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The self-policing nature of these ethical codes gives them little clout except to expel a member from the particular society. However, many state licensing boards for engineers have adopted "rules of professional conduct" that closely mirror these codes of ethics, so that a proven violation can now result in reprimand, suspension, or revocation of one's license to practice engineering (91). These "rules of professional conduct" for engineers are similar in scope to the "code of professional responsibility" that each state bar has adopted for its attorneys (92).

The content of engineering ethics codes is controversial. They vary among engineering societies, seemingly dependent upon the degree to which its members tend to practice engineering outside of a large corporate hierarchy. For instance, the NSPE has many members who practice engineering in small consulting engineering firms, usually of the partnership nature, so their code is quite long and detailed and contains considerable information designed to self-regulate the profession (88). In contrast, The American Institute of Chemical Engineers (AIChE) consists mostly of members employed by large corporations; no pecuniary influencing clauses are present in its code of ethics (87). Slowter and Oldenquist have reviewed many engineering codes of ethics from the philosophical viewpoint and concluded that three types of clauses should occur (93). These are:

- public interest responsibility
- qualities of truth, honesty, and fairness
- professional performance standards.

Thus, Slowter and Oldenquist would delete any pecuniary type information as being improper for a code of ethics.

When can an ethical responsibility as given in a code of ethics become illegal? For the engineer this was answered by the U.S. Justice Department's antitrust case against NSPE (94). The controversy concerned section 11(c) of the NSPE Code of Ethics, which stated:

Section 11—The Engineer will not compete unfairly with another engineer by attempting to obtain employment or advancement or professional engagements by competitive bidding. . . . (c) He shall not solicit or submit engineering proposals on the basis of competitive bidding. Competitive bidding for professional engineering services is defined as the formal or informal submission, or receipt, or verbal or written estimates of cost or proposals in terms of dollars, man days or work required, percentage of construction cost, or any other measure of compensation whereby the prospective client may compare engineering services on a price basis prior to the time that one engineer, or one engineering organization, has been selected for negotiations. The disclosure of recommended fee schedules prepared by various engineering societies is not considered to constitute competitive bidding. An Engineer requested to submit a fee proposal or bid prior to the selection of an Engineer or firm subject to the negotiation of a satisfactory contract shall attempt to have the procedure changed to conform to ethical practices, but if not successful he shall withdraw from consideration for the

proposed work. These principles shall be applied by the Engineer in obtaining the services of other professions.

The government alleged this was a per se violation of the Sherman Antitrust act (95):

Every contract, combination in the form of trust or otherwise, or conspiracy, in restraint of trade or commerce among the several states, or with foreign nations, is declared to be illegal . . .

The NSPE defense was based upon the Rule of Reason, as its brief stated (94):

18. (a) The principles and standards contained in the NPSE Code of Ethics, particularly those contained in that part of the NSPE Code of Ethics set out above, are reasonable, necessary to the public health, safety and welfare insofar as they are affected by the work of professional engineers, and serve the public interest.

(b) Experience has demonstrated that competitive bidding for professional engineering services is inconsistent with securing for the recipients of such services the most economical projects or structures. Testing, calculating and designing the most economical and efficient structures and methods of construction is complex, difficult and expensive. It is cheaper and easier to design and specify inefficient and unnecessarily expensive structures and methods of construction. Consequently, if professional engineers are required by competitive pressures to submit bids in order to obtain employment of their services, the inevitable tendency will be to offer professional engineering services at the lowest possible price. Although this may result in some lowering of the cost of professional engineering services it will inevitably result in increasing the overall cost and decreasing the efficiency of those structures and projects which require professional engineering design and specification work.

(c) Experience has also demonstrated that competitive bidding in most instances and situations results in an award of the work to be performed to the lowest bidder, regardless of other factors such as ability, experience, expertise, skill, capability, learning and the like, and that such awards in the case of professional engineers endanger the public health, welfare and safety.

(d) For the aforesaid reasons, the provisions of the NSPE Code of Ethics set out above are not, in any event, an unreasonable restraint of interstate trade or commerce.

The Supreme Court rejected these arguments as a misapplication of the Rule of Reason:

Contrary to its name, the Rule [of Reason] does not open the field of antitrust inquiry to any argument in favor of a challenged restraint that may fall within the realm of reason. Instead, it focuses directly on the challenged restraint's impact on competitive conditions.

The court refused to accept any professional project exceptions.

The fact that engineers are often involved in large-scale projects significantly affecting the public safety does not alter our analysis. Exceptions to the Sherman Act for potentially dangerous goods and services would be tantamount to a repeal of the statute. In our complex economy the number of items that may cause serious harm is almost endless—automobiles, drugs, foods, aircraft

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components, heavy equipment, and countless others cause serious harm to individuals or to the public at large if defectively made. The judiciary cannot indirectly protect the public against this harm by conferring monopoly privileges on the manufacturers.

Further, the crack in antitrust analysis suggested by the *Goldfarb* case, which implied that a profession may be treated differently from ordinary business in antitrust situations, was effectively closed with (96):

By the same token, the cautionary footnote in *Goldfarb* cannot be read as fashioning a broad exemption under the Rule of Reason for learned professions. We adhere to the view expressed in *Goldfarb* that, by their nature, professional services may differ significantly from other business services, and, accordingly, the nature of the competition in such services may vary. Ethical norms may serve to regulate and promote this competition, and thus fall within the Rule of Reason. But the Society's argument in this case is a far cry from such a position. We are faced with a contention that a total ban on competitive bidding is necessary because otherwise engineers will be tempted to submit deceptively low bids. Certainly, the problem of professional deception is a proper subject of an ethical canon. But once again, the equation [sic] of competition with deception, like the similar equation [sic] with safety hazards, is simply too broad; we may assume that competition is not entirely conducive to ethical behavior, but that is not a reason, cognizable under the Sherman Act, for doing away with competition.

Technical societies are justifiably concerned that competitive bidding may degrade public safety, not only when large and expensive technical projects are concerned, but also when insufficient engineering analysis enters into bidding specifications. However, the Supreme Court readily indicated that the approach used was overly broad and in this instance illegal, and any improvement along these lines must come from Congress.

A further antitrust concern for professional groups can be based upon the *Radiant Burner* case (97). Here the American Gas Association, a trade group, effectively refused to test Radiant's gas burner for safety, utility, and durability. The test standards were determined by the trade group itself. The Supreme Court said that Radiant had a valid cause of action under federal antitrust law, thus, judgment for failure to state a claim upon which relief can be granted by the district court and affirmed by the appellant court, was reversed. The implication is that private groups, such as a professional association, cannot make their own standards in restraint of trade, and that this type of public safety standard can only come from a governmental body under legislative authorization (98).

A recent Supreme Court decision has further clarified this critical issue. In *American Society of Mechanical Engineers [ASME] vs. Hydrolevel Corp.* a severely divided court affirmed the Second Circuit Court of Appeals finding that the ASME was guilty of antitrust violations (99). The facts of the case were that certain members, including the

chairman, of the ASME subcommittee, who were also officers in a company competing with Hydrolevel, and who had the power to interpret the widely based ASME Boiler and Pressure Vessel Code, used their committee positions to conspire against Hydrolevel by issuing a misrepresentation of the compliance of Hydrolevel's product with the subject code. The conspiracy was started by a member of the chairman's company, who requested an opinion about the Hydrolevel product. The chairman had prior knowledge of the request. Subsequently, the case against the individuals and their respective companies was settled out of court, leaving ASME as the only defendant.

The district court's jury decision found ASME guilty on the legal agency theory of actual authority. Here the jury ruled that since the committee's opinion was sent out on ASME letterhead and over the signature of an ASME employee, the society had ratified the committee's actions. The Court of Appeals affirmed but changed the legal theory to that of apparent authority, reasoning that this took a lesser degree of proof than actual authority, so that the jury would also have returned a guilty decision based upon this question.

A divided Supreme Court ruled 6-3 to affirm the Court of Appeals. In terse and sometimes caustic language, the majority opinion and the dissent chastised each other's legal theories. The majority felt apparent authority was sufficient reason to impose vicarious antitrust liability on the principal, even in the case of a nonprofit organization. The dissent reasoned, based upon congressional intent, apparent authority was an insufficient basis to apply antitrust liability, especially where in a nonprofit setting the principal gained nothing economically. However, the majority did agree with the Court of Appeals that the trial court's \$7.5 million damage was excessive, especially since ASME later reversed the opinion with full committee action and sent a retraction letter. The majority stated:

We hold that the apparent authority is consistent with the congressional intent to encourage competition. ASME wields great power in the nation's economy. Its codes and standards influence the policies of numerous states and cities, and, as has been said about "so-called voluntary standards" generally, its interpretations of its guidelines "may result in economic propriety or economic failure, for a number of businesses of all sizes throughout the country," as well as entire segments of industry... ASME can be said to be "in reality an extra-governmental agency, which prescribes rules for the regulation and restraint of interstate commerce."... When it cloaks its subcommittee officials with the authority of its reputation, ASME permits those agents to affect the destinies of businesses and thus gives them the power to frustrate competition in the workplace. [citations omitted]

The majority essentially infers that ASME has performed so excellently in the standards business that it must be regulated by government action. Since ASME is not a public utility subject to economic regulations, the antitrust

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laws must serve to represent the public interest. The classic *Munn v. Illinois* case suggested that an enterprise could become "clothed with a public interest" and thus be subject to public regulation (100). The majority reasons that ASME's very success with its Boiler and Pressure Vessel Code has subjected it to the need for public regulation.

A further aspect of the majority opinion is that ASME can impose internal controls sufficient to prevent the Hydrolevel controversy from recurring. In fact, as a result of the trial court's decision, ASME did use new procedures for its standards committees. Thus, the majority penalized a subsequent remedial remedy similarly to its use against the defendant in product liability suits involving strict liability. (101). On the other hand, the dissent reacted with:

The Court today adopts an unprecedented theory of antitrust liability, one applied specifically to nonprofit, standard-setting association but a theory with undefined boundaries that could encompass a broad spectrum of our country's concept of "apparent authority," would impose the potentially crippling burden of treble damages. In this case, the Court specifically holds that standard-setting organizations may be held liable for the acts of their agents even though the organization never ratified, authorized, or derived any benefit whatsoever from the fraudulent activity of the agent and even though the agency acted solely for his private employer's gain. In my view such an expansive rule of strict liability, at least as applied to nonprofit organizations, is inconsistent with the weight of precedent and the intent of Congress, unsupported by the rules of agency law that the Court purports to apply, and irrelevant to the achievement of the goals of the antitrust laws. Accordingly, I dissent.

Here the use of the phrase "rule of strict liability" implies that in comparison with product liability theory, the actions of the defendant are immaterial, and only the result that any economic injury to a third party will leave the nonprofit organization liable.

Punitive damages is the term the dissent associates with treble antitrust damages and notes further that punitive damages have not been normally allowed for apparent authority liability up to now.

The Supreme Court decision poses serious concerns for all professional organizations, not just engineers, whether to continue their voluntary standards programs by using members with expertise in the appropriate subject matter. These member volunteers feel that they have a moral responsibility, in the traditional subjective sense, as knowledgeable persons in the field, to set safety requirements for the benefit of the public.

Perhaps ASME's basic problem is a reliance on the concept of professionalism that implies that an engineer "will be realistic and honest in all estimates, reports, statements, and testimony" (94). Thus, even in a situation where personal conflict of interest could occur, the engineer can still give an opinion in this professional sense. In contrast, in the legal profession, with which the court judges naturally concur,

the Code of Professional Responsibility Canon Nine is "a lawyer should avoid even the appearance of professional impropriety," implying that sufficient checks and balances should be placed upon a group, even professionals, so that a conflict of interest will not be possible. Thus, maybe ASME volunteer standards can survive if more bureaucratic multiple review procedures are employed to ensure that conflicts of interest cannot occur. Naturally, then, efficiency declines and costs increase. But to the engineer a one-shot occurrence is insufficient reason to drastically change a well-functioning procedure. He or she requires a significant continuing probability of difficulty before change can be justified. In the collective responsibility sense, where does the moral responsibility of the engineer and his or her employer corporation lie?

Conclusion

From the discussions in this overview, no clear-cut line exists where the engineering profession's legal responsibility ends and its moral responsibility continues. The closest approximation to a concrete division lies in the field engineering area, where contract terms try to limit legal liability, but the ethical duty to prevent foreseeable harm is still present. Naturally, if control is extended beyond the contract limits, liability will follow this morally based action.

Conversely, when legal liability is predicated upon strict liability concepts, the engineering profession suffers monetarily from the imposition by the courts of egalitarian ethical ideas upon their utilitarian views. Because the engineering profession generally possesses a utilitarian ethical value system, with strong overtones of meritocracy, the courts' use of the "deep pocket doctrine," requiring the manufacturer to be in essence the insurer of his products, creates a bewildered engineering profession that wonders why society is picking on it. The profession's answer has been to fight back with help of its utilitarian friends in the insurance industry by using the political process to have state legislatures pass "product liability acts." These acts essentially reintroduce the concepts of negligence into the product liability arena and shift the balance of justice more toward a utilitarian viewpoint.

On a separate front, the engineering profession, in attempting to apply its utilitarian ethical principles to the establishment of behavior guidelines for its members and to the establishment of technically sound standards (both done in the interest of having the profession act in a manner most advantageous to the public), runs afoul of the libertarian antitrust principles and laws. Antitrust ideas can have utilitarian supporters when monopolistic situations work against the overall good of the public. But when antitrust laws are stretched to bring in peripheral parties clearly outside of the action according to utilitarian conflict-of-interest principles, again the engineering

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profession wonders why society is picking on it.

How should the profession respond? Should it change its ethical value system to egalitarian? Of course not! The business of risk imposition can only be handled with a utilitarian viewpoint. Thus, the engineering profession will have to learn to live with a certain amount of litigation fostered mainly by the egalitarian elements of society. In addition, society is making strong implications that engineers need to do a better job of analysis and synthesis in creating their work product, which further implies to the engineer that society is willing to pay the increased cost associated with more engineering services. However, society also seems to say that engineers should accept more of a continuing responsibility for their work product that should include a further search for methods to lower, not only the uncertainty associated with any risk imposition, but the actual risk itself.

Philosophers have been unable to show clearly and convincingly that either utilitarianism or egalitarianism is a superior approach (102). Society must live with this conflict of values. Indeed, the Constitution states that Congress can pass laws designed to produce the maximum good for society as a whole, but these laws are limited by the rights enumerated and implied in the Bill of Rights. And, many of the most famous Supreme Court cases have dealt, ultimately, with this conflict of values. We hope we have explained here the origin of some of these value conflicts and why technologists are naturally inclined to a utilitarian value system. One major source of the technologists's dilemma is that his or her utilitarian moral value system often conflicts with a legal system that is in large part based upon nonutilitarian moral principles.

Acknowledgments

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side of CCK's action will not retard the development of morphine tolerance, the problem of tolerance may be mitigated by a reduction in the total amount of morphine needed to alleviate pain.

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9. The BSA-immunized group controls for the antibodies developed in the CCK-immunized group against BSA as well as for a general stress effect of the immunization procedure.
10. Samples (10 μ l) of serum from the tail vein or cerebrospinal fluid from the cisterna magna were incubated in Veronal buffer (pH 8.5) with [¹²⁵I]CCK octapeptide (10,000 count/min; New England Nuclear) for 48 hours. Bound radioactivity was precipitated with goat antibody to rat immunoglobulin G. Specific binding was calculated by subtracting nonspecific binding (that measured in normal rat serum) from total binding. The normal concentration of circulating CCK in rat is not known. However, resting values for dogs and humans are approximately 64 and 26 pg/ml, respectively [G. M. Fried *et al.*, *Gastroenterology* 85, 1113 (1983); P. N. Maion, A. C. Selden, V. S. Chadwick, *Regul. Peptides* 4, 251 (1982)]. Thus it is likely that the binding capacity of serum from our experimental animals (~ 50 pg/ml) was high enough to sequester a large percentage of the endogenously released CCK. It is also important to note that serum from our CCK-immunized rats could not have bound morphine, since this would have resulted in a decrease in free morphine and hence a decrease in analgesia rather than the observed potentiation.
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Incidence of Low Birth Weight Among Love Canal Residents

Abstract. The incidence of low birth weight among white live-born infants from 1940 through 1978 was studied in various sections of the Love Canal. A statistically significant excess was found in the historic swale area from 1940 through 1953, the period when various chemicals were dumped in this disposal site. Potential confounding factors such as medical-therapeutic histories, smoking, education, maternal age, birth order, length of gestation, and urban-rural difference did not appear to account for this observation. Low birth weight rates were comparable to those of upstate New York from 1954 through 1978, the period when there was no deposition of chemical wastes.

Concern about adverse health effects that might be associated with hazardous chemicals dumped at sites such as the Love Canal has been growing. Over 200 chemicals have been found in the Love Canal dump site (1) and many, such as benzene (2) and lindane (3), have been shown to have toxic effects on man in industrial settings. The spectrum of human hazards that might be associated with other compounds isolated in the canal, such as certain isomers of dioxin (4), is not known.

Two major difficulties encountered in designing epidemiologic studies of chronic diseases in multichemical settings are the uncertainty in selecting appropriate end points and the long induction period between exposure and clinical diagnosis. Certain adverse reproductive events, however—low birth weight is an example—are objectively identifiable in a relatively short period of time. We analyzed data on the incidence of low birth weight among infants born in the Love Canal area from 1940 through 1978. This time span includes periods of active dumping at the site (1940 through 1953) and no formal dumping (1954 through 1978).

The study population included all peo-

ple residing in single-family houses located in a series of parallel streets (97th Street through 103rd Street), bounded on the north and south respectively by two avenues (Colvin and Frontier) (5). Backyards of 99 houses on 97th and 99th streets directly abut the canal.

Because there are no historical environmental data on houses in the study area, we had to infer which subsets of the study population might have maximum exposure to chemicals. We reasoned that one group might be the families who lived on 97th and 99th streets directly adjacent to the chemical dump site. The accumulation of rain and ground water, facilitated by either natural or man-made activity, could have raised the level of chemical wastes to the topsoil layer, thus facilitating lateral migration. This slowly overflowing bathtub effect could result in the transport of waste products to adjacent backyards and basements.

Another possibility was that certain chemicals in the dump site might have spread preferentially to houses located on the natural drainage pathways in the area. Before the development of housing in this area, a number of natural shallow depressions traversed the area, some of

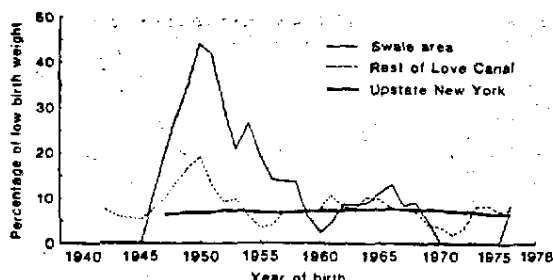


Fig. 1. The 5-year moving averages for percentages of low birth weights among infants born in the Love Canal swale area ($n = 174$), the rest of the Love Canal area ($n = 443$), and upstate New York.

which intersected the Love Canal itself. The locations of these depressions, commonly referred to as swales, were determined from aerial photographs taken in 1938, 1951, and 1966. The photographs were independently interpreted by a group at the Cornell University School of Civil and Environmental Engineering who had no knowledge of the hypotheses being tested. These depressions served as drainage ways and produced ponding in certain sections during times of high water. Additional verification of historical drainage pathways was obtained from interviews with area residents and review of their photographs and motion pictures. As the area was developed, the contour and extent of these swales was substantially modified. By 1956, the major swale which intersected the upper section of the canal was eliminated. The identification of houses located on these natural depressions was established from serial aerial photographs taken between 1938 and 1966. Still another possibility was that residents in the entire study area might have been exposed to toxic vapors emanating from the dump site. Accordingly, we hypothesized that there was an excessive incidence of low birth weight infants who were conceived and born in each of these areas.

In an effort to identify and interview all individuals who resided in the study

area at any time from 1940 through June 1978, the following sources were used: a review of all property records on file at the assessor's office in Niagara Falls, New York; city directories for all available years in the study period; calls to hot lines indicating individuals with prior residency in the area; and residents identified by those who lived in the area and were interviewed in 1978. Birth files from vital records at the New York State Department of Health were searched manually for all surnames identified through these sources, for the years 1940 through 1978. In addition, all available computerized vital record birth files (1958 through 1978) were surveyed to identify live births in the study area as a check on the other data. No additional births were found for the period. With use of a prepared questionnaire, adult residents (18 years of age and older) were interviewed about past medical, therapeutic, social (smoking, alcohol, and educational), and occupational histories. Pregnancy histories were obtained from all females. The same field investigators conducted the interviews throughout the study.

Of the 1295 adult females who were identified as having resided in the study area, 1201 (92.7 percent) were located and interviewed. Forty-one (3.2 percent) were located but refused to be inter-

viewed, and 53 (4.1 percent) could not be located. There were 383 women who had a total of 617 children [612 (99 percent) white, 4 black, and 1 American Indian] born alive in the study area from January 1940 through June 1978. They had resided in the area an average of 11.0 years (range 1 to 30 years) during their reproductive period (15 through 44 years of age). Birth certificate information for all infants born to women who had lived in the area for at least 9 months before the time of the birth of the child was obtained from the State's Bureau of Vital Records. The address was reviewed and the birth weight shown on the certificate recorded. If the resident address on the birth certificate was not a study area address, the birth was not considered in the analysis. Infants who weighed 2500 g (5 pounds, 8 ounces) or less were considered low birth weight children.

The proportion of low birth weight infants among all live births was established for the entire study area, the swale area, and the area abutting the canal. The average proportion of all white infants of 2500 g or less at birth for upstate New York (that is, New York State, excluding New York City) from 1945 through 1978 (6) (5,088,556 live births, $351,682 \leq 2500$ g, 6.9 percent low birth weight) was used in comparisons to indicate whether there was an excess of low birth weight children in the various study areas. As another comparison, the proportion of low birth weight white children for all cities of population 25,000 or greater (1970 census) in upstate New York from 1953 through 1978 (7) was calculated (1,043,066 live births, $80,938 \leq 2500$ g, 7.8 percent low birth weight). Sex ratios (male rate divided by female rate) were calculated for each Love Canal study area, for upstate, and for the urban group. Binomial probabilities of the observed number or more of low birth weight children were established for each study area on the basis of these rates. Probabilities of differences between areas within the canal were also established by the normal approximation of the difference between two proportions (z test, one-tailed). This was also done for differences when smoking history of mothers and household education (highest number of years of school completed by either parent) were considered. An examination of the past medical, therapeutic, social, and occupational histories of adult females with live births did not reveal any unusual patterns, such as radiation therapy or known infection during pregnancy, in any of the areas studied.

The expected number of low birth

Table 1. Total live births and children born with low birth weights in the swale area compared with the rest of the Love Canal (that is abutting the canal and nonswale) and by the known smoking and educational histories. The P values are based on one-tailed z tests for two proportions. Numbers in parentheses are percentages.

History	Number of births				P
	Swale		Rest of canal		
	Live	Low birth weight	Live	Low birth weight	
All live births	174	21 (12.1)	443	32 (7.2)	0.027
Smoking					
Never smoked	70	7 (10.0)	174	7 (4.0)	0.035
Smoked	102	13 (12.7)	265	25 (9.4)	0.175
Household education					
<12 years	41	6 (14.6)	105	3 (2.9)	0.004
12 to 15 years	124	14 (11.3)	285	24 (8.4)	0.179
≥16 years	7	1 (14.3)	44	0 (0.0)	

weight children by age of mother was determined from the proportion of low weight children in each age group in upstate New York and the number of live births by age of mother in each area. The probabilities of the differences were calculated (χ^2 test). The same analyses were done for birth order. Gestational age (under 37 weeks) of low birth weight children was examined for each area and for upstate New York. Finally, temporal trends in each study area were evaluated by calculating 5-year moving averages of the percentage of low birth weight children by year of birth.

Among the 617 children born in the entire study area, 53 (8.6 percent) had low birth weights. In the houses abutting the canal, there were 124 live births with 8 (6.5 percent) low birth weight infants, and among the 174 live born infants in the swale area, 21 (12.1 percent) had low birth weights.

The binomial probabilities of the numbers of low birth weight children observed for the entire study area as well as for the area abutting the canal were within chance variation ($P > 0.05$ for all) when compared with upstate New York or the urban areas. The χ^2 probabilities of the distributions by maternal age and by birth order when compared with upstate New York were also within chance variation ($P > 0.05$ for both). However, the number of low birth weight infants born in the swale area was significantly more than both upstate New York (binomial, $P = 0.009$) and the urban area group (binomial, $P = 0.029$) (8). When the data were analyzed by age of mother and by birth order, the number observed in this area was also significantly more than upstate New York for each [respectively, $\chi^2(1) = 7.0514$, $P = 0.008$; $\chi^2(1) = 6.7438$, $P = 0.009$].

Swale area residents had significantly more low weight children than did the residents of the rest of the canal ($P = 0.027$) (Table 1). This was also true among women who had never smoked ($P = 0.035$). Results for educational level are also shown in Table 1. The proportions of low birth weight children for whom gestational periods were under 37 weeks were similar in the swale area and the rest of the canal: 52.4 and 53.1 percent, respectively. The percentages in both areas were consistent with that of upstate New York (48.9 percent) ($P > 0.05$ for both).

The sex distributions for all live births and low birth weight children in the swale area and the rest of the canal were all within chance variation (z test, two-tailed, $P > 0.05$ for each) when compared to those of upstate New York and the urban areas. The average length of residence for all women with live births was 10.8 years for the swale area and 10.3 years for the rest of the canal. For women who had a low weight child the averages were 10.9 years for swale area residents and 11.4 years for residents of the rest of the canal. For those without a low weight child the average residence was 10.8 years for swale residents and 10.2 years for the rest of the Canal. None of the differences between areas, or within area by weight of child, was statistically significant ($P > 0.05$ for all).

The 5-year moving average of the percentage of low birth weights indicated that in the swale area there was a marked excess of these births starting in 1946 and ending in 1958 (Fig. 1), peaking in 1950 (8 of 18 infants, 44.4 percent). The rest of the canal area also showed a peak in 1950, but the magnitude was not as large (4 of 21 infants, 19.0 percent) and the time span, 1947 to 1953, was shorter. For the period of active dumping (that is, prior to 1954), the swale area's percentage of low weight births was higher than in upstate New York (z test, $P < 0.0001$) and the rest of the canal (z test, $P < 0.012$). Low birth weights in the rest of the canal were not significantly higher than in upstate New York ($P > 0.05$).

It is important to emphasize that the low birth weight data used for all analyses were obtained from birth records and not through interview. There are several major difficulties in study design that limit the interpretation of results. It is not certain that all infants born in the area during the study period were included in this investigation. Although it is clear that human exposure to a specific toxic agent can result in an adverse reproductive outcome (9, 10), it is exceedingly difficult to define exposure in multi-chemical settings such as the Love Canal. In addition, the evidence associating low birth weight with toxic chemical exposure is limited (11). Other variables, for which there are no objective data, can influence the frequency of the end point. Although we found no convincing evidence that educational level, smoking, occupation, past medical or thera-

peutic histories influenced the results, most of these data were obtained from interviews and are, therefore, subject to recall bias. In addition, it was impossible to examine other important variables such as alcohol ingestion before and during the pregnancies included in this study.

Despite these limitations, our findings suggest that a real excess of low birth weights occurred in the swale area during a time period when there was active dumping at the Love Canal. Whether other objective health end points, such as congenital defects, will show similar results is not yet known. In any event, our study also suggests that infants born alive in the Love Canal study area between 1960 and 1978 were at no greater risk of low birth weight than were those born in upstate New York.

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8. Stillbirths were excluded from our analysis because there were only a total of seven among residents of the Love Canal area during the study period. Four were born to residents of the swale area of which two were low birth weight. Of the three born to residents of the rest of the canal, one was low birth weight, one was not, and the status of the third was not known. In order to determine whether their exclusion could significantly distort the frequency of low birth weight infants in one or more of the study areas, we analyzed total births (including stillbirths) and found that our findings were not altered ($P = 0.008$ for the period of active dumping in the historical swale area compared to the rest of the canal).
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urged attention at the early stage of development, noting that if a substance is permitted into the environment it is then too late to do anything about it. However, Wilkinson added that he does not think there are actual "risks" (See July 24, Page 20).

Davis said an SAP sub-panel with specific expertise in the field has been formed, and that this sub-panel will be involved in consideration of small-scale tests.

FDA Commissioner Dr. Frank E. Young commented that EPA lacks a classical microbiology branch, saying, "It is a difficult time." EPA's Dr. Elizabeth L. Anderson, Director of the Office of Health and Environmental Assessment, replied that her office contains experts.

Dr. Angelo Turturro of the National Center for Toxicological Research asked how EPA conducts risk assessment, and Davis replied that a small-scale trial can be utilized. Conceding that the "Catch-22" is that the risk in conducting the experiment cannot be known without conducting the experiment, Davis replied that "greenhouse experiments" are satisfactory. He said that "peer review in that area is a key . . ."

Davis said biotechnology permits "unique regulatory challenges," stating that the agency's goals are a "credible scientific review mechanism . . .," a "regulatory approach that doesn't lead to . . . over-regulation . . .," and maintenance of public confidence. Lack of public confidence leads to restrictive regulation, he indicated. Davis reviewed EPA's proposed policy on biotechnology regulation, which was published late last year (See Jan. 2, Page 5), calling for the "building of confidence in the process" under a "meaningful and minimal regulatory structure."

Wilkinson commented that different government agencies are "suddenly getting into the act," expressing the view that agency guidelines are being developed "too hastily and without a great deal of thought."

URL 02928

EPA TO HOLD WORKSHOPS ON USE OF RISK ASSESSMENT

EPA is arranging a series of workshops on how to use risk assessment information, the agency's Dr. Elizabeth Anderson, Director of the Office of Health and Environment Assessment, told the Toxicology Forum in Aspen, Colo. (See preceding and following stories).

The agency official said she is "concerned" that numbers can be "applied inappropriately" in making risk assessments.

Discussion of risk assessment at the Toxicology Forum mainly dealt with the practical difficulties in extrapolating animal data to man and in making realistic risk assessments. Details of this discussion were carried in the July 29 issue of FOOD CHEMICAL NEWS, a companion publication.

Stating that there is "consensus" about EPA's risk assessment guidelines, Anderson described them as an attempt to reduce the "unknowns in scientific data . . ." She called for consistency, avoidance of a "cookbook" approach, flexibility on a case-by-case basis, and openness of the process.

Anderson said EPA is trying to work out safety factors, stressing that EPA's guidelines on carcinogenicity are consistent with those of the White House Office of Science and Technology Policy. The goals, she said, are to balance risks and benefits, set target levels of risk, establish priorities, determine residual risk, and establish the urgency of public health risks, such as in crucial uncontrolled waste sites.

PESTICIDE & TOXIC CHEMICAL NEWS

Although quantitative risk assessment "can be a doubled-edged sword," Anderson stressed flexibility, noting that EPA found benzene represented only a minor risk, FDA found lead acetate to present only a "trivial risk," and FDA is attempting to use risk assessment to find that color additives are in a "de minimis risk situation." The EPA-er said it "would be a mistake to attempt to back away from quantitative risk assessment."

Consultant Dr. Albert C. Kolbye, Jr., expressed concern that states might base enforcement actions on the numbers. Anderson replied that the cut-off line on use of numbers depends on the weight of the evidence.

Dr. Robert A. Neal, Chemical Industry Institute of Toxicology, discussed a risk assessment made on formaldehyde by CIIT, and hitting government failure to consider mechanism (See July 17, page 8). FDA's Dr. Robert Scheuplein said formaldehyde is a complicated example of quantitative risk assessment, commenting that the Interagency Risk Management Council Working Group has appointed a working group to consider the matter. The FDA-er said that CIIT separated the effects, noting a non-linear increase in DNA binding. He added that there is no agreement yet on the proper administered dose of formaldehyde for testing.

TSCA Retrospective Review to Cover 69 Non-Polymers, 31 Polymers

EPA's Charles M. Auer, of the Office of Toxic Substances, said the retrospective review of toxicity predictions under TSCA will exclude certain polymers, covering approximately 69 non-polymers and 31 polymers (See July 24, Page 32). Under TSCA, he noted, the agency must make toxicity assessments on the basis of limited test data. He said the PMN system under Section 5 of TSCA is "most useful in screening chemicals . . ."

The retrospective review, funded by EPA and the National Toxicology Program, will be completed in 1987 or 1988, Auer said. It is designed to determine whether the EPA assessment of toxicity would have changed if more tests results had been available, based on a comparison between the toxicity assessments and the results of a battery of tests designed to control "false positives" and "false negatives," he explained.

Auer added that selected chemicals will undergo systemic toxicity tests and a genetic test battery. If concerns arise, he said, additional tests will be considered, noting that this may be limited by funding constraints. In addition to comparing test results with toxicity predictions, Auer said, specific toxicities will be compared.

In the second part of the program, dealing with long-term effects, the EPA-er said a study will be designed to increase EPA's ability to predict toxicity. A "confirmatory laboratory study" may be conducted for substances being subjected to NTP testing.

Dr. Ernest E. McConnell, of the National Institute of Environmental Health Sciences, called the retrospective review a "very important study," commenting that the lack of data on substances reviewed under TSCA has been a "best kept . . . secret."

AGENT ORANGE "POLITICAL" INVOLVEMENT STRESSED AT TOX FORUM

Some of the studies on Agent Orange and dioxin effects on Viet Nam veterans were conducted for "political reasons," Dr. Michael Gough, of the Congressional Office of Technology Assessment (OTA), alleged at the Toxicology Forum held in Aspen, Colo. (See preceding stories).

UPL 02929

ASPECTS OF TOXICITY AND TOXICOLOGY

Chemistry and Industry, 1/17/83, p. 52

Skin problems in the chemical industry

*File: Risk
Gen*

Theodore Gadian

Of all the many hazards of the chemical industry, cancer receives by far the most attention. Its emotive effect singles it out from all other diseases, and makes it totally unacceptable. Consequently, a very high proportion of the limited medical, nursing, and hygiene manpower and expertise that is available is devoted to it. Yet dermatitis is by far the commonest, and in many ways now the most important, of all the hazards. Occupational dermatitis* comprises more than 60 per cent of all cases of industrial disease.

Much has been achieved in bringing the hazard of occupational cancer in the chemical industry under very strict control. So much so that although it may be unpopular to do so, an important question has now to be asked. It is whether, by continuing to devote so much time, money, and effort to reduce the risk of, say, bladder cancer in the dyestuffs manufacturing industry from its present minute level to one marginally still more minute, it is at the expense of other occupational diseases, such as dermatitis? Even the most enlightened companies must set some limit to their budget for safety, and undue emphasis on one type of hazard may prejudice the efforts to control the others. We must question whether what were the priorities of 10, and certainly of 30, years ago must necessarily remain the absolute priorities of today. This is not a plea to abandon or neglect cancer research and prevention — it is a plea to get the balance right.

The control and avoidance of dermatitis is one of industry's most important tasks in the medical field. Dermatitis is the cause of much ill-feeling between management and unions; of litigation, sickness absence, unemployment and unemployability; and, of course, of skin irritation and cosmetic embarrassment.

Skin sensitisation

Some of the misunderstandings which arise between worker and management occur because companies which do not have a medical officer, may be unaware of the basic difference between skin irritation and skin sensitisation. Consequently, when, after recovering from a rash or other

affection of the skin, the question of returning to their old jobs arises, men are sometimes treated in the same way from whichever of the two they have suffered, whereas the placement of the two categories should be quite different. The distinction is a fundamental one. In everyday life we are familiar with the fact that some people develop a rash when they eat strawberries, others when they eat plums; and the severe reactions of still others to primula and to penicillin are well known. Similarly, in industry, some men will react to certain chemicals by developing a rash even when the exposure is slight, while others are not affected at all, even by higher exposure. Moreover, once sensitised by a first attack, subsequent exposure to even minute concentrations may provoke a reaction, and with each fresh attack the tolerance to the chemical is lowered, and the range of substances which will provoke a reaction may increase.

Sensitisation thus involves a special relationship between a particular person and a particular chemical, or perhaps a family of chemicals. Once this is definitely established, the man must avoid contact with the substance. In severe cases, he can become so sensitised that he has to avoid even going too near to the building in which the chemical is being used. It is, therefore, as essential to avoid his further exposure as it is essential to ensure that the person who is sensitive to penicillin is not given it in any form — not even as highly diluted eye drops — and that the one who is sensitive to strawberries or plums never eats them — not even one.

This is in direct contrast to the worker whose skin has been burned by, say, a corrosive acid, or highly irritated by bromine. Once his skin has healed there is no increased risk in his working again with the acid or with bromine, because further skin injury will not cause a more violent reaction than the first. He will be affected no differently from the man who has never previously been burned. To take another example from everyday life, the man who is pricked by a rose thorn can continue to dead-head and prune his roses, because if he is pricked again he will not react more intensely than he did the first time.

The question, then, of where to employ a man who has

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*Occupational Dermatitis, Prescribed Disease No. 42, is described in the National Insurance (II)(PD's) Regulations, 1st schedule, Part 1 as 'Non-infective dermatitis of external origin (including chrome ulceration, but excluding dermatitis due to ionising particles or electro-magnetic radiations other than radiant heat)'.

developed a rash would appear to be simple. If it is due to sensitivity, he must be taken off the process. If it is due to skin irritation, he can go back to his old job. In practice, however, it is not so simple. It is not always easy to be sure that a skin eruption is due to a man's work, and not to some other cause. In almost all industrial diseases, dermatitis also occurs outside industry. The worker's rash may be due to the use of detergents at home, or to the use of a hair shampoo, a wristlet watch strap, a ring, make-up, or a suspender strap (the worker with a rash is not necessarily a man).

Not all rashes in workers are necessarily dermatitis. In factories one sometimes meets with infectious diseases, such as German measles, chicken pox, or scarlet fever; also with skin diseases which arise from some built-in constitutional factor, such as psoriasis, lichen planus and pityriasis. A case of German measles in a workplace where there may be women in early stages of pregnancy can have terrible consequences, and the rash may come and go in a couple of days with no accompanying malaise; it is therefore important for the medical officer to be on the look out for the possibility that the patient is suffering from German measles.

It is also important to be certain that in a genuine case of occupational dermatitis, the responsible chemical is correctly identified, and that the patient is removed from contact with that chemical, and not from some innocent material, as has been known to happen.^{*} The identification of the responsible chemical, or even of the particular part of the process, may not be easy, especially in workers such as maintenance men, who work in many different areas. Patch testing is not as conclusive as it might seem, and false positive and false negative results can be obtained for various reasons such as human error, wrong dilutions, or the effects of the solvent used. It may also cause a severe flare-up of the dermatitis. It should always be carried out by a well-trained person, and even then one sometimes gets the maddening report that the subject appears to be sensitive to nothing at all, or else to almost everything tested. In spite of these limitations, however, patch testing does sometimes prove to be of considerable value.

It may be asked why we do not attempt to desensitise the sensitised individual, as is done with some non-industrial substances, such as pollen. This cannot normally be attempted in industry, because the responsible chemicals are usually too toxic to inject, and the principle of desensitisation is to inject gradually increasing doses of the material into the patient.

As is often the case, simple common sense methods may be more effective than highly technical ones. Much is at stake both for the worker, and for a conscientious company, and between them every effort must be made to solve the problem. The trial and error method can be very useful. It involves returning the man, after the rash has disappeared, to the same job that he was doing at the time it erupted. If the rash then re-occurs, it is reasonable to presume that it is due to his work, and it may then be easier to pin-point which chemical, or which process or part of the process, is the cause. He is then removed permanently from it. It is surprising how often the rash does not re-appear, which

means that the suspected chemical is not, in fact, the cause. It is essential that the whole procedure should first be explained to the man and discussed with him. This should be done by the medical officer if there is one, and failing that, by the safety officer. The method should only be used with the man's full knowledge and consent. It may be argued that the worker is being used as a guinea-pig. To some extent this is true, but in my opinion the counter-arguments effectively outweigh this:

- The worst that can happen is a flare-up of the rash. This, however, will clear when the man is removed from further contact, and one then knows that he must not again be exposed to the same process.

- One should never lightly remove a man from a job to which he has become accustomed, and at which he may have become skilled. Apart from presenting the personnel department with a problem, it is usually to the worker's disadvantage to change jobs. He may be averse to moving away from a place where he has made friends with his workmates, and where he has come to understand the requirements of his supervisor. He might also suffer a loss of earnings, by no longer doing process work, or overtime.

- Even moving to another plant may involve some risk, because in many chemical companies similar chemicals are used in different buildings.

Litigation

It is important to consider the legal position of a company in these circumstances, when they return a man after his rash has disappeared to his old job, or move him to one where he may be in contact with similar chemicals, and he develops dermatitis again. There have been cases where this has been the issue.

In *Mullings v the Clayton Aniline Company* (1977),² the plaintiff developed dermatitis in each of three different buildings, and was considered to be sensitised to dyestuffs intermediates. He was advised to leave, but asked to be tried in yet another building. This was agreed, and soon after commencing work there, the rash developed again. The judge ruled as follows: 'There was no negligence or breach of duty on the part of the defendants in continuing to employ the plaintiff at his request, and in transferring him to other buildings. It was the plaintiff who wished to remain with the defendants, despite advice to the contrary. It was known that the plaintiff was susceptible - both plaintiff and defendants knew this.' The action was therefore dismissed.

This judgement was on similar lines to that in the case of *Withers v Perry Chain Co.* (1956).³ The plaintiff had previously been employed by the company, and had contracted dermatitis a number of times from doing various jobs involving contact with grease. Some time after she left the company, they hired her to do similar work, again with contact with grease, to which she agreed. She developed a rash, and sued the company. The judge held that the duty of an employer towards a servant who is susceptible to a disease does not extend to refusing to employ him in work which involves a risk. The court had borne in mind the case of *Paris v Stepney Borough Council*,⁴ and then said that if the servant knows there is a risk and decides to take it, that is a matter for him. It was for the employee to weigh it against the desirability or necessity of the employment. It is

^{*}Wilson & Cronin (1971)¹ described cases of dermatitis occurring in nurses from their blue uniforms. The blue dye was the obvious suspect, but it was eventually found that the responsible chemical was a green anthraquinone dye used as a shading component.

¹In this case, the responsibility of a company to a one-eyed employee was at issue.

doubtful whether the same decisions would have been given had the hazard been cancer. It would throw too great a burden on the employee to decide what to do. It is equally doubtful, however, whether a responsible company would, in fact, subject him to the stress of making such a decision, or his taking such a risk.

Dermatitis is the cause of much litigation, and can sour industrial relations in a company. There are two main reasons for this. Firstly, dermatitis is such a common industrial disease that difficult cases are bound to arise from time to time. Secondly, both parties frequently have what seems to them to be a good and legitimate case, and to have right on their side. The employee maintains that he has developed his disability only through working for the company, and he would not have contracted it had he worked elsewhere or been better protected. The company, on the other hand, can point to the vast majority of its workers who do not contract dermatitis and could maintain that the problem is due solely to the employee's unusual susceptibility. It is, therefore, of the greatest importance that the possible risk is explained clearly to the worker beforehand, and that he should be carefully trained by the safety department in the avoidance of contamination.

Avoidance of contamination

The avoidance of contamination demands painstaking training of the individual by the safety and medical departments, the enforcement of strict precautions, and the provision of many, and often costly, safety devices. As with other industrial hazards, the classical methods of avoiding exposure to potentially harmful substances must be used in the prevention of skin disease.

Medical history and examination

A careful medical history must be taken. Anyone with a previous record of dermatitis or eczema should be rejected, in his own interest as well as that of the company. An allergic diathesis, as shown by previous attacks of urticaria, or asthma, or of severe hay-fever, requires much consideration. In the case of psoriasis, exposure to skin irritants or sensitisers can sometimes light up a previously dormant condition (the Koebner phenomenon). These cases should be decided individually on their own merits.

Substitution

Wherever practicable, a non-sensitising or less sensitising chemical should be used instead of a potentially potent one. Acrylates and epoxy resins can be very strong sensitisers, but not all to the same degree. In some cases, a less active acrylate or epoxy resin can be substituted for a more active one, although this is not always technically possible.

Communication and training

An employee should always be told, in plain language, the nature of any hazard to which he may be exposed, what precautions are taken to protect him, and what his own contribution to his safety, and that of his fellow-workers must be. This should be done before he is exposed to any risk.

Protective clothing

Dermatitis begins most commonly on the hands, and gloves are the most important protection against such contact as cannot be avoided by other preventive measures. Gloves should be of the right material to protect against the

particular chemicals concerned and they should fit well. If they are too tight they will cause discomfort and sweating, and the wearer is tempted to remove them. If they are too loose the chemical may get between the glove and skin. No obstacle should be put in the way of a man wishing to change his gloves for any reasonable cause. Where necessary, gauntlets should be provided, elasticated to ensure that the chemical has no way of access through looseness. The safety department should inspect the gloves regularly to ensure that they have no holes. Other exposed parts of the body must be protected by appropriate measures. The face, neck and upper chest may be affected by dust, while the hands may be clear.

Baths, showers, wash-basins

These should be readily available, in sufficient numbers, wherever their use is appropriate. The difficult question may be not whether a bath or shower should be allowed, but when – immediately after the operation, or at the end of the shift. With goodwill and common sense it can be solved, not so much by fixed rules but rather by dealing with individual cases and circumstances on their own merits. Intelligent and sensible behaviour by supervisors, who authorise the baths, is essential. Once the question goes higher up the line of management, the element of confrontation enters into a situation where it really has no place at all.

Barrier creams

Barrier creams are a useful adjunct to safety, but have a limited value. They are in no way a substitute for good industrial hygiene. They supplement, but do not replace, the other methods.

Plant design and ventilation

As with any other hazard, the incidence of skin disease can be reduced by appropriate plant design. Enclosure should be maximal – complete if possible. Local exhaust and general ventilation should be skilfully installed.

Unforeseen circumstances

By careful use of the above methods, the incidence of skin disease can be reduced to a small level. Nevertheless, cases do occur, sometimes because of a failure by the worker to use all the protective measures provided and sometimes because of unforeseen circumstances.

The skin can be damaged by the use of strong bleach. In the dyestuffs manufacturing industry, men's hands can become coloured red, green, or blue by the end of a shift, because of some failure of the protective measures. Men do not like to go home with coloured hands, and are tempted to use strong bleach or turpentine to remove the colour. This can dissolve a protective layer of the skin, and make it more vulnerable to irritants and sensitisers. A diluted bleach, of a maximum strength of 10 per cent available chlorine should be provided as otherwise men will turn to the concentrated form. This diluted bleach or 'bleach liquor' has been used for many years with, as far as one knows, no ill effect.

Skin cancer

Dermatitis is not the only skin hazard in industry, although it is by far the commonest. Skin cancer was among the early occupational diseases to be investigated and written up. Percivall Pott in 1775 described cancer of the scrotum in chimney sweeps. It is now known that the carcinogen was

3,4-benzpyrene. Skin cancer can occur in workers with pitch, tar, anthracene and creosote, in shale-oil workers, cotton mule-spinners, and tool-setters. Owing to the stringent precautions that have been introduced, much of this, like chimney sweep's cancer and mule-spinner's cancer has become largely of historical interest only. The extraction of the mineral action from shale-oil has rendered this free from the carcinogenic agent. The prognosis of skin cancer, diagnosed and treated early, is extremely good. Routine and compulsory examination of the skin of the whole body of all those at risk should be done by a medical officer.

Papillomata, or warts, are benign skin tumours, which may occur in handlers of tar, pitch, asphalt, creosote and anthracene. They are multiple and recurrent and if untreated may become malignant – as is the case with papilloma of the bladder. The use of precautions along the lines described earlier, should eliminate this hazard. Routine skin inspections will ensure that any case which might arise will receive the early treatment which so improves the prognosis.

Chloracne, a particularly disfiguring skin condition, affecting the face as well as other parts of the body, can result from exposure to polychlorinated aromatic hydrocarbons, and from dioxins. Cases occurred after the Seveso incident in Italy, owing to the release of the particularly

potent 2,3,7,8-tetrachloro dibenzo-*p*-dioxin. This, and other less harmful dioxins may be present in minute amounts as impurities in the agricultural herbicide 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), but responsible companies now ensure that the degree of contamination is so slight as to be unmeasurable. Despite much lobbying, the government – rightly on the available evidence – refuses to ban the manufacture and use of 2,4,5-T.

Occupational skin disease is now much less common than it was, particularly skin cancer. In the case of dermatitis, although most companies do everything possible to protect their workers, and cases are fewer than they were, there is still much room for improvement, and for increased research. The funds for this are limited by a company's budget. It is therefore important that there should be a realistic review of the relative priorities of the various hazards to which their employees are exposed.

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Harmonisation of toxicological testing in chemical safety evaluation

Christopher P Patrick

In recent years, considerable effort has been directed towards the international harmonisation of chemical control policies.* The OECD Chemicals Programme concerned with general industrial chemicals is probably the best known activity in this area but attention has also been focussed on pharmaceuticals and pesticides within the EEC and on a wider scale through the United Nations agencies, WHO and FAO. These programmes of harmonisation cover various aspects of chemical regulation, but I will concentrate on one particular aspect, that of the toxicological testing required by regulatory authorities for the safety evaluation of products before they are marketed. Before looking in detail at individual programmes, some discussion of the background to harmonisation is appropriate.

There is general agreement between regulatory authorities on the basic pattern of toxicological testing which is required for chemicals intended to have an effect on biological systems. This pattern covers tests for toxic effects after single (acute) and repeated (subchronic and chronic)

exposure and special tests to investigate areas such as reproductive toxicity, mutagenic and carcinogenic potential, and allergenicity. However, within this basic framework, a company wishing to market its products internationally is faced with a plethora of differing requirements set down by national regulatory authorities in the form of regulations, recommendations, standards and guidelines. Consequently, there is a wide variation between countries in both the tests required for product approval and the protocols to be followed in conducting these tests. Some of these differences are illustrated for pharmaceuticals – one class of products for which governments have over the years developed distinct testing requirements in the belief that their own particular 'package' is necessary for an adequate safety evaluation of the chemicals concerned (Table 1). The consequences of these differences are obvious – the development of products takes longer and is more costly, without necessarily achieving any additional assurance of a product's safety-in-use. In addition, the different national requirements can create non-tariff barriers to trade, especially if

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* The term chemical is used here in its broadest sense to cover general industrial chemicals as well as substances developed for specific use in products such as pharmaceuticals, agrochemicals, foods and cosmetics.

The ABCs of occupational skin disease—Part I

Dermatitis is the major occupational disease in the U.S. Chemical process industries are full of potential irritants. Check the risk in your workplace against the following information.

Kenneth J. McNaughton, Editor

□ In the first part of this two-part series,* we will look at the incidence of skin disease in the U.S., the physiology of the skin, the causes of occupational dermatosis, and some related governmental, medical and legal factors. Part II will show how to help prevent occupational skin disease through techniques of cleanliness, and will examine the use of specific cleansers in the chemical process industries.

Incidence of occupational skin disease

The skin is the largest organ of the body and is the first exposed to environmental irritants. Because of this, dermatosis is widespread. (Dermatosis is the general name for skin disease. The term dermatitis refers specifically to an inflammation of the skin.)

National statistics on occupational illnesses and injuries are projected by data from a mandatory record-keeping system, provided for by the 1970 Occupational Safety and Health Act (OSHA) and compiled by the U.S. Bureau of Labor Statistics. In the mid-1950s, skin ailments accounted for 50 to 70% of diseases contracted on the job. Although recent statistics show a decline, skin disease remains the most frequently occurring occupational illness nationally recognized and reported (see graph, p. 148).

The National Institute for Occupational Safety and Health (NIOSH) attributes the decline in cases of skin disease during the past two decades to automation, enclosure of industrial processes, and educational efforts. While these improvements have reduced the risk, especially in manufacturing, new chemicals and materials are continually being introduced that may be skin irritants or sensitizers.

Dermatitis is costly. Of all occupational diseases reported by the State of New York Workers' Compensation

*Part II of the series will appear shortly. This material has been adapted with permission from "The Prevention of Occupational Skin Diseases," copyright 1981, The Soap and Detergent Assn., 475 Park Ave. S., New York, NY 10016, for (\$2.50).

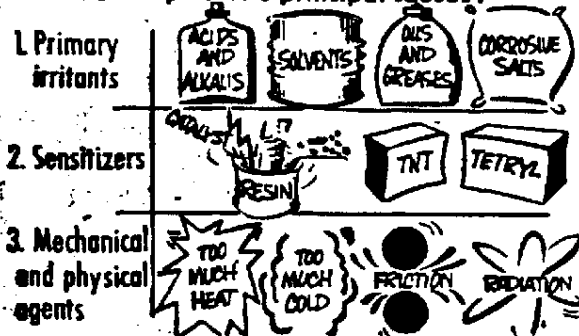
tion Board in 1978, dermatitis, with 23% (363 cases), had the second frequency. (Loss of hearing—27%—was first.) Compensation payment in the same year for dermatitis patients in the state amounted to \$1,700,933 (an average of \$4,686 per case) which was 14% of the total paid for occupational-disease cases.

The skin

Nature has surrounded the human body with a remarkably protective shield—the skin. Occupying some 2,880 square inches of area on the average adult, it is outranked only by the blood as the most powerful weapon the body has for fighting off a vast host of menacing forces.

What can cause DERMATITIS?

Examples of 3 principal causes:

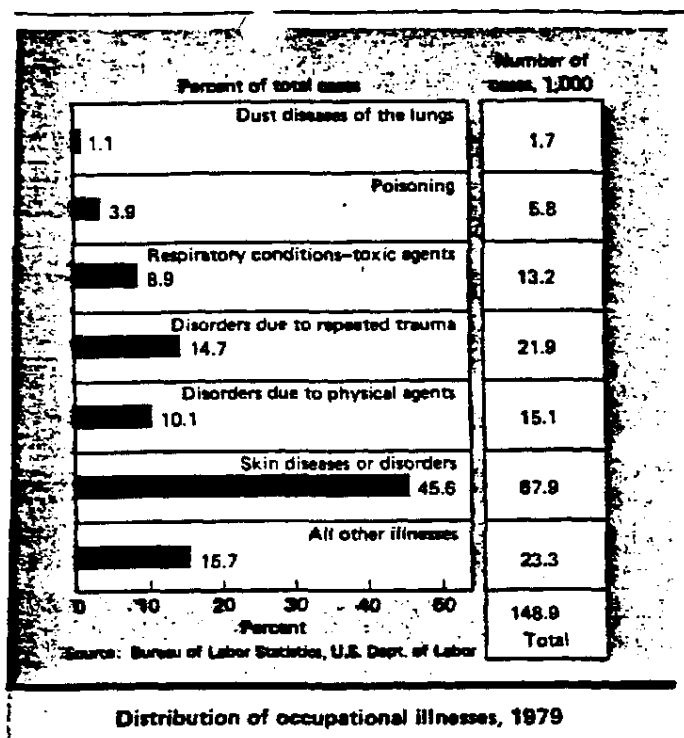


The skin performs an amazing variety of life-support functions with such ease that it goes largely unnoticed during good health. Because of its barrier action, it fends off injury from germs, physical forces and adverse chemical substances. This barrier, which is a relatively waterproof covering for the body, allows human beings—who are some 67% water by weight—to live in a dry environment without drying out. The skin allows us to cope quickly and almost effortlessly with severe extremes in the environment, as well as the normal assaults of wind and weather.

Another skin function, formation of pigment, defends the body against damage by the sun's rays. Finally, the skin's ability to reproduce its epidermal layers repre-

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sents a most important part of protection through its self-repair capability.

Causes of occupational dermatosis

The causes are divided into two main groups: predisposing and direct:

● **Predisposing**—There are several factors that may predispose a person to dermatosis.

Sex. Sex is a factor in the susceptibility of certain individuals to develop dermatoses. Women's skin has a tendency to be less oily than men's, thus making it more sensitive to many irritants, especially solvents. Yet, there have been fewer reports of occupational dermatoses per capita among women than men. This may be due to less employment of women in occupations showing high risk of occupational dermatoses. However, of equal or greater relevance is the fact that women are more likely to seek first aid and medical attention for skin diseases, thus preventing more-severe and prolonged types of dermatoses.

Season of year. Occupational dermatoses are more prevalent in warm weather, when less clothing is worn and contact with external irritants is more likely to occur. Excessive perspiration with resulting skin damage is also greater in warm weather.

Winter, with its lower temperatures and humidities, brings chapping from exposure to cold and wind. Overheated rooms and low humidity, at home and at work, cause skin to lose moisture and become dry. These factors increase the incidence of skin irritation. Further, workers are less inclined to take showers before going outside into the cold.

Existing or pre-existing skin diseases. Individuals who

have a history or presence of certain skin diseases are more susceptible to occupational dermatoses. Skin diseases unrelated to an individual's present occupation may be aggravated by exposure to some industrial environments. Pre-existing skin diseases such as psoriasis, chronic fungus infections, and others, predispose the skin to superimposed contact dermatitis.

Lack of cleanliness. Lack of cleanliness, both personal and environmental, is probably the most frequent predisposing cause of occupational dermatitis. Clean working environments and personal cleanliness diminish worker susceptibility.

Dirty underclothes and workclothes, and failure to properly clean the skin after working with chemical irritants, are important factors in causing occupational dermatitis. Contact with clothes that have been saturated with chemicals during an employee's work period may spread dermatitis to other members of the household. Clothing contaminated at work should be changed at once and thoroughly laundered before reuse. Contaminated work clothing should never be washed with the family clothing.

Allergy. Cutaneous allergy is the specifically acquired alteration in the capacity of an individual to react to even minute amounts of an allergen. The sensitivity is related to heredity. Allergenic substances (certain chemicals, plants, drugs, etc.) account for 20-25% of all occupational dermatitis.

Age. Besides the particular susceptibility to acne during adolescence, age seems to also influence sensitivity to external irritants. Many young and new workers are affected with acute occupational dermatitis. This may be the result of their not having become accustomed to the chemicals or, more likely, because they are less careful in handling them. Chronic scaling and flaking dermatitis usually occurs in older workers.

■ **Direct**—The following are direct causes of occupational dermatoses.

Mechanical and physical. Injuries caused by mechanical agents result in abrasions, bruises, wounds and the introduction of foreign bodies into the skin. Wounds of the skin can readily become infected with bacteria and certain fungi.

Physical agents such as high temperature, cold and radiation can cause occupational dermatoses. For example, high temperatures cause perspiration and softening of the outer horny layer of the skin. This can lead to so-called "heat rashes" common among workers exposed to hot humid weather, electric furnaces, hot metals, etc. Radiologists, doctors, dentists and technicians, and some industrial workers can be subject to radium and X-ray exposure. Laundry workers and dishwashers are subject to excessive immersion of the skin in hot water, which weakens the skin barrier.

Sunlight exposes construction workers, farmers, fishermen, foresters and others who work outdoors to skin-damaging radiation.

Manufacturers and users of fiberglass and asbestos products must take stringent measures to protect their workers from contacting these agents.

Chemical agents. Chemicals are the most frequent cause of occupational dermatitis because most chemicals can cause skin irritation in certain individuals under certain

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conditions. Chemicals can act as primary skin irritants and/or cutaneous sensitizers (see photo* p. 147).

A *primary irritant* causes dermatitis by direct action on the normal skin at the site of contact, if permitted to act in sufficient intensity and quantity for a sufficient length of time. Primary irritants cause skin damage by dissolving or extracting from the skin some of its essential components. Examples of primary skin irritants are strong acids and alkalis, corrosive salts and solvents.

A *cutaneous sensitizer* does not necessarily cause a noticeable skin change on first contact, but after five or more days, further contact on the same or other parts of the body may cause dermatitis. The difference between the irritant and the sensitizer, therefore, is a matter of both time and mode of action. Examples of common sensitizers are certain aniline dyes, nickel, chromium, mercury, poisonous plants, and plastics such as uncured epoxy resins.

Primary skin irritants may also act as sensitizers, but pure sensitizers are not primary irritants. Thus, certain primary skin irritants may so sensitize a person that he

Biological agents. Biological agents of bacterial, viral, fungal or insect origin may cause or complicate occupational dermatoses. An example of industrial bacterial skin disease is anthrax, contracted by handlers of skins or hides from infected animals. Farmers and horticultural workers may contract fungal diseases from cattle, plants and soils. Food and grain handlers often contract grain or straw itch from handling produce infected with mites.

Medico-legal aspects

Because of the increasing costs of workers' compensation coverage, insurance protection, sickness and accident benefits, and the loss to the employer through absence by the worker, it is important that employers take all reasonable steps to protect workers from dermatitis. Further, since the adoption of the Occupational Safety and Health Act, many of the recognized protective measures, such as the use of protective clothing and proper cleaning agents, are now requirements for employers, enforceable by penalties imposed by federal law. Employers subject to the Act should familiarize themselves with the standards issued pursuant to the Act and take all steps necessary to ensure compliance.

Governmental impact

By requirement of the Federal Hazardous Substances Labeling Act, hazardous materials are labeled so that the hazard is made known to the workers who will be handling them. These labels often include the emergency measures to follow in case of accidental contact or spillage of the chemical.

Under the 1972 Amendments to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the U.S. Environmental Protection Agency (EPA) regulates the labeling of materials such as pesticides, disinfectants and similar chemicals. It also requires a statement of the hazards and emergency measures to be followed, and a statement of the ingredients in the compound.

The U.S. Dept. of Transportation (DOT) Act requires hazardous materials to be packaged in such a manner that they can be safely handled without undue danger from leaking containers.

The Occupational Safety and Health Act of 1970 has had greater impact on the prevention of occupational dermatoses than any other single piece of legislation. The Act is administered by the Occupational Safety and Health Administration (OSHA) of the U.S. Dept. of Labor.

OSHA requirements extend from requiring disclosure by the employer of any hazardous materials contained in chemical compositions, to requiring installation of safe equipment, and to the supplying of approved safety clothing and other protective devices. Failure to meet OSHA standards can result in large fines and even closing of a facility.

OSHA influence extends into the area of adequate sanitation and wash-up facilities, which, as we will see in the next article, are of vital importance in the prevention of dermatoses (see photo this page*).

*The two illustrations in this article are photographs of color slides available from The Soap and Detergent Assn. Cleanliness posters and other worker-training visual aids are also available.



develops dermatitis from extremely low concentrations of compounds that could previously be handled without difficulty.

Some chemicals can sensitize the skin to light so that sunburn occurs more easily. Those affected may also develop various rashes, including hives and blisters, when their skin is exposed to sunlight. Chemicals that act in this manner are called photosensitizers, examples of which are coal tar, certain dyes, crude petroleum, and some plants, grasses, vegetables and fruits.

A small percentage of occupational dermatoses may result from breathing or swallowing certain particles and dusts. Examples of this are quinacrine hydrochloride, sulfa compounds and some antibiotics encountered in the pharmaceutical trades.

Plant poisons. Several plants and woods are known to cause contact dermatitis. The widest known offenders are poison ivy and poison oak. Other plants such as wild parsnip and diseased (pinkrot) celery are photosensitizers. Woods such as West Indian mahogany, silver fir and spruce have been reported to cause dermatitis, especially when being sandpapered and polished.

The ABCs of occupational skin disease—Part II

If a chemical irritant or sensitizing agent is not allowed to contact the skin, it cannot cause dermatosis. Overall, cleanliness is the most important factor in the prevention of occupational skin disease.

Kenneth J. McNaughton, Associate Editor

☐ In the first part of this article,* we looked at the incidence of occupational skin disease in the U.S., the physiology of the skin, the causes of occupational dermatosis, and some medical, legal and governmental factors. The subject of this followup is the prevention of occupational skin disease through proper techniques of cleanliness.

Environmental cleanliness

Environmental cleanliness is important to maintain good morale, reduce contact dermatitis, and set an example of cleanliness for workers. Regular cleaning of floors, walls, ceilings and light fixtures maintains the best possible conditions and reduces accident hazard.

Good housekeeping duties are best carried out by special maintenance personnel assigned direct responsibility for maintenance cleaning. To be most effective, the cleaning should be planned and should be done on schedule. Management must provide maintenance personnel with proper equipment and cleansers, and adequate training in their use, to assure optimum results. Equipment to spray, rinse, wet-vacuum, and automatically proportion the cleaning material (to avoid misuse) should be available. It will save time and money while giving more satisfactory results than manual methods.

Personal cleanliness

Prompt and efficient removal of industrial soil from the skin prevents prolonged contact of chemical irritants. Quick removal can be encouraged by providing enough easily accessible, strategically placed washing facilities, proper cleansers and towels.

Where irritating chemicals are present in the work environment, it is necessary for workers to shower at the end of each shift (or more often), should the skin be-

come contaminated with chemical irritants. Where highly corrosive chemicals are handled, a safety shower must be available in an easily accessible area.

Personal clothing, including undergarments worn on the job, should be changed daily and washed thoroughly before reuse. In some exposures, it is necessary to provide clothing and laundry service to ensure daily change. Suitable change areas should be provided by management.

Protective creams, lotions and ointments

While barrier creams and lotions are popular with workers, the degree of protection they afford is much less than comes from properly designed and maintained protective clothing. Nevertheless, there are many instances where a barrier cream can be valuable: where use of a face shield might be cumbersome; where gloves would interfere with the sense of touch required; or when the degree of protection required is minimal.

Protective lotions can be divided into four types:

Vanishing cream—Contains soap, which remains in the pores and on the surface of the skin and thus facilitates removal of the soil when washing.

Water repellent—Leaves a thin film of a water-repellent substance such as lanolin, beeswax, petrolatum or silicone on the skin and helps to prevent ready contact with water-soluble irritants such as acids, alkalis and certain metallic salts.

Solvent repellent—Contains ingredients that will repel oil and solvents. Lanolin has some oil-repellent as well as water-repellent properties and may be used as an ingredient. There are two types of solvent-repellent barrier preparations, one leaving an ointment film and the other a dry, oil-repellent film.

Special types—Some protect against the photosensitizing action of coal-tar distillates. Others offer some protection against poison ivy, or act as insect repellents. Perhaps the best-known class of protective lotion contains chemicals that filter out the sun's ultraviolet rays and thus prevent sunburn and chronic skin damage.

Protective clothing

Despite safety engineering efforts, handling of irritating materials sometimes cannot be avoided. In this situation, properly-designed protective clothing will provide a good barrier against industrial irritants.

Closely-woven fabrics are suitable for protection against irritating dust. Gloves and aprons of impervious

*This material has been adapted, with permission, from "The Prevention of Occupational Skin Diseases," copyright 1981, The Soap and Detergent Assn., 475 Park Ave. South, New York, NY 10016 (\$2.50). Part I appeared in CE's Mar. 22 issue, pp. 147-150.

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materials such as rubber or plastic offer protection against liquids, vapors and fumes. Natural-rubber gloves, aprons, boots and sleeves are impervious to water-soluble irritants, but soon deteriorate when exposed to strong alkalis and solvents. Synthetic rubbers, such as neoprene and many of the newer plastics, are more resistant to alkalis and solvents. However, some films are adversely affected by chlorinated hydrocarbon solvents. Appropriate materials should be selected to afford protection from the particular solvents used. When workers are wearing rubber or plastic gloves, they should wear replaceable liners of soft cotton to absorb perspiration and be more comfortable.

Leather gloves give good protection against injury and irritating solids or dusts. The leather should be soft and pliable and the seams should have a smooth finish to prevent skin irritation by mechanical friction. Gloves to protect the hands from chemicals should reach well up the forearm. If impervious sleeves or gauntlets are worn, fasten them at the wrist over the gloves.

Management is required to keep protective clothing clean and in good repair. Workers should be instructed to report any tears or holes in gloves, coveralls, sleeves, aprons and other protective clothing. Each worker should have at least two sets of protective clothing.

Plant design

A process involving chemicals known to irritate the skin should be designed so that harmful materials are handled in a closed system. Liquid and dry materials should be brought into the plant in sealed containers and transferred by closed systems into storage sheds, tanks or bins. They should be pumped or sucked by closed systems to the reaction vessels simply by opening valves or turning on a switch. Modern production trends toward automation and continuous-reaction systems minimize manual contact with harmful materials.

Proper ventilation must be provided to remove toxic or irritating vapors and dusts. Care must be taken to comply with the requirements of the Environmental Protection Agency and any local regulatory agency for emissions into the atmosphere.

Existing plants may need to be modified to meet U.S. Occupational Safety and Health Administration standards as well as prevent industrial contact dermatoses. Local exhausts may be installed in areas where exposure is likely to take place.

It is frequently possible to substitute less-irritating materials. A good example is the substitution of high-flash naphtha for benzene in making rubber cement. In certain instances, it has been necessary, because of government action, to completely prohibit the use of certain chemicals. Additionally, there are severe restrictions on the use of some materials (e.g., vinyl chloride, some pesticides, ethyl benzene, toluene and xylene).

Medical department

Large industrial plants rely heavily on their medical departments to assist in the prevention and control of occupational diseases. In any case, medical assistance should be provided, whether the company has its own, or contracts for its medical services.

The physical examination for new employees is the

first step in the prevention of occupational disease. The skin is an important part of this physical examination because there are many existing skin conditions that can be aggravated by placing the individual in an adverse work environment. Recurrence of some previous nonoccupational skin condition may be claimed as a result of the present occupation. Careful records of pre-placement examinations may be very useful to disprove false claims.

When, despite all precautions taken, a case of occupational dermatosis does arise, the medical department must not only treat the condition but must also work closely with the worker and other departments to find the cause of the dermatosis. The physician who treats occupational dermatoses should visit the plants, where the cases arise. Much can be learned about the causative factors that produce the occupational dermatoses, but even more important, the physician can help develop an active strategy of preventive measures.

The physician must also be alert to the possibility that the true sensitizing or irritating agent may be found away from the job—at home, in pursuit of hobbies, or in moonlighting.

Industrial cleansers

Measures to protect the skin from irritating and sensitizing substances depend greatly on skin-cleansing preparations. It is essential that hands be thoroughly cleansed after work to prevent prolonged contact with contaminants and to avoid the risk of irritation, infection or contact dermatitis.

The basic requirements of industrial skin cleansers are to: remove industrial soil quickly and efficiently; not harmfully dehydrate, abrade or irritate the skin by normal application; flow easily through dispensers; be adequately preserved against microbial contamination; not clog the plumbing.

There are various types of hand cleansers available: lotion skin cleansers; heavy-duty hand cleansers—cake abrasive type, powder, waterless hand cleansers (cream and liquid); synthetic detergents; antimicrobial hand cleansers; cake toilet soaps and liquid toilet soaps.

Consultation with a reliable manufacturer's well-trained representatives will aid in selection of an appropriate cleanser.

Education

It is not sufficient to merely provide workers with protective clothing, barrier creams and industrial cleansers; they must be instructed in proper use as well.

Instructions on proper safety procedures and skin care should be a regular part of the training program. The hazards of the job should be explained to the worker, and appropriate procedures for dealing with the hazards should be taught. Emergency procedures for accidental spills and other exposures should be gone over thoroughly.

Management must realize the importance of preventing dermatoses, including the economic losses incurred if skin diseases are not controlled. If all levels of management are not convinced of the necessity for a safety program, then it will be only partially enforced and will not be as effective. ●

Biodegradation of Chemicals of Environmental Concern

Martin Alexander

A variety of synthetic chemicals are present in inland and marine waters and in agricultural and other soils. Some of these compounds are toxic or may be converted to hazardous products in nature. Government regulatory agencies have been controlling the use of pesticides for some time, and the U.S. Environmental Protection Agency (EPA) has initiated a program to establish proce-

aquatic environments photochemical reactions may be significant. However, nonenzymatic reactions rarely lead to appreciable changes in chemical structure, and it is the biodegradative sequences that bring about major changes in the structure of the introduced chemical. Current evidence suggests, furthermore, that the indigenous microbial populations are the chief agents of change of

Summary. Microorganisms in soils and waters convert many synthetic organic chemicals to inorganic products. Other compounds are transformed only by cometabolism. These microbial processes may lead to environmental detoxication, the formation of new toxicants, or the biosynthesis of persistent products. Type reactions are proposed for major categories of enzymatic transformation of synthetic chemicals in soils, natural waters, and sewage. Some organic molecules are resistant to microbial attack, and explanations for the persistence of such compounds are suggested.

dures for assessing the environmental impact and health hazards of chemicals not classified as pesticides. In response to public and government concern and because of the intriguing research problems presented, environmental scientists, biologists, and chemists have been giving increased attention to identifying and determining the behavior and fate of organic compounds in natural ecosystems. Progress is hindered by the enormous number of chemicals that are used in industry, farming, and the home; current estimates suggest that tens of thousands of different compounds are used in commerce. Many of these substances are deliberately or inadvertently released into waters and soils. Moreover, many of them represent classes of molecules that biologists and biochemists have not previously investigated.

An organic chemical introduced into a terrestrial or aquatic ecosystem may be subjected to nonenzymatic or enzymatic reactions brought about by the inhabitants of the environment. Several types of abiotic mechanisms for chemical change have been described, and in

molecules that are metabolized in waters and soils. Although plants and animals metabolize a variety of chemicals, the activities of the higher organisms are often modest by comparison with the transformations effected by heterotrophic bacteria and fungi residing in the same habitat.

Role of Microorganisms

The mineralization, or complete biodegradation, of an organic molecule in waters and soils is almost always a consequence of microbial activity. Few abiotic mechanisms of importance in nature totally convert organic compounds of any degree of complexity to inorganic products, and mineralization sequences characterize the microbial metabolism of several classes of synthetic compounds. As they convert the organic substrate to inorganic products, the responsible populations make use of some of the carbon in the substrate and convert it to cell constituents. At the same time, energy is released, and the populations increase in numbers and biomass as they assimilate some of the carbon and acquire energy for biosynthesis. As a consequence, min-

eralization is typically a growth-linked process. Detoxication is a common outcome of mineralization except when one of the products itself is of environmental concern, as in the case of nitrate in certain waters or sulfide under anaerobic conditions.

With many chemicals, a microbial conversion quite different from mineralization takes place. Interest in this type of conversion rose markedly when it was found that many compounds are acted on biologically in soils and waters but no microorganisms able to use the compounds as sources of nutrients or energy could be isolated. The evidence for a microbial role in the transformations is the finding that the compound is transformed in nonsterile but not in sterilized samples of the natural environment or is transformed more rapidly in the nonsterile circumstances. Compounds that are thus modified in nonsterile but not sterilized environmental samples, or are acted on more readily when viable organisms are present, include DDT, 2,4,5-T, aldrin, heptachlor (1-3), and many other chlorinated and nonchlorinated molecules. Microorganisms able to use these chemicals as nutrients or for energy have yet to be isolated. The finding that chemicals are subject to microbial action and yet do not apparently sustain growth of the responsible populations has led to considerable research on the phenomenon, which has been termed cometabolism, or sometimes cooxidation (4). The populations presumably are growing on another substrate while performing the transformation known as cometabolism.

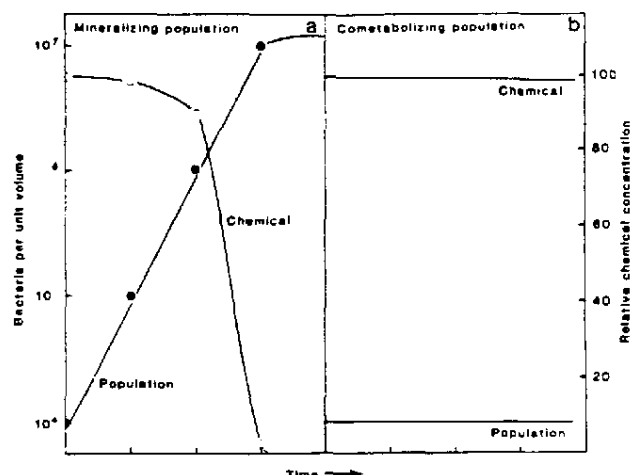
Objection to this term has been voiced inasmuch as it does not describe a new metabolic phenomenon (5). Granting that from the biochemical viewpoint cometabolism is merely biotransformation, the environmental consequences of cometabolism are such that maintaining a separate term is defensible. Two environmental consequences stand out. First, the populations responsible for the transformation do not increase in numbers or biomass as a result of the introduction of the chemical into water or soil. This lack of increase is a reflection of the inability of the organisms to use the chemical for biosynthetic purposes, and it is in marked contrast to the increase in population size or biomass when a mineralizable substrate is introduced into the same environment. Because populations acting on many synthetic chemicals are usually small, a compound subject to cometabolism is characteristically modified slowly, and the rate does not increase with time, again in contrast with a substrate acted

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on by mineralization (Fig. 1). The points in Fig. 1a represent the commonly observed population increase and chemical disappearance when bacteria are provided with a compound they can use as a carbon and energy source for growth. In Fig. 1b, a hypothetical model for cometabolism is used to show the lack of increase in bacterial population size and the very slow decline in concentration of a chemical that is cometabolized by bacteria which use some other compound in the natural ecosystem as a source of carbon and energy; in the model it is assumed that the size of the population of cometabolizing bacteria is at a steady state because of the continuous availability of small amounts of the growth substrate. Second, products structurally similar to the introduced chemical accumulate because the responsible organisms do not have a sufficient array of enzymes to bring about its extensive transformation, particularly to intermediates in normal metabolic sequences. Accumulations of products of this type have been observed in natural environments, model ecosystems, and microbial cultures in artificial media. Such modest changes in the molecule often do not result in detoxication because they are not sufficiently great to remove the structural features associated with toxicity to one or another species.

Direct evidence for cometabolism in nature has been largely lacking, however. The evidence for its occurrence in natural ecosystems consists of the activity in nonsterile but not sterilized samples of the environment, the inability to isolate a microorganism that uses the compound as a nutrient or energy source, and the demonstration that isolated microorganisms growing on other organic compounds carry out a reaction analogous to that in the natural ecosystem. Recent studies with soil and sewage, on the other hand, have provided direct evidence that this phenomenon is taking place. With sewage amended with certain ^{14}C -labeled herbicides, for example, the added pesticides are converted almost stoichiometrically to organic products and no microbial cell material is formed; failure of microorganisms to use the introduced compound as a carbon source was shown when it was observed that the ^{14}C label was not found in the nucleoside fraction of the organic matter in the sewage model ecosystem (6). In investigations of cometabolism in soil, ^{14}C -tagged carbon monoxide was introduced into the gas phase over samples of soil. These studies were initiated to provide additional evidence that microorganisms in soil are major agents in the destruction

Fig. 1. Hypothetical model for population changes and metabolism of a chemical modified by mineralizing and cometabolizing populations.



of this atmospheric pollutant (7). The conversion of CO to CO_2 in these test systems was not the result of microorganisms using the gas as a carbon source, because essentially none of the ^{14}C was recovered in the organic matter-microbial cell fraction of soil. Moreover, the CO was not oxidized by autotrophic bacteria because its oxidation did not enhance the rate of CO_2 fixation by soil microorganisms, a necessary consequence if the reaction was autotrophic. The process is thus brought about by organisms that oxidize CO but obtain neither carbon nor energy from the reaction, that is, by a cometabolic sequence (8).

The physiological basis for cometabolism is not clear; that is, why microorganisms, which commonly grow on the substrate they metabolize, are unable to proliferate at the expense of the compounds they act on by cometabolism. In view of the large number of synthetic chemicals that apparently can be cometabolized, establishing the physiological explanation is quite important. The most likely hypothesis is related to enzyme specificity. Many enzymes present in microbial cells catalyze reactions involving several different but chemically related substrates (9). If the product of the action of one of these enzymes is not a suitable substrate for any other enzyme in the organism, that compound will accumulate, although the initial enzyme characteristically converts its natural substrate to products that provide energy and a source of carbon for the active species (4).

Ecological Consequences

Ecological and public health considerations have resulted in great attention being given to certain categories of mi-

crobial transformations. When the chemical introduced into waters or soils is toxic, a common consequence of microbial action is detoxication. In modifying the chemical, the detoxifying microorganisms destroy its actual or potential deleterious influence on one or more susceptible animal, plant, or microbial species. Although mineralization of toxicants is characteristically detoxication, intermediates in the sequence may endure for some time, for example, in the conversions of phenoxy herbicides in soil to yield phytotoxic intermediates (10). Some of the intermediates in mineralization that accumulate are known to be nontoxic, but often their potential hazard to animal, plant, or microbial life has not been assessed. Cometabolism of a toxicant may also result in detoxication, and certain synthetic compounds that appear to be cometabolized in nature are converted to products that are not of ecological concern (11).

Certain chemicals that are themselves innocuous are converted enzymatically to products that are hazardous to one or another species. Toxicants may be generated from innocuous precursors (by a process that is often called activation) in a mineralization sequence, although the intermediates usually do not persist, and activation also may occur during cometabolism. Microbial activation is evident in the methylation of inorganic mercury in aquatic sediments and other environments to yield the more toxic mono- or dimethylmercury—compounds that are not only harmful but are also readily taken up from the sediments by aquatic animals (12). Inorganic arsenic may also be methylated, and the products of this microbial process are the far more toxic methyl arsenes; this reaction occurs in microbial cultures as well as in natural ecosystems (13, 14).

We have been investigating a reaction sequence leading to the conversion of innocuous compounds to potent carcinogens. The reactions are in part enzymatic and, apparently, in part nonenzymatic but related to microbial cells or activities. This transformation is the *N*-nitrosation of secondary amines. It is of particular importance because the inorganic and organic precursors of nitrosamines are widespread. The organic precursors are secondary and tertiary amines or quaternary nitrogen compounds, and these substances are present in higher plants, phytoplankton, animal wastes, and a number of synthetic compounds that are introduced in large quantities into natural ecosystems. The inorganic precursor, nitrite, is continually generated in soils and waters from ammonium during nitrification or from nitrate. *N*-Nitrosation has now been demonstrated to take place in samples of soil, water, and sewage, and the secondary amines that can be nitrosated in these model ecosystems to yield the carcinogens include

simple dialkylamines and diethanolamine. The nitrosation reaction may be catalyzed enzymatically, but microbial cell constituents or other complex organic materials may also effect nitrosation (15-17).

These compounds are of potential environmental concern not only because of their toxicity and the ubiquity of their precursors, but also because the nitrosamines are reasonably long-lived in natural ecosystems. The persistence of some nitrosamines illustrates another feature of certain microbial transformations: they may convert a readily metabolizable compound to a product that is not quickly destroyed. Thus, although the *N*-nitroso derivatives may endure for some time, the dialkylamine precursors are readily transformed microbiologically in natural environments (18, 19). Moreover, should the nitrosamines be generated in soil, they could affect humans, because plants may assimilate the carcinogens from soil or the compounds may leach downward through soil and

enter the ground water used for drinking (20).

Another category of ecologically important transformations involves the conversion of toxicants that are active against one type of organism into products that affect another. Because of such transformations, as well as activation, it is essential to identify environmentally generated products inasmuch as the putative environmental detoxication, in these instances, has not been achieved and new species have been placed under stress. A notable example of this category of transformation is the dehalogenation and oxidation of pentachlorobenzyl alcohol, a compound introduced in Japan to control a fungus pathogenic to rice. This antimicrobial agent was not harmful to the rice plants to which it was applied, but when the plant residues containing the fungicide were incorporated into the soil, tri- and tetrachlorinated benzoic acids were formed. These products were not antifungal, but they suppressed the development of plants sown after the

Table 1. Type reactions for transformation of chemicals of environmental importance.

Category	Reaction*	Example†	Reference
Dehalogenation	$RCH_2Cl \rightarrow RCH_2OH$	Propachlor (S,M)	(29)
	$ArCl \rightarrow ArOH$	Nitrofen (S)	(30)
	$ArF \rightarrow ArOH$	Flamprop-methyl (S)	(31)
	$ArCl \rightarrow ArH$	Pentachlorophenol (S,M)	(32)
	$Ar_2CHCH_2Cl \rightarrow Ar_2C=CH_2$	DDT (M)	(33)
	$Ar_2CHCHCl_2 \rightarrow Ar_2C=CHCl$	DDT (G,W,M)	(3, 33)
	$Ar_2CHCCl_3 \rightarrow Ar_2CHCHCl_2$	DDT (G,S,M)	(3, 33, 34)
	$Ar_2CHCCl_3 \rightarrow Ar_2C=CCl_2$	DDT (W,S,M)	(33, 35)
	$RCOCl \rightarrow RCOOH$	N-Serve (S), DDT (W,M)	(3, 33, 36)
	$HetCl \rightarrow HetOH$	Cyanazine (S)	(37)
	$ArNH_2 \rightarrow ArOH$	Fluchloralin (S)	(38)
	$ArCOOH \rightarrow ArH$	Bifenox (S)	(39)
	$Ar_2CHCOOH \rightarrow Ar_2CH_2$	DDT (M)	(40)
	$RCH(CH_3)COOH \rightarrow RCH_2CH_3$	Dichlorofop-methyl (S)	(41)
Decarboxylation	$ArN(R)COOH \rightarrow ArN(R)H$	DDOD (S)†	(42)
	$RCH_3 \rightarrow RCH_2OH$ and/or $\rightarrow RCHO$ and/or $\rightarrow RCOOH$	Bromacil (S), diisopropylnaphthalene (G), pentachlorobenzyl alcohol (S,M)	(21, 43)
Methyl oxidation	$ArH \rightarrow ArOH$	Benthocarb (S), dicamba (W)	(44)
	$RCH_2R' \rightarrow RCH(OH)R'$ and/or $\rightarrow RC(O)R'$	Carbofuran (S), DDT (S,W,G)	(3, 45)
	$R(R')CHR'' \rightarrow R(R')CH(OH)(R'')$	Bux insecticide (S)	(46)
	$R(R')(R'')CCH_3 \rightarrow R(R')(R'')CCH_2OH$	Denmert (S)	(47)
β oxidation	$ArO(CH_2)_nCH_2CH_2COOH \rightarrow ArO(CH_2)_nCOOH$	ω -(2,4-Dichlorophenoxy)-alkanoic acids (S,M)	(10, 48)
Epoxide formation	$RCH=CHR' \xrightarrow{O} RCH-CHR'$	Heptachlor (S,M)	(49)
Nitrogen oxidation	$R(R')NR'' \rightarrow R(R')N(=O)R''$	Tridemorph (S)	(50)
Sulfur oxidation	$RSR' \rightarrow RS(O)R'$ and/or $\rightarrow RS(O_2)R'$	Aldicarb (S,M)	(51)
$=S$ to $=O$	$(AlkO)_2P(S)R \rightarrow (AlkO)_2P(O)R$	Parathion (S,M)	(52, 53)
Sulfoxide reduction	$RC(S)R' \rightarrow RC(O)R'$	Ethylene thiourea (S)	(54)
Reduction of triple bond	$RS(O)R' \rightarrow RSR'$	Phorate (S)	(55)
Reduction of double bond	$RC=CH \rightarrow RCH=CH_2$	Buturon (S,M)	(56)
Hydration of double bond	$Ar_2C=CH_2 \rightarrow Ar_2CHCH_3$	DDT (W,M)	(57)
	$Ar_2C=CHCl \rightarrow Ar_2CHCH_2Cl$	DDT (W,M)	(3, 33)
Nitro metabolism	$Ar_2C=CH_2 \rightarrow Ar_2CHCH_2OH$	DDT (W,M)	(57)
	$RNO_2 \rightarrow ROH$	Nitrofen (S)	(58)
Oxime metabolism	$RNO_2 \rightarrow RNH_2$	Pentachloronitrobenzene (S,M), Sumithion (S,W,M)	(59)
	$RCH=NOH \rightarrow RC=N$	Aldicarb (S,M)	(51)
Nitrile amide metabolism	$RC=N \rightarrow RC(O)NH_2$ and/or $\rightarrow RCOOH$	Bromoxynil (S,M), Dichlobenil (S,W)	(60)

*Abbreviations: R, organic moiety; Ar, aromatic; Alk, alkyl; Het, heterocycle; waters (W) 43-(2,5-Dichlorophenyl)-5,5-dimethylisoxazolidine-2,4-dione.

†Reaction demonstrated in sewage (G), microbial culture (M), soil (S), or natural

original rice crop was harvested. The process is apparently microbial and co-metabolic (21). From the standpoint of public health, the conversion of the widely used antifungal compound, thiuram, to the carcinogenic dimethylnitrosamine in model ecosystems is noteworthy. The reaction sequence in this instance appears to involve both microbial and nonenzymatic mechanisms (15).

Enzymatic "defusing" may also occur. This refers to the conversion to a nontoxic product of a compound that might otherwise be activated; that is, the potential for toxicity is biologically destroyed before the molecule is converted to the inhibitor. Defusing takes place in the microbial cleavage in culture of 4-(2,4-dichlorophenoxy)butyrate to yield the nontoxic 2,4-dichlorophenol before the phytotoxin 2,4-dichlorophenoxyacetate is generated (22). Enzymatic defusing in natural ecosystems or in models thereof has yet to be shown.

Type Reactions

A major problem facing investigators who deal with the biodegradation and environmental metabolism of synthetic chemicals is that few biochemical precedents exist for many of the molecules of environmental concern. Even among the priority water pollutants established by the EPA and the compounds or classes of chemicals on the priority list for testing under the Toxic Substances Control Act, few chemicals have been studied to ascertain how they are metabolized in microbial cultures, let alone natural ecosystems. The precedents that have been

established are useful in determining what microorganisms may do to other representatives of a particular class of chemicals.

The pathways of metabolism are often delineated in microbial cultures because the investigations are easier to conduct and the data are less equivocal, but the transformations must be established in natural ecosystems or models of them. These ecosystems include sewage, soils, fresh waters, estuaries, and oceans. Sewage transformations are of particular environmental significance, for it is in sewage that many chemicals are first subjected to biological transformation and may be destroyed or converted to new toxicants. Soils receive a multitude of chemicals from agriculture, municipal wastes, food processing industries, and discharges from manufacturing and from the transport of materials from place to place. Many compounds are introduced into fresh, estuarine, or oceanic waters by industries, transportation activities, and municipal or industrial sewage treatment operations in which the compounds are incompletely destroyed.

Investigators dealing with environmental metabolism must use a somewhat different approach from that employed in classical biochemistry and microbiology. They are interested not only in compounds that are generated within the microbial cell but in compounds that are both formed and excreted so that they appear outside the cell. Moreover, they must persist outside the cell long enough for the intermediate to appear in quantities sufficient for detection and potential toxicity. It is still not clear why only certain compounds in a metabolic se-

quence accumulate outside the active organisms and why others are confined to the interior of the responsible species. Moreover, it is not yet possible to establish generalizations about which of the likely intermediates will accumulate. In addition, few meaningful predictions can be made of which steps in a mineralization or cometabolic sequence will be slow and which fast. Because of these difficulties, predictions of which intermediates will appear outside the cell and accumulate are tenuous at best.

A few of the type reactions are given in Table 1. Several types of cleavage reactions are listed in Table 2. These represent sequences that have been established in model ecosystems or, in some instances, by direct measurements of soils or waters. For some of the reactions or sequences only a single example exists, but for others many different compounds undergo the transformation. The chemical listed may itself be modified as indicated in the type reaction, or the reaction may apply to a late step in the degradation or transformation of the listed chemical. Moreover, in some instances, the data are not sufficiently rigorous to show that the reaction is microbial, because some of the processes may be partly or wholly nonenzymatic. The types of products listed are found only outside the cell and at concentrations that are readily detectable; that is, these are the products that are of potential environmental importance, not just those that are generated intracellularly.

In view of the multitude of chemicals that are discharged and the unfeasibility of testing each one rapidly, the ability to predict metabolic fates and products of

Table 2. Type reactions for cleavage of chemicals of environmental importance.

Substrate	Reaction	Example	Reference
Ester	$RC(O)OR' \rightarrow RC(O)OH$	Malathion (M), phthalates (W,M)	(61)
Ether	$ArOR \rightarrow ArOH$	Chlormethoxynil (S), 2,4-D (S,W,M)	(1, 62, 63)
	$ROCH_2R' \rightarrow ROH$	Dichlorofop-methyl (S)	(41)
C-N bond	$R(R')NR'' \rightarrow R(R')NH \text{ and/or } \rightarrow RNH_2$	Alachlor (S,M), trimethylamine (G,M)	(64, 65)
	$RN(Alk)_2 \rightarrow RNHAlk$	Chlorotoluron (S), trifluralin (S,M)	(66, 67)
	and/or $\rightarrow RNH_2$		
	$RNHCH(R')R'' \rightarrow RNH_2$	Imugam (S)	(68)
	$RNH_2CH_2R' \rightarrow RNH_2$	Glyphosate (S,W)	(69)
Peptide, carbamate	$RNHC(O)R' \rightarrow RNH_2 \text{ and/or } HOOCH_2R'$	Benlate (S,M), dimethoate (S)	(70)
	$R(R')NC(O)R'' \rightarrow R(R')NH + HOOCH_2R''$	Benzoylprop-ethyl (S)	(71)
=NOC(O)R	$RCH=NOC(O)R' \rightarrow RCH=NOH$	Aldicarb (S,M)	(51)
C-S bond	$RSR' \rightarrow ROH \text{ and/or } HSR'$	Benthicarb (S), Kitazin P (S,M)	(72, 73)
C-Hg bond	$RHgR' \rightarrow RH \text{ and/or } Hg$	Ethylmercury (S,M), phenylmercuric acetate (S,M)	(74)
C-Sn bond	$R_3SnOH \rightarrow R_2SnO \rightarrow RSnO_2H$	Tricyclohexyltin hydroxide (S)	(75)
C-O-P	$(AlkO)_2P(S^*)R \rightarrow AlkO(HO)P(S^*)R$	Gardona (S), malathion (S,M)	(76)
	and/or $\rightarrow (HO)_2P(S^*)R$		
	$ArOP(S^*)(R)R' \rightarrow ArOH \text{ and/or } HOP(S^*)(R)R'$	Diazinon (S), parathion (S,M)	(53, 77)
P-S	$RSP(O)(R')OAlk \rightarrow HOP(O)(R')OAlk$	Hinosan (M), Kitazin P (M)	(73)
Sulfate ester	$RCH_2OS(O_2)OH \rightarrow RCH_2OH \text{ and/or } HOS(O_2)OH$	Sesone (S,M)	(78)
S-N	$ArS(O_2)NH_2 \rightarrow ArS(O_2)OH$	Oryzalin (S)	(79)
S-S	$RSSR \rightarrow RSH$	Thiram (S,M)	(80)

*Sulfur or oxysulfur

breakdown is critical to government regulators and industrial scientists endeavoring to select which of several chemicals are less likely to be of ecological concern. These type reactions provide a basis for such predictions, but too few type reactions are known.

Considerable progress has been made in defining the pathways of biodegradation of a variety of synthetic chemicals in laboratory cultures of individual microorganisms (23). For example, there is much information on how individual microbial species cleave simple aromatic molecules in culture and how they bring about the destruction of aliphatic hydrocarbons. Such studies of single populations in artificial media are reasonably simple, in contrast to environmental investigations of metabolic fate, because the test compound is frequently present in high concentration, the microorganisms are acting individually, and none of the complexing materials and surfaces that characterize soils, sediment, sewage, and even natural waters is present. By use of pure cultures and test solutions, a wealth of information has been gathered on the pathways of breakdown of a number of environmentally important synthetic chemicals, including pesticides, aliphatic and aromatic compounds containing various substituents, and several heterocyclic compounds that appear to be of ecological concern.

Nevertheless, it is difficult to predict the effect of surfaces, which of the several metabolic pathways demonstrated in culture operate in nature, the impact of predation and parasitism on the metabolic functions of the dominant species in soils and waters, and whether the low chemical concentrations in nature will support dissimilar populations using metabolic pathways different from those studied in the laboratory. One of the chief limitations of extrapolations based on studies of axenic cultures in artificial media is the inability to predict which of the products formed during biodegradation will appear outside the microbial cell and accumulate in nature to concentrations sufficient to be of ecological importance. Hence, although studies of metabolism with pure cultures in laboratory media are useful and greatly simplify the establishment of pathways of biodegradation in nature, they are merely the first phase of the testing activity; the final phases include use of model ecosystems and then assessment of products in the natural environment.

Not all the processes effected by microorganisms in soils and waters are degradative. A number of compounds are known to be modified to yield

methyl, simple acyl, nitro, and nitroso derivatives. Dimers may be formed, and the formation of nitrogen heterocycles has recently been demonstrated. Type reactions are summarized in Table 3. In addition, oligomers and polymers appear to be generated, giving rise to "bound" residues and uncharacterized brown or black products that are probably polyaromatics.

Recalcitrant Molecules

A few years ago, a conflict developed between microbiologists and individuals who monitor synthetic chemicals in waters and soils. Microbiologists were convinced, on the basis of their earlier successes in obtaining active organisms, that every organic compound was able to sustain microbial growth and would be mineralized. Monitoring studies, however, revealed the longevity in soils, waters, or both, of plastics, other synthetic polymers, chlorinated aromatic compounds of various sorts, pesticides, and other industrial chemicals. If microorganisms were so catabolically versatile, it might have been expected that every organic chemical would have been destroyed after sufficient time had elapsed or before the compound was transported for some distance from the original point of discharge. The finding of such an array of dissimilar molecules that persisted in waters and soils revealed the surprising lack of catabolic omnipotence of microbial communities. The weight of field evidence became so great that the conflict has been resolved: many synthetic organic molecules are mineralized very slowly or not at all, and hence they persist for long periods and are of potential ecological concern. Organic chemicals that endure for long periods in natural ecosystems owing to the inability of microorganisms to degrade them rapidly, if at all, are known as recalcitrant molecules. A few of these recalcitrant substances are toxic, and the microflora of waters and soils either does not bring about detoxication or does so slowly. A few of the persistent compounds are not hazardous but are aesthetically undesirable—for example, many plastics and other synthetic polymers.

Some recalcitrant molecules are not toxic at the concentrations found in waters and soils, but they are subject to biomagnification. If the compounds were not persistent, they would not have endured to undergo biomagnification and accumulation in the tissues of higher animals and plants. At the high levels pres-

ent in such tissues, these recalcitrant molecules have deleterious effects on species at or near the top of food chains. Furthermore, a compound that is not readily destroyed in nature can be transported for some distance; thus, many recalcitrant chemicals introduced originally into soil are present in waters some distance away from the site of first application, and other recalcitrant compounds that are introduced into a river, stream, or sewage treatment plant move to waters far from the original point of introduction. Another problem is that it is not possible to rid natural ecosystems of their content of a recalcitrant chemical should new knowledge in toxicology indicate that a compound that was previously thought to be innocuous is in fact hazardous; in contrast, should a readily mineralizable compound be found to be ecologically unsafe, the supply in natural ecosystems will be destroyed by the indigenous microfloras once the discharge or use of the compound is terminated. Hence, owing to the persistence of toxicants and substances that are aesthetically objectionable, the susceptibility of recalcitrant compounds to biomagnification and distant transport, and the inability to remove them readily, if at all, from natural ecosystems if they are found to be harmful, considerable interest has been focused on the biochemical or ecological bases for molecular recalcitrance. Industrial researchers and technical staffs of regulatory agencies are endeavoring to understand the bases for recalcitrance and to predict which molecules may not be subject to microbial transformation, especially to mineralization.

The persistence and lack of rapid microbial attack on a chemical may be attributable to chemical or environmental causes. The molecule may be completely refractory to microbial destruction. Absolute recalcitrance is probably a property of synthetic polymers such as polyethylene, polyvinyl chloride, and others widely used in manufacturing or in fabrics of importance in the home. Some recalcitrant molecules may be acted on enzymatically, but the reaction is cometabolic; the responsible organisms do not proliferate, the rate of transformation does not increase with time, and the substrates are likely to be persistent. Certain chemicals that are readily biodegradable in one environment are long-lived in another because of environmental factors; thus, the absence of oxygen is occasionally associated with the resistance of even carbohydrates to microbial destruction (24). The durability of peats, as long as they are under water, attests to the recalcitrance of organic compounds in cer-

Table 3. Conjugation and other model reactions involving chemicals of environmental concern.			
Reaction type	Reaction	Example	Reference
Methylation	$\text{ArOH} \rightarrow \text{ArOCH}_3$	Pentachlorophenol (S,M)	(81)
	$\text{CH}_3\text{As(O)(OH)}_2 \rightarrow (\text{CH}_3)_2\text{AsH}$ and/or $(\text{CH}_3)_3\text{As}$	Methylarsonate (S,M)	(14)
Ether formation	$\text{Hg}^{2+} \rightarrow \text{CH}_3\text{Hg}^+ \rightarrow (\text{CH}_3)_2\text{Hg}$	Mercuric ions (S,M)	(82)
	$\text{RCH}_2\text{R} \rightarrow \text{R(R)CHOCH(R)R}$	Diphenylmethane (M)	(83)
N-Acylation	$\text{ArNH}_2 \rightarrow \text{ArNHC(O)H}$	Bifenox (S), Nitrofen (S)	(30, 84)
	$\text{ArNH}_2 \rightarrow \text{ArNHC(O)CH}_3$	DCNA (2,6-dichloro-4-nitroaniline)	
Nitration	$\text{ArNH}_2 \rightarrow \text{ArNHC(O)CH}_2\text{CH}_3$	(S,M), 3,4-dichloroaniline (S)	(85)
	$\text{ArH} \rightarrow \text{ArNO}_2$	Chlormethoxynil (S)	(62)
N-Nitrosation	$(\text{Alk})_2\text{NH} + \text{NO}_2^- \rightarrow (\text{Alk})_2\text{NNO}$	Chlorodimeform (S)	(86)
	$2\text{ArNH}_2 \rightarrow \text{ArN}=\text{NAr}$	Dimethylamine (S,G,M)	(16, 87)
Dimerization	$\text{RSH} \rightarrow \text{RSSR}$	Propanil (S,M), trifluralin (S)	(67, 88)
		Denmert (S), Prothiocarb (S)	(47, 89)
Nitrogen heterocycle formation	$\text{CH}_3\text{CH}_2\text{C}=\text{CNHR} \rightarrow \text{CH}_2=\text{C}(\text{NR})\text{CH}_2$	Alachlor (M)	(64)
	$\text{CH}_3(\text{CH}_2)_n\text{CH}_2\text{N(R)C}=\text{CNO}_2 \rightarrow \text{CH}_3(\text{CH}_2)_n\text{CH}_2\text{N(R)C}=\text{C}(\text{NR})\text{CH}_2$	Dinitramine (S,M), Oryzalin (S)	(79, 90)

tain anaerobic deposits (25). In addition, certain classes of chemicals, when sorbed to surfaces of colloidal materials present in natural ecosystems, are not readily attacked microbiologically and chemical analysis shows their prolonged persistence (26).

Several explanations have been advanced and a number of mechanisms proposed to account for the non-degradability or the longevity of recalcitrant molecules. Biological evolution has explored a narrow range of chemical pathways, and hence it is plausible to believe that various synthetic compounds are too far from the mainstream of catabolic pathways to be substrates for any species. If no enzyme has evolved to convert a molecule to an intermediate in an existing biochemical pathway, it is unlikely that the compound will be acted on biologically. Enzymes are specific in the substrates they act on, and the scope of genetic capabilities of natural populations is great but apparently not all-encompassing; hence, it is likely that certain compounds do not sustain growth of any organism, are not acted on by catabolism, and do not serve as the basis for the selection of new genotypes able to cope with biochemically novel compounds. A molecule that cannot penetrate the microbial cell and is not modified by an extracellular enzyme is recalcitrant, and the lack of penetration, coupled with the absence of a suitable extracellular enzyme, is a plausible basis for a molecule being refractory. Such an explanation may account for the lack of microbial destruction of polyethylenes,

which represent the higher molecular weight homologs of aliphatic hydrocarbons; the latter do penetrate the microbial cell and are degraded by intracellular enzymes.

Microorganisms require energy to maintain themselves; that is, they must carry out oxidations to obtain sufficient energy to carry out their essential functions. Should the ambient concentration of a chemical be very low and the rate of its penetration into the cell thus provide too few molecules per unit time to allow the organism to get enough energy to maintain itself, a species able to metabolize the chemical may not replicate and may even die out; hence, some compounds at minute concentrations may persist. This hypothesis to account for the longevity of water-soluble compounds present at low concentrations may also apply to chemicals having very low water solubilities or to those not emulsified to allow for rapid penetration into the cell; if such a substrate does not enter the cell at a rate sufficient to allow the microorganism to get energy rapidly enough for maintenance as well as growth, persistence is a likely outcome. There is evidence which suggests that certain compounds present in the aqueous phase at trace concentrations are very slowly attacked, although the small amount present should be destroyed readily (27).

Other hypotheses to account for the resistance of persistent molecules to microbial breakdown include complexing of the normally available substrate with resistant polyaromatics and inacces-

sibility of the site on the substrate at which the enzyme should function. A number of compounds that are normally readily degradable are rendered resistant when they are complexed with resistant organic materials. Moreover, resistance may be attributable to inaccessibility of the end of a large molecule belonging to a class of chemicals in which biodegradation is initiated at the terminal portion of the molecule, or it may be ascribed to cross-linkages that mask the site at which the enzyme might otherwise function (28).

As industry seeks replacements for persistent compounds and as additional chemicals are sought for new purposes, it is necessary to know which features of the molecule are associated with resistance to biodegradation. These practical interests, coupled with the interest of academic scientists in establishing the bases for recalcitrance, have led to attempts to predict biodegradability from chemical structure. At present, these predictions are somewhat tenuous. Nevertheless, empirical observations provide a basis for suggesting which structural features and substituents underlie resistance and which may make an otherwise resistant molecule into a readily available substrate (28).

Conclusion

Interest in biodegradation of chemicals of environmental concern is growing. Regulatory agencies are requiring information, industry is asking questions

that can only be answered experimentally, and university scientists are seeking to establish appropriate generalizations. The presence of industrial chemicals, manufacturing wastes, and other unwanted chemicals in water and of pesticides on land and in crops has convinced the public that pollution by synthetic organic molecules is a problem of major importance. Monitoring studies have demonstrated that industrial effluents are sources of chemicals found in drinking water supplies and that chlorinated organic compounds may be formed from natural products as the water is treated before human consumption. The Toxic Substances Control Act and other federal regulations have played a catalytic role in promoting research on biodegradability. In view of this large amount of activity, one can look forward to new technologies and approaches designed to minimize environmental pollution while maintaining the benefits to society of synthetic chemicals.

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Risk Management Strategy under the Toxic Substances Control Act and the Federal Insecticide, Fungicide, and Rodenticide Act¹

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INTRODUCTION

The Federal government has at its disposal a variety of statutes which address themselves to the management of risks attendant on the use of chemical substances in our technologically complex society.

Key among these are the Food, Drug, and Cosmetic Act (FDCA), the Federal Meat Inspection Act (FMIA), the Federal Hazardous Substances Act (FHSA), the Consumer Product Safety Act (CPSA), the Occupational Safety and Health Act (OSHA), and the several statutes under the purview of the Environmental Protection Agency (EPA). The present discussion is concerned with risk management strategies under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA).

The legal restrictions on risk management options vary considerably over the various statutes listed above. If one examines the listed statutes in a chronological series, there is a suggestion of an evolution in legislative thinking as science and society have become more sophisticated. There is certainly a world of difference between the zero risk simplicity of the Delaney clause in FDCA [21 USC 348(c) (A)] and the risk-benefit balancing mandated by TSCA [15 USC 2601 *et seq.*] and FIFRA [7 USC 136 *et seq.*].

Before proceeding with the discussion of risk management concepts under TSCA and FIFRA, it is worthwhile to place some perspective on the question of risk-benefit balancing as practiced by EPA.

Many persons believe that risk-benefit balancing is the balancing of economic costs vs human health risks. This is simply not feasible since it requires placing a dollar value on human health. By saying "not feasible" it is not to imply that people do not associate dollar values with their health—anyone who purchases health or life

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insurance does just that. As used here, "not feasible" means that it would be too contentious to value human health as public policy since such valuations tend to be highly individual choices.

The EPA has adopted the more fruitful approach of avoiding comparison of economic benefits to health risks. This requires a two-stage analysis (described in more detail in the discussions which follow). Essentially, the EPA develops an estimate of the degree and types of risks posed by a chemical-related activity. Direct health (or environmental) benefits attendant on such activity are estimated. Sometimes this benefit analysis becomes complex. As an example, a particular chemical activity may pose some risk but be less risky than alternatives {[47 FR 47669 (Oct. 27, 1982) (EBDC PD/4); [48 FR 124 (Jan. 3, 1983) (PCB Railroad Transformer)]; [47 FR 46980 (Oct. 21, 1982) (PCB Controlled Manufacturer and Waste Rule)]}. The considerations of effects on the availability of a nutritious food supply, quality health care, and similar—but not immediately obvious—health (or environmental) benefits is important.

By comparison of health (or environmental) risks and benefits, the EPA arrives at an initial risk mitigation goal (assuming the judgement is made that risk mitigation is needed). The most cost-effective way of achieving this goal is then sought. Economic factors play a prominent part in this. The constraints of real world considerations also factor; a useful control needs to be perceived as being "practical" if it is to be societally acceptable. Technical realities are a further consideration. It is unrealistic to deal in control strategies which place one below the limit of detection or for materials for which analytical methodology does not exist.

As a practical matter, EPA in implementing TSCA and FIFRA utilizes three sorts of general risk mitigation goals. The first pertains to noncancer health endpoints. The EPA's Office of Pesticides and Toxic Substances (OPTS) seeks generally to establish a no-observable-effect level (NOEL) based on animal data. An appropriate margin of safety (also termed an uncertainty factor by some) is then applied to generate an allowable exposure limit, often expressed as the allowable daily intake (ADI). It is important to remember that under this approach the presumptive residual risk is zero for exposures below the stated limit. The margin of safety accommodates for uncertainty in interspecies comparisons and also provides protection in the event of temporary excursions above the stated limits of exposure.²

The second sort of general risk goal pertains to the environment. OPTS has generally used the avoidance of significant negative impacts or of irreversible impacts on the ecosystem as a broad goal. This means that (except for members of endangered species) there may be some impact on individuals in an ecological community but it is the stability of the community as a whole that is the primary concern.

The third sort of risk management is that of carcinogenic substances. A full discussion of this difficult area is beyond the scope of this presentation. OPTS does seek to reduce risks (generally by reducing exposure) posed by carcinogens to levels where the incremental risk (also called excess risk) is sufficiently low as to be insignificant. For practical purposes, these are risk levels which are not realistically expected to add to an individual's cancer burden. OPTS does not employ any predetermined statistical risk level since this will vary depending on a variety of factors. In the narrow

² The Office of Pesticides and Toxic Substances uses a safety factor of 100 for endpoints which have a demonstrable no-effect level with the exception of cholinesterase inhibition in which case a safety factor of 10 is used.

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area of setting water quality criteria, the Agency has traditionally used a target of 1×10^{-5} as a lifetime risk [45 FR 79318 (Nov. 28, 1980) (Water Quality Criteria)]. If it is considered that an individual in the United States has a 0.33 lifetime risk of contracting some form of cancer (American Cancer Society, 1981; Reif, 1981), that about 10% of this risk is genetic in origin and that about 70-75% of this risk could be reduced by changes in diet and lifestyle then the individual is faced with a basal lifetime risk of circa 0.10. (Office of Technology Assessment, 1981; Higginson and Muir, 1979; Wynder and Gori, 1977). Viewed in this light, the target of 1×10^{-5} represents an incremental risk of 0.01% above the basal risk and is perhaps not unreasonable. To state this differently, the individual has 10,000 times more risk of developing cancer from a variety of factors than from chemical exposure at the 10^{-5} risk level.

With this brief perspective on the sorts of consideration which enter into risk management at OPTS, it is possible to turn to an examination of the programs under FIFRA and TSCA.

GENERAL CONSIDERATIONS IN RISK MANAGEMENT UNDER TSCA AND FIFRA

There are many factors that enter into making decisions in the public realm. One can make an analogy to an operational amplifier circuit for simulation purposes. Figure 1 represents an operational amplifier which is set up for integrating signals. The output of this circuit is supposedly a regulatory decision. As in most types of computing, the basic axiom applies: garbage in and garbage out. One can not get a good decision unless there are good inputs; and what sorts of inputs does one deal with? First of all, there is that large taskmaster, "policy." This is what drives, filters, and screens the whole process. Then there is risk analysis, some good, some not so good. Risk analysis, of course, requires a data base, requires professional judgment, and requires peer review. If the science is well done, one has a chance of arriving at a sound regulatory decision. If the science is faulty, the regulatory decision can only be a poor one.

Under TSCA and FIFRA, benefits must be taken into account. EPA also must consider what is in fact feasible. As stated previously, regulation must be practical if it is to be effective. Finally, since we are an open society, we have feedback, and this comes—in the EPA arena—from Congress and from members of the general public.

The system can work well if the inputs are good and if the feedback is informed and reasonable. However, as in any feedback situation, when the feedback blows up, the system shuts down. None of the inputs then matter. The basic point that underlines this discussion is then: when events move out of the realm of science and into the realm of public emotion, science may become foreclosed.

OVERALL STRUCTURE OF TSCA AND FIFRA

The basic structures of the Toxic Substance Control Act and the Federal Insecticide, Fungicide, and Rodenticide Act are, in fact, very similar in principle and operational design to the structure of the Food, Drug, and Cosmetic Act which EPAs colleagues at FDA administer and to many other sorts of chemical control statutes. Basically,

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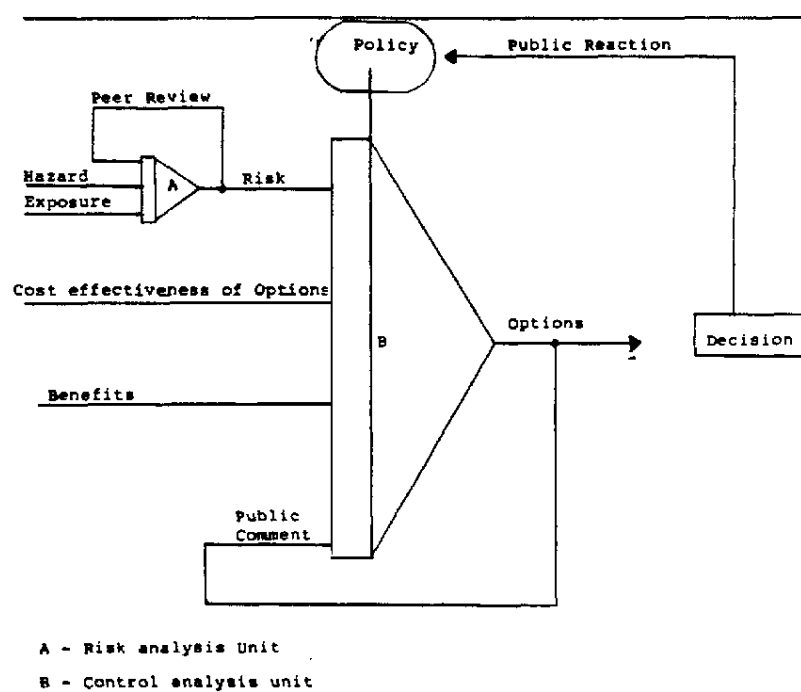


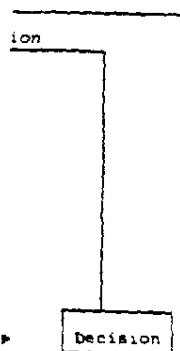
FIG. 1. Decision elements in the management of risks posed to human health and the environment by chemical substances.

one has a system which screens materials before they enter into the stream of commerce. Also, in TSCA, FIFRA, and some other chemical-related statutes, there are activities designed to be retrospective.

This is very important. In most industrialized nations, a very well-developed chemical and drug industry exists. These countries also seem to enjoy very high levels of general health. Industrialized society has thus come to its present state of development having fortuitously done things reasonably well from a public health view. That is not necessarily a guaranty for the future, and it does not say that there are not specific problems that have to be dealt with that arise out of some past practices. One needs chemical control programs that are both prospective and retrospective. The operations of TSCA and FIFRA can be readily represented by a diagram (Fig. 2). When one compares these two statutes, the basic structural similarity to the Food, Drug, and Cosmetic Act and to the Sixth Amendment of the European Economic Community becomes apparent (Table I).

NEW CHEMICAL SCREENING PROGRAM

The screening of new chemicals under TSCA is achieved through the process of premanufacture notification (PMN). Under FIFRA the corresponding activity (Fig.



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RISK MANAGEMENT STRATEGY FOR TOXIC SUBSTANCES

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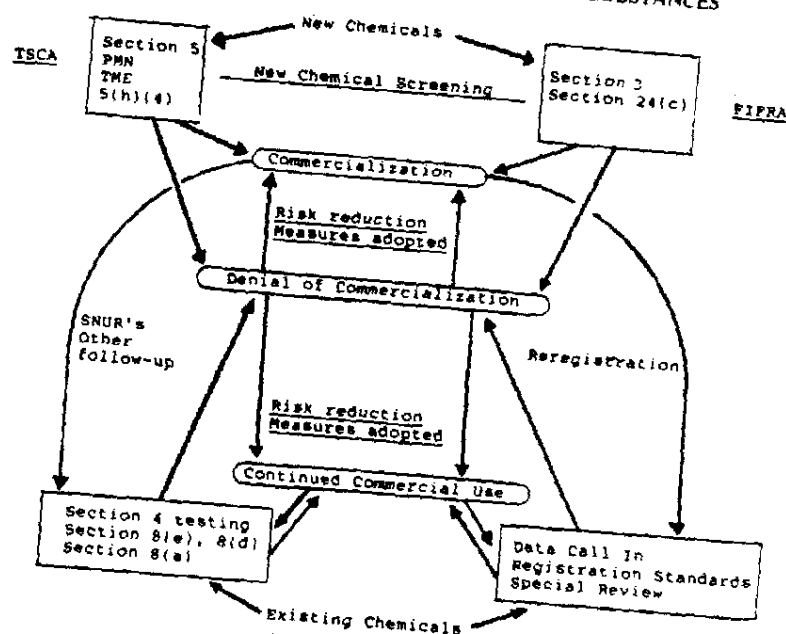


FIG. 2. Operational elements of TSCA and FIFRA.

2) is termed registration. There are, of course, differences in these two processes. Pesticide registration is a licensing procedure for materials which are being commercialized, whereas premanufacture notification is a screening program for materials that are not yet in manufacture and may never be commercialized. EPA estimates that some 40-50% of what goes through the PMN process is actually commercialized at some point.

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TABLE 1
COMPARISON OF TSCA, FIFRA, FDCA, AND EEC SIXTH AMENDMENT PROGRAMS

Element	TSCA	FIFRA	FDCA	EEC
New Chemical Review	Section 5 (Intent to manufacture)	Section 3 Section 24(c)	IND NDA	Notification at 1 metric ton sales annually
Old Chemical Review	Section 4 tests Section 8	Data call-in Registration Stds.	GRAS review, etc.	NONE
New Chemical follow-up	SNUR's Section 5(e), Section 5(f), Section 8(a).	Reregistration	Case reports, Surveillance	Step-sequence
Specific control authorities	Section 5(f), Section 6, 7	Label changes, Cancellation	Withdrawal of approval	NONE

The basic principle remains, however, that there is review of a chemical before it is introduced to the human environment. As needed, data is developed so that an informed judgment can be made as to for which uses and under what conditions there will be reasonable safety. For the registration of pesticides, which applies to materials being commercialized for a well-defined and limited set of uses, it is possible to specify the data requirements ahead of time in more detail than is practical under the PMN program.

One also needs a mechanism for reviewing chemicals more than just once, since use conditions may change during the commercial life of a chemical. Accordingly, EPA has initiated, under the present Administration, a follow-up program under TSCA which will allow EPA to look at specific materials which may go through the PMN process but which EPA would want to review again, should use or exposure change, because of their inherent toxic potential. Similarly, under FIFRA there is a statutory program which has not really been implemented. That particular statute requires materials to be reevaluated through registration every 5 years. It is a provision which the agency to date has not implemented because of a higher priority which has been given to the review and reregistration of materials registered prior to 1972. The EPA does expect to be able to address cyclic reregistration, a follow-up action, in the very near future.

EXISTING CHEMICAL REVIEW

Retrospective review is referred to as the existing chemical program under TSCA and as the registration standards and data call-in program under FIFRA. These programs acknowledge the fact that for many materials which have entered commerce in the past, the data base is not uniform. This makes toxicological comparisons difficult at times and can leave interesting questions unanswered. As a result, these programs put EPA initially into an information gathering mode.

Under the TSCA program, EPA issues test rules and/or negotiated agreements for chemicals which are selected by an interagency testing committee (ITC). This committee is composed of members from various federal agencies. The ITC designates chemicals for which it believes additional information is needed which can be obtained by testing. Substances can be designated, for instance, on the basis of an environmental concern or a human health concern.

Under the registration standard program in the pesticide area EPA has a similar objective. Under this program the agency identifies gaps in the data base for previously registered materials (generally those registered prior to 1972). The data gaps are identified in a guidance document and letters are issued requiring that those who wish to maintain their registration for those products fill the data gaps or come to some agreement with the agency to address the agency's stated concerns. Once the gaps are filled, a registration "standard" is completed which guides future review of specific formulations.

Both the TSCA and FIFRA programs allow EPA to look for specific problems in existing chemicals and to correct them.

THE ROLE OF PROFESSIONAL JUDGEMENT

Any risk management strategy is confronted with complex judgemental issues, risk analysis, and responsiveness to feedback. The scientist has certain professional re-

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responsibilities both to see that information is properly evaluated and—just as importantly—to see that the evaluation is properly and adequately translated for consumption by a public that often is not well equipped to deal with the complexities of the scientific issues.

Oliver Wendell Holmes once wrote, "Science is a very first rate piece of furniture for a man's upper chamber if he has common sense on the ground floor." It appears that those words are pertinent, especially as they pertain to chemicals and the levels and types of risk associated with some of them. When we say, "chemical risks," what we are really considering is unreasonable risks to the health of people or to the environment. One has to make distinctions concerning environmental effects, various human health effects, and that great nightmare, the risk of cancer. One also has to consider risks versus benefits. Also, many toxicological effects do not have the same spectrum of activity across different compounds. For instance, some compounds may pose a carcinogenic concern; others may pose an environmental concern. Under the charge given the agency by TSCA and FIFRA, a broad-balanced perspective is required. Yet, public concern may misdirect attention from areas where a public health or environmental impact can be made to areas where little or no impact can be had. It is important that regulatory science strive to be both up to date and interdisciplinary. This is the best safeguard against taking up an inappropriate cudgel to deal with a regulatory concern.

THE USE OF RISKS/BENEFIT BALANCING

Some regulatory decisions are fairly clearcut with respect to risks and benefits. The FDA recently faced a series of concerns over DPT vaccine which presents probably as clearcut a case of risks and benefits as can be found.

This concern was initiated by a television program which dealt with the potential risks inherent in the use of DPT vaccine (Gonzalez, 1982). The response of the public health community to this particular show was one of concern. The program was discussed editorially and otherwise in the Journal of the American Medical Association. The medical community was properly concerned that the program might put people off of DPT vaccination. The problem with the program is that it was a scare package. The footage that was aired was very dramatic. It was "good television"; that is entertaining. The presentation was not, unfortunately, balanced. The show did not say very much about the fact that 40 years ago, 7000 children died annually from pertussis. It said very little about the fact that since the introduction of the pertussis vaccine that number has dropped to some 5 or 20 annually. In short, if the vaccine had not been developed, even given better medical treatment, thousands of children might still die annually.

What types and level of risk are associated with the vaccine? The Center for Disease Control estimates that about 1 in 100,000 injections will produce some neurological reaction. However, the severity may vary. In rough terms, if 1 million children are treated, one may have 10 incidents of neurological reactions (since this risk index is in fact a clinical expectancy).

As an absolute level of risk that would appear to be a low level. It seems lower still in comparison to the thousands of deaths and hundreds of cases of permanent

brain damage which could be expected annually, (from the pertussis itself), if pertussis were allowed to remain endemic.

With DPT vaccine, the benefits are very clearcut. The risks are well understood, and they are low. Professional judgement and common sense resulted in continued use of the vaccine. Unfortunately, in some European countries, public emotion overrode science and the same set of concerns led to temporary turndowns in vaccination rates and, shortly following, increases in pertussis incidence. This degree of clarity in defining risks and benefits does not, unfortunately, extend to many chemical regulatory decisions.

In administering TSCA and FIFRA, the EPA regularly must make decisions on chemicals under conditions where the risks and benefits may not be completely defined. The role of regulatory risk management becomes one of identifying the most probable set of outcomes associated with various decision options and selecting an option which will, in fact, have a public health or environmental benefit.

There are several approaches EPA takes, depending on the types of effects involved. OPTS' general concerns were defined in some detail in the introduction to this article. These can briefly be summarized.

For environmental effects, the agency attempts to prevent significant or irreversible adverse effects on the environment. This is overlain by the rubric of the Endangered Species Act.

Toxicological effects tend to fall into two groups: noncancer and cancer. For non-cancer effects, the agency uses the approach of setting a safe exposure level based on a margin of safety applied to a no-effect level of exposure. For cancer, a no-effect level has been difficult to establish. The agency has considered, therefore, that at any level of exposure there is some degree of risk. That is not to say the risks are of sufficient magnitude to be concerned about relative to other risks. It is to say a no-effect level is not established. The question of no-effect levels for carcinogens is in a state of flux and is beyond the scope of this discussion. FDA has adopted such a level for selenium in animal feed [38 FR 10458 (April 27, 1973); 21 CFR Part 121 (Selenium in Animal Feed)] and Pitot has discussed the concept of a "practical threshold" based on Druckery's data (Pitot, 1981; Druckery, 1967).

EPA has attempted to avoid comparison of risk to benefit on the basis of weighing economic factors against human health. In the human health area the approach of the agency has been to compare health risks against health benefits to select a suitable risk mitigation goal. Generally, this is some risk level which is for practical purposes nonexistent or of no significance. If it is decided that regulatory action is needed to reach the stated risk goal, then economic risks are balanced against economic benefits and the most cost effective regulatory option is selected.

CONCLUSION

Risk management is very often the art and science of distinguishing the relevant from the less relevant or irrelevant. In a sense it is the institutional ability to look into the night and distinguish the real forms from the shadows. In that, risk management is like any other scientific or technical endeavor. It is the task of the scientist to sift through mountains of "fact" and discern that thread of reality which leads through the mountains to understanding.

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How LDL Receptors Influence Cholesterol and Atherosclerosis

The receptors bind particles carrying cholesterol and remove them from the circulation. Many Americans have too few LDL receptors, and so they are at high risk for atherosclerosis and heart attacks

by Michael S. Brown and Joseph L. Goldstein

Half of all deaths in the U.S. are caused by atherosclerosis, the disease in which cholesterol, accumulating in the wall of arteries, forms bulky plaques that inhibit the flow of blood until a clot eventually forms, obstructing an artery and causing a heart attack or a stroke. The cholesterol of atherosclerotic plaques is derived from particles called low-density lipoprotein (LDL) that circulate in the bloodstream. The more LDL there is in the blood, the more rapidly atherosclerosis develops.

Epidemiologic data reveal the surprising fact that more than half of the people in Western industrialized societies, including the U.S., have a level of circulating LDL that puts them at high risk for developing atherosclerosis. Because such concentrations are so prevalent, they are considered "normal," but clearly they are not truly normal. They predispose to accelerated atherosclerosis and heart attacks or strokes.

What determines the blood level of LDL, and why is the level dangerously high in so many Americans? Some answers are emerging from studies of specialized proteins, called LDL receptors, that project from the surface of animal cells. The receptors bind LDL particles and extract them from the fluid that bathes the cells. The LDL is taken into the cells and broken down, yielding its cholesterol to serve each cell's needs. In supplying cells with cholesterol the receptors perform a second physiological function, which is critical to the development of atherosclerosis: they remove LDL from the bloodstream.

The number of receptors displayed on the surface of cells varies with the cells' demand for cholesterol. When the need is low, excess cholesterol accumulates; cells make fewer receptors and take up LDL at a reduced rate. This protects cells against excess cholesterol, but at a high price: the reduction in the number of receptors decreases the rate at which LDL is removed from the circulation,

the blood level of LDL rises and atherosclerosis is accelerated.

We have proposed that the high level of LDL in many Americans is attributable to a combination of factors that diminish the production of LDL receptors. Recognition of the central role of the receptors has led to a treatment for a severe genetic form of atherosclerosis, and it has also shed some light on the continuing controversy over the role of diet in atherosclerosis in the general population.

The story begins with the discovery of LDL receptors in 1973 in our laboratory at the University of Texas Health Science Center at Dallas. We were studying tissue cultures of the human skin cells called fibroblasts. Like all animal cells, cultured fibroblasts need cholesterol as a major building block of their surface membrane (the plasma membrane); they had been shown to get the cholesterol by extracting it from lipoproteins in the serum of the culture medium. There is a mixture of various lipoproteins in human serum, but we found that the fibroblasts derive most of their cholesterol from a particular lipoprotein: LDL. We were able to attribute this to the presence on the cells of highly specific receptor molecules that bind LDL and related lipoproteins.

LDL is a large spherical particle whose oily core is composed of some 1,500 molecules of the fatty alcohol cholesterol, each attached by an ester linkage to a long-chain fatty acid. This core of cholesteryl esters is enclosed in a layer of phospholipid and unesterified cholesterol molecules. The phospholipids are arrayed so that their hydrophilic heads are on the outside, allowing the LDL to be dissolved in the blood or intercellular fluid. Embedded in this hydrophilic coat is one large protein molecule designated apoprotein B-100.

It is apoprotein B-100 that is recognized and bound by the LDL receptor, a

glycoprotein (a protein to which sugar chains are attached). The receptor spans the thickness of the cell's plasma membrane and carries a binding site that protrudes from the cell surface. Binding takes place when LDL is present at a concentration of less than 10^{-9} molar, which is to say that the receptor can pick out a single LDL particle from more than a billion molecules of water. The receptor binds only lipoproteins carrying apoprotein B-100 or a related protein designated apoprotein E.

How is LDL taken into the cell? Our collaborator Richard G. W. Anderson discovered in 1976 that the receptors are clustered in specialized regions where the cell membrane is indented to form craters known as coated pits (because the inner surface of the membrane under them is coated with the protein clathrin). Within minutes of their formation the pits pouch inward into the cell and pinch off from the surface to form membrane-bounded sacs called coated vesicles; any LDL bound to a receptor is carried into the cell. (Receptor-mediated endocytosis, the term we and Anderson applied to this process of uptake through coated pits and vesicles, is now recognized as being a general mechanism whereby cells take up many large molecules, each having its own highly specific receptor.)

Eventually the LDL is separated from the receptor (which is recycled to the cell surface) and is delivered to a lysosome, a sac filled with digestive enzymes. Some of the enzymes break down the LDL's coat, exposing the cholesteryl ester core. Another enzyme clips off the fatty acid tails of the cholesteryl esters, liberating unesterified cholesterol, which leaves the lysosome. As we have indicated, all cells incorporate the cholesterol into newly synthesized surface membranes. In certain specialized cells the cholesterol extracted from LDL has other roles. In the adrenal gland and in the ovary it is converted

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into respectively the steroid hormones cortisol and estradiol, in the liver it is transformed to make bile acids, which have a digestive function in the intestine.

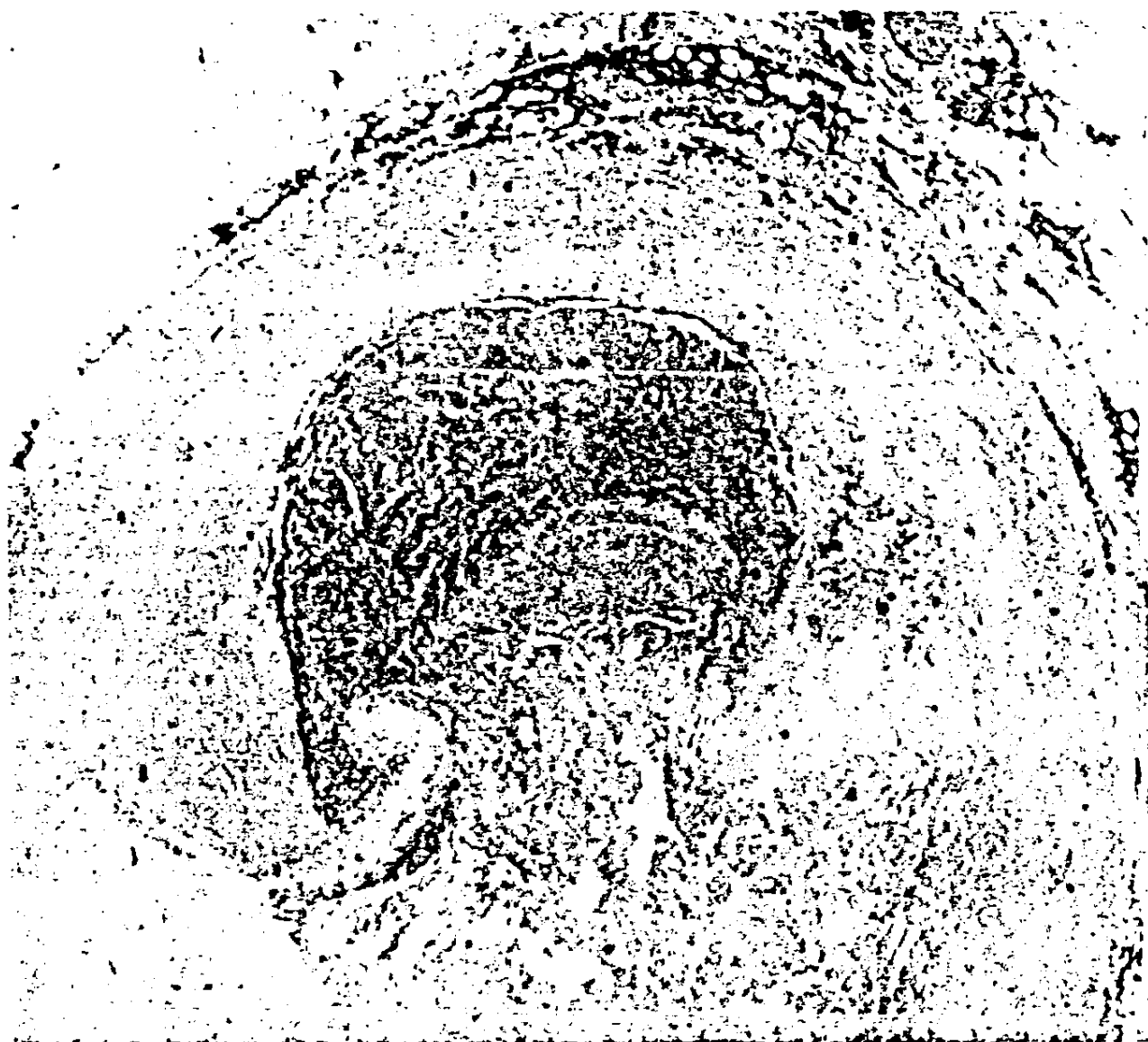
The amount of cholesterol liberated from LDL controls the cell's cholesterol metabolism. An accumulation of cholesterol modulates three processes. First, it reduces the cell's ability to make its own cholesterol by turning off the synthesis of an enzyme, HMG CoA reductase, that catalyzes a step in cholesterol's biosynthetic pathway. Suppression of the enzyme leaves the cell dependent on external cholesterol derived

from the receptor-mediated uptake of LDL. Second, the incoming LDL-derived cholesterol promotes the storage of cholesterol in the cell by activating an enzyme called *ACAT*. The enzyme reattaches a fatty acid to excess cholesterol molecules, making cholesteryl esters that are deposited in storage droplets.

Third, and most significant, the accumulation of cholesterol within the cell drives a feedback mechanism that makes the cell stop synthesizing new LDL receptors. Cells thereby adjust their complement of receptors so that enough cholesterol is brought in to meet their varying demands but not enough

to overload them. For example, fibroblasts that are actively dividing, so that new membrane material is needed, maintain a maximum complement of LDL receptors (some 40,000 per cell). In cells that are not growing the incoming cholesterol begins to accumulate, the feedback system reduces receptor manufacture and the complement of receptors is reduced as much as tenfold.

Our observations in tissue cultures were confirmed when the receptor system was shown to have an important role in the body. Soon after we found the LDL receptor on cultured fibroblasts it was shown to be present on circulating



BLOOD CLOT in a coronary artery took the life of a 76-year-old man with advanced atherosclerosis. Over the decades cholesterol carried by low-density lipoprotein (LDL) particles had infiltrated the wall of the artery, forming a bulky deposit (pale pink) that narrowed the channel. The clot formed suddenly, obstructing blood flow and causing the death of the heart muscle that had been supplied with

oxygen and nutrients by this artery. The formation of the clot (dark red) appears to have been triggered by a rupture of the lining of the channel that exposed the flowing blood to crystals of cholesterol (white needle-shaped objects). The photomicrograph, in which the sectioned artery is enlarged 37 diameters, was made by L. Maximilian Buja of the University of Texas Health Science Center at Dallas.

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human blood cells and on cell membranes from many different tissues of mice, rats, dogs, pigs, cows and human beings. The relative number of receptors and their functioning can be assessed in living animals and in human volunteers by injecting into the bloodstream LDL labeled with a radioactive isotope and measuring its rate of removal from the circulation. The rate has been shown to depend on the total number of LDL receptors displayed on all cells in the body. This can be demonstrated by modifying the apoprotein B-100 before the LDL is injected, so that it can no longer bind to receptors. James Shepherd and Christopher J. Packard of the University of Glasgow showed that the modified LDL circulates much longer than normal LDL.

Where is the LDL taken up? Daniel Steinberg of the University of California School of Medicine at San Diego and John M. Dietschy of the Health Science Center at Dallas have shown that in rats, rabbits, guinea pigs and squirrel monkeys about 75 percent of the receptor-mediated removal of LDL takes place in the liver. We have measured the number of receptors directly, in cell

membranes isolated from different tissues. Most tissues are found to have some receptors, but those of the liver, adrenal gland and ovary—the organs with particularly large requirements for cholesterol—have the highest concentration of receptors.

What is the origin of circulating LDL? The mechanism of its production is more complex, and as yet less well understood, than the mechanism of its uptake and degradation. LDL is one component of the system that transports two fatty substances, cholesterol and various triglycerides, through the bloodstream. The fat-transport system can be divided into two pathways: an exogenous one for cholesterol and triglyceride absorbed from the intestine and an endogenous one for cholesterol and triglyceride entering the bloodstream from the liver and other nonintestinal tissues.

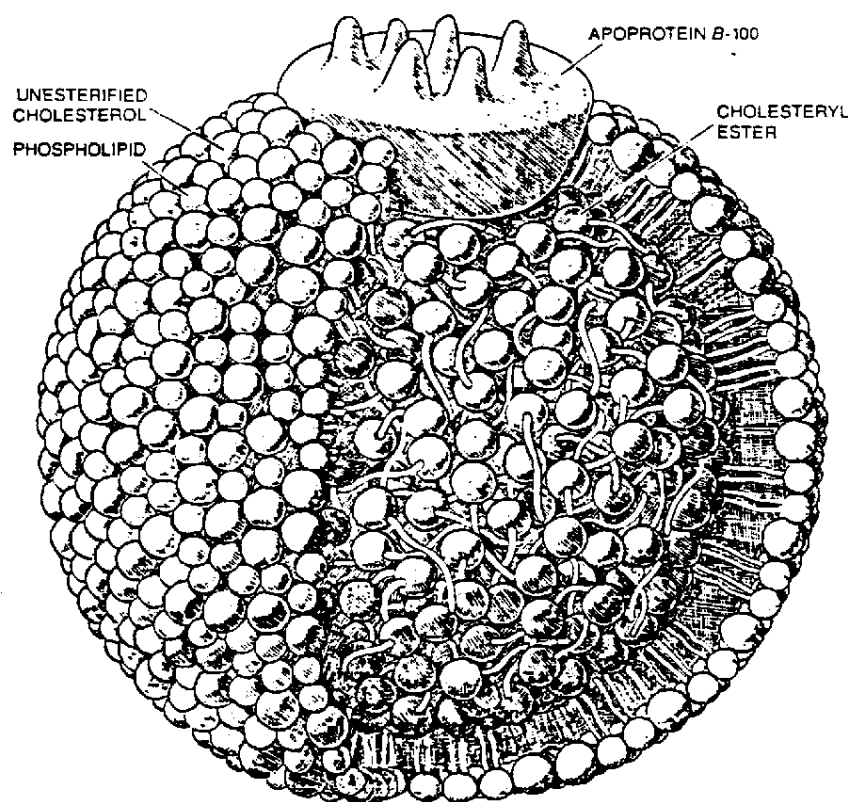
The exogenous pathway has been mapped by Richard J. Havel of the University of California School of Medicine at San Francisco and by others. It begins in the intestine, where dietary fats are packaged into lipoprotein particles

called chylomicrons, which enter the bloodstream and deliver their triglyceride to adipose tissue (for storage) and to muscle (for oxidation to supply energy). The remnant of the chylomicron, containing cholesteryl esters, is removed from the circulation by a specific receptor found only on liver cells. This chylomicron-remnant receptor does not bind LDL or take part in its removal from the circulation.

LDL is a component of the endogenous pathway, which begins when the liver secretes into the bloodstream a large very-low-density lipoprotein particle (VLDL). Its core consists mostly of triglyceride synthesized in the liver, with a smaller amount of cholesteryl esters; it displays on its surface two predominant proteins, apoproteins B-100 and E, both of which can be bound by LDL receptors. When a VLDL particle reaches the capillaries of adipose tissue or of muscle, its triglyceride is extracted. The result is a new kind of particle, decreased in size and enriched in cholesteryl esters but retaining its two apoproteins; it is called intermediate-density lipoprotein, or IDL.

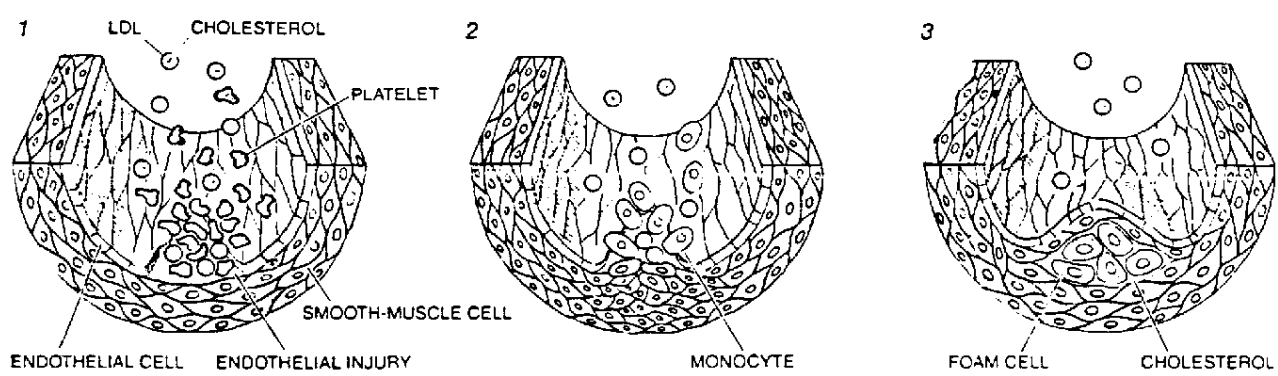
In human beings about half of the IDL particles are removed from the circulation quickly—within from two to six hours of their formation—because they bind very tightly to liver cells, which extract their cholesterol to make new VLDL and bile acids. Robert W. Mahley and Thomas L. Innerarity of the University of California School of Medicine at San Francisco have shown that the tight binding is attributable to apoprotein E, whose affinity for LDL receptors on liver cells is greater than that of apoprotein B-100. IDL particles not taken up by the liver remain in the circulation much longer. In time the apoprotein E is dissociated from them, leaving the particles, now converted into low-density lipoprotein (LDL), with apoprotein B-100 as their sole protein. Because of B-100's lower affinity for LDL receptors, the LDL particles have a much longer life span than IDL particles: they circulate for an average of two and a half days before binding to LDL receptors in the liver and in other tissues.

The central role of the LDL receptor in atherosclerosis was first appreciated when we showed that its absence is responsible for the severe disease called familial hypercholesterolemia (FH). In 1939 Carl Müller of the Oslo Community Hospital in Norway identified the disease as an inborn error of metabolism causing high blood cholesterol levels and heart attacks in young people; he recognized that it is transmitted as a dominant trait determined by a single gene. In the 1960's Avedis K. Khachadurian at the American University in Beirut and Donald S. Fredrickson at the U.S. National Heart and Lung Insti-



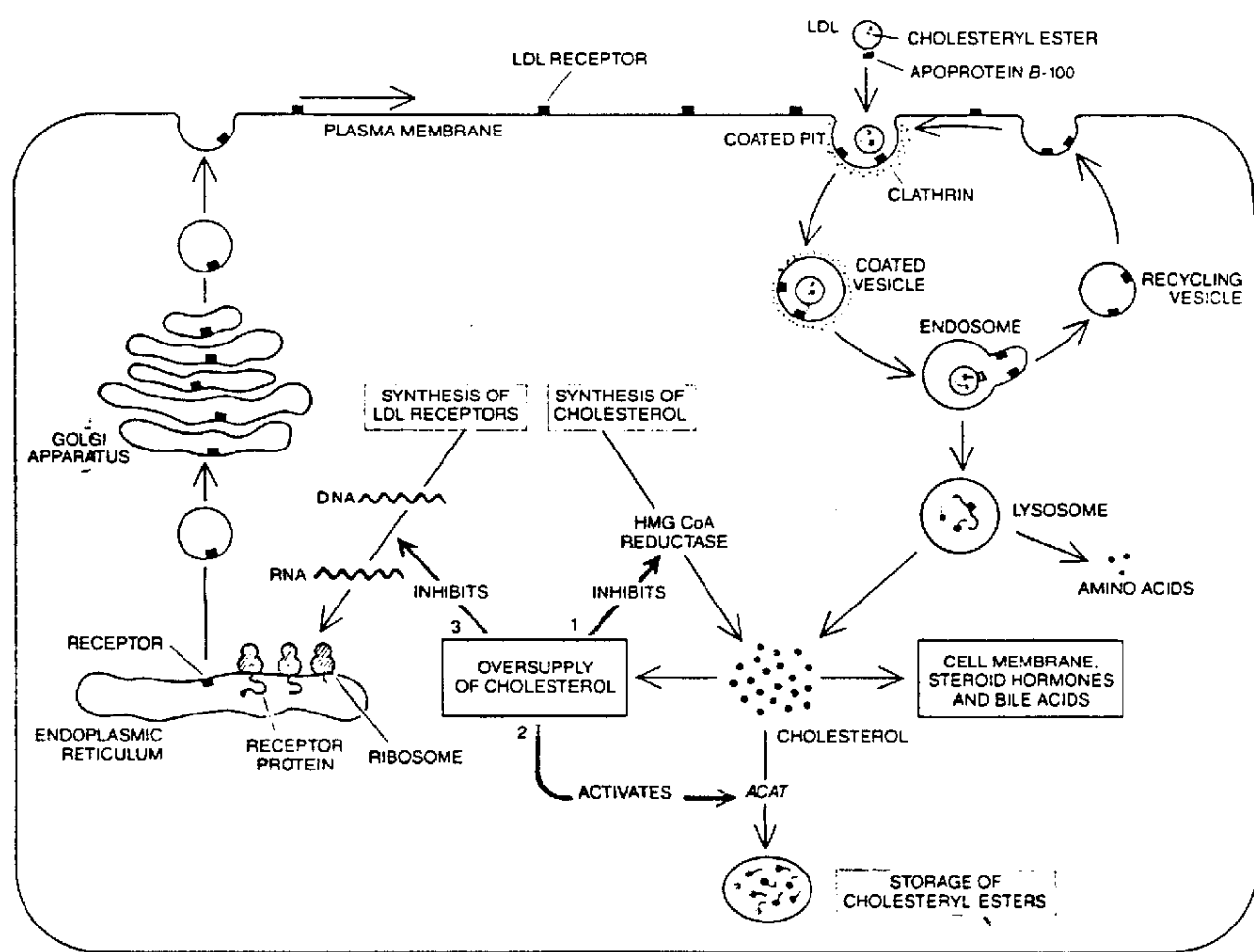
LDL, MAJOR CHOLESTEROL CARRIER in the bloodstream, is a spherical particle with a mass of three million daltons and a diameter of 22 nanometers (millionths of a millimeter). Its core consists of some 1,500 cholesteryl esters, each a cholesterol molecule attached by an ester linkage to a long fatty acid chain. The oily core is shielded from the aqueous plasma by a detergent coat composed of 800 molecules of phospholipid, 500 molecules of unesterified cholesterol and one large protein molecule, apoprotein B-100. When blood cholesterol is elevated, increasing the risk of atherosclerosis, the reason is almost always an increase in circulating LDL.

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ATHEROSCLEROTIC PLAQUE develops slowly. Damage to the thin layer of endothelial cells that lines an artery initiates plaque formation. According to a model originally proposed by Russell Ross and John A. Glomset of the University of Washington School of Medicine, the damaged endothelium becomes leaky and is penetrated by low-density lipoprotein (LDL) particles and blood platelets (1). In response to the release of such hormones as platelet-derived growth factor, smooth-muscle cells in the layer below the endothelium multi-

ply and migrate into the damaged area (2); at the same time white blood cells called monocytes invade the area and are activated to become scavenger cells called macrophages. The smooth-muscle cells and macrophages ingest and degrade LDL and become foam cells. If the blood LDL level is too elevated, cholesterol derived from the LDL accumulates in and among the foam cells. The accumulated cholesterol, cells and debris constitute an atheroma (3), which in time can narrow the channel of the artery and so lead to thrombosis.



CIRCULATING LDL (top right) is taken into a cell by receptor-mediated endocytosis. LDL is bound by a receptor in a coated pit, which invaginates and pinches off to form a coated vesicle. Fusion of several vesicles gives rise to an endosome, in whose acidic environment the LDL dissociates from the receptor, which is recycled to the cell surface. The LDL is delivered to a lysosome, where enzymes break down the apoprotein B-100 into amino acids and cleave the ester bond to yield unesterified cholesterol for membrane synthesis

and other cellular needs. The cellular level of cholesterol is self-regulating. An oversupply of cholesterol has three metabolic effects. It inhibits the enzyme HMG CoA reductase, which controls the rate of cholesterol synthesis (1); it activates the enzyme ACAT, which esterifies cholesterol for storage (2), and it inhibits the manufacture of new LDL receptors by suppressing transcription of the receptor gene into messenger RNA (3), which would ordinarily be translated on ribosomes of the endoplasmic reticulum to make the receptor protein.

tute showed there are two forms of the disease, a heterozygous form and a more severe homozygous form. Heterozygotes, who inherit one mutant gene, are quite common: about one in 500 people in most ethnic groups. Their plasma LDL level is twice the normal level (even before birth) and they begin to have heart attacks by the time they are 35; among people under 60 who have heart attacks, one in 20 has heterozygous FH.

If two FH heterozygotes marry (one in 250,000 marriages), each child has one chance in four of inheriting two copies of the mutant gene, one from each parent. Such FH homozygotes (about one in a million people) have a circulating LDL level more than six times higher than normal; heart attacks can occur at the age of two and are almost inevitable by the age of 20. It is notable that these children have none of the risk factors for atherosclerosis other than an elevated LDL level. They have normal blood pressure, do not smoke and do not have a high blood glucose level. Homozygous FH is a vivid experiment of nature. It demonstrates un-

equivocally the causal relation between an elevated circulating LDL level and atherosclerosis.

By what mechanism is the LDL level elevated? What is the particular function of the mutant gene? When we looked at cultured skin fibroblasts and circulating blood cells from FH homozygotes, we saw that the cells have either no functional LDL receptors at all or very few and therefore cannot bind, internalize and degrade LDL efficiently. The defective gene, in other words, encodes the protein of the LDL receptor. Homozygotes, having inherited two defective receptor genes, cannot synthesize any normal receptors. The cells of FH heterozygotes have one normal receptor gene and one mutant gene; they synthesize half the normal number of receptors and can therefore bind, internalize and degrade LDL at half the normal rate.

Although all FH patients studied to date have a mutation in the gene encoding the LDL receptor, the mutations are not always the same. Depending on the particular site that has undergone mutation, the receptor may not be synthesized at all or it may be synthesized but then fail to be transported to the cell surface, fail to bind LDL or fail to cluster in coated pits.

Studies with radioactively labeled LDL show that the particles survive in the bloodstream of FH homozygotes about two and a half times as long as they do in people with a normal LDL-receptor gene. (Eventually the LDL is removed from the circulation by alternate but much less efficient pathways.) The predictable slowdown in the removal and breakdown of LDL is one major reason for the extremely high LDL level characteristic of FH, but it does not account for the entire rise. In addition to degrading LDL more slowly, a person homozygous for FH actually produces about twice as much LDL per day as a normal person. How can a defect in the LDL receptor lead to the overproduction of LDL? The answer to this question came from studies of a remarkable strain of rabbits with a genetic defect resembling the one in human FH.

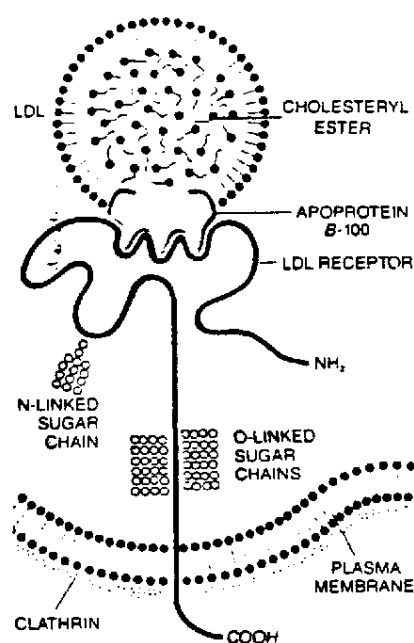
The rabbits were discovered in 1978 by Yoshio Watanabe of the Kobe University School of Medicine and are called WHHL rabbits (for "Watanabe heritable hyperlipidemic"). They are homozygous for a mutant LDL-receptor gene and produce less than 5 percent of the normal number of receptors; they have high circulating LDL from the time of birth and develop atherosclerosis leading to heart attacks by the age of two. Studies done by us in collaboration with Toru Kita and David W. Bilheimer and by Steinberg and his colleagues showed that the rabbits, like their human counterparts with homozygous

FH, make too much LDL as well as taking too long to break it down.

To learn the reason for LDL overproduction, Kita injected radioactively labeled VLDL, a precursor of LDL, into WHHL rabbits and normal animals and tracked the radioactivity through the fat-transport pathway. He found that triglyceride was removed from the VLDL, generating IDL, at the same rate in both groups. In normal rabbits the vast majority of the IDL particles disappeared rapidly from the circulation as they bound to LDL receptors on liver cells. In the WHHL rabbits, however, the liver cells lack LDL receptors, and so more IDL particles remained in the circulation and were eventually converted into more than the normal amount of LDL. In other words, a reduction in receptors has two effects in the rabbits—increased production and decreased removal of LDL—that act synergistically to raise the LDL level, which therefore rises disproportionately. Nicholas B. Myant and his colleagues at Hammersmith Hospital in London have shown the same thing is true in FH homozygotes.

Knowledge of the receptor deficiency in FH suggested a way to help the large number of patients with the heterozygous form of the disease. Perhaps we could stimulate the heterozygote's one normal gene to direct the synthesis of twice as many receptors as usual and so provide the patient with a normal complement of functional receptors. The possibility of such treatment was raised by something we had learned from cultured skin fibroblasts, namely that the feedback regulation of receptor synthesis takes place at the level of transcription. An excess of cholesterol reduces transcription of the LDL-receptor gene into messenger RNA, the nucleic acid that is subsequently translated by the cell's protein-synthesizing machinery to make the receptor protein; a cholesterol deficiency stimulates transcription and thus steps up the manufacture of receptors. We found we could get cultured cells from FH heterozygotes to make a normal number of LDL receptors (by making more messenger-RNA molecules from their single receptor gene) when we reduced the amount of cholesterol in the culture medium. How might we create an analogous cholesterol deficiency in the FH patient?

The liver takes up and degrades more cholesterol than any other organ because of its large size and its high concentration of LDL receptors. The bile acids into which most of the cholesterol is converted are secreted into the upper intestine, where they emulsify dietary fats. Having done their work, the bile acids are not simply excreted, however; they are largely reabsorbed from the intestine, returned to the bloodstream,



LDL RECEPTOR, a glycoprotein embedded in the plasma membrane of most body cells, was purified from the adrenal gland by Wolfgang J. Schneider in the authors' laboratory. David W. Russell and Tokuo Yamamoto cloned complementary DNA derived from its messenger RNA. The DNA's nucleotide sequence was determined and from it the 839-amino-acid sequence of the receptor's protein backbone was deduced. Sites of attachment of sugar chains to nitrogen (N) and oxygen (O) atoms were identified, as was a stretch likely to traverse the membrane. The actual shape of the receptor is not yet known; the drawing is a highly schematic representation.

taken up by the liver and again secreted into the upper intestine. This recycling of bile acids ordinarily limits the liver's need for cholesterol. We reasoned that if the recycling could be interrupted, the liver would be called on to convert more cholesterol into bile acids and this should lead the liver cells to make more LDL receptors.

A class of drugs that interrupt the recycling of bile acids was already known. They are the bile-acid-binding resins, gritty polymers carrying many positively charged chemical groups. Taken orally, these resins bind to the negatively charged bile acids in the intestine; because the resins cannot be absorbed from the intestine, they are excreted, carrying the bound bile acids with them. The first bile-acid-binding resin, cholestyramine, was synthesized more than 20 years ago and was found to lower the blood LDL level by an average of 10 percent. (A recent 10-year prospective study done by the National Heart, Lung, and Blood Institute indicated that such a reduction was enough to cut the incidence of heart attacks in a test group of middle-aged men by 20 percent.) What we had learned about LDL metabolism provided the missing rationale for such results: the interruption of bile-acid recycling increases the number of LDL receptors on liver cells.

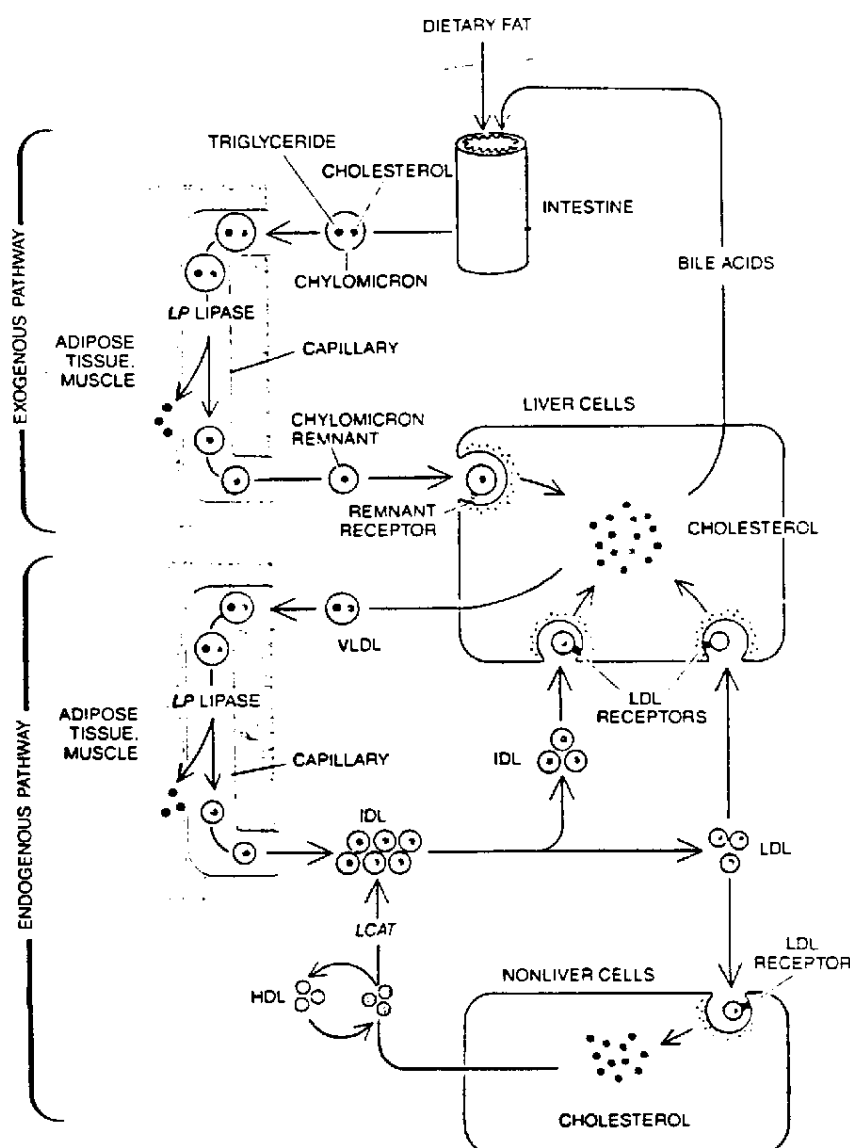
The 10 percent drop in LDL level attainable with cholestyramine and other such resins was encouraging, but clearly a more profound reduction is necessary for treating FH heterozygotes. The limited efficacy of the resins stems from the dual response of the liver to a cholesterol deficiency. In addition to making more LDL receptors the liver increases its manufacture of HMG CoA reductase and makes more of its own cholesterol. We reasoned that this increased *de novo* synthesis of cholesterol partially satisfies the resin-induced demand for more cholesterol and so prevents the liver from maximally increasing the number of LDL receptors.

We thought inhibition of cholesterol synthesis might force the liver to rely more on LDL uptake and thus stimulate greater production of receptors. To block cholesterol synthesis we took advantage of the discovery by Akira Endo, now of the Tokyo University of Agriculture and Technology, of a remarkable natural inhibitor of HMG CoA reductase. In 1976 he isolated from a penicillin mold a substance called compactin. A side chain of the compactin molecule closely mimics the structure of the natural substrate of HMG CoA reductase, and so it binds to the enzyme's active site and inhibits the enzyme's activity. Alfred W. Alberts of the Merck Sharp & Dohme Research Laboratories and his colleagues isolated from a different mold a structural rela-

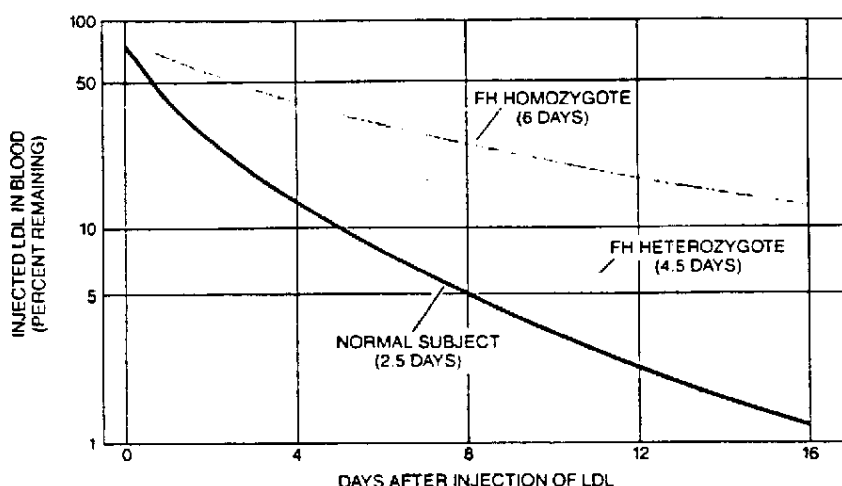
tive of compactin, called mevinolin, that is an even more potent enzyme blocker. Compactin and mevinolin were shown, by Endo and Alberts respectively, to lower the blood LDL level in animals. If our idea was correct, the drugs should be even more effective in conjunction with a bile-acid-binding resin.

In collaboration with Petri T. Kova-

nen we administered a bile-acid-binding resin to dogs either alone or along with one of the enzyme inhibitors. After two weeks we assessed the number of LDL receptors by measuring the ability of biopsied liver membranes to bind radioactive LDL. We found, as expected, that the resin alone generated a modest rise in the number of receptors. When the



EXOGENOUS AND ENDOGENOUS fat-transport pathways are diagrammed. Dietary cholesterol is absorbed through the wall of the intestine and is packaged, along with triglyceride (glycerol ester-linked to three fatty acid chains), in chylomicrons. In the capillaries of fat and muscle tissue the triglyceride's ester bond is cleaved by the enzyme lipoprotein (LPL) lipase and the fatty acids are removed. When the cholesterol-rich remnants reach the liver, they bind to specialized receptors and are taken into liver cells. Their cholesterol either is secreted into the intestine (mostly as bile acids) or is packaged with triglyceride in very-low-density lipoprotein (VLDL) particles and secreted into the circulation, inaugurating the endogenous pathway. Again the triglyceride is removed in fat or muscle, leaving cholesterol-rich intermediate-density lipoprotein (IDL). Some IDL binds to liver LDL receptors and is rapidly taken up by liver cells; the remainder stays in the circulation and is converted into LDL. Most of the LDL binds to LDL receptors on liver or other cells and is removed from the circulation. Cholesterol leaching from cells binds to high-density lipoprotein (HDL) and is esterified by the enzyme LCAT. The esters are transferred to IDL and then LDL and are eventually taken up again by cells.



NUMBER OF LDL RECEPTORS in the body is assessed by injecting LDL labeled with a radioactive isotope and measuring the amount of radioactivity in blood samples for several weeks; the loss of radioactivity reflects the cellular uptake of LDL and hence the number of LDL receptors. The curves trace the removal of LDL from the circulation in patients with the homozygous and heterozygous forms of familial hypercholesterolemia (FH) and in normal subjects. In each case the mean life span of an LDL particle is shown in parentheses.

enzyme inhibitor was given too, the number of receptors rose much more. At the whole-body level this led to a marked increase in the rate of removal of LDL from the circulation. Together the two drugs caused a remarkable 75 percent decline in the dogs' LDL level.

With Bilheimer and Scott M. Grundy we went on to administer a resin and mevinolin to patients with heterozygous FH. Their LDL level fell by approximately 50 percent, into the normal range. Tests with radioactive LDL showed the drop was caused by an increase in LDL receptors. The single normal gene had been made to work twice as hard as usual, producing enough receptors to allow LDL to be removed from the circulation at a normal rate.

As might be expected, FH homozygotes, lacking even one normal receptor gene, do not respond to this two-drug treatment. Another approach must be found if they are to be helped. Thomas E. Starzl of the University of Pittsburgh School of Medicine has tested a surgical approach, following up on a suggestion that the homozygote's lack of receptors might be partially corrected if the patient could be given a liver from a normal donor. He transplanted the liver of a child killed in an accident into a six-year-old girl suffering from severe homozygous FH. (The patient had already had several heart attacks and her heart was so weakened that a heart transplant was necessary at the same time.) More than six months after the operation the patient was maintaining a total blood cholesterol level in the range of 300 milligrams per deciliter, compared with a preoperation level of about 1,200. Obviously liver transplantation is not an ideal treatment, but the results to date

make it clear that receptors on the cells of the transplanted liver are functioning to remove LDL from the circulation.

What about the vast number of people in Western industrial societies who suffer heart attacks or strokes without having any genetic defect in the LDL receptor? Is what we have learned about FH relevant to the high incidence of atherosclerosis in the general population? We believe it is. The LDL-receptor hypothesis states that much of the atherosclerosis in the general population is caused by a dangerously high blood level of LDL resulting from failure to produce enough LDL receptors. The inadequate number of receptors can be attributed to subtle genetic and environmental factors that limit receptor manufacture even in people without FH. One environmental factor is a high dietary intake of cholesterol and of saturated fats derived from animal tissues.

Epidemiologic surveys done in many countries over the past 30 years have uniformly shown that atherosclerosis becomes severer as the mean LDL level rises in a population. As long ago as 1958 Ancel Keys of the University of Minnesota Medical School studied populations, in seven countries, in which the mean total cholesterol level varied from a high of 265 milligrams per deciliter to a low of 160. (He did not measure LDL cholesterol specifically, but because the level of lipoproteins other than LDL does not vary much, one can assume that the variations in total cholesterol reflected differences in LDL level.) Keys recorded the cholesterol level of 12,763 age-matched men in the seven countries, and 10 years later he determined which of the men had had a heart attack.

Two variables were found to correlate strongly with cholesterol level: the incidence of coronary atherosclerosis (as measured by fatal heart attacks) and the dietary intake of animal fats. In two villages (in Japan and Yugoslavia) where the mean total cholesterol level was 160 the incidence of fatal heart attacks was less than five per 1,000 men per 10 years. In eastern Finland, where the mean total cholesterol level was 265, the incidence of fatal heart attacks was 14 times as high. In populations with intermediate cholesterol levels (as in the U.S.) the incidence fell between the two extremes.

The correlation between cholesterol level and dietary intake of animal fats was even stronger than the correlation between cholesterol and atherosclerosis. Populations consuming small amounts of animal fats (as in Japan and Yugoslavia) had low cholesterol levels. Populations with a high intake of such fats (as in eastern Finland) had high levels. Subsequent studies of many different populations have confirmed Keys's findings: high LDL levels are the rule in populations that consume a large part of their calories as fats from meat and dairy products.

The LDL-receptor hypothesis provides a likely explanation of the epidemiologic data. A high average intake of cholesterol makes cholesterol accumulate in liver cells. The accumulation seems to be accentuated by ingestion of animal fats rich in saturated fatty acids. Even a modest accumulation of cholesterol in the liver would partially suppress the manufacture of LDL receptors. This could lead to an increase in the average LDL level that would be detectable in an entire population.

Animal experiments by our group and by Mahley and Innerarity support the hypothesis that a high-fat diet reduces LDL receptors in the liver. In baboons, rabbits and dogs maintained on low-fat diets the number of LDL receptors is high and the animals degrade injected LDL rapidly; their LDL level is much lower than it is in human beings. When rabbits and dogs are fed diets high in cholesterol, their manufacture of receptors in the liver is suppressed by as much as 90 percent, and the result is a buildup of both IDL and LDL in the bloodstream. At birth human infants have LDL concentrations similar to those of other animal species; apparently newborn human beings make a large number of LDL receptors. During the childhood and early-adult years in industrialized societies, however, the LDL level rises three- or fourfold. Studies in adults injected with LDL suggest that the increase is attributable to a decrease in the number of receptors with age.

The causes of the acquired receptor deficiency in human beings are not all known. The high dietary intake of ani-

mal fats seems to be an important factor, but it is not the only one: even in people raised on diets extremely low in fats the LDL level tends to be higher than it is in other species. Such hormones as estradiol and thyroid hormone are known to stimulate the manufacture of LDL receptors in the liver, and it is possible that subtle abnormalities in these and other hormones contribute to the age-related decrease in receptors.

The concentration of LDL eventually attained in most middle-aged adults in the U.S. and in similar societies is associated by epidemiological data with accelerated atherosclerosis. Experiments with cultured cells show why. The receptors bind LDL optimally when it is present in the blood at a concentration below 50 milligrams per deciliter. The receptors in animals and in humans

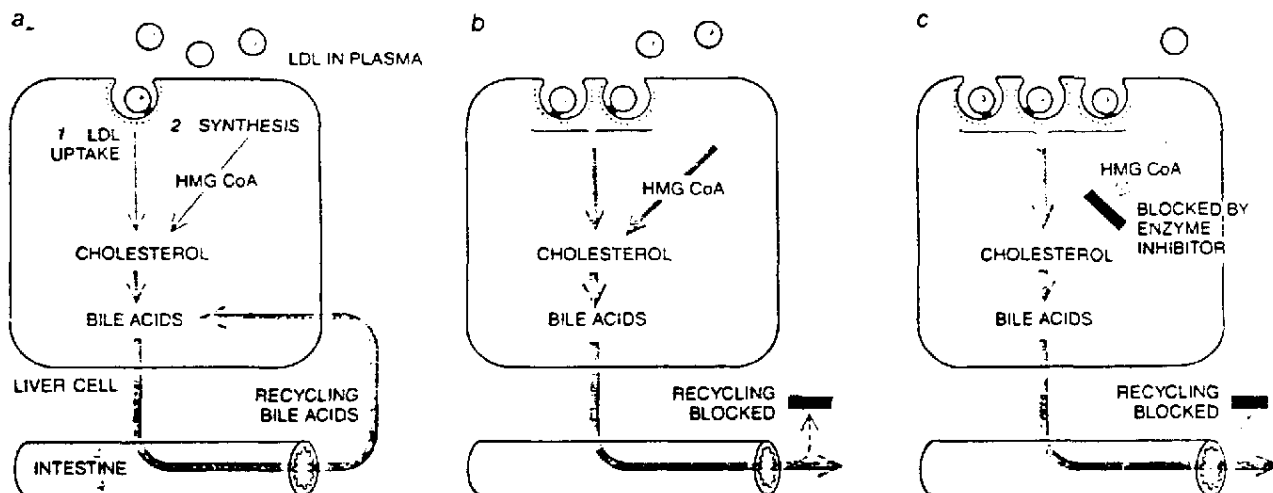
(judging by the LDL level in human infants) have apparently been selected by evolution to function at just such levels. Yet in Western industrial countries the average "normal" LDL level in adults is about 125 milligrams per deciliter, considerably above the concentration at which receptors bind LDL most efficiently.

One finding that is consistent with the LDL-receptor hypothesis has been reported by William R. Hazzard of the Johns Hopkins Hospital and his colleagues. They showed that ingestion by adults of a high-cholesterol diet (including three egg yolks per day) does lead to a decrease in the number of LDL receptors, which they measured directly in circulating lymphocytes. A definitive test of the hypothesis will, however, require a comprehensive and well-con-

trolled study of the rate of metabolism of injected VLDL and LDL in members of populations with low-fat and high-fat diets and with varying LDL levels. That has not yet been done systematically.

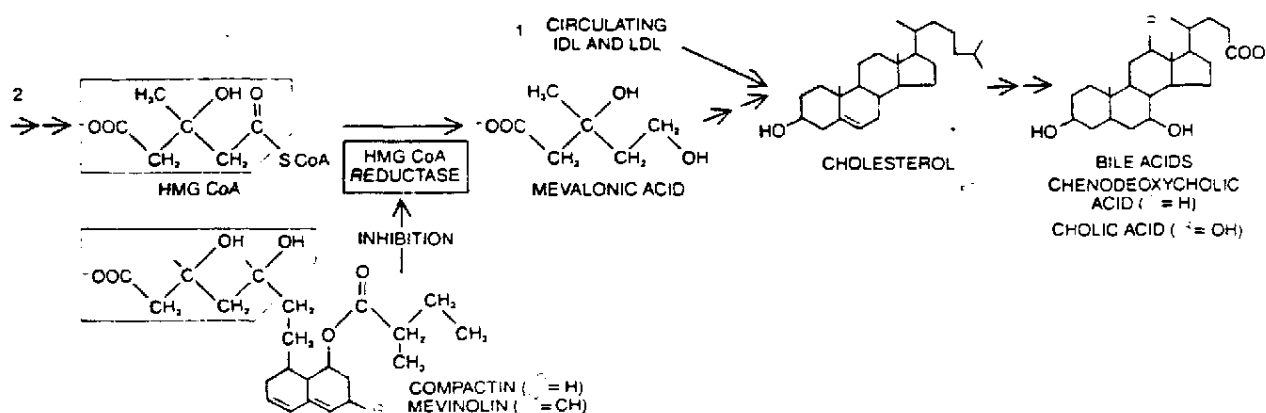
If the LDL-receptor hypothesis is correct, the human receptor system is designed to function in the presence of an exceedingly low LDL level. The kind of diet necessary to maintain such a level would be markedly different from the customary diet in Western industrial countries (and much more stringent than moderate low-cholesterol diets of the kind recommended by the American Heart Association). It would call for total elimination of dairy products as well as eggs, and for a severely limited intake of meat and other sources of saturated fats.

We believe such an extreme dietary



LIVER GETS CHOLESTEROL for conversion into bile acids from IDL and LDL taken up from the circulation (1) or by synthesizing it de novo (2). A key step in the long synthetic pathway is reduction of HMG CoA to mevalonic acid, a reaction catalyzed by the enzyme

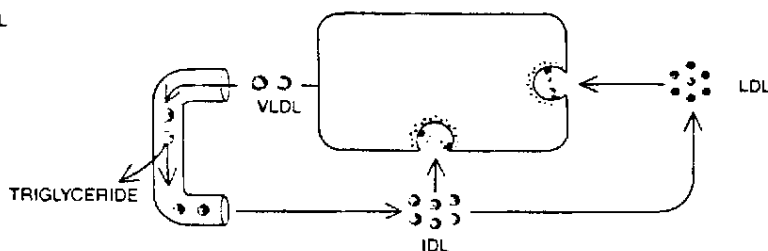
HMG CoA reductase. The enzyme is inhibited by the drugs compactin or mevastatin, whose side chain is so similar to that of HMG CoA (colored frames) that it blocks the enzyme's active site. Enzyme inhibition leaves liver dependent on uptake of IDL and LDL.



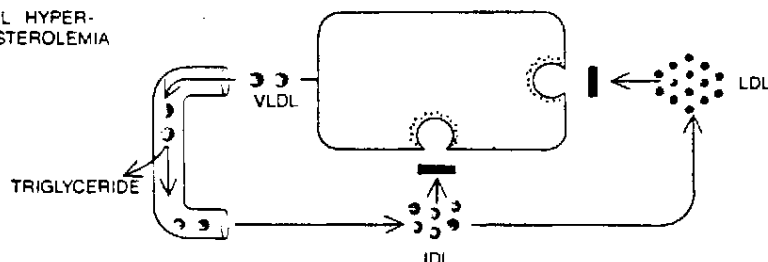
HETEROZYGOUS FH can be treated with a combination of drugs that stimulates manufacture of LDL receptors. Ordinarily the liver's demand for cholesterol is modified by the recirculation of bile acids (a). If the recirculation is prevented by a bile-acid-binding resin (b),

more cholesterol is needed. Liver cells respond by increasing the number of LDL receptors, but also by increasing the rate of cholesterol synthesis. If a second drug is given to block enhanced synthesis (c), still more receptors are made and the blood LDL level is lowered.

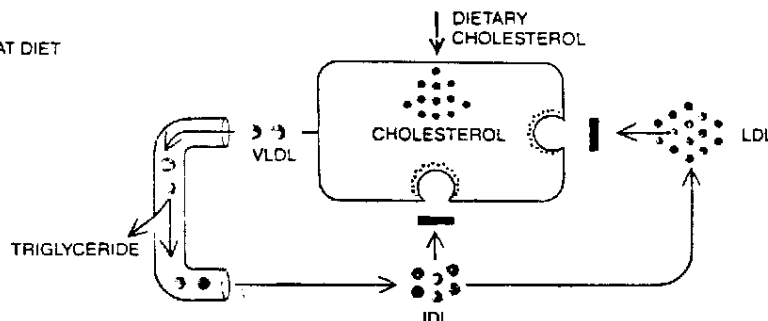
NORMAL



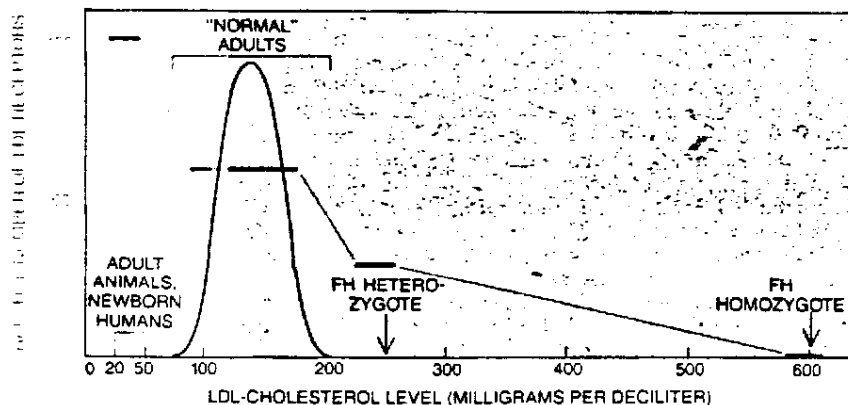
FAMILIAL HYPER-CHOLESTEROLEMIA



HIGH-FAT DIET



LDL-RECEPTOR DEFICIENCY, whether genetic or acquired, has two synergistic effects that combine to raise the blood LDL level. VLDL secreted by the liver is converted into IDL in fat and muscle. In normal people about half of the IDL particles are taken up by LDL receptors on liver cells; the rest are converted into LDL (*top*). In FH (*middle*) a genetic defect diminishes the number of receptors on liver cells; an analogous deficiency is caused by diets that fill liver cells with cholesterol and so reduce receptor synthesis (*bottom*). In either case there are the same two consequences. IDL not taken up by liver cells remains in the circulation and is converted to yield increased amounts of LDL; the LDL in turn is removed more slowly.



RANGE OF LDL LEVELS in "normal" adults in Western industrial societies, indicated by the curve, is compared with the range in adult animals and human infants and with the levels seen in FH patients. Levels in the shaded region of the chart are above the threshold associated with accelerated atherosclerosis; more than half of the adults have LDL levels above the threshold. The LDL level is inversely associated with the number of LDL receptors (*color*).

change is not warranted for the entire population. There are several reasons. First, such a radical change in diet would have severe economic and social consequences. Second, it might well expose the population to other diseases now prevented by a moderate intake of fats. Third, experience shows most Americans will not adhere voluntarily to an extreme low-fat diet. Fourth, and most compelling, people vary genetically. Among those who consume the current high-fat diet of Western industrial societies, only 50 percent will die of atherosclerosis; the other 50 percent are resistant to the disease.

Some individuals resist atherosclerosis because their LDL level does not rise dangerously even though they consume a high-fat diet: they may inherit genes that somehow circumvent the usual feedback system and maintain receptor manufacture at an adequate level. Barbara V. Howard of the National Institutes of Health Clinical Research Center in Phoenix has shown, for example, that Indians of the Pima tribe have relatively large numbers of LDL receptors, and maintain low LDL levels, in spite of a high-fat diet. In other individuals the arteries apparently resist the damaging effects of elevated LDL. For example, 20 percent of men with heterozygous FH do not have a heart attack before the age of 60 even though their blood LDL is very high.

Given these reasons for constraint, what can be done to prevent accelerated atherosclerosis? One approach is to individualize dietary recommendations. A diet moderately low in animal fats would seem to be prudent for most people. The diet proposed by the American Heart Association, for example, would reduce blood cholesterol levels by as much as 15 percent and should somewhat lessen the incidence of heart attacks. On the other hand, people who have a strong family history of heart attacks or strokes, and who may therefore be particularly susceptible to the damaging effects of LDL, might well be encouraged to follow a diet extremely low in cholesterol and saturated fats—even if their LDL level is near the mean "normal" level. One can hope additional research will identify factors that either sensitize people to the ill effects of LDL or protect them from those effects.

Finally, therapy with drugs that increase the number of LDL receptors may turn out to be appropriate for at least some people who do not have FH but in whom the number of receptors is reduced by diet or other factors. If it is shown that these drugs do prevent diet-induced suppression of receptors and if the drugs can be shown to be safe for long-term use, it may one day be possible for many people to have their steak and live to enjoy it too.

UHL 02963

Which Risks Are Acceptable?

THOMAS H. JUKES

PEOPLE WILL ACCEPT voluntary risks, such as driving a car, crossing a street, or even smoking cigarettes, but refuse to accept involuntary risks that they perceive as being imposed on them without consent. The environmentalist and consumerist organizations have been highly successful in persuading the public that industry seeks to impose involuntary risks for reasons of profit.

I have been personally involved with environmentalism for many years. I have been a life member of the Sierra Club since 1939, and my wife and I started the first chapter of the Sierra Club outside of California, when we lived in Suffern, New York, in 1950. During the fifties and sixties, I watched the transition as environmental groups, originally dedicated to the outdoors and to preserving wilderness—a philosophy to which I gave my support—grew into a broad-based antitechnological movement led by professionals. In 1959, the Sierra Club published a book, *This Is the American Earth*, which attacked technology. For example, it spoke against medical research that kept people alive by means of in-

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This article is adapted from a talk presented to the American Industrial Health Council on March 19, 1980, in Washington, D.C.

jections; it said the earth was being destroyed by chemical fertilizers, and that not enough manure was being used.

The movement against chemical technology gained much strength with the publication in 1962 of Rachel Carson's *Silent Spring*. As I pointed out in 1971, DDT came to be widely regarded by the public as a dangerous poison instead of a life-saving chemical.¹

The number of new laws passed—and the new agencies born—just in the past ten years, prompted a recent speaker to address his audience thus:²

Just sit back and try to imagine a world without:

- the National Highway Traffic Safety Administration to recall Pintos or Firestone tires;

Imagine, if you can, a world without:

- the Consumer Product Safety Commission to warn about asbestos in hair dryers;

Imagine a world without:

- OSHA to teach that manure is slippery;

Imagine a world without:

- the Federal Election Commission to tell us who paid to elect the candidates of their choice;

Imagine a world without:

- the EPA to require catalytic converters on cars;

Imagine a world without:

- the National Environmental Policy Act to require environmental impact statements;

Imagine a world without:

- the Endangered Species Act to protect the snail darter, or the Santa Cruz long-toed salamander.

Such a world existed only ten years ago when none of these agencies or laws existed.

Aminotriazole and Rats

First, a little history:

In November 1959, Dr. Boyd Shaffer, the head toxicologist at American Cyanamid Company Laboratories, informed the Food and Drug Administration that the weed killer aminotriazole caused enlargement and adenoma of the thyroid gland in rats. These results were obtained in a two-year study of rats fed high levels of aminotriazole at the Hazleton Laboratory under contract with the American Cyanamid Company. The finding was unexpected, but it was not novel. The same effect on thyroid glands of rats is pro-

duced by any goitrogenic substance and, indeed, by iodine deficiency. Goitrogenic substances are present naturally in foods such as soybeans, turnips, and cabbage. Synthetic goitrogens are used to control overactivity of the thyroid gland in human patients. One of these, thiouracil, was actually cleared by the FDA as an animal feed additive around 1950. Aminotriazole itself was in use as an experimental antithyroid drug in the late Dr. Edwin Astwood's clinic at Tufts University Medical School in Boston in 1959.

Yet adenoma of the thyroid gland, induced by dietary means, can eventually result in carcinomatous changes in some rats that receive a goitrogen for many months. This fact is not considered hazardous in the clinical use of goitrogens as antithyroid drugs, for it is recognized that subacute or short-term dosage with goitrogens does not produce the excessive enlargement of the thyroid glands that precedes the onset of carcinomatous changes in rats. The enlargement is actually caused by an indirect hormonal effect. Goitrogens inhibit the uptake of iodine by the thyroid gland. As a result, the pituitary gland works overtime to stimulate the thyroid gland to resume thyroid hormone production at normal levels. This stimulation of the gland by the pituitary hormone, thyrotropin, results in enlargement of the thyroid. In today's climate, any enlargement or hyperplasia is regarded as a potential cancer.

Aminotriazole had been introduced in the spring of 1959 as a herbicide for weed control in various crops, including cranberry bogs. The permitted use called for stopping the spraying several months before harvest time. A few growers did not take this precaution, and, as a consequence, small traces of aminotriazole were suspected in less than 0.34 percent of the cranberry crop.

The rest is, literally, history. Mr. Arthur Flemming, secretary of Health, Education, and Welfare under President Eisenhower, took to the radio and warned the people of America against eating cranberries. He threatened his listeners with cancer unless they avoided cranberries at Thanksgiving. The result was a panic from which United States consumers have never fully recovered. The interpretation was that a chemical company was planning to make money by giving people cancer. A Cyanamid salesman reported that a service station attendant refused to sell him gasoline. Hundreds of tons of cranberries that contained no aminotriazole were bulldozed underground. A writer denounced "the poisoned cranberries of Madison Avenue." An official of a chemical company told

his wife to throw away her cans of cranberries "just in case." Even in the small percentage of cranberries that contained aminotriazole, the antithyroid effect was probably no greater than that of cole slaw. A woman in Maryland started to plan a book. Her name was Rachel Carson.

In the years before the cranberry incident, various authors had written about the dangers of chemicals, including pesticides, but the idea had never caught on. However, Mr. Flemming's warnings were the official voice of the government.

I regard Arthur Flemming as the innovator who made it possible for Rachel Carson to destroy public confidence in pesticides, and, eventually, in many products of the chemical industry. He had no scientific training—his background was in journalism and public administration—but his political ambition enabled him to reach cabinet rank in the Eisenhower administration. How far we have come since Flemming and the cranberries is illustrated by a recent incident at the Environmental Protection Agency. The agency distributed, at public expense, 30,000 copies of a pamphlet prepared by the League of Women Voters that starts with the following paragraph:

Darlene Cody, in her first trimester of pregnancy, went hiking on a national forest trail. Part of the area through which the trail wound was very smoky, as it was being subjected to a controlled burning by the U.S. Forest Service. Unbeknownst to Mrs. Cody, the area had also been sprayed with the herbicides 2,4,5-T and 2,4-D. Mrs. Cody's baby was born with a cleft palate.

The Codys suspect dioxin as the cause of their baby's birth defect. Particularly toxic chemicals known to cause tumors and birth defects in test animals, dioxins are unavoidable impurities produced in manufacturing 2,4,5-T.

The EPA has 200,000 more copies on hand.

The remarkable thing about the current negative attitude toward acceptable risks is that this atmosphere of public paranoia has been created by imagination rather than by the measurable effects of chemicals. A few years ago, we could point out that there was not a single case of any consumer having been injured by a pesticide that had been applied in accordance with the regulations. There have, of course, been cases of industrial accidents from pesticides, including injury to applicators, but not to consumers. Today, such reassuring statements count for nothing. We

are told that it is impossible to connect cause and effect, especially since cancer may take thirty years to develop following the original exposure. Mr. Jimmy Carter, during his presidential campaign in the summer of 1976, informed an audience that pesticide residues in foods were an example of a carcinogenic hazard. A prominent scientist has repeatedly stated that the carcinogenic effects of dieldrin will not start to appear in human beings until several years from now.

Where are all the sick people? Apparently they are busy lobbying Congress to raise the retirement age from 65 to 70. That is, the older ones. The young ones are breaking world records in sporting events. In the world as a whole, the birth rate is so much higher than the death rate, and life expectancy is increasing so rapidly, that the human species has created an ongoing and insoluble population crisis. When the growers of marijuana in Northern California complained that 2,4,5-T was making their men sexually impotent, and producing miscarriages in their women, someone asked how the women became pregnant. In my opinion, the prospect of winning damage suits has a powerful effect on the imagination.

The "Single Molecule Myth"

One of the traps into which we have been led by the carcinologists is the "single molecule story." This was used with dramatic effect at Congressional hearings, in reference to diethylstilbestrol (DES), and was publicized by Morton Mintz in the *Washington Post*. Recently, it was reaffirmed by Dr. Arthur Upton, former director of the National Cancer Institute, as follows:

No scientific method currently available can accurately determine how much of a carcinogen, if any, may be safely added to our food supply without increasing the risk of cancer in the human population. Many scientists believe there is no "safe" level of a carcinogen. Transformation of a normal cell into a cancer cell could conceivably occur with one molecule of a carcinogen acting on a single cell.

By "could conceivably occur," perhaps he means there is a one chance in a million possibility of one molecule causing cancer. Surely the chance could not be much more remote than this, if it is worth scaring people about.

I have made some calculations with regard to arsenic, which is listed by the International Agency for Research in Cancer as a known human carcinogen (Cancer Research 40:1-12, 1980). In trace amounts, arsenic is considered to be a nutritionally essential element, but this does not inhibit the carcinogenologists. For example, it has been stated that the essential daily intake of selenium, chromium, and arsenic, all classified as carcinogens, does not represent safe levels of these substances, but is dangerous, and "is the price we have to pay in order to stay alive," according to Dr. W. Lijinsky, of the National Cancer Institute.

The arsenic content of a normal healthy human being is 4.4 mg, using the lower figure quoted by Professor E. J. Underwood, professor of biochemistry at the University of Western Australia. This is 9×10^{18} molecules of arsenic as As_1 . One would think that this staggering figure, which is two million times the human population on the earth, would give Dr. Upton pause. Let us try some calculations.

If each molecule of arsenic has a one-in-a-million chance of transforming a normal cell into a virulent cancer cell, then the odds are 9 trillion to 1 (dividing 9×10^{18} by 1 million) that we shall all get cancer from arsenic normally present in the body. Perhaps it is statistically possible to escape this, but the chances are very small—about 1,000 to 1 against the possibility that anyone in the world will escape developing cancer from arsenic.

This sounds pretty grim. Perhaps, however, each cell in the body must receive one molecule of arsenic before the danger of cancer develops. There are about 1 trillion cells in the body, each of which, on the average, should contain 9 million molecules of arsenic. But not all of these cells might be potential cancer cells.

Shall we say that one cell in every billion could become a virulent cancer cell? According to this, 1,000 cells would be at risk. Each of these has a 9-to-1 chance in favor of being transformed, even if the odds are a million to one against a possibility of any single arsenic molecule in the cells carrying out the transformation. So there are still odds of 9,000 to 1 that everyone will get cancer from the arsenic normally present in the body, according to Dr. Upton's theory.

If arsenic will not do the job, there are numerous other carcinogens present in the body. Among these are cadmium—30 mg per person—and chromium—6 mg per person. Then there is ura-

nium. It is present in our bodies, because we are a part of the solar system.

If you try to convince people that they are not in danger from single molecules of dioxin (as EPA has recently suggested), they usually reply: "Well you don't know," or "It might be that just that one molecule will hit the dangerous spot." I believe it is more effective to point out that we are continually exposed to huge numbers of carcinogenic molecules.

The list does not stop with inorganic elements.

Of Mice and Estrogens

Estrogens are carcinogenic or co-carcinogenic in tests with mice. Yet the same natural estrogens that produce cancer in the mouse tests are also made by the human body. The daily production is 20 to 400 micrograms of estradiol, depending upon the age and sex of the individual. The lowest level, 20 micrograms, corresponds to 7×10^{15} molecules produced per day. The FDA has warned against dangers of cancer resulting from natural estrogen therapy in postmenopausal women. What are the chances of one molecule of estrogen causing cancer? (Remember that we are talking about one additional molecule taken in with our food supply.) This invading molecule would have to compete with 7×10^{15} molecules that are already there, and are produced every day. What is the meaning of such a number?

First, if one molecule of an estrogen could cause cancer, then everyone should develop cancer from estrogens that are produced in the body naturally. Second, odds of one against 7×10^{15} can best be illustrated by imagining someone tossing a coin. If you watched a coin tossed twenty times, and it came down heads every time, you would conclude that the coin had heads on both sides. What would your conclusion be if it were tossed forty times, and it came down heads every time? The chances are one trillion to one against this, and that is still far less than 7×10^{15} .

Each cell contains many million molecules of carcinogens. There has to be a definite principle that stops cancer from developing inevitably in every cell. This "threshold principle," which Dr. George Claus correctly points out is a law of nature, is not overcome until enormous numbers of molecules bombard the target, which is probably DNA.

It cannot be true that there is no such thing as a "no-effect level" for carcinogens, because every living organism contains carcinogens at all times.

DES in Beef Production

I have been involved for about eight years with the matter of the ban on DES in beef production. DES is a synthetic female sex hormone, an estrogen. It came into use because it is far cheaper than the natural steroid estrogens and, unlike them, it is quite effective when given by mouth. DES is metabolized to its glucuronide, which is excreted in the bile and in the urine. This is important, because it means that DES is not cumulative. It came into use in clinical medicine in the 1940s and was introduced into beef production in the early 1950s, because small quantities of DES, fed or injected, increased the production of lean beef. Before that, it had been given to chickens, in which it increased the fat content of the carcass—the exact opposite of what it does to beef cattle. Its use in chickens was discontinued many years ago.

From the beginning it was known that DES, like all other estrogens, could be classified as a carcinogen on the basis of tests with laboratory animals. The test animals are usually C3H mice, a strain that carries the mammary tumor virus so that these mice spontaneously develop breast cancer. The percentage of mice with breast cancer increases when the mice are given estrogens. DES was permitted in beef production, however, because no residues were detectable in the meat when the hormone was used according to directions. These directions specified a withdrawal period before the animal was sent to market. An alternative method was to implant a DES pellet in the ear of the animal. The ears were discarded when the cattle were slaughtered, and no residues could be detected in the meat.

When the Delaney Clause was passed in 1958, it was pointed out that although DES, an additive in cattle feed, was a carcinogen, no residues could be found in beef. Accordingly, a special "no-residue exception" was made for this use of DES. However, as assay methods became more sensitive, traces of DES were found in beef liver, usually when the withdrawal period had not been observed for feed containing DES. The average amount in beef liver seems to be not more than 0.25 ppb. It is not detectable in

muscle meat, but a "guesswork figure" is that the amount in muscle may be 10 percent of the amount in liver. This estimate may be too high. Thus, my estimate of the maximum exposure to consumers is not more than 3.4 nanograms per day.

DES in Clinical Use

Public alarm over DES in clinical medicine became very great when it was discovered by Dr. Arthur Herbst, of the Harvard Medical School, in 1971 that vaginal cancer developed in a small percentage of "DES daughters." These were children of women who had been given large doses of DES during pregnancy to prevent threatened miscarriage. The treatment was found ineffective, since the same percentage of miscarriages occurred in untreated controls. Nevertheless, at least a million women received the DES treatment, mostly in the late 1950s. The alarm over this monumental piece of medical malpractice continues to mount. DES daughters are reported to have had a significantly higher percentage of deformed uteri. Genital abnormalities have been reported in male offspring.

Public reaction to this disaster involved demands, including one by Senator Edward Kennedy, that DES be banned in beef production. He was supported by Dr. Frank Rauscher, then director of the National Cancer Institute, and the FDA issued a ban. However, the producers of DES successfully challenged the ban on grounds that the FDA did not hold hearings. Subsequently hearings did take place in which I participated, and the ban was issued on June 29, 1979, accompanied by a decision of more than 300 pages. Astonishingly, the FDA still permits the use of DES pills in clinical medicine. A single pill, containing one mg of DES, contains more than 200,000 times the daily intake of DES from beef products, according to my estimates.

But perhaps even the small amount of DES present in beef is an unacceptable risk? To decide this question, we must consider two points: first, what is the normal exposure of human beings to estrogens, and second, does DES have unique cancer-causing properties different from the known carcinogenic effects of natural estrogen at high doses?

To answer the first question, the normal production of natural estrogens in the body is equivalent to between 70,000 and 200,000

nanograms of DES daily. The answer to the second question has been provided by experts in the mechanism of action of estrogens. Their opinions were ignored in the ban issued by FDA in 1979. Professor Elwood Jensen, director of the Ben May Laboratory for Cancer Research at the University of Chicago, said in sworn testimony, "there is no evidence of any fundamental difference between the hormonal action of DES and that of estradiol." He said that he knew of "no instance in which it is established that the cancer-enhancing effect of DES cannot be duplicated by an appropriate dose of a steroidal estrogen." He pointed out that the biological action of the estrogenic hormones, which are natural cell-regulating agents, is quite different from that of foreign chemical carcinogens, which are metabolized to compounds that combine with DNA, and that the action of an estrogen must show a threshold below which the fraction of receptors occupied in each cell will be too small to elicit biochemical response. Physiological agents, he said, such as estrogens, vitamin D, or insulin, show a spectrum of dose response effects. He concluded that "the continued use of DES as a growth promotant for livestock presents no threat to the consumer."

Two other investigators, Okey and Bondy, of the University of Windsor (Canada), who used cell cultures from C3H mice, found that "binding of DES did not appear to be fundamentally different from the binding of natural estrogens," and that the "apparent affinity of receptor for DES was essentially the same as that for estradiol."

Another interesting circumstance consists of the presence of natural estrogenic substances in numerous plant foods, such as soybeans, green leaves, and vegetable oils. These have the same effect as DES or steroid estrogens when added to the feed of immature, normal mice, i.e., they produce an enlargement of the uterus. (They have not been tested for cancer.) For example, when soybean meal is fed by mouth, the estrogenic effect corresponds to a content of more than 20 ppb of DES. An FDA employee has suggested that the maximum amount of DES permissible in meat would be one part per trillion. The estrogenic potency of soybean meal is equivalent to more than 20,000 times this level.

For brevity's sake, one can state that three levels of the effect of estrogens evidently exist. First, a no-effect level, as with the natural estrogens normally present in meat. Second, a physiological

level), corresponding to the normal production of estrogens within the body. Third, the effect from excessive quantities used in clinical medicine, such as DES in pregnancy, or the natural estrogen preparations administered to postmenopausal women. This is the only level that presents a risk. The amount of DES that reaches consumers in beef products is at the no-effect level.

However, to justify the use of DES in beef production there must be a benefit to the public. This is twofold. First, the FDA estimated that the ban on DES would cost the public \$503,000,000, presumably on an annual basis, because of increased prices of meat resulting from less efficient production. Second, the fat content of carcasses of beef from animals receiving DES is lower than that from control animals. Both the secretary of HEW and the surgeon-general called attention in 1979 to the need for lowering the animal fat content of human diets. Some cancer experts state that animal fat is a carcinogen that increases the risk of cancer of the large bowel, one of the most common forms of cancer in the U.S.A. If the increased fat intake from the DES ban were to result in a single additional cancer case per year, this would far outweigh the risk from DES used in meat production.

There is no indication that the more vociferous consumerists will pay the slightest attention to these arguments. One of them, James Turner, has said that DES in beef production should be banned even if no residues are present. Other consumerists routinely point to the use of DES in beef production as one of the horror stories of agri-business. To reinforce their arguments, they often trot out the "single molecule" theory.

Evidently, where DES in meat production is concerned, there is no acceptable risk, even if the risk is nonexistent.

Pesticides

Public concern over pesticides continues to be provoked by industrial accidents, some of which are due to carelessness. As a result, there is no lack of ammunition for those who favor bans.

Among obvious examples are Agent Orange, PCBs, DBCP, kepone, and polybrominated biphenyls. The toxic effects of one chemical are often assumed to apply to its chemical relatives, without scientific justification. For example, newspaper articles about PCBs

usually identify them as "a chemical that resembles DDT." The herbicides 2,4,5-T and 2,4-D are lumped together in spite of the fact that 2,4-D has never been shown to be harmful, and is not contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Consequently, the future of many chemical pesticides is uncertain. Many consumerists claim that pesticide residues in foods contribute to the number of cancer cases. With pesticides, as with DES, the question of acceptable risk is still unresolved. The question of PCBs is particularly interesting. These compounds, polychlorinated biphenyls, are used for heat transfer in electrical transformers, and for other industrial purposes. In contrast to pesticides such as DDT, the use of PCBs was never regulated in the 1960s. As a result, discarded PCBs from drained transformers were regarded in the same manner as discarded crankcase lubricants, and were used to lay dust on roads, for example. The difference in toxicity between PCBs and DDT was demonstrated in controlled experiments reported in *Poultry Science* by Professor Milton Scott, of Cornell University. He showed that PCBs depressed hatchability of hens' eggs when fed at a level of 10 ppm of diet, and reduced hatchability to near zero levels at 20 ppm. In the same experiment, DDT had no effect when fed at 200 ppm, and methyl mercury caused eggshell thinning.

In 1966, Elwood Jensen detected PCBs in the eggs of wild birds in Sweden. His work was continued and extended in England in 1967. PCBs were found to accompany DDT in peregrine falcon tissues and eggs, yet DDT was blamed and PCBs were soft-pedaled. Scare stories about DDT in seawater appeared in 1969, and "the end of the oceans" was predicted. However, the level of DDT in seawater was found to be less than 1 part per trillion (ppt), compared with 20 ppt for PCBs, which were being used in boat paints. PCBs continue to make headlines as food contaminants. No acceptable levels of risk have been determined, and there are no benefits from allowing PCBs to come in contact with the food supply.

DDT

The procedure used to obtain a ban on DDT was "The Big Lie." The Big Lie was the only method that could have succeeded, for DDT has saved more lives and prevented more illnesses than any chemical in history. The EPA states that DDT is dangerously poi

sonous to human beings. Actually, DDT has been a leading cause of the world population explosion.

The use of DDT in disease control was started by the U.S. Army. As a result, more lives were saved than were lost in World War II from military action, not including the Holocaust. This was completely ignored by Rachel Carson when she wrote *Silent Spring*. The campaign against DDT was greatly helped by the media, including the *New York Times*, and *Science*. Newspaper cartoonists drew pictures of skeletons labeled "DDT." Dan Rather has referred to DDT as "that deadly poison." (He was not referring to mosquitos!) And yet DDT has not caused a single human death except for suicides, who were probably killed by the solvent. Even in 1980, DDT is still good for a scare story. The *Chicago Tribune*, of February 3, 1980, ran a long article headed "Towns' Population Poisoned by DDT." However, when the details were examined, the reader learned merely that residents of Triana, Alabama, had DDT levels fourteen times higher than the national average. The article did not mention that such levels have been found harmless to factory workers exposed to DDT for up to twenty years.

The Center for Disease Control (CDC) reported that DDT levels were found to increase with age, and that there was no noticeable equilibrium level. CDC called this "the most dramatic finding of the study" of the residents of Triana, Alabama. Other findings were that persons with higher DDT levels tended to have higher serum cholesterol and triglyceride levels. (This makes DDT sound about as toxic as ice cream.) They also tended to have higher levels of gamma-glutamyltranspeptidase—a liver enzyme. This unusual enzyme is used in tests of liver function. CDC said: "These changes are small and may not affect the health of individuals in Triana." So much for the poisoning of the population by DDT. The mayor of the town has commented: "We don't know if the DDT or the bureaucrats who have converged on us, studying us like mice in a cage, are what's driving up our blood pressure."

Antibiotics in Feeds

Another example of a massive falsehood is the following statement from a 1970 book by one of Ralph Nader's colleagues:³ "Unless Edwards and his crew review closely every decision about antibiotics—as human drugs, as additives to feeds and as animal

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drugs—people will continue to be injured and to die from excessive and improper use of antibiotics."

At the time the statement was made, there was ample information on the effect of feeding low levels of antibiotics to infants and children. The main result was that morbidity was decreased and, as reported by some researchers, lives were saved. The scientific reports began to appear in 1951, and continued through 1958. I summarized them in a 1973 article for *Advances in Applied Microbiology*.⁴

Residues of tetracycline antibiotics in meat are unstable, and are destroyed by cooking. Tetracycline antibiotics were used legally for several years to postpone spoilage in poultry meat and in fish. No problems were reported: indeed, in one publication, *Salmonella* contamination of chickens was reported greatly decreased by dipping them in a weak solution of chlorotetracycline. Using antibiotics in animal feeds is said to be risky because this may spread "infectious resistance," in which harmless bacteria transmit resistance to pathogens. However, there is no evidence of this effect from animal feeds. Resistance problems with antibiotics, such as penicillin resistance in gonorrhea, can be traced back to clinical medicine.

The National Academy of Sciences has just issued a valuable scientific report: "The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds" (March 18, 1980). The committee said: "There are no data linking human illness with the subtherapeutic use of antimicrobials in any aspect of animal husbandry," but added that hazards may still exist, therefore adequate research is needed to explore this possibility.

The Delaney Clause Viewed in 1980

The Delaney Clause, sometimes called the Delaney Amendment, is part of the Food Additives Amendment of the Food, Drug, and Cosmetic Act, and it became law in 1958. The clause says that "No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal." An addition to the clause states that the prohibition against carcinogenic additives does not apply to ingredients of the feed of food animals, provided that

no residue of such additives is found by approved methods of analysis in the food derived from the animals.

The Delaney Clause, therefore, applies to food additives, but the principles involved in it have played a part in all risk assessments involving cancer. Briefly, these are (1) that there is no such thing as a safe level of any carcinogen, and (2) that it may take twenty, or thirty, or forty years for cancer to develop after the first exposure to a carcinogen. There is some talk of modifying or changing the Delaney Clause, but the clause has strong supporters, who say that if an attempt is made to change the clause, they will counterattack by proposing that it be extended to include mutagens and teratogens. Among its supporters are consumer activists and cancer researchers. People who seek to change the clause are accused of being in favor of cancer, or interested in selling carcinogens.

I don't think anyone disagrees with the purpose for which the clause was introduced; obviously, no food additive should be used if there is a chance that it will cause cancer in human beings. But suppose the risk is only one case in 100 years in the entire United States population? Suppose there are benefits, such as the prevention of botulism through use of nitrites in cured meats and fish?

Perhaps the most serious problem is that carcinogenic effects keep being discovered for substances that will not be banned. I have mentioned the essential trace mineral elements, such as chromium, selenium, and arsenic. Many organic ingredients of foods, such as estrogens and goitrogens, can also be shown to be carcinogenic or co-carcinogenic. Alcohol is in this class and, according to recent information, so is formaldehyde. Quercetin, a common flavonol present in plants, is mutagenic and carcinogenic in laboratory tests. Black pepper is carcinogenic to mice, according to a recent test in which 28 mg of black pepper extract was applied cutaneously over a three-month period. A notorious carcinogen, aflatoxin, is produced by a mold that grows on peanuts and corn. It is impossible to exclude aflatoxin from the food supply entirely, it is only possible to keep it at low levels. However, cancer can be produced in rats by 20 ppb of aflatoxin, a level sometimes found in peanut butter. Other molds produce carcinogens, and pyrrolizidine alkaloids have been found in honey.

I believe the Delaney Clause, in its strict sense, is unenforceable.

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I have never advocated its repeal, however, because I believe the request for any change must come from the regulatory agencies and from previous supporters of the Delaney Clause.

Conclusion

I have drawn attention to the basic conflict between producers and regulators, and I said "the success of a bureaucracy, including its budget, is measured by the number of regulations it devises." Such a conflict should represent a dynamic balance that has a favorable effect on consumers, who receive a flow of products that have been tested for safety, and have been found to have a favorable risk-benefit ratio.

However, the regulatory agencies seem to be proliferating beyond all reason or expectation. For example, *FDA Consumer* stated in January 1980:

[T]he federal government plans to concert the efforts of 35 agencies and departments to control chemicals that cause cancer and reduce the threat to public health. It's all mainly a matter of coordination and deliberate actions that will identify the chemical culprit and develop systematic ways to control them.⁶

Another problem is that, as FDA has asserted, the laws "have not authorized FDA to consider the economic benefits" of substances used to increase food production. Evidently, efforts to increase the food supply with the help of chemistry will be opposed, not encouraged, by the federal government. The agencies have a large number of amateur helpers to assist them in devising bans and other restrictive regulations. For example, the Environmental Protection Agency has an Office of Pesticides and Toxic Substances, which has \$687,000 available for a public participation program. This includes a \$147,000 carry-over from fiscal 1979. Some of the beneficiaries from this well-filled public trough will be the National Wildlife Federation, Association of New Jersey Environmental Commissions, Center for the Hudson River Valley, Rutgers University Journalism Resources Institute, and the League of Women Voters in Houston, Baton Rouge, and North Carolina, to educate residents about toxic substances. Others are the Friends of the Everglades, Tennessee Environmental Council, Environmen-

tal Action Foundation, and Sierra Club, the last-named to receive a grant of \$95,000 to provide training and education materials.

This largesse comes at a time when funds for basic research are being cut by the federal government.

NOTES

1. In my article for *Environmental Affairs*, 1: 534 (1971), I wrote:

The National Audubon Society printed 700,000 copies of a leaflet urging that the export of DDT be stopped. This leaflet was distributed at about the same time a resolution requesting the continuation of the use of DDT was passed at a meeting of the WHO Regional Committee for Southeast Asia held in 1969 in Nepal, attended by representatives of eleven tropical countries totaling over 700 million in population—about 1000 people for each Audubon leaflet.

Many people have become self-constituted authorities on DDT as a result of exposure to mass media. For example, the chief judge of the Circuit Court of Appeals in Washington, D.C., announced in January, 1971, that DDT kills honeybees and is dangerous to people. Yet, while other insecticides, such as parathion and Sevin, do kill bees, DDT's effect on these insects is only minimal. As regards DDT's effects on people, the principal consequence has been to increase population, not endanger lives.

What are the facts of this strange paradox? What motivates those who crusade against the most useful chemical in history? Is the attack on DDT partly directed against its role in accelerating the population explosion?

The organizations that are most active in the movement to ban DDT include some of the large conservation groups. Despite the size of some of these groups, they do not speak for all segments of the population. Some environmental groups, in fact, have recently been challenged by organizations which represent racial minorities The needs of the urban poor are not likely to be assuaged by the Thoreau-like preoccupations of many of the conservation associations. . . .

The National Audubon Society, which appears to have a predominantly white and middle-class membership, is one of the most active anti-DDT organizations The Society stated recently that one of its two main purposes is "the education of man regarding his relationship with and his place within the natural environment as an ecological system" The Audubon Society has no program for the relief of suffering among millions of human beings in the tropics.

Two other organizations that have attacked DDT are the National Geographic Society and the Sierra Club. The National Geographic Magazine advertises plush overseas tours for the wealthy people. The magazine has beautiful photographs of wild animals, birds, and underdressed natives in picturesque attitudes. These pic-

tures do not show the ravages of tropical diseases that can be controlled by DDT. The Sierra Club, which is seeking legal action to obtain a ban on DDT, also features expensive outings to remote lands, again largely for the healthy and economically secure. The motivation of conservation organizations is primarily to protect the landscape and its wildlife. This may be in conflict with combatting hunger and disease in human beings.

2. R. Main, "Excessive Regulations," Address to Pest Control Operators of California at San Jose, 8 February 1980.
3. J. Turner, *The Chemical Feast*.
4. *Advances in Applied Microbiology*, 16: 1 (1973).
5. *FDA Consumer*, January 1980, p. 11.

Handy, Handy Book

Complete Guide To PEST CONTROL

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CHAPTER 3

THE PESTICIDES

The proposed decoctions and washes we are well satisfied, in the majority of instances, are as useless in application as they are ridiculous in composition . . .

Editorial, *Practical Entomologist*,
Oct. 30, 1865.

Most pesticides are synthetic, though a few are produced naturally by plants. The U. S. Environmental Protection Agency (EPA) had more than 1200 pesticides registered in 1980. Of these 275 were herbicides, 400 were insecticides, 200 were fungicides and nematocides, 100 were rodenticides, and 225 were disinfectants. These are sold in the form of 30,000 products or formulations, and 5 pounds of pesticides are used each year to feed, clothe, and protect every man, woman, and child in the United States alone. Part of these 5 pounds are used at home by the homeowner as do-it-yourself pest control, and that is what part of this book is about.

Pesticides have become extremely beneficial tools to the urbanite, the home gardener. He depends on pesticides, perhaps more than he realizes: for algae control in the swimming pool, weed control in his lawn, flea collars and powders for pets, sprays for controlling a myriad of garden and lawn insects and diseases, household sprays for ants and roaches, aerosols for flies and mosquitoes, soil and wood treatment for termite protection by professional exterminators, baits for the control of mice and rats, woolen treatment at the dry cleaners for clothes moth protection, and repellents to keep off biting flies, chiggers, and mosquitoes when camping or fishing.

These chemical tools are used by the homeowner as intentional additions to his home and garden environment in order to improve environmental quality for himself, his animals, and his plants, giving him the advantage over his pest competitors. Pesticides are used in agriculture to increase the ratio of cost/benefit in favor of the grower and ultimately the consumer of food and fiber products — the public. Pesticides have contributed significantly to the increased productive capacity of the U.S. farmer, each

of whom produced food and fiber for 3 persons in 1776, 37 in 1965, and 59 persons in 1980. Where can one find a more successful story of technology?

THE LANGUAGE OF PESTICIDES

To one person the word pesticide may suggest the insecticide malathion. To another it may conjure up the herbicide dalapon, and still another the garden fungicide maneb. All are correct, however only in part, for the uses and effects of these three materials are totally unrelated.

"Pesticide" is an all-inclusive, but nondescript word meaning "killer of pests". The various generic words ending in "-icide" (from the Latin, *-cida*, to kill) are classes of pesticides, such as fungicides and insecticides. In the table below are listed the various pesticides and other classes of chemical compounds not commonly considered pesticides. These others, however, are included among the pesticides as defined by federal and state laws.

Pesticides are legally classed as "economic poisons" in most state and federal laws and are defined as "any substance used for controlling, preventing, destroying, repelling, or mitigating any pest". Should you ever pursue the subject of pesticides from a legal viewpoint they would be discussed as economic poisons.

The pesticide vocabulary not only includes all of the commonly-used pesticides, but also includes groups of chemicals which do not actually kill pests, as shown in Table 3. However, because they fit rather practically as well as legally into this umbrella word, pesticides, they are included.

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CHAPTER 8

The single factor that determines the degree of harmfulness of a compound is the dose . . .

Ted A. Loomis,
Essentials of Toxicology, 1974

THE HAZARDS OF PESTICIDES

All pesticides are toxic, but their use is not necessarily a hazard. Let's get it straight at the outset. There is a marked distinction between *toxicity* and *hazard*. These two terms are not synonymous. *Toxicity* refers to the inherent toxicity of a compound. In other words, how toxic is it to animals under experimental conditions. *Hazard* is the risk or danger of poisoning when a chemical is used or applied, sometimes referred to as *use hazard*. The factor with which the user of a pesticide is really concerned is the use hazard and not the inherent toxicity of the material. Hazard depends not only upon toxicity but also upon the chance of exposure to toxic amounts of the material.

Webster defines the word poison as "any substance which introduced into an organism in relatively small amounts, acts chemically upon the tissues to produce serious injury or death." One can immediately spot several flaws in this definition. The "relatively small amount" statement is open to wide interpretation. For instance, many chemical agents to which man is exposed regularly could be termed poisons under this definition. An oral dose of 400 milligrams of sodium chloride per kilogram (mg/kg) of body weight, ordinary table salt, will make a person violently ill. A standard aspirin tablet contains about 5 grains of aspirin, chemically known as acetylsalicylic acid. A fatal dose of aspirin to man is in the range of 75 to 225 grains or 15 to 45 tablets. Approximately 85 deaths occur every year (about one-third are children) as a result of overdoses of aspirin. To take a third example, let us consider nicotine. A fatal oral dose of this naturally occurring alkaloid to man is about 50 milligrams (mg), or approximately the amount of nicotine contained in two unfiltered cigarettes. In smoking, however, most of the nicotine is decomposed by burning, and, thus, it is not absorbed by the smoker.

Here man is not exposed during ordinary use to amounts of salt, aspirin, and nicotine which cause toxicity problems. Therefore, it is obvious that the *hazard* from normal exposure is very slight even though the compounds themselves would be toxic under other circumstances.

There's a better definition for the term "poison": "A chemical substance which exerts an injurious effect in the majority of cases in which it comes into contact with living organisms during normal use." The compounds mentioned above would obviously be excluded by such a definition and so would the majority of pesticides.

By necessity, pesticides are poisons, but the toxic hazards of different compounds vary greatly. As far as the possible risks associated with the use of pesticides are concerned, we can distinguish between two types: First, acute poisoning, resulting from the handling and application of toxic materials, and second, chronic risks from long-term exposure to small quantities of materials or from ingestion of them. The question of acute toxicity is obviously of paramount interest to people engaged in manufacturing and formulating pesticides and to those responsible for their application. Supposed chronic risks, however, are of much greater public interest because of their potential effect on the consumer of agricultural products.

Fatal human poisoning by pesticides is uncommon in the United States and is due to accident, ignorance, suicide, or crime. Fatalities represent only a small fraction of all recorded cases of poisoning, as demonstrated by these recent United States statistics, Table 31. It will be noted that in 1965, 2.8% of deaths from accidental poisoning were from pesticides, while in 1977 this cause had dropped to 1.0%. When the children's part of these statistics are viewed, it becomes a much more serious matter.

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TABLE 31. Total Deaths from Accidental Poisonings by Solids and Liquids.

POISONING CLASSIFICATION	1968 (base)	1974	1975	1976	1977
Antibiotics & other anti-infectives	15	9	27	20	23
Hormones & synthetic substitutes	8	28	32	26	20
Systemic & hematologic agents	27	53	61	58	58
Analgesics & antipyretics (Salicylate & congeners)	390 (120)	967 (83)	1275 (98)	1067 (79)	526 (58)
Sedatives & hypnotics (Barbiturates)	827 (321)	620 (330)	557 (266)	508 (224)	363 (208)
Autonomic nervous system & psychotherapeutic drugs (Tranquilizers)	99 (68)	165 (106)	178 (103)	190 (92)	193 (88)
Central nervous system depressants and stimulants (Amphetamines)	25 (13)	40 (18)	37 (11)	36 (11)	39 (10)
Cardiovascular drugs	46	143	158	138	157
Gastro-intestinal drugs	7	6	3	4	4
Other & unspecified drugs & medicants	248	711	804	792	831
TOTAL DRUGS	1692	2742	3132	2839	2214
Alcohol	182	370	391	337	337
Cleaning & polishing agents	23	13	12	14	10
Disinfectants	9	8	6	6	5
Paints & varnishes	2	1	5	0	1
Petroleum products and other solvents	70	54	54	45	52
Pesticides, fertilizers or plant foods	72	35	30	31	34
Heavy metals (and their fumes)	53	23	13	15	21
Corrosives and caustics	28	13	16	22	17
Noxious foodstuffs and poisonous plants	10	5	6	6	7
Other & unspecified solid & liquid substances	442	752	1029	846	676
TOTAL NON-DRUG SOLID AND LIQUID SUBSTANCES	891	1274	1562	1322	1160
TOTAL ALL SOLIDS AND LIQUIDS	2583	4016	4694	4161	3374

Source: Mortality Statistics — Special Reports
Division of Vital Statistics
National Center for Health Statistics, Health Resources Administration
Public Health Service, Food and Drug Administration

In 1968, 11% of all accidental poisoning deaths were children under 5 years of age, while in 1977 that figure had dropped to 2.8%, a remarkable improvement. Still another good statistic is that of the less-than-5-year-olds poisoned in 1968, 11% again were from pesticides, while in 1977 that percentage had dropped to 7.4%. On the grimmer side is the statement that of all deaths attributed to accidental

poisoning by pesticides in 1977, 20% were children under 5 years of age (Table 32).
Let's examine another type of data for 1973. Of 117,589 reported accidental ingestions among children under 5 years of age, pesticides were responsible for only about one half the number attributed to cosmetics or two-thirds of those attributed to aspirin (Table 33).

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TABLE 32. Deaths from Accidental Poisoning by Solids and Liquids in 1977.

POISONING CLASSIFICATION	Under 5 Years of Age	5 Years and Over*	Total Deaths All ages
Antibiotics & other anti-infectives	1	22	23
Hormones & synthetic substitutes	0	20	20
Systemic & hematologic agents	8	50	58
Analgesics & antipyretics (Salicylate & congeners)	16 (11)	510 (47)	526 (58)
Sedatives & hypnotics (Barbiturates)	4 (3)	359 (205)	363 (208)
Autonomic nervous system & psychotherapeutic drugs (Tranquilizers)	9 (2)	184 (86)	193 (88)
Central nervous system depressants and stimulants (Amphetamines)	1 (0)	38 (10)	39 (10)
Cardiovascular drugs	5	152	157
Gastro-intestinal drugs	3	1	4
Other & unspecified drugs & medicines	<u>10</u>	<u>821</u>	<u>831</u>
TOTAL DRUGS	57	2157	2214
Alcohol	0	337	337
Cleaning & polishing agents	2	8	10
Disinfectants	3	2	5
Paints & varnishes	0	1	1
Petroleum products and other solvents	12	40	52
Pesticides, fertilizers or plant foods	7	27	34
Heavy metals (and their fumes)	3	18	21
Corrosives and caustics	6	11	17
Noxious foodstuffs and poisonous plants	0	7	7
Other & unspecified solid & liquid substances	<u>4</u>	<u>672</u>	<u>676</u>
TOTAL NON-DRUG SOLID AND LIQUID SUBSTANCES	37	1123	1160
TOTAL ALL SOLIDS & LIQUIDS	<u>94</u>	<u>3280</u>	<u>3374</u>

* Includes Unspecified Age

Source: Mortality Statistics — Special Reports
 Division of Vital Statistics
 National Center for Health Statistics, Health Resources Administration
 Public Health Service, Food and Drug Administration

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TABLE 33. Accidental Ingestions Among Children Under 5 Years of Age

Type of Substance	1973	
	No.	%
Medicines	52,113	44.3
*Internal	42,215	35.9
*Aspirin	7,763	6.6
*Other	34,452	29.3
*External	9,898	8.4
Cleaning and Polishing Agents	19,132	16.3
Petroleum Products	4,974	4.2
Cosmetics	10,362	8.8
Pesticides	5,591	4.8
Gases and Vapors	140	0.1
Plants	7,032	6.0
Turpentine, Paints, Etc.	6,988	5.9
Miscellaneous	10,517	9.0
Not Specified	740	0.6
Total	117,589	100.0

Source: Individual case reports submitted to the National Clearinghouse for Poison Control Centers: 1973, from 517 centers in 45 states.
Bull. Natl. Clearinghouse for Poison Control Centers, U.S. Food and Drug Admin. Bur. Drugs, H.E.W., May-June 1974.

Regardless of your attitude toward pesticides and their presumed hazard, they have an excellent safety track record, and it grows better each year, mainly through education and labeling of containers.

PESTICIDE EFFECTS ON MAN

Pesticides were developed to kill unwanted organisms, and are toxic materials which produce their effects by several different mechanisms. Under certain conditions they may be toxic to man, and an understanding of the basic principles of toxicity and the differences between toxicity and hazard is essential. As you already know, some pesticides are much more toxic than others, and severe illness may result when only a small amount of a certain chemical has been ingested, while with other compounds no serious effects would result even after ingesting large quantities. Some of the factors that influence these are related to (1) the toxicity of the chemical, (2) the dose of the chemical, especially concentration, (3) length

of exposure, and (4) the route of entry or absorption by the body.

Early in the development of a pesticide for further experiments and exploration, toxicity data are collected on the pure toxicant as required by the Environmental Protection Agency. These tests are conducted on test animals that are easy to work with and whose physiology, in some instances, is like that of man, for example, dog. Test animals include white mice, white rats, white rabbits, guinea pigs, and beagle dogs. For instance, intravenous tests are determined usually on mice and rats, whereas dermal tests are conducted on shaved rabbits and guinea pigs. Acute oral toxicity determinations are most commonly made in rats and dogs, with the test substance being introduced directly into the stomach by tube. Chronic studies are conducted on the same two species for extended periods, and the compound is usually incorporated in the animal's daily ration. Inhalation studies may involve any of the test animals, but rats, guinea pigs, and rabbits are most commonly used.

These procedures are necessary to determine the overall toxic properties of the compound to various animals. From this information, toxicity to man can generally be extrapolated, and eventually some micro-level portion of the pesticide may be permitted in his food as a residue, which is expressed in parts per million, that is parts of a chemical per million parts of a particular food, by weight.

Toxicologists use rather simple animal toxicity tests to rank pesticides according to their toxicity. Long before pesticides are registered with the Environmental Protection Agency and eventually released for public use the manufacturer must declare the toxicity of their pesticide to the white rat under laboratory conditions. This toxicity is defined by the LD₅₀, expressed as milligrams (mg) of toxicant per kilogram (kg) of body weight, the dose which kills 50% of the test animals to which it is administered under experimental conditions.

This toxicity value, or LD₅₀, is measured in terms of oral (fed to, or placed directly in the stomachs of rats), dermal (applied to the skin of rats or rabbits), and respiratory toxicity (inhaled). Using two of these tests, oral and dermal, a toxicologic ranking is shown for the organophosphate and organochlorine insecticides in Fig. 26-27. The materials on the top of the list are the most toxic and those at the bottom the least. The size of the dose is the most important single item in determining the safety of a given chemical, and actual statistics of human poisonings correlate reasonably well with these toxicity ratings.

ESTIMATING PESTICIDE TOXICITY TO MAN

In addition to toxicity, the dose, length of exposure, and route of absorption are the other important variables. The amount of pesticide required to kill a man can be correlated with the LD₅₀ of the material to rats in the laboratory. In Table 34 below, for example, the acute oral LD₅₀ expressed as mg/kg dose of the technical material, is translated into the amount needed to kill a 170 lb. man. Dermal LD₅₀s are included for a better understanding of the relationship of expressed animal toxicity to human toxicity.

In a manner of generalizing, oral ingestions are more toxic than respiratory inhalations which are more toxic than dermal absorption. Additionally,

there are physical and chemical differences between pesticides which make them more likely to produce poisoning. For instance, parathion changes to the more toxic metabolite paraoxon under certain conditions of humidity and temperature. Parathion is more toxic than methyl parathion to field workers, yet there is not that great a difference in their oral toxicities. Workers' exposure is usually dermal, which explains why many more illnesses are reported in workers exposed to parathion than those exposed to methyl parathion. So, we see that toxicity, route of absorption, dose, length of exposure and the physical and chemical properties of the pesticide contribute to its relative hazard. Hazard, then, is an expression of the potential of a pesticide to produce human poisoning.

TABLE 34. Combined Tabulation of Pesticide Toxicity Classes.

Toxicity Rating*	Routes of Absorption		
	LD ₅₀ Single ORAL Dose Rats mg/kg	LD ₅₀ Single DERMAL Dose Rabbits mg/kg	Probable Lethal Oral Dose for Man
6 - Super toxic	less than 5 mg	20 mg or less	A taste, a grain
5 - Extremely toxic	5 - 50 mg	20 - 200	A pinch - 1 teaspoon
4 - Very toxic	50 - 500	200 - 1,000	1 teaspoonful - 2 tablespoons
3 - Moderately toxic	500 - 5,000	1,000 - 2,000	1 ounce - 1 pint
2 - Slightly toxic	5,000 - 15,000	2,000 - 20,000	1 pint - 1 quart
1 - Practically nontoxic	>15,000	>20,000	>1 quart

* Modified from: Clinical Toxicology of Commercial Products, 2nd Edition 1963. Gleason, M. N., Gosselin, R. E., and Hodge, H. C. The Williams and Wilkins Company, Baltimore, Maryland.

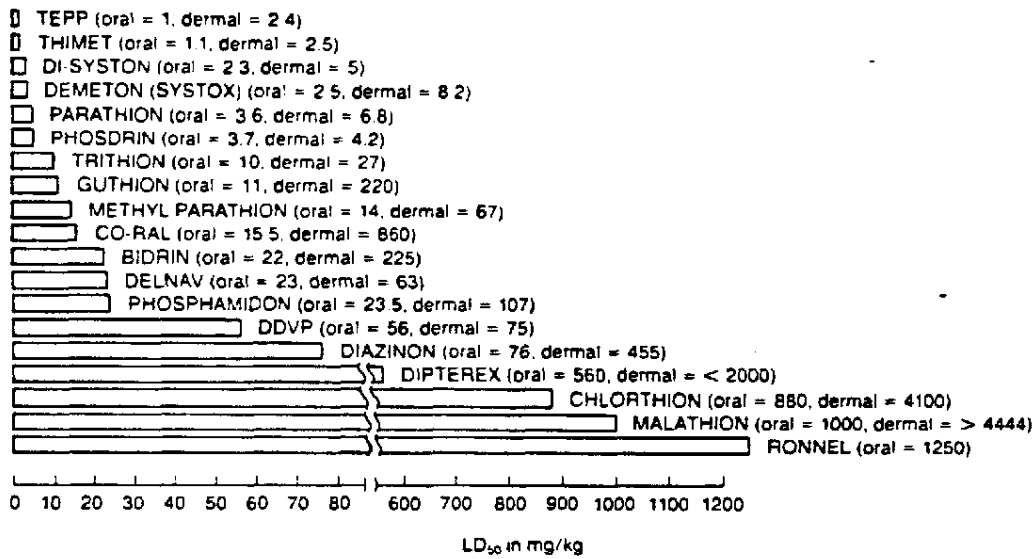


FIGURE 26. Acute Oral and Dermal Toxicity Values to Rats for Some Organophosphate Pesticides.¹

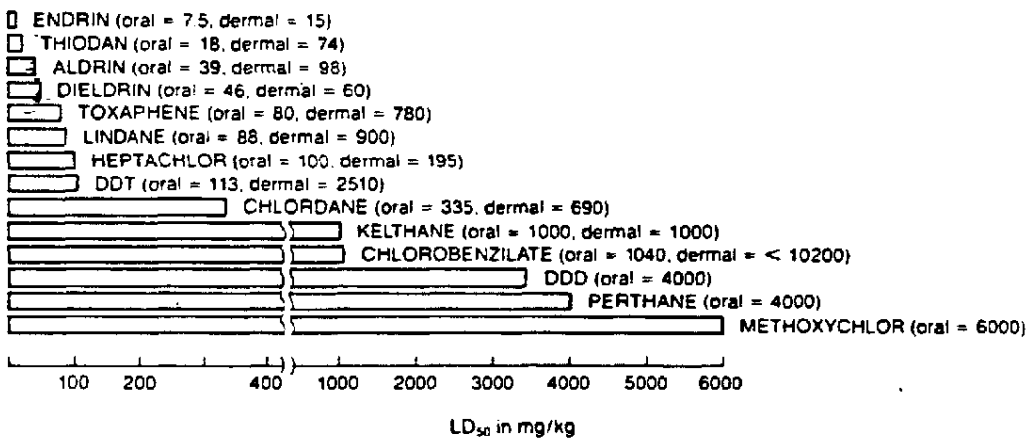


FIGURE 27. Acute Oral and Dermal Toxicity Values to Rats for Some Chlorinated Hydrocarbon Pesticides.¹

¹ Source: Unpublished chart prepared by the Bureau of Occupational Health, State of California Department of Public Health. Reproduced by permission.

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THE 8 SURPRISES or Has the World Gone to Hell?

JAN 3 1975

by
JOHN J. McKETTA
The E.P. Schoch Professor
Department of Chemical Engineering
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UPL 02987

... An address delivered to the
Lion's Club of Austin, Texas
May 16, 1974 and repeated
on subsequent occasions.

from Jefferys
Dr. General 11/1/73

THE 8 SURPRISES

or

HAS THE WORLD GONE TO HELL??

by John J. McKetta

On March 27, 1973, I heard Garner Ted Armstrong say over the television:

"There is no way you can have any optimism for the continuation of life on this earth because of the pollution, over population, and results of technological advances."

It bothers me that there are so many purveyors of gloom who talk about the hopelessness of our future.

There is an entire spectrum, from zero to infinity, of views and actions on almost any problem. Let's take the pollution problem, for example. We all know there are still some companies and cities who put toxic gases and liquids into our air and streams. It's almost unbelievable that many of our large cities still discharge raw sewage, or only partially treated sewage into our streams. Both industry and the cities should be stopped immediately from these flagrant violations. On the other extreme we have those people who wish to have distilled water in the streams and zero particulates in the atmosphere. These are impossible concentrations and could not be attained even if we had no people on this earth. The answer, obviously, is somewhere between these two extremes. Just like most of you, I am a family man. My lovely wife and I have four wonderful children. It is my wish that they have clean air to breathe and clean water to drink. Not distilled water nor absolutely pure air, but I do want them to have odorless, non-toxic, clean air, and clean water. I believe we still have a great deal of environmental work to do in the U.S.A. I believe, however, that extremism is bad on either end.

We're all deeply concerned about reports of the destruction of our environment as a result of technological recklessness, over-population, and the lack of consideration to the preservation of nature. As Chairman of the National Air Quality Commission I have to read great amounts of technical

literature in this area. I've turned up a lot of evidence that I'd like to share with you.

Some of the people, who are filled with gloom and believe we have no future, blame our apparent demise on the Judeo-Christian ethic that it is God's will that man exploit nature for his proper ends and that we have overdone it. Others recommend that we return 2500 years and embrace the practices of druidism. Many many people express a disdain for science and mistrust in technology in general.

They say our automobiles are no longer a wondrous method of freeing man from his immobility, but instead have become terrible polluters and ultimately piles of junk to desecrate the landscape. Electricity, which has been the most convenient form of energy ever available, has come into disrepute. The bad industry that produces electricity is looked upon as an evil organization of the establishment whose objective is to create new radiation hazards with nuclear power plants, cut down trees, stick poles into the ground and pump smoke into the air to poison all of us.

It's a gloomy picture indeed. But I've found out this outlook is not justified. This is what I'd like to talk to you about. I hope you'll understand that I'm speaking to you as one who understands elementary science and engineering and not as an emotional supporter of any particular "side" of ecology. Some of the facts I will mention will surprise many of you. I can assure you that my conclusions are supported by evidence that is difficult to interpret in any other way. They may be verified by anyone who wishes to do so. I'll leave a list of literature citations with the chairman of your group.

1. WHY IS THE OXYGEN DISAPPEARING??

My first surprise concerns the air we breathe. You have been reading that we are seriously depleting the oxygen in the atmosphere and replacing it with toxic substances such as carbon monoxide.

Throughout my formal education I have always been taught that oxygen in our atmosphere is supplied by green plants using the process of photosynthesis. It is known that plants take in carbon dioxide and through activation by sunlight, combine CO_2 with water to make starches and cellulose, and give off oxygen. In this way the whole chain of plant and animal life is sustained by

energy from the sun. When the vegetable or animal materials thus produced are eaten, burned, or allowed to decay, they combine with oxygen and return to the carbon dioxide and water from whence they came. We all know this. Then, what is the surprise?

Surprise number one is that most of the oxygen in the atmosphere *doesn't* come from photosynthesis. The evidence is now overwhelming that photosynthesis is just inadequate to have produced the amount of oxygen that is present in our atmosphere. The reason is that the amount of oxygen produced by photosynthesis is just exactly enough to convert the plant tissue back to the carbon dioxide and water from which it came. In other words, the net gain in oxygen due to photosynthesis is extremely small. The oxygen in the atmosphere had to come from another source. The most likely possibility involves the photodissociation of water vapor in the upper atmosphere by high energy rays from the sun and by cosmic rays. This process alone could have produced (over the history of the earth 4.5×10^9 years) about 7 times the present mass of oxygen in the atmosphere.^{2,11}

The significance of this information is that the supply of oxygen in the atmosphere is virtually unlimited. It is not threatened by man's activities in any significant way. If all the organic material on earth were oxidized, it would reduce the atmospheric concentration of oxygen by less than 1%. We can forget the depletion of oxygen in the atmosphere and get on with the solution of more serious problems.⁷

2. CARBON MONOXIDE WILL KILL US ALL!

As you know, the most toxic component of automobile exhaust is carbon monoxide. Each year man adds 270 million tons of carbon monoxide to the atmosphere. Most of this comes from automobiles. The scientists are concerned about the accumulation of this toxic material because they know that it has a life in dry air of about 3 years. For the past several years, monitoring stations on land and sea have been measuring the carbon monoxide content of the atmosphere. Since the ratio of automobiles in the northern and southern hemisphere is 9:1 respectively, it was expected that the northern hemisphere would have a much higher concentration of atmospheric carbon monoxide. The true measurements show however that there

is no difference in CO amounts between the hemispheres and that the overall concentration in the air is not increasing at all. In fact, they've found higher concentrations of CO over the Atlantic and Pacific Oceans than over land????

Early in 1971 scientists at the Stanford Research Institute^{1,3} in Palo Alto disclosed that they had done some experiments in smog chambers containing soil. They reported that carbon monoxide rapidly disappeared from the chamber. Next, they sterilized the soil and then found that now the carbon monoxide did not disappear. They quickly identified the organisms responsible for CO removal to be fungi of the aspergillus (bread mold and penicillin types). These organisms, on a worldwide basis, are using all of the 270 million tons of the CO made by man for their own metabolism, thus enriching the soils of the forest and the fields.¹

This does not say carbon monoxide is any less toxic. It does say that, in spite of man's activities, carbon monoxide will never build up in the atmosphere to a dangerous level except on a localized basis. To put things in perspective, let me point out that the average concentration of CO in Austin, Texas, is about 1.5 parts/million. In downtown Houston, in heavy traffic, it sometimes builds up to 15 to 20 ppm. In Los Angeles it gets to be as high as 35 ppm. In parking garages and tunnels it is sometimes 50 ppm.⁶

Here lies surprise number two for you — do you know that the CO content of cigarette smoke is 42,000 ppm? The CO concentration in practically any smoke-filled room grossly exceeds the safety standards we allow in our laboratories. I don't mean to imply that 35 to 50 ppm CO should be ignored. I do mean that there are so many of us who subject ourselves to CO concentrations voluntarily (and involuntarily) that are greater than those of our worse polluted cities, including Holland Tunnel in New York, without any catastrophic effects. It is not at all unusual for CO concentrations to reach 100 - 200 ppm range in poorly ventilated, smoke-filled rooms. Incidentally, if a heavy smoker spends several hours without smoking in a highly polluted city air containing 35 ppm of CO concentration, the concentration of CO in his blood will actually decrease!¹⁰ In the broad expanse of our natural air, CO levels are totally safe for human beings.

Incidentally, 93% of the CO comes from trees

and greeneries (3.5 billion tons/year). Only 7% comes from man (270 million tons/year).

3. OXIDES OF NITROGEN WILL CHOKO US!

I have been extremely impressed by the various research efforts on the part of petroleum, automotive, and chemical companies to remove oxides of nitrogen from the products of combustion in the tailpipe gas of our automobiles. I've read about the brilliant work of Dr. Haagen-Smit that showed that the oxides of nitrogen play a critical role in the chain reaction of photochemical smog formation in Los Angeles.⁸ Oxides of nitrogen are definitely problems in places where temperature inversions trap the air.

But we've all known for many years that nature, in addition to man, also produced oxides of nitrogen. The number three surprise (and shock) is that most of the oxides of nitrogen come from nature. If we consider only nitric oxide and nitrogen dioxide, the best estimates are 97% is natural and only 3% are man-made. If we also consider nitrous oxide and amines, then it turns out that 99+% is natural and less than 1% is man-made.^{8,9}

Nature makes oxides of nitrogen in several ways. Biological action and organic decomposition produce most of the N_2O and NO . In fact, the great saltpeter deposits of South America are a result of perpetual thunderstorms over the Andes. Oxides of nitrogen in rain water react with minerals of the soil and end up as saltpeter when the water evaporates.

The great abundance of marine life between Antarctica and the tip of South America is also attributed to the nitrate run-off from the Andes which initiates plankton growth, thus setting off a whole chain of fishes which eat each other ending on the top with the blue whale.

The significance of this is that even if we are 100% successful in our removal of the oxides of nitrogen from combustion gases, we will still have more than 99% left in the atmosphere which is produced by nature. *Sometimes I think nature laughs at us.*

4. THE DEATH OF LAKE ERIE

We've all read for some time that Lake Erie is dead. It's true that the beaches are no longer swimmable in the Cleveland area and the oxygen con-

tent at the bottom of the lake is decreasing. This is called eutrophication. The blame has been placed on phosphates as the cause of this situation. Housewives were urged to curb the use of phosphate detergents. In fact, for several years phosphate detergents were taken off the market. There's been a change in law since scientific evidence proved that the phosphate detergents were not the culprits and never should have been removed from the market in the first place.

Now let's look at the scientific evidence that I've been able to find on the subject. The study shows that the cause of the eutrophication of Lake Erie has not been properly defined. This evidence suggests that if we totally stopped using phosphate detergents, it would have no effect whatever on the eutrophication of Lake Erie. Many experiments have now been carried out that bring surprise number four—that it is the organic carbon content from sewage that is using up the oxygen in the lake and not the phosphates in the detergents.^{4,5}

The reason that the Cleveland area beaches are not swimmable is that the coliform bacterial count is too high, not that there is too much detergent in the water.

Enlarged and improved sewage treatment facilities by Detroit, Toledo, Sandusky and Cleveland will be required to correct this situation. Our garbage disposal units do far more to pollute Lake Erie than do the phosphate detergents. If we put in the proper sewage treatment facilities, the lake will sparkle blue again in a very few years.

Incidentally, we've all heard that Lake Superior is so much larger, cleaner and nicer than Lake Erie. It's kind of strange then to learn that in 1972 and 1973 more tons of commercial fish were taken from Lake Erie than were taken from Lake Superior.

Governor Gilligan of Ohio declared war on pollution in general and on thermal pollution in particular. Investigation of the thermal pollution problem reveals that, beyond any question of doubt, the sun is by far the greatest thermal polluter of Lake Erie. Governor Gilligan announced that he would "back legislation making it unlawful to increase the temperature of the water by more than one degree over the natural temperature." I don't know what he will do with the sun breaking the law since, as we all know, the natural temperature of Lake Erie is changed by the sun more than 40°F every year between winter (33°F) and summer

(75°F+). The natural life in the lake accommodates this change in great fashion, as it has for many thousands of years. According to my calculations, if we would store up all of the electricity produced in Ohio in a whole year and use it exclusively for heating Lake Erie all at one time, it would heat the entire lake less than 3/10ths of 1°F.

In terms of localized heating, we must remember that we already have hundreds of power plants pouring warm water into streams and lakes. Forty of these are nuclear power plants. Evaluation of the effect of these from an ecological point of view is that "thermal pollution" is a less descriptive and less appropriate term than is "thermal enrichment." There are no species disappearing. No ecological catastrophies or problems have appeared. Some of the best fishing locations in the country are near the warm water outlets of these power plants.

5. DDT IS THE WORST THING THAT EVER HAPPENED TO US???

DDT and other chlorinated compounds are supposedly endangering the lives of mankind and eliminating some bird species by the thinning of the egg shells of birds. There is a big question mark as to whether or not this is true. From the readings that I have done, the experiments were conducted in such a manner that positive conclusions could not be drawn from them. Even if it is true, it's quite possible that the desirable properties of DDT so greatly outnumber the undesirable ones that it might prove to be a serious mistake to ban entirely this remarkable chemical.

Many of you heard of Dr. Norman E. Borlaug, the Nobel Peace Prize winner. He is opposed to the banning of DDT. Obviously he is a competent scientist. He won the Nobel Prize because he was able to develop a new strain of wheat that can double the food production per acre anywhere in the world that it is grown.

Dr. Borlaug said, "If DDT is banned by the United States, I have wasted my life's work. I have dedicated myself to finding better methods of feeding the world's starving population. Without DDT and other important agricultural chemicals, our goals are simply unattainable."

As I read into this matter, I find that DDT has had a miraculous impact on arresting insect-borne diseases and increasing grain production from

fields once ravaged by insects. According to the World Health Organization, malaria fatalities alone dropped from 4 million a year in the 1930's to less than 1 million per year in 1968. Other insect-borne diseases, such as encephalitis, yellow fever, and typhus fever showed similar declines. Surprise number five is that it has been estimated that 100 million human beings who would have died of these afflictions are alive today because of DDT. Incidentally, recent tests indicate that the thinning of bird egg shells may have been caused by mercury compounds rather than DDT! Oh hum!

6. WE'RE KILLING OFF TOO MANY SPECIES!

Many people feel that mankind is responsible for the disappearance of the animal species. It is possible that in some instances man *may* hasten the disappearance of certain species. However, the abundance of that evidence indicates that he has very little to do with it. About 50 species are expected to disappear during this century. It is also true that 50 species became extinct last century and 50 species the century before that and so on . . . Dr. T. H. Jukes of the University of California points out that about 100 million species of animal life have become extinct since life began on this planet, about 3 billion years ago. Animals come and animals disappear. This is the essence of evolution as Mr. Darwin pointed out many years ago. Mankind is a relatively recent visitor here. Surprise number six is that he has had nothing to do with the disappearance of millions of species that preceded him.

In fact, one of man's failures is that he has *not* been successful in eliminating a single insect species — in spite of his all-out war on certain undesirable ones in recent years.

7. MAN IS THE REAL POLLUTER!

Here's the *seventh surprise!* The late Dr. William Pecora has calculated that all of man's air pollution during his thousands of years of life on earth does *not* equal the amount of particulate and noxious gases from just three volcanoes (Krakatoa, Japan—1883; Mt. Katmai, Alaska—1912; Hekla, Iceland—1947).

Dr. Pecora pointed out that nature's pure water is not so pure after all. Here are a few of his examples:

1. The natural springs feeding the Arkansas and Red Rivers carry approximately 17 tons of salt *per minute*.
2. The Lemonade Springs in New Mexico carry approximately 900 pounds H_2SO_4 per million pounds of water. (This is more than ten times the acid concentration in coal mine discharges.)
3. The Mississippi River carries over 2 million tons of natural sediment into the Gulf of Mexico *each day*.
4. The Paria River of Arizona makes the Mississippi look like a trout stream. It carries 500 times more natural sediment than the Mississippi River — yes — 1 billion tons of sediment per day.

LET'S GO BACK TO THE GOOD OLD DAYS

Don't believe the trash about the happy lives that people once had before all this nasty industrialization came along. There was no such thing. One of my 19-year-old students once asked me, "What has all these 2000 years of development of industry and civilization done for us? Wouldn't we have been happier in 100 B.C.?" I said, "No, chances are 97 out of 100 that, if you were not a poor slave, you'd be a poor farmer, living at bare subsistence level."

When people think of ancient times, they think of themselves as members of aristocracy. They are sitting in the Agora in Athens listening to Socrates, in the Senate House in Rome debating with Cicero, riding on horses as knights of Charlemagne time. They are never slaves, never peasants, *BUT* that's what most of them would be.

My wife once said to me, "If we lived a hundred years ago we'd have no trouble getting servants." I said, "If we'd lived 150 years ago, we'd be the servants."

Let's consider what life was really like in America just 150 years ago. For one thing, we didn't have to worry about pollution very long — because life was very brief. Life expectancy of males was about 38 years of age. It was a grueling 38 years. The work week was 72 hours. The women's lot was even worse. They worked 98 hours a week scrubbing floors, making clothes by hand, bringing in fire wood, cooking in heavy iron pots, fighting off insects without pesticides. Most of the clothes were rags by present-day standards. There were no

fresh vegetables in winter. Vitamin deficiency diseases were prevalent. Homes were cold in winter and sweltering in the summer.

Epidemics were expected yearly and chances were high that they would carry off some members of the immediate family. If you think the water pollution is bad now, it was *deadly* then. In 1793 one person in every five in the city of Philadelphia died in a single epidemic of typhoid as a result of polluted water. Many people of that time never heard a symphony orchestra, or traveled more than 20 miles from their birthplace during their entire lifetime. Many informed people do not want to return to the "paradise" of 150 years ago. Perhaps the simple life was not so simple.

WE ARE PRACTICING WITCHCRAFT

In every age we have people practicing witchcraft in one form or another. I used to think that the people of New England were irrational in accusing certain women of being witches without evidence to prove it. Suppose someone accused you of being a witch? How could you prove you were not? It is impossible to prove unless you can give evidence. It is precisely this same witchcraft practice that is being used to deter the construction of nuclear power plants. The opponents are saying that these plants are witches and it is up to the builders and owners to prove that they are not. The scientific evidence is that the nuclear power plants, constructed to date, are the cleanest and least polluting devices for generating electricity so far developed by man. We need electricity to maintain the standard of living we have reached but to the extreme environmentalists we are witches. We should be burned at the stake.

We hear the same accusations about lead compounds from the gasoline engine. Our Environmental Protection Agency has no evidence that there has ever been a single case of death, or even illness from lead in the air coming from burning of gasoline, but they still insist that we must remove the lead from the gasoline. To the EPA we are witches — they have no evidence — no proof — we are pronounced guilty! And yet you know that gasoline needs some additives to prevent engine knocks. If we don't use tetraethyl-lead, we'll have to use aromatic compounds. Some aromatics are carcinogenic. We know that! The use of unleaded gasoline also used up to 20% more crude oil.

(Incidentally, the real reason for removing lead from gasoline was because it was suspected that lead poisoned the catalyst in the emission control unit. Now we have good evidence that it isn't the lead but ethylene bromide which is the poisoner.)¹²

From what we read and hear, it would seem that we are on the edge of impending doom. A scientific evaluation of the evidence does not support this conclusion. Of course, we have some undesirable problems attributed to technological activities. The solution of these problems will require a technical understanding of their nature, not through emotion. They cannot be solved unless properly identified, which will require more technically trained people — *not less*.

I agree, as Thomas Jefferson did, that if the public is properly informed, the people will make wise decisions. The public has not been getting all of the facts on matters relating to ecology. This is the reason why I am speaking out on this subject today — as a technical man and as a citizen. Some of the things you have heard today are contrary to your beliefs, but I'm willing to support my conclusions on evidence good enough for me to stake my reputation on it.

8. THE LAST SURPRISE (#8) — WE'RE GOING TO LIVE!

In summary, let me state that we are not on the brink of an ecological disaster. Our O₂ is not disappearing. There will be no build-up of poisonous CO. The waters can be made pure again by adequate sewage treatment plants. The disappearance of species is natural. A large percentage of pollution is natural pollution and would be here whether or not man was on this earth. We cannot solve our real problems unless we attack them on the basis of what we know rather than what we don't know. Let us use our knowledge and *not our fears* to solve the real problems of our environment.

There is a moral to the effect that those who misrepresent facts are not believed when they speak the truth. We've heard many cries of "wolf" with respect to our oxygen supply, the build-up of CO, the disappearance of species, DDT, the oxides of nitrogen, phosphates in the lakes, thermal pollution, radiation effects from nuclear power plants, lead in gasoline, mercury in fish, filth in our streams, to name a few. For the most part, these cries of wolf have not been malicious, but have

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Pesticides and human welfare

EDITED BY

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AND

J. G. R. STEVENS

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Abbreviations

Throughout the text the initials FAO have been used for the Food and Agricultural Organization of the United Nations, Rome, and WHO for the World Health Organization, Geneva. Abbreviations for titles of journals are in accordance with the fourth edition of the *World list of scientific periodicals* (Butterworth and Co. 1963-5).

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PART I

THE PROBLEMS

15 Hazards to people

by J.M. Barnes



Plate 15.1. A bioassay being carried out on animal tissues. Before a new pesticide is put on the market, laboratory tests on animals give a reliable picture of its likely toxicity to man. (Shell photograph)

Compared with other industries, agriculture has a high accident rate in the developed countries. As well as the more obvious severe and fatal accidents with tractors and other heavy machinery, there are hazards from chronic trauma to the spinal column from ill-sprung tractors driven over rough ground and damage to hearing from noise. Farm animals may inflict physical injury as well as transmit infections such as brucellosis or anthrax, while a serious and unpleasant infection, leptospirosis, may be acquired from wild rats.⁷

Acute or subacute injury to the lung may occur from exposure to the oxides of nitrogen emitted from silo towers, and the farmer and members of his family may also develop a chronic, recurrent, and ultimately fatal pulmonary mycosis from the inhalation of spores from mouldy hay: 'farmers lung'. The accident rate among children on farms is unnecessarily high because they are allowed, and sometimes even encouraged, to play with farm equipment as they never could with other industrial machinery.

Thus the arrival some 30 years ago of a few acutely poisonous pesticides among the agricultural community represented an addition to a wide range of dangers which continue to receive much less attention than they deserve. There was no reason to expect that procedures recommended for the safe handling of pesticides would be followed any more conscientiously than those for the safe handling of other sources of hazard on the farm. The remarkable record of the safe use of pesticides on British farms therefore bears witness to the very limited toxic hazard that pesticides present.^{3, 12} In some of the developing countries the use of pesticides may involve the first contact of a community with any toxic chemical and some of the consequences flowing from this are referred to below. Regrettably few communities make any attempt to record accidents from pesticides among agricultural workers.⁹

Nature of the toxic effects of pesticides

The immediate toxic effect of a pesticide in a poisoned person is usually related to its mode of action on the target organ. Nicotine,

lindane, dieldrin, endrin, parathion, and aldrin produce by different biochemical mechanisms an acute disturbance of the nervous system which, if it is severe enough to interfere with respiration, may be fatal. The symptoms and course of poisoning differ, but if the patient recovers, function is fully restored and no permanent injury results. The absence of any structural damage to the nervous system or elsewhere is confirmed by observations on experimental animals exposed to larger or more frequently repeated doses than are encountered by the occasionally poisoned person.

Pesticides of another group interfere with energy transformation in the tissues. There is a large group of substances interfering with oxidative phosphorylation and of these only dinitro *ortho*-cresol (DNOC) and pentachlorophenol are known to have killed people. Again, there is no irreversible damage remaining in people or animals who recover. Of the poisonous pesticides still in use, girdyl and ethyl mercury fungicides are outstanding in producing permanent injury to the nervous system, while the fumigants carbon tetrachloride and methyl bromide may in cases of severe poisoning produce some damage to the kidney and nervous system respectively. With these exceptions, those pesticides that are toxic to man are because of acute damage depending for their effects upon a disturbance of function and not the destruction of vital tissues.

The great majority of pesticides in widespread use are not, however, serious **poisons for people**. They are selectively poisonous for the target organism. Sometimes the basis of their selective toxicity is well understood. In the case of malathion the mammal but not the insect has a metabolic pathway which hydrolyses malathion before it is activated to the toxic malaoxon. In the case of many herbicides the site of action is a system that exists in plants but has no counterpart in animals, and animals degrade and excrete the herbicide by processes that exist to rid the organism of the dozens of unwanted substances that are absorbed from a variety of sources during normal life.

Occasionally a substance which is normally used quite safely may show an unexpected effect when absorbed in a higher dose. Paraquat is an example of a substance that has been safely applied over millions of hectares by thousands of people without harm to them other than occasional injury to the eye or skin if unprotected from splashes of concentrate. However, less than a mouthful of the concentrate accidentally swallowed may cause a severe, progressive, fatal injury to the lungs. This toxic effect was observed in the animal tests carried out before

paraquat was marketed. The point to be emphasized here is that the 'toxicity' - the capacity to produce damage - is one thing and the 'hazard' - the probability that damage will be produced under any particular circumstances - must be considered separately. The introduction of any new chemical into the human environment must be phased and this is the purpose of most pesticide regulatory schemes. Substances cannot be simply labelled 'safe' or 'dangerous'. Their toxic properties together with their manner of use will determine whether they can be used safely.

The evidence available from the data compiled for over 20 years in the U.K. is that pesticides can be used safely and that the details from overturning factors alone are greater in any one year than all reports of illness arising from exposure to pesticides. There have been no deaths from pesticide poisoning. Reports are compiled of all cases where men have been off work for illness attributed to exposure to pesticides. The majority of these cases arise from irritation or inflammation of the skin or eyes resulting from splashes while mixing concentrates. Among the substances used as pesticides there are a few which can induce sensitization in people who come in contact with them; such individuals may have to avoid all future contact with a particular compound.

There are a number of relatively common serious human diseases for which no general cause has yet been established: leukaemia, aplastic anaemia, and peripheral neuritis are three examples. When a patient presents such an illness the doctor often seeks by enquiry some possible cause. As a result there are scattered in the medical literature claims that exposure to a pesticide has led to the development of one or other of these diseases. There is no epidemiological evidence to support such claims; in other words, the disease is not seen among those most heavily exposed or surviving acute poisoning by the compound. The aplastic anaemia reported in individuals said to have been exposed to BHC has been attributed to benzene which does cause aplastic anaemia, but BHC is based on cyclohexane which does not cause anaemia. There is no epidemiological evidence that exposure to pesticides causes cancer.

Circumstances under which poisoning by pesticides has taken place

Although large amounts of a pesticide in its most concentrated form are encountered in the manufacturer's plant, it is not difficult to protect workers from exposure in a modern chemical factory, and few people may be at any risk when a process is largely enclosed. Protection may be less adequate in some formulation plants, in which the active pesticide

is mixed with inert dusts or made into a solution or emulsifiable concentrates, particularly when dry powders and dusts are being produced. Acute poisoning has been reported among men formulating some of the more toxic insecticides.

There have been reports from all parts of the world of poisoning among those applying pesticides in the field.¹⁰ The exposure is greatest among those who dilute and mix the concentrates and the same applies to those who load aircraft for aerial applications. Occasionally pilots have been poisoned from leaks from pipes in badly designed spraying aircraft. Those who maintain spraying machinery may also be at risk if the machines are not properly cleaned at the end of the operations. Knapsack sprays and pumps may leak and contaminate the clothing of those who operate them. There have been occasional reports of illness among agricultural workers who have been pruning, thinning, or picking recently sprayed crops such as peaches and grapes. Such episodes have been confined to crops sprayed with parathion, one of the most toxic insecticides still in general use.

While fatal and non-fatal poisoning has followed the careless application of pesticides for the proper purpose of helping the better growth of crops or the storage of harvested products, there are other circumstances under which casualties, often on a dramatic scale, have occurred. Seed that had been dressed with pesticides to ensure better germination and growth, particularly if it is not issued to the farmers for sowing until after the correct sowing time, has been eaten in the place of their own grain which they had already sown. In Iraq in 1972, hundreds of deaths occurred and thousands of men, women, and children were permanently disabled after consuming grain dressed with a methyl mercury fungicide.¹¹

In other episodes dressed seed has been stolen and sold as edible material. In one instance the dressed seed was fed to livestock and a family who ate a pig became severely affected. It is not surprising that in a recent report WHO and FAO recommended the withdrawal of all methyl mercury seed dressings except for use in seed 'banks'.¹²

Other outbreaks of poisoning have resulted from the contamination of human food, usually flour or sugar inessian sacks, from leaking or broken containers in ships and vehicles. Even the separation of the pesticide from the food by storage in different holds (which, however, by no means always took place) was not enough to prevent one outbreak where the pesticide concentrate dripped through the flour of the hold and soaked into sacks of flour.¹³

There have been many cases of poisoning from pesticides among children, though many fewer in the U.K. than in the U.S.A.¹⁴ Whether or not this difference is linked to the greater freedom of entrance of American children is not certain. What is certain is that many such episodes stem from the gross carelessness of adults in leaving so-called 'empty' containers available as playthings.

Insecticides found to be obviously so effective against an agricultural pest have been incorrectly and dangerously applied for the eradication of others, such as bed bugs or body lice, with a consequent dangerous or fatal poisoning of members of a household. In some communities an 'empty' 25-litre drum may represent a valuable addition to household equipment; if the first use to which such a drum is put is the mixing of drinks for a wedding party, the outcome will be disastrous.

Finally, the presence of poisonous pesticides in a community may provide a new and convenient means of suicide or homicide.

Thus, it is clear that pesticides can and do kill or seriously poison people. The most dramatic and serious episodes have resulted from misuse, whereas their legitimate application on an ever-increasing scale for pest control purposes appears to be associated with fewer reports of accidents. It is worth turning aside to enquire into the reasons for this.

Developments which have reduced hazards

There is little doubt that knowledge about the ways in which people are actually exposed when they apply pesticides has been crucial in the development of safer methods. Because so many applications of pesticides are by means of sprays, either of suspensions of wettable powders or of diluted emulsions, it has been widely believed that pesticides are dangerous because they might be inhaled. Careful studies with measurements made during various operational procedures showed conclusively that the main route of exposure was the skin and not the respiratory tract.¹⁴ In operations that varied from indoor spraying to applications in orchards, ground crops, and the soil itself the amount of material on the skin or clothing exceeded many-fold the quantity that would have entered the mouth and nose. The explanation is simple: namely, that particles that will settle on leaves or any other surface must exceed a certain mass, whereas only very much smaller particles which would not impinge and settle on surfaces can enter the lungs. Thus, the only pesticides that are a potential danger by inhalation are those few preparations which are released as smokes or vapours and

against which special protection by respirators can be provided.

Knowledge that the skin is the principal route of exposure for pesticides means that attention can be focused on simple protection of the exposed areas and an insistence on regular washing during any prolonged period of exposure. Except when handling concentrates, heavy-duty rubber protective clothing is not needed -- and would be intolerable to wear in many circumstances. However, light cotton will prevent droplets reaching the skin. Another consequence of this knowledge has been the attention paid during the toxicological testing of new pesticides to the ability of a substance to pass through the intact skin. This can rarely be predicted from chemical structure or physical properties of a compound. Those pesticides that have proved dangerous to use (other than volatile ones) have an acute toxicity by the dermal route that is not greatly different from that by the oral route, whereas for the great majority of compounds in common use it may be difficult to elicit any serious acute toxic effects in animals after skin application alone.⁴ In accepting new compounds for use as pesticides attention is paid to their acute dermal toxicity to laboratory animals. In some countries it is feasible to insist that certain protective measures are provided for those employed in the application of the more toxic pesticides. Where compulsory protective measures, including the provision of special garments, need not be recommended when less toxic analogues are applied, an important sales incentive for the development of less toxic pesticides is provided. However, where very toxic substances have an important role as pesticides, attention has been paid to safer formulation such as adsorption on to inert granules or incorporation into other solid bases to provide a slow-release device. The fact that fewer safety precautions are needed for the use of such preparations may partly override their greater cost.

Another important factor in reducing hazards is the greater control being exercised by a number of governments over the introduction, marketing, distribution, and labelling of pesticides, accompanied by better field services and advice to users. It is becoming less frequent for the local salesman to be the only source of information about a new pesticide. Where there is a more intensive and commercially important agricultural enterprise in a region there may be opportunities for training in the practice of using pesticides. This may often be done to make certain that the correct applications are made to ensure that the residues of pesticide in the treated crops do not exceed the limits set by prospective buyers. All such training is likely to encourage the use of

methods providing greater safety for those applying the materials.

Knowledge of the mode of action of the anticholinesterase insecticides* has made it possible in the case of the organophosphorus compounds to devise a simple field method for detecting exposure long before serious or dangerous toxic effects appear, and thus permit a man to be withdrawn from further danger. Such arrangements are practicable only during the trial introduction of a compound. There are, however, effective antidotes to acute poisoning by both the anticholinesterase compounds and the convulsive chlorinated hydrocarbon insecticides, so that if agricultural workers do become ill and are taken to hospital it is unusual for them to die. However, the best protection against poisoning by new pesticides is the large amount of information that is acquired about their toxicity before they ever become commercially available.

Value of laboratory tests on animals.

During the past 50 years it has become increasingly customary to examine the toxicity of new substances on laboratory animals before the compounds are introduced into the human environment. Although such screening was first done, albeit on a very limited scale, on compounds destined for use in industrial processes where men might be exposed to vapour or liquids, there were until recently many compounds in wide commercial use for which there were few toxicity data. For modern pesticides there has always been some information on mammalian toxicity. This is exemplified by the early studies of the effects of DDT on the common laboratory species including monkeys, as well as on man himself. These investigations were carried out within two or three years of the introduction of DDT in 1945.⁵ The early organophosphorus anticholinesterases were recognized as close chemical relations of lethal 'nerve gases' and no one was surprised at the great toxicity of parathion and TEPP. The early casualties among people who first applied parathion, often with no more regard to safety than they gave to the use of DDT, encouraged the search for compounds that killed insects but were less acutely toxic to mammals. The result is that now there are compounds such as malathion or phoxim for which the margin of safety is enormous. This is related to differing rates of activation and degradation in the whole animals -- insects or rats. Such vital information would never come to light if preparations such as tissue culture replaced rats in tests for toxicity.

One of the earliest herbicides, DNOC, caused some deaths from

*See p. 263.

acute poisoning about 1950 among those spraying cereals in hot weather. When used as a slimming agent 20 years earlier, DNOC killed some patients but it was not until it was used as a selective herbicide that a proper study of its mammalian toxicity was undertaken. By contrast, 2,4-dichlorophenoxyacetic acid was shown in the same period to have a very low mammalian toxicity, and it has had a long history of safe use. From this early work there developed an increasingly complex pattern of tests on laboratory animals exposed both acutely and by repeated or prolonged application; and it can now justifiably be stated that laboratory tests on mammals give a reliable picture of the likely toxicity to man, although animal tests may not indicate that a compound can induce skin sensitization in man.

Toxicity tests on animals have thus made it possible to foresee and forestall the hazards of acute poisoning from occupational exposure; but this has not prevented people from expressing anxiety about the possible late effects of a prolonged exposure to small amounts of a pesticide that occasionally remain as a residue in food prepared from treated crops. Since tests on animals give a good indication of the possibility of acute poisoning it is irrational to assume that they are inadequate as indicators of possible chronic toxic effects. When pressed for examples of a toxic effect from a chronic exposure to low doses most people mention only cancer.

However, it is also known from extensive studies on chemicals other than pesticides that laboratory animals can respond by producing cancers resembling those seen in man. The response of animals to a prolonged heavy exposure to a new substance thus provides a reasonable basis for deciding whether the compound has the properties of a chemical carcinogen. At the present time, however, a great deal of disagreement exists about the significance of lesions produced in the livers of mice by a whole range of substances including DDT. While the tumours in the livers of these mice have many pathological features of liver cancers, the behaviour of the lesions and of the animals as a whole do not resemble those accompanying the evolution of a true cancer. Any compound being developed as a pesticide which during the course of toxicity tests on animals showed the capacity to produce cancer would be withdrawn from further development. At the present time there are no grounds for labelling as carcinogens DDT and half a dozen other pesticides that in large doses produce liver tumours only in mice.

Part of the alarm about chemical carcinogens as hazards rests upon the undoubted fact that for people exposed to carcinogens in industry,

just as for many smokers, the first evidence of a toxic effect is the appearance of the cancer, possibly at an incurable stage. Coupled with this fear is a widespread belief that there is no 'safe dose' of a chemical carcinogen because a single molecule homing on a sensitive DNA molecule might start a cancer. Recent work on the capacity of damaged DNA to undergo repair indicates, however, that there is likely to be a dose-response relationship for chemical carcinogens similar to that for other toxic substances. With respect to other toxic effects, the very extensive laboratory tests, including lifetime studies on rats continuously exposed to pesticides now in use, amply demonstrate the existence of fairly steep dose-response relationships. This indicates that if the people receiving the heaviest exposure during the application of a pesticide show no ill-effects, then it is extremely improbable that those absorbing minute traces in food will suffer any ill-effects.

Contemporary evidence for assessing hazards

There are unfortunately no good figures for the incidence of acute or any other sort of poisoning of people by pesticides, but from poison control centres it is evident that pesticides are responsible for only a very small proportion of cases of poisoning, both fatal and non-fatal, from chemicals.

From hospital reports there is no evidence that unusual or prolonged effects follow recovery from the acute pesticide poisoning from whatever cause, although the follow-up of acute poisoning is only for very short periods.

The recognition of long-term toxic effects from substances to which people are occupationally exposed is difficult, even when it is a rare tumour in a comparatively closed population. It is therefore not feasible to set up a study that is likely to provide evidence, negative or positive, that exposure to a pesticide can eventually lead to cancer in man. Agricultural populations are widely scattered, and hospital and general medical services are likely to be minimal in rural areas. Most important of all, this exposure to pesticides will be mixed, intermittent, and to a constantly changing group of compounds. While this last factor makes a follow-up difficult, it also protects the individual, for he will not be exposed to any particular substance over a long term. The only groups of people who have had a continuous and unusually heavy exposure to a single pesticide are the men who have formulated DDT since 1948 and others in malaria control programmes who have applied

DDT as an indoor spray year after year. One group of formulators has been followed-up in the U.S.A., and WHO are attempting to do the same for groups of sprayers in Brazil and India... but establishing the cause of death in a country where autopsies are not done has its problems.

As mentioned above, there has been much concern expressed about pesticide residues in food.² This stems partly from the widespread practice of having 'tolerances' or limits which pesticide residues in treated crops should not exceed. It is popularly believed that if these 'tolerances' are exceeded then that food is dangerous to eat. In practice a tolerance is established as the level which need not be exceeded if the crop has been treated as recommended in order to control a particular pest. With the improvement of analytical techniques the practice of doing analyses on market basket samples has increased. In this procedure the food as actually consumed is analysed. When this is done it is found that most pesticide residues have disappeared: for example, 'Extensive data show that most pesticides leave little or no residue in the majority of foods and most of the residues present are removed in storage, preparation and processing.'¹¹

Outlook for the future

While the continued clamour about hazards from pesticides may well seem to be quite out of proportion to the dangers that accompany their use, there is no doubt that attention will remain focused on better and safer methods of using them. Unfortunately it is unlikely that such advances will take place first in those communities where the dangers are greatest. Where there is little or no control of the introduction and distribution of pesticides the cheapest and most effective materials may be used by people untrained and ill-equipped to apply toxic compounds, but it is to be hoped that eventually most of the really dangerous compounds will no longer be marketed by reputable organizations.

The more extensive use of less dangerous materials should not be the pretext for abandoning care in the handling and application of pesticides. They should all be treated with respect, because it is never possible to be absolutely sure that substances shown to be safe in the short term will not have some deleterious effects in the long term if exposure has been heavy.

It is vain to hope for the ultimate replacement of existing pesticides by compounds that are more highly selective in their action, although for many herbicides this is already the case. What we may reasonably

expect is that the most persistent materials will be replaced by more biodegradable counterparts. While the control of pests continues to depend extensively on the use of chemical agents, it is reasonable to predict that the emergence of resistant strains of pests will ensure repeated changes in the nature of the substances used, thus avoiding long-term exposure to any particular pesticide.

The toxic effects of all pesticides continue to be scrutinized with great care, and as much is known about their behaviour and metabolism in animals as is known about many things to which people are more widely and more heavily exposed.

There have been cases of acute poisoning under circumstances which occasioned no surprise, either because of the toxicity of the particular pesticide involved or the gross carelessness and disregard for elementary safety associated with the incidents. Proper methods of handling avoid serious risks to people, and the probability of accidents diminishes with a greater general awareness of potential hazards.

The effective use of pesticide does not lead to the gross contamination of human or domestic animal food. The minute traces measured in parts per million that are sometimes found in food are of no toxicological significance even in the case of the poorly biodegradable organochlorine compounds. The use of such persistent compounds will gradually disappear for general aesthetic reasons and no case based on the toxicological hazards they present can be made for any immediate or drastic action to effect this change.

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16 Pest resistance to pesticides

by James R. Busvine

I can clearly remember first hearing of DDT-resistant houseflies from the late Professor Missiroli in Rome in 1947. This was only five years after our initial tests of the new insecticide and, such was the reputation of DDT at that time, it was difficult to accept his story; but he kindly supplied me with some of the portentous flies and we soon verified the fact. Furthermore, it was not long before reports began to multiply of similar immune strains of flies and other insects. The obvious seriousness of the matter began to change the common usage of the word 'resistance' among those concerned with pest control. Formerly, we had used it to describe normal variations in tolerance due to environmental changes, to which insects are very prone; alternatively, it was used as a characteristic of particular species of pest, some of which can withstand much higher doses of poison than others. Now, however, it is convenient to use the words 'susceptibility' or 'tolerance' for these familiar concepts and to reserve the word 'resistance' for abnormal strains selected by extensive pesticide usage.

The phenomenon is not entirely novel. As long ago as 1911 there was evidence that extensive fumigation of citrus trees had selected a strain of scale insect resistant to hydrogen cyanide gas; and there were perhaps four or five other cases before the Second World War. But the growth in incidence of resistance since 1947 was very much larger and faster, as a result of the introduction on a vast scale of new synthetic insecticides. This growth of resistance is illustrated in Fig. 16.1 by the numbers of species involved; it refers to insects of medical importance only, because their early resistance was better documented than that of the agricultural pests. It seems that 52 species of agricultural pests had developed resistant strains by 1958 and 228 by 1969: the first figure about equalled that of medical pests; the second far outstripped them.

Within a few years, resistant houseflies had been reported from very many countries; and similar troubles had been reported for lice, fleas, certain culicine mosquitoes, and various agricultural pests. Without discussing the practical importance of these figures at this point, it need hardly be said that the phenomenon soon caused concern. In particular, officials of the World Health Organization, who

Risk

Summer '70

A Point of View

*Toxic Substances: The "Raucous Truth"
About Uncertainty*

STEVEN D. JELLINEK*

"The public . . . demands certainty. It must be told definitely and a bit raucously that this is true and that is false. Yet there are no certainties."
— H. L. Mencken (1919)

I have heard it said, perhaps a bit cynically, that controlling the risks of toxic chemical substances is like trying to count grains of sand in a desert.

While there is no comparison, of course, between the two tasks in terms of their relative value to society, the analogy still has some validity. Given the enormous number of chemical substances in existence today, the shifting priorities for those that cause the most concern, and the universe of scientific and other unknowns that must be dealt with in assessing their hazards, the job of preventing unreasonable chemical risks to human health and the environment is—like counting sand in the desert—remarkably awesome.

Of all the obstacles that must be overcome if we as a nation are to succeed in reducing the significant risks of exposure to toxic chemicals, uncertainty is the greatest. Although—as Mencken said—absolute certainties probably do not exist, our efforts to come to grips with the real hazards of toxic chemicals must nonetheless be backed and justified by the best degree of certainty we can achieve.

Uncertainty in all its forms is therefore a major target of many

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of the powerful new authorities entrusted to EPA under the Toxic Substances Control Act of 1976 (TSCA). As Congress clearly recognized when it passed this law, relatively little is known about most of the chemicals used by our society—how they are used, who gets exposed to them and how, and what are the results of such exposure. Under TSCA, EPA for the first time has the necessary authority to gather certain kinds of basic information on chemicals—information that has never before been gathered in one place for public use, covering the roughly 70,000 commercial chemical substances manufactured or processed in up to 115,000 establishments nationwide.

TSCA gives EPA the authority to identify substances as harmful and—when other federal laws cannot control the specific sources of exposure—to control those substances whose risks of injury to public health and the environment outweigh their economic and social benefits. EPA can not only ban the production of the most hazardous substances already in existence, but it also can take a number of alternative actions to attack problems of toxic substances in our society. Under TSCA, EPA can:

- Review new substances to identify and prevent any unreasonable risks they may pose;
- Require reporting of any significant new uses of existing chemicals, and limit or prohibit any uses that might present unreasonable risks;
- Require that industry, at its own expense, test certain chemicals and classes of chemicals for adverse health and environmental effects;
- Control the distribution and disposal of any chemical that, uncontrolled, might pose an unreasonable risk.

In addition to the conflicting pulls inherent in TSCA—primarily through the law's requirement that chemical risks be weighed against chemical benefits—EPA must also contend with a number of other tensions in carrying out its responsibilities under TSCA—not just political tension or tension between our environmental and industrial constituencies, but tension between “good science” and “good regulatory policy.”

Good science and good regulatory policy, of course, are not

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mutually exclusive. But neither are they synonymous. While EPA cannot fulfill its public trust by waiting for science to provide all the answers to support our regulatory policy decisions, neither can it act responsibly without a firm scientific basis.

Most of EPA's focus—both scientific and regulatory—has traditionally been on the waste products of our industrial society and on the application of science and technology to controlling residuals. With the passage of TSCA, however, this focus is shifting to the potentially adverse effects of otherwise socially beneficial products. Congress recognized the difference between these approaches, and gave EPA a stiffer legal test to pass before it can act. That test, of course, is “unreasonable risk.”

Making unreasonable risk determinations exacerbates the tension between good science and good regulatory policy—and between certainty and uncertainty. Making such determinations requires three basic steps: (1) assessing the risks of a chemical; (2) assessing the benefits of a chemical; and (3) weighing the risks and benefits to arrive at a final regulatory decision.

Although EPA is relying heavily on the scientific community to help assess chemical risks, and TSCA's powerful testing and information powers will be used to narrow the gaps in our knowledge, we will never be able to answer every question with absolute certainty. Nor will every question be answered to everyone's satisfaction.

In the long term, though, one of TSCA's major contributions will be to extend the body of scientific knowledge of chemicals. In this way, everyone—industry included—stands to benefit from TSCA's role in reducing uncertainty. Among the areas that will gain from the increased knowledge are:

- Detection and monitoring (How does the chemical get into the environment? How does it change once there? Where does it go? Who is affected by it?);
- Testing (How can we predict more accurately, rapidly, and inexpensively the chronic effects of chemicals on health and the environment?);
- Health effects (Which chemicals cause cancer, birth defects, gene mutations, etc.? What are the relevant biological mechanisms involved?); and

- Ecological effects (Which chemicals affect the relationships among living systems, and what is the potential, long-term result of even the most subtle perturbations?).

The "raucous truth" about uncertainty's role in mitigating chemical risks, therefore, is that it is both antagonist and protagonist. We must act in its presence and, alternatively, against its presence; knowing which course to take as each tough decision-making situation comes along under TSCA has much to do with the ultimate success of our efforts.



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Risk Assessment—A Familiar Concept

JEROME H. HECKMAN†

THERE ARE SOME things in life that are just too good, or work too well, to become outmoded and cast aside. These old standbys simply reappear on the scene, repackaged and relabeled to be heralded as something exciting and novel. Have you ever considered how the "Hustle" is but a jazzed-up jitterbug; hair stylists are simply overpaid barbers; eligible bachelors now swing as "singles"; and pancakes are devoured as crepes?

And so it goes with risk assessment. Take away its official and scientific-sounding cloak and we are left with a familiar concept that all of us use every day. Risk assessment techniques are applied, if only unconsciously or subconsciously, when we decide how to get to work or whether or not we should even go. Likewise, they come into play when we determine what to order for lunch, or where to live.

Risk assessment has been around for such a long time and seen so many places that it now goes under multiple aliases. Common

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This is adapted from a speech to the American Chemical Society panel on Legal Aspects of Chemical Health and Safety, September 12, 1979, Washington, D.C. Reprinted with permission.

sense, horse sense, sixth sense—are all synonyms. My favorite is the phrase "Rule of Probability," as stylized by Louis Nizer and popularized by characters such as Perry Mason and Columbo. Early in his book, *My Life in Court*, Nizer discusses the process whereby, on the basis of cumulative experience, we anticipate with reasonable certainty the reactions to a given stimulus. By applying this "knowledge" to any set of facts, we can judge whether the conduct described is probable.

Those of you who have watched Perry Mason may have wondered how, without exception, he was able to confront the guilty party with the vivid and grisly details of his or her crime. Nizer in real life, and Mason on TV, simply utilize the rule of probability to reconstruct past events by determining the most likely course of human conduct. This is really the best we lawyers can do. I submit that it is, in truth, the best that science can do, too, and, more important, that it is far better to move on the basis of risk assessment or the rule of probability, reasonably applied, than it is to make the equally definitive and risky decision to do nothing, or consciously delay an action.

Given the fact that we really must use risk assessment techniques daily, it is mildly surprising that there is such reluctance to recognize and acknowledge their use on the food safety scene. I suspect this is another case where we might all look around and ask: "What are we pretending not to know?" Obviously, public relations, political, and sociological considerations are involved in this subterfuge, but it is becoming clearer that the pretense can be as dangerous as the facts.

Public Anxiety

We live in a time when each day seems to herald the addition of yet another putative carcinogen to an ever-growing list. "Prematurely issued" reports by government agencies, widely and often hyperbolically publicized by the hot news media, have, according to an editorial in the most recent issue of the *Journal of the American Medical Association*, "heightened public anxiety whenever evidence, no matter how tenuous or unconfirmed, is presented linking a commonly available substance with cancer."

URL 03004

The editorial, entitled "Science Reporting to Alarm the Public," observes that the tests that form the basis of these reports "are often conducted with dosages that exceed any to which man could be exposed, are administered for periods that equal the natural life span of the test animals, are given by inappropriate routes, and are finally evaluated by persons of questionable expertise in the field of tumor histopathology." The editor, Dr. William R. Barclay, perceives the problem to be of sufficient severity to warrant among major medical journal editors the organization of a suitable truth squad to counteract the fear factor.

The public is confused, and understandably so. They are informed, by familiar and trusted sources, that their favorite soft drink is laced with carcinogens; equally trusted sources then proceed to discount the findings by attacking the relevancy of feeding rats "huge" amounts of a substance used in the beverage to induce observed effects. Add to this confusion the government's inconsistency in allowing demonstrably more potent carcinogens to remain on the market while less harmful products are removed, and a growing disillusionment with science as having all the answers. At least as I see it, the result is that we have reached a point where we can no longer pretend. All of us will have to acknowledge that conscious applications of risk assessment in the area of food safety are a necessity; no one can assure or continue to pretend to assure absolute safety, since there is no such thing.

The saccharin and nitrite episodes are examples. Cynics might say that these are cases where industry happened to be successful in creating the appearance of grass roots support to open Pandora's box. But the stockpiling of diet sodas, and bumper stickers protesting that the Canadians have determined that saccharin is dangerous to your rat's health, belie such cynicism. The public is simply demanding that a sensible approach be taken and that the risks posed by these substances be put into some kind of perspective. Congress has obliged with its Saccharin Study and Labeling Act; similar legislation urging a moratorium against banning nitrites is now before it. As I see it, what has happened is that no Pandora's box has been opened at all; instead, a corner of the veil that surrounds the little black box I call the scientific mystique has been lifted, and necessarily so.

Bolder FDA Policy

URL 03005

Taking its cue from the public, FDA has revitalized a six-year-old proposal to regulate carcinogenic residues in edible products of food-producing animals. In 1973, FDA treaded softly when it came to application of the rule of probability to food safety. Today, the agency walks more boldly and waves a banner of risk assessment—the scientific jargon of the day which seems to be gaining acceptability in most parts of the body politic.

Although not apparent from its title, "Criteria and Procedures for Evaluating Assays for Carcinogenic Residues," the modified proposal is cast in the scientific aura of risk assessment. It is more commonly called "SOM" ("Sensitivity of Method") because any assay which measures presence or absence of a carcinogen is useful to the extent that it is sensitive enough to detect the carcinogen at a level of consequence. As written, the proposal would establish procedures and minimum criteria to ensure the absence of cancer-causing residues in products of food-producing animals to which drugs, food additives, or color additives have been administered. In keeping with the agency's tentative espousal of risk assessment techniques, the former Commissioner and current Acting Commissioner have stated that the principles outlined in the proposal have potential applicability for regulating all chemical carcinogens.

In the minds of many, the SOM proposal is the most comprehensive endeavor, to date, to bring risk assessment to the area of food safety. Conceptually, SOM aptly highlights the advantages of risk assessment in this particular context, while underscoring some of the difficult problems which remain to be resolved.

The basic intent of the proposal is to describe the procedures which will be required to assure that there will be "no residues" of carcinogenic drugs or their metabolites in the edible tissues of animals that have been treated with these drugs. The proposal would require chronic studies with experimental animals to measure the dose-response in test animals to the drugs or their metabolites. From the observed data, a linear extrapolation would be performed to yield a "virtually safe" dose for which the risk of a carcinogenic response will not exceed one in one million. The "virtually safe" dose will be expressed as a concentration in the

diet. This proposal requires that an analytical procedure be used that is sensitive enough to ensure that the safe dose will not be exceeded in the daily diet. A finding of "no residue" in edible tissues at the prescribed analytical sensitivity is required, thereby assuring that the edible animal products do not contain carcinogenic "food additives."

The proposal also provides a "screening" mechanism which establishes the procedure for assessing whether a new substance poses enough of a carcinogenic potential to require full-scale toxicological testing, or something less. This initial determination is resolved by a weighted decision involving three points: a use factor that relates to the probability or extent of human exposure to the substance; the level or intensity of exposure which reflects the quantity of the substance that might be present in food; and the probable toxicological significance of the substance based on an assessment of its chemical structure, its likely metabolites, and other suitable information. If this threshold assessment indicates that a substance might pose a significant potential carcinogenic risk, it must then be tested by oral, lifetime dose-response studies on two suitable test animal species to establish an appropriate SOM or establish noncarcinogenicity.

Obviously, the SOM proposal embodies fundamental precepts of risk assessment. It squarely rejects the concept of absolute zero—a concept which, in the past, FDA has zealously pretended it had to embrace. This has led to especially unfortunate results in its regulation of indirect additives, such as food packaging.

The revolutionary refinements over the past twenty years in analytical methods for detection of trace substances in foods have effected a qualitative difference in the meaning of the law. Trace migrants undiscoverable ten, five, or two years ago and now found in parts per trillion are banned if, at enormously higher levels, they are known or suspect carcinogens. Although science has progressed to the point of identifying such substances, it has not made the parallel advancement of providing guarantees that at such levels there is zero, or at least only an insignificant, risk. Nor is it realistically likely to be able to prove this negative.

The SOM proposal puts law and science on a more equal footing. Increased scientific sophistication has continually altered the meaning of the law to make its impact much more severe than

most would say Congress ever intended. The SOM proposal would "stabilize" legal construction. Under it, once a substance is cleared because it is "non-detectable" (i.e., there is "no residue present"), with an acceptable assay, the status would not be changed if improved analytical capabilities measure residues at lower, previously undetectable levels. Only new evidence of toxicity at lower levels would trigger a reassessment of safety.

Another basic principle embodied in the SOM proposal is the analog to zero risk—the concept of relative safety. SOM's acknowledgment of relative safety is evident in the proposal's examples of estimated acceptable total dietary levels of several known or suspect carcinogens that would provide a lifetime risk of one in a million or less.

Similarly, the proposal's screening mechanism shows a deference to relative safety. There are certain substances which, given their limited conditions of use, are unlikely to pose a problem. Scarce resources should be directed toward testing other and more potentially harmful substances. Not all substances under the sun can, or should, be tested.

Risk-Benefit Analysis

The risk assessment techniques embodied in the SOM proposal are not to be confused with risk-benefit analysis—another popular term of the day. Risk assessment supplies us with a common denominator to calculate and compare fractions of risk. Risk-benefit picks up where risk assessment leaves off. It takes our risk assessment fractions and interjects totally new calculations, in the form of benefit assessments. The equation is changed, and the answer is necessarily different.

As I see it, except in those relatively rare situations where a food or an additive is unique, it would be difficult, if not impossible, to quantify benefits for a substance. I also feel that Congress and the courts have wisely steered the administrative agencies away from such subjective value judgments whenever possible.

The popularity of a product or the extent of its constituency should and does determine whether a product stays on the market. This is simply the law of supply and demand. But to hinge a product's survival (and in many cases, the manufacturer's) on

bureaucratic perception of a particular food's value would be to seriously undermine all free competition.

From a practical standpoint, how could FDA fairly administer such a policy of assessing the benefits of individual foods? Under a famous Supreme Court decision in the area of administrative law, *Ashbacker Radio Corporation v. Federal Communications Commission*, FDA would, arguably, be required to hold comparative hearings to simultaneously assess the risk-benefit ratio of competing products prior to determining the lucky products to remain on the market. I shudder at the vision of a group of manufacturers and their lawyers making 100,000-page hearing records to try to prove their product is "more better" than a competitor's.

SOM is one tool for risk assessment, but obviously it is applicable primarily to what are called "incidental additives" of one type or another. What about the food supply proper? Here, too, especially with respect to the many food additives which are essential to an adequate, healthful diet, risk assessment, not risk-benefit will have to serve as our yardstick—a continuum which allows us to gauge and compare risks. The difficulty with its application as regards direct food additives, or food itself, could be compounded or lessened by the fact that public debate is more likely when one discusses whether things like saccharin or nitrates are to be used and deemed to present an acceptable risk. There is also the fundamental question of what the scientific community and the regulators will decide are reasonable guidelines for risk acceptance.

Unfortunately, applying risk assessment techniques is not merely a matter of dividing our yardstick into "go" and "no go" regions when you try to apply it to foods or things intentionally added to them. Assume, for purposes of discussion, that we adopt the same lines of demarcation suggested by many of the risk assessment advocates of today; any chance smaller than one in one million of getting cancer is an acceptable level of risk, while any substance posing a risk of one in 50,000 or greater must be banned.

What about those chemicals which could pose a lifetime risk of considerably greater than one in one million, or even one in 50,000, but which are naturally occurring, such as tannic acid in tea, cholesterol in eggs and selenium in feeding? To ban such alleged carcinogens would put a serious dent in our food supply

—a result which I venture that even the most diehard health fanatic would be unwilling to accept. As a practical necessity, and one which FDA currently observes, these foods, complete with naturally occurring toxins, remain on the market.

Phaseout Alternative

So far so good, but what about those substances which are "uniquely functional additives" yet, according to a risk assessment model and acceptance criterion, would have to be banned? A long-range phaseout coupled with some type of government incentive to develop substitute products is one possible approach. Unfortunately, like most things with merit, it too has its complications.

On the political side, phaseout authority would clearly require an act of Congress. FDA recently asked the Department of Justice whether it has the authority to phase out nitrites, or any other substance for that matter, under the Federal Food, Drug and Cosmetic Act. To the surprise of a few, the Justice Department responded that FDA has no phaseout authority, express or implied, to remove proven carcinogens from the marketplace.

On the practical side, it is probably advisable to limit the phaseout approach to those substances which lack market substitutes that have been fully tested and labeled "safe." Otherwise, we will be faced with the phenomenon, common today, where manufacturers, who, notwithstanding a long history of satisfactory use of a particular additive, switch to a new and less well tested product at the drop of a hat. In short, we need to encourage some old-fashioned "wait to switch."

The slope gets more slippery as we enter the gray area bounded on one side by the "relatively absolutely safe" risk of one in one million and smaller, and on the other, by that last outpost of relative safety at one chance in 50,000 (or wherever else it is set).

Other Options

Various approaches have been suggested for dealing with this intermediate zone, among the more prominent of which is cautionary labeling. Labeling may be effective for that special por-

tion of the population who not only know, but who don't pretend not to know. Most will ignore the labeling; but the less fortunate will suffer from an information overload which may well later manifest itself in the form of more of the "heightened public anxiety" decried by the AMA in its JAMA article.

Others point to educational programs which, if implemented at an early enough point, will encourage good nutritional habits. Such programs are needed, but even in conjunction with full ingredient labeling, their impact may prove too modest for many.

It has been suggested that by voluntarily undertaking such risks as x-rays, driving fuel misers rather than the more massive gas guzzlers, or ordering martinis, we tacitly consent to incur risks of similar magnitude from the food we eat. In my judgment, this approach inaccurately assumes some awareness on the part of the public of risks that might be posed by particular foods.

At least to add to the options list, I would propose that substances in this gray area be assessed as follows: if they have a long history of use and there is no reason, other than an animal study, to suspect that they have an adverse effect on humans, they should stay on the market, labeled in the usual manner. My experience is that lack of safety of a substance for human exposure is not the deep dark secret some would have us believe. If something is dangerous, we often find out about it first in the laboratory and the chemicals never enter the food supply, or disappear promptly after evidence develops to indicate a possible risk. In other words, my suspicion is that our gray area is not nearly as significant in reality as it might appear from the mathematical models.

This approach is not without shortcomings. For example, on its face, it could discriminate against new products, which lack the saving grace of a track record.

In the case of new or recently developed products which fall in the gray zone, I would propose that their use continue to be limited. Rather than rely solely on the less effective voluntary restrictions on use, which the labeling and/or educational approach would offer, we can simply continue use limitations such as those now included in most direct additive regulations. By thus lowering the "use factor" of a risk assessment model—and I believe all of them do or should include use as a factor—we will have simply

"regulated up" substances into our safe zone of less than one in one million. Some monitoring of consumption patterns would be necessary so that new uses will not become "runaways" without safeguards, but this should not be a serious obstacle.

Crucial to any of the alternatives being discussed is the accuracy of the premises upon which they are based. The risk assessment models must, to the greatest extent possible, simulate real world conditions. Prior to resolving even the most seemingly "purely scientific" issues, there must be a basic recognition that issues of science and policy are intertwined in all phases of the risk assessment approach.

To suggest that scientists will provide the ground rules upon which the policymakers will act, as many writers have suggested, is an oversimplification. The ground rules will necessarily be the culmination of crucial policy decisions.

In the case of SOM, the proposed ground rules include, for example, the most conservative extrapolation model, a 99 percent confidence level for regulatory assays, and the assumption that all tumors in test animals are to be counted in assessing carcinogenicity. In the minds of many, the net effect of such built-in conservatism is an acceptable level of risk which is magnitudes smaller than the stated one in one million level.

Like the computer printout, which is only as good as its programmer, the rule of probability is only as valuable as the underlying information to which it is applied. Infusing policy factors at the ground level is like shooting craps with loaded dice; the probability of a given outcome is necessarily skewed.

Reasonable scientists, like reasonable lawyers, will, of course, differ. Such varied opinions should be brought to bear to ensure that each ground rule simulates with the greatest accuracy the probable outcome in real life. This is what is meant when one observes that on the basis of cumulative experience, we anticipate with reasonable certainty the reaction to a given stimulus. The rule of probability demands that the subset of factors which make up cumulative experience be as accurate as possible.

Who Should Set Policy?

The fact that risk assessment calls into play important policy issues has persuaded some, including those within FDA's own

ranks, to advocate that Congress, and not the FDA, should determine what is and what is not an acceptable risk. Congress, they claim, is the only appropriate body to make such decisions.

I disagree.

From a practical point of view, it is doubtful that Congress will want anything to do with such decisions. Congressman Martin of North Carolina put it aptly:

Until FDA proposed to ban saccharin, no politician (and few scientists) dared publicly to challenge Delaney. Anyone questioning the validity of this absolute safety dogma would be terrorized and quickly wilted by the simple suggestion that 'your constituents deserve better than to be represented by someone who favored a little bit of cancer.'

Administrative agencies determine policy on a daily basis in areas of fundamental importance. They do it under the aura of their respective areas of expertise. FCC and FTC regulate free speech; OSHA regulates the workplace; EPA determines how many and what kinds and levels of pollutants and effluents will be tolerated.

But apart from the precedent for administrative policymaking, the agencies have a statutory mechanism, or indeed a statutory duty under the Administrative Procedure Act, to ensure that the public is heard. When it comes to risk assessment, the success of FDA in determining appropriate levels of risk will depend on whether it can accurately gauge what the public considers to be appropriate levels of risk. It has the means to do so.

It is most appropriate that the very decision to adopt risk assessment techniques in the area of food safety is the result of a risk assessment analysis. On the one hand, we have our existing system of ad hoc decisionmaking. There are no uniform ground rules which are brought to bear in assessing and comparing substances. It is probable that this ad hoc approach will continue unless there is a conscious effort to change it. Regrettably, the courts have consistently upheld the power of FDA and other agencies to proceed on a case-by-case basis in the area of public safety, even where such activities discriminate against competitors and produce inconsistent results.

On the other hand, the adoption of uniform ground rules for applying the risk assessment yardstick offers a more objective mechanism for responding to public opinion and maintaining the safety of our food supply while better allocating scarce scientific and regulatory resources on a priority basis. The choice, it seems to me, is easy, but the scientific community will have to help make it. Then all of us will need to work more closely together to bring about the enactment of any new rules (or, to a minor extent, laws) necessary.

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Fred Dorrell
NEWS & VIEWS

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THE DDT DEBATE: THE BEGINNING OF THE BIG BAN ERA

by Helen E. Kelly

It has been incontrovertibly shown to prevent human illness on a scale hitherto achieved by no other public health measure entailing the use of a chemical.

*—British Medical Journal editorial
Chemicals used as sprays are like devils
that create chains of poison and death.*

—Justice William O. Douglas

Both of these allegations refer to the same substance. A paradox? Perhaps. A prototype for conflict? Absolutely.

The substance is DDT, and the statements above epitomize the heart of the battle over the banning of DDT, a battle that gave birth to and nurtured the environmental movement that is now in full bloom. The DDT controversy may seem like ancient environmental history today, but its form can be traced in virtually every environmental conflict since then. It is this role as prototype that makes the DDT debate so fascinating and so worthy of study. Now, almost two decades after the appearance of *Silent Spring*, environmental contests take the form of ritual drama, the script of which was written during the fight over an ordinary-looking white powder—dichloro diphenyl trichloroethane.

DDT was first synthesized in 1874, but 65 years passed before it was tested as an insecticide in 1939 in Switzerland. The following year, in 1940, it was patented as a contact insecticide by Dr. Paul Muller, who received the Nobel Prize in medicine in 1948 for his discovery.

DDT began its life of use as a public health insecticide during World War II. In 1943 the U.S. began manufacturing the chemical for military use in the fight against two devastating insect-borne diseases: typhus and malaria. General worldwide use of DDT began after 1945. At first the emphasis was still on the medical benefits of the insecticide, primarily in terms of malaria control, but also against the vectors of yellow fever, sleeping sickness, plague, typhus, dengue, and encephalitis, all of which are transmitted by insects. However, the low cost and wide effectiveness of DDT guaranteed that its use would be extended to pest control in agriculture and forestry. In



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many cases, the use of DDT greatly increased crop yields, as in the case of rice production in the Philippines, Thailand, and Venezuela. In the U.S., the greatest but by no means sole use of DDT was in the South, to combat the insect destroyers of cotton, peanuts, and soybeans. DDT was also found to be an effective agent against the spruce budworm, pine weevil, tussock moth, and gypsy moth, which have the capacity to devastate woodlands.

Since DDT was not the only insecticide available by the early 1950s, one might wonder why it continued to dominate the scene, especially for use in public health programs. There were three reasons why DDT remained the preferred insecticide for many uses, not the least of which was its extraordinarily low cost. In 1968 one pound of DDT cost 17½ cents. Since, for many purposes, the recommended application level of DDT was one pound per acre, enormous areas of land could be treated at a minimal expense. At the height of the DDT controversy it was generally acknowledged, even by opponents of DDT, that no available alternative could be obtained as cheaply.

The second reason for the overwhelming success of DDT was, ironically, the very property which was to become ammunition for those who sought to ban its use in the late 1960s, namely, the exceptional stability and persistence of DDT in the area sprayed. This ability of DDT to remain active for many months after application eliminated the need for frequent respraying. While this made DDT use efficient for both forestry and agriculture, it was in the area of malaria eradication that the persistence of the insecticide was most vital. In many cases, the areas to be sprayed were far removed from civilization and difficult to reach, and the need for constant respraying would have crippled anti-malaria programs. The long-term residual effect of DDT made it possible for long intervals to elapse between sprayings of dwellings. Without the advent of DDT or some other equally effective and persistent insecticide, it is dubious whether large-scale malaria eradication programs would ever have been attempted.

As it stands now, DDT has been credited with saving 100 million lives as a result of its use against insect-borne diseases. Some idea

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DR. JOHN HIGGINSON TALKS WITH ACSH

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Environmental Update

John Higginson is the founding director of the World Health Organization's International Agency for Research on Cancer (IARC). Born in Belfast, Northern Ireland, in 1922, Dr. Higginson received his Medical Degree from Trinity College, Dublin, in 1946. Prior to joining IARC, Dr. Higginson was a research pathologist at the University of Glasgow and the South African Institute for Medical Research, Johannesburg, and later, American Cancer Society professor at the University of Kansas. He is widely recognized as one of the originators of the environmental theory of cancer causation.

ACSH:
WHAT ARE THE GOALS OF IARC?

HIGGINSON:

The IARC was established as a research institute by a group of governments to try to develop and execute a coordinated international program in cancer research with special emphasis on epidemiology, causation, and prevention.

ACSH:
HOW DO IARC'S RESEARCH AND PUBLIC
EDUCATION PROJECTS DIFFER FROM
THOSE OF OUR NATIONAL CANCER INSTI-
TUTE OR THE AMERICAN CANCER
SOCIETY?

HIGGINSON:

Although the budgets are very different (the Agency being a somewhat "peanut" operation), all nonetheless have the same goals in the field of environmental carcinogenesis. Because of our limited budget, however, the Agency has no clinical program and does not treat patients. The Agency is essentially a scientific research body, publishing in the scientific literature. The practical value to the general community comes from public health measures for prevention. These can be applied, as a result of that research, either through government action or through educational programs. For example, we can educate people about the carcinogenic dangers of excessive drinking.

ACSH:
IS CANCER A SERIOUS HEALTH PROBLEM
WORLDWIDE?

HIGGINSON:

Well, the relative importance of cancer as a health problem keeps changing in different countries. Thus in the United States, about one in four persons will develop cancer today. These figures are similar to those in Western Europe and the Soviet Union.

In contrast, in the developing world, changes can take place extremely rapidly, as illustrated in the case of Singapore. Cancer was a relatively unimportant cause of death in Singapore in 1950. By 1965 it had become the most important cause of death on the island.

Later, it was overtaken by heart disease, which had previously been of less importance. This was possibly due to changing lifestyle conditions associated with increased prosperity. In India, the number of cancers is increasing markedly due to improved life expectancy. However, the relative importance of this increase is diminished by the large number of children and young people in that country. The importance of cancer will become more obvious as the population pyramid stabilizes as a result of birth control.

ACSH:
HOW DO YOU REACT TO THE SEEMINGLY
ALARMIST REPORTS THAT THE UNITED
STATES IS CURRENTLY EXPERIENCING A
"CANCER EPIDEMIC"?

HIGGINSON:

I have discussed these reports with numerous epidemiologists. We are all agreed that there has been an epidemic of lung cancer related to cigarette smoking over the last two to three decades. This is partly offset by a marked decline in stomach cancer. For most other cancers, there are only slight trends up and down, which are difficult to evaluate due to registry artifacts, etc. As a generality, it could be stated that in the U.S. in whites, tobacco-related cancers are still increasing. In black males, there are marked increases in lung and esophageal cancers and some increases in prostatic cancer. In black females, lung cancer is increasing but others are decreasing. Some of these latter changes may be due to lifestyle factors. I do not believe that there is an epidemic, as is often implied, apart from lung.

ACSH:
THE AMERICAN ATTITUDE TOWARD CAN-
CER IS CALLED BY SOME A "CANCER-
PHOBIA"—IS IT UNIQUE TO THE UNITED
STATES?

HIGGINSON:

I don't think it's unique to the United States. However, when you have a population where over 20-25 percent of the people get cancer, practically everyone has had personal contact with the disease. Thus, fear of cancer has largely replaced fear of tuberculosis (the white death, as it was known in the past). Naturally, people are very worried about a disease whose nature they do not understand. I think that vocal cancerphobia is probably more extreme in the U.S. than in other countries in the sense that people feel that few improvements have taken place in treatment and understanding of the disease. This attitude is partly media-engendered, and partly due to over-expectations as to the immediate results of modern research.

ACSH:
DO YOU THINK IT IS BECAUSE A "CURE"
HAS NOT BEEN FOUND?

HIGGINSON:

I think that there have been definite over-expectations as to the possibilities of an immediate cure, although many people believe that if enough money is spent, cancer can be prevented, controlled, and cured very soon. Unfortunately, people don't recognize how much in fact has been done, and how much could be done by applying available knowledge. For example, in the United States, if skin cancer is included, we probably could prevent nearly 40 percent of all cancers in males with certain changes in cultural habits and lifestyles. The proportion theoretically preventable in females is much smaller, say 20 percent. Unhappily, such changes often involve individual action which people don't want to carry out. This indicates the discrepancy which exists between a vague fear of an event in the long-term future, and a present pleasure, such as smoking. People's fears and their willingness to do something about those fears do not always operate rationally. So, cancer prevention should be considered in addition to gradual improvements in therapy. Certain skin cancers are deemed virtually 100 percent curable today.

ACSH:

IN ONE OF YOUR MANY ARTICLES YOU TALK ABOUT THE GENERAL UNWILLINGNESS OF GOVERNMENT TO APPLY CURRENT KNOWLEDGE OF CANCER RISKS WHERE IT OFTEN AFFECTS PERSONAL PLEASURES OR MATERIAL WELL-BEING. YET YOU ALSO STATE THAT IN SUCH CASES IT IS THE GOVERNMENT'S RESPONSIBILITY TO TAKE THE NECESSARY DRACONIAN MEASURES. IS THIS A SOLUTION OR A PARADOX?

HIGGINSON:

It's a paradox and not easy to resolve, and I am not optimistic that it can be resolved in the short term. I do suspect, however, that it can be gradually resolved in the long term with improved education and positive modification in certain lifestyles. It is informative to look at the consumption of cigarettes in the United Kingdom over the last 15 years. In the population group with the highest education, e.g., professionals and college graduates, cigarette smoking has fallen to approximately one half of that in the early sixties. In contrast, in the group with the least education, there has been practically no change. This indicates that with education, people will listen. I believe it is the responsibility of the government to provide a total educational plan regarding health hazards. Thus, children should not be permitted to smoke at school. In my time, you could get expelled for smoking. Draconian efforts to control smoking among children are being tried in France. Teachers are not allowed to smoke in class, but only in a special room. All of us have seen the marked changes that are taking place in airline travel, and it is interesting to note that many smokers prefer the non-smoking seats for short trips. Unfortunately, the group on which education has had the least effect is the young female.

ACSH:

IS IT LIKELY THAT THERE IS YET SOME UNDISCOVERED FACTOR THAT IS RESPONSIBLE FOR A LARGE NUMBER OF CANCERS?

**HIGGINSON:**

Certainly, but you have to consider each site individually, and separate possible causative factors from an understanding of mechanisms. We don't understand the mechanisms of breast cancer, a very important female cancer, nor the external factors involved. We suspect the involvement of hormones, which may be altered by sexual and behavioral patterns such as number of children, age at first pregnancy, and so on, and also diet. But our knowledge does not at present permit definitive recommendations as to prevention. Similarly, for cancers of the stomach and large intestine. Again, there are many hypotheses, but few of them are supported by adequate data, especially in relation to lifestyle.

ACSH:

CAN YOU COMMENT ON THE RECENT REPORT BY THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY ON COLON CANCER AND THE LOW FIBER DIET?

HIGGINSON:

In all studies on colon cancer, the only risk factor that seems consistent is low fiber; high fiber seems to have a protective effect. However, there are many different types of fiber. There are lots of hypotheses regarding the action of fiber besides regularity. I am sufficiently convinced of the possibility that I now take All Bran at breakfast, which I didn't do before. That is the sum total of the dietary changes that I have made, apart from not over-eating, in the last 30 years, and the only ones for which I would say that the evidence is sufficiently satisfactory. Further, the action is certainly not going to do any harm, and may do some good. Forty years ago I was told that roughage was a good thing, and as a kid I was made to have roughage for breakfast. I was taught in medical school that it prevented all sorts of diseases of the large intestine. Then it dropped out as old-fashioned medicine, granny stuff. Now it's back in again.

ACSH:

YOU HAVE PREVIOUSLY MADE THE STATE-

MENT, "IN OTHER WORDS, I BELIEVE THAT OVEREMPHASIS ON CHEMICALS HAS DISTORTED OUR APPROACH TO THE ENVIRONMENTAL THEORY FOR MANY CANCERS."

HIGGINSON:

This statement obviously excluded discussion of point-source exposures such as occupation and medical drugs, which represent a different problem. However, the belief that the great burden of cancer of so far unknown cause is largely due to diffuse chemical pollution of food, water, and air, and can be controlled through identification and avoidance of one synthetic carcinogen only, has little support. Thus, studies of the vast number of compounds that are present in the general environment do not suggest that any individual compound is a predominant factor for most sites. The possibilities of guaranteeing prevention through such action are extraordinarily low. About 1500 compounds have been identified in alcoholic beverages and more than that in average municipal water. These include many animal carcinogens. It is impossible to evaluate the impact of each of these compounds on an individual basis. However, it may be possible to evaluate their impact on the total burden in man. When this is done, you will find that there is no real difference in terms of cancer between people served by polluted and non-polluted water, as in the case of arsenic in Taiwanese water. In Utah there is no difference in overall cancer incidence in Mormons in urban and rural areas in contrast to national differences in non-Mormons. Even where there is obvious evidence of pollution, e.g., as in the air of Los Angeles, evidence of a major impact on lung cancer in non-smokers remains to be proven. On the other hand, this does not imply that unnecessary pollution should be tolerated. No one wishes to drink unnecessarily dirty water or breathe sooty air. People have forgotten, however, that things have gotten a lot better. There have been vast improvements in London, and also in some U.S. cities. But if such pollution is not the cause of 70-80 percent of cancers in women and 40-50 percent of cancers in men, those of unknown origin, then what are the causes? At this point, the problem becomes completely different. Thus, while recognizing the difficulties of identifying specific factors which may have initiated a specific cancer, we now accept the possibility of modulating factors associated with diet and lifestyle, and their role on cancer mechanisms. The effect of diet on fetal life, infancy, and childhood, is only just beginning to be recognized. We know people vary widely in their ability to metabolize and modify certain foodstuffs, and further that the latter have a marked effect on the metabolism of cancer-producing agents. While the role of lifestyle does not represent a chemical or industrial carcinogen in the classical sense, as represented by occupational exposures or cigarette smoking, it does reflect a biochemical background. These comments don't mean that you shouldn't control pollution and waste disposal, etc. That's another question. But the point is, that concentration only on polluting factors is unlikely to permit control of a great portion of the cancer burden, and that a whole new field of research is opening up. ■

URL 03012

THE FOOD INDUSTRY AND NUTRITION

by Kathleen A. Meister

Many people who are interested in nutrition think that the food industry doesn't share this interest, and that food manufacturers are unresponsive to consumer needs in this area. This impression is false. The industry is very aware of the increasing public interest in nutrition, and virtually every company has made systematic efforts to provide consumers with nutrition information about its products. Many have gone far beyond this basic responsibility and have undertaken substantial nutrition-related activities that benefit the consumer. These include establishment of corporate nutrition policies and nutrition advisory boards, involvement in basic nutrition research, and publication of educational materials.

However, the food industry's involvement in nutrition also has a negative side. A company's main goal, of course, is to sell its products at a reasonable profit. As public interest in nutrition has become increasingly intense, it has provided opportunities for exploitation of this interest for marketing purposes. This has led to distortions of nutrition facts that can mislead and confuse consumers.

Nutrition Activities of Food Companies

Increasing numbers of packaged foods carry nutrition labelling, but even if a product doesn't have this kind of label, nutrition information is almost always available from the manufacturer. Most companies take consumer complaints, requests for information, and other inquiries seriously. For instance, Best Foods has a stated policy of responding to all consumer correspondence within 48 hours of receipt.

Most large food companies have developed corporate policy statements on nutrition, dealing with such topics as accuracy of nutrition information in advertising, support for nutrition research, and provision of nutrition information to consumers. These policies tend to be general and innocuous. Few deal with specific nutrition topics or take stands on controversial issues. The primary significance of these statements is that they indicate that the company realizes nutrition is important enough to demand an official corporate policy.



Today, nutrition commands this kind of attention even in firms that produce relatively limited lines of food products. For instance, a nutrition policy statement is currently being developed at Frito-Lay. Procter and Gamble, which sells only a few grocery products, has an informal (unpublished) nutrition policy, and maintains an active program of basic nutrition research.

In addition to forming a committee within the company to determine nutrition policy and guide research and development, some food manufacturers, such as Universal Foods and Kraft, have established advisory boards of outside experts to provide additional scientific input in nutrition matters. Best Foods established such a board more than forty years ago.

Food processors have worked closely with government agencies in nutrition research efforts ranging from the design of enrichment programs in the 1940s to the development of uniform nutrition labelling in the 1970s. Today, the larger food com-

panies have extensive nutrition research programs. Many research efforts are directly aimed at meeting consumer needs. For instance, at Oscar Mayer, the corporate nutrition task force is investigating ways to reduce or replace sodium in processed meats, while retaining acceptable product quality. This project was undertaken in response to expressed health professional and consumer concerns about sodium and hypertension.

Some segments of the food industry are involved in nutrition activities that go beyond the promotion or development of specific products. Numerous companies support and participate in the activities of professional organizations such as the National Nutrition Consortium and the Institute of Food Technologists. Trade organizations, such as the National Dairy Council, the Sugar Association, the Cereal Institute, and Grocery Manufacturers of America, publish nutrition information for

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professionals and consumers. Some individual companies have similar programs, of which the following are only a few examples.

Foremost Foods produces a high-quality quarterly publication entitled *The Professional Nutritionist*.

Kraft publishes an extensive line of booklets for consumers on topics such as food and nutrition terms, food selection, storage and preparation, and guidelines to good health.

General Mills publishes a monthly newsletter called *Contemporary Nutrition*. It is designed for health professionals and each article is written by an expert on the specific subject.

Nabisco has recorded a set of radio spots on nutrition, distributed them to stations throughout the country, and published them in a consumer brochure.

As part of a continuing public affairs program on food issues, General Foods recently took out a series of full-page ads in major newspapers, reprinting and explaining the federal government's Dietary Guidelines. Federal health officials praised these ads as "intellectually honest."

Nutrition Exploitation

Some manufacturers have capitalized on popular ideas about nutrition that don't coincide with scientific facts. For instance, popular wisdom condemns sugar, but scientific evidence implicates it in only one health problem, tooth decay, and even then only when consumed in a sticky form in between meals, not when consumed as part of a meal. Nevertheless, some companies exploit the lack of sugar in their products as a major selling point. A recent television commercial for Aunt Millie's spaghetti sauce based its entire pitch around the rather irrelevant fact that this brand of sauce contains no sugar, while a major competitor's product does.

Consumer attitudes may also influence product formulation. One yogurt manufacturer complained that the mention of sugar on the labels of his fruit-flavored yogurts was damaging to the products' image. He considered substituting honey, because it has a better image, even though he acknowledged that honey is merely sugar in another form.

Another form of exploitation has become so common that this entire newsletter could easily be devoted to listing examples. This, of course, is the extensive use of such terms as "all-natural,"

"organic," "no additives," and "no artificial anything" in food advertising and labelling. Many consumers believe that such products are of better quality and more nutritious than other products. In fact, there is little difference. Sometimes a "natural" product may even be of inferior quality if a preservative which would otherwise have lengthened its shelf life has been omitted. However, many people think that "natural" products are always better, and food manufacturers and advertisers reinforce this misconception.

Although the nutrition information presented in food company publications is almost invariably accurate, each manufacturer tends to emphasize the nutritional advantages of its products and ignores the disadvantages. Different companies may also present nutrition information in different ways, to favor their own products. Unfortunately, this may confuse consumers.

For example, informational booklets published by Oscar Mayer (producers of meat products) and Best Foods (manufacturers of peanut butter and many other packaged foods) both include tables listing the fat contents of a variety of foods. However, the Oscar Mayer table lists the *percentage of fat* in each food (bologna 30 percent, peanut butter 52 percent) while the Best Foods table lists the *percentage of calories from fat* (bologna 82 percent, peanut butter 74 percent). Both sets of figures are correct, and nutrition experts do not agree about which system more effectively conveys information about the fat content of foods. Although there is no overt deception here, most people would be very confused about the relative "fattiness" of bologna, peanut butter, and the other foods listed after reading both tables.

Addition of nutrients to specific food products has been an effective way of correcting some forms of malnutrition. However, indiscriminate fortification of food products, for the purpose of generating impressive figures to put on nutrition labels, does little to improve public health. Overfortification can encourage careless eating habits and, since some nutrients are toxic in excess amounts, it may even be directly harmful to health. Fortunately, many food manufacturers realize this. The nutrition policies of Kraft, Oscar Mayer, Kellogg, General Mills, and many other companies include statements that nutrient additions

will be made only when appropriate. However, it should also be noted that Kellogg and General Mills each produce one breakfast cereal (Most and Total, respectively) so highly fortified that it must be labelled as a *supplement* rather than a food. The suitability of these products is subject to question.

Selling Nutrition in the 1980s

It has been said many times in the past that "you can't sell nutrition." There is increasing evidence that this is no longer true. The Second (1980) *Woman's Day* Survey indicated that one out of two consumers uses nutrition labelling to compare food brands. According to a General Mills study, over 40 percent of consumers check the nutrient content of a product before buying it for the first time. A recent study by Arthur D. Little, Inc., concluded that public interest in the nutritional value and healthfulness of food is genuine and here to stay and predicted that products with a healthful image will sell well in the 1980s. Many recently introduced nutrition-oriented products and advertising campaigns have been successful. *The New York Times* has reported that increasingly large sums of money are being invested in the research, development, and advertising of nutrition by food companies in response to the growing recognition that nutrition sells.

An editorial column in the November 1980 issue of the trade journal, *Cereal Foods World*, pointed out that food manufacturers would have much to gain in terms of sales, credibility, and relations with government agencies if they regarded themselves as members of the "health care team." If food companies adopt this attitude toward the marketing of nutrition, both producers and consumers will benefit. However, if food manufacturers regard nutrition as merely the latest food fad to be exploited in product development and advertising, without regard to the real nutritional needs of the public, they will be failing to meet their responsibilities to their customers. ■

Kathleen Meister, M.S., is a research associate with ACSH.

UPL 03014

BOOK REVIEWS

TITLE: *Three Mile Island: The Hour-by-Hour Account of What Really Happened*
AUTHOR: Mark Stephens
PUBLISHER: Random House, New York, 1980
COST: \$11.95 (hardcover)
REVIEWER: Helen E. Kelly, M.P.H.

It was inevitable that the March 1979 incident at the Three Mile Island nuclear power plant would spawn a book such as Mark Stephens' *Three Mile Island*. There is no need to append a subtitle to insure that the reader will know the book's content. The title alone is testimony to the extent to which the incident at Three Mile Island is considered common knowledge.

Perhaps predictably, *Three Mile Island* purports to tell "what really happened during the accident at Three Mile Island." Disclaiming any particular bias, Mark Stephens presents his book as an anatomy of the Three Mile Island (TMI) incident, considering the actions of the utility officials, the government, and the press. Such an impartial dissection of the contributions of the press, government, and industry to the TMI incident and its impact on the American public is greatly needed. Public understanding of what occurred at TMI, both technically and politically, is limited. Much of the confusion has resulted from the contradictory versions of the incident issued by each of the primary players: press, utility, and government. If this book had given an honest critical appraisal of all three groups, it would have provided a great service to truth-seekers everywhere. As it is, Stephens subjects both utility and government to illuminating microscopic examination but leaves the media virtually untouched, rather like a well-feathered fowl beside two uncomfortably plucked comrades. The first inkling that the press will emerge unscathed appears in the prologue of the book where we learn that we will see "how the press tried to do its job." The phrasing of this fragment automatically exonerates the press from any unsavory role in the proceedings. After all, they were only nobly trying to do their job.

However, rather than harp on Stephens' failure to unflinchingly examine those who are, after all, his colleagues (Stephens is a journalist and professor of public affairs communication), it is worthwhile to consider his successes.

For a book which must necessarily deal with innumerable complicated technical processes and even more complicated political processes, *Three Mile Island* is quite readable. At its best, it is as compelling as any popular thriller. Stephens relies heavily on the personalities of the individuals involved in the TMI drama to add interest to the aspects of the incident which might otherwise be less than fascinating to the lay reader. While the technique is effective, Stephens overdoes it. Two hundred and forty names are listed in the index

of *Three Mile Island*, among them Attila the Hun, Groucho Marx, Teddy Roosevelt and, of course, Jane Fonda. The greatest difficulty of the reader is keeping track of this enormous cast of characters.

While Stephens' technical descriptions of what he always refers to as "the accident" are well and simply written, it will probably still be difficult for many readers to visualize the sequence of events in the Unit 2 reactor at Three Mile Island. Illustrations would have been helpful, especially if they included a simple step-by-step flow diagram.

Where Stephens really excels, however, is in his penetrating look at the actions and interactions of the technicians, scientists, and politicians who both dealt with and exacerbated the problems at Three Mile Island. *Three Mile Island* details the incredible lack of coordination between the local and federal governments, the Metropolitan Edison Utility Company, the Nuclear Regulatory Commission (NRC), and a plethora of other agencies which

became involved with TMI. It rapidly becomes evident that much of the blame for the needless psychological damage done to the residents of the TMI area must be laid at the feet of the NRC, an agency which the book portrays as suffering from a sort of organizational St. Vitus' dance.

Stephens says in his prologue that "the story of TMI is generally one of information—its presence, absence, and evasive nature." In a sense, the same may be said of his own book. The absence of a critical review of the vital role the press played in disseminating information and misinformation, and the failure to address the question of the media's responsibility in such events as TMI, prevent the unqualified recommendation of *Three Mile Island* as a fair and complete look at "what really happened." With this reservation, however, the book can be recommended for its thorough examination of the behavior of the utility and the government. After all, two out of three isn't bad.



TITLE: *Atomic Energy: A New Start*
AUTHOR: David E. Lilienthal
PUBLISHER: Harper & Row, New York, 1980
COST: \$8.95 (hardcover)
REVIEWER: Robert V. Kline, Ph.D.

TITLE: *Brain Allergies: The Psychonutrient Connection*
AUTHORS: William H. Philpott, M.D. and Dwight K. Kalita, Ph.D.
PUBLISHER: Keats Publishing, Inc., New Canaan, Connecticut, 1980
COST: \$15.00 (hardcover)
REVIEWER: Betsy McPherrin, M.S.

As founding director and chairman of the Tennessee Valley Authority (TVA) from 1933 to 1947 and the first chairman of the Atomic Energy Commission (AEC), David E. Lilienthal had a long and successful career in administration. In particular, he witnessed and nurtured the development of both the civilian and military nuclear energy programs. In doing so he had to cope with many technical and human difficulties generated by the wide spectrum of uses to which nuclear energy would be put. Civilian versus military control and government versus private development of nuclear energy are two of the thorny issues that had to be dealt with along the way. It is this wide perspective that Lilienthal shares with us in this book.

The TVA is cited as an organization that works well, being run by conscientious, responsive people who are trained on the job. The AEC on the other hand is seen as an organization traditionally devoted to promoting nuclear energy whatever the cost:

Our main objective in the past was to produce electricity with a cheap atom, the cheapest possible, one that would be economically and environmentally competitive with other forms of energy at a time when foreign oil was absurdly cheap and plentiful. This simple formula was shortsighted and dangerously wrong, as we have learned to our cost.

The author contends that, in the rush to implement nuclear energy, safety issues were given short shrift, and cites the Three Mile Island incident as one consequence of this. The anecdotal material brought to bear in support of this contention draws from the author's long experience and is the most interesting aspect of the book.

After quitting the AEC, Lilienthal became a vociferous critic of the agency. In about 1963 he attacked the agency's conflicting role as both promoter and regulator of nuclear energy. Partly as a result of this conflict of interests, the U. S. Congress eventually disbanded the AEC and formed the Nuclear Regulatory Commission.

The theme of the book, and presumably the reason why it was written, is contained in the following:

Our new objective must be to find a safer, "healthier" method of producing peaceful energy from the atom by a method that also minimizes or eliminates the present risk of furthering the spread of nuclear weapons. If it is also cheap, or relatively cheap, fine; but first it must be safe.

At this point nuclear energy, as an energy source, becomes a thing unto itself: "ordinary

standards are not good enough for nuclear power." Apparently because of the potential connection with nuclear weapons, the concern for safety becomes both an obsession and a conceptual trap. In at least ten other places in the book an appeal is made for someone to develop a fundamentally new method of obtaining energy from nuclear material, one that is inherently safe. Just how is not even a matter of speculation.

The author's desire to place nuclear energy in a category by itself is, however, a conceptual trap. No method of producing energy is without risk. The magnitude of the risk can only be reasonably determined by looking at an energy system in its entirety. Total risks incurred by each system must be compared. Coal-fired power plants incur risks associated with mining, transportation, pollution, waste and ash disposal, etc. Viewed in this way, nuclear energy may be inherently no more dangerous than any other; the problems are simply different.

The importance of energy in our society is not minimized. In a short summary of the energy options available today, the author acknowledges the necessary role that nuclear energy will have to play in the foreseeable future: "We cannot reject out of hand any possibility, including nuclear power. But it must be safe."

The importance of affordable energy is waved away, however, when it is said: "If it is cheap, or relatively cheap, fine." To be acceptable, any energy system must be both safe and produce energy that is economically competitive with other methods of production. A safe system producing expensive energy is of limited interest.

Parts of the book are entertaining, but overall the hindights are more interesting than the foresights. The author fails to recognize that existing nuclear power plants can be made safer for a relatively small increase in cost. The author's vague calling, in the book's title, for a fundamentally new approach to nuclear power production is, realistically, little more than wishful forecasting. ■

Robert Kline, Ph.D., is a Fellow of the Interdisciplinary Program on Health at Harvard University.

The authors of *Brain Allergies* seek "to acquaint the lay reader, as well as the concerned physician, with the concepts of orthomolecular medicine and human ecology." The book does, indeed, "acquaint," but the thoughtful reader will wish for greater documentation and less side-stepping of vital questions.

Human ecology, according to Philpott and Kalita, is the scientific examination of man's environment in order to discover sources of environmentally produced illness. They believe that up to 60 percent of the symptoms attributed to such mental illnesses as schizophrenia are actually "allergic" reactions to various environmental stimuli such as foods, inhalants, animals, etc. (The term "maladaptive reaction" is used, since the reactions are not necessarily allergies in the classical sense, wherein a specific "allergen" such as pollen elicits antibody production.) Philpott claims that of 250 consecutive patients, most had "maladaptive reactions," including 92 percent of the schizophrenics. One third of his patients reportedly react to common environmental chemicals (insecticides, preservatives, additives, chlorine in water, etc.).

Philpott, Kalita, and others hypothesize that maladaptive reactions result from "addiction" to certain foods or chemicals. When the addictive substance is used frequently, all is well. Maladaptive reactions occur in response to "chronic stress" such as an overload of the "allergen," harbored infection, or other physical and emotional stress.

Abnormalities in blood sugar level (diabetes and hypoglycemia), are said to be allergic responses to specific foods, which are not necessarily carbohydrates.

Philpott tests for such maladaptive substances by fasting patients for four days, then exposing them to the substance, whereupon susceptible individuals show an "immediate reaction with an allergic-like quality." For example, one patient responded to wheat with sneezing, laughing, and pacing, to black olives with a two-hour headache, and to dates with a running nose and "hard-to-please" attitude. (Classic allergists apparently refer to this as "presumptive evidence" of a cause-and-effect relationship, since the patients are aware they are being challenged with suspect foods.)

The "cure" for such addiction is what the authors call the "diversified rotation diet." Foods or food families that evoke responses are avoided for three months or more. After that, if a food is eaten infrequently, say once every four days, no symptoms are evoked. The testing and therapy appear similar to those used by conventional allergists.

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UJRL 03016

HEALTH WATCH

Contempt of Court

An ACSH member from Ohio sent us an article from the *Cleveland Plain Dealer* about some extraordinary goings-on in the juvenile courts of Licking County, Ohio. One of the judges there believes that hostility and aggression in children can be attributed to their consumption of certain foods, including milk, flour, chocolate, sugar, and gelatin, and applies these scientifically unfounded beliefs on the job. Juvenile offenders who come into his court are required to fill out a diet questionnaire, and if the results indicate that food "might be a factor in behavior," they are put on a restricted diet. According to the judge, "It's got to be cold turkey all the way."

We're getting accustomed to health hogwash, but it's disturbing to find out that in some places, it has the forces of law behind it.

Physicist's Rx for Herpes

A *News & Views* reader from Washington, D.C. provided another excellent addition to our hogwash file: an article from the magazine *Sexology Today* entitled "Controlling Herpes with Food."

Herpes type II is a virus that can cause painful, recurring outbreaks of blisters, mostly in the genital region. No cure for this sexually transmitted disease has been found, and the symptoms tend to come and go. These characteristics and the personal nature of the problem make it a perfect target for home remedies, folk "cures," and the kind of nutritional nonsense found in the magazine article. According to the magazine, herpes sufferers should avoid sugar, vitamin E, and fat, and increase their intake of vitamin C to levels of questionable safety. One should also eat more of the amino acid lysine and less of the amino acid arginine. What this means, in practical terms, is to avoid chocolate-covered peanuts, which apparently have an unfavorable lysine/arginine ratio, and can supposedly "precipitate recurrence of active herpes the next day."

Scientific evidence to support these menu suggestions is lacking. However, the article gives the impression that this information has a scientific basis because it is drawn from a public presentation by a university physicist. Of course, training in medicine or nutrition is not required for a degree in physics, and a lecture at an "alternate lifestyles convention" is a far cry from a publication in a peer-reviewed scientific journal. Unfortunately, it is unlikely that most readers of this magazine article appreciated these distinctions.

USDA Boss on Food Safety

In an interview published in the February issue of the Washington newsletter, *Nutrition Intelligence*, John Block, the new Secretary of Agriculture, was asked his opinion on the subject of using risk-benefit analysis to make food safety decisions. Secretary Block replied, "I think we almost have to move to something

like that, because there's risk in almost anything we do or eat... Still, a lot of these things we have to have. Vitamin D is an example. If you eat too much vitamin D, it's a carcinogen. But we have to have it."

Mr. Block's comments are an example of the new, more realistic approach to food safety issues that we've been hoping to see.

Rare Courage

We have noted before (see "Conspiracy of Silence?", *ACSH News & Views*, Volume 1, No. 2) that most magazines devote little attention to the hazards of cigarette smoking. It's a pleasure to be able to point out an exception to this rule. The December 1980 issue of the personality magazine *Modern People* featured a hard-hitting cover story on the dangers of cigarettes, entitled "How the Tobacco Companies Are Sending You to an Early Grave." In addition to presenting the medical evidence against smoking, the article captured readers' attention with pictures of celebrities, including John Wayne, Humphrey Bogart, Betty Grable, and Nat King Cole, who died of smoking-related diseases. The striking cover showed pictures of eight convicted murderers and a cigarette pack, with the caption "All of These Killers Are Dead or in Prison Except One." *Modern People* also ran a follow-up story in its next issue on how to quit smoking. Many readers of the first article were undoubtedly receptive to that kind of information.

Clear Vision at FDA

Some people fear that the new administration will threaten public health with its efforts to cut down on government regulation. We disagree. There are some truly necessary regulations which must be kept in effect, and we think that the administration realizes this. However, there is a real need to stop the overwhelming flow of unnecessary regulations, which create problems rather than solve them.

A good example of the latter occurred when an administrator at the Food and Drug Administration (FDA) had salt tablets used in the care of soft contact lenses taken off the market. The FDA decided that people couldn't be trusted to prepare their own solution for storing and cleaning their lenses. By taking away the tablets, FDA forced contact lens wearers to buy prepared salt solutions. Unfortunately, these solutions cost six times as much as the tablets, and they contain a preservative that can cause bothersome allergic reactions in some people. On the other hand, doctors have reported no problems with the salt tablets as long as they were used properly.

After receiving many complaints from the public, a House subcommittee conducted an investigation of this incident and concluded, quite reasonably, that there was no basis for withdrawing the salt tablets from the market. We certainly need regulatory agencies to pro-

(continued on page 11)

EDITORIAL:

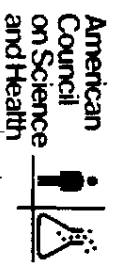
At the present time there is unprecedented interest in the subject of nutrition in this country. Our people, consumer advocate groups, health food devotees, voluntary health agencies, the United States government through its various departments and institutes, congressional committees, and the National Academy of Sciences are concerned about nutrition practices and policy. Why has this come about in the last decade? Possibly because Americans, since Vietnam, have become disillusioned with the conventional institutions of government, industry, medicine, and education, and have increasingly devoted their attention to self and self-entitlement. Since adequate food is clearly required for personal health, much attention has been centered on the value of foods.

Mythology of food is an ancient and recognized phenomenon and postulates that foods have powers of healing beyond their nutritional values. Because of the emotional and cultural values of foods, nutrition is subject to more political action than many other branches of natural science. Politics deals with the defense of the party (institution, political group, cult, or position) whereas science deals with the investigation of truth.

Why is nutritional science so susceptible to the intervention of politics? There are several reasons. First, nutrition is big business not only for the production of foods but also health foods. Second, food mythology fosters beliefs rather than understanding and leads to emotional investments in given nutritional concepts, i.e. cultism, whether the concept is scientifically valid or not. Third, the press plays a big role in nutrition education and individual food writers wield significant power in determining nutrition policy. Some journalists believe that because they write about nutrition they are, *de facto*, experts in the science. Many are consumer activists and naturopaths. Finally, nutrition programs get votes.

A prime example of politics in nutrition is the reception given to the recent report of the 15-member Food and Nutrition Board of the National Academy of Sciences on the relationship of diet to disease. "Toward Healthful Diets," released on May 28, 1980, summarized a critical scientific review of over 400 medical papers to determine what advice should be given to the American public about diet aimed at prevention of the chronic degenerative diseases. Using as its principal criterion that proof of benefit should be demonstrated for a public health measure before it is generally recommended to the public, the Board advised healthy Americans to: (1) eat a variety of foods to obtain each day's nutritional requirements, (2) eat moderately to maintain desired weight,

From
A B C D



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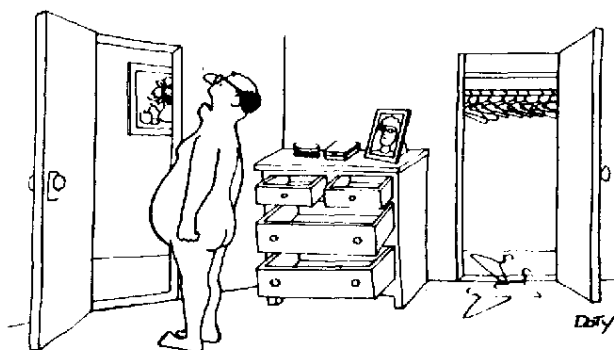
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The American Council on Science and Health (ACSH) is working to bring some *common sense* back to the evaluation of food additives, pesticides, and other aspects of our contemporary lifestyle.

Saccharin, for example, has been one recent focus of our attention. The Food and Drug Administration has recommended that this popular artificial sweetener be banned. **ACSH** analyzed all the information on the health effects of saccharin and concluded that there was no scientific evidence to ban it. And we made our findings known to the American consumer, the scientific community, the media, and our government representatives and regulators.

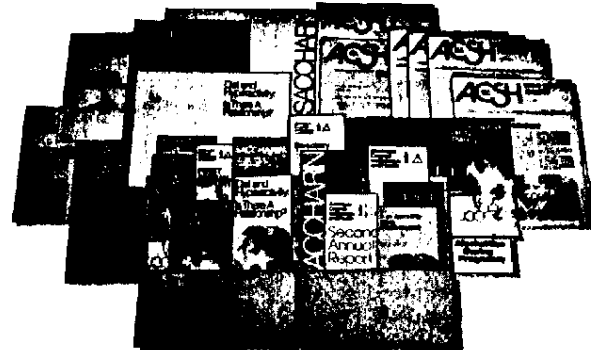
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"You mean they've banned everything?"

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The Science and Politics of Nutrition

(3) avoid alcohol, sugar, fats, and oils if one needs to lose weight or has a very sedentary occupation, (4) increase physical activity fitness, and (5) use salt in moderation.

Although these modest recommendations were supported by the American Medical Association and by a segment of the food industry, the report elicited a storm of criticism from the American Heart Association, consumer advocates, the government Departments of Agriculture and Health, and many journalists.

In its June 3, 1980 editorial entitled "A Confusing Diet of Fact," *The New York Times* stated, "The National Academy of Sciences is supposed to be an authoritative, impartial source of scientific advice to both the public and the government, the supreme court of science. But its latest report on healthful diets is so one-sided that it makes a dubious guide in national nutrition policies." Dr. Mark Hegsted, administrator, Human Nutrition Center of the USDA, said on July 31 that "the Food and Nutrition Board is irresponsible in not making a recommendation on dietary cholesterol." Although the American Heart Association admitted in a news conference on August 8 that "the scientific evidence is lacking that cholesterol-lowering will reduce or prevent heart attacks," it nonetheless endorsed its previous position, urging Americans to reduce total fat, saturated fat, and dietary cholesterol in the hope of preventing coronary heart disease. Representative Fred Richmond of the House Subcommittee on Domestic Marketing, Consumer Relations, and Nutrition stated on June 18 that he felt that the Food and Nutrition Board had overstepped its charter and violated its authority by putting forward a public policy advising the American people about what kind of diet to follow. Several consumer advocates made *ad hominem* attacks on Board members, alleging that their consultantships with segments of the food industry proved industry bias. All these were political arguments that did not deal with the scientific content of the report.

This furor illustrated the extent to which the field of nutrition is dominated by politics rather than by science. Vested interests took precedence over scientific criticism and the report was attacked in order to advance those interests. Most scientists would argue in general that if data are incomplete or unconvincing, as are the data relating diet modification to prevention of heart disease, then it is better to withhold final conclusions and particularly advice to the public until there is tangible proof of benefit. Intervention in susceptible populations with both diet and drugs to alter overall mortality rates from a variety of chronic diseases by changing serum

cholesterol levels has uniformly failed.

The data linking *dietary* cholesterol to cardiovascular disease are very weak. The intake of dietary cholesterol in the United States has not changed appreciably in 70 years and does not correlate with the rise in the incidence of coronary heart disease that occurred in this country between 1920 and 1963 nor with its fall from 1963 to the present time. Furthermore, in the U.S. no correlation has been made between any component of diet, including saturated fat and cholesterol intake, and the risk of coronary heart disease. In free-living populations it has been shown that wide-range altering of dietary cholesterol has little, if any, effect on serum cholesterol. Although LDL-cholesterol in plasma is a risk factor for coronary heart disease, the Board decided, in company with five other national expert committees from Canada, England, Australia, New Zealand, and Norway, that dietary cholesterol is not a risk factor for coronary heart disease.

It is my view that science will eventually triumph over politics in scientific disputes, although in the case of Galileo it took centuries. The Food and Nutrition Board report has stimulated considerable debate and dissent in professional circles in the past several months. Dr. Thomas James, in his 1980 presidential address to the American Heart Association (AHA) entitled "Sure Cures, Quick Fixes, and Easy Answers: A Cautionary Tale About Coronary Disease," said, "Today I want to share with you my growing concern about overpromise in coronary disease. My remarks center around the credibility of the AHA and medical science generally." He continued by making four main points in his address: (1) we should be more explicit, i.e. make full disclosures of the basis for public recommendations; (2) we should distinguish between risk reduction and true prevention for individuals; (3) we should be aware of the coercive power of public advice, i.e. in generating regulation, and (4) we should admit that we do not know the full effects of dietary restriction in childhood.

Atherosclerosis and its principal clinical expression, coronary heart disease, is a disease of unknown cause and is contributed to by many factors in addition to diet. Coronary heart disease is not a nutritional disease like rickets or pellagra. Only 50 percent of the risk of suffering a heart attack is accounted for by all the risk factors, which include family history of heart disease, obesity, diabetes, hypercholesterolemia (high plasma LDL-cholesterol), high blood pressure, cigarette smoking, and inactivity. Platelets, little cellular particles in the blood, play an important part in the initiation of the disease. The public must understand that the solution to the medical riddle of atherosclerosis is not for

politicians but for scientists to solve by careful investigations of true cause-and-effect relationships in the body. An entirely new strategy of prevention may be needed!

One hopeful development is that the mortality rate from coronary heart disease has been decreasing in our country over the past twenty years at the rate of 1-2 percent per year. The National Institutes of Health has concluded this positive result is not due to any single factor. Even when the slight changes in diet, serum cholesterol, smoking, blood pressure, and physical activity are summed, the result exceeds expectations. Further scientific research is needed to understand even the good things that are happening to the U.S. population.

Robert E. Olson, M.D., Ph.D.
St. Louis University School of Medicine

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MISLEADING MEGADOSES

by David B. Roll, Ph.D.

Although one expects to find the advocacy of megadoses of vitamins in the health cult literatures, it is disappointing to discover uncritical endorsement of this practice in literature directed at health professionals. Yet, such an article recently appeared in *American Pharmacy* (Vol. NS 19, No. 9, p.498, 1979), a publication of the American Pharmaceutical Association (APhA). One would hope that the editors of such a prestigious publication, aimed at health professionals having a minimum of five years of college education, would show more sophistication in their selection of articles or at the very least submit them for peer review prior to publication.

The fallacy of megadosage is well covered by Ron Deutsch in his excellent book *Realities of Nutrition* (Bull Publishing Co., Palo Alto, CA, 1976) in which he points out that, since mankind was successful in evolving on the food readily available, we would not expect to find large natural barriers preventing access to foods needed for health. The following table shows some of the recommendations made in the paper cited in *American Pharmacy*. Also included is the amount of food (in all cases an excellent source of the vitamins was used in the calculations) that would be required to obtain the quantity recommended.

Vitamin	Quantity Recommended	Food Needed to Obtain Quantity Recommended
E	840 IU	15.2 lb. of wheat germ
C	5280 mg	18.9 lb. of oranges
B ₁	52 mg	19.8 lb. of roast pork
B ₂	52 mg	68.0 lb. of whole milk
Niacinamide	32 mg	3.7 lb. of peanuts

Keeping in mind that the energy requirement for a 23-year-old male is 2700 calories (2000 calories for a female), it is interesting to note the approximate number of calories that would be found in these quantities of food, namely, wheat germ (25,000 calories); oranges (4800 calories); pork (12,400 calories); milk (20,400 calories); peanuts (9500 calories).

Such quantities of food are not compatible with life, and make the advocacy of such high quantities of vitamins suspect at best. Is it not reasonable to ask why, after our reasonably successful evolution, it is now necessary to rely on megadoses of nutrients that we have not required in the past?

Among the alleged benefits cited in the article for such a regimen are "better" health and metabolism and more energy, with the evidence for such claims being largely anecdotal. When the quantities of food noted are considered, one might add to the list massive obesity. Obviously this would not lead to better health even if we could tolerate such tremendous quantities of food.

It is our hope that APhA will reevaluate its editorial policies with the aim of insuring that scientific inquiry and not just personal opinions and anecdotes is retained as the foundation upon which all legitimate health professions are based.

Dr. Roll is Professor of Medicinal Chemistry at the College of Pharmacy, University of Utah.



Book Review

(continued from page 7)

Philpott believes that "super" nutrition, via intravenous and oral megadoses of individual nutrients, reduces the incidence and severity of maladaptive reactions. This is the "orthomolecular" part of the treatment. For example, a woman who was maladaptive to wheat reportedly had no symptoms when wheat was eaten after receiving intravenously 7.5 grams of Vitamin C (125 times the Recommended Dietary Allowance) and one gram each of pyridoxine and niacin (500 and 77 times the RDA, respectively).

Book chapters describe "the healing powers of Vitamin C," "the perils of toximolecular medicine," and a theory of "the disease process."

The authors' observations (bizarre case histories appear throughout the book) are fascinating, but they are merely observations. Philpott and Kalita recognize "the need for long-term, intense—and necessarily expensive—scientific evaluations of clinical orthomolecular-ecologic medicine as applied to chronic degenerative diseases." They are less credible when they state that "without double blind studies, we have believable evidence of a cause-and-effect relationship," and when they recommend the rotation diet to everyone because "Americans are eating... foods with a frequency that is beyond our biological capability to handle in a healthy way." If there are controlled studies which support the latter statement, they are not mentioned in the text.

Philpott delves little into mechanisms which might explain his observations, stating that "even when there is a demonstrated evidence of symptom production on exposure to a food or chemical, we still do not know why," and postulating the causes as "immunological, metabolic errors, enzyme deficiencies, nutrient deficiencies, toxins, infections, or something else."

They say you can't argue with success, but it is not clear that the orthomolecular-ecologic approach has been successful. All of the case histories have happy endings, but there is no mention of failures or long-term follow-up, and the authors claim no specific rate of success. The rotation diets are potentially safe and nutritious, but many of the specific foods allowed each day are seasonal, prohibitively expensive, or otherwise unavailable in most parts of the United States. Different cooking oils, herbs and spices, and sweeteners must be used on each day of a four- or seven-day cycle. Most prepared foods, even those as basic as bread and cereals, are unacceptable. The alternative is "cooking from scratch" (using special recipes) or doing without. How many patients could adhere to such a stringent and time-consuming diet?

The book aroused this reader's interest in allergy and the brain-nutrient connection. However, I would not recommend it to people who don't know the difference between a study and a story.

Betsy McPherrin, M.S., is a nutritionist and free-lance writer.

Health Watch

(continued from page 8)

fect us from hazards that are beyond our control. But we don't need them to protect us from ourselves, on the insulting assumption that we are incapable of reading and following directions.

TV Touts Feingold

We were deeply disturbed by a recent segment of the syndicated TV show *PM Magazine* entitled "Diet for Problem Kids." The program consisted of interviews with children who were on the Feingold diet and with their parents (members of a New England area Feingold Association), who were very enthusiastic about the diet's effects on their children. The show not only lacked scientific balance, it lacked science, period. No physician or other professional with expertise in hyperactivity was interviewed. Viewers were never even told that the diet had been tested scientifically, let alone that it had been found to be ineffective. The controversial nature of the Feingold regimen was never mentioned.

This kind of careless approach to a serious problem that deeply troubles many families can only be described as irresponsible journalism.

Caffeine Confusion

ACSH found itself in the midst of confusion last month when our report on caffeine, which concluded that this food and drug component is not a threat to human health, was released just after the publication of a Harvard School of Public Health study suggesting a statistical link between coffee consumption and pancreatic cancer.

Actually, there is no contradiction between the two studies. Our report focused specifically on caffeine, a compound found in tea, cocoa, some soft drinks, and some medications as well as in coffee. The Harvard study focused specifically on coffee, a complex mixture of more than three hundred substances, one of which is caffeine.

The Harvard study was preliminary, as its authors pointed out. It raised a hypothesis that is worthy of further study, but it certainly did not establish a definite link between any coffee component and pancreatic cancer. However, if such a link is established in the future, it is highly unlikely that caffeine will be the implicated substance. In the Harvard study, pancreatic cancer risk was not elevated in tea drinkers, and tea contains substantial amounts of caffeine.

—E.M.W.

PROFILE

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We think the ACSH scientists are a unique and interesting group of people that you, our readers, would enjoy getting to know. To help you become acquainted, each issue of *NEWS AND VIEWS* will feature a biographical PROFILE of one ACSH Director or Advisor.

Recent Publications... "Silent nucleotide substitutions and the molecular evolutionary clock," *Science*, 1980; "Silent nucleotide substitutions during evolution," *Naturwissenschaften*, 1980.

Research... "Molecular evolution and the sequences of DNA molecules."

Turning Point... "The most recent turning point took place in December 1961 at a meeting of the Enzyme Club at Rockefeller University when Dr. Severo Ochoa gave a talk on 'Synthetic polynucleotides and the amino acid code.' I promptly decided to stop what I was doing and enter this new field. For the same reason, I resigned from my job about a year later to organize a new research group at the University of California, Berkeley. It led me into molecular evolution."

Personal Health Code... "I stopped all use of tobacco in 1953 which was easy because I smoked only one cigarette a day. I gave up coffee about ten years ago, not because of any particular health concern, but because it was a nuisance that 'did nothing for me.' I have no special dietary fads. My food list for heavy exercise on high mountain backpacking trips includes one half pound of sugar per day, starting in 1938. I have no tendency to overeat, apparently, because my weight is approximately normal without 'dieting.' I don't regularly consume either alcohol or vitamin pills. I have a very active family life with my wife, three children, and five grandchildren."

Major public health concerns Americans face... "Cigarette smoking, overeating, quackery, misinformation, and alcoholism."

What do you think will be the most important public health accomplishments in the coming years? "In the coming years, new discoveries in immunology have great potential and so has the development of recombinant DNA technology—not for 'changing individuals,' but for more general applications."

Why did you join the American Council? "I helped start the Council because of the great need for authentic information on matters involving public health, especially nutrition. The need arose from the tremendous amount of misinformation by 'special interest groups,' such as consumerists and environmentalists who start scare stories as a way of life."

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ENVIRONMENTAL UPDATE

Drugs: The controversy over the benefits and risks of estrogen therapy in preventing osteoporosis in postmenopausal women continued unabated with a report in the February issue of the *American Journal of Public Health*. From their study of women enrolled in the Kaiser-Permanent Medical Care Program in Portland, Oregon, authors Johnson and Specht concluded that estrogen replacement therapy reduces the risk of hip fractures. They acknowledged, however, that the small number of study cases limits the strength of their conclusion and that the protective effect among hysterectomized women was smaller than that for the entire study group. Hysterectomized women generally receive greater exposure to exogenous estrogen and would presumably benefit the most from its protective action.

Hip fractures due to osteoporosis, a process of bone thinning resulting from calcium loss, are ten times more frequent in females than males. Although osteoporosis occurs in both males and females beginning around age 35, the rate of bone loss increases significantly in some females after menopause. This acceleration is presumed to be a function of the decrease in natural estrogen that accompanies menopause. However, the exact process by which estrogen influences bone density is not known. To further complicate matters, there are numerous other factors, including insufficient dietary intake of calcium and vitamin D, cigarette smoking, and inactivity which accelerate bone loss in postmenopausal women.

The real controversy, though, lies in the trade-off between estrogen therapy's preventive benefits and its risks of causing endometrial cancer. Epidemiological studies conducted since 1975 have shown an association between long-term (more than 2 years) estrogen use and this form of uterine cancer. Yet among elderly women, endometrial cancer results in far fewer deaths (2700) than those attributed to hip fractures (15,000). Many clinicians advocate prophylactic long-term estrogen therapy for most women who have reached menopause. Even the Food and Drug Administration, through its Endocrine-Metabolic Advisory Committee, has ruled that "estrogens are effective in preventing postmenopausal bone loss and the risks are acceptable."

Many questions about estrogen use to prevent bone fractures remain unanswered. While it is clear that estrogen therapy is an aid in reducing bone loss, it has not been conclusively established that this treatment prevents fractures. The lowest effective dose, minimum duration of treatment, and perhaps most important, a well-defined population at risk are still unknown. Thus, as with the

cholesterol-heart disease controversy, it may be premature to advocate long-term estrogen therapy for most women without more evidence of benefit.

Lifestyle: With the publication of an epidemiological study in the *New England Journal of Medicine* (304(13):745, March 26, 1981), another of life's simple pleasures joins the growing list of cancer hazards. This time it's snuff, a finely ground or powdered tobacco used by many to get "that real tobacco taste."

In a comparison of drinking, cigarette smoking, and snuff dipping habits between a group of North Carolina women with oral and pharyngeal cancer and a control group, researchers found a 4-fold increase in cancer risk associated with snuff dipping in white nonsmokers. Among women using snuff for more than 50 years, the risk for cancer of the gums and oral mucous membranes increased almost 50-fold. A dose-related increase in oral cancer risk was also noted for those who smoked but did not use snuff, and for those who smoked and drank only. White women had a greater increase in cancer risk than black women, apparently because they used snuff in greater amounts over a longer period of years.

The authors identified N-nitrosornicotine (NNN) as the prime suspect responsible for oral cancer. NNN has tumor initiating properties in laboratory animals and is found in tobacco smoke condensate, chewing tobacco, and snuff. It is formed by bacterial or enzyme action on tobacco during curing and from the mixing of snuff with salivary nitrites.

The original hypothesis linking snuff dipping with oral cancer stems from the geographical distribution of oral cancer deaths generated by the National Cancer Institute's *Cancer Atlas*. Male deaths from this type of cancer are concentrated in the Northeast and are generally thought to result from the combination of cigarette smoking and alcohol use. In contrast, female oral cancer deaths are concentrated in the South, particularly North Carolina, Georgia, and Alabama. This new study suggests that as much as 31 percent of oral cancer in North Carolina is attributable to snuff dipping alone.

The researchers noted that total production of smokeless tobacco products in the U.S. rose from 98 million pounds in 1971 to an estimated 134 million pounds in 1980, with a 3-fold increase in finely cut tobaccos. They expressed concern about the heavy advertising campaigns by the tobacco industry and reports in the medical literature recommending these tobacco products as substitutes for cigarettes. We wholeheartedly concur with the authors' recommendations to educate the public about this hazard. The only safe tobacco product is the one that is not consumed.

Pesticides: Spring is here and with it comes the annual plague of gypsy moths in the Northeast. The voracious larvae of this insect pest defoliated more than 400,000 acres of park and woodlands in New Jersey alone last year and are expected to cause record damage again this year. But despite the availability of an inexpensive and safe pesticide, carbaryl (more popularly known by Union Carbide's trade name, Sevin), many communities are apparently opting for the moths.

Last year we reported that aerial spraying of Sevin was discontinued in many areas because of an alleged relationship with birth defects. Based on this public concern, the Environmental Protection Agency reevaluated the literature on carbaryl and human health. It concluded that there is no evidence that use of this pesticide poses any health risks to humans. Unfortunately, this decision and others by various state environmental agencies did not satisfy carbaryl's critics, and the debate continues.

In our own community of Summit, New Jersey, Sevin has been accused of "a litany of horrors" including Reye's syndrome, birth defects, miscarriages, lowered sperm counts, liver disorders, and "a personal testimony of Sevin-induced blindness." The city council, which approved the use of Sevin, also stands accused of disregarding the rights and health of pregnant women and opting for a "quick fix" because of Sevin's undisputed cost-effectiveness.

If the pragmatic consequences of this fervid emotionalism were not so serious, there would be a great tendency to shake one's head in disbelief. But there is a disturbing schizophrenia towards science that is clearly obvious in this debate. On the one hand, anti-pesticide activists are more than willing to quote vague, allegedly scientific sources which support their contentions. However, more reasoned scientific opinions not in accord with their own are regarded as profit-motivated or "inconclusive." As has been stated many times, Americans today seem willing to accept any opinion of our technological society, as long as it is bad.

—T.S.

URL 03023

The DDT Debate

(continued from page 1)

of the incredible effectiveness of DDT in reducing the incidence of malaria can be seen in India, where ten years of insecticide use reduced the malaria death rate from 750,000 to only 1500. Even more dramatic was the case of Ceylon. With the use of DDT, malaria incidence declined from 2.8 million cases in 1946 to 110 cases in 1961, when the battle was considered won and spraying was abandoned. Seven years later, malaria incidence in Ceylon was back up to 2.5 million, and DDT spraying had to be reinstated.

The final reason that DDT enjoyed such popularity as a pesticide was the fact that it combined high toxicity for insects with low toxicity for other organisms, including man, a fact which may well seem amazing in light of the infamous reputation which this chemical was ultimately to have with the lay public. Thousands of individuals, military and civilian, had their clothing dusted with 10 percent DDT powder while they wore it, without ill effect. More pertinent to the safety issue was the absence of any DDT-related fatality or chronic disease among individuals employed as DDT sprayers in anti-malaria programs, a group estimated at one time as consisting of 130,000 men annually. Nor was any toxic effect noted in the 600 million to one billion people who lived in repeatedly sprayed dwellings. Poisoning with DDT was a rarity, and the only documented instances were the result of massive accidental (and sometimes suicidal) ingestion of the insecticide.

However, despite this generally clean bill of health, DDT use was not completely problem free. For one thing, certain insect strains began to develop resistance to DDT. By 1969, insect resistance to DDT necessitated the use of alternative insecticides in 1 percent of the areas where DDT had originally been used for disease eradication. Of course, it should be remembered that the problem of resistance was not peculiar to DDT, and has been shown to occur with repeated use of any chemical. The occurrence of resistance in some insect species, though disturbing, cannot be considered a rationale for banning a chemical, just as few would suggest discontinuing the general use of penicillin due to the emergence of several penicillin-resistant strains of bacteria.

The greatest problem associated with DDT, however, was that, in a few instances, enthusiastic use became enthusiastic overuse, primarily in the area of agriculture. "If some is good, more is better" was the rationale of some farmers. In addition, whether by accident or carelessness, a few incidents occurred in which concentrated pesticides found their way into lakes and streams. While DDT was not specifically involved in all of these mishaps, its reputation with the public nevertheless suffered from guilt by association.

Proper and responsible application and disposal of DDT were the rule rather than the



exception. Even the increased applications of DDT to cropland, considered damning evidence by those opposed to the pesticide, were sometimes a legitimate, and accepted, response to the development of insect resistance. However, the incidents of carelessness and misuse, both real and exaggerated, inevitably provided ammunition for individuals opposed to DDT use, and were often luridly portrayed to the lay public.

It was this perceived pesticide abuse which helped Rachel Carson's *Silent Spring* to gain acceptance. Considering how effectively this book aided the environmental movement, perhaps a more accurate title would have been "Silent Springboard." The infant environmental movement saw its opportunity when *Silent Spring* was published in 1962, and, by riding the wave of interest and concern generated by Carson's book, gained a position of considerable prominence and power in a relatively short period. It is unknown whether Carson herself would have supported the call for a total ban on DDT around which the environmentalists rallied in the late 1960s; Rachel Carson died in 1964. While *Silent Spring* is certainly hard on DDT, often inaccurately so, it is even harder on certain other pesticides which, it states, make DDT "seem by comparison almost harmless." Ironically, though *Silent Spring* never specifically advocates a ban on DDT or any other pesticide, the Audubon Society's Rachel Carson Memorial Fund was used to support one of the first legal suits for a ban on DDT use.

By the late 1960s, the DDT ban crusade was in full swing, led primarily by the fledgling Environmental Defense Fund (EDF). The popularity of the anti-DDT movement led a 1970 *Nature* editorial to quip, "In the last few months resistance to insecticides has been growing almost faster among people than insects." In 1969, Michigan was the first state to actually ban the chemical, followed by Wisconsin, Arizona, and California. It was in 1969, too, that the EDF, Sierra Club, National

Audubon Society, and a Michigan environmental group petitioned then Secretary of Agriculture Clifford Hardin to ban DDT, alleging it to be a carcinogen. A Commission on Pesticides and Their Relationship to Environmental Health, called the Mark Commission, was appointed by the Secretary of Health, Education, and Welfare in the same year. On the basis of the recommendations of that commission, the Agriculture Secretary announced a plan for phasing out the use of DDT by December 31, 1970, with the exception of uses essential to protection of public health and welfare. Under this ban, the use of DDT in health-related mosquito control programs and on certain crops, such as cotton, continued to be permitted.

It might be helpful to pause here and briefly describe the basis for opposition to continued use of DDT. The previously mentioned persistence of the insecticide became a thread of fear woven through many other concerns about DDT. While DDT's lengthy residual life was in itself harmless, it was the idea of this persistence linked to the claims of harm to the environment and human beings that generated the real hysteria. It was generally acknowledged that DDT was present throughout the world environment, although this is true for other compounds as well. Small concentrations of DDT were found to be present in the U.S. population, but, according to the Mark Commission's report, "no reliable study has revealed a causal association between these residues and human disease."

At first, the main concern about DDT revolved around some studies suggesting that it was responsible for causing thin eggshells and, therefore, declining populations of certain bird species such as the brown pelican. Even now there is no scientific consensus as to the validity of this claimed effect; opinions vary on the adequacy of the studies cited as evidence. (Other environmental pollutants, such as PCBs and mercury, may have been responsible for many of the effects.) However,

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The DDT Debate

(continued from preceding page)

this point was probably not the major source of conflict. Nor was the fact that, at some concentrations, DDT is toxic to many crustaceans and fish. Had the environmentalists concentrated only on these dangers to wildlife, there probably would have been far fewer fireworks. But as the movement against DDT gained momentum, other more controversial and frightening hazardous effects were added to the list of DDT's alleged sins. Foremost among these was the assertion that DDT was a carcinogen and posed a substantial threat to human health. DDT does cause liver tumors in mice fed large quantities, but there was and is no evidence that DDT causes cancer in humans, even among those individuals occupationally exposed to very high doses over long periods.

The ban on DDT that was recommended by the Mark Commission was based, as was stated in the Commission report, more on "suspicion of danger" than on proof. In exempting certain essential uses of DDT from the ban, the commission was careful to note that "the current evidence is not sufficient to justify unqualified banning of the insecticide."

The partial ban of DDT, extensive though it was, did not satisfy the environmental groups, who subsequently pressed the newly formed Environmental Protection Agency (EPA) to cancel the remaining registered uses of DDT. Such an action would amount to a total ban on the use and sale of DDT, and would effectively eliminate DDT use worldwide.

It is worth noting that, though the incidents of pesticide overuse which motivated the anti-DDT crusade occurred solely in developed nations such as the U.S., the real hardship of a total DDT ban would fall on poor and starving Third World countries where human existence

is more fragile than thin pelican eggshell. The same economic considerations that made DDT so appealing, and essential, for use in developing nations tended to militate against the wasteful overuse of the chemical by those poorer countries, whether in agriculture or mosquito control campaigns. In fact, the use of DDT for malaria control entails almost no environmental contamination, as spraying is restricted to the inner surfaces of dwellings. In pushing for a total DDT ban then, American environmental elitists were essentially pursuing a course which would punish developing nations for the occasional pesticide excesses of the United States. Time and again the World Health Organization stated that a total ban on DDT would mean the demise of programs against insect-borne disease in Third World nations, and the death of millions of people.

It was this push for a total ban that created the real controversy. In 1971 a hearing was scheduled so that each side could present its case. It is revealing that, while EPA was meant to decide the question of the ban on the basis of the recommendations of the hearing examiner, EPA ultimately participated in the hearings on the anti-DDT side, along with the EDF and conservation groups.

In April of 1972 the hearing examiner, Edmund Sweeney, recommended to EPA that no more extensive ban of DDT was necessary or desirable, based on the evidence presented at the hearings. Yet less than two months later, on June 14, 1972, then Administrator of the EPA William Ruckelshaus banned all of the remaining uses of DDT with the exception of uses related to essential public health purposes. This ban did not affect the sale of DDT to developing nations.

Why Ruckelshaus ignored Sweeney's recommendations is not clear, but his action may have stemmed from a desire to establish the authority of the infant EPA through some muscle flexing. Ruckelshaus' motive was especially perplexing to those who remembered his stated position on DDT two years previous:

DDT is not endangering the public health and has an amazing and exemplary record of safe use. DDT, when properly used at recommended concentrations, does not cause a toxic response in man or other mammals and is not harmful. The carcinogenic claims regarding DDT are unproved speculation.

By making an example of DDT, Ruckelshaus may have hoped to give warning to various environmental bad boys that the new agency meant business, while simultaneously garnering brownie points from environmentalists. Regardless of the intent of the move, it set a precedent for caprice at the EPA which has cropped up in later actions of the agency.

By now, DDT and the furor that surrounded the ban have been largely forgotten, but the reputation of DDT as pariah of the insecticides seems as persistent as the chemical itself. As recently as last August, a magazine article accused U.S. chemical companies of exporting cancer in the form of DDT, thus giving new life to that tired old sophistry.

At the time of the DDT ban, much was made of the need for more reliable research, particularly on the human health effects of DDT exposure. However, in a classic example of what happens when cautionary bans are instituted pending more data, studies on DDT waned following the ban. *Ex post facto* research rarely excites much interest or research grant funding.

In retrospect, it is difficult to say whether the ban on DDT was harmful. Other pesticides were available, and relatively affordable, in this country, and the continued availability of DDT for export insured the maintenance of vital food and public health programs in developing nations. On the other hand, misconceptions about the alleged hazards of DDT were also effectively exported to Third World countries, and may have discouraged truly essential uses of the pesticide.

But however uncertain the effects of the ban itself, the process of the debate was disastrous. The DDT conflict set a pattern for environmental decisions based less on scientific evaluation of risk than on hysteronics, mud-slinging, and hyperbole. The rigid dichotomizing of issues and the enshrinement of The Cause are by now honored traditions, stemming from the format of that prototypic contest, the DDT debate. ■

Helen Kelly, M.P.H., is a research associate with ACSH.

ZIGGY



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Tom Wilson

LETTERS TO THE EDITOR

March 26, 1981

Dear Editor:

I am writing to you about the article by Ruth B. Schwartz entitled "Callifano's Curious Cancer Estimates" that appeared in the November/December issue last year of *ACSH News & Views*. I object most strongly to being associated with the quantitative estimates that appeared in what Schwartz calls the "estimates paper." If she had telephoned me in France, she would have discovered that I was not a member of the group which formed in 1977 to look at occupational factors, and which "worked frantically in the summer of 1978 to prepare testimony for OSHA." I arrived in the United States in late August 1978 to spend a year at the NCI (National Cancer Institute) on sabbatical leave from my home institute, the International Agency for Research on Cancer.

Soon after my arrival I was shown a draft of the paper. Since the paper made some useful points, although the quantitative estimates were clearly absurd, and since, like most of the others named by Schwartz, I was under the impression that major revision, to which I could contribute, was foreseen, I volunteered an appendix giving the epidemiological and statistical rationale for some statements in the report. The next I knew, again like most of the others, was that the document had been widely released, following a statement by Callifano, with my name attached as contributing the appendix. I have said consistently, since my first contact with the article, that the numerical estimates and the methods used for deriving them were untenable. The wide publicity the document has been given, and the uses to which it has been put by other

agencies, has been harmful to the science of epidemiology. My paper with Dr. Brown in the *JNCI [Journal of the NCI]*, "Multi-stage models and the primary prevention of cancer," has nothing to do with the estimates paper, and I certainly do not regard it as a revision of the appendix. The appendix simply used some of the ideas I was developing at the time, but a careful reading of the *JNCI* paper would have shown that the situation is much more complex than the estimates paper indicates.

Yours sincerely,

N. E. Day, Ph.D.
Head, Biostatistics Programme
Division of Epidemiology and Biostatistics
International Agency for Research on Cancer
Lyon, France

Editor's Note:

We sincerely regret that we did not call Dr. Day in France for his view of the "Estimates" paper, which agrees with ACSH's. It is unfortunate that he did not refuse to permit the use of his name in any connection with "Estimates," as Dr. Brown did.

Dr. Schneiderman suggested that the JNCI article, "Multistage Models and Cancer Prevention," was a revision of the "Estimates" Appendix. The ACSH article points out how difficult it would be to recognize that JNCI report as such a "revision."

March 31, 1981

Dear Editor:

I have just read "The Pitfalls of Shortcut Science" in the January/February 1981 *ACSH News & Views*. It is a most timely piece. We need all the support we can get in the efforts to get the regulatory agencies to act only on the basis of reasonably valid scientific and technical data. The advocates of a riskless society have left us a sad legacy in the general cynicism with which the American public now views governmental regulatory actions, particularly in the public health area. We can only hope that the pendulum reached the extreme of its swing with the type of examples cited in your article and that we may now see the reemergence of reason and thorough scientific studies to replace the unfounded allegations and scary scenarios as a basis for governmental action.

Keep up the good work.

Sincerely,

Robert K. Best
Deputy Director
Pacific Legal Foundation
Sacramento, California

ACSH wants to know your opinions and concerns on health and environmental issues. We welcome letters to the editor and other contributions to the newsletter. Please send them to the American Council on Science and Health, 1995 Broadway, New York, New York 10023.

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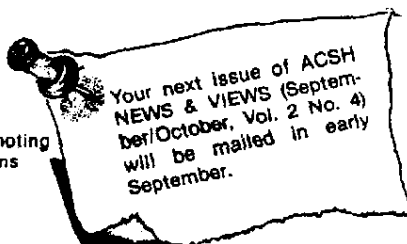
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THE SCIENCE OF THE POSSIBLE

Paul B. Weisz

It correlates

I began my days in research as a physicist. I was studying cosmic radiation a few years after Professor Victor Hess undertook balloon flights, during which he carried sensitive radiation detectors into the upper atmosphere. He expected the radiation level from natural terrestrial radioactive sources to decrease as he rose from the earth. Instead, the intensity climbed. In 1936, Hess received the Nobel prize in physics for the discovery of cosmic radiation. Suddenly we scientists became aware of a source of radiation bombarding us constantly with energies ranging to multiples of BeVs to GeVs (10^9 to 10^{12} eV) or more, which were capable of penetrating many meters of solid matter. It was an exciting time.

Had the radiation fear psychology of our decade prevailed then, one of the immediate questions raised would have been: "How much harm does it do to us?" Instead, the psychology of inquiry was a happier one. There was curiosity as to whether such radiation exposure—provided to us by the creator, after all—had a beneficial effect. In 1938, we heard of experiments done in Austria: Rabbits were raised deep down in a mine shaft and shielded by additional lead. Statistical analysis of the results indicated a significant *reduction* in life expectancy. Ergo, here was correlative proof: less radiation, less life.

A little while later we heard the sequel to the story: Autopsies indicated that a significant number of rabbits had suffered from lead poisoning. The correlation between mortality and radiation intensity was upset by another parameter.

It is hard enough to establish a clean cause-consequence relationship in a "controlled" laboratory experiment. It is

immensely more difficult outside the laboratory, in a world of innumerable parameters. Often we are not even aware of which other variables may be operative and which may have causative effects on the relationship under investigation. Nevertheless, all too often correlations have been used to point a finger at suspects that might add increments of mortality to the human race.

Do small changes in environmental temperature affect mortality? Well, to answer this question, why not begin with the customary correlative investigations? There are ample vital statistical data of annual mortality rates (1) classified by state, major cities, causes of death, etc. Also, we can find ample meteorological data on temperatures for various locations (2). Thus, there was little difficulty cross-plotting mortality rates vs. some representative average temperature. (We chose the average daily temperature in January averaged for various locations for each state.)

The data for deaths due to cancer or to cerebrovascular complications (Figures 1 and 2) represent classical shotgun patterns. There is no significant correlation. However, the data on pulmonary involvements (pneumonia and flu) (Figure 3), reveal a definite correlation. A computer regression (or a sensible visual estimate) provides a slope of 10 to 13 more casualties per million population per year for every degree Fahrenheit drop in temperature.

It seems reasonable, furthermore, that there is a link between pneumonia and flu and temperature exposure. Interestingly, our correlative result stands reinforced by an incidental observation reported in a book-length study (3) intended to examine correlations between air pollution and mortality. For a study on Chicago, it says, [The effect of the]

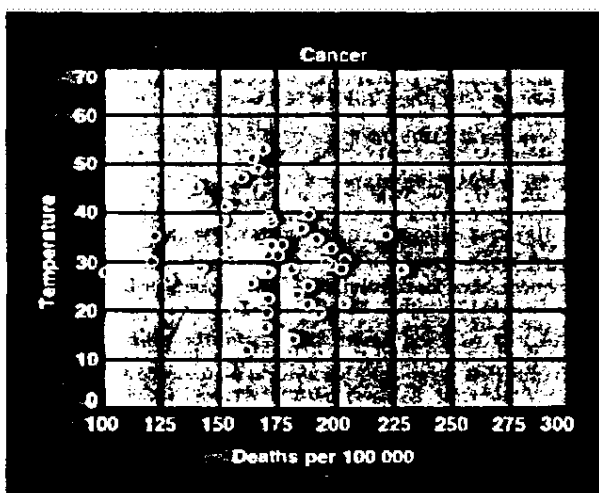


Figure 1. U. S. mortality due to cancer, plotted against average January temperature of U.S. localities

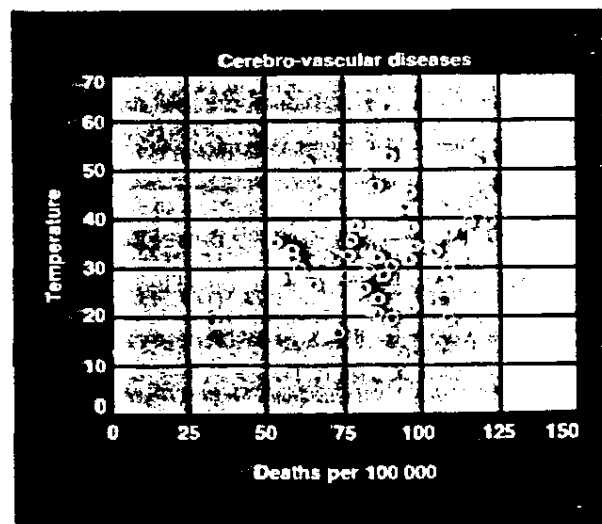


Figure 2. U.S. mortality due to cerebrovascular conditions

"mean temperature was statistically significant (indicating that, as the daily mean temperature increased, the daily number of deaths decreased)."

With only a little arithmetic, and with no more irresponsibility than has been practiced in reporting some other correlative observations, we could state that every measure that lowers the environmental temperature by one degree "may result in some 2000 to 2600 more deaths per year in the U.S. population."

If such a conclusion were followed up as seriously as has been the case in arguments about chemicals or radiation, there could develop a vast set of new issues, actions, arguments, lawsuits, expenses, incomes, heartaches, etc., for plaintiffs, defendants, lawyers, politicians, and people. The defendants might conceivably include the head-of-household who moved his or her family from Florida to Oregon in a job transfer, or the president, who asked us to turn down our thermostats a few degrees.

Many parameters can interfere, directly or indirectly, with a correlation, including our temperature study. With some imagination, we can think of many examples: One type of ethnic background may have more sensitivity to pulmonary implications than another. Perhaps Scandinavian ancestry (prevalent in cooler Minnesota) is more prone than Latin ancestry (in warm Florida). Or, perhaps the frequency of pulmonary implication is linked to the ease of infection, related to population density, which in turn may correlate to north-south geography, and thus to temperature or with time spent outdoors, etc.

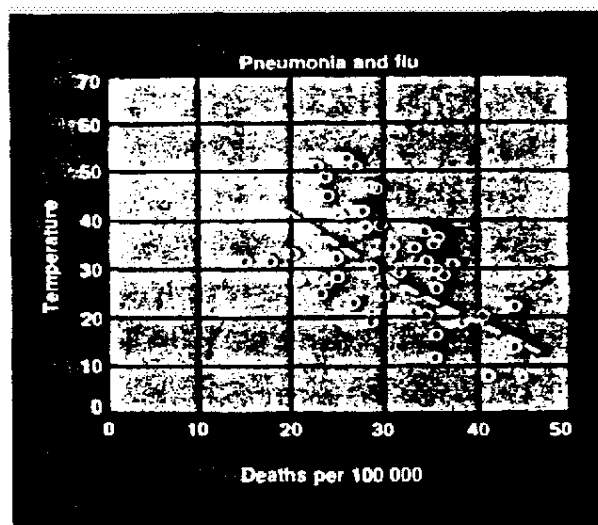


Figure 3. U.S. mortality due to pneumonia and flu

Correlations seldom provide answers without a great deal of research and experienced judgments. But they can pose challenging questions. Take, for example, some challenging results we encountered in the above study when we plotted U.S. mortality figures for cirrhosis of the liver (Figure 4). There is no suggestion of a dependence on environmental temperature, but the points that crowd the lowest figures (solid circles) are those of states in what H. L. Mencken termed the "Bible Belt" (4). However, while most of the nation is characterized by 12 ± 4 deaths per 100 000 of cirrhosis, there is one solitary and outstanding point with four to five times this mortality figure. It is Washington, D.C.

... Which illustrates a case of "fallout" from research. Sometimes we don't get conclusive results concerning the questions posed, but we discover some answers to questions we didn't really mean to raise.

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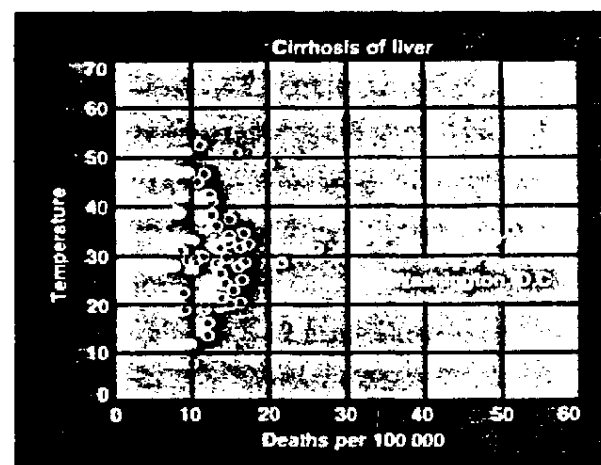


Figure 4. U.S. mortality due to cirrhosis of the liver for diverse U.S. localities; solid dots correspond to states of the "Bible Belt"

Toxicology in Business Decision Making

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More than ever before, toxicology and its sister health sciences and technologies are needed as members of the business team to ensure sound business decision making for both new and existing businesses. Yet the marriage of toxicology and business is an uneasy one since toxicology is both the bringer of bad news and a major resource for the solution of problems. Both business and toxicology have much to learn about each other to make the marriage work and to make full use of toxicology's scientific advice in reaching sound decisions on the safe production, distribution, and handling of a company's products. Toxicology also has a central and difficult role in helping business navigate the turbulent waters of regulation or of potential or actual litigation. From his own experience in organizing a corporate health, safety, and environmental department, the author describes the concepts that must be understood and the marshaling of resources needed to ensure that toxicology can play its full role in business decision making.

INTRODUCTION

Bis-chloromethyl ether, vinyl chloride, asbestos. . . . These and other widely publicized substances are materials of great usefulness in our society. All three of these and a number of other materials are *known* human carcinogens, and beyond these there are the *potential* human carcinogens, materials for which some indication of carcinogenicity may have been found with animal tests. In addition, there are various official lists containing hundreds, sometimes thousands, of additional names; some are of synthetic chemicals, some are of naturally occurring materials, some are commonly known, some are hardly heard of, but all supposedly offer some form of hazard for human beings, though whether this is so or not often remains to be seen. Increasingly in the last decade, we have been hearing of these new hazards of chemical species, and not with respect to carcinogenicity alone. Words heretofore reserved for the specialist have been appearing in the public press: mutagenicity, teratogenicity, oncogenicity, neurotoxicity, and behavioral toxicology, to name only a few. Products old or new, by-products, wastes, and emissions of every sort may be found in many places and exhibit a variety of toxicities. Toxic effects can include these new terms and others.

Thinking of the production, transportation, distribution, marketing, use, and disposal of chemical substances of all types related to practically every industry under the sun soon brings us to the conclusion that toxicology must be an important subject. This understanding raises new issues for business and can incur new costs. These costs must enter into the thinking of business management if it is to plan and conduct its business successfully in ways which are protective of employees and of the numerous other members of the public who may come in contact with the results of business operations in one way or another.

SOME NEEDED ADAPTATIONS

Business organizations and toxicology—indeed, all of the health sciences and technologies, which include occupational medicine and industrial hygiene, for example—have much to learn from each other if they are to work together effectively.

In my own case, one of the first things I had to become accustomed to was the fact that a well-known workhorse of a chemical, vinyl chloride, known to be hazardous in various ways and therefore treated with respect in our everyday work with it, could cause serious adverse health effects even when long-term exposures did not exceed what was considered to be safe in earlier days. The lessons of vinyl chloride, among other things, set me and my company thinking about how we were organized to meet other similar potential problems. As it happened, we had most of the skills and resources needed to cope with the new problems, but we had to organize them differently, and understand them better, to make effective use of them. *All of management must come to understand the facts and implications of chronic as well as acute toxicity.*

Another thing that *all members of management must become accustomed to is that we now have laws*, some of them relatively new, which cover nearly every aspect of business operations and of the ultimate fate of products, by-products, and other materials. These laws are implemented through regulations. In some cases the regulations are very complete and detailed, whereas in other cases they are still being developed. They are there to be complied with in any event, and they often include heavy civil and even criminal penalties for noncompliance. Members of management must therefore accustom themselves to the fact that they could, in some circumstances, unless they recognize the existence and importance of these laws and regulations, find themselves facing serious legal charges. It is also, therefore, a fact that the laws and regulations themselves must be taken into account in corporate decision making.

Beyond the specific requirements of the health, safety, and environmental laws and their regulations, conscientious companies wish to protect their workers and the public from not only the traditional hazards but also from the new hazards, the so-called "chronic health effects." Chronic health effects are adverse impacts on health which come about as a result of low-level or long-term chronic exposures to specific materials. It is unthinkable and, for any sound businessman, unwise to fail to try to produce products safely, to make their safe use possible, and to concern himself with the potential toxic impacts of his business in general. Society will, in time, reject businesses which fail in this respect. In addition to this, management must understand that our courts of law are almost daily developing new dimensions

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in the administration of our product liability laws. Increasingly, litigants are seeking significant awards for increased risk of *future* damage and for the fear which such claims are said to engender.

Management needs to appreciate all of the factors which give proper importance to the impact of modern toxicological knowledge on business operations, plans, and decisions.

There's a significant but ironic concept to which the management of any company must also become accustomed. Much effort will be directed to determining how safe their operations or products might be and how they might be made safer. Yet, when a hazard is identified, the law itself frequently requires that it be reported. It is also usually necessary to warn of the hazard to protect those who might be exposed. Thus it appears to be necessary to conduct lengthy and costly studies only to turn around and incriminate your own operations or products! At first blush, these two things, the need to search for and find hazards and the need to report and warn of them, appear to lead to a "damned if you do and damned if you don't" situation. If no report or warning is given, frequently there are serious penalties, either in the law or as a result of liability. And if a report or warning is made, the information can adversely affect the business, one way or another. This is a situation which modern management must become accustomed to and cope with. The concept that health information per se is confidential is certainly not the concept of today's world, nor is it so that one can fail to search it out. This circumstance must impact business decision making within any firm today.

It is obvious from the foregoing that toxicology, too, and its sister health sciences and technologies have much to learn on entering the business world. *Scientific studies on matters relating to human health can no longer be regarded, or carried out, in isolation from the world in which business lives.* The possibility exists that any experiments toxicology conducts on chemicals or mixtures of chemical species will be used and misused, however exploratory they may be, however far removed from the levels or routes of exposure likely for humans their conditions may be, and however much explanation toxicology may offer as to the inapplicability of the results directly to human risk assessment.

The fact that serious misuse of toxicology's work can occur in such important arenas as regulation or litigation does not mean that work should not be done. Real health effects exist and they must be found, studied, and dealt with. *Toxicology*, however, must learn to work with all the many differing types of expertise, including business expertise, to help determine what are the questions that need to be answered. It must then design its investigations not only to answer those questions but also so the results, whether positive, negative, or equivocal, will be as interpretable as possible in terms of human health under real conditions of possible exposure right from the start. All of this calls for serious and thoughtful review of the traditional approaches to protocol design on the part of toxicology and a considerable expansion of both the thinking and the role of toxicology.

All of the *new concepts* and the new circumstances must be kept in mind when conducting existing business, planning for future business, and making decisions on a day-to-day basis. Carefully thought through, these concepts may permit a business to continue, profitably, while also requiring profound modifications in a product line, the end uses into which products are sold, and the ways in which products are made and distributed. At times they can lead to the decision that a given line of

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business is no longer desirable and that the best decision is to get out of that business and deploy the freed resources in other directions. These are clearly difficult decisions, not always accompanied by fully calculable factors and yet, difficult though they may be, they must be made regarding both the viability of existing businesses and the feasibility of entering new businesses.

All too often, the *experts* who assess the health, safety, and environmental factors associated with a company's operations and products cannot bring forth simple, reassuring answers. At best, because of the high degree of uncertainty in the fields with which the experts deal, the answers are disturbing and difficult to cope with. At worst, from a psychological viewpoint, the experts are the ones who bring the news that a product may be hazardous. Nonetheless, these are the people and the resources needed to help govern a business intelligently in this new world. In this case, it is wise not to cut off the head of the messenger who brings the bad news, because it is that messenger's head, healthy and functioning, that is needed most of all in trying to solve the problems which he brings to management's attention.

I would now like to describe the resources needed to provide the basis for sound decisions, how they might be marshaled, and how decision-making management should view and use them.

THE RESOURCES NEEDED

A large firm can usually marshal internally many of the types of expert people needed to assess the problems which the broad field of toxicology poses for business and to work with the operating and business functions to find solutions for these problems. The small firm has similar problems, but must approach them differently. I would like to discuss briefly what some of these necessary areas of expertise are before discussing how to marshal the resources in an effective way.

Occupational medicine is a specialized branch of medicine which deals not only with the physical but also with the toxicological aspects of occupational health. The diseases which occupational medical experts encounter are often not those caused by viruses or bacteria, but are rather those which may be caused by exposure to different agents encountered in the work place or elsewhere, singly or in combination. Tracking down precisely what may have caused a given effect in a specific individual is a most difficult task, and the difficulty is compounded by the fact that it is not always easy to distinguish between conditions caused by normal disease vectors and occupational disease vectors. Special training is needed, however, to cope with the problems of diagnosis where diseases may be caused by chemical contact and to prescribe proper treatment. The occupational medical specialist must work very closely with two other key specialties: industrial hygiene and toxicology. Moreover, epidemiology is today a vital partner of occupational medicine in determining the likelihood and source of toxicologically caused disease. Epidemiology is the discipline which deals with the discovery and description of the sources and vectors of disease in populations.

Industrial hygiene is a discipline which blends the biomedical and physical sciences and engineering. The industrial hygienist is a specialist, among other things, in methods for detecting potentially hazardous agents in the workplace and elsewhere, in the measurement and monitoring of these agents, in determining their

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sources, and in determining how best to abate exposure to humans through engineering means, personal protection, work practices, or other techniques. Industrial hygienists thus work hand in glove with the occupational medical specialists and epidemiologists in attempting to determine the causes of particular adverse effects under actual circumstances and in finding ways to reduce risks.

Toxicology is another member of the health science team, along with occupational medicine and industrial hygiene. Toxicology devotes itself to studying the effects of chemicals on species other than man, including single-celled organisms and mammals. The object is to obtain indications of the types of effects to be expected in human beings. Clearly, the toxicologist is a strong and essential support to both the industrial hygienist and the occupational medical specialist in providing data for the ultimate assessment of hazard and risk.

To do a complete toxicological study, however, requires more than individuals labeled "toxicologists." The toxicologist may well be an experimental toxicologist, a genetic toxicologist, or other type of toxicologist and must work closely with and be supported by other disciplines: veterinary pathology, to determine what effects have been found, if any; biostatistics, to measure the effects, where these are measurable, and determine their significance; genetics; biochemistry; synthetic organic chemistry; analytical chemistry; and many other ancillary fields to make sound experiments possible and to determine the meaning of them. All of these specific fields work as a unit to produce and interpret toxicological results. Together with industrial hygiene, occupational medicine, and epidemiology, these skills of toxicology are needed, ideally, to most effectively design the right experiments and to gather information and interpret it in relation to human health in actual settings with relation to chemical substances.

The health sciences listed above provide basic input data to the decision-making process. However, other important capabilities are involved in major ways before the operators and businessmen get involved. These others are: specialists in *regulatory matters*, a field which is rapidly becoming an almost free-standing body of knowledge generally involving people with scientific and technical backgrounds who have worked in the regulatory field; specialized legal counsel; public affairs experts; and public relations specialists. Environmental sciences, technology, and, again, the associated regulatory fields are also important in determining the fate of chemicals in the environment and how they can ultimately contact people, as well as how to deal with such chemicals and comply with relevant regulations. These may not all be centralized in a single organization in a large corporation, but must work together in any case. All of these several diverse areas of work must be combined in their capabilities to help business management make sound decisions with respect to its business when faced with health, safety, or environmental problems.

There are *two other areas* which must be mentioned in which special expertise is required as a result of the health, safety, and environmental problems facing business today. These are *information accumulation and retrieval and the management of all of the combined resources*.

The amount of information which is needed to cope with a single problem in this field is enormous. Its sources and literature are almost endless: scientific and academic institutions and their publications, legal decisions, regulatory actions, internal company studies, epidemiological studies, medical records, and the reports of numerous types of agencies, both private and public. In addition to this, there

are legal requirements for the maintenance of records for long time periods, up to several decades, for many types of data. All of this requires increasingly sophisticated systems for the orderly accumulation and rapid retrieval of data and these, in turn, require highly trained information specialists, properly managed to do their job effectively for the entire organization.

Finally, management effort must be devoted single-mindedly and exclusively to the management of the diverse activities to pull them together in a coherent and integrated fashion, enabling them to give strong and useful support to the operating and business segments of any corporation as they go about the business of making their decisions. *Even with all of this, management must recognize that answers provided by their best experts will still include large uncertainties.* This is the nature of these fields and it is the state of the art today.

MARSHALING THE RESOURCES

Most large corporations in the *oil and chemical industries* have, at least over the last few years, examined what resources they need and how to marshal them in this multidisciplinary area. There is no one obvious right way which can be uniformly recommended for all corporations. Different divisional structures and degrees of centralization and decentralization will demand that the resources be parceled out differently under the various managements involved. One thing is true, however, and that is that the resources—the experts—are expensive and some are exceptionally scarce. Therefore, care should be taken to ensure that they do not duplicate each other unnecessarily and that they are properly coordinated throughout the corporation. This latter point is especially important in another sense: from the outside, a corporation always appears to be a single entity and the fact that it may be divisionalized and decentralized does not make much difference when the corporation is viewed by the public at large or by public institutions. Therefore, however decentralized the corporation may be and however decentralized the health, safety, and environmental forces within it may therefore also be, some form of central focus must be provided to coordinate the overall views of the corporation in these areas and to respond accordingly to the outside world.

It must also be recognized that there are some types of activities which are not centralizable, no matter what the organization of the corporation. While there may be health and safety experts available in a head office to support the corporation at large, these people cannot readily serve the day-to-day needs of employees in field locations. *Suitable resources must be supplied directly at the field locations, available on call.* There are other aspects to the safe operation of plants, distribution terminals, and other facilities in this toxicological era which are not centralizable. A further example is the proper training of the individual operators. The training of operators must be carried out in some reasonably uniform and compatible fashion, but it is on the spot, on the job, and in the field itself where that training pays off in terms of protection for the operators themselves. Clearly, the responsibility for the conduct of training adapted to local conditions belongs to local operating management and cannot be centralized. However, training materials and training guidance and expertise in training methods can be supplied by a central organization. For each corporation's structure, the proper balance must be struck.

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Providing for good and timely *communications* across divisional lines is vitally important in considering how to organize a health, safety, and environmental effort within a corporation. Good communications must be a two-way affair: from the health, safety, and environmental organizations to the operating and business organizations and from the operating and business organizations back to the health, safety, and environmental organizations. It cannot be accomplished on an arm's-length basis, or on the basis of expert advice given "take it or leave it." Only by close communication in working sessions, so that the objectives of each group may be understood and possible courses of action explored, can the real degree of communication required for the successful prosecution of business objectives in this day and age be achieved. In some relatively complex organizations, it may be necessary to provide people whose main purpose is to facilitate close interactions, to marry those who need a particular resource with the resource, and to enter directly into planning and decision making at their beginnings.

The communications between the health, safety, and environmental organizations and the operating and business organizations are not the only ones that must be strong. Close interaction with the *legal organization* and its specialized attorneys is a must. Moreover, the effectiveness of communications with employees and the public must be high. This requires close ties to both the personnel and the public relations organizations. Health and safety matters are of obvious interest to the employees concerned. Good communication must be maintained with them so that they understand the hazards of the materials with which they work and so they understand how to work with them safely. At the same time, the same matters have proven to be of great public interest. This is evidenced by numerous articles and stories in the press and programs on television devoted to these subjects. *An effort to communicate with the press and to be able to answer its questions understandably is a very important part of today's business world.* The ability to communicate well and to make positions clear and understandable will affect the ability not only to make sound decisions, but also to carry them out.

Because of the public interest as well as the legislative interest in health, safety, and environmental matters today, the field of *public affairs* is one in which health, safety, and environmental matters have become enmeshed; it is therefore essential to maintain public affairs experts within the corporation in close working relation to the health, safety, and environmental experts. Time and effort must be assigned to manage this linkage to assure that the corporation is able to make its views known to governmental bodies as new laws or regulations develop. Only in this way can businesses hope for regulations that are both necessary and effective: to keep silent is to accept what others deem feasible.

One of the most significant and useful pathways to making an individual corporation's views known is through appropriate *national trade associations*. A large corporation will frequently belong to many trade associations which have relevance to its operations. Such associations usually strive to maintain clear awareness in this as well as many other fields of the trends of legislation within the houses of Congress and of the actions of regulatory agencies in Washington. Moreover, there are in many instances similar trade associations at the state level with whom contact must also be maintained in order to know what is happening in each of the many jurisdictions which might affect a company's business. There is no question that this problem is a very large one. The number of different actions which can proceed

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within the legislatures of the fifty states and at the same time at the federal level is extremely large, and there is no guarantee that there will be anything resembling a comparable underlying philosophy for each of these. It is almost a certainty that they will differ significantly from each other in detail. Organizing this effort must be of concern to the managements of companies today. Legislative and regulatory initiatives and, indeed, the political climate all affect the abilities of business to survive and grow and must impact business decisions. In the last several years, health and environmental matters have proven to be fertile ground for political thrusts.

The *large firm* can marshal its resources to cope with these many problems, although many difficulties are still encountered; being certain that the management is indeed aware at all times of the obligations and pitfalls it faces and the decisions it must make is a very difficult business. The *small firm* clearly has a different order of magnitude of capability to cope with toxicological matters of importance in its business decision making. Nonetheless, the small firm must find ways to keep itself in compliance with current regulations and to assess the risks it runs in its business. Where a major liability suit, for example, may be a serious problem to a large firm, it may be a matter of life or death for a small firm. Where regulatory strictures, the burden of paperwork, or the slowness of registration or permitting may seriously hamper the large firm, they may also be matters of life or death for the small firm.

In spite of the overwhelming nature of the problem, the small firm cannot simply ignore the problem and hope that it will go away. This would be a bad decision. The small firm might find itself out of business and with its management indicted. While the small firm cannot possibly maintain the resources internally that it might need to answer all the questions it might wish to have answered, it can, through the use of *consultants and legal counsel*, at least maintain itself aware of the problems and provide itself with some of the resources it needs to answer specific questions at specific points in time. Consultants are available in the many fields mentioned above who can serve on a part-time basis to survey the operations of small firms and advise management as to whether there are specific problems that need to be dealt with and to give at least some indication of the sizes and significances of these problems. Moreover, although no one attorney can have all the knowledge needed in the specialized fields of health, safety, and environmental law, a good attorney can at least identify the problem areas and seek specialized assistance so that appropriate actions can be advised. The management of the small firm, being aware of what these actions are, can then assess whether they can be taken within the confines of the business as it exists, examine its options, and make its decisions.

Belonging to appropriate national and local trade associations is another means for the small firm to maintain an awareness of the important new regulations with which it must be in compliance, the main terms of these regulations, the penalties involved, and the dates at which they become effective. Most trade associations provide such information to advise their members of significant legislative and regulatory moves. At the very least, a small firm must ensure that it is in compliance with relevant laws and regulations. The small firm also has the ability, as does any other firm, to ask the regulatory agencies about their views on given regulations and on their interpretation. It must be understood, however, that while these views may be given, they are not generally binding upon the agency. While individuals within regulatory agencies may be very conscientious and do their best to help, generally

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speaking their advice will not guarantee that the agency, through its enforcement or inspection arms, will necessarily find the firm to be in compliance. This advice, while useful, must therefore be taken in the proper context.

In the *final analysis*, then, all firms, large and small, must find ways to keep themselves aware of the legislative and regulatory activities in the health, safety, and environmental areas and of the requirements for compliance. Beyond that, they must also maintain themselves in a position to assess the problems that toxicity may cause with respect to their products, processes, and operations, to protect their workers and the public, and to protect themselves in the area of product liability as best they can.

There is no question but that it is more difficult and more costly to maintain an ongoing business today, whether it is a large one or a small one, or to cause it to grow, than it was in the past.

HOW TO VIEW AND USE THE RESOURCES

As mentioned before, many of the types of specializations mentioned are rare or in heavy demand and therefore tend to be costly. This is to say that while the more common specializations are costly, the rare ones are particularly costly and must be used particularly effectively to aid in business decision making. For this reason, the way in which the health, safety, and environmental forces of a company are organized and are set up to communicate with the rest of the company is very important indeed. Beyond this, and assuming that an effective organization with effective communications has been devised, there is still a *cost* to this new organizational feature of the modern business and the question is: What is the attitude to take toward it?

As mentioned earlier, it is not wise to behead the messenger when he arrives with disturbing news. The best way to deal with the messenger, his disturbing news, and the cost of keeping him on the payroll is to make him part of the business team and to make his costs part of the business costs. Just as plant maintenance is a running cost that must somehow be recovered in the price of the product, just as distribution, marketing, advertising, or any of all the many other costs that any business must now bear must be clearly defined, reported, accounted for, and recovered in the market place, so must the cost of the health, safety, and environmental resources of the company. Beyond that, the advice that such an organization can give to the rest of the company on what resources will be needed in the future to prosecute the ongoing business, what risks there may be because of health, safety, and environmental factors, and what the necessary reduction of such risks will likely cost are all pieces of information which will not always be pleasant but which nonetheless need to be known to the business decision makers so that they can take proper account of them and decide how to manage the business portfolio of the firm. This is true not only in short term and in the annual budgeting process, but is also true in longer-term planning.

Here, too, in *longer-term planning*, the health, safety, and environmental factors, and the toxicological implications of these factors for human health, become a necessary part of business planning. Any plan which does not take full account of these factors, ranging from the need for compliance with relevant regulations to the

difficult art of predicting risks which have not as yet been experienced, is bound to be unrealistic. Any estimate of future profitability which does not take such factors into account is not worthy of being reported to senior management or to the board of directors. Moreover, the means whereby the health, safety, and environmental experts in a company are able to express their views on the risks that must be coped with in the future must be clearly defined and openly available to them. Many of these risks, and the costs of coping with them, are far too serious and far too subtle for them to be filtered out at some point along the way before they reach the ultimate decision makers in the company. This is not to say that the health, safety, and environmental organizations must sit on the board of directors, bypassing important layers of management. It does say that however the company is structured, *the health, safety, and environmental experts must have a voice and a presence on the business teams at appropriate levels*. For this voice to be heard, management must indicate that it wishes to hear what that voice has to say. This desire must be clearly expressed from the topmost layers of management to the bottommost layers of management, and the communication links should be kept sound. Decision-making management must receive what it pays for to do its own job.

Health, safety, and environmental expertise is not unique in the importance of being heard. It is simply as true in this field as in any other. For example, if there were some risk about the engineering features of a new plant which might make it less reliable than a more costly one, this type of information should certainly be available to the decision-making management of a company. The same is true of information relating to any potential risk in a new venture or in the maintenance of current operations.

CONCLUSION

The costs of the health, safety, and environmental forces in a company must be clearly known and clearly set forth so that management may see them and know what they are paying and satisfy themselves that they are getting what they pay for. Management must fully recognize that what they pay for, while helpful in forming the best decisions, is information of a highly uncertain nature. In addition to this, the health, safety, and environmental forces must be considered to be members of the business teams in a company and their voices must be clearly heard in the making of decisions at the appropriate levels within the corporation and, ultimately, through whatever channels may be appropriate for a given company, at the decision-making level. All of this must be true in the face of the fact that the health, safety, and environmental organization frequently must have, because of its nature, a unique obligation to report adverse information outside of the company. This consideration does not take the health, safety, and environmental forces off of the business team, nor make them any less supportive of the true and fundamental objectives of the company, but it is a matter which requires a considerable degree of understanding on the part of management.

Environmental Health Risk Management in Canada¹

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The legislative basis of the federal Canadian government's control of toxic chemicals is described and examples are given of the practical application, ranging from recommendations to a ban on the sale of the product. The ordered sequence of risk assessment and the application of risk estimation techniques are considered. It is clear that the ultimate political decision is not amenable to simplistic scientific analysis, although risk analysis is valuable in defining, rather than solving, the problem.

INTRODUCTION

Risk—its analysis and its management—has become one of the most talked about topics in the field of environmental health. Largely this is to the good, for it promises to bring order and rationality into our thinking about environmental hazards and to create an understanding, both in the professional and public community, that will lead us to considered and socially acceptable solutions. The caveat must be that societal judgments are often complex and can rest on deeper emotional springs rather than on reason. This is a lesson that the proponents of nuclear energy have learned to their cost.

The Canadian approach to risk management derives from our legislative authority—both federal and provincial—with the understanding that the regulatory mode can be replaced, or amended, by economic or educational options. In general, the Canadian political system adopts a liberal democratic view of the state. It accords to market forces the primary initiative in the introduction of new products and goods—and hence of new hazards. The state does, of course, referee the process and, on occasion, assumes direct involvement through public enterprise. Control of toxic substances can be applied from manufacture to disposal. Federal jurisdiction, particularly the criminal law, trade, and commerce powers, provides the basis for the major Acts (Table 1) designed to protect the health of Canadians from environmental hazards. In all, for toxic substances, there are some 27 federal statutes which exercise some form of control and the ten provinces have enacted 99 pieces of legislation.

¹ Presented at the Toxicology Forum, Aspen, Colorado, July 1982.

TABLE I
MAJOR FEDERAL ACTS FOR TOXIC CHEMICALS

Canada Water
Clean Air
Fisheries
Ocean Dumping Control
Environmental Contaminants
Food and Drugs
Hazardous Products
Pest Control Products
Transportation of Dangerous Goods
Canada Shipping
National Health and Welfare

The six-year-old Environmental Contaminants Act is intended to control hazards that are not effectively dealt with under other legislation and provides broad powers to collect data and conduct investigations with respect to substances entering or likely to enter the environment in concentrations which may endanger human health or the environment. Uses of PCBs, PCTs, Mirex, and chloro-fluorocarbons have been prohibited under this Act. Regulations under the Food and Drugs Act prescribe standards for the quality of food and maximum levels for such toxic chemicals as lead, arsenic, and aflatoxin. In contrast, the Hazardous Products Act relies on schedules (such as the prohibition of the sale of urea-formaldehyde foam insulation, or tris (2,3-dibromopropyl) phosphate)) and regulations rather than broad powers of prohibition. It must be emphasized that regulatory strategies range from outright banning, through setting emission standards or maximum allowable concentrations, to recommendations or guidelines—the least severe control. In all cases, the authority derives from the basic federal acts.

There appear to be few limitations on what the Parliament of Canada can do under the criminal law power and it can legitimately be applied to the regulation of the production and distribution of hazardous substances. In 1933, the British Columbia Court of Appeal upheld federal legislation that prohibited the use of sulfur dioxide in meat products despite the fact that the evidence showed that it was not harmful to health. The Court reasoned that adulteration of food had historically been dealt with by the criminal law. That being so, Parliament had jurisdiction and it was up to Parliament alone to determine how best to deal with the problem and which adulterants could be tolerated. The same approach was taken in 1974 when the federal regulations limiting the use of cyclamates in foods were contested by Berryland Canning Company Ltd.; the Court judged that the Department had acted in the public interest.

Although the pressure for deregulation is felt in Canada as elsewhere it is noteworthy that the recent report of the Economic Council of Canada on this issue chose to exempt environmental pollution from the general conclusion to reduce and restrict regulation. Our experience has been that most manufacturers and employers are serious in their efforts to comply with prevailing regulations and standards. In fact, in areas of high technology—as with radiation-emitting devices—the industry follows the promulgated regulations so effectively that wide-ranging surveillance on our part is not required.

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All new federal regulations in the area of health, safety, and fairness that have a major effect on the Canadian economy—set at the present at \$10 million a year—are subject to socioeconomic analysis. Except for emergencies, summary analyses are to be published in the Canada Gazette, together with the draft regulations, and the public is given 60 days to comment. In principle, the socioeconomic analysis covers the use of several different methods, including cost-benefit, cost-effectiveness, and risk-benefit analyses. It should be remembered, however, that with the best will in the world the ultimate cost of a regulation can be startlingly different from that initially calculated.

ENVIRONMENTAL HEALTH DECISIONS

The legislative powers described are similar in their intent to those found in many other western countries. Differences are more commonly found in the application and enforcement of these powers. In illustration, here are some recent examples of federal environmental health decisions ranging, in the ordered sequence, from recommendations to guidelines to regulations and, finally, to bans of the sale of the products.

Recommendations

In 1975, reports were received in Canada that certain models of TV receivers manufactured by Panasonic could emit X rays at potentially hazardous levels (above 0.5 mR/hr at 5 cm) if certain circuit components failed and that under these circumstances a picture would still be visible. As this problem was not covered by a standard at this time, no regulatory action was possible. However, the Minister has the authority and the duty to warn the public of a potential health hazard. A press statement was issued and the manufacturer voluntarily agreed to replace the defective components. More recently, in an investigation of point-of-use water purifiers we have found that pathogenic bacteria, such as *Flavobacterium* and *Pseudomonas aeruginosa*, can proliferate on granular carbon filters. To control this potential hazard the Department issued an Information Letter to the trade in May 1981, proposing that the sale of these devices be prohibited under the Hazardous Products Act. The industry response to this letter, in particular the Canadian Water Quality Association and their U. S. counterparts, was extremely cooperative. Recommendations are to be made by the industry to ensure that activated carbon filters are not used on microbiologically unsafe water, or with water of unknown quality. A joint Departmental/Water Quality Associations' workshop to identify remaining microbiological problems was held. The Department considers that these actions obviate the need to ban these devices at the present time.

In both instances, public health interests were served by recommendation.

Guidelines

In Canada, the provinces have the primary authority to legislate for municipal water supplies while the Department has the responsibility for research and coordination. Guidelines for Canadian Drinking Water Quality were published in 1978 as

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a result of some four years work by a federal/provincial group of scientists, technologists, and water engineers operating under the aegis of the Federal/Provincial Advisory Committee on Environmental and Occupational Health. Limits for more than 50 parameters of water quality covering physical, chemical, microbiological, and radiological characteristics were given in terms of "maximum acceptable concentrations" for many of the contaminants. These guidelines have largely been implemented by the provinces, as is their responsibility, and this commitment is surely a result of their own involvement in the genesis of the criteria and guidelines. In Canada, at least 90 percent of the industrial workforce is under provincial jurisdiction so that when the Minister of National Health and Welfare recommended in 1975 that the workplace standard for asbestos should be 2 fibres/cm³ (time-weighted average length greater than 5 µm) he wrote to his provincial colleagues asking them to reexamine their own occupational exposure standards. This value has been adopted as a regulation or guideline by the provinces: it is under review at the present time.

Regulations

Federal regulatory, and hence enforceable, limits have been established for a range of environmental contaminants: for mercury in fish at 0.5 ppm; for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) at 20 ppt in fish; for lead in gasoline at 0.77 g/liter; and for asbestos emitted to the outside environment from mining and milling operations at 2 fibres/cm³. The rationale for this type of decision will be considered later.

Bans

The most stringent of all regulatory actions is to remove products from the marketplace. This action is only taken when the potential health impact is high and/or safer replacements are available. The sale of urea-formaldehyde foam insulation was banned in Canada in December 1980 under the Hazardous Products Act because of a range of reported and potential adverse health effects, largely but not solely ascribed to formaldehyde. Safer and more effective insulating materials were, of course, available. The carcinogenic properties of asbestos are well established. The use of asbestos in children's toys, modeling clays, dry-wall joint cements, or simulated ashes has been banned under the same Act. Similarly, the use of PCBs as microscope immersion oils were banned in 1976 and, in 1980, all new uses of PCBs—including use in make-up or filling fluid—were banned under the Environmental Contaminants Act.

RISK IDENTIFICATION

These, then, are examples of federal regulatory control measures. To understand their rationale, it is instructive to consider the whole question of risk assessment in the ordered sequence of risk identification, risk estimation, risk evaluation, and, finally, risk management (Whyte and Burton, 1980). Once the hazard is recognized, a scientific determination of risk is performed before the ultimate political judgment on the acceptability of the risk and its consequences. In real life, of course, the steps

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The choice of the chemical, device, or product to be tested is one that traditionally has been made after an integration of factors by qualified, experienced staff on the basis of their knowledge, but not usually in a formal manner. At its worst, this can lead to "the hazard of the week" syndrome where the programs are initiated idiosyncratically following media intervention. More rigorous methods of priority setting are being developed in many countries. In Canada, a List of Priority Chemicals to be considered under the Environmental Contaminants Act is gazetted annually. Three sets of criteria are applied: toxic effects to human health or environment, persistence, and quantity and use.

On the basis of submitted comments, a joint Interdepartmental Health and Welfare/Environment Committee develops a list of priority chemicals. To date, a list of some 22 chemicals and groups has been established, classified as: Category I—regulations being developed; Category II—under investigation; Category III—further study or information required; and Candidate Chemicals—potential problems. It must be remembered that chemicals already controlled under other federal legislation, such as food additives, drugs, or pesticides, or as environmental contaminants, such as arsenic, mercury, and oxides of nitrogen and sulfur, or that are controlled under other mandates, are excluded from this list. Although the system of priority setting is less rigorous and less time consuming, the final list is similar to that derived by the Interagency Testing Committee of the U. S. A. Toxic Substances Control Act. This latter system is based on some 34 scoring subsystems. Other lists have been developed by international organizations and the WHO/ILO/UNEP International Programme on Chemical Safety has provided a priority list of over 100 industrial chemicals and groups of chemicals.

RISK ESTIMATION

The scientific risk estimation rests on three major sources of evidence: epidemiology—in the occupational or general environment; animal experimentation; and *in vitro* testing. To some extent, supportive information can be provided by correlations between chemical structure, in terms of functional groups, and biological activity. Although epidemiology can, in principle, provide the most definitive evidence on a chemical's risk to human health, its main deficiency is in relating long-term effects to a specific cause. Accurate estimates of exposure, the delayed effect of many chemical insults, the ubiquitous nature of environmental contaminants, and the wide range of chemical entities present in food all serve to confound the problem.

Nevertheless, epidemiological evidence has implicated asbestos as a human carcinogen and led to the regulatory decisions described. The cumulative results of five epidemiological studies of industrial populations, chosen by Schneiderman *et al.* (1981) as the most authoritative, give an estimated excess lifetime risk of cancer of 10^{-6} for exposure to levels of 10^{-5} to 10^{-4} fibres/cm³, based on a linear dose-response model. This environmental level could be regarded as an acceptable risk. The standard for mercury in fish is based, in part, on the tragic events at Minamata as well as on animal studies, all of which were used to derive the Joint FAO/WHO Expert Committee on Food Additives (1972) recommendation of a tolerable weekly intake of

200 µg methyl mercury per 60-kg adult. Human, as well as animal, data on the toxic properties of lead, particularly the impairment of behavioral abilities, have led to a proposal under the Clean Air Act to reduce its concentration in gasoline, of which we in Canada use some 10,000 metric tons annually.

Animal carcinogenesis studies were the basis of recommended maximum acceptable levels for trihalomethanes and nitrotriacetic acid in the drinking water guidelines (National Health and Welfare, 1979). In each case, the maximum cancer risk of drinking water containing the maximum level of contaminant, using conservative statistical linear extrapolation procedures, is of the order of one to two cancers per year in a population of 2 million. The Departmental regulatory level of 20 ppt of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in fish was derived from rodent studies. In this instance, an "effect level" for carcinogenicity with a safety factor of 2000 was adopted because there is no evidence that the TCDD is a genotoxic carcinogen, i.e., does not alter the integrity of the genome. Following the ban on the sale of urea-formaldehyde foam insulation, the Department recommended an indoor air guideline of no more than 0.1 ppm formaldehyde. This was based on a safety factor of one-twentieth of the workplace standard and on knowledge that the mathematical models based on nasal passage carcinoma in rodents would give a cancer risk at this level of less than that from smoking one-third of a cigarette each day.

However, a cautionary note must be sounded. Seductive as it may be, we cannot, at the present time, predict the quantitative human risks from laboratory data. They can be used to buttress decision-making—but not to actuate it. Munro and Krewski (1981) have shown that the shape of the dose-response curves derived from different statistical and stochastic models has a profound effect on the estimate of risk. The well-known analysis by the National Academy of Sciences on saccharin ingestion (at 120 mg/day) showed that the expected number of cases of bladder cancer in the United States over the next 70 years could range from 0.22 to 1.14 million! This is hardly useful as a guide to decision-making when exaggerated to this level.

It has been suggested by Doll and Peto (1981) that "priority setting" would be a more honest name for this exercise than "risk assessment" and that what is of more value is a measure of potency of a chemical which could be multiplied by a crude estimate of human exposure to yield an index of human hazard. Such a potency index has been proposed by Clayson (1980), based on the dose that will induce an excess of 50 percent over the spontaneous response rate. By focusing on a dose corresponding to relatively high response rates, the problem of low-dose extrapolation is circumvented. It is well-established that carcinogenic potencies can differ markedly between species, as well as between sites so the problem of interspecies extrapolation remains.

RISK EVALUATION

It is when one comes to the issue of societal judgement—the ultimate political decision point—that the defined rules of the scientific method have to be deserted. Unfortunately, some systems analysts, particularly from the nuclear energy industry, consider that mathematical comparisons of totally unrelated risks or even of alternative risks will convince the public—and hence their elected representatives—to pursue a desired policy objective. The reality is that complex social phenomena cannot be reduced to single-scale risk rankings. The nuclear energy debate has shown with

blinding clarity the distinction between objective and subjective risks, and the attendant philosophies based on different values, ideologies, and—frankly—naked competition for power. These issues have been described by one at the center of the fight. Carl Tham (1979), the Swedish Minister for Co-ordination and Energy, has given an honest account of the travail of the Swedish Energy Commission to achieve an agreed policy on energy.

In conclusion, in Canada we have used the formal procedures of risk estimation to aid the societal judgment based on our legislative authority. The techniques are valuable and will certainly be refined and strengthened. Risk analysis is a powerful tool for categorizing and assessing risks but its role in decision-making is, as yet, limited. Whether or not greater scientific knowledge will radically alter this situation is debatable, but that should not detract, to the smallest extent, from our pursuit of a better understanding of the risk assessment process.

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Science, Regulations, and the Safe Handling of Chemicals¹

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Diverse scientific, technical, and technological factors must be considered when developing chemical safety regulations which may have to bridge many segments of industry. The handling and disposal of chemical wastes, too, have their own unique problems at every stage in the chain. Unfortunately, regulatory initiatives based on sound scientific and factual evaluation have often been lacking in the regulatory process. Some examples of ill-conceived regulations are the Occupational Safety and Health Administration's original generic cancer policy; the Environmental Protection Agency's 1979 proposal for an airborne carcinogen policy; and a move by the Food and Drug Administration in 1979 to regulate carcinogen residues in meat and poultry on the basis of unproven science. Industry realized that poor regulations would be far worse than no regulations at all. As one response, the American Industrial Health Council (AIHC) was formed to promote the integration of sound science into regulatory policies and decisions relating to chronic health hazards. This paper, presented as a speech before the Industrial Research Institute in May of 1982, describes the AIHC's proposals. The AIHC defined a logical decision process consisting of four steps leading to the selection of appropriate regulatory responses. The first three steps, Hazard Identification, Hazard Evaluation, and Risk Evaluation, are called the risk assessment process. The final stage is Regulatory Response. Use of this process can bring about the right kind of partnership between science and society in the regulatory process. These principles are so general they can be applied in regulatory areas beyond those originally intended, such as the problems of hazardous waste sites. An example of a bad approach to dealing with hazardous waste is the Love Canal waste site. In this case, the regulators did not first seek sound scientific facts on which to base societal value judgments. A positive example of hazardous waste site management implementing this four-step process is the McColl disposal site in Fullerton, California. While some aspects of the investigation are still in the Hazard Identification stage, others have moved into the second stage of Hazard Evaluation. This is a case where there has been a deliberate avoidance of leaping to conclusions before the existence and the degree of hazard have been determined so that the risks can be assessed and the proper responses made. A framework for decision making represents a common-sense approach. The AIHC's principles have not been fully embedded in the legislative or regulatory processes of this country, but the opportunity now exists to get these principles and methodologies embedded in the laws as they are amended, in regulations as they are created, and in policies as they are devised.

INTRODUCTION

Chemicals are not just the concern of their basic manufacturers—everyone handling them is involved, to some degree. And the user, not the manufacturer, often

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has the more difficult job of handling chemicals safely. It is obvious, therefore, that diverse scientific, technical, and technological factors must be considered, among others, when developing chemical safety regulations which may have to bridge many segments of industry.

The handling and disposal of chemical wastes, too, have their own unique problems at every stage in the chain.

When I say "handling" I refer to all the ways we move and contain chemicals whether as raw materials or as they are transformed during manufacturing and processing; as they pass down the distribution chain or as they are disposed of as products, by-products, effluents, or wastes. References to handling chemical substances must, therefore, be considered not just in one isolated environment such as the workplace, in the air, in effluent streams, and so on, but every place they might come into contact with people or the environment.

For the word "safe," as in "safe handling," I like Lowrance's definition: "A thing is safe if its risks are judged to be acceptable" (Lowrance, 1976). This straightforward and simple-seeming sentence is profound, direct, and complete. It includes the idea that, except for highly restricted and special circumstances, absolute safety cannot generally be achieved.

Unfortunately, regulatory initiatives based on sound scientific and factual evaluation have often been lacking in the regulatory process. It must seem incredible to scientifically knowledgeable people that highly technical regulatory decisions can be made without first examining the available scientific information. However, in the recent past, proper scientific input has been severely constrained by the policies of regulatory agencies. Not to elevate these practical problems to too high a plane, I see, nonetheless, some parallel with the problem faced by Galileo!

Starting in the early 1970s, there was a strong regulatory drive and, as a matter of convenience, a kind of "short-cut science" was developed to deal with chronic health risks. For example, *all* risks were to be regulated since this abbreviated science did not distinguish any degrees of risk. This simplistic policy led to some potent examples of ill-conceived regulations.

One prime example is the carcinogen policy as initially proposed by the Occupational Safety and Health Administration in 1977 (OSHA, 1977). As an example, this policy ruled that any substance causing a tumor, benign or malignant, in any animal species, at any dose level, via any route of administration, should automatically be considered a potential human carcinogen and regulated as such. Such a standard would have constrained the independent exercise of scientific analysis by its rigid, universal criteria which ignored all other current knowledge and precluded incorporation of new scientific knowledge. In addition, it was potentially one of the most costly regulations ever issued, it did not provide for priority setting on the basis of relative risks, and it would have resulted in an unproductive diversion of billions of dollars in an attempt to regulate chemicals which, under normal conditions of use, do not pose a risk of cancer in humans.

OSHA's regulatory proposal started a trend toward such so-called "generic" proposals for controlling potentially carcinogenic materials by other federal agencies including the Environmental Protection Agency (EPA) and the Consumer Product Safety Commission (CPSC). The imposition of highly conservative constraints on scientific assessment in these proposals is echoed in a 1979 proposal of the Food and Drug Administration (FDA).

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In 1979, the EPA proposed a generic airborne carcinogen regulation under Section 112 of the Clean Air Act in which one conservative premise was piled on another, obscuring any real scientific assessment (EPA, 1979). The FDA moved to regulate carcinogen residues in meat and poultry based on unproven science and a commitment to the unrealistic goal of a practically risk-free environment (FDA, 1979). Also, the CPSC moved forward with a proposal based substantially on the OSHA model but in some ways going even beyond it. This initiative was later withdrawn (CPSC, 1978).

The Interagency Regulatory Liaison Group, an informal group of five agencies, issued a report proposing a series of policy constraints on the scientific evaluation process (IRLG, 1979). The report was published for public comment and extensive comments were filed but never evaluated. Yet the Regulatory Council based its policy on it (Regulatory Council, 1979), and the unevaluated criteria were used by the EPA for assessing the carcinogenic potential of airborne chemicals. Most of these assessments did not survive later peer review (EPA Science Advisory Board, 1980).

The sciences involved in health hazard evaluation are fraught with uncertainty. The only way agencies seemed to know how to deal with this was through the implementation of fixed rules based on rigid criteria, whether reasonable or not. Only by accepting science as a starting point of the regulatory process can these uncertainties be dealt with and understood.

INDUSTRY INVOLVEMENT

It was soon apparent to industry that poor regulations would be far worse than no regulations at all. Faced with tremendous potential costs and misdirected effort, industry realized it had to devote some of its time and resources toward a workable solution.

One highly focused effort began with the formation of the American Industrial Health Council (AIHC) in the Fall of 1977. This association mobilized the technological and scientific capabilities of approximately 100 diverse companies to the task. Their objective is to promote the integration of sound science into regulatory policies and decisions relating to chronic health hazards. To accomplish this, AIHC has developed a set of rational, clear-cut principles which have been applied successfully in testimony and comments in many areas such as the Food Safety Law amendments, regulations under Section 112 of the Clean Air Act, Regulatory Reform legislation, and the OSHA Carcinogens Policy which was reopened for comment again just this Spring.

The principles have been explained in detail in a volume prepared last Fall, labeled a "Draft for External Review," (AIHC, 1981). The volume is available, and AIHC is seeking comments because it is not the last word to be said on this issue. Thinking on this subject is continually evolving; but, to date, this is the best compendium available of AIHC's thoughts.

I cannot emphasize too strongly that AIHC was formed to develop sound principles and not to simply resist regulation. These principles represent constructive alternatives to past approaches that did not work.

In Fig. 1, I have summarized the key principles needed to ensure a successful regulatory outcome.

- 1 ESTABLISH SCIENTIFIC NEED BEFORE REGULATING
- 2 INDEPENDENT/INTERACTIVE ROLES
 - (a) SCIENTIFIC EVALUATION
 - (b) REGULATORY DECISION-MAKING
- 3 FLEXIBILITY TO ACCOMMODATE NEW SCIENTIFIC KNOWLEDGE
- 4 MECHANISMS FOR VALIDATION OF ALL RELEVANT SCIENTIFIC DATA
- 5 LOGICAL DECISION PROCESS FOR IDENTIFYING HAZARDS EVALUATING RISKS AND SELECTING REGULATORY RESPONSES
- 6 THE REGULATORY FUNCTION MUST MANAGE THE REGULATORY PROCESS

FIG. 1. Key principles needed to ensure a successful regulatory outcome

First, *establishing scientific need* prior to initiating the regulatory process is good common sense. Sound scientific evaluation of all the information available is the only basis for identifying hazards and for making rational decisions to control significant associated risks.

Second, it is important to *distinguish the role of independent scientific evaluation* from that of regulatory decision making. To integrate sound science into the regulatory process, the scientific and regulatory functions must be recognized as separate but interacting. Scientific evaluations must be as objective as possible and should not include or be limited by societal values or judgments. Scientific evaluation should result in a "best" assessment of the available information, include descriptions of the ranges of the uncertainties, and explicitly display all assumptions. Science cannot fulfill the whole task of risk assessment; it must not include conservative assumptions or safety factors. These assumptions and factors are part of the role of the regulator which science must not usurp. Societal decisions are ultimately made by the regulator.

Third, it is necessary to maintain flexibility in any regulatory process to *accommodate the development of scientific knowledge*. Rapid advances in science make rigid criteria a barrier to some regulatory decisions. For example, in 1958 detection at one part per million was good science. Now the improvement in technology permits measurement, in many cases, of parts per trillion. Our understanding of the biological sciences also moves forward by leaps and bounds.

Fourth, it is necessary to have explicitly established *mechanisms for validating all relevant scientific data* needed to evaluate chronic health hazards. Such mechanisms assure the maximum objectivity and least bias in the scientific assessments used in determining regulatory responses. I will illustrate some of these mechanisms in Fig. 2.

Fifth, it is necessary to have a *logical decision process* which starts with the initial scientific identification of a potential hazard and moves, step-by-step, to the ultimate selection of appropriate regulatory responses. I will discuss this process in greater detail later.

And finally, in this list of principles, one of the most important ones to remember is that the *regulatory function itself must manage the overall regulatory process*. This includes posing the questions, launching the process, utilizing the scientific results as they emerge from the independent scientific process, reaching the ultimate conclusion

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- THE SCIENCE PANEL
 - INDIVIDUAL INDEPENDENT SCIENCE PANELS
 - AGENCY SCIENTIFIC CAPABILITIES
 - PUBLIC AND PEER REVIEW
 - WORKSHOPS AND SYMPOSIA - PRE-REGULATORY PHASE
 - COOPERATIVE PROGRAMS FOR TESTING AND SCIENTIFIC EVALUATION
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FIG. 2. Six AIHC recommended mechanisms to validate scientific data.

as to level of risk, and deciding on the necessary regulatory action. It is necessary for scientific assessments to be independent, and indeed, it is only this type of assessment that is a good tool for the regulator.

Turning to Fig. 2, I have listed a number of AIHC's recommended mechanisms to validate scientific data. The Science Panel is conceived as an independent entity consisting of excellent scientists drawn from the appropriate disciplines and from academia, industry, or government, supported by a staff, and located organizationally outside of the regulatory agencies but fully accessible to them. It would be used for major regulations, and its conclusions, while not mandatory, would be such that if the agencies reached a different assessment they would be obliged to explain, for the record, why they did so.

The establishment of individual independent science panels attached to the relevant agencies is also encouraged since these can assist in handling a large amount of necessary scientific evaluation relevant to the specific regulatory processes. These panels, too, would be composed of scientists not only from government but also from industry, academia, and other institutions, each highly qualified in a discipline relevant to the task in hand.

The establishment of the above panels would require improvements in the agencies' own scientific capabilities, if gaps exist, to assure fruitful communication between the agencies and the panels and sound and credible work within the agencies. It is also desirable that public review of important health initiatives and other means of peer review be utilized, as necessary. In the preregulatory phase, it is urged that the agencies establish workshops and symposia in order to fully understand the state of the art in any chronic health area even before embarking on the first stage of establishing a scientific need prior to regulation.

Cooperative programs for testing and for the scientific evaluation of data among industry, government, and academia are also strongly encouraged.

A FOUR-STAGE DECISION-MAKING PROCESS

The logical decision process or framework which I noted earlier is illustrated in Fig. 3 and is composed of the four numbered stages in that figure. The entire regulatory process, as shown in the left-hand side of the figure, stretches from the top line to the bottom line and begins, as indicated by the arrow at the top, with the need to identify a hazard, if one exists, before proceeding further down the chain toward regulation. The first three steps in the four-step process, Hazard Identification, Hazard

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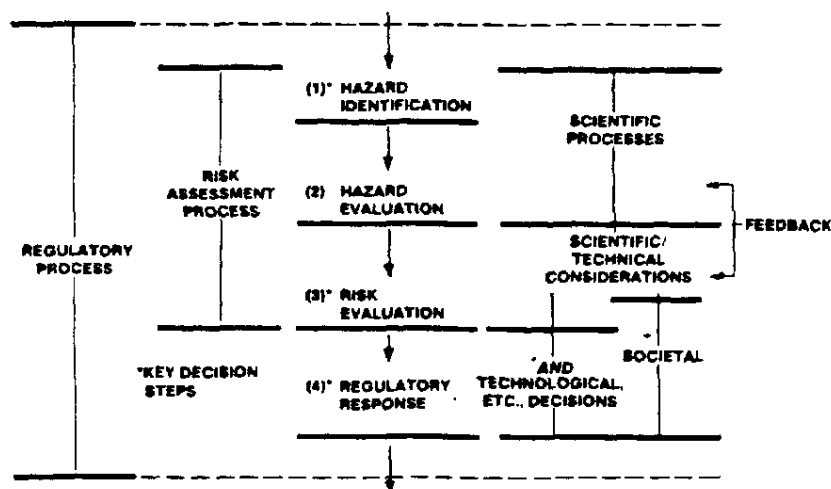


FIG. 3. The logical decision process or framework.

Evaluation, and Risk Evaluation, are called the *risk assessment process*, as indicated in the figure.

Hazard Identification is the scientific process of gathering and validating data on the hazard of a substance, which is the potential to do harm to humans or the environment, and drawing conclusions as to whether a hazard exists or not. Validation mechanisms are vital in this step as in the later steps. This is a key decision step, for if no hazard is identified, the remaining steps need not be taken, no regulatory action is required, and resources may be used to address other potential hazards.

If a hazard is identified, then it must be evaluated to determine its characteristics under different circumstances and how they might be expressed in terms of human health effects or environmental effects. This is accomplished in the second stage, *Hazard Evaluation*. Succinctly, when considering human health effects, this involves the scientific effort to determine from the available information and theories what kinds and ranges of human responses might be expected under laboratory-like exposure conditions if it were possible to obtain such information. Such an evaluation process must be objective and unbiased and should not include or be limited by societal values, judgments, or constraints. This stage must also include procedures for input by industry scientists and from the academic and public sectors.

The third stage calls for *Risk Evaluation* to determine whether and to what extent the potential hazard of a substance is realized in the real world. Technical information on actual exposure levels, frequencies, and routes, on who is exposed in what numbers and where, is required. The degree of risk of the hazard may be assessed through a categorization procedure. When it has been determined whether the risk is significant or not and therefore whether regulation is needed, rational decisions can be made as to the necessary control measures. This step is also a key decision step for determining whether or not to proceed to stage 4. Here, too, the validation of data through scientific peer review is needed.

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On the right-hand side of the figure it is indicated that the first two stages are both scientific processes, whereas the third stage involves scientific and technical considerations. At the very last segment of the third stage, societal considerations, must play a part in the final assessment of the *acceptability* of the degree of risk. Here, in the public policy arena, is where Lowrance's definition of safety comes fully into play.

As indicated in the diagram, feedback is necessary between the first three stages and, indeed, there may be occasions when the sequence is performed more than once.

The final stage is *Regulatory Response*. Here the regulator considers further relevant factors in deciding whether to regulate and what amount and kind of regulation are needed, making this the final key decision stage.

Under existing law, no two regulators will consider identical factors in this fourth stage. Frequently this is because of the specific legislative mandates under which they operate. More generally, however, these factors should be of a technological nature such as technical feasibility, cost effectiveness, or other economic and societal considerations of all types, including the acceptability of the ultimate outcome.

In summary, then, the first two stages are scientific in character, the third requires scientific, technical, and some regulatory considerations, while the fourth is the province of the regulator responsible of making societal value judgments based on scientific, technological, and public input.

A rational, ordered thought process such as this is the only feasible approach to take in dealing with the fact of the uncertainties inherent not only in the basic scientific information but also in the regulatory process itself. This process, as outlined, can bring about the right kind of partnership between science and society in the regulatory process.

Such a process helps accelerate the setting of priorities through risk assessment which determines whether there is a significant risk that can be significantly abated through regulation. It also accelerates the process of achieving sound and workable regulation with real relevance to the abatement of risks to human health.

Risk assessment has already been sanctioned by the Supreme Court which has upheld its use in two important, separate cases. The Court set aside the OSHA Benzene Standard, holding that OSHA's regulatory criteria on identification and control of potential carcinogens resulted in regulation of risks regardless of their significance (*Industrial Union Dept., AFL-CIO vs American Petroleum Institute*, 1980). This finding was reaffirmed in the Cotton Dust case which stated the regulation should be directed at significant risks (*American Textile Manufacturers Institute vs Donovan*, 1981).

The principles I have discussed have so far been specifically addressed only to some of the issues involved in only some of the many areas of regulation. The principles are so general, however, that they can be broadly applied even to areas beyond those contemplated when they were originally drawn up. I have in mind not only other regulatory areas, but also their application in individual companies.

Within my own company we utilize our own system for risk assessment and response (Deisler, 1982) which, while being far more detailed as to technique, is very similar to the one I have described; and we have had considerable success in applying it internally to those situations where regulatory guidance did not seem to be sufficient. One of the details is worth mentioning. We are not in a position, as a company, to

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determine what risk is acceptable. We can, however, consider comparative risks and define goals for risk reduction to help ourselves in the pragmatic characterization of risks. This aids in deciding what responses may be needed to abate the risk from an identified hazard.

THE LESSON OF LOVE CANAL

To illustrate the generality of these principles in other regulatory areas, I would like to discuss one of the messiest and most complex problems now facing the public, government, and industry. This is the problem of hazardous waste sites. In this field there are some bad examples of how not to go about the solution of the problems, but some good examples are beginning to appear as well.

Among the best known of the bad examples is the Love Canal site. This is a well-worn example, and I certainly do not propose to review it in detail. But certain aspects are worth discussing within the context of what I have previously stated.

Dr. Lewis Thomas, head of the Memorial Sloan-Kettering Cancer Center, was asked by New York Governor Hugh Carey to head a commission to review the so-called scientific studies relating to Love Canal (New York State, 1980).

These studies have become the basis for widespread publicity and for the compounding of apprehension within the Love Canal community. In its report, the Commission finds most of them to be fatally flawed. Among the shortcomings: failure, in some cases, to provide adequate controls; failure to validate through proper medical methods the illnesses that were found; the use of scientifically invalid methodology; and the drawing of unfounded conclusions from reports which, at times, were impossible to interpret. The Commission noted that the damage done by this combination of bad work and bad management is perhaps beyond mending, and that many of the Love Canal residents have become so distrustful of government agencies and their scientific reliability that they are unwilling to believe anything except the worst news about themselves.

Clearly, scientific approaches taken to deal with the Love Canal waste site were grossly inadequate. The Lewis Thomas Report, itself, is at times scathing in its criticism. The Commission concluded that the critical failure is the inconclusiveness of studies carried out to date. Where improvements in public and decision-maker understanding might have been achieved, only further questions and debates on scientific credibility have been the result.

Love Canal is a classic case of value judgments being placed ahead of good scientific judgment. In fact, value judgments came in at the very beginning, before valid scientific determinations were made. The studies did not even address the first stage, Hazard Identification. They leaped immediately to stage 4, Regulatory Response, basing statements and proposed actions purely on assumptions.

In this case, the regulators did not seek sound scientific facts on which to base any societal value judgments. Within the context of the risk management process, the regulator's job is defined in two parts: (1) to manage, from the beginning, the process that brings the scientific facts into consideration, to identify hazards, evaluate hazards, assess risks, and determine if action is needed; and (2) to manage the process which ultimately results in this value judgment and in the needed course of action.

REGULATOR VS SCIENTIST ROLE

Regulators have the critical responsibility for ensuring that societal value judgments are considered at the end of the regulatory process. Yet they have been reluctant to do this. The scientists have gotten caught in the void created by the regulator's hesitancy and, out of necessity, have been forced to make value judgments.

The role of the regulator has not been clearly defined or understood. This has resulted in the regulator expecting too much of science, asking it for societal value judgments while constraining its full exercise to "ensure," somehow, that only "safe" decisions are made.

On the other hand, scientists often do not stop to consider what is their role. They may think very clearly in the specifics of their science, but they are only human. When the scientist gets into an area where his scientific assessment could result in some number of people falling prey to a serious disease, it is difficult to separate emotions from judgment. This could result in the scientist unwittingly usurping the role of the regulator. Scientists should be asked to produce only their best scientific estimates since these are the best tools available to the regulator.

This explains the concern which AIHC, in stating its principles, exhibits so strongly—trying to distinguish and separate the independent scientific role and the regulatory role while insisting that the regulator must be the overall manager of the process to ensure that it is conducted correctly. The responsibility of the regulator is a clear and a heavy one!

CURRENT APPLICATIONS OF AIHC PRINCIPLES

Going beyond the Love Canal example, can assessment and abatement approaches be taken that are more effective scientifically and less unsettling socially?

I believe that the implementation of principles such as those I have discussed is the only answer now available to this question. Currently, I am aware of the handling of waste sites in both Tennessee and California which are proceeding by a process parallel to the AIHC risk assessment and management step-by-step process. I would like to think that these sites, as well as others, will use this rational process to achieve successful solutions. I would like to describe briefly where each one of them is in the process.

In Memphis, a project team from Johns Hopkins University, along with the Tennessee Department of Health, is determining whether a health effects study is feasible (Johns Hopkins University, 1981). Four different investigational plans are being prepared based on proximity of residents to waste sites, environmental sampling, and measuring of bodily presence of chemicals and of adverse health effects. Throughout this planning study, substantial efforts are being made to coordinate the work of all involved organizations and to consult the local public. This is in stark contrast to the procedures which were followed in the case of Love Canal.

Efforts are being somewhat hampered, however, by procedural barriers to investigation of health effects at the waste sites, such as denial of access for environmental sampling. In addition, the negative environment created by lawsuits is interfering with the exchange of medical and health-related information between qualified professionals. The investigation is, at the moment, still in the first stage, Hazard Identification. Difficult and tortuous as the real path to a sound solution may be, or even

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to the accomplishment of Hazard Identification, progress is being made, and the necessary stages can, in due course, be accomplished.

An investigation of the McColl disposal site in Fullerton, California, has uncovered considerable information on chemical composition and environmental impact (Stephens, 1981; Dreith, 1982). The study was undertaken using the task force approach, with public agencies performing tasks relating to five identified study areas. As in the case of Memphis, there have been difficulties in developing meaningful health data. Citizens' emotions are a factor; however, the continued effort to communicate the nature and progress of the study to the citizens is clearly the solution to this part of the problem. Environmental monitoring is continuing, although it has so far failed to establish the presence of substances in concentrations sufficient to cause adverse health effects to the public at large. Other aspects of hazard identification are going forward, such as the study of the site itself from the geological and hydrological standpoints, to establish not only whether there are hazards present at the moment, but whether there is the possibility of hazards arising in the future.

The evaluation of a waste site involves applying the four-stage process in parallel to various aspects of the site. This is because a site is so complicated, from both the health hazard and environmental standpoints as well as from hazards which may exist not only today, but in the future because of the migration of the materials in the site. Thus, while some aspects of the investigation at the McColl site are still in the Hazard Identification stage, others have moved into the second stage of Hazard Evaluation. This is a case, like Memphis, where there has been a deliberate avoidance of leaping to conclusions before the existence and the degree of hazard have been determined so that the risks can be assessed and the proper responses made. My company is one of those which has involved itself in assessing the McColl site, along with public governmental bodies, and I am hopeful we can all keep on the steady track toward an ultimate satisfactory solution that has so far been our course.

One item I should mention in the evaluation of a waste site is nuisance. This could include odor or unsightliness, for example, and depending on such factors as location, could lead to some form of action even if the evaluation of health or environmental risks would not do so.

While there is no simple and rigid methodology on how to determine the potential hazard of chemicals at a waste site, the risk of exposure now and in the future, and the potential health effects from such exposure, a rational process based on sound scientific efforts and a step-by-step evaluation offers the best hope of arriving at workable solutions. Such a process has been outlined by the AIHC, and as I noted earlier, it appears to have practical common-sense application to areas well beyond those conceived by its originators.

CONCLUSION

A framework for decision making represents a common-sense approach. It offers demonstrable progress and is more acceptable to those affected who can understand what is being done, more so than with the hit-or-miss, rigid rules of the past. Fear of the unknown is what causes irrational emotions. While science is not going to solve political problems, the use of common sense in defining the problems and the answers, and assisting science to do its proper job, can help gain the necessary public support and cooperation.

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Industry has accomplished quite a bit in its efforts to seek sound and responsible regulation. In fact, the concepts industry has put forward through trade associations such as the AIHC are the most fruitful we have to date.

I hope I have not left the impression that the AIHC or any other trade association or industry group has come up with the ultimate solution to all of our problems and we can now go home and forget about it. I would like to emphasize that these principles have *not* been fully embedded, by any means, in the legislative or the regulatory processes of this country, nor is it true that there is uniform awareness of the importance of doing so within the agencies. The climate today is more receptive, however, and now, with this receptive climate, we have the opportunity to get these principles and methodologies embedded in the laws as they are amended, in regulations as they are created, and in policies as they are devised.

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A Systematic Approach to Reducing the Risk of Industrially Related Cancer

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One specific concern that has received public attention in recent times is the possible risk of cancer from exposure to industrial chemicals. Although it is not known presently how much cancer is caused by exposure to chemicals from industry, and although the amount is believed by many to be low, responsible corporate actions to reduce the threat of industrially related cancer must be a part of daily business. Even though the personal and emotional impacts of cancer pose a great difficulty in dealing with its risk, if we take a realistic view, it is possible to place the risk into a more manageable perspective and thereby not impede our efforts toward abating it.

To that end, we have developed a four stage process for making decisions about cancer risk and actions to reduce it, together with a system for classifying risks as "high," or "low," or "insignificant." The four stages are: hazard identification, hazard evaluation, risk evaluation and risk response.

A proper understanding and use of this systematic process by legislative and regulatory bodies could lead to more rational decisions about how to best allocate society's finite resources so as to reduce cancer risks as soon as possible for the largest number of people. Use of this process will also accelerate the handling of the most significant risks first and, until our complex societal mechanisms move to determine what is acceptable risk, it will give us in industry a means for setting priorities and moving in a clearly desirable direction.

PREFACE

The purpose of this paper is to present the approach developed by the Shell Oil Company (hereafter referred to as Shell) to reducing the risk of cancer from exposure to industrial chemicals to the extent that, and whenever, such a risk exists. We believe that this approach is rational, systematic and, if incorporated into the lawmaking and regulatory processes, will have the effect of reducing such risk as soon and as effectively as possible for the most people.

Although industrially-related cancer is now believed to be a small contributor to the total amount of cancer, enormous attention nevertheless has been paid to it by the Congress, regulatory agencies and the media. Various federal agencies have pro-

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posed regulations attempting to address this topic. However, some of these initiatives, like the original OSHA cancer policy (OSHA, 1977), would not deal effectively with the problem of industrially related cancer. Yet, if these measures had been implemented as originally conceived, it is estimated they would have cost the nation billions of dollars per year and they would have created a serious adverse financial impact on the chemical industry and on Shell to no good end.

But the story isn't all history. Right now the OSHA cancer policy is being reconsidered, and there is a group in the Administration charged with trying to develop a national cancer policy. The continuing regulatory effort in this and in almost every health and environmentally related area makes us see that this is a topic of significant regulatory importance. It is a topic that won't go away because many people think that exposures to potential carcinogens are more controllable in industry than elsewhere. It is easier to think that than to worry about such things as smoking or eating habits. Such habits are hard to control, as we well known.

In spite of the fact that cancer incidence from exposure to industrial chemicals is a small part of the total, it's more feasible politically to say that industry will solve all our problems than to say quit eating this or quit smoking that. *It is easier to regulate industry than anybody else.*

If any of our chemicals do cause cancer, then we must certainly pay attention to the problem. But we are more than a little amazed at the tremendous amount of emphasis which has been placed on the small industrial contribution when there are other, larger causes that clearly should be dealt with. Because of the tremendous emphasis which has been placed on this issue, the tremendous potential costs involved, and the ineffectiveness of the regulatory proposals that have been made so far, this is a big problem for industry and for Shell. We must pay attention to it.

What makes this a nationally important topic is that it will have a large impact on the development of regulatory schemes for other kinds of health effects. This topic is the leader. It is a pattern setter. The pattern of regulation established concerning this topic will carry over into other health areas and set the pattern for their regulation. So what we do in this area—what we think and say about this topic—is quite important. Because of these reasons, we felt impelled to develop our own views on how to think about this problem and how to develop effective regulations.

We also believed it essential that we be in a position to tackle problems we recognize which might not be covered by regulation. And we've done so—in those few instances where we found a problem.

Readers should recognize that these are our views at this time, based on our current knowledge and understanding. Additional knowledge and/or changing conditions could affect the future validity of conclusions derived from this material.

INTRODUCTION

Technical and scientific achievements in the past 100 years have resulted in dramatic benefits which enable people in our society to live more comfortably and for longer lifetimes. Yet concern exists about the growth of technology and any potential adverse health impact resulting from it.

One specific concern that has received public attention in recent times is the possible risk of cancer from exposure to industrial chemicals. It is known that some

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chemicals can cause cancer if people are exposed to them at certain levels. However, it is not known presently how much cancer is caused by exposure to chemicals from industry. The amount is believed to be low, according to noted authorities (Doll and Peto, 1981). Cancer is believed to result, for the most part, from our lifestyles: smoking or our eating and drinking habits, for example. Much of it may, in fact, prove to be preventable through actions we can take.

To the extent that risks to health, safety and the environment might result from the manufacture, distribution and use of our products, Shell must be concerned—because much of what we produce often ends up in the public's hands.

In Shell's July 1980 *Shell Views* on cancer ("Reducing the Risk of Cancer—a goal for the '80s")¹ Shell set forth its understanding of cancer and its causes. Shell concluded that responsible corporate actions to reduce the threat of industrially related cancer must be part of daily business. Industry must take into account health risks, along with all other elements, in doing its work in order to be a truly responsible part of society. Wise use of industry's resources is needed so that whatever risks of cancer its activities may engender, those risks are reduced as soon as possible for the largest number of people.

The personal and emotional impacts of cancer pose a great difficulty in dealing with its risks. We dread this disease which can be a lengthy, suffering, often terminal illness. However, in spite of our natural emotional response, if we take a realistic view of the risk of cancer, it is possible to place the risk into a more manageable perspective and thereby not impede our efforts toward abating it.

UNDERSTANDING RISK

Risk is an inevitable fact of life. Risk in industry is the same as risk in everyday life—it is the chance that something may prove to be unsafe, that some adverse effect may occur.

You drive your car to work safely, day after day. There is always the chance you will have an accident—if you're a good driver and lucky, you won't; but there's always the chance. It can happen. That's one example of risk.

Either consciously or subconsciously we all make judgments on acceptable risks to our lives. We are aware of relatively high mortality risks in such activities as smoking, rock climbing, excessive eating or motorcycling. On the other hand, generally we recognize very low risks of death from tornadoes, lightning, earthquakes, fishing, air travel or drinking municipal water.

Most of us tend to mix our emotional response to the event with our judgment of the risk and, for example, may be very frightened of lightning or earthquakes, but face smoking, excessive eating or motorcycling with greater equanimity. To some, smoking is a personal risk choice—in other words, it is a risk over which they *perceive* they have *some degree of control*. While the risk of being struck by lightning is very low, it represents much less of a personal risk choice. It is a risk over which people *perceive* they have *little control*. The perception of control or lack of control over risk affects our decision—both as individuals and as a society—as to the *acceptability* of a risk.

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The most widely used quantitative technique for stating risks to life is odds of death for a wide statistical sample. To the person who has lost a loved one in a car accident, or the individual suffering from cancer of the bladder, such statistics seem like a cruel hoax. However, to a society which has limited resources, such statistics have to be the foundation on which rests the allocation of its resources. Abatement of cancer from industrial chemicals, just as abatement of other risks to life, must be viewed in the context of intelligent allocation of resources.

Estimates of risks to people can be improved using epidemiological data when they are available. Epidemiology is the science that deals with the distribution and causes of a disease in a population. If the calculated results predict effects which could have been detected by an epidemiological study at an appropriate confidence level, and no such effects have been observed, then the subsequent risk evaluation should reflect this finding. We must bear in mind, however, that the absence of indicative results in an epidemiological study does not necessarily mean that no effect is possible. It just may not be measurable yet or the laws of chance may have acted to obscure it.

Industry has made significant progress in reducing risks in the workplace. That progress has depended on the results of scientific studies by industry, universities and government which identify hazards. Unfortunately, having identified hazards, the bluntness of the scientific tools available makes risk evaluation very imprecise. Thus, there are many disagreements about how to estimate the extent of risk.

SHELL'S DECISION PROCESS TO EVALUATE RISKS AND MAKE APPROPRIATE RESPONSES

There are many problems in evaluating and reducing risk. The key problem is we don't know all we need to know about the magnitude of risk, and yet decisions for action have to be made.

In making these decisions, we separate the different aspects of the decision process (Figure 1) into four stages (Deisler, 1982a):

1. Hazard identification
2. Hazard evaluation
3. Risk evaluation
4. Risk response.

Stage 1: Identifying a Hazard

Risk results from exposure to a hazard. A hazard is the existence of the potential for an adverse effect. The first step in dealing with risk is to identify the hazard.

For example, a cliff can be a hazard. So can a car or a loose skate. Similarly, a chemical substance, natural or man-made, may be a hazard.

Some agents have already been identified as human cancer hazards; for example, asbestos, vinyl chloride and benzene. Nature has its own chemicals which have been found to produce cancer such as aflatoxin which may be found in peanuts, corn and elsewhere.

Stage 1 is very important. In this step, existing data are examined to determine whether or not a hazard exists. If it does appear to exist, the decision process moves

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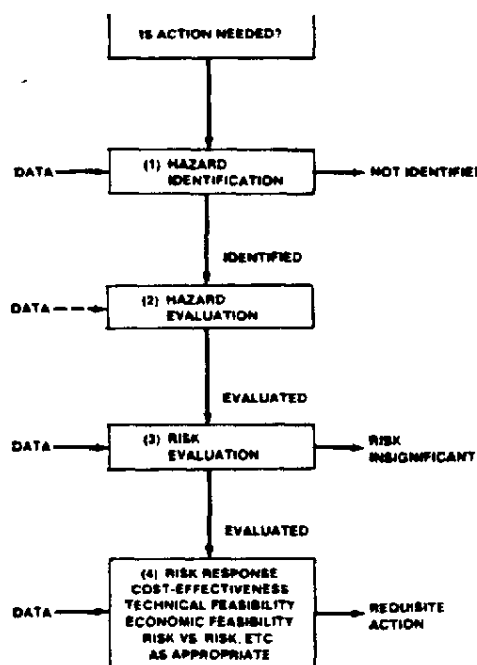


FIG. 1. Process for risk evaluation and response determination.

to the next stage; if not, resources can be re-allocated appropriately to deal with other potential hazards or to develop additional information to help identify the hazard under consideration.

Stage 2: Evaluating a Hazard

If the first step identifies a potential hazard, the second step is to evaluate that hazard to determine the likelihood for an adverse effect to result under specific conditions. The speed of a car, its location and direction of travel and its braking ability all bear upon the likelihood of it causing adverse effects. In the case of a potential human cancer hazard, evaluation involves estimating the ranges of carcinogenic response that might occur in humans under various levels of exposure.

How are human cancer hazards identified and evaluated? Some are first identified by case histories and they may be further evaluated by several means, including epidemiology.

Case histories have been a primary source of health hazard identification and evaluation in the past. Cancer of the scrotum was discovered in chimney sweeps in England 200 years ago as a result of case histories. Studies of these histories led to the conclusion that soot, or something associated with soot, was a cancer-causing agent—a carcinogen.

There are factors which can cause a hazard to be years or even decades before it is identified.

We hope that the impact of our work will be felt where early information is needed for experiments with humans. We hope to establish a system for the identification of hazards.

Single Case

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Animal Test

Animal Test

Other than informative models for the identification of hazards.

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There are limits to epidemiological studies. Often there are many confounding factors which obscure cause and effect. Epidemiological correlations may be suggestive of cause and effect, but they seldom demonstrate clear-cut relationships. Also, there has to be an observed effect on man before disease is recognized, and it may take years or even decades of exposure before such effects may be observed.

We hope to see cancer hazards identified and their risks reduced *before* we see an impact on man. After all, it would not be right to wait until such effects are observed where earlier indications are available. For this reason, we turn to additional sources of information for hazard evaluation. These include *single cell tests* and *animal experiments*. A full hazard evaluation requires the *extrapolation* of these results to humans, utilization of historical human data and the critical task of scientifically establishing biological plausibility.

Single Cell Tests

One of the best known single cell tests is the Ames test. Its purpose is to furnish quick, inexpensive screening to determine the mutagenic potential of a test compound.

In the Ames test, genetically-altered bacteria are exposed to the test material. These test bacteria have been altered in such a way that they are unable to reproduce. If the bacteria do reproduce in the presence of a test compound, it is evidence that a mutagenic change has occurred.

However, the results of these and other single cell tests cannot be directly extrapolated to whole animals or humans. Bacterial test cells are not the same as human cells. Bacteria used in the Ames test have been stripped of a major part of their normal defense mechanisms; mechanisms that human cells, and human bodies, *do* have. What happens to a single cell bacterium, or other single cell, in a particular kind of test may be very different from what happens to an animal or human cell, especially when embedded in its own, whole animal or human body with all the many forms of defense of which whole bodies are capable.

Thus, a positive result in the Ames test, by itself, is not indicative of human carcinogenicity. It can be used in conjunction with other single cell tests to provide information on the possible processes by which a compound may act. These results, other information and tests with animals can yield more definitive evidence about the possibility of human carcinogenicity.

Animal Tests

Other than historical observation in humans, animal tests provide the most direct information about the existence of a potential hazard, though animals are only rough models for each other and for human beings, at best.

A species of animals (such as rats) is exposed to a test compound at various dosage levels and the results observed. Usually the dosage levels used are far above those expected in human exposures because of the need to limit animal populations to manageable sizes and still be able to observe significant results. After having done this, it is then necessary to decide what such results might mean to humans. This is commonly referred to as "extrapolation from animal to man" and involves two steps:

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extrapolation from high test doses to the low doses of interest for people; and interpretation of the effects in terms of how humans might respond. The order in which these steps should be taken is not predetermined.

There are obviously many problems with this type of testing. It is costly because it involves many trained people testing many animals over a period of years, and it yields highly uncertain results. The largest animal experiment ever made involved more than 24,000 mice and took four years to complete. And the results are still not definitive. Even if they were definitive for the test animals, the differences in metabolic reactions and physiological functions between animals and humans could still have to be considered. The significance to the human system is a key, though difficult, determination.

Nevertheless, results from well-executed animal tests are considered to be important indicators for assessing human cancer potential. They are the best indicators we have at this time, even though indirect and uncertain.

Extrapolation

A key step in the use of animal data for human hazard evaluation is the extrapolation from the generally high experimental dose range for animals to the generally low dose range of interest for humans. This is normally done using mathematical equations, often called models, to represent possible biological responses. Currently used equations are very limited and simple, at best, compared to the underlying biological processes involved.

Simplistic selection of models and incautious interpretation of the resulting calculations can lead to highly distorted results. To try to minimize this distortion, we recommend taking at least the following two steps.

First, the most probable dose-response relationships and the uncertainties involved for each of several known models which appear to span the range of possible biological responses in the case considered should be calculated. Only those models which statistically fit the data well in the experimental range and which are not thought to be biologically unsound should be considered further.

Second, the results of those calculations should be used in combination with all other available, valid information to narrow the range of answers as much as possible.

By following these steps, one can get an estimate of the *ranges* of likely animal responses related to doses that people might encounter. In using these ranges, one must bear in mind that the *true* model is not really known; the true model's extrapolation could lie even outside of the calculated ranges, high or low. For example, there might be an exposure threshold, in a given case, below which no practical effect will occur.

Figure 2a illustrates the results of an experiment wherein rats were fed the compound ethylene thiourea (Graham *et al.*, 1975). $P(D)$, the fraction of animals exhibiting lesions at dose D , is plotted versus dose D (in ppm). $P(D)$ also represents the probability of an animal showing a lesion when exposed to dose D over the course of the experiment. It is, therefore, a measure of risk to the animals under study. Of the two models shown in the figure, the so-called One-Hit model represents the data very poorly and the Weibull model represents the data very well. The One-Hit model should be rejected from further consideration in this case.

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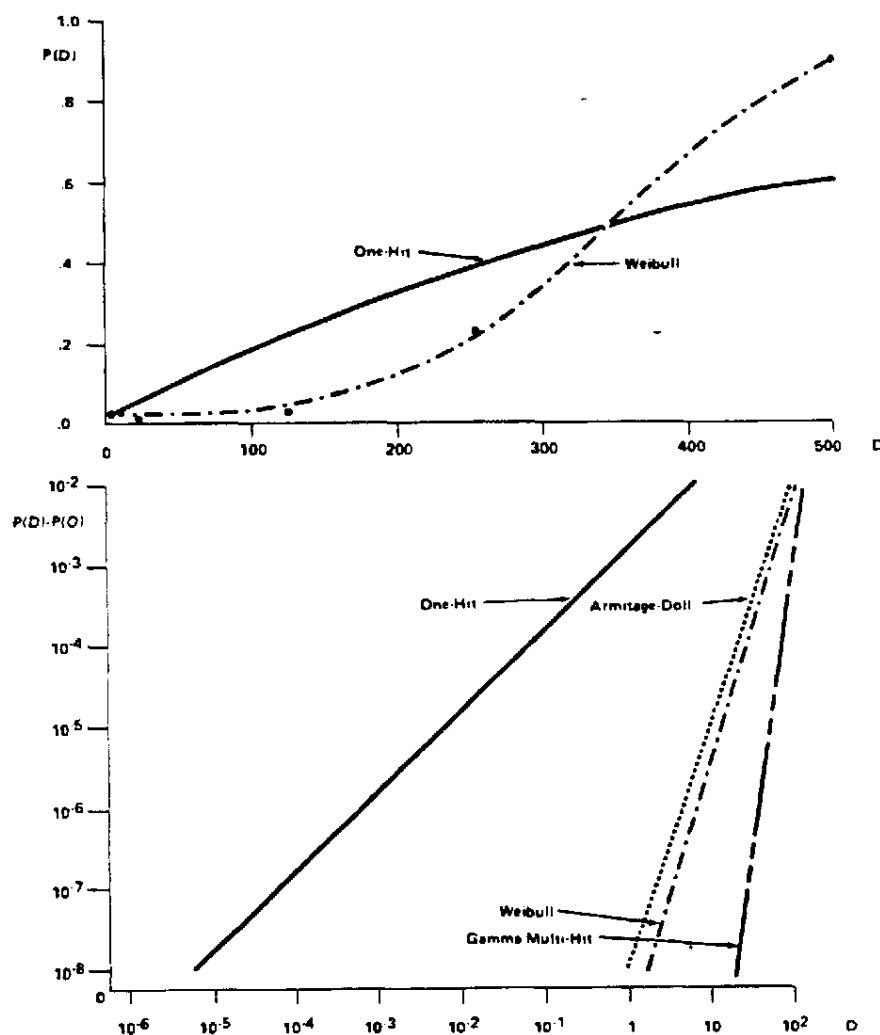


FIG. 2. Source: *Proposed System for Food Safety Assessment*. Final Report of the Scientific Committee of the Food Safety Council. Food Safety Council, Washington, D. C. June 1980. p. 152.

In Figure 2b, $P(D) - P(0)$, the rate of lesion occurrence at dose D minus the rate of occurrence in the control, is plotted versus dose D . The above two models and two others are shown, extrapolated to low dose levels, and the additional two models also fit the data well. In fact, in this case, the steepest model fits best of all. If these were all the rational models conceivable, then the ranges in which risks to rats might lie, expressed as probabilities, are indicated by the vertical distances between the Armitage-Doll and Gamma Multi-Hit lines in Figure 2b, plus the error margins due to experimental uncertainty (not shown). Here at a given dose level, the response

ranges may be several orders of magnitude wide and any additional information which helps to narrow these ranges is clearly desirable.

Beyond these two steps, recalculation of doses into equivalent human dosages by all reasonable means, together with an assessment of relative interspecies sensitivities, are needed to display what knowledge exists of the possible ranges of response which humans might exhibit. The assessment of relative sensitivities is very important—but scientific information is very limited in this area. The better designed the experiments, and the more information available on relative metabolic and other interspecies comparisons, the better will be these interpretations.

The further the extrapolation results lie from the actual data, the greater will be the divergence between models and the wider will be the estimated ranges of human response. It is desirable to use any data which increase the chances of validity of a particular model, rule out some models, or set bounds on where the extrapolations, in fact, might lie.

What must be done, then, in reaching a hazard evaluation is to give progressively less weight to the calculated results as extrapolations are extended. This requires us to use not only all valid information, but also the best scientific judgment. Correspondingly, more weight is given to other evidence which has a bearing on the evaluation of the hazard.

Stage 3: Evaluating Risk Associated with a Hazard

Once a hazard has been both identified and evaluated, comparisons can be made with known or potential exposure levels, the modes of exposure and the number of people potentially exposed. From this, the best estimated range of risk to humans in the real world can be expressed. Classifying these real risks is the desired end product of the third stage.

We classify risks by using the concept of risk regions (Deisler, 1982a; Deisler, 1982b): high risk, low risk and insignificant risk as shown in Figure 3. From the above discussions it is obvious that our measurement tools are too blunt for any finer divisions; yet two regions are too few for setting priorities in a truly useful way. While we cannot decide by ourselves what risks are acceptable, society, one way or another, might do so. A societal scale could thus have similar regions denoted "unacceptable risk," "variously acceptable risk," and, again, "insignificant risk."

Deciding whether a risk is insignificant or not is a most difficult, case-by-case, matter. Such factors as the number of people possibly affected and whether further reduction in exposures to the risk-causing agent is likely to yield significant improvements in safety must be considered.

More straightforward benchmarks are available for us to gauge the boundary between the high and low risk regions. Comparison with known risks of similar kind and effect is an important benchmark. Another is to select the boundary so that the corresponding risk level, if met or exceeded in all identified exposure situations, leads to an attribution of cancer to industrially-related causes which is small—and not really determinable—when compared with total cancer from *all* causes.

The proper definition of this boundary between the high and low risk regions should be considered when trying to answer the question of what is unacceptable risk to individuals *as individuals* and not, as is the case of the lower boundary, when trying

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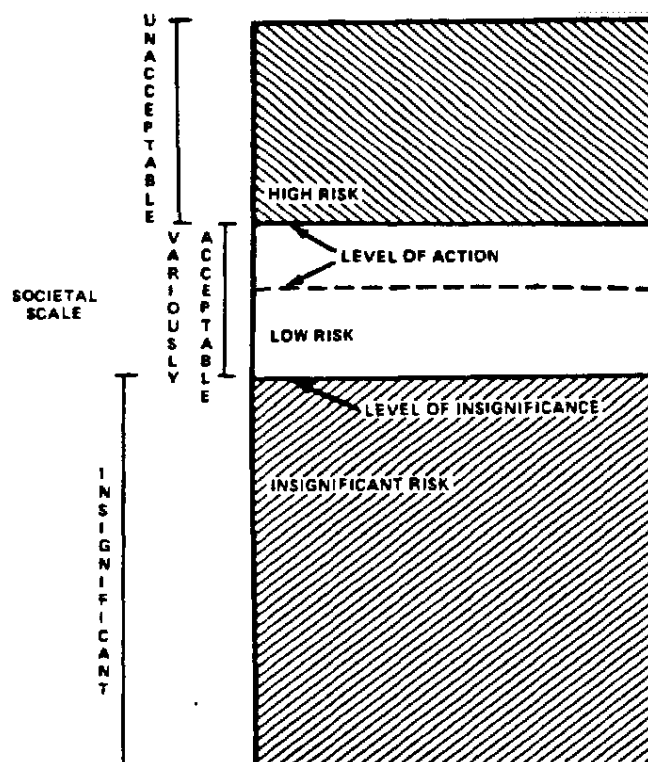


FIG. 3. Three risk regions.

to determine what individual risk is an insignificant risk when applied to *groups of individuals*.

In Shell, we use the concept of risk regions where other guidance is not available. Where a law or regulation sets an exposure limit below that developed from our risk assessment, we comply with the law. If we have information that suggests the need for a lower exposure level than that required by regulation, we carefully evaluate that information and may set an internal standard that is indeed lower than that required by regulation. For example, the *regulated* "time weighted average" exposure limit for epichlorohydrin is 5 ppm—Shell's limit is 1 ppm.

Given the ranges of expected responses, and a system for classifying risks such as the one described, the best judgment then must be exercised to conclude what level of risk we have to deal with: high, low or insignificant.

Stage 4: Risk Response

The fourth and final stage in dealing with risk is the response—what decisions do we make? It is here that we address all the fully evaluated scientific data, the technical and economic feasibility of ways to reduce risk and the resultant societal impacts.

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Out of this flows a decision on what actions are required to deal with the risk.

It is easy to say "let's eliminate all risk." But as previously noted, risk is inherent in everything we do. The philosopher William James once wrote: "It is only by risking our persons from one hour to another that we live at all." An unstated goal of society is to keep risk to a reasonably acceptable minimum since we know instinctively we cannot eliminate all risk or do without that which creates risk—life itself.

In Shell, as elsewhere in industry and society, there are finite resources—not just money, but also the number of experts and the amount of time and technology available. Thus, we must set priorities and handle the most important and opportune targets first. Our risk classification system helps us set priorities.

Discovery of a risk in the high risk region requires action to reduce or eliminate the risk because the risk is high, by our definition, and unacceptable. No action is taken in the insignificant risk region, but the door is left open for future consideration of any new data which may become available. For risks in the low risk region, exposures are reduced to the extent indicated by consideration of technical feasibility, cost-effectiveness, economic impacts and other relevant factors.

CONCLUSION

Shell is working toward a three-part goal which emphasizes the most effective allocation of our resources:

- (1) deploy our resources and information so as to protect the most people from the risk of cancer as soon and as effectively as possible;
- (2) lay a foundation for continuing risk reduction and control; and
- (3) as a desired, long-term end point, reduce the contribution to total cancer from industrially-derived agents to an insignificant level.

We believe our system is effective in reducing exposures for the most number of people in the shortest time, in handling the most significant risks first and in making maximum use of our finite resources of expertise, time and money. Also, it is designed to be compatible with the highly imprecise information with which we must deal.

No system is perfect. While our system provides a framework for ordering our thinking about risk, for inducing consistency and for making it possible to deal with exceptions and new knowledge, it can make no guarantees.

In using our system, we do not preempt society's right to determine what is acceptable risk. Until such time as our complex societal mechanisms move to address these situations, our methods give us a means for setting priorities and moving in a clearly desirable direction.

We believe that principles such as these, if incorporated into the processes by which laws and regulations are developed, will have the effect of reducing the risk of industrially-related cancer as soon and as effectively as possible for the most people.

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ARE YOUR GENES RIGHT FOR YOUR JOB?

*An employee's genetic makeup may
prevent him from getting a job —
or keeping the one he has*

By Chris Goodrich

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Jack, a young man in good health, applies for a blue-collar job at a vegetable oil processing plant. The company doctor gives him the routine physical examination—EKG, chest X-ray, eye and sight examinations, blood test. Two weeks later Jack gets a form-letter rejection; the company has hired someone more suitable for the job.

Jack does not know it, but he lost the job because of his genes. The company performed a genetic screening test on Jack's blood and discovered he might develop an antibody which, because of a potent chemical allergen found in the plant, would increase his risk of getting occupational asthma by three or four times. The company decided not to hire Jack because he might get sick on the job, thus preserving Jack's

health—and decreasing the chance of an injury-related employee lawsuit.

Although this case is hypothetical, it comes very close to reality. According to a survey on genetic screening use among the nation's largest industries, released in June 1982 by the Congressional Office of Technology Assessment, 59 corporations said they would begin some form of genetic screening of their workers within the next five years; 17 said that they had previously used the procedure, and six said they used it currently. The OTA's final report, *The Role of Genetic Testing in the Prevention of Occupational Illness*, has just been published.

Most of the parties involved in the survey—scientists, union leaders, politicians, industrialists—expressed sur-

prise that genetic screening was already so widespread. While most researchers were assuring the subcommittee that the technology is still embryonic, some industries seemed to be making employment decisions based, at least in part, on workers' genetic makeup. The initial curiosity about genetic screening turned into suspicion as its far-reaching implications began to emerge: Can an employer refuse to hire someone because he *might* get a disease? Can a worker insist on taking a job, even if it endangers his health?

The two major factions in the genetic screening debate are poles apart in their perceptions. The industrialists say the technology can be a great boon for worker safety, if and when it becomes precise in predicting susceptibil-

Genes

ity to occupational illnesses. If testing determines that a person is "hypersusceptible" to a hazardous substance, the industrialists reason, that person should not work anywhere near it. They regard genetic screening as a way to help them separate susceptible workers from potentially harmful chemicals.

The unions agree that workers should not be exposed to dangerous chemicals, but insist the business world is approaching the technology from the wrong direction. They say that industry should remove the hazard from the workplace, not the worker. The unions, and other opponents, see genetic screening as another step on the road to a corporate Big Brother. "If we know enough about a person's genetic profile, we could exclude him or her from almost any job," testified Dr. Howard Sloan, associate professor of pediatrics at Ohio State University, before the House Subcommittee on Investigation and Oversight of the Committee on Science and Technology.

How can a worker—or a fired worker, or a rejected applicant—find out whether his company has tested him for a genetic "susceptibility" or "deficiency"? What right does a company have to probe the most personal aspect of a worker's life—his genes, those bits of DNA which make him an individual?

Genetic screening is a direct spinoff of another technological advance that has worried many people—genetic engineering. Genetic engineering has made it possible to cut a gene's DNA into segments of known length by introducing a specific restriction enzyme into the gene. If a DNA fragment of unusual length is found, the DNA tested is abnormal. So far, only a few diseases have been identified with particular gene abnormalities, but it is possible that most genetic diseases will be identified with a specific DNA mutation. A person carrying the abnormal gene may be at greater risk of developing a specific disease—a form of cancer, for example—when exposed to hazardous chemicals.

It is also true, however, that an abnormal gene may be harmless. Some traits are healthful and harmful at the same time; sickle-cell trait, for instance, carried by 8 percent of the American black population, provides a measure of protection against malaria but may lead to blood damage in low-oxygen environments. (Blacks with sickle-cell trait were not admitted to the Air Force Academy until 1980; it was feared that as pilots

they might pose a danger to themselves and other servicemen should their aircraft lose pressurization.) But on the grounds that any genetic abnormality could lead to health problems and, potentially, a lawsuit, an employer might decide to exclude certain workers from an applicant pool even though his genetic mutation was completely benign.

Testing methods

There are two kinds of genetic screening, one called biochemical testing and the other cytogenetic testing. Biochemical testing, performed only once, tests whether the individual carries a particular trait that might make him more susceptible to harm from hazardous chemicals; cytogenetic testing, performed at intervals over a period of months or years, tests whether an individual's genetic makeup is changing over time, and may enable the physician to determine how exposure to hazardous substances has affected the patient's genes. (The terminology is further complicated by OTA's decision to restrict its definition of genetic screening to biochemical testing, and to replace the term cytogenetic testing with genetic monitoring.) Biochemical testing is fairly reliable; cytogenetic testing, according to the OTA report, is merely "suggestive."

The simplicity with which a genetic test is performed stands in stark contrast to the complex issues it presents. According to testimony before the House Subcommittee on Investigation and Oversight,

chaired by Albert Gore Jr. (D-Tennessee), pre-employment physical exams are given to almost half of all employees, and often entail the taking of blood samples. A small quantity of blood is all that is needed to perform genetic testing. Robert L. Jennings Jr., a former OSHA attorney now practicing with Baskin & Sears in Pittsburg, says "There are no laws saying what can be tested for."

Legal issues

The present legal status of genetic screening is moot. Case law is almost nonexistent. The only statutes governing the tests are a handful of sketchy state laws and there is no federal regulation. An applicant denied a job because of his genes may, nonetheless, have a wide range of state and federal legislation under which to sue: the Occupational Safety and Health Act of 1970, the Rehabilitation Act of 1973, Title VII of the Civil Rights Act of 1964, some state privacy and confidentiality statutes, and various state laws regarding discrimination, occupational safety and health, and the rights of the handicapped.

"This is going to be one of the most important areas of occupational health litigation in the future," says Michael S. Baram, a professor at Boston University School of Law. Baram is co-chair of a conference titled "Biological Monitoring and Genetic Screening in the Industrial Workplace," to be held in Washington, D.C., in May.

The most sensitive area in which law-

'Whole classes of able-bodied individuals will be rendered unemployable.'



Chris Goodrich is assistant editor of California Lawyer.

suits are likely to occur involves Title VII, which prohibits employment discrimination based on race, color, religion, sex or national origin. This is so, says Geoffrey M. Karny, project director of the OTA's biological applications program, because possibly deleterious traits show up in particular ethnic populations or aggregate by sex.

The classic example is the sickle-cell trait among blacks, and it was the most frequently used test uncovered by the OTA survey. Carrying one sickle-cell trait does not cause anemia—sickle-cell anemia is a result of carrying two such traits, one from each parent. However, scientists have yet to decide whether a single sickle-cell trait is harmful, or lowers the carrier's resistance to anemia. Because anemia can be aggravated by certain workplace chemicals, a company might wish to screen out workers who carry the sickle-cell trait. If a black were denied a job because he had the trait, Karny says, he could establish a prima facie case of discrimination against the employer because the screening practice had a "disparate impact" on his race.

Karny, an attorney, told the Gore subcommittee that in such a case an employer "would have the burden of justifying the screening program by demonstrating its relation to legitimate job requirements or business needs. It is presently unclear whether avoiding tort liability or the cost of engineering controls (in the workplace) is a business necessity or whether the employee's capacity to perform the job without a risk of future illness is a job-related characteristic.... Since genetic screening is currently of low or uncertain predictive value, a program that had disparate impact on the employment opportunities of the classes protected by Title VII would violate that Act."

The Rehabilitation Act could afford grounds for a genetic discrimination suit, Karny says, "if the individual's genetic makeup could be read as a handicap." If it met that standard, the courts would then have to rule on whether a handicapped person could be denied a job because of a "reasonable probability of future illness." Karny notes that the Rehabilitation Act affects only employers who receive federal funds—which still involves millions of people—but that in most states similar statutes offer even broader protections to the handicapped.

Most of the state laws relating to genetic screening deal only with the sickle-cell trait. North Carolina, Florida and Louisiana all have statutes that prohibit employment discrimination on the basis of the trait. New Jersey instituted a broader rule in 1981, prohibiting discrim-

ination against any person who carries atypical hereditary blood traits, and specifies sickle-cell, hemoglobin-C, Tay-Sachs, thalassemia and cystic fibrosis traits.

Much of this legislation stemmed, at least in part, from a 1980 *New York Times* series on genetic screening ("The genetic barrier: job benefit or job bias?" February 3-6). The most controversial of the four articles discussed the sickle-cell screening of black employees at E.I. du Pont de Nemours & Company. According to Dr. Bruce W. Karrr, du Pont's corporate medical director, the company started the testing in 1972 at the request of black workers, when there was scientific debate over whether a single sickle-cell trait might be harmful.

Companies using genetic screening are not volunteering their identities.

The *Times* article implied that du Pont used the testing for "nefarious purposes," but Karrr says the tests—still given to new employees on request—are "unrelated to job placement, hiring and firing, or any employment decision." He told the Gore subcommittee that du Pont's physicians "did not routinely tell the black applicant that sickle-cell testing was being done, but if the sickle-cell test was positive, he was given the results."

In 1974 du Pont began to monitor for glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, which predisposes the carrier to anemia, and serum alpha₁-antitrypsin (SAT) deficiency, which predisposes the carrier to emphysema. A physician in the company's Deepwater, New Jersey plant suggested these tests be implemented, Karrr says, to see whether test results might predict the likelihood of future illness being caused or worsened by certain chemicals in the facility. The tests were discontinued in 1981.

The *Times* stories were also a significant impetus behind the October 1981 hearings on genetic screening. The Gore subcommittee eventually suggested that an anonymous questionnaire be circulated to find out what was being done with the procedure, and it was this survey that catalyzed the screening furor. The survey disclosed not only that genetic screening was in much greater use than anyone had imagined, but that it had been used, in most cases, for more than research. Though the most common action resulting from the screening was to inform the employee of the test results, in

five cases an employee was transferred and in two cases it was suggested that an employee seek another job.

Karrr says the results of the four-page survey, which was sent to the Fortune 500 companies and the nation's 50 largest private utilities, were "blown all out of proportion." The 59 companies that said they planned to institute genetic screening within five years may well have meant they would do so only after the technology had been perfected, says Karrr. He adds, however, that he was surprised that five other companies, besides du Pont, were already using genetic screening.

Because the survey was anonymous, no one seems to know the names of the other companies currently using genetic screening—and they are not volunteering their identities. But the number of companies screening at the time of the survey do not represent a particularly narrow range of industry; two were chemical companies, two were utilities, and two were in the electronics industry. Half of the companies that said they had tested in the past were chemical manufacturers, and many chemicals—such as benzene, vinyl chloride, and toluene—are known to cause or aggravate cancer, emphysema and other diseases.

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There is an ironic twist to the legal implications of genetic screening: In some cases pre-employment screening might be required. A parallel can be drawn with the practices of railroad companies, which routinely X-ray prospective employees for back problems when a job entails a large amount of back stress. Under the Federal Employers Liability Act, a railroad company cannot assign a worker to a job that is hazardous to the worker, other employees or the public. A similar standard could arguably be applied to job assignment or job rejection made on

Genes

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There are also unavoidable standards for employment in certain occupations. Railroad switchmen, for instance, cannot be colorblind or color-impaired, since they must be able to distinguish between red and green. Certain physical requirements—referred to as bona fide occupational qualifications, or BFOQs—may indeed exclude some applicants from specific jobs, and such requirements have been upheld in court.

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Will regulation be effective?

No one knows how much of a legal snarl genetic screening is going to create, of course, or whether the snarl can be anticipated by timely legislation. An important pending federal case is *Christman v. American Cyanamid Co.* (ND W Va, No. C-80-0024-PH) in which a number of women allege they underwent sterilization in order to comply with the company's policy of prohibiting fertile women from working near substances that could endanger the health of a fetus.

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VII can provide enough protection. It is difficult to say, too, whether federal legislation would be effective, since advances in identifying the genetic sources of disease may be achieved much faster than controlling regulations. The City of Hope National Medical Center in Los Angeles, for instance, has recently announced a new technique for detecting genetic diseases which researcher R. Bruce Wallace says may enable scientists to isolate the problem genes for 10 different diseases by the end of 1983.

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ARE YOUR GENES RIGHT FOR YOUR JOB?

*An employee's genetic makeup may
prevent him from getting a job —
or keeping the one he has*

By Chris Goodrich

Jack, a young man in good health, applies for a blue-collar job at a vegetable oil processing plant. The company doctor gives him the routine physical examination—EKG, chest X-ray, eye and sight examinations, blood test. Two weeks later Jack gets a form-letter rejection; the company has hired someone more suitable for the job.

Jack does not know it, but he lost the job because of his genes. The company performed a genetic screening test on Jack's blood and discovered he might develop an antibody which, because of a potent chemical allergen found in the plant, would increase his risk of getting occupational asthma by three or four times. The company decided not to hire Jack because he might get sick on the job, thus preserving Jack's

health—and decreasing the chance of an injury-related employee lawsuit.

Although this case is hypothetical, it comes very close to reality. According to a survey on genetic screening use among the nation's largest industries, released in June 1982 by the Congressional Office of Technology Assessment, 59 corporations said they would begin some form of genetic screening of their workers within the next five years; 17 said that they had previously used the procedure, and six said they used it currently. The OTA's final report, *The Role of Genetic Testing in the Prevention of Occupational Illness*, has just been published.

Most of the parties involved in the survey—scientists, union leaders, politicians, industrialists—expressed sur-

prise that genetic screening was already so widespread. While most researchers were assuring the subcommittee that the technology is still embryonic, some industries seemed to be making employment decisions based, at least in part, on workers' genetic makeup. The initial curiosity about genetic screening turned into suspicion as its far-reaching implications began to emerge: Can an employer refuse to hire someone because he *might* get a disease? Can a worker insist on taking a job, even if it endangers his health?

The two major factions in the genetic screening debate are poles apart in their perceptions. The industrialists say the technology can be a great boon for worker safety, if and when it becomes precise in predicting susceptibil-

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ity to occupational illnesses. If testing determines that a person is "hypersusceptible" to a hazardous substance, the industrialists reason, that person should not work anywhere near it. They regard genetic screening as a way to help them separate susceptible workers from potentially harmful chemicals.

The unions agree that workers should not be exposed to dangerous chemicals, but insist the business world is approaching the technology from the wrong direction. They say that industry should remove the hazard from the workplace, not the worker. The unions, and other opponents, see genetic screening as another step on the road to a corporate Big Brother. "If we know enough about a person's genetic profile, we could exclude him or her from almost any job," testified Dr. Howard Sloan, associate professor of pediatrics at Ohio State University, before the House Subcommittee on Investigation and Oversight of the Committee on Science and Technology.

How can a worker—or a fired worker, or a rejected applicant—find out whether his company has tested him for a genetic "susceptibility" or "deficiency"? What right does a company have to probe the most personal aspect of a worker's life—his genes, those bits of DNA which make him an individual?

Genetic screening is a direct spinoff of another technological advance that has worried many people—genetic engineering. Genetic engineering has made it possible to cut a gene's DNA into segments of known length by introducing a specific restriction enzyme into the gene. If a DNA fragment of unusual length is found, the DNA tested is abnormal. So far, only a few diseases have been identified with particular gene abnormalities, but it is possible that most genetic diseases will be identified with a specific DNA mutation. A person carrying the abnormal gene may be at greater risk of developing a specific disease—a form of cancer, for example—when exposed to hazardous chemicals.

It is also true, however, that an abnormal gene may be harmless. Some traits are healthful and harmful at the same time; sickle-cell trait, for instance, carried by 8 percent of the American black population, provides a measure of protection against malaria but may lead to blood damage in low-oxygen environments. (Blacks with sickle-cell trait were not admitted to the Air Force Academy until 1980; it was feared that as pilots

they might pose a danger to themselves and other servicemen should their aircraft lose pressurization.) But on the grounds that any genetic abnormality could lead to health problems and, potentially, a lawsuit, an employer might decide to exclude certain workers from an applicant pool even though his genetic mutation was completely benign.

Testing methods

There are two kinds of genetic screening, one called biochemical testing and the other cytogenetic testing. Biochemical testing, performed only once, tests whether the individual carries a particular trait that might make him more susceptible to harm from hazardous chemicals; cytogenetic testing, performed at intervals over a period of months or years, tests whether an individual's genetic makeup is changing over time, and may enable the physician to determine how exposure to hazardous substances has affected the patient's genes. (The terminology is further complicated by OTA's decision to restrict its definition of genetic screening to biochemical testing, and to replace the term cytogenetic testing with genetic monitoring.) Biochemical testing is fairly reliable; cytogenetic testing, according to the OTA report, is merely "suggestive."

The simplicity with which a genetic test is performed stands in stark contrast to the complex issues it presents. According to testimony before the House Subcommittee on Investigation and Oversight,

chaired by Albert Gore Jr. (D-Tennessee), pre-employment physical exams are given to almost half of all employees, and often entail the taking of blood samples. A small quantity of blood is all that is needed to perform genetic testing. Robert L. Jennings Jr., a former OSHA attorney now practicing with Baskin & Sears in Pittsburgh, says "There are no laws saying what can be tested for."

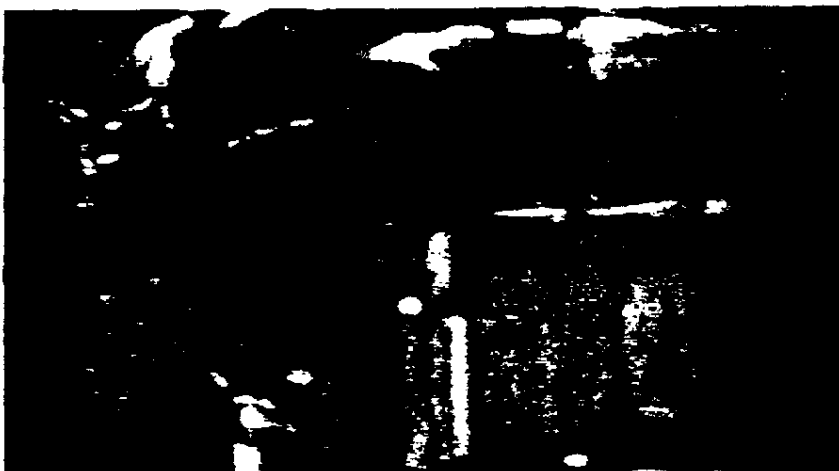
Legal issues

The present legal status of genetic screening is moot. Case law is almost nonexistent. The only statutes governing the tests are a handful of sketchy state laws and there is no federal regulation. An applicant denied a job because of his genes may, nonetheless, have a wide range of state and federal legislation under which to sue: the Occupational Safety and Health Act of 1970, the Rehabilitation Act of 1973, Title VII of the Civil Rights Act of 1964, some state privacy and confidentiality statutes, and various state laws regarding discrimination, occupational safety and health, and the rights of the handicapped.

"This is going to be one of the most important areas of occupational health litigation in the future," says Michael S. Baram, a professor at Boston University School of Law. Baram is co-chair of a conference titled "Biological Monitoring and Genetic Screening in the Industrial Workplace," to be held in Washington, D.C., in May.

The most sensitive area in which law-

**'Whole classes of able-bodied individuals
will be rendered unemployable.'**



Chris Goodrich is assistant editor of California Lawyer.

suits are likely to occur involves Title VII, which prohibits employment discrimination based on race, color, religion, sex, or national origin. This is so, says Geoffrey M. Karny, project director of the OTA's biological applications program, because possibly deleterious traits show up in particular ethnic populations or aggregate by sex.

The classic example is the sickle-cell trait among blacks, and it was the most frequently used test uncovered by the OTA survey. Carrying one sickle-cell trait does not cause anemia—sickle-cell anemia is a result of carrying two such traits, one from each parent. However, scientists have yet to decide whether a single sickle-cell trait is harmful, or lowers the carrier's resistance to anemia. Because anemia can be aggravated by certain workplace chemicals, a company might wish to screen out workers who carry the sickle-cell trait. If a black were denied a job because he had the trait, Karny says, he could establish a *prima facie* case of discrimination against the employer because the screening practice had a "disparate impact" on his race.

Karny, an attorney, told the Gore subcommittee that in such a case an employer "would have the burden of justifying the screening program by demonstrating its relation to legitimate job requirements or business needs. It is presently unclear whether avoiding tort liability or the cost of engineering controls (in the workplace) is a business necessity or whether the employee's capacity to perform the job without a risk of future illness is a job-related characteristic.... Since genetic screening is currently of low or uncertain predictive value, a program that had disparate impact on the employment opportunities of the classes protected by Title VII would violate that Act."

The Rehabilitation Act could afford grounds for a genetic discrimination suit, Karny says, "if the individual's genetic makeup could be read as a handicap." If it met that standard, the courts would then have to rule on whether a handicapped person could be denied a job because of a "reasonable probability of future illness." Karny notes that the Rehabilitation Act affects only employers who receive federal funds—which still involves millions of people—but that in most states similar statutes offer even broader protections to the handicapped.

Most of the state laws relating to genetic screening deal only with the sickle-cell trait. North Carolina, Florida and Louisiana all have statutes that prohibit employment discrimination on the basis of the trait. New Jersey instituted a broader rule in 1981, prohibiting discrim-

ination against any person who carries atypical hereditary blood traits, and specifies sickle-cell, hemoglobin-C, Tay-Sachs, thalassemia and cystic fibrosis traits.

Much of this legislation stemmed, at least in part, from a 1980 *New York Times* series on genetic screening ("The genetic barrier: job benefit or job bias?" February 3-6). The most controversial of the four articles discussed the sickle-cell screening of black employees at E.I. du Pont de Nemours & Company. According to Dr. Bruce W. Karrh, du Pont's corporate medical director, the company started the testing in 1972 at the request of black workers, when there was scientific debate over whether a single sickle-cell trait might be harmful.

Companies using genetic screening are not volunteering their identities.

The *Times* article implied that du Pont used the testing for "nefarious purposes," but Karrh says the tests—still given to new employees on request—are "unrelated to job placement, hiring and firing, or any employment decision." He told the Gore subcommittee that du Pont's physicians "did not routinely tell the black applicant that sickle-cell testing was being done, but if the sickle-cell test was positive, he was given the results."

In 1974 du Pont began to monitor for glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, which predisposes the carrier to anemia, and serum alpha₁-antitrypsin (SAT) deficiency, which predisposes the carrier to emphysema. A physician in the company's Deepwater, New Jersey plant suggested these tests be implemented, Karrh says, to see whether test results might predict the likelihood of future illness being caused or worsened by certain chemicals in the facility. The tests were discontinued in 1981.

The *Times* stories were also a significant impetus behind the October 1981 hearings on genetic screening. The Gore subcommittee eventually suggested that an anonymous questionnaire be circulated to find out what was being done with the procedure, and it was this survey that catalyzed the screening furor. The survey disclosed not only that genetic screening was in much greater use than anyone had imagined, but that it had been used, in most cases, for more than research. Though the most common action resulting from the screening was to inform the employee of the test results, in

five cases an employee was transferred and in two cases it was suggested that an employee seek another job.

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CHAPTER TWENTY-EIGHT

Industrial Toxicology: Retrospect and Prospect

JOHN A. ZAPP, JR. Ph.D.

Industrial toxicology is a comparatively recent discipline, but its roots are shadowed in the mists of time. The beginnings of toxicology, the knowledge or science of poisons, are prehistoric. Earliest man found himself in environments which were at the same time helpful and hostile to his survival. He found his food among the plants, trees, animals, and fishes in his immediate surroundings; his clothing from the skins of animals; and his shelter mainly from caves. His earliest tools and weapons were of wood and stone.

1 THE BEGINNINGS OF TOXICOLOGY

It was in the very early period of prehistory that man must have become aware of the phenomenon of toxicity. Some fruits, berries, and vegetation could be eaten with safety and to his benefit, whereas others caused illness or even death. The bite of the asp or adder could be fatal, whereas the bite of many other snakes was not. Man learned from experience to classify things into categories of safe and harmful. Personal survival depended on recognition and avoidance, so far as possible, of the dangerous categories.

In a unique difference from other animals, man learned to construct tools and weapons that facilitated his survival. Stone and wood gave way in time to bronze and then to iron as materials for the construction of these tools and weapons. The invention of the bow and arrow was a giant step forward in weaponry, for it gave man a chance to kill animals or other men from a safe distance. And man soon used his knowledge of the poisonous materials that he found in his natural environment to enhance the lethality of his weapons.

One of the earliest examples of the deliberate use of poisons in weaponry was the smearing of arrowheads and spearpoints with poisons to improve their lethal effectiveness. In the Old Testament we find at Job 6:4, "The arrows of the Almighty find their mark in me, and their poison soaks into my spirit" (The New English Bible version). The Book of Job is generally dated about 400 B.C.

L. G. Stevenson (1) cites the Presidential Address of one F. H. Edgeworth before the Bristol Medico-Chirurgical Society in 1916, to the effect that Odysseus is credited in Homer's *Odyssey* with obtaining a man-killing poison from Anchialos, king of the Taphians, to smear on his bronze-tipped arrows. This particular passage does not occur in modern translations of the *Odyssey* and, according to Edgeworth, was probably expurgated from the text when Greece came under the domination of Athens, at which time the use of poisons on weapons was considered barbaric and not worthy of such a hero as Odysseus.

Because the earliest literature reference to Homer is dated at 660 B.C., well before the Pan-Athenian period, an early origin of the use of poisoned arrows can be assumed. Indeed, the word "toxic" derives from the early Greek use of poisoned arrows.

The Greek word for the bow was *toxon* and for a drug was *pharmakon*. An arrow poison was, therefore called *toxikon pharmakon*, or drug pertaining to the bow. Many Latin words are derived from the Greek, but the Romans took only the first of the two Greek words as their equivalent of "poison," that is, *toxicum*. Other Latin words for poison were *venenum* and *virus*. In the transition to English, *toxicum* became "toxin," and the knowledge or science of toxins became "toxicology."

There were practicing toxicologists in Greece and Rome. Stevenson (1) refers to a book by Sir T. C. Albutt (2) according to which the professional toxicologists of Greece and Rome were purveyors of poisons, and dealt in three kinds: those which acted quickly, those which caused a lingering illness, and those which had to be given repeatedly to produce a cumulative effect. These poisons were of vegetable or animal origin, with the exception of arsenic. Although the toxicity of lead was described by Hippocrates, and of mercury by Pliny the Elder, these metals were apparently not deliberately employed as poisons before the Renaissance.

There is little doubt that the customers of the early toxicologists were interested in assassination or suicide. Poisons offered a safer means, for the assassin, of disposing of an enemy than the more visible alternatives which posed the risk of premature discovery and possibly effective retaliation. As a means of suicide, poison often seemed more acceptable than other available means of self-destruction. Although poisons have continued to be used for both homicide and suicide, their popularity for these purposes has decreased as the popularity of firearms has increased.

The use of poisons as adjuncts to other weapons such as the spear or arrow appears to have ceased in western Europe long before the discovery of firearms. It has persisted to this day in primitive civilizations such as those of the African pygmies and certain tribes of South American Indians. The use of poison on a large scale as a primary weapon of war occurred during World War I, when poison gases were employed by both sides. In the interval between World War I and World War II, the potential of chemical and biological agents as a means of coercion was thoroughly studied by most of

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the powers, and both sides were prepared to use them, if necessary, in World War II. Although their use in future wars has apparently been renounced, it should not be forgotten that the chemical and biological toxins remain viable means of coercion which could be utilized under appropriate circumstances in future conflicts. It would not be prudent to forget this in thinking in terms of national defense.

The early and sinister uses of poisons did result in contributions of toxicology. Furthermore, the knowledge obtained did not require extrapolation to the human species, since man was the subject in early experimentation.

As mentioned above, the professional toxicologists of Greece and Rome had recognized and dealt with poisons which produced acute effects, those which produced lingering effects, and those which produced cumulative effects. We recognize these categories today. The "dose-effects" relationship was also recognized. In Plato's well-known description of the execution of Socrates (3), Socrates is required to drink a cup of hemlock, an extract of a parsley-like plant bearing a high concentration of the alkaloid coniine. When Socrates asks whether it is permissible to pour out a libation first to any god, the jailor replies, "We only prepare, Socrates, just as much as we deem enough."

The ancients also had some concept of the development of tolerance to poisons. There have come down through the ages the poison damsel stories. In one of these, related by Stevenson (1), a king of India sent a beautiful damsel to Alexander the Great because he guessed, rightly, that Alexander was about to invade his kingdom. The damsel had been reared among poisonous snakes and had become so saturated with their venom that all of her secretions were deadly. It is said that Aristotle dissuaded Alexander from doing what seemed natural under the circumstances until Aristotle performed a certain test. The test consisted in painting a circle on the floor around the girl with an extract of ditany, believed to be a powerful snake poison. When the circle was completed, the girl is said to have collapsed and died. The poison damsel stories continued to appear from time to time, and even Nathaniel Hawthorne wrote a short story about one entitled "Rappaccini's Daughter."

Kings and other important personages, fearing assassination, tried sometimes to protect themselves from this hazard by attempting to build up an immunity to specific poisons by taking gradually increasing doses until able to tolerate lethal doses, sometimes—it is said—with disastrous results to the queen. Other kings took the precaution of having a slave taste their food before they ate. When slaves became too scarce or expensive, they substituted a dog as the official taster, and found that it worked about as well. Perhaps we have here the birth of experimental toxicology in which a nonhuman species was deliberately used to predict human toxicity.

2 FROM AGGRESSION TO PREVENTION

2.1 The Middle Ages

Little of importance to the science of toxicology developed during the Middle Ages. Such research as was done was largely empirical, and involved the search for such things as

the Philosopher's Stone, the Universal Solvent, the Elixir of Life, and the Universal Remedy. The search for the Universal Remedy is rumored to have been abandoned in the twelfth century when the alchemists learned how to make a 60% solution of ethyl alcohol through improved techniques of distillation, and found that it had some remarkable restorative properties.

2.2 The Sixteenth to the Nineteenth Centuries

Although modern science is generally held to have had its beginnings in the seventeenth century with the work of Galileo, Descartes, and Francis Bacon, there was a precursor in the sixteenth century of some importance to toxicology. This was the physician-chemist Phillipus Aureolus Theophrastus Bombastus von Hohenheim, known as Paracelsus. Born in 1490, the son of a physician, Paracelsus studied medicine with his father, and alchemy at various universities. He was not impressed with the way that either medicine or alchemy was being taught or practiced, and decided that more could be learned from the study of Nature than by studying books by ancient authorities.

Through travel and observation, Paracelsus learned more than his contemporaries about the natural history of diseases, to the cure of which he applied his knowledge of both medicine and alchemy. He advocated that the natural substances then used as remedies be purified and concentrated by alchemical methods to enhance their potency and efficacy. He also attempted to find specific therapeutic agents for specific diseases, and became highly successful as a practicing physician; in 1526 he was appointed Town Physician to the city of Basel, Switzerland, and a lecturer in the university. Being of an egotistical and quarrelsome disposition, Paracelsus quickly antagonized the medical and academic establishment.

Syphilis in the sixteenth century was a more lethal disease than it was to become later, and the medical profession had no interest in it or cure for it. Paracelsus introduced and advocated the use of mercury for the treatment of syphilis, and it worked. The establishment, however, was outraged and denounced Paracelsus for using a poison to treat a disease. Paracelsus loved an argument and responded to this and other accusations with a series of "Defenses," of which the Third Defense (4) contained this statement with respect to his advocacy of the use of mercury or any other poison for therapeutic purposes: "What is it that is not poison? All things are poison and none without poison. Only the dose determines that a thing is not poison." Paracelsus lectured and wrote in German, which was also contrary to prevailing academic tradition. When his works were eventually translated into Latin, the last sentence of the above quotation was usually rendered: "Dosis sola facit venenum" or "The dose alone makes a poison." This principle is the keystone of industrial hygiene, and is supported by experimental toxicology.

Mercury soon became and remained the therapy of choice for syphilis for the next 300 years until Ehrlich discovered on his 606th trial an arsphenamine, Salvarsan, which was superior. Antimony was widely used as a therapeutic agent from the seventeenth to the nineteenth century, with the medical profession sharply divided as to whether it was more poison than remedy or more remedy than poison.

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for syphilis for the next 300 years, Salvarsan, which was introduced in the seventeenth to the eighteenth century as to whether it was

The period from the seventeenth to the nineteenth century witnessed little decline in the use of human subjects for the initial evaluation of remedies. In 1604, a book said to have been written by a monk named Basile Valentine, but more probably by an anonymous alchemist, was published under the title *The Triumphant Chariot of Antimony*. The book states that the author had observed that some pigs fed food containing antimony had become fat. He therefore gave antimony to some monks who had lost considerable weight through fasting, to see if it would help them to regain weight faster. Unfortunately, they all died. Up to this time, the accepted name for the element had been stibium (from which we retain the symbol, Sb), but it was renamed antimony from the words *anti-moine* meaning "monk's bane." The Oxford English Dictionary agrees that this might be the popular etymology of the word. I am indebted to H. W. Haggard (5) for this anecdote.

2.3 The Nineteenth Century to the Present

Experimental toxicology as we know it followed the rise of organic chemistry, the beginning of which is usually dated around 1800. The rise was very rapid, and it is estimated that by 1880, some 12,000 compounds had been synthesized, and of these some turned out to be very toxic, and in some cases proved fatal to the chemists who prepared them. Two of the war gases employed on a large scale in World War I, that is, phosgene, COCl_2 , and mustard gas, bis(β -chloroethyl) sulfide, had been prepared in 1812 and 1822, respectively.

The early organic chemists were not deliberately looking for poisons, but for dyes, solvents, or pharmaceuticals, for example. Toxicity was an unwanted side effect, but if it was there it was there, and had to be recognized. The sheer number of new organic compounds being synthesized in the laboratory, along with a growing public disapproval of the practice of letting toxicity be discovered by its effects on man, led to a more extensive use of convenient and available animals such as the dog, cat, or rabbit as the surrogates for man, much as some of the ancient kings used dogs instead of slaves to test their food before they dined.

Loomis (6) credits M. J. B. Orfila (7) with being the father of modern toxicology. A Spaniard by birth, Orfila studied medicine in Paris. According to Loomis:

He is said to be the father of modern toxicology because his interests centered on the harmful effects of chemicals as well as therapy of chemical effects, and because he introduced quantitative methodology into the study of the action of chemicals on animals. He was the author of the first book devoted entirely to studies of the harmful effects of chemicals (Orfila, 1815). He was the first to point out the valuable use of chemical analyses for proof that existing symptomatology was related to the presence of the chemical in the body. He criticized and demonstrated the inefficiency of many of the antidotes that were recommended for therapy in those days. Many of his concepts regarding the treatment of poisoning by chemicals remain valid today, for he recognized the value of such procedures as artificial respiration, and he understood some of the principles involved in the elimination of the drug or chemical from the body. Like many of his immediate followers, he was concerned primarily with naturally occurring substances for which considerable folklore existed with respect to the harmfulness of such compounds.

A reading of some of the earlier nineteenth century reports indicates a lack of recognition of and concern with either intraspecies or interspecies variation. Sometimes it is not possible to determine from the report what species of animal was tested. Some reports were based on dosage of only one animal, it being assumed that all others would react similarly. In reports of inhalation toxicity, a lethal concentration might be identified without designating the length of the exposure time.

The initial experience of biological variability came more from study of the action of drugs than from study of the action of chemicals as such. The increased interest in the action of drugs resulted from the availability of so many new organic compounds that could be explored for possible therapeutic activity.

In the second half of the nineteenth century the phenomenon of biological variability was recognized by pharmacologists, as was also the necessity for establishing the margin of safety between a therapeutically effective dose and a toxic dose of a drug. Clinical trials of new drugs, with adequate controls, began to be accepted as good science. The traditional wisdom and beliefs about therapeutic practice were reexamined by the pharmacologists, but as Clark stated in the introduction to his 1937 monograph on general pharmacology (8):

The energy of pharmacologists during the second half of the nineteenth century was largely expended on this task which was both wearisome and thankless. Neither the clinicians or the drug manufacturers were grateful to the pharmacologist who hampered their freer flights of fancy by captious criticism.

The thanklessness of the pharmacologist's task becomes understandable in light of the economic and social theory prevailing during the nineteenth century. Adam Smith's book, *An Inquiry into the Wealth of Nations*, published in 1776, had argued that a laissez-faire policy was the best way to assure growth of capital, increasing production, and increasing prosperity, and this doctrine became the accepted belief of the Industrial Revolution. It did work well up to a point, but the increasing prosperity went to the capitalists rather than to the workers.

C. T. Thackrah, M.D. (9), a pioneer in British industrial medicine writing in 1831, stated: "Most persons who reflect on the subject will be inclined to admit that our employments are to a considerable degree injurious to health. . .," and "Evils are suffered to exist, even when the means of correction are known and easily applied. Thoughtlessness or apathy is the only obstacle to success."

But laissez-faire was defended even by prominent clergymen of the time. In 1850, Archbishop Whately, in England, wrote: "More harm than good is likely to be done by almost any interference in men's money transactions, whether letting and leasing, or buying and selling of any kind" (10).

And the Reverend Horace Bushnell advised the businessman to conduct his business according to the laws of trade, "and never let his operations be mixed up with charities."

By the closing years of the nineteenth century, however, strict laissez-faire economics was being seriously questioned, and the Church was beginning to preach the Social

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Gospel. At the same time Science was being looked to as the great hope for bringing about Utopia, and scientific research was encouraged.

It was also in the latter part of the nineteenth century that a change in attitude occurred toward occupational disabilities. As the Industrial Revolution brought more and more men, women, and even children, into work environments that were productive of occupational disabilities, and as the disabled were discharged and thrown upon public charity in strict adherence to laissez-faire policy, it began to appear reasonable to legislators in various industrialized countries that the industry responsible for occupational disabilities should bear their cost rather than the general public.

Germany led the way in 1883 with the passage of a Workingmen's Insurance Law which set up an insurance fund into which both employers and employees paid up to 6 percent of employee earnings. For this the workers obtained free medical care, as well as some compensation during periods of disability.

Since insurance premiums depend on the payout, and since both workers and employers were paying the premiums, each now had an incentive for minimizing the payout, and each group developed an interest in applying available remedies that would reduce disabilities.

England passed a similar Workman's Compensation Law in 1897, but in the United States the first State Workman's Compensation Law was not enacted until 1910, and the most recent in 1948. The National Safety Council was established in 1911, and in 1914, the U.S. Public Health Service set up its Division of Industrial Hygiene.

In the year 1914, the first American book on occupational diseases was published (11). It was written by W. G. Thompson, M.D., and shows a rather modern outlook as shown by the following:

It is quite true that many of the processes of manufacture will always involve risks to health, as many trades involve risk to limb and life. One cannot handle white lead without risk of disease, just as one cannot use dynamite without risk of injury. Yet, in each case, the workman has the right of warning against the hazard, the right of such protection as modern scientific knowledge affords, and should have the right of compensation when disabled as a result of the lack of such warning and protection.

The Occupational Safety and Health Act of 1970 (OSHA) affirmed these rights, but responsible industry had moved in that direction long before OSHA. It was about the time that Dr. Thompson's book appeared that some of the larger chemical companies began hiring corporate medical directors and physicians to provide on-site medical services directed not only to therapy, but also to prevention of occupational disabilities. No law, at that time, required that they do so.

There had been no organic chemicals industry in the United States prior to World War I. It was born just after World War I because we had felt, during that war, the effects of deprivation of such useful things as aniline dyes (used for printing our stamps and currency, among other things) and pharmaceuticals (including even aspirin), which we had been importing from Germany. There was a natural desire to free ourselves

from future dependence on such items, much as we have felt about oil imports since 1973. Fortunately, manpower and facilities used during the war for manufacture of munitions were available after 1918, and several companies decided to use both the manufacturing facilities and manpower to get into the organic chemicals business. And since neither employers nor workers had any previous experience in making and handling organic chemicals, the side effects of unanticipated toxicity began to be encountered. That toxicity was not wanted; it was counterproductive; it was a problem among other problems. Problems had to be managed if the industry was to survive.

To manage a problem, it must be anticipated, the causes must be identified and analyzed, and practical means of overcoming the problems must be available. As a means to this end, industrial preventive medicine, industrial toxicology, and industrial hygiene became valuable tools.

By the mid 1930s, three of the large chemical companies in the United States had established in-house laboratories of industrial toxicology. The companies were Du Pont, Dow, and Union Carbide. The purpose of these laboratories was to provide management with sufficient information about the toxicity of new chemicals to enable management to make prudent business decisions. Could the engineers design safe plants and processes for the manufacture and handling of the chemical? Could the final product be used safely for its intended use? If not, management could expect only trouble when the toxicity became manifest. No prudent management welcomes trouble.

By 1938, there were enough government affiliated people engaged in the practice of industrial hygiene on the federal, state, and local levels, to make possible the formation of the American Conference of Governmental Industrial Hygienists (ACGIH). In 1939, the American Industrial Hygiene Association (AIHA) was founded. These societies sought to bring collective knowledge and skills together in order to achieve a sound basis for all to carry out their responsibilities for recognizing, evaluating, and controlling those hazards of the workplace which cause occupational illness and disability, or even discomfort and reduction in efficiency. Above all, they believed in the possibility of controlling hazards through reduction of exposure to an acceptable level.

The *Journal of Industrial Hygiene* began publication in 1918, and the *American Industrial Hygiene Association Journal* began publication in 1939. Papers on industrial toxicology were accepted by both these journals.

The experience of the early industrial toxicologists and industrial hygienists was consistent with Paracelsus' principle that the dose alone makes a poison. Both in the toxicology laboratory and in the workplace it was observed that certain levels of exposure produced toxic effects but certain lower levels of exposure did not. Prevention of injury in the workplace could be accomplished, therefore, if exposure of workmen could be kept below a level which produced toxic effects. Industrial hygiene has operated by means of this method of control.

Following World War II, there was a marked expansion of the organic chemicals industry, particularly in the fields of organic pesticides, elastomers, and other synthetic polymers for use in textile fibers or plastic films. Food technology changed to meet increasing demands for food that kept well, was convenient to prepare, was attractively

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INDUSTRIAL TOXICOLOGY: RETROSPECT AND PROSPECT

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packaged, and looked, felt, and tasted good. Questions soon arose, however, about the safety of the new pesticides and food additives, and in particular about possible toxic effects from long-term low-level exposure.

By 1950, Congress was considering the necessity for amending the Food, Drug and Cosmetic Act of 1938 to meet the changed conditions, and the Food and Drug Administration had begun asking manufacturers to conduct "lifetime" exposure of at least one species, usually the rat, to establish "proof of safety" before marketing a new food additive or pesticide.

The Food Additives Amendment of 1958 required that any new intentional or unintentional food additive have FDA approval, usually in the form of a regulation, published in the *Federal Register* as a response to the manufacturer's petition for the proposed use, before the material could be marketed. Pesticide chemicals which leave a residue in or on raw agricultural commodities were soon brought under the same system of control. The FDA would establish a tolerance level for food additives or pesticides at either a presumed no-effect level or the lowest level required to produce the desired effect, whichever was the lower of the two levels. The Delaney clause, added to the Food Additives Amendment of 1958 on the floor of the House, prohibited the FDA from setting any tolerance other than zero, however, for any substance found to induce cancer when ingested by man or other animal. Initially, substances generally recognized as safe (GRAS) or substances covered by prior FDA approval (prior sanctions) would not be considered food additives under the Amendment, but subsequently, prior sanctions were cancelled and many substances from the original GRAS list were brought under the formal regulation process.

As time went on, the protocols acceptable to the FDA for toxicity tests offered as proof of safety for a proposed product became increasingly complex and expensive. The Occupational Safety and Health Act of 1970 (OSHA) was brought about in part by a concern for toxic effects on workers by long-term exposure to chemicals in the work environment. At the same time, the National Institute for Occupational Safety and Health was established in the Department of Health, Education and Welfare, to advise OSHA on the health aspects of chemical hazards of the workplace, and to recommend standards for the control of such hazards. The Toxic Substances Control Act of 1976 seeks to "regulate commerce and protect human health and the environment by requiring testing and necessary use restriction on certain substances, and for other purposes" (from the preamble to the act). The Environmental Protection Agency (EPA) took over from the FDA responsibility for establishing tolerances for pesticides and administers the Toxic Substances Control Act.

We have seen that during the nineteenth and twentieth centuries, industrial toxicology has come of age, and is no longer an option affordable by a few concerned industries resolved to protect their employees and the public by anticipating the possible toxic side effects of otherwise marketable commodities. Now, with the current laws and regulations, no industry can ignore toxicity as a key factor in business planning. Many in-house toxicology laboratories have been, and are still being, established since the 1930s. Commercial toxicology laboratories have multiplied to serve those who have no in-house

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laboratories, and some universities have set up institutes to carry out toxicity testing on a contract basis.

Whereas in the beginning toxicology served the purposes of aggression, the coin has now been reversed and in our time the largest number of toxicologists are serving the purposes of prevention, based on supplying accurate information and advice on the toxic potential of the multitude of chemical substances in man's environment.

3 THE DEVELOPMENT OF INDUSTRIAL TOXICOLOGICAL TESTING

Knowledge of the toxic effects of chemicals on man developed along two lines of investigation. The first was direct observation of effects produced in man. Even up to the nineteenth century substances thought to have therapeutic value were administered directly to man with often disastrous results. Haggard (5) tells of King Mithridates of Pontus, who in the second century B.C. had the ambition to discover a universal antidote for poisons. He is said to have sent men to search throughout the known world for all kinds of alleged poisons, and he administered these to slaves, observed the effects, and tried out various antidotes. He came up with a recipe for an antidote, found after his death, it contained 37 to 63 ingredients, all now believed to be worthless.

Direct observation of toxic effects on humans is still attempted through the discipline of epidemiology, but this involves only the observation of populations, and not the deliberate administration of chemicals to humans to observe their toxic effects.

The second method of obtaining knowledge of the toxic effect of chemicals on man is indirect. The substances are administered to animals, and the results are extrapolated to humans. This is the only acceptable method today, and is the method employed by industrial toxicology.

The question that industrial toxicologists were asking toward the end of the nineteenth century was "How much of this substance is safe?" rather than "How much is toxic?" Their thinking, however, was directed mainly to the question of acute toxicity. With the recognition that there was such a thing as intraspecies variability, experiments were directed toward estimating the minimum lethal dose, which was the largest dose that would kill only the most susceptible member(s) of the species. Something a little less than this might then be the largest dose that would *not* kill any members of the species. To approximate the minimum lethal dose, one obviously had to expose a number of animals to the same dose, and to use several different dose levels.

Consideration of the efficient use of laboratory facilities and cost control led to a shift away from the use of dogs, cats, and rabbits for acute toxicity experiments and to the use of rats, mice, and guinea pigs as the preferred test species. The albino rat emerged as the preferred species for most studies, at least in their preliminary stages. It is worth mentioning that much progress has been made in the commercial breeding of experimental animals for use in toxicity testing. The rats, mice, guinea pigs, and rabbits now available for purchase are relatively free from the diseases that commonly afflict these

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species, so that any pathological changes induced by the test chemical are more readily discernible than was the case even 25 years ago.

It was only in the twentieth century that a clear understanding of the quantitative aspects of biological variation developed. For any individual the effects of a given drug or poison would increase with increasing dose and decrease with decreasing dose. This had been known for a long time. But by 1937, Clark (8) could note:

One of the most familiar facts in medical practice is that no two persons respond in exactly the same manner to drugs. The use of biological methods for standardizing drugs has necessitated the measurement of the extent and distribution of individual variation in response to drugs, and in consequence a large [amount of] literature has accumulated.

What this large amount of literature had demonstrated was that for a population divided into subgroups receiving graded doses, a plot of a selected response, such as percent mortality, against dose (or most often the logarithm of the dose) usually assumed an S, or sigmoid, or ogival shape characteristic of the cumulative form of the normal curve of error. The greatest increase in mortality for a given increment of dose occurs around the 50% mortality point; hence the lethal dose for 50% of a population, the LD_{50} , can be calculated with greater precision and with fewer animals than any other percentage point. For these reasons, acute toxicity is usually expressed in terms of the LD_{50} , although for many purposes it might be more desirable to estimate, say, the LD_{01} or LD_{99} . If the data fit the theoretical curve fairly well, it is possible to calculate statistical confidence limits for the values obtained.

The sigmoid curve of response versus dose can be converted into a straight line if percent response is expressed as the corresponding multiples of the standard deviation. A probability graph paper soon became available on which percent response could still be plotted on the ordinate, but with the percents spaced so as to correspond to the appropriate multiples of the standard deviation. These techniques had been worked out by the middle 1930s.

There are other mathematical models besides the normal curve of error which provide reasonable approximation to observed dose-response data, but the LD_{50} remains the point that can be determined most efficiently, and it is therefore the usual index of acute toxicity. The slope of the dosage-mortality curve provides an index of potency.

If animals are exposed by the inhalation route, there are two variables that determine lethality. These are the concentration of the toxin in the air, and the time over which the animals are exposed. For a given exposure time, the most efficient measure of acute toxicity is the concentration causing 50% mortality, or LC_{50} . But for each LC_{50} the exposure time must be specified.

World War I stimulated a great many studies of acute inhalation toxicity for chemical warfare purposes. The number of compounds examined during World War I as possible chemical warfare agents is estimated to have been between 3000 and 4000, and of these, 54 were used in the field at one time or another. The German chemist Fritz Haber

proposed that for a given effect such as death, the inverse relationship between concentration and exposure time could be expressed by the simple equation $Ct = k$, where C is concentration and t is exposure time. This relationship holds fairly well over a relatively narrow range of concentrations and times. The information gained through the testing for military purposes had, of course, post-war value for industrial toxicology.

Some of the World War I chemical warfare agents were selected for their irritancy to skin or eyes, rather than for systemic toxicity, and both the techniques developed for their study, as well as the information gained, were useful to postwar industrial toxicology.

Although chronic, or cumulative, toxicity had been recognized for centuries, it received much less attention than acute toxicity until recent times, possibly because acute toxic effects were more likely to occur and be recognized than were chronic effects. Chronic toxicity could, however, be investigated by any relevant route of exposure provided the dosages used were small enough to permit the animals to survive their repeated assaults over a sufficiently long period of time to permit the chronic damage to appear. The most perplexing question was, "How long should a prolonged exposure be to gain all the necessary information?" Opinions differed, but the majority of toxicologists seemed to feel that 90 days of repeated exposure would be sufficient to elicit all the important manifestations of chronic toxicity in the rat or mouse provided the daily doses were sufficiently high but still consistent with survival.

In 1938, as a consequence of the elixir of sulfanilamide tragedy, in which a number of persons died as a result of taking a solution of sulfanilamide in diethylene glycol for therapeutic purposes, the U.S. Food and Drug Administration undertook a comprehensive investigation of the toxicity of the glycols. This investigation culminated in a "lifetime" feeding study with diethylene glycol in rats. In 1945, Nelson et al. (12) reported the results at a meeting of the Federation of American Societies for Experimental Biology. A surprising result of the study was the finding that some of the rats fed a diet containing 4% diethylene glycol had developed bladder stones, and that some of those with bladder stones had also developed fibropapillomatous tumors of the bladder. Since neither bladder stones nor tumors had been found in tests of shorter duration, it became obvious that, for some lesions, 90 days was not a sufficient time of exposure. By 1950, the Food and Drug Administration had begun recommending lifetime studies, for which they considered 2 years in the rat to be proper, as part of proof of safety of proposed new intentional and unintentional food additives and pesticides. As a guide to the perplexed, members of the FDA staff prepared an article entitled "Procedures for the Appraisal of the Toxicity of Chemicals in Foods, Drugs and Cosmetics," which was published in the September, 1949, issue of *Food Drug Cosmetic Law Journal* (13). It contained a section on how to do long-term chronic toxicity studies, and recommended a period of 2 years for the rat, plus 1 year for a nonrodent species such as the dog.

Although not an official regulation, the article advised everyone of the FDA's expectations with respect to data submitted to it as proof of safety of the proposed new food additive or pesticide. A revision of the article appeared in 1955 (14), and a third revision

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was published in 1959 as a monograph put out by the Association of Food and Drug Officials of the United States (15).

During the same period, the Food Protection Committee of the National Academy of Science/National Research Council was publishing and revising "Principles and Procedures for Evaluating the Safety of Food Additives" (16) which were, in general, consistent with the FDA staff's guidelines. One common thread ran through both sets of recommendations. With each revision, the complexity of the tests increased and so did the cost.

The FDA's recommended protocol in 1959 (15) for a "lifetime" test with rats called for four groups of a minimum of 25 males and 25 females each. There would be a control group, a low-dose group (a no-effect level, it was hoped), a high-dose group (chosen to be an effect level), and a mid-dose group. All animals would be necropsied for gross pathology. Selected organs would be weighed, and selected organs would be preserved for histopathology. During the course of the experiment, food consumption and weight gains would be measured, blood and urine would be monitored for deviations from normality, and any behavioral changes would be noted. A three-generation reproduction study would be carried out at all dose levels. Also, a similar experiment would be carried out with four groups of six to eight dogs each for an exposure period of 2 years, to determine whether a nonrodent species responded differently from the rat. Dog reproduction studies were not required. The lifetime of the rat was considered to be 2 years for the purposes of the test. So it was in 1959.

In the ensuing two decades, the complexity and cost of the tests has again increased. On August 22, 1978, the Environmental Protection Agency published in the Federal Register proposed guidelines for registering pesticides in the United States (17). Though they are directed to pesticides, EPA states that it believes these guidelines to be consistent with those under preparation by other federal regulatory agencies and the Interagency Regulatory Liaison Group (IRLG). They provide, therefore, a glimpse of what all federal regulatory agencies may be requiring in the near future. Nor do the EPA guidelines differ much from the procedures recommended in 1977 by the National Academy of Sciences/National Research Council in their publication "Principles and Procedures for Evaluating the Toxicity of Household Substances" (18), which was prepared at the request of the Consumer Products Safety Commission.

Considering only the "lifetime" feeding study with rats, we find that both sets of guidelines call for 50 animals of each sex for the control and for each of the three dosage level groups, which is double the number recommended in 1959. Under certain circumstances it might be advisable to start the testing in utero, by feeding the test substance to weanling rats, breeding these, and then starting over with their offspring (17, 18).

If there is any suspicion that the test compound is oncogenic, the EPA guidelines would require a second chronic toxicity test with the mouse or hamster, or another species if appropriate. The mouse would be the normal choice, and the duration of the test would be 18 to 24 months, and the test groups would consist of at least 50 animals of each sex per group.

It is obvious that chronic toxicity testing has come a long way in only three decades, and the burden of carrying out these tests has fallen largely upon industry, whether the tests be carried out in-house or by contract. It is not so obvious that the cost of the testing is borne ultimately by the consumer.

As of 1979, it may be said that techniques are available for carrying out, with experimental animals, tests that will answer almost any question that might be asked regarding the various aspects of toxicity to the test species. The techniques encompass acute toxicity, short-term or subchronic toxicity, chronic toxicity, oncogenicity, mutagenicity, teratogenicity, neurotoxicity, skin irritation and sensitization, and eye irritation, among others. References 17 and 18 discuss these methodologies in detail. The complete battery of tests on one compound could consume 500 to 1000 animals, could cost in excess of \$500,000, and would require 3 to 5 years for completion—if all went well.

It follows that with such complexity and cost and time, it is not possible to test completely all compounds of interest with the available personnel and facilities, or even the potentially available, within the foreseeable future; therefore, problems remain.

4 CONTEMPORARY PROBLEM AREAS

4.1 How much Toxicity Testing is Optimum?

If an industry is attempting to develop a pesticide or a chemical warfare agent, toxicity to the target species is an asset. But in most cases toxicity in an industrial product is not the desired effect but rather an unwanted side effect which, if unrecognized, could create major problems for the manufacturer.

A prudent management should therefore seek answers to the following toxicity-related questions before investing capital in the production and marketing of a new product:

1. Can it be manufactured safely?
2. Can it be used safely for its intended purpose?
3. Can it be disposed of safely into the environment during manufacture and after its intended use?

If the answer to any of these questions is "No," it would not be prudent to invest capital in the project, no matter how useful and profitable the proposed product might appear to be if there were no side effects, for toxicity would be a tangible and significant product defect.

A prudent management must therefore take toxicity into consideration from a purely business point of view. But because the cost of toxicity testing becomes a part of the cost of product development, and eventually of cost of product to the consumer, management would like to keep that cost as low as possible. On the other hand, if frugality leads to inadequate testing, the business decision process is jeopardized, and a wrong decision could be very costly.

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But though all industry has its own need for valid toxicity information, not all industry has had the benefit of competent toxicological advice. In its absence, persons not trained or competent in toxicology have decided what tests, if any, are required, and have directed contract laboratories to carry out just these tests. Usually they have not been able to judge the competence of the testing laboratory, nor have they been able to properly interpret the reports submitted. Hence errors of omission and commission have occurred, and problems have arisen that have affected not only the industry but the public as well. And when problems arise that affect the public, or are even perceived as a potential threat by the public, the public demands that the government do something about it.

The government responds to public demands. Each of the laws and regulations requiring toxicity information from industry has been a response to a perceived public need for government restriction of industry's freedom to make its own decisions. Under these laws, government regulatory agencies, not industry, decide whether a material can be made, used, and disposed of safely. The Occupational Safety and Health Administration (OSHA) decides whether or under what conditions a substance can be made safely; the Food and Drug Administration (FDA) decides whether or how much of a substance can be permitted in food or drugs; the Environmental Protection Agency (EPA) decides whether or how much of a substance can be used as a pesticide, and under what conditions it can be made and used without harm to health or the environment. The Department of Transportation decides what special precautions are necessary in moving a material from one place to another.

The advantage to society of having an impartial review by experts of the basis for an industry decision that a proposed new product can be made, used, and disposed of safely is obvious, but the problem is whether the government is likely to be the source of the required impartial expertise.

In the first place, industry decides from evidence, in its judgment sufficient to reach a decision, whether a new product can or cannot be made, used, and disposed of safely. And here industry can make two kinds of error, both important for business decisions. It can decide erroneously that the product is unsafe and should therefore not be made. This would be a Type I error. Or, industry can decide erroneously that the product is safe when in fact it is not safe. This would be a Type II error. The penalty to industry for a Type I error would be loss of a potentially profitable business, and to the public, loss of a potentially useful product. The penalty to industry for a Type II error could be financial loss, as well as loss of credibility and public confidence, and to the public, harm to health and/or the environment. Industry therefore must seek to avoid both kinds of error.

The government regulatory agencies, on the other hand, have little incentive for avoiding Type I errors, but are greatly concerned to avoid Type II errors, for these could lead to, in addition to harm to health or the environment, public criticism, political disadvantage, and possible loss of jobs. To protect themselves against Type II errors, regulatory agencies usually demand a greater degree of proof of safety than industry might think sufficient to reach a reasonable judgment.

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Even so, at present consumer advocates and environmental activists are pressing the agencies to demand evidence that proposed new products are *absolutely* safe, and such evidence cannot be obtained and will never be obtainable, as Aristotle pointed out centuries ago. As one government toxicologist put it, "The one thing I worry about is finding myself someday on the witness stand without a piece of paper in my hand that would justify my decision to approve this product." It is therefore understandable that regulatory agencies tend to require protocols that minimize their chance of committing Type II errors. Nor are the regulatory agencies inhibited by increasing the cost of, and time required for, expanded toxicity testing, because the initial expense must be borne by industry, although the bulk of it will eventually be passed on to the public which may not as yet realize that this is happening.

But may not the regulatory agencies take the position that the avoidance of Type II errors is their mandated job, and that they have no concern with Type I errors? An affirmative answer to this question might be proper if the number of suspect materials were small, and their loss of no importance. But on the contrary, thousands of substances are viewed as suspect because the *possibility* of one or more harmful effects has not been conclusively eliminated.

Under these circumstances, undue emphasis on the avoidance of Type II errors does carry penalties for society. If, for example, the FDA delays approval of a proposed new drug for 5 years in their effort to avoid making a Type II error, and if it is then found that this new drug can save 1000 lives a year, the penalty for a 5-year delay in approval is 5000 unnecessary premature deaths. A recent statement, prepared and approved by the Committee on Chemistry and Federal Policy of the National Academy of Sciences' section on chemistry, deals with broader aspects of the problem, and is worth reading in its entirety, but the following excerpts (19) are relevant:

In his annual report to the members of the National Academy of Sciences this year, president Philip Handler stressed that 'the falloff in industrial productivity, the decline of innovative new industrial starts has become a matter of widespread concern. It is clearly a threat to the vitality of the U.S. economy and, hence, to much else that we cherish. . . .'

Potentially a very significant factor is the ever-growing impact of federal regulatory actions, which have already diverted resources from basic to defensive research. Every high-technology company has experienced the necessity to develop new testing methods, new criteria for safety, and new ways to meet environmental requirements, all of which have added substantially to the time, effort, and cost of developing new products. The end result for whatever reasons has been a startling decline in innovative research and products. More broadly, 204 new publicly financed small technical companies came into being in 1969; by 1975 this number had dwindled virtually to zero. . . .

The question is not whether we need federal regulation of industrial products and processes, but whether we can put such regulation on a sounder scientific basis.

There is yet another aspect to the problem. The minimum number of rats, for example, required to carry out a "lifetime" chronic toxicity test doubled from 1959 to 1979. This means that in a given facility and a given number of personnel, twice as

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many "lifetime" tests could be carried out by the 1959 protocol as by the 1979 protocol. Given the existing backlog of compounds waiting to be tested, is it better to have the small increment of safety incorporated in the 1979 protocol, or to have tested more compounds by the 1959 protocol?

Perhaps the answer to these problems will come about eventually through risk/benefit analysis, which is now achieving some popularity. But it must be remembered that a particular risk may be avoidable only at the cost of creating other risks of as great or greater importance, and the benefit to be obtained from a particular course of action may cancel other benefits (20).

The question of how much toxicity testing is optimum is certainly a contemporary problem area worthy of serious consideration not only by scientists, but also by government policy makers and by the public.

4.2 Shortcuts

One way out of the dilemma posed in the preceding section concerning how much toxicity testing is optimum, would be to find new approaches to toxicity testing that would give reliable answers to the questions all concerned parties think must be answered, but with the expenditure of less time, effort, and cost, and a decreased commitment of facilities. If this were possible, the advantages would be obvious, for more compounds could be tested in a given time period, thus decreasing the possibility of toxic effects from materials not yet subjected to the kind of comprehensive testing advocated in proposed federal regulatory guidelines (17).

Of the various kinds of toxicity tests needed, it is the long-term chronic, or "lifetime," test that uses up the most time, laboratory space, and money. A question of current interest is whether tests of shorter duration than lifetime can reliably estimate a no-effect dosage that would be confirmed by a lifetime study if such were carried out. McNamara (21) has discussed the possibilities and concludes that, for most purposes, tests of about 4 months' duration should be satisfactory to establish long-term no-effect doses, although in certain special cases, lifetime testing might still be prudent.

The most important question is whether tests of no more than 4 months' duration could reliably estimate the possibility of carcinogenicity. McNamara makes the point that the malignant transformation in tissues is preceded by precancerous lesions which may be used as indicators of impending carcinogenicity, and at least justify the necessity for more detailed testing.

Another approach to shortening the time necessary for the detection of carcinogenicity in mammals has been the advocacy of in vitro tests for mutagenicity in cultures of bacteria, yeasts, or isolated mammalian cells, it being assumed that mutagens are highly likely also to be carcinogens. McNamara believes, however, that observations made during short-term testing with mammals may ultimately be more reliable.

At present it seems doubtful that the regulatory agencies would be willing to accept anything less than the most detailed tests in order to minimize their possibility of making a Type II error. But McNamara cites evidence that his recommended battery of

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short-term tests could estimate a lifetime no-effect level for 95 percent of the compounds. If so, the more detailed tests required by the regulatory agencies would raise the level to somewhere between 95 and 100 percent, but could not guarantee 100 percent for humans because of the necessity for extrapolating results from one species to another. And if short-term tests were considered acceptable, more untested compounds could be tested within the same time frame at no greater cost in a given facility. Which serves the greater public interest?

A thoughtful article by Wildavsky (20) entitled "No Risk is the Highest Risk of All" postulates that an overcautious attitude toward new technological developments may paralyze scientific endeavor and end up leaving us less safe than we were before. His thesis is that the elimination of one risk may exaggerate other and more serious risks, and that the distribution of risk, like the allocation of uncertainty, becomes an ordinary object of political contention.

There is no "scientific" answer to the question of how much risk is acceptable with respect to a given hazard. Since the public pays for the elimination of specific risks in taxes and prices, it is likely that the public, through its elected representatives, will eventually provide the answer.

4.3 Thresholds

Most toxicologists have accepted the dictum of Paracelsus that "the dose alone makes a poison" and the implication that for all poisons a dose can be found that produces no toxic effects. Industrial hygienists have operated on the validity of this principle, and the Threshold Limit Values (TLV) promulgated by the American Conference of Governmental Industrial Hygienists (ACGIH) are based on it. OSHA has incorporated the 1968 TLV List in its initial regulations. Yet in recent years, a "new" toxicology has arisen which proclaims that for certain effects, at least, no dose other than zero is safe, and no dose other than zero can be tolerated for substances that produce irreversible effects such as cancer. The Delaney Clause of the Food Additives Amendment of 1958 incorporated this concept.

In a 1977 book entitled *Ecological Sanity* by Claus and Bolander (22), the authors discuss the merits of the no-threshold concept. They quote the following from Kühnelt (23) as a concise statement of the "new" toxicology:

... We should remember that there are three different types of toxins. (1) Concentration poisons: their effects increase in proportion to the dose. To these belong the largest majority of all known toxins, and also such materials which are usually regarded as nonpoisons, which can, however, in large quantities also produce toxic manifestations (e.g., table salt). (2) Cumulative poisons: they do not produce in small quantities any observable poisonous manifestations, but they become stored in organisms and show their effects when they have reached a certain concentration or when, through a change in metabolism, they are mobilized. To these belong, for instance, DDT, which is stored in the body fat; also chlordane, aldrin and dieldrin. For these materials there is therefore no tolerance dose because each uptake of the toxin, no matter how small, adds to the

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cumulative effect, which, in the course of time, must become manifest. (3) Summation poisons: they are destroyed or eliminated from the organism, but they cause—even in very small amounts—tissue damages which are definitely irreversible, and which will be exacerbated through further doses. Such materials act mainly as carcinogens. For these there is absolutely no harmless, minimal dosage [translation by Claus and Bolander].

Claus and Bolander point out that the negation of a threshold dosage for group 2 takes no account of the possibility of elimination or detoxification of these compounds. They consider the conclusion with respect to the absence of any harmless, minimal dosage for group 3 as "bordering on the ludicrous," and cite several literature references, as well as some calculations of their own, in support of this position.

There is, indeed, a body of respectable scientific opinion which holds that thresholds exist even for carcinogens. Although a single molecule of a carcinogen may induce a malignant transformation in a single molecule of DNA, there is a long step between a molecule and an intact organism. The organism possesses defenses that a molecule does not possess. Carcinogens may be detoxified before they reach target cells. Genetic damage can be repaired. If a cell does become malignant, it may be dealt with by the body's immunologic defenses, which are known to exist. Old (24) has reviewed the status of the immunologic defenses in a 1977 article. In 1975, Selikoff (25) spoke of the paradox of Rehn:

In 1895, Rehn reported the first three cases of cancer of the bladder among aniline workers. When additional cases of this association were identified in the next 15 years in Germany and Switzerland, it was projected that the developing chemical industry, with its increasing number of synthetic chemicals new to the human environment, would bring with it a host of problems and an unhappy harvest of cancer. This prediction in the next decades seemed far from unreasonable when our colleagues demonstrated carcinogenicity in literally hundreds of chemicals in animal test programs. Yet, by and large, the prophecy was not seen to be fulfilled in the first half of the 20th century. Even until recently, human cancers have been relatively few and seemingly restricted in type and number, almost as exceptions to the broad spectrum of human cancer, viz. betanaphthylamine and benzidine bladder cancer, radium neoplasms, coal tar skin cancers, etc.

Thus, until recent years, we were faced with something of a paradox; Rehn and his contemporaries had shown that human cancer could result from chemical industry exposure, laboratory studies indicated that the agents could be varied and numerous, yet human experience had not demonstrated this to be a major problem.

In recent years, the problem has again been put before us in pressing terms. Do experiences with vinyl chloride, bis-chloromethyl ether, chromates, etc., demonstrate that the prophecies were really correct, merely premature? We do not yet know, but the question is an important one and must now be addressed.

The paradox of Rehn could be resolved on the hypothesis that human exposures to the many and varied carcinogens have, for the most part and for one reason or another, been in the no-effect dosage range for development of cancer within the human lifetime. Nevertheless, the debate over the existence or nonexistence of thresholds continues, and must be listed as a contemporary problem area.

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4.4 Extrapolation

Webster defines "extrapolate" as "to project, extend, or expand known data or experience into an area not known or experienced so as to arrive at a usually conjectured knowledge of the unknown area by inferences based on an assumed continuity, correspondence, or other parallelism between it and what is known." Young scientists are, or were, warned that extrapolation is a risky procedure, and should never be carried far beyond the observed data base. That advice is still sound, but in the field of toxicology some extrapolation is necessary because the usual question is, "What dosage will be harmless to humans?" and there is no ethical or legal way of using humans as experimental subjects in investigating the potential toxicity of a new chemical.

Two kinds of extrapolation are involved: first, the extrapolation of results obtained on a test animal species to the human species; and second, the extrapolation of a no-effect dosage obtained on a relatively small number of the animal species to the much larger number of human beings that might be exposed.

With regard to interspecies extrapolation, there are some who hold that it is futile. Man is so unique and different from other mammalian species, that any attempt to extrapolate from these species to human beings must be purely speculative. However, people holding this opinion have generally had little or no biological training, and do not realize how much man does have in common with other mammals. Even the rodents have brains, livers, hearts, kidneys, and other organs that perform the same functions by the same chemical reactions as these same organs perform for humans. Damage by a toxin to one or more of these organs in the rodent is quite likely to be of the same type as the damage to these same organs in man. There may, however, be quantitative differences. Human beings may be more (or less) susceptible to the same mg/kg dosage because of, for example, different enzyme concentrations.

Historically, toxicologists both within and outside government regulatory agencies have dealt with the problem of interspecies extrapolation in two ways. First, it must be demonstrable that the chosen test species, for example, the rat, metabolizes the test compound in the same way as man. Second, it is assumed that man may be as much as 100 times more sensitive to the effects of the test chemical as is the rat. The Food and Drug Administration incorporated the hundredfold margin of safety into the Regulations to the Food Additives Amendment of 1958. On this basis, a test chemical found to produce no observable toxic effects when fed to rats at 100 ppm of the diet over their lifetime would be presumed to produce no observable toxic effects in humans at a level of no more than 1 ppm over their lifetime. As specified by the Amendment itself, however, no substance found to induce cancer in man or other animal could receive a tolerance other than zero (the Delaney clause). For toxic effects other than cancer, the hundredfold margin of safety rule appears to be acceptable. There has been no serious attempt to challenge it as inadequate for regulatory purposes, except in the matter of carcinogens.

Carcinogenesis is, for several reasons, a special case. Cancer is the second most prevalent cause of death for American men and women. It is an unpleasant and expensive way to die which few would choose if they had a choice. It is demonstrably caused by

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environmental factors if these are taken to include such factors as diet and cultural practices, as well as chemical carcinogens per se. It should be possible, therefore, to decrease the probability of dying of cancer in favor of dying of some other cause. Some of the methods for accomplishing this are clearly under the control of the individual even now, for example, the elimination of cigarette smoking, modification of the prevailing diet, and elimination of excessive exposure to sunlight. The elimination of chemical carcinogens, however, is not within the power of the individual, and is a concern of industry and government. The question at issue is whether a particular finite level of exposure to a chemical carcinogen poses no risk, or some minimal acceptable risk, or a risk so great as to be unacceptable.

In laboratory experiments with carcinogens, the dose-effect relationship is observed. As the dose of carcinogen is increased, the proportion of animals developing tumors is increased. As the dose of carcinogen is decreased, the proportion of animals getting tumors decreases. In human populations carcinogenic effects are also dose related, for as Selikoff (25) has noted, "Occupational disease is not an all-or-none affair. On the contrary: it is clear that even for occupational carcinogenesis there is a dose:disease response relationship."

In the laboratory it is possible to find a dosage level that does not induce an excess of tumors within the lifetime of the animals. Even in human populations exposed to known carcinogens epidemiological evidence suggests that exposure can be lowered to a point where no tumors develop within the lifetime. But the question is raised as to whether in large populations there may be individuals more sensitive than any individual in the group under epidemiological study. An answer to the question of what dose might be expected to produce, say, one cancer per million of exposed population is not determinable through either laboratory or epidemiological investigation, because the result would not be observable against the noise background of the population. A speculative answer must be attempted through the process of extrapolation. Various formal models have been suggested as appropriate for this purpose.

The most conservative model postulates that zero response can be obtained only at zero dosage, and that a linear straight-line relationship exists for all doses between zero and an observed low-effect dose. In a model suggested by Hoel et al. (26) in 1975 for interim use, it is not even necessary to have an observed effect dose. These authors postulate a hypothetical experiment in which 100 mice are fed a diet containing 1 percent of a chemical and no tumors result (0/100). They do not accept that this experiment indicates noncarcinogenicity, but rather that one should accept the upper 99 percent confidence limit of the 0/100 result, that is, 4.5/100, as the probable "true" outcome, and extrapolate from this to a dose that would produce 1 tumor in a population of 1 million, by the simple arithmetic ratio:

$$\frac{x \text{ ppm}}{10^{-6}} = \frac{10^4 \text{ ppm}}{4.5 \times 10^{-2}} \quad \text{or} \quad x = 0.22 \text{ ppm} \quad (1)$$

And according to Hoel et al., "Thus, any chemical tested in only 100 animals could not be introduced into the human food supply at a level exceeding 0.22 ppm, even if there

were no evidence of its carcinogenicity, assuming the risk level of one per million were 'acceptable'."

This rather horrendous conclusion, however, takes no notice of another well-established factor in carcinogenesis, namely, induction time, or time to appearance of tumor since the latter is the observable manifestation of induction. Yet it is an observed fact that time to appearance of tumor is inversely related to dose. The lower the dose, the longer the time to appearance of tumors until finally no tumors appear within the life-span of the animals. Druckrey (27) in 1967 expressed this relationship by a simple equation:

$$Dt^n = k \quad (2)$$

where D = total accumulated dose, t = time to appearance of tumors (either median time or time to appearance of first tumor), and n = an exponent greater than 1 (often about 3) related to the potency of the carcinogen. If n were 3, a thousandfold reduction in dose would result in a tenfold increase in time to appearance of tumor.

The principle involved in the Druckrey relationship has been verified by a number of investigators (28-34). Some investigators have suggested modifications of the Druckrey formula in the interests of generalization while retaining the general principle of inverse relationship between dose and time to appearance of tumor. A World Health Organization Scientific Group (35) in 1974 commented as follows:

The summation effect described by Druckrey and others is not questioned and his equation characterizing potency may be accepted. Nevertheless, every organism has a limited life span and in this sense there is, for each individual a real threshold.

It would appear that extrapolation from animal data to a safe level of exposure for humans to carcinogens might involve a smaller departure from the observed data base, and hence less uncertainty, if it were based on time to appearance of tumor rather than dose. Certainly, induction time for tumors is a real phenomenon and should not be ignored.

Extrapolation, by definition, will always remain a problem area. Unfortunately, there is no way of completely escaping it.

4.5 Political Toxicology

The rigid application of the scientific method has been proved over the years to be a reliable method of arriving at the realities of nature (36). If these realities differ from commonly accepted beliefs, so much the worse for the beliefs, says the scientist. But those in authority look at it differently. Will a new scientific discovery promote or weaken their authority? Will it promote or interfere with their political, moral, and social goals? If it interferes, so much the worse for the science. Galileo found this out.

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INDUSTRIAL TOXICOLOGY: RETROSPECT AND PROSPECT

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In recent years toxicity has come to be perceived by the public as a major threat to its well-being. What concerns the public becomes a matter of interest to the media, and media interest becomes a matter of interest to those who seek to control public opinion and action. There is opportunity, therefore, for toxicology to serve political interests. This is all right so long as Toxicology in the Service of Politics does not conflict with Toxicology as Science. Opinions will differ as to whether Political Toxicology is a current problem area, but the potential is there, and it should be looked for.

4.6 Public Attitudes

Public attitudes are a problem area in several respects. First, the educational system has dealt with toxicology only as an advanced subject, and the general public has little understanding of what it is all about. Second, the public depends on the media for most of its information, and the media is often naïve with respect to toxicological matters, and often overreacts. Third, the public tends to view toxicity as perhaps a greater hazard than it actually is, compared with other hazards to which the public is exposed.

Better education appears to be the only answer to these problem areas.

5 PROSPECTS

Toxicology has come of age in our time in that its importance is recognized by industry, the government, and the public. Industry needs a knowledge of toxicity as an important input to prudent business decisions. Government is firmly established as the regulator which tells industry what it must and must not do to preserve health and the environment. The public fears toxicity and demands the right to know the hazards to which it may be subjected and adequate protection against those hazards.

There appears to be little prospect that the problem of toxicity will be forgotten by any of the involved groups in the foreseeable future. One might well advise son or daughter to consider the profession of toxicology as a possible vocation which promises reasonable job security for the competent.

Advances in the science of toxicology will undoubtedly occur, for like all science it is dynamic, and as Lord Macaulay wrote in 1837: "... it is a philosophy which never rests, which has never attained, which is never perfect. Its law is progress." Macaulay, of course, was speaking of science in general, but his words are applicable to toxicology.

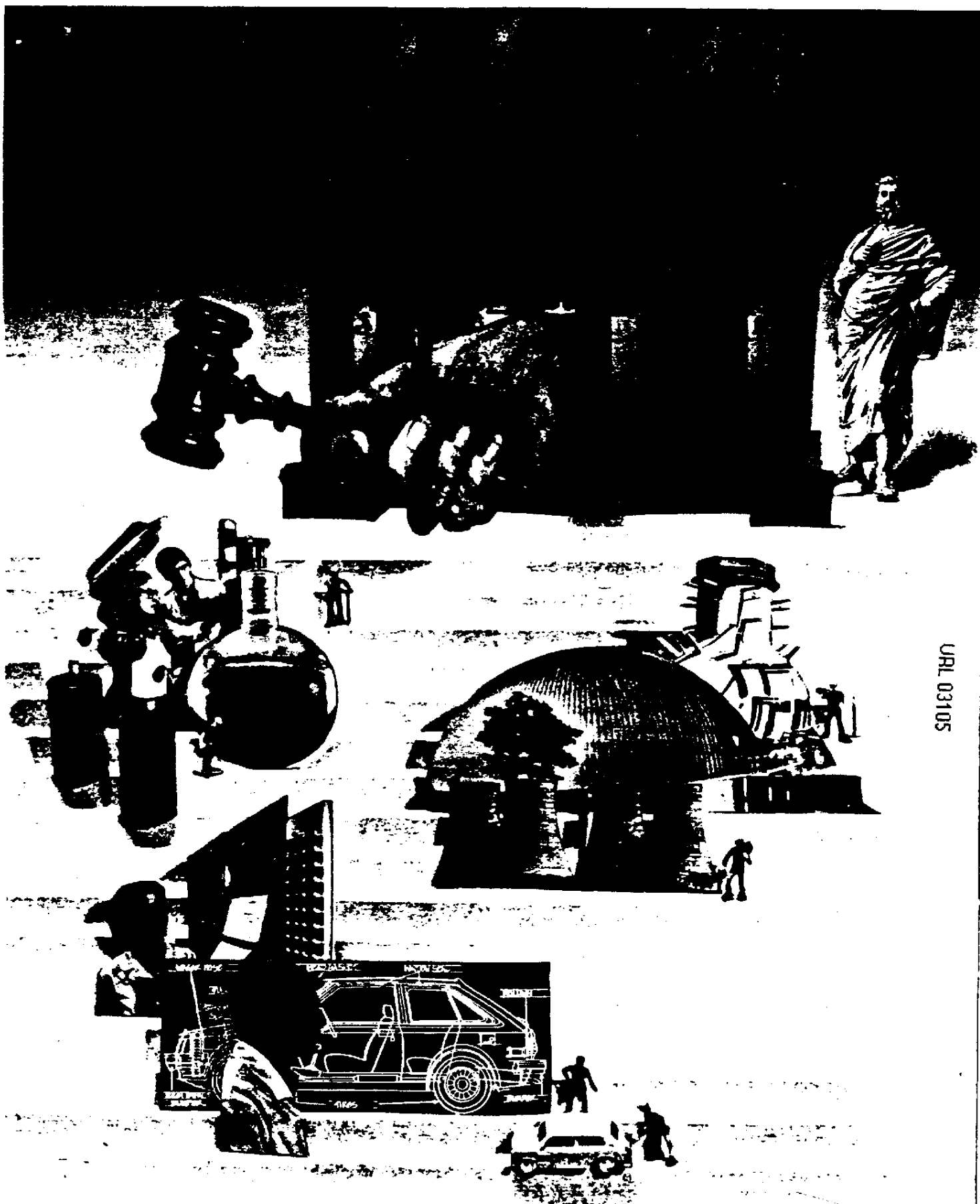
We can anticipate more efficient methods for arriving at the truth, the realities of the situation rather than opinion and speculation. We can hope that they will supply valid answers at lower cost and in less time than do the currently available methods. We can hope that the public and the media will become better informed and able to distinguish between fact and fiction concerning problems of toxicology. And we can hope that government will view and deal with problems of toxicity in proper perspective against the broad spectrum of other problems.

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URL 03105

The responsibilities of the technologist

Part 1

J. Mingle
C. Reagan

Every technologist is responsible for how his or her work affects others. This responsibility is both legal and ethical, two aspects that may not overlap at all times. This overview of technologists' responsibility focuses on the practice of engineering, but its concepts are equally valid for all chemical professionals.

Here we introduce the question of legal and moral responsibility and discuss negligence in detail. In a forthcoming installment, we will address liability, and examine various forms of moral responsibility, individual and collective. Finally, we will look at the legal aspects of a professional code of ethics.

In modern society, technology has become an intimate part of daily life, whether one considers transportation, things we use, banking, agriculture, or any other necessary endeavor. The driving force behind this technology is a special kind of person, whose activities Webster's dictionary defines, under engineering, as "the science by which the properties of matter and the sources of energy in nature are made useful to man in structures, machines, and products" (1). Here we direct particular emphasis to the phrase "useful to man."

With the concept of making its work product useful to man, the technologist becomes intertwined in the relationship between moral and legal responsibility to society. A concern for a high degree of moral responsibility is paramount to the concept of professionalism. However, what is the relationship between legal responsibility and moral responsibility? Can situations occur when moral responsibility has ceased but legal responsibility continues? Further, are there situations in which the concepts of moral and legal responsibility cannot be separated?

In order to consider moral responsibility, the ethical value system of the engineer must be included in the discussions. This will bring forth the various ways engineers (and other technologists) view legal responsibility, as well as their response to ethical value systems other than their own.

What is responsibility?

In this paper we divide responsibility into legal responsibility and moral responsibility. As far as courts are concerned (2), "legal responsibility is virtually synonymous with liability." We will thus often use the two interchangeably. Many times legal responsibility will arise from a valid contract, which is "a promise or a set of promises for the breach of which the law gives a remedy, or the performance of which the law in some way recognizes as a duty" (3). This definition, applied to engineering service contracts, results in an implied duty for the engineer to perform adequately. Of course, duty concepts are implicit to the field of tort law, as when the "duty of care" criterion for negligence is under consideration. Additionally, legal responsibility can rest under the causes of action of warranty and strict liability.

The concept of moral responsibility is a basic premise from philosophy (4a). Moral responsibility can be divided into the traditional or subjective concept and the future-oriented or objective concept (4b). For the traditional concept, a person is accountable for a state of affairs if and only if the action is performed under no excusing conditions, such as ignorance of the consequences of an act, or under such circumstances as were beyond the individual's control (4c). In the objective concept, a person is justifiably blamed for having performed an act if the sanctions will have a good effect on the person's future conduct (4b). This objective theory of moral responsibility has certain similarities with the legal concept of negligence.

Moral responsibility can be further refined into four basic areas (5a):

Role responsibility is that responsibility associated with some "distinctive place or office in a social organization to which specific duties are attached" (5b). Thus, parents, police officers, sea captains, and university deans, for example, have specific duties by virtue of their social roles. Frequently, these duties are explicitly enumerated in detail.

Like other professionals, engineers (and chemists) have certain responsibilities over and above those of the nonprofessional. Precisely what those additional responsibilities or duties are will depend on the particular role, i.e., social or professional, that the engineer is playing. Note however, that the technologist may have multiple roles to play.

Causal responsibility is caused or produced. For example, one may say: "The high floodwater was responsible for the weakened foundation" or "The poor design was responsible" or "An incompetent engineer was responsible." So here responsibility is attributed to events, acts, conditions, or objects, as well as to human beings. While the sense of this use is clear, deciding what caused something to happen can be enormously difficult in real cases. This concept appears similar to standard legal causation theory.

The important notion of *liability-responsibility* is that of being "blameworthy" and "morally bound to make amends or pay compensation." This sense seems to follow naturally from the first two meanings. If a person has some obligations, the neglect of which causes harm to befall someone else, clearly he or she owes some compensation to the wronged party. While this principle is clear, its application is much more complicated. Many of these complications have led precisely to the current state of liability laws and practices that we will consider later. Further, a person also may be liable to make amends for damages he or she has done accidentally, where no moral blame may be attributed. A common example occurs when one may be responsible—in the sense of being liable for damages—for something done by someone else, on the grounds that one stands in a certain relation to that person.

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Parents' liability—responsibility for the deeds of their minor children is an example of this.

Capacity-responsibility is having the capacities required for being responsible for one's actions. Those capacities "are understanding, reasoning, and control of conduct: the ability to understand what conduct legal rules or morality require, to deliberate and reach decisions concerning these requirements, and to conform to decisions when made" (5c).

One way philosophers have studied responsibility is to look at the various ways imputations of responsibility are defensible; that is, what kinds of excuses are acceptable. Typical excuses appropriate to each of the senses for responsibility would be: "It wasn't my job to look after that." "The part I designed did not cause the accident." "Not liable for fire, theft, or vandalism." "He is mentally incompetent and unable to control his violent tendencies" (6). Tort law is designed to handle these types of excuse and to resolve them in a legally satisfactory manner.

Moral and legal responsibility do not coincide. There are occasions when moral responsibility is imputed, but the law does not hold the person legally liable. In other instances, notably with *strict liability*, a person is made to pay compensation or is held to be legally liable when moral responsibility appears to be missing. Thus, "all legal systems in response either to tradition or to social needs both extend responsibility and cut it off in ways which diverge from the simpler principles of moral blame" (7).

We will examine the further philosophical concept of collective responsibility later, when we shift the perspective from the individual engineer to his or her parent company.

Legal responsibility

Legal responsibility or liability can be divided into the standard causes of negligence, warranty, and strict liability. In this overview we will discuss warranty and strict liability together, not only to accentuate their difference from principles of negligence, but also because they tend to be associated with products generated by engineering services rather than the services themselves.

Negligence

To prove a negligence case against an engineer, the plaintiff must establish that the engineer had a duty of care toward the plaintiff, and that the engineer breached this duty of care which then causally produced harm, usually in the form of physical injury, to the plaintiff (8). Generally, in this negligence situation the engineer has provided engineering services, such as design, supervision, or consultation, and the person receiving the injury often is not the person for whom the services are rendered. For instance, in a typical field engineering situation, the agent engineer is on site, where he or she is inspecting construction.

An injury for any reason to a construction worker may trigger a legal action against the engineer who is alleged to have had a duty to this third-party construction worker to see that the site is a safe place to work. Many modern cases on this third-party type of construction accident have occurred. Some typical examples follow where, in this construction liability content, the words architect and engineer can be used interchangeably, for either may be liable under the same negligence principles (7).

In *Swartout vs. Beard* a workman was killed when an excavation caved in (9). The architect's contract required

inspection of the work as well as the authority to stop work if necessary. The contractor's project engineer pointed out to an engineer employee of the architect the unshored excavation, specifically indicating the cracking condition because of wet clay. The employee engineer indicated corrective action would be taken, but nothing was done before an accident occurred several days later. The court held that liability for negligence resulting in death may be based upon the supervisory activities of the architect, and privity of contract was not a prerequisite to liability. Further,



Figure 1. Basic areas of moral responsibility.

one of the contract provisions was specifically to maintain any excavations in a safe condition, so the court ruled that the architect breached this contract duty and was guilty of negligence.

In contrast, in *Parks vs. Atkinson* (10) an apprentice carpenter fell from a scaffold that was not designed by the architect but was erected by the contractor. In a suit against the architect, the court held that for him to be liable to an employee of an independent contractor, the architect must first be found to have the duty to supervise the method and manner of actually doing the work. Here, the architect had only those controls necessary to assure that the results of the contractor's work complied in technical detail with the plans and specifications prepared by the architect. In the subject situation, the architect had the power and did stop work twice before the accident occurred, but only to force proper construction and not to enforce safe methods or procedures. Summary judgment for the architect was affirmed.

The engineer in *Krieger vs. J. E. Greiner Co.* (11) who had designed a bridge and supervised its construction was held not liable for the injuries of workmen when a subcontractor negligently erected steel reinforcing bars. Under the contract, the court ruled the engineer had no duty to supervise methods of construction, which included safety considerations.

An interesting case is *Slifer vs. Wheeler and Lewis* (12), in which a welder was injured on a school project when a section of the roof collapsed because of a lack of shoring for the building frame. Evidence showed that the architect had knowledge of this condition, but had visited the construction site only once prior to the accident. The court held that the architect's duty of supervision required him to assure himself

that the required bracing and shoring were erected. Here the contract required the architect, through his duty of supervision, to assure the school district of substantial performance of all contract requirements, including safety. Thus, since the contract between the school district and the contractor called for the contractor to be responsible for the prevention of accidents, the architect, because of the misfeasance of the contractor, was also liable for the accident. The broad contract language had created a duty to see that the contractor guarded his workers against accidents.

For this series of field engineering cases the key issue is "what legal duty has been created by the contract language?" The engineer becomes disheartened when a liberal court takes carefully worded contract language and extends its meaning to pull the engineer under an indirect duty of care requirement for a distant site worker, as occurred in the *Skifer* case (13). Of course, others would tell the engineer that society is deeming that he or she has at least an ethical duty to ensure "safety in the workplace," which seems to become a legal duty in the eyes of the court if any shoddy performance by the engineer is shown (14). We'll discuss the engineer's moral responsibility in a later section.

Another aspect of the field engineering cases brings out the general principal-agent status that exists, for the field engineer is normally under an employment contract to a larger firm (15a). Rarely is the engineer employed as an individual alone unless he or she serves as an independent contractor consultant. Naturally, in tort theory this principal-agent situation becomes a master-servant relationship, and the employer pays the judgment on a vicarious liability theory (15b).

Another area of engineering practice involves the concept of design. If a manufactured product is being considered, then product liability overtones creep into the discussion; we'll cover this aspect subsequently. At this point let us only consider the concept of negligence in design, in which the engineer is to exercise such care, skill, and diligence in his or her design effort, as do persons engaged in the engineering profession ordinarily exercise under similar circumstances (16).

An objective standard is employed as to what the prudent, reasonable engineer would do under the same circumstances, and requires expert testimony by others in the profession. For instance, in *Seaman Unified School Dist. No. 345 vs. Casson Construction Company* (17a), the appellate court remanded for a new trial when expert testimony about drainage problems around a construction site because of heavy rains was excluded. The court said (17b):

The common knowledge that water runs downhill does not give a jury the ability to understand the technically complicated excavation, grading, and drainage plans of a gymnasium construction project.

This standard is referred to as the professional standard, so that the client who hires a professional purchases reasonable service, not insurance guaranteeing a perfect job (18).

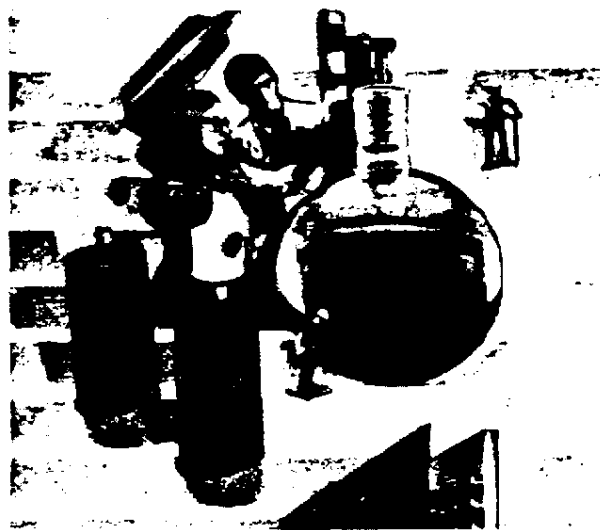
Negligence in design many times is referred to as defective design, an unfortunate choice of words because it immediately triggers a view toward strict liability. In many instances the difference between defective design in negligence and strict liability is that in the former case the accent is upon the behavior of the defendant, and whether his or her design included a reasonable foreseeability into

the future and so anticipated the plaintiff's injury; whereas in the latter situation the expectations of the plaintiff as to whether the product's design was unreasonably dangerous may govern the case (19).

A case showing the difficulty the jury has in applying negligence principles to design is *Self vs. General Motors Corporation* (20a). Here, a man driving under the influence of alcohol and drugs hit a parked 1962 Chevrolet station wagon that had just stopped on the shoulder of a freeway because of a flat tire. The station wagon was knocked into a gully, its fuel tank ruptured, and the vehicle caught fire. Two occupants were killed and two were severely burned. Action was brought against the Chrysler driver for negligent driving and against General Motors for defective design of the Chevrolet station wagon because of the fuel tank placement in the left rear fender section. The jury verdict was for the plaintiffs against both defendants. The judge denied General Motors' motion for judgment notwithstanding a verdict (*j.n.o.v.*), but approved a new trial for them based upon a juror's concealment of information on *voir dire*. Both sides appealed. The appeals court affirmed the trial court in awarding a new trial for General Motors, but denied the *j.n.o.v.* claim. The case brings up the interesting concept of "design by jury," as the dissent stated (20b):

I agree that "a lawsuit is a poor way to design a motor vehicle," but to permit this issue to go to a jury gives the jury the power to do so with no guarantee that a jury can come to grips with the difficulties and hard choices inherent in designing a complicated product.

It is a matter of common knowledge that there is no place on an automobile where a tank holding 20 or so gallons of volatile gasoline



can be "safely" located. Should General Motors then be held to have defectively designed the automobile because it required gasoline as a fuel? Absolutely not.

Thus in each case the involvement of the gas tank will depend on the circumstances of the particular crash. Plaintiff's expert testified that in this case the area below the floor of the vehicle was not appreciably damaged. From this it is argued that it was negligent not to have put the tank there. But what if the angle of the collision had been different or Prior's vehicle had been a low-slung sports car that went beneath the rear bumper and struck the area which plaintiff contends is the "safe" area? Would plaintiff's expert then say in that case that it would be negligent

to have the tank in such a position and that the tank should have been in the fender?

Clearly the fortuitous circumstances of a particular mishap should not be the controlling factor. General Motors' liability should not depend upon the direction or manner in which Prior impacted the target vehicle. The testimony of plaintiff's expert created no factual issue.

Thus the retrial may well degenerate into a debate over the probabilities as to which type of impact is most likely to occur or which kind of accident is the "most foreseeable," i.e., front, rear, side, etc.

The question of defective design is not whether the vehicle was designed to minimize the damage from the particular accident that did occur but whether on balance the vehicle is designed to minimize damage in the usual and foreseeable mishaps.

Naturally, the design engineer agrees with this dissenting judge that "design by jury" is essentially random design.

The majority based their opinion on the legal doctrine that when substantial credible evidence is presented on both sides, the jury's verdict on defective design will not be disturbed (20c). The majority did not agree with the dissent that "the testimony of plaintiffs' expert created no factual issue." The majority concluded:

[D]efective design is an amorphous and elusive concept once we have progressed beyond the ideas of fitness for intended use, its contours certainly include the notions of excessive presentable danger when an automobile's fuel tank has been located in a position relatively more hazardous than others, when the added hazard of its location has been recognized by the industry, when the danger is well-known to the designers, and when the tank could have been readily relocated in a safer position, a jury could conclude that the location of the fuel tank made the design of the automobile defective.

The real issue is that to the majority the defective gas tank design was a question of fact for the jury to decide, while to the minority it was a question of law on which the judge should rule. The technical designer reads this opinion and comes to the conclusion that the court is looking at foreseeable accidents from a subsequent view, so that if "sometimes" ever occurs, it was foreseeable and should have been designed against. The *Self* case seems to be not a negligence case but only one of strict liability where the court is trying to justify using General Motors' "deep pocket" or otherwise a large corporation can afford to pay the judgment even if they are not at fault!

In Part 2 of this series we will examine the legal responsibility involving warranty concepts and strict liability. While negligence focuses on the behavior of the defendant, both concepts we'll discuss concentrate instead on the product. This view is shared by the law and the technical practitioner.

Substantial portions of this work originally appeared in *Jurimetrics*, 1982, 23(2). © 1982 by John O. Mingle and Charles E. Reagan. All rights reserved.

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SPACE BUS

The secret military payload on the [July 1982] shuttle flight (which is generally known to have contained the Air Force's CIRRIS infrared sensor, being developed to spot missile launches) was a visible reminder of what all the concern was about. Critics say that the shuttle, with its dual role, has effectively erased the line between civilian and military space missions. And they see NASA's acceptance of a substantial Department of Defense (DoD) role, first in the design specifications and now in the operations of the shuttle, as having been a Faustian bargain: NASA received

support for a big engineering project of the sort it thrives on, but is now having to pay the price of sacrificing its civilian role more and more to military interests. . . . The chief fear of supporters of the civilian space programme is that with the increased emphasis on these military uses of space, NASA may end up doing little more than running a bus service, and may become in effect a "vassal" of the Air Force.

Stephen Bodiansky

Nature

July 15, 1982

A chemist conducts a health inspection

Mary Ann Solstad

People are growing increasingly aware of "bad" effects from even low-level, chronic exposures to chemicals. There's uncertainty about the effects of many substances, and thus a certain aura of fear. Today resource material to guide you in safety inspections of your own lab is generally available. (See Hedberg and Bussell; the two articles by Kaufman; Reich and Harris; and the Safety Committee of the New York Section of the ACS, all in the supplemental reading list.) This information won't make you a safety expert, but it will help when one is not around. What I've done to help you is work out an inspection system that's applicable to schools, small labs, craft shops, or workshops for home artisans, as well as to larger installations.

Provided that at least the following conditions are met, the moderately inquisitive chemist can use the system. With it, colleagues can take formal turns being safety inspectors.

First, you must have reason to suspect there is a problem (i.e., somebody complained); there is likely to be little or no industrial hygiene measuring equipment available; and OSHA compliance or other legal issues must not be involved. Most important, you must have enough sense to know when you are out of your depth and need to call in the experts.

Your investigation may have three possible results: First, you may get the reassurance that there is a minimal health hazard or none at all; second, that there is a problem, but that it can be alleviated; and finally, that the situation bears further investigation. If you are faced with the last of these three there are a number of people you can turn to for help, including occupational physicians and nurses, industrial hygienists, or health and safety consultants. Most of these people are available through state departments of industry or labor, insurance companies (especially in matters involving workman's compensation), and as independents.

I became interested in toxicology following an exposure that I later suspected might have caused a lingering illness. My unscientific survey, conducted at scientific meeting social hours, indicates that a majority of safety consultants similarly began learning in the school of hard knocks. Their unplanned and sudden initiation to the field, which included contact with explosive reactions, electrical grounding problems, chemical spills, and the use of protective clothing, seems to coincide frequently with their fields of expertise. The problems caused by low-level exposure to chemicals are less obvious than those listed above, and are frequently overlooked or attributed to other causes, particularly by primary care physicians or nurses.

A field survey

Let's suppose someone calls me because they have headaches, skin rashes, nausea, dizziness, irritability, lassitude, or eye or throat irritation that they suspect may be related to some chemical. Would I take a look at the workplace? Of course. You can come along to take notes.



First impressions

Odor. Rate its intensity, irritability, and disagreeableness. Note these at once, because many substances cause olfactory fatigue; after a few minutes of exposure their smell isn't even noticed.

Noise. Intensity, pitch, duration, and character (intermittent or continuous).

Equipment location. Is it logically placed for good work flow and safe movement about the room?

Work habits. Meticulous or sloppy? Smoking or eating in the work area? Food or cigarettes stored in work space?

Medical history

Current symptoms. Focus on their intensity, onset, duration, and frequency. I use conversation, interview, or written forms to get some measure of these admittedly subjective complaints. Also note medications, prescribed or otherwise, and any recent changes in them.

Signs that a medical professional could objectively note or measure, including blood pressure or red throat, come in a gray area more properly left to doctors, nurses, or

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paramedics. The point of the medical history is *not* to play doctor, but to look for a common thread of complaints among workers in an area, or any time or space relationship between symptoms and work.

Workplace history

Questions about the workplace also apply to home:

- Recent remodeling?
- Changes or adjustment in the ventilation system?
- Additional insulation, or tightening for energy conservation?
- New workers?
- Change in procedures?
- Change in chemicals?
- Processes and materials used, past and present?

In at least one case, home exposure to a paint remover, after occupational exposure to carbon monoxide, triggered a fatal heart attack. Methylene chloride in the paint remover and carbon monoxide combine preferentially with hemoglobin some 200 times greater than oxygen does to form carboxyhemoglobin, and also to inhibit the release of oxygen from the blood to the tissues. Carbon monoxide in cigarettes also reduces the oxygen available to the tissues and any combination of the above has an additive effect (1).

Ventilation

General dilution ventilation is the type found in most public buildings. Air comes in and air goes out at so many calculated air changes per hour. It will then meet local or state building codes, which have little or no relation to health and safety in a lab, only comfort. Even so, it helps in offices, for instance, to check the air flow. I use a bamboo pole with a fine ribbon on the tip. This saves climbing and stooping.

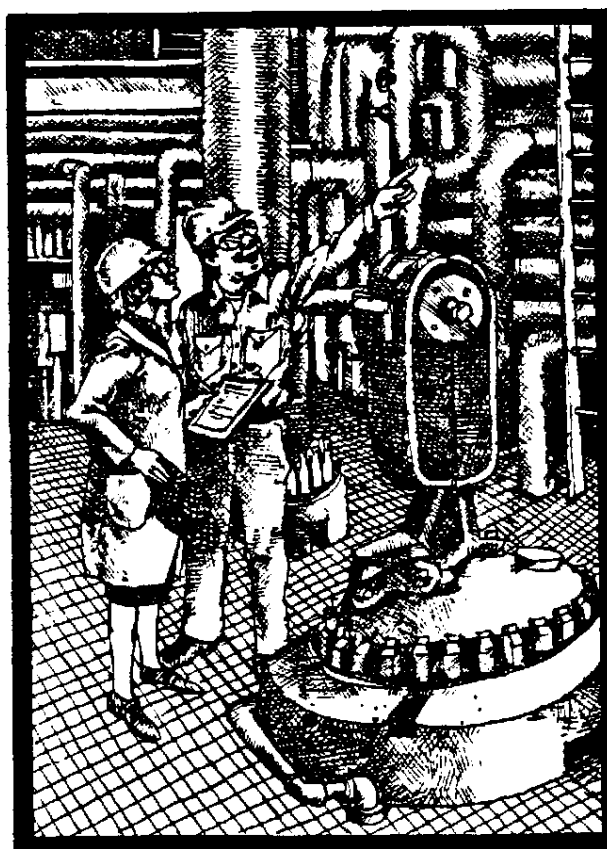
Local exhaust ventilation is exemplified by the laboratory hood or an enclosure around a grinding wheel with an exhaust duct, sometimes called a snorkel or elephant trunk. We will see whether the work area is enclosed, ideally on three sides, whether the work area back is at least 4 inches from the hood face, and whether the flow of air is away from the breathing zone. Other questions include: Does the exhaust design keep inquisitive heads away from the route between work and the exhaust duct? Is the exhaust duct close to the work? With a snorkel this will mean closer than one duct diameter to work or source (2)?

Next, we will check the air flow. In the absence of a velometer, I use my handy-dandy flow indicators: fine ribbons, commercially available smoke tubes, or dry ice in water to give an indication of air flow at the work area. In fact, they're better than a velometer to dramatically illustrate disturbances in this air flow caused by workers, lab traffic, or doors opening and closing. Since air is being exhausted a source of makeup air is necessary. Its location is important: large diffusers in the ceiling or on an opposite wall have been recommended as most effective (3).

For the acid test, mercaptan or pyridine could be opened in the hood. This is guaranteed to make the inspector unpopular, maybe even thrown out. I've sometimes used a cheap perfume, but wintergreen is effective and more pleasant. In any case, all these air flow indicators are also effective in retraining lab workers to use hoods correctly.

The roof. Nearly every industrial hygienist has found the answer to a problem up here. Go up and look around to see the location of the hood's exhaust, the location of any nearby smokestack, and the location of the fresh air intake. Is it in proximity to either of the above? Is a neighbor emitting noxious fumes (for example, phenols from tarring a roof)? Use the handy-dandy air flow indicators.

As we walk through I've noticed the type of work space, e.g., teaching lab, R&D, artist's studio, or workshop. I've also watched for the size of the operation, from micro quantities to vats, and any process that may disperse materials into the air, such as evaporating, pouring, mixing, grinding, or cleanup sweeping or dusting. Wet cleanup is usually preferred, and is almost imperative whenever toxic or irritative respirable particles between 1-10 μm might be



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present. HEPA (high-efficiency particle air) filters may be in some installations—use them only for their design purpose. The surgical-type mask is useless for toxic vapors or fine dusts.

I then ask for a complete list of chemicals in use or in storage. Double-check this, and pay particular attention to identification, dating, and precautionary labeling; also note storage space and arrangement. (We're getting into the realm of safety now. Perhaps it's well to have the safety officer along, if there is one, or use one of the available safety lists, such as those cited in the first paragraph of the article.

Personal protection

What is available, and what is being used?

Work clothes are used to protect the skin and street clothes, and to protect the laboratory. This is especially important in biological work. They also protect other areas such as the home or lunch room from chemicals. Therefore, don't eat in lab clothes, don't keep cigarettes or snacks in them, and never keep snacks in the lab refrigerator.

Gloves. Are they made of the right material? Consult a list (Table 1) (4). To double-check, put some solvent into a glove finger to test its strength and permeability. Are they in good condition, rinsed before each removal, and inspected each day? Defective gloves may well be more hazardous than no gloves at all, because they can hold a solvent in contact with the skin (doctors call it an occlusive dressing) and can give a false sense of security.

Safety glasses. Are they worn when appropriate, which, like seat belts, is more often than most users do?

Respirators. If they need to be in regular use, the process needs redesigning. I would go to a professional for selection of proper type, and instruction in fit, use, and maintenance. Beards can present a problem in gas-tight fit. Again, the surgical-type mask is useless for toxic vapors or fine dusts.

Reference and study time

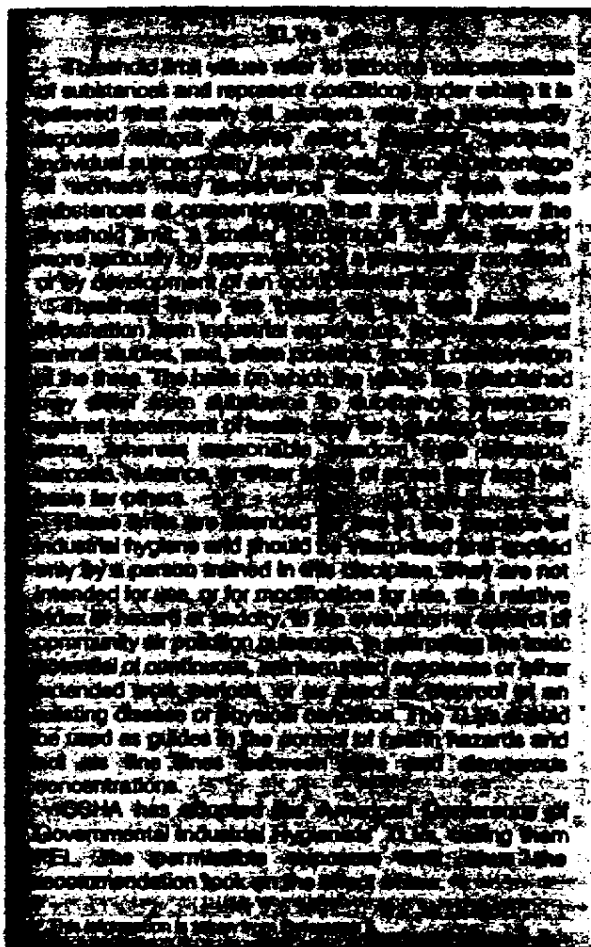
Go to the library and do your homework. My bibliography is not at all exhaustive, but it is useful. For quick reference I prefer "The Merck Index" (7th ed.) or M. Gleason's book. A literature search should always include a check for the latest recommended exposure with the threshold limit values (TLVs), and the summary of animal experiments in the National Institute of Occupational Safety and Health's (NIOSH) "Registry of Toxic Effects." For background on a chemical I read Patty's Volume II and the "Documentation of TLVs," as well as NIOSH's "Criteria Documents" when available. For general background, NIOSH's "The Industrial Environment: Its Evaluation and Control" and the National Research Council's "Prudent Practices" are invaluable. T. A. Loomis has a good introduction to toxicology. And no chemist should be without the ACS's "Safety in the Academic Laboratory."

You will have read that some chemicals interact synergistically; for example, one alcoholic drink after an exposure to chlorinated hydrocarbons may be a literal knockout. At the top of the synergistic hit list is tobacco. Due to the ever-increasing number of materials found to have a harmful synergistic effect with smoking, I feel anyone who works with chemicals is foolish to smoke at all. There are long-delayed consequences of exposure to many 1-10- μ m

Table 1. Safety equipment survey: Gloves

Chemical	Natural rubber or latex	Neoprene rubber	Latex/neoprene	Butyl rubber	Buna-N or NBR	Nitrile	Polyvinyl chloride
Acetic acid	G	G	G	G	G	G	G
Acids (dilute)	G	G	G	G	G	G	G
Acids (concentrated)	NR	NR	NR	NR	NR	NR	NR
Alkalis	G	G	G	G	G	G	G
Alcohols	G	G	G	G	G	G	G
Aromatic hydrocarbons (toluene, xylene)	NR	NR	NR	NR	G	G	NR
Chlorinated hydrocarbons (methylene chloride, methyl chloroform)	NR	NR	NR	NR	NR	G	NR
Ketones (e.g., acetone)	G	NR	NR	G	NR	NR	NR
Lacquer thinner	NR	NR	NR	NR	G	NR	NR
Paint and varnish remover	NR	NR	NR	NR	G	G	NR
Paint thinner	NR	G	G	NR	G	G	NR
Petroleum distillates	NR	G	G	NR	G	G	NR
Phenol (carbolic acid)	NR	G	G	NR	G	G	G
Polyester resin	NR	NR	NR	NR	G	G	NR
Turpentine	NR	G	G	NR	G	G	NR

Note: G = good; NR = not recommended.



particulates, especially for smokers.

Exposure occurs through inhalation and skin contact more commonly than through ingestion. Some classes of compounds act rapidly on the central nervous system; others are slow destroyers of liver and kidneys. But since these organs have a reserve capacity, the effects may not show up for weeks, months, or years. Some effects are transient but frightening. Exposure to fresh, finely divided metal oxides, as in welding, can produce a severe flu-like illness that commonly strikes at night. It's self-limiting, however, and recovery is quick.

Sherlock Holmes

The facts are in, but how to make sense of them? That's hard to explain. I use a combination of curiosity, solid facts, tenacity, horse sense, and intuition. It's likely that the solution or clues to the solution will be found in one or more of the following:

- the medical symptoms and timing
- the homework
- the roof arrangement
- inadequate local exhaust ventilation
- remodeling with particle board and decorating or insulating, all of which can create unacceptable levels of HCHO from urea-formaldehyde resin
- sloppy work habits
- a hunch
- psychosomatic illness, sometimes called mass hysteria.

The solution is to change the process by using materials that are less toxic or to limit exposure by enclosure or increased ventilation. At the absolute minimum I advise anyone with recurrent headaches at work to get fresh air periodically. If a solution does not seem obvious there are two choices: Look for the offbeat solution, but you must ask the right question to get the right answer. Or call in a health and safety consultant, industrial hygienist, or an occupational health physician or nurse. Psychosomatic illness is probably less common than thought, but if the symptoms go away shortly after the inspection begins, it might be because of a placebo effect.

For many noxious chemicals the human being is a better detecting device than many field instruments. Low-level exposures to many substances can lead to subtle but measurable decreases in fine motor coordination, short-term memory, response to stress, and judgment—rather like having one too many drinks. Home artisans often let toddlers play in the studio. Don't allow it. Remember, a young child or fetus is highly susceptible to toxins that have little effect on adults.

Higher exposures can lead to nausea, headaches, dizziness, lassitude, urinary tract irritation, reduced pulmonary function, numbness in the extremities, or irritated eyes. These levels will approach or exceed TLVs (5). The symptoms can come from an assault on the central nervous system, liver, kidney, lungs, or any one of our enzyme systems. The body has only a limited number of ways it can respond to physical, emotional, or chemical stress.

Let me illustrate the Sherlock Holmes approach at its best, when measurements and traditional approaches fail.

The Eastern Airlines Red Rash. In early 1980 Eastern Airlines flight attendants on a newly delivered group of planes were worried about a red rash. It was limited to the hands, arms, and face of cabin attendants in that one plane model, only on over-water flights. It was gone in 24 hours and caused no additional skin problems. Doctors were in a quandary, industrial hygienists could measure nothing, airline officials were soothing, but impotent, and the union threatened action because the attendants were upset, worried, and felt singled out by some malicious force. After about six weeks it was traced to red ink on the new demonstration life vests. Careful observation and a dash of intuition triumphed over technology. This is one of the few instances in which the illness was partially psychosomatic, since seeing the red rash made the crew feel ill.

The High School Art Room. The project that launched my consulting career involved a cluster of complaints of upper respiratory irritation, headaches, nausea, and other nonspecific symptoms among students and staff in a new school addition. After months of memos, it was only when a male supervisor joined the female teachers for a meeting and suffered an attack of blurred vision that a state agency was called in to check out the area.

Initial investigation in conjunction with the state industrial hygienist pointed to the misuse of art materials as the source of the complaints, both because the complaints were centered in this area, and because of the potentially hazardous nature of many art supplies. The art curriculum was reduced to sketches and watercolor; the darkroom was closed. An engineer who visited during a school vacation week attributed the occasional wafts of "sulfurous fumes" to "random mixing by a 'playful' student" of developer and sulfuric acid (6).

My more extensive independent investigation, which included searching records at the Weather Bureau and the state's Department of Environmental Quality Engineering (DEQE), meeting with members of the school committee, school building subcommittee, teacher's associations, nurses, and administrators, as well as making simple measurements and conducting simple experiments, showed that the new ventilation intake was downwind of the school boiler stack when the early morning breeze came from the sea. The symptoms were compatible with low-level exposures to sulfur dioxide mist and carbon monoxide, and their onset corresponded with light wind from the suspect direction. That the ventilation module was built contrary to DEQE edict had been overlooked. The art room was directly under the ventilation intake, and thus received the highest concentrations of pollutants. The fluky nature of the wind meant that investigators who spent only a brief time on the site overlooked the true source of the problem. The hard part of the investigation was getting initial approval to be on the flat-roof.

All the measurements taken by the state hygienist did not find the true source of the symptoms, which included central nervous system depression and airway irritation. The hygienist did not examine the roof. The recommendations, however, did serve as a wedge to teach students and teachers safer handling of art supplies, and to force installation of local ventilation for silkscreen cleanup—a substantial fringe benefit of the background material provided to the school. The engineer called in did not arrange to see classes at work, nor ventilation in action.

Empathy was as necessary an ingredient in the solution as expertise. Since the teachers had been disbelieved for so long, they needed to be reassured that their symptoms were real. A shoulder for crying on was part of my equipment. The three teachers had three separate physicians, so no connection of symptoms was made. They were usually not examined until the signs and symptoms had subsided, certainly not on-site. The toxicology of the exposures the art teachers experienced was undoubtedly not known by the doctors. This is where a health and safety consultant or occupational health nurse could fill in the pieces. Since then two of the three teachers closely involved resigned. The effects from chronic exposure to a toxin are frequently larger than the immediate health effect.

Proof that the culprit I discovered (proximity of



ventilation intake to boiler stack) was the primary cause of the symptoms came when, as an interim solution, the ventilation intake was turned off whenever the boiler was firing. Result: no more problems. The sad part is that the ventilation plans had never received final approval because the DEQE had predicted unacceptable levels of SO_2 at the air intake. The government's system had relied on the technical literacy of the decision makers; that literacy was evidently lacking. Had the DEQE authority commensurate with its responsibility, the design would never have been implemented.

The windup

Before leaving a project, review good work habits, process modifications, and their reasons. Try to go over findings with everyone concerned. The simpler the solution, the more likely it is to be implemented. Frequently a simple change in work habits—such as bringing work closer to an exhaust duct, not smoking on the job, or moving a desk—will alleviate a problem. A change in solvents, to one less volatile or less toxic, may be the solution that avoids costly ventilation or process changes. Receiving raw materials such as clay or fabric dyes in wet rather than powdered form will sharply reduce inhalation exposure to hazardous dusts. I have found that in the beginning, and in my follow-up, people need most to know I'm interested and concerned.

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DEFINITION: EDUCATION

Education is learning to appraise data critically, to try to think up an intellectual framework, to be able to test it, to be able to marshal facts, to be able to write about them, to be able to communicate with people

who may—and almost certainly will—have less knowledge of those facts than you have, because they will be asking you questions about them with a view to taking some action.

Sir Frederick Dainton

File: Risk, Perspective
Copy: Risk, Cancer
Agent Orange pp 661-662

Research policy and public policy

F. H. Tachleay

Let's start with the question of whether policy shapes the nature of research or if research shapes policy. The answer is yes. Things have worked both ways in the past, and we can expect that both will do so in the future.

Public policy is difficult to define in manageable terms. In the broadest context, policy makers include the Congress, the executive branch, the courts, state and local governments, and perhaps most important, the American public, which is heard both by voting and through a diverse set of public interest groups. These range from small, loosely knit local organizations to large, cohesive national ones. They represent the interests of environmentalists, consumers, businesses large and small, and a host of others.

Though all of the groups faithfully claim they are acting in the public interest, their efforts usually are directed more toward self interest. Imaginative minds can always define self interest in terms of the public good, or at least the interests that they feel the greater public should have. These comments are not meant to be flippant or derogatory. They merely reflect the natural attitudes of individuals and groups; personal beliefs invariably are ennobled when expressed in terms of social welfare.

In our system, one must conclude that in the long term, policy is made by the people, even though short-term aberrations frequently arise. We may question the capability of the public to understand the complexities inherent in high technology, but I agree with Thomas Jefferson, who said: "... and if we think them not enlightened enough to exercise their control with a wholesome discretion, the remedy is not to take it from them but to inform their discretion."

Scientists generally recognize the importance of the public role in making decisions that lead to policy. But most scientists have not recognized that many important issues of today transcend science and that the judgments of science can best be incorporated as Jefferson recommended by informing the discretion of the public.

Weinberg (1) defined issues that transcend science as those in which questions can be asked of science that science cannot answer. Such issues arise frequently with pesticides because of uncertainty in such areas as estimating exposure and extrapolating test data from animals to humans. Accepting the fact that many issues transcend science is difficult for many scientists. The public long accepted the

development of increasingly sophisticated technology without question, at the most offering mild rebukes. That attitude has changed dramatically in the past 20 years. The nonscientific laity now challenges science directly and forcibly. Little wonder that scientists are threatened by the new order. We do not willingly leave the comfortable cocoon of unquestioned omniscience that enveloped us for so many years.

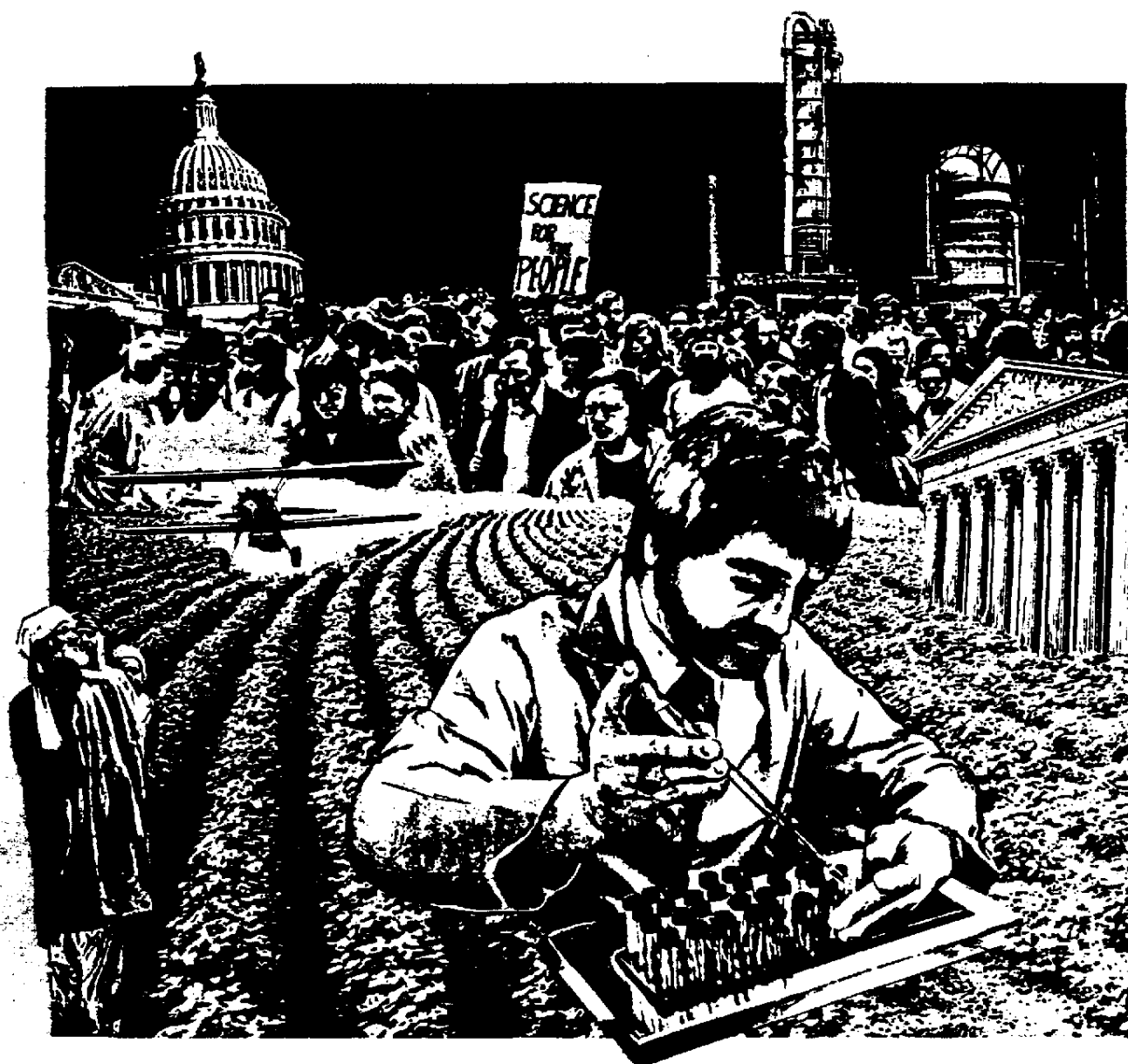
The new order has wrought profound changes in the form and substance of policy development. I want to explore with you three areas of policy development that seem important in today's society: the activities of special interest groups, the adversary process in judicial affairs and administrative procedures, and the resolution of disputes on issues that transcend science.

Pesticides and the decade of environmentalism

Special interest groups have been a part of the American scene for all of our history, but their complexion has changed profoundly in the past 20 years. Once such groups could be classified predominately on the basis of management and labor, the major components of our private enterprise system. The last 20 years have seen the formation of many more groups whose efforts are directed to the improvement of, among other areas, consumer rights and the environment. In 1973 the Council on Environmental Quality (2) reported there were perhaps 5000 environmental organizations in the U.S., more than half formed during or after 1969. A survey of their activities showed that about half testified at public hearings and 17 percent engaged in lobbying activities. National groups such as the Natural Resources Defense Council and the Environmental Defense Fund were established specifically to provide a legal challenge to the established ways of doing business by private industry and government.

In terms of legislation enacted, one can only conclude that environmental special interest groups have been eminently successful. The National Environmental Policy Act was enacted in 1969; Clean Air Amendments in 1970; the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, in 1972; the Federal Water Pollution Control Act in 1972; the Endangered Species Act, adding plants to a former act protecting endangered fish and

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wildlife, in 1973; the Toxic Substances Control Act in 1976; and a variety of other acts related directly or indirectly to environmental quality. The fact that all of the acts cited here have some influence on the use of pesticides is not merely coincidental. Who would question the appropriateness of labeling the 1970s the decade of environmentalism?

The surge of environmentalism and concern about the effects of pesticides have profoundly influenced the nature of pesticide research. Previously the principal question asked about a pesticide was "does it kill the pest?" Suddenly we were addressing questions concerning their metabolism, persistence in the environment, bioaccumulation, residues in food and feed commodities, and effects on nonpest species. Many scientists active today owe their professional careers to Rachel Carson's writings and the resulting ground swell of public concern about pesticides distributed in the environment.

It is interesting to note that the documentation of benefits—increased yield of agricultural commodities—in the early public hearings following cancellation of the

organochlorine insecticides was extremely difficult. Scientists involved in plant protection research in the early days of the synthetic organic pesticide era simply knew intuitively that dead bugs translate into increased yield. But data to support their theory were scanty. Research methodology to define the yield increases attributable to effective plant protection is still beset with many problems, but we are much more proficient today at estimating losses due to pests—and thus the benefits of control—than we were 10 years ago. Whether the research methodology to determine crop losses has indeed been improved, or we have simply learned to express our ignorance more intelligently, is debatable. I prefer to believe the former, but suspect the latter is not without truth.

These comments are not meant to be disparaging; they simply point out the extreme difficulty of separating the effects of crop protection practices from the numerous other factors that influence yield. An example is that losses in corn production in Illinois in 1965 were estimated to be 20%, one of the highest estimates ever. Nevertheless, ideal weather

for corn production that year led to a bumper crop so that most farmers had the largest yield and biggest profit in history—despite the 20% loss to stalk rot (3).

A note on carcinogenicity

In recent years the rebuttable presumption against registration (RPAR) process developed by EPA for assessing risk and benefit prior to reregistration of pesticides forced intensive efforts on quantifying benefits. RPAR also forced a substantial effort on determining the degree of exposure to pesticides by users. Studies of exposure were not conducted so much because of acute toxicity, but rather because of possible chronic effects, especially carcinogenicity, mutagenicity, and teratogenicity.

The subject of carcinogenicity merits further comment because an acceptable policy on the management of carcinogens by all agencies of the government has not yet been established. The death rate from cancer in the U.S. is about 175 per 100 000, high enough that each of us probably has a friend or relative who has or had cancer. It is a wasting disease causing great pain for those who suffer from it and emotional trauma for those who witness their plight. Fear of cancer is a natural human reaction. But that fear has been exacerbated by stories of a phenomenal increase in cancer incidence, with the cause being attributed to exposure to a variety of chemicals, pesticides predominant among them.

There are, I believe, three important reasons for concentrating on chemicals as the principal causes of cancer. First was the postulate by Higginson in the 1950s that about two-thirds of all cancers were caused by environmental factors and thus were theoretically preventable. As time went on most people connected the words "environment" and "chemical," a misinterpretation that Higginson has taken some pains to correct (4). In using the word "environment," Higginson meant everything that surrounds and impinges upon people—chemicals being only one component of a large array of factors.

Second was an exploitation by environmental organizations of the public's inherent fear of cancer, associating cancer with rising public concern that followed the publication of "Silent Spring" in 1962. There seemed to be a rightness, if not a righteousness, in the belief that chemicals cause pollution. Pollution is bad, therefore chemicals must be the cause of that bad disease we call cancer.

The third reason for the chemical-cancer association was the war on cancer declared by President Richard M. Nixon in the early 1970s. Many millions of dollars were appropriated for cancer research with the objective of finding causes and cures. Results were expected quickly and research oncologists had to respond. Chemicals already were uppermost in the American consciousness, and they offered a relatively simple and easily manageable tool for cancer research. Cancers with clearly defined etiology such as smoking, benzo(a)pyrene, and aflatoxin are clearly much simpler to deal with than such nebulous, fuzzy entities as diet and behavior, which Higginson identifies as the most important components of life-style associated with carcinogenesis. As a result Nixon's war on cancer led to a concentration on chemicals in cancer research and intensified the already existing belief that chemicals are the major cause of cancer.

I suspect that most people in the U.S. believe that the cancer rate is increasing rapidly and that exposure to



chemicals is the cause. But statistics of the National Cancer Institute do not support this. In fact, when the number of men dying of lung cancer is subtracted from the total number of cancer deaths, we see no increase in the cancer death rate during the past 30 years. Remember that smoking is the major cause of lung cancer. For women the age-adjusted total cancer death-rate in the U.S. has declined slightly during the same period despite the fact that lung cancer deaths among women have increased about 10-fold.

The same 30-year period saw production of pesticides increase about 12 times, synthetic rubber about five times, and plastics about 35 times (5). And total synthetic organic chemical production rose from about 50 billion pounds to about 350 billion pounds. Cancer incidence increased from about 125 to 175 per 100,000 during the same 30-year period, and most of that is attributed to smoking. Although the long lag-time from exposure to development of cancer prevents a positive statement, the evidence strongly suggests that the association between chemicals and cancer is more apparent than real. You shouldn't interpret these remarks to mean that no chemicals cause cancer, because of course some do. I do believe, however, that chemicals per se have been unfairly maligned by undue emphasis on them as carcinogens.

For or against

Originally a cornerstone of the judicial system in the U.S., the adversary process has expanded substantially into administrative procedures and significantly into daily discourse among individuals and groups. Formal procedures such as judicial cases or administrative hearings have arbiters (a judge or administrative law judge) whose function it is to weigh the evidence given by two sides and find truth that will result in a just decision.

There are those in the legal profession who believe that the process has devolved into one of gamesmanship in which the discovery of truth has become secondary to winning for the client (6). I could cite numerous instances to support this belief. But even if gamesmanship is an exaggeration, I believe the adversary process is poorly designed to deal with uncertainty—the principle issue at hand in disputes concerning pesticides.

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In the adversary process one has to be either for or against something. That is the case as well if one is to testify during court proceedings or an administrative hearing. Lawyers prepare cases for their clients. Potential witnesses are interviewed and then selected only if their testimony will support the position already taken. Having given testimony, they are subject to cross examination, which usually is comparatively mild in administrative hearings although it occasionally becomes offensive. Scientists testifying on opposite sides of an issue have no opportunity to discuss their differences with each other. They are in fact prevented from doing so by the adversary process. That is foreign to the discovery of truth as scientists have learned it. The process of peer review prior to and after publication of experimental results is the cornerstone of scientists' search for truth. That avenue is not open in the adversary process. As a consequence, many scientists refuse to testify when called, or do so only under duress. Those who do testify often become even more firmly set in their views because the subtle reasons for differences in interpreting a body of data are not elicited during either direct or cross examination. Thus the adversary process in a public hearing perpetuates and intensifies differences.

Scientists are trained to deal with uncertainty and do so daily. Lawyers, on the other hand, are not. They operate in a system that recognizes only black and white. Understanding between attorney and scientist witness is frequently difficult because of their different approaches.

After a public hearing is completed, the administrative law judge evaluates the evidence and provides recommendations to the head of an agency—called the administrator at EPA—who must make a final decision. The administrator is in a particularly difficult position for making that decision, because of the constraints on seeking the counsel of experts who participate in hearings. Because attorneys for the two sides sign up all the best witnesses in advance, the range of choices for expert counsel open to the administrator is extremely limited, if it exists at all. After a decision is made, the winners are elated and the losers enraged. The losers appeal the decision and the second round of testimony, by experts who again may not discuss their differences with each other, begins. Some decision, commonly by a court, ultimately becomes the final one that must be accepted. But the controversy remains. Simply put, the system has forced acceptance of a decision but has done nothing to resolve differences.

Pesticide issues are extremely complex, particularly in the area of chronic toxicology. Can a nonscientist attain the depth of understanding needed to make good decisions on complex issues in which he has no training? This question has been raised repeatedly, but never satisfactorily answered. The legal community is itself divided on the issue. Some believe that the courts can contribute most by strengthening administrative procedures (7); others believe that the courts should play a more substantive role (8). The question is important, but I doubt that we will soon see any profound change in the judicial system.

The administrator's position is extremely difficult, for he or she must make decisions on issues that may transcend science. The decision by EPA Administrator William Ruckelshaus to ban DDT is an excellent example of what I mean. Ruckelshaus has since stated that the DDT decision was political rather than scientific. Not political in the sense of votes gained or lost, but rather, I prefer to believe,

"socio-political." DDT had become a social cause. The only way to defuse the emotion surrounding that cause was to deny further use. Fine! I have never objected to the DDT decision, but have always felt that the right decision was made for the wrong reasons of record. Support for the decision rested in largest measure on its potential as a human carcinogen, despite testimony by then Surgeon General Jesse Steinfeld supporting continued use of DDT for protection of human health. At its worst interpretation, the DDT decision prostituted science to support a decision made for a different reason; at the least, it did not interpret the scientific data the way most oncologists would. Can we fault Ruckelshaus? Probably not—at least not as much as we can fault the system. Suppose he had cited socio-political reasons to support his decision. An appeal would have been made immediately and gleefully, and there is no question but that the Appellate Court would have found his decision arbitrary and capricious.

Public hearings became a part of FIFRA procedures for admirable reasons: They give everyone the opportunity to participate in the decision-making process, and they afford all parties an opportunity to redress a perceived wrong resulting from an administrator's decision. But man's inventiveness in devising the system of hearings and appeals neglected an unavoidable trap within the maze—implementation by the adversary process.

Process affects decision

I must add a final point on the adversary process as it operates in administrative hearings. The regulatory agency takes a position at the time a cancellation or suspension notice is issued. That then triggers an administrative hearing under Section 6(d) of FIFRA, assuming a request for a hearing is filed by the registrant. From then on, EPA's efforts are directed to defending its position. Attorneys from the Office of the General Counsel prepare the defense, assisted as needed by the scientific and technical staff. Although the administrator stands aside from this effort, I find it difficult to believe that the concentrated defense activity by loyal employees of his agency does not have some influence on his decision. I believe that the administrative public hearing, as it has operated under FIFRA, is little more than a protracted and expensive public showcase to support a decision that was made at a much earlier time.

I have faith that reasonable people can resolve differences and reach conclusions that best serve society's interests and needs. Moreover, I have faith that most people are reasonable. Extremists with small bands of vociferous followers will always be around, but they are a minority that society can tolerate. Their voices will be muted when reasonable people with honest differences find the courage to shun the adversary process, communicate openly, and work to resolve their differences. Freed from the constraints of the adversary process, reasonable people would work to understand and then to resolve their differences. They would rely on research to reduce uncertainty in those areas where differences could not be resolved.

The saga of 2,4,5-T represents to me a classic case of the misuse of science to support a decision made for different reasons. A notice of cancellation of uses of 2,4,5-T was first issued by EPA in 1973. It was withdrawn on June 24, 1974, the day the public hearing was to start, because of the lack of sufficient evidence. On March 1, 1979, EPA issued an emergency suspension of 2,4,5-T use in forests, pastures, and rights of way. The suspension action was taken on the basis

of an EPA study (commonly referred to as Alsea II) that showed an association between exposure to 2,4,5-T and the incidence of spontaneous abortion. The Alsea II study has been reviewed by numerous individuals and groups, none of whom supported the conclusions reached in the report (10).

The arguments were not restricted to domestic use of the herbicide. I believe that the suspension and cancellation orders exacerbated an existing fear among Vietnam veterans that their health was damaged by exposure to Agent Orange. While these veterans should be compensated for any ills they suffer resulting from serving their country, they should not be compensated for the wrong reason. And the available evidence fails to support the veterans' contention that Agent Orange caused the wide variety of ills alleged.

But the veteran's fears are real. The suspension and cancellation orders and coverage in the press contributed to those fears. Some have suggested that court awards for injury be made for excessive regulation (9). Should that ever come to pass, 2,4,5-T would make an interesting test case.

An alternative for solving problems

I have been involved with three dispute resolution conferences in which disputants were brought together to discuss differences outside the adversary process. The herbicide 2,4,5-T was the subject in two of them, the third involved the imported fire ant and its control. I think all three had some measure of success in influencing regulatory decision makers by exposing people to a nonadversary process, and, most important, by helping us learn to develop better procedures for resolving disputes. I'd like to share with you the important lessons learned from those conferences as follows:

- Invited participants must represent all sides of the issue. Discussion groups for specific topics may be composed of scientists, politicians, and the nonprofessional laity.
- All discussions must be open to the public. Numbers of invited participants must be limited simply for logistics' sake, but many others will be interested in the process, the issue, and the conclusions reached.
- Uninvited members of the public should be treated as participants in the process. They must be given the opportunity to comment, question, or provide other input they deem important, but without disrupting the process.
- Reports should be developed during the course of the conference with drafts turned in before participants leave. Edited versions should be completed promptly—not more than two months after the conference closes. This requires substantial preparation beforehand by active participants and adequate clerical support during the conference.
- Usually several specific topics will be discussed concurrently. Liaison must be provided among groups and specific groups should report to the conference as a whole. These procedures reduce duplication, permit everyone to know what progress is being made, and frequently stimulate insight that might not otherwise result. In some situations it may be profitable to interchange invited participants among two or more groups.
- Particular care must be taken to ensure that no participant feels threatened. It is usually difficult to achieve proportional representation from the various interest groups without either sacrificing expert knowledge of the

available data or making the group unmanageably large. For example, if there are three interest groups, a single individual representing one group may feel overwhelmed and might charge the conference with bias in selecting the group. The appearance of bias in establishing groups must always be avoided as diligently as bias itself.

- There must be vigorous and imaginative efforts to attract the press. This isn't easy and I have never been very successful at it. After all, the conference has been organized to resolve dispute and downplay controversy, so you can't promise harsh words and fist fights on the hour to enliven the proceedings. I'm confident that the press can be attracted, but not by casual, unimaginative efforts. Public information specialists should be intimately involved from the first planning sessions through the end of the conference.

Conclusion

There are some instances in which pesticide research has shaped public policy. More frequently, however, policy has shaped the direction and nature of research. Neither procedure is inherently good or bad. In many instances, pesticide research that was forced by policy was research that ought to have been conducted earlier. Disputes about pesticides and their use will continue. The most critical policy need that I see is the development of mechanisms and institutions to resolve rather than perpetuate dispute.

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*Calculations
in
Toxicology*

CLINICAL AND DIAGNOSTIC VETERINARY TOXICOLOGY

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CALCULATIONS IN TOXICOLOGY

The ability to accurately manipulate numbers is fundamental to the practice of medicine. The practitioner is constantly calculating drug dosages based on estimates of body weight and food consumption. Similarly, the toxicologist is faced with the problem of relating the level of contamination in a feed to the clinical signs observed in a suspected poisoning. In this section several guidelines will be developed to help the toxicologist and practitioner interpret the significance of numbers resulting from laboratory analyses or estimates of probable exposure.

Terminology

In veterinary toxicology the preferred method of expressing concentrations of most toxicants in feeds, water, solvents, sprays and animal tissues is to use parts per million or related terms such as parts per billion or parts per trillion. Occasionally when high concentrations are involved, such as with insecticide concentrates, the concentration is expressed as a percentage on a weight/weight basis. A part per million, abbreviated ppm, is one part of X in 999,999 parts of Y on a weight/weight basis. Using metric units, then 1 ppm is 1 mg per 1,000,000 mg or, more simply, 1 ppm is equal to 1 mg/kg. This relationship is fundamental and must be firmly committed to memory. If this basic relationship is understood, then the toxicologist can calculate the equivalent in any other units of weight. For example, 1 microgram (µg) per gram is also 1 ppm.

The definition of 1 part per billion, abbreviated ppb, follows in a similar manner, namely 1 part in 1,000,000,000 parts or 1 µg/1,000,000,000 µg which progressively reduces to 1 µg/1,000,000 mg = 1 µg/1,000 grams = 1 µg/kg. Again this is a basic relationship that should be firmly retained. The definition of 1 part per trillion (ppt) follows in a similar manner.

Fortunately there is a direct relationship between percentage concentration and parts per million. This relationship can be discovered by calculating the percentage equivalent of 1 ppm as given in Example 1.

Example 1: Determining percentage equivalent of 1 ppm.

- a. 1 ppm = 1 mg/kg = 1 mg/1,000,000 mg.
- b. $1 \div 1,000,000 = 0.000001$.
- c. Convert to % by multiplying by 100.
- d. $0.000001 \times 100 = 0.0001\%$.
- e. Therefore, 1 ppm is the same as 0.0001%.

From this relationship a conversion table can be calculated as given in Table 1.

TABLE 1
Relationship Between PPM and Percentage

PPM	Percentage
0.001 ppm = 1 ppb	0.0000001%
.01 ppm = 10 ppb	0.000001%
.1 ppm = 100 ppb	0.00001%
1 ppm	0.0001%
10 ppm	0.001%
100 ppm	0.01%
1,000 ppm	0.1%
10,000 ppm	1.0%

A rule of thumb that is most useful is: to convert ppm to percentage, move the decimal point 4 places to the left. And, to convert percentage to ppm move the decimal point 4 places to the right. Using this rule of thumb it is easy to see that 124 ppm is the same as 0.0124% and that 0.5% is the same as 5000 ppm.

A commonly encountered situation in clinical veterinary toxicology is the addition of drugs to animal feeds where the concentration is expressed as grams of drug per ton of feed. Example 2 shows how this can be expressed on a ppm basis.

Example 2: Show that 1 gm/ton is equal to 1.1 ppm.

- a. Basic definition: 1 ppm = 1 mg/kg.
- b. 1 gm/ton = 1000 mg/2000 pounds.
- c. $= 1000 \text{ mg}/2000 \text{ pounds} \div 2.205 \text{ pounds/kg}$.
- d. $= 1000 \text{ mg}/907 \text{ kg}$.
- e. $= 1.102 \text{ mg/kg}$.

- f. = 1.102 ppm, therefore 1 gm/ton is equal to 1.1 ppm.
- g. And furthermore, 100 gm of drug/ton is equivalent to 110 ppm.

This provides another useful rule of thumb; namely, that 100 gm/ton gives a concentration equivalent to 110 ppm.

Example 3 shows several ways of using the above information in solving an applied problem.

Example 3: Preparation of 2 tons of pig grower feed containing 400 ppm arsanilic acid.

Method 1—Use rule of thumb that 100 gm/ton is equal to 110 ppm.

- $\frac{400 \text{ ppm}}{110 \text{ ppm}} = \frac{X \text{ gms/ton}}{100 \text{ gms/ton}}$
- $X = \frac{400 \times 100}{110} = 364 \text{ gms/ton}$
- Therefore, you need $2 \times 364 = 728$ grams of arsanilic acid to prepare 2 tons of medicated feed.

Method 2—Use the rule of thumb in converting ppm to percentage.

- 400 ppm = 0.04%.
- 2 tons = 1814 kg.
- $1814 \text{ kg} \times 0.04\% = 1814 \text{ kg} \times 0.0004 = 726 \text{ grams.}$

(Answers differ because of rounding error)

Either method is correct and each individual needs to decide which method he personally prefers to use.

Expressing Concentrations of Substances in Body Fluids

The lack of uniform methods among toxicologists for expressing concentrations of substances in blood or other fluids can lead to appreciable confusion. Units used include ppm, mg%, mg/100 ml, milliequivalent, mg/liter, $\mu\text{g}/100 \text{ ml}$, and probably others. Example 4 shows different ways of expressing blood lead levels.

Example 4: Assume you have a report on the analysis of a whole blood sample from a dog suspected of having lead poisoning and the report comes back as 0.8 ppm. What are the other ways of expressing this residue?

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- As mg/100 ml
 - 0.8 ppm = 0.8 mg/kg.
 - 0.8 ppm = .08 mg/100 ml.
(Assuming specific gravity of blood to be 1, although we know that the specific gravity of blood of domestic animals is in the range of 1.039 to 1.061)
 - This is also the same as 80 $\mu\text{g}/100 \text{ ml}$.
- As $\mu\text{g}/\text{ml}$
 - 0.8 ppm = .08 mg/100 ml.
 - 1 mg = 1000 micrograms.
 - .08 mg/100 ml = 80 $\mu\text{g}/100 \text{ ml}$.
 - = 0.8 $\mu\text{g}/\text{ml}$.
- As mg%
 - 1 mg% = 1 mg/100 ml.
 - 0.8 ppm = .08 mg/100 ml.
 - = 0.08 mg%.

Problems Encountered in Expressing Exposure

Frequently animal toxicology studies are done with the toxicant administered on a weight of drug per unit body weight basis (i.e., mg drug/kg body weight). However, in field cases encountered in veterinary toxicology the estimated exposure is often based on a feed analysis which results in X ppm toxicant in the feed. The problem then is to estimate how much of the suspect feed the animal consumed and to calculate an estimated dosage. Fortunately, sources of information are available for estimating the average amount of feed each of the common domestic animals consumes during various stages of its life cycle. One source is the information published by the National Academy of Sciences—National Research Council, as follows:

- Nutrient Requirements of Beef Cattle, Fourth revised edition, 1970.
- Nutrient Requirements of Poultry, Sixth revised edition, 1971.
- Nutrient Requirements of Dairy Cattle, Fourth revised edition, 1971.
- Nutrient Requirements of Sheep, Fourth revised edition, 1968.
- Similar documents are available for horses, swine, dogs, rabbits, mink, and foxes.

Another publication of the NAS/NRC that contains extensive data on animal feeds is "United

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States—Canadian Table of Feed Composition," Second revision, 1969.

The general formula for converting a level of drug in feed (ppm) to the estimated equivalent on a mg/kg basis is:

$$\frac{(\text{Level in feed (ppm)}) \times (\text{kg feed eaten/day})}{\text{body weight in kg}} = \text{mg drug/kg body wt}$$

One additional factor to consider when making these conversion estimates is the increased toxicity that may occur when the dose is given in one, single oral exposure rather than more uniformly throughout the daily eating period. By the same token, a toxicant given in one dose may induce vomiting (organic mercurials) while the same amount incorporated in the daily food may be tolerated by the stomach to the detriment of the organism.

Example 5: If the toxic level of drug XYZ in the feed is 25 ppm for a 10 pound pig, what is the estimated toxicity of drug XYZ on a mg/kg body weight basis? [Assumptions: feed is air dried, drug is evenly distributed in feed, 10 pound pig eats 0.8 pounds feed/day (8% of body weight), and the drug does not depress appetite.]

- Formula = $\frac{(\text{level in feed in ppm}) \times (\text{kg feed eaten})}{\text{body weight in kg}}$
- 25 ppm = 25 mg/kg
- $\frac{(25 \text{ mg/kg}) \times (.8 \text{ pound} \div 2.205 \text{ pounds/kg})}{(10 \text{ pounds} \div 2.205 \text{ pounds/kg})}$
- $= \frac{(25 \text{ mg/kg}) \times (.3628 \text{ kg})}{(4.535 \text{ kg})}$
- $= \frac{9.07 \text{ mg}}{4.535 \text{ kg}}$
- $= 2.0 \text{ mg/kg}$

Conversely, the toxicologist may have data on the toxicity of a drug expressed as mg drug per kg body weight and in this case wishes to know what the equivalent level in the feed would be in order to produce similar toxicologic effects. In this case the formula is given as:

$$\text{ppm in feed} = \frac{(\text{mg drug/kg body wt}) \times (\text{wt of animal in kg})}{(\text{wt of animal in kg}) \times (\text{percentage of body wt eaten as food/day})}$$

In the numerator the total number of mg of drug per animal is determined and in the denominator the amount of food eaten per day is calculated. The quotient is then mg drug/kg feed or ppm drug. However, inspection of the formula shows that by removing the weight of the animal from both the numerator and the denominator the formula is simplified to yield:

$$\text{ppm in feed} = \frac{\text{mg drug/kg body weight}}{\text{percentage of body wt eaten as food per day}}$$

Therefore, if the toxicologist knows what the toxicity of a drug or chemical is on a mg drug/kg body weight basis and can estimate the feed intake, then the equivalent exposure on a ppm basis can be calculated. In clinical situations the problem is encountered from a slightly different perspective. The clinical situation requires the toxicologist to determine, often using chemical analysis, the amount of chemical in the feed and then to make a judgment of whether or not the levels found are sufficient to cause the veterinary toxicologic problem under consideration.

Example 6: Assume that you know, based on published information, that the toxicity of a new feed additive is 2 mg/kg body weight for young pigs. At this dose the pigs become anorexic. You are called in on a case where pigs being fed the new drug have become anorexic and are scouring. The person responsible for mixing the feed claims to have added the appropriate amount to achieve a drug level of 10 ppm. However, based on a report of a chemical analysis you suspect the level is 30 ppm. Would 30 ppm be a high enough level to cause the problem? First you might determine what the feed level would be to give an exposure equivalent to 2 mg/kg. This can be determined using either of the two formulas given above. Assume that this case involves 10 pound pigs eating an amount of feed equivalent to 8% of their body weight/day. Calculate the level in the feed required to give an exposure of 2 mg/kg.

Method 1—

$$\text{a. ppm in feed} = \frac{(\text{mg/kg}) \times (\text{wt of animal in kg})}{(\text{wt of animal}) \times (\% \text{ of body wt eaten as feed})}$$

$$\text{b.} = \frac{(2 \text{ mg/kg}) \times (10 \text{ pounds} \div 2.205 \text{ pounds/kg})}{(10 \text{ pounds} \div 2.205 \text{ pounds/kg}) \times (.08)}$$

$$\text{c.} = \frac{(2 \text{ mg/kg}) \times (4.535 \text{ kg})}{4.535 \text{ kg} \times 0.08}$$

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d. = $\frac{9.070 \text{ mg}}{.363 \text{ kg}}$

e. = 24.98 mg/kg $\cong$ 25 ppm

Method 2—The problem can be solved more directly by using the simplified formula:

a. ppm in feed = $\frac{\text{toxicity of drug in mg/kg}}{\text{percent body wt eaten as feed}}$

b. = $\frac{2 \text{ mg/kg}}{.08}$

c. = 25 ppm

Since you have reason to believe that the level actually fed (30 ppm) exceeds the toxicity of 2 mg/kg or 25 ppm in feed, you would seriously consider the involvement of the drug in this instance.

Feed consumption by an individual animal will vary with body weight, ambient temperature, disease conditions, type of feed and a host of other conditions. However, it is necessary to have some estimate of feed consumption under normal conditions. The estimated feed consumption values presented in Table 2 are guidelines and should be used with due caution, especially if you have reason to suspect that unusual conditions exist in a particular situation.

TABLE 2
Estimated Feed Consumption Rates for Beef, Swine and Chickens Under Ideal Conditions
Numbers Based on NRC Nutrient Requirement Data

Species	Body Weight		Weight of food eaten per day expressed as percentage of body wt.
	Pounds	Kilograms	
Beef	300	136	2.3
	450	204	2.5
	650	295	2.4
	1000	454	2.1
Swine	10-25	4.5-11.3	8
	50	23	6.4
	100	45	5.3
	150	68	4.5
	200	91	4
Chicken	0.5	.23	14
	1.0	.45	11.4
	1.5	.68	9.7
	3.5	1.59	6.7
	5.5	2.50	5.0

Estimating Dosages When Exposure Is Based on Consumption of Green Forage That Has Been Sprayed

A difficult situation is encountered when the toxicologist is faced with a field problem involving "sick" or dead animals "associated" with the spraying of forages with a chemical. One must estimate the amount of forage eaten and make an estimate of the uniformity of the sprayed material on the forage. Short grass may be uniformly sprayed, whereas, tall weeds or grasses may have spray material concentrated at the top with little material reaching the lower portions of the plant.

Palmer and Radeleff (1969. The Toxicity of Some Organic Herbicides to Cattle, Sheep, and Chickens, ARS, Production Research Report No. 106) estimated that a high quality improved pasture would yield 0.1 pound (45 grams) of air-dry forage/square foot or about 2 tons per acre. Application rates of 1 pound of chemical/A would result in 10.4 mg chemical per square foot. (1 A = 43,560 square feet) They further assumed a forage consumption factor of 3% of body weight and total availability of the chemical (maximizes exposure). This results in an equivalent exposure of 7 mg/kg for each pound of chemical/A. (1 kg $\times$.03 = 30 grams of forage consumed per kg body weight; 45 grams of forage from 1 square foot contains 10.4 mg or 30 grams contains 6.9 mg which rounds off to 7 mg.)

On a ppm basis the forage would be estimated to contain 230 ppm of chemical. [(1000 gm/kg $\div$ 45 grams) $\times$ (10.4 mg) = 230 mg/kg] Thus another useful rule of thumb is that 1 pound of chemical per acre results in an exposure in a grazing animal of approximately 7 mg of chemical per kg body weight. Therefore, if a herbicide were applied at 2 pounds per acre and cows were allowed to graze the sprayed forage, the herbicide exposure would be approximately 14 mg/kg. If the no effect exposure level is 300 mg/kg for the herbicide, then the toxicologist would rightly conclude that the herbicide would not be responsible for any adverse health effects seen in the cattle.

Conversion Factors

Table 3 contains some commonly used conversion factors or numeric constants frequently or occasionally needed in veterinary toxicology.

CALCULATIONS

9

TABLE 3
Equivalents, Constants and Prefixes

Length	Capacity—Liquid
1 inch = 2.54 centimeters	1 minim = 0.062 milliliters
1 foot = 30.48 centimeters	1 ounce = 8 drams
1 yard = 91.44 centimeters	1 ounce = 29.57 milliliters
1 furlong = 660 feet	1 dram = 3.697 milliliters
1 rod = 16.5 feet	1 gill = 4 ounces
1 mile = 5280 feet	1 quart = 0.946 liters
1 mile = 1609.3 meters	1 quart = 256 drams
1 chain = 66 feet	1 quart = 57.75 cubic inches
1 centimeter = 0.3937 inch	1 gallon = 3.785 liters
1 meter = 39.37 inches	1 cubic foot = 7.48 gallons
1 meter = 3280.8 feet	1 cubic foot = 59.84 pints
1 micron = 1×10^{-6} meter	1 cubic foot = 28.32 liters
1 micron = 1×10^{-3} = 0.001 millimeter	1 bushel = 9.309 gallons
1 angstrom = 1×10^{-5} = 0.00001 micron	1 barrel (oil) = 42 gallons
	1 barrel (US liquid) = 31.5 gallons
	1 acre-foot = 3.259×10^5 gallons
	1 liter = 1.057 quarts
	1 liter = 270.5 drams
	1 liter = 33.81 ounces
	1 liter = 0.264 gallons
	1 liter = 61.03 cubic inches
	1 liter = 1000 milliliters
	1 teaspoon = 5 milliliters
	1 tablespoon = 15 milliliters
Area	Capacity—Dry
1 acre = 43,560 square feet	1 bushel = 8 gallons
1 acre = 4,047 square meters	1 bushel = 4 pecks
1 hectare = 2.471 acres	1 bushel = 35.24 liters
1 hectare = 10,000 square meters	1 bushel = 1.24 cubic feet
1 square mile = 640 acres	1 cubic foot = 0.804 bushel
	1 cubic foot = 28.316 liters
	1 cubic foot = 25.714 quarts
	1 peck = 8 quarts
	1 quart = 1.101 liters
	1 liter = 0.908 quarts
	1 liter = 61.03 cubic inches
	1 cubic meter = 35.314 cubic feet
	1 cubic inch = 16.387 milliliters
Weight	
1 grain = 64.8 milligrams	
1 ounce = 28.35 grams	
1 ounce = 16 drams	
1 pound = 453.59 grams	
1 short ton = 2000 pounds	
1 short ton = 907.18 kilograms	
1 long ton = 2240 pounds	
1 long ton = 1016.05 kilograms	
1 metric ton = 1000 kilograms	
1 metric ton = 2204.6 pounds	
1 gram = 15.43 grains	
1 kilogram = 2.205 pounds	
Miscellaneous	
Degrees Centigrade = $(^{\circ}\text{F} - 32) \times 0.55$	
Degrees Fahrenheit = $(^{\circ}\text{C} \times 1.8) + 32$	
1 Calorie = 0.003968 BTU	
1 BTU = 252 Calories (Gram) (15°C)	
1 atmosphere = 33.90 feet of water	
1 atmosphere = 29.92 inches of mercury	
1 atmosphere = 14.7 pounds/square inch	
1 horsepower = 745.7 watts	
1 gallon water = 8.3453 pounds	

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TABLE 3 (Cont.)

Prefixes Applied to Metric System Units

Multiples	Prefix	Symbol
10 ¹²	tera	T
10 ⁹	giga	G
10 ⁶	mega	M
10 ³	kilo	k
10 ²	hecto	h
10	deka	da
10 ⁻¹	deci	d
10 ⁻²	centi	c
10 ⁻³	milli	m
10 ⁻⁶	micro	μ
10 ⁻⁹	nano	n
10 ⁻¹²	pico	p
10 ⁻¹⁵	femto	f
10 ⁻¹⁸	atto	a

Density of Dry Feed Ingredients*

Product	Pounds/cubic foot	Product	Pounds/cubic foot
Alfalfa meal	18	Oat, seed	30
Alfalfa pellets	42	Oat, ground	22
Barley, whole	41	Oat, rolled	21
Barley, ground	25	Pellets, 0.25 inch	39
Calcium carbonate	75	Phosphate	75
Corn, shelled	45	Rye, bran	17
Corn, ear chopped	35	Rye, middlings	42
Corn, meal	39	Salt, fine	75
Cottonseed oilmeal	38	Sorghum, seed	33
Dairy, concentrates	43	Soybeans, ground	30
Fishmeal	35	Soybeans, seed	47
Hay, loose	5	Soybean oilmeal	38
Hay, pressed	8	Tankage	49
Linseed oilmeal	29	Urea	38
Milk, powdered	20	Wheat, whole	49
Millet	39	Wheat, bran	13
Milo, seed	42	Wheat, ground	39
Milo, ground	34	Whey, dry	41
Molasses, feed	23		

*Source: Feed Manufacturing Technology, 1970.

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1 inch 9 in.

SPECIAL REPORT

Sprayed-on asbestos-containing insulation coats ceiling beam. Such friable material, often seen exposed in parking garages, crumbles easily

General Institute of Technology photo

ASBESTOS

The fiber that's panicking America

Pamela S. Zurer, C&EN Washington

March 1984—The Environmental Protection Agency assesses a \$24,000 fine against three schools in Goffstown, N.H., for failing to comply with EPA's rule concerning asbestos in schools.

December 1984—The District of Columbia files a \$400 million lawsuit against asbestos manufacturers and distributors to recoup the cost of removing asbestos from city buildings.

January 1985—Fairfax County, Virginia, government announces it will spend \$5 million to \$6 million to remove asbestos from three public buildings, even though it says air levels are not hazardous.

Demand for asbestos in the U.S. last year was only about 30% of what it was at its peak in 1973. Fear of the material's toxicity and the health-related lawsuits it has engendered are largely to blame. But demand has been mushrooming for the services of the asbestos abatement industry, as property owners rush to remove asbestos

that was used as fireproofing and insulation in many buildings built before the mid-1970s. Demand for legal expertise is increasing, too, with property damage suits multiplying rapidly.

Two decades ago, concerns about asbestos hazards centered on workers who had been exposed to huge amounts of fibers in their jobs. In the 1960s, landmark epidemiological studies by Irving J. Selikoff of Mount Sinai School of Medicine and E. Cuyler Hammond of the American Cancer Society showed that insulation workers who had dealt with asbestos for 20 years or more were dying of cancer and the complications of asbestosis at alarming rates. Later, a few people whose only contact with the material was that they lived in the same house as asbestos workers were found to be dying of mesothelioma—a rare cancer of the lining of the lung or abdomen.

In 1971, asbestos became the first material to be regulated by the then-new Occupational Safety & Health Administration. In 1982, lawsuits filed by workers suffering from asbestos-related diseases led Manville Corp.—once the largest U.S. asbestos producer but since

1983 out of that business—to look for an escape from the rising costs in bankruptcy court.

Today, although there is still concern that people who work with asbestos are not protected adequately, fear is mounting over the long-term effects of exposure to asbestos in the general environment. Asbestos fibers can be found in the air almost anywhere if you look hard enough. Sources of asbestos in outdoor air range from natural rock to mining and manufacturing operations to particles released from the brake linings of cars and trucks. Indoors, aging or damaged building materials can release asbestos into the air.

Anxiety over asbestos in buildings began to grow in earnest last spring when the Environmental Protection Agency started highly publicized efforts to enforce its asbestos-in-schools rule. That regulation requires school administrators to inspect their buildings for asbestos-containing materials that crumble easily. If any is found, the schools must notify employees and parents that friable asbestos is present. EPA doesn't require that the material be removed, because the mere presence of asbestos is not necessarily hazardous, but recommends each school be evaluated on a case-by-case basis.

Telling parents that there is asbestos in their children's school but authorities aren't going to do anything about it, however, is like saying there's dynamite in the basement but there's no need to worry because the fuse isn't lit. Many parents have been frightened by statements that breathing a single fiber of asbestos can cause cancer years later. Panic and pressure ensue, and the result in many cases has been school closings and hasty removal of asbestos.

Similarly, asbestos is being taken out of many private and public office buildings. Often owners are motivated by fear they will be held liable for future asbestos-related diseases in the buildings' occupants. The bill for all this ripping out of asbestos may come to \$20 billion, a staff member of the House Appropriations Committee estimates.

Yet no one is really sure how hazardous low levels of asbestos in the air are. And asbestos removal is a complicated task that, if done improperly, can leave higher air levels of asbestos in the building than existed before the work started.

Evaluating the risks that asbestos poses to the general population requires extrapolating data gathered in the workplace, where approximate fiber levels are known, to a much larger group of people exposed to much lower concentrations that are essentially unknown. Unlike the case with many toxic chemicals, a large amount of information on occupational hazards of asbestos is available. Even with that massive body of literature, however, it is very difficult to pin down accurately the risks to people who are exposed outside the workplace.

For example, last year a National Research Council (NRC) Committee on Nonoccupational Exposure to Asbestiform Fibers tried to quantify the risks of inhaling low levels of asbestos. The panel concluded that breathing the asbestos present in ambient air may be hazardous and some deaths from cancer probably will result. In contrast, a Canadian report by the Royal Commission on Matters of Health & Safety Arising from

the Use of Asbestos in Ontario, also issued last year, finds "no evidence that disease afflicts individuals who breathe asbestos in outdoor air or inhale it as occupants of asbestos-containing buildings."

Although the NRC panel's stated conclusions are considerably more alarming than those of the Canadian group, the NRC committee states in the body of its report that the number of deaths expected to result from nonoccupational exposures to asbestos are very uncertain. In fact, in calculating the quantitative risks of developing cancer from such exposures to asbestos, the NRC panel estimated the risk could be as high as 1700 per million or could be nil.

"You must realize you can't pin down any specific numbers within that range," says committee member Jeremiah Lynch, manager of industrial hygiene for Exxon Chemical. As with all quantitative risk assessments, so many assumptions were necessary that the panel found it impossible to be exact.

Because of the weight a report from the prestigious NRC can carry with policy makers struggling to regulate asbestos, it's important to look at all the ifs, ands, and buts of the study. "A danger we all recognized when we worked on this was that people will overlook all the qualifiers," Lynch says.

Risk assessment complications

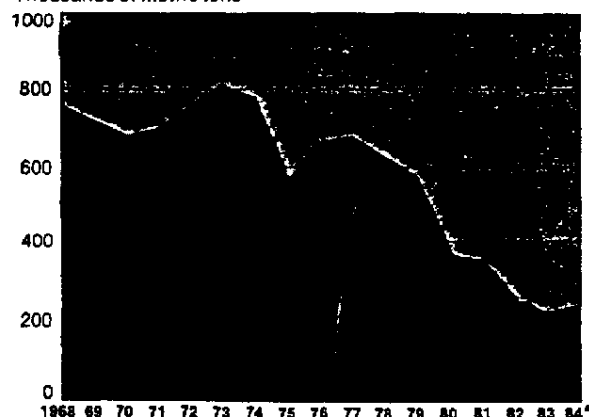
To assess the health risk of a substance, its toxic effects must be identified, the relationship between dose and disease clarified, and the dose the population is exposed to determined. Uncertainties abound at every step.

In the case of asbestos, the toxic effects of high exposures are well documented. Among them are asbestosis, a type of pulmonary fibrosis or scarring of the lungs. Victims become short of breath and may eventually struggle so hard to breathe that they die of heart failure.

Asbestosis, which may develop after years of intense

U.S. consumption of asbestos peaked in 1973

Thousands of metric tons



a Estimate. Source: Bureau of Mines

URL 03129

Special Report

What's in a name? Even defining asbestos is difficult

Asbestos is not a discrete chemical compound or even a single group of minerals. The term is an imprecise commercial one that refers to several fibrous inorganic materials that are valued in industry for their high tensile strength and resistance to heat.

Unfortunately, sometimes minerals that do not meet mineralogists' criteria for asbestos also are lumped under the collective term. With medical scientists, federal regulators, industrial hygienists, contractors, unions, school boards, and even parent-teacher associations trying to tackle the problem of indoor exposure to asbestos, imprecise definitions only make a complicated problem even more difficult to handle.

The several mineral forms that are known commercially as asbestos vary in composition, fiber size, and crystal structure. They share what mineralogists call the "asbestiform habit"; that is, under certain rare conditions the minerals crystallize in bundles of hundreds or thousands of strong, flexible fibrils that look like organic fibers. However, the same minerals can—indeed usually do—crystallize in nonfibrous, rocklike forms.

Other minerals (for example, talc) also may sometimes form fibers under certain geological conditions. These fibers ought not to be called asbestos, mineralogists argue, because they lack the unique flexibility and tensile strength of true as-

bestos varieties. Asbestos fibers tend to cleave along the long axis of the fiber, yielding the thinner component fibrils, rather than break across the fiber axis into shorter lengths.

All commercial varieties of asbestos are silicates, that is, minerals where SiO_4 tetrahedra form the backbone of the crystal lattice. Silicate minerals are classified according to their crystal structures. Asbestiform mineral varieties occur as members of two groups: the serpentine and amphibole minerals.

Only one commercial asbestos mineral, chrysotile, belongs to the serpentine group. Serpentine is a magnesium silicate, in which layers of linked silica tetrahedra alternate with layers of magnesium oxide-hydroxide octahedra. In serpentine rock, the double layers result in platy crystals that tend to cleave into sheets like mica. In the asbestiform variety, however, the double layer rolls up on itself, curling as it grows to form long hollow tubes that are characteristic of chrysotile.

Chrysotile asbestos also is called white asbestos. Most asbestos being produced today is chrysotile, primarily from Canada and the U.S.S.R.

The other types of commercial asbestos all belong to the amphibole mineral group. Amphiboles are characterized by

Some silicates can crystallize as asbestos fibers

Mineral name	Chemical formula	Asbestiform variety
SERPENTINE GROUP		
Serpentine	$\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$	Chrysotile (white)
AMPHIBOLE GROUP		
Riebeckite	$\text{Na}_2\text{Fe}_3^{2+}\text{Fe}_2^{3+}\text{Si}_8\text{O}_{22}(\text{OH},\text{F})_2$	Crocidolite (blue)
Cummingtonite-grunerite	$(\text{Mg},\text{Fe}^{2+})_7\text{Si}_8\text{O}_{22}(\text{OH})_2$	Cummingtonite-grunerite asbestos (amosite, brown)
Tremolite-actinolite	$\text{Ca}_2(\text{Mg},\text{Fe}^{2+})_5\text{Si}_8\text{O}_{22}(\text{OH})_2$	Tremolite-actinolite asbestos
Anthophyllite	$(\text{Mg},\text{Fe}^{2+})_7\text{Si}_8\text{O}_{22}(\text{OH},\text{F})_2$	Anthophyllite asbestos

Source: Bureau of Mines

exposure, was the first toxic effect of asbestos to be uncovered. Early occupational standards were designed to protect workers from that disease.

"Asbestosis occurs, for all practical purposes, only after exposure in the workplace," says Arthur M. Langer, a mineralogist who is associate director of the environmental sciences laboratory in Mount Sinai School of Medicine and a member of the NRC panel. The committee did not try to quantify the risk of asbestosis in its report on nonoccupational hazards, as it considered such risks in the general population to be nil.

Epidemiological studies have shown that occupational exposure to asbestos also can produce lung cancer, frequently occurring after a latency period of 10 to 30 years. Hammond and Selikoff documented that smoking cigarettes multiplies the risks of developing lung cancer from asbestos exposure. Lung cancer in asbestos-exposed workers could be cut significantly if they did not smoke cigarettes.

Mesothelioma is a very rare, always fatal, form of cancer of the lining of the lungs and abdominal cavity. The National Cancer Institute estimates there are only about 970 cases a year in the U.S. It is often called a

"marker disease" for asbestos because most cases develop 20 to 40 years after exposure to that material.

However, in 10 to 30% of all mesothelioma victims no exposure to asbestos can be documented. Nevertheless, most researchers believe there would be few cases of mesothelioma in the absence of asbestos exposure.

Unlike lung cancer, the risk of developing mesothelioma is not tied to smoking. However, the risk seems to increase with the amount of time that passes after an individual is first exposed. That is what makes parents so fearful for their children's health. For if it takes, say, 40 years to develop mesothelioma, a child exposed to asbestos at age 10 would be more likely to get that cancer before dying of something else than an adult exposed at age 25.

Dose-response curves

The health risks of breathing high amounts of asbestos fibers are clear. What is less certain is the relationship between the amount of fiber inhaled and the amount of disease—that is, the dose-response curve.

Some occupational studies have complete enough data on dose levels to indicate that the risk of disease drops



Minerals that under certain geological conditions crystallize as asbestos fibers more often form typical rocks. Cummingtonite (right) is the mineral that may sometimes crystallize as asbestos fibers known as amosite (left)

strips of cations (usually calcium, sodium, magnesium, iron, or aluminum) sandwiched between two strips of linked silica tetrahedra. All the amphiboles have about the same basic structure but are substituted with different cations. Amphibole strips of asbestos are thought to grow in single crystal whiskers, often in veins of massive nonfibrous rock.

Only two amphiboles have been ex-

ploited commercially as asbestos to any significant degree. Crocidolite (blue asbestos), the asbestiform variety of the mineral riebeckite, currently is mined only in South Africa. Cummingtonite-grunerite asbestos (brown asbestos)—produced only in the Transvaal province of South Africa—is often called amosite from the acronym for the company Asbestos Mines of South Africa. Other amphiboles, such

as anthophyllite and the tremolite-actinolite series, also occur in asbestiform varieties, but only rarely.

Further complicating matters is that minerals rarely occur as their pure, ideal composition but may contain a wide variety of contaminant ions. Batches of chrysotile from different mines, for example, are never identical.

Mineralogists themselves differ on the details of defining asbestos. But the fine points are even more likely to be obscured when the term asbestos is used by medical scientists or regulatory agencies. For instance, the legal regulatory definition of asbestos created by the Occupational Safety & Health Administration in setting occupational exposure limits is broader than the definition mineralogists and some other government agencies prefer. OSHA defines the minerals chrysotile, crocidolite, amosite, and all forms of anthophyllite, tremolite, and actinolite as asbestos.

"OSHA's terminology is so broad it includes a great deal of Earth's crust," says Malcolm Ross, mineralogist with the U.S. Geological Survey. OSHA is considering modifying its definition by adding the word "asbestiform" in front of anthophyllite, tremolite, and actinolite. That would bring OSHA's practice into line with the Mine Safety & Health Administration and the Consumer Product Safety Commission.

with decreasing exposure to asbestos. But there is no evidence in occupational studies to show there is a threshold level below which there are no adverse effects. "The problem is we haven't observed any safe levels," says Langer.

Some researchers think there are no safe levels of asbestos in the air. "As long as there's any exposure, there will be illness," says Selikoff. Accordingly, in formulating its report, the NRC committee chose to make the conservative assumption that no threshold level exists below which there isn't any risk of developing lung cancer or mesothelioma from asbestos.

Another problem in establishing a dose-response curve is the inaccuracy of old dose measurements. "We can't even be sure what was in the workplace 30 years ago," Langer says. "We only have good measurements since 1972," when OSHA began requiring them.

The shape of the dose-response curve at low doses isn't known and must be extrapolated from the high occupational exposures. "When extrapolating down to zero dose you must be careful," Langer says. "You are going beyond the hard data and extrapolating through doses for which no biological data are available."

As is often done in estimating the environmental risks of carcinogens, the NRC panel assumed the response was linear. This again is a conservative assumption that tends to overestimate the incidence of cancer at low doses.

The most controversial assumption in the NRC report is the panel's decision to lump together all forms of asbestos. The term asbestos is a commercial one that includes a number of mineral varieties that crystallize as strong, flexible fibers. A very vocal minority asserts that the type of asbestos most commonly used in the U.S., chrysotile, causes significantly less mesothelioma than other forms of asbestos, known as amphiboles. By grouping all the types together, these critics charge, the overall risks from asbestos are exaggerated.

"The [NRC] report is dangerous," says Andrew Churg, a pathologist at the University of British Columbia. "It ignores the difference between chrysotile and the amphiboles so it makes the mesothelioma risk seem much higher." Churg thinks the Canadian report, which cites only a weak association between chrysotile fibers and mesothelioma, is more accurate.

Churg's opinion is shared by others who object to the different species of asbestos being classed together.

Special Report

Malcolm Ross, a mineralogist with the U.S. Geological Survey, has made something of a crusade of his belief that chrysotile is not a significant health threat in a nonoccupational setting.

"When the public is led to believe that only the tiniest bit [of asbestos] will kill them, they're going to demand its removal," Ross says. "I'm troubled about where we are putting our money relative to the risks."

Ross says that to estimate accurately the health effects of each kind of asbestos separately, epidemiologists must look at the experience of asbestos miners and millers. He points specifically to chrysotile miners at Thetford Mines in Quebec. An epidemiological study of about 11,000 miners there by J. Corbett McDonald of McGill University found very few deaths from mesothelioma. In contrast, other studies have shown up to 10% of workers exposed to the amphibole called crocidolite die from mesothelioma.

The view that chrysotile asbestos is much less hazardous than the amphiboles forms the basis for regulation of asbestos in the U.K. and other members of the European Economic Community, where occupational standards allow higher levels of chrysotile than the amphiboles. The recent Ontario report recommends banning amphibole asbestos in Ontario, but not chrysotile. (The Canadian province of Quebec is a major producer of chrysotile asbestos; Ontario is not.) But in the U.S., Ross' position invites heated reaction.

"There's not a shred of evidence that some forms are less hazardous than others," Selikoff says. He points to a new study by Churg as the "smoking gun" that proves chrysotile is just as deadly as other forms of asbestos when it comes to mesothelioma. Churg and his co-workers found that of 90 chrysotile miners autopsied between 1980 and 1983, six died of mesothelioma.

Churg himself, however, says his data should not be used to judge the incidence of mesothelioma. "These are selected autopsies," he says. "You have to conclude that chrysotile ore causes mesothelioma, but it's very dangerous to draw conclusions on incidence" because the autopsies are not a representative sample.

Even though there are substantially fewer deaths from mesothelioma tied to chrysotile, the NRC panel decided not to weigh the risk of the various forms of asbestos separately. That is largely because, considering smokers and nonsmokers together, the most common kind of cancer associated with asbestos is lung cancer, and chrysotile appears to be just as potent in causing lung tumors as the other types of asbestos. However, the risk of lung cancer in nonsmokers, according to the NRC panel, is less than that of mesothelioma.

"I think that Ross' basic assertion that the amphibole asbestos minerals produce more mesothelioma is correct," says committee member Langer. "But that doesn't mean chrysotile is a safe fiber. The lung cancer rate in some industries that use this fiber is very high. We still have to contend with it."

Langer also suggests that different disease rates experienced by miners as compared to industrial workers may be caused by variations in fiber properties. "The physical dimensions and surface characteristics may vary from industry to industry," he says, "and these may be important factors in chrysotile asbestos's differential toxicity." The Canadian report also notes differences in disease rates in different industries.

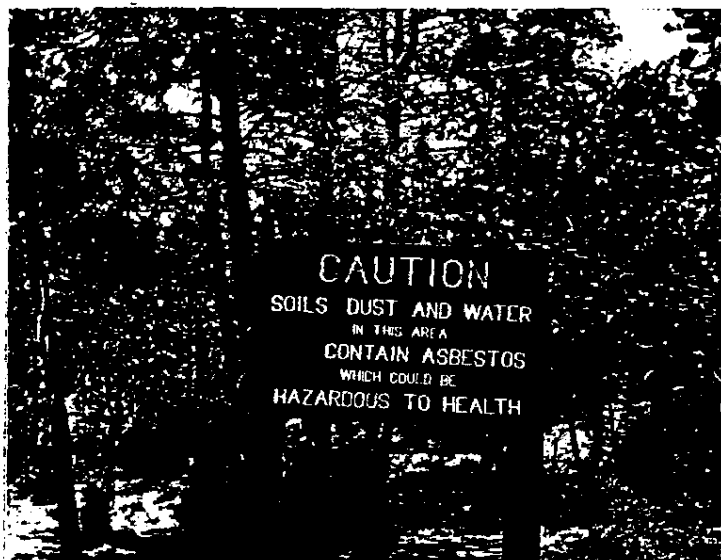
Exposure measurements

The nature of the fiber is only one factor in gauging the risk of low-level exposure to asbestos. Just as important are the intensity and duration of exposure. Measuring the amount of asbestos in ambient air is not a trivial problem, however. Neither is relating ambient air levels to the amounts of asbestos found in occupational settings.

Asbestos levels in the workplace are measured as the number of fibers in a given volume of air. For instance, OSHA's permissible exposure limit currently is two fibers of asbestos per cubic centimeter of air.

OSHA counts the number of fibers more than 5 μ m long and at least three times longer than they are wide, using an optical microscope. Most fibers—perhaps 95%—in an occupational air sample are shorter than 5 μ m, but OSHA reasons the longer fibers are a fair index of the entire amount.

The light microscopy technique normally used in occupational settings is phase-contrast microscopy. "It allows you to visualize materials with a long aspect ratio (ratio of length to width) that are greater than 0.2 μ m in width," says John A. Small, a research chemist with the National Bureau of Standards. "But it doesn't distinguish among fibers of different origins. Under the phase-contrast counting methodology, glass, cellulose, and carbon fibers may be counted as asbestos," he says. Despite that limitation, phase-contrast microscopy is not a bad technique for an asbestos mill or plant, where one can reasonably assume that most of the fibers in the air are asbestos.



Sources of asbestos fibers in ambient air include natural rock. Rock outcrops near this park north of Coalinga, Calif., have been estimated to contain up to 50% short-fibered chrysotile asbestos

However, it was discovered early on that measuring asbestos in ambient air is very difficult. "It's a problem of a needle in a haystack," says Exxon's Lynch. "You find a little bit of asbestos in the presence of an enormous amount of particulate matter."

Therefore, electron microscopy techniques are used to measure asbestos accurately in ambient air. Samples are collected and treated to remove organic materials. Clumps of fibers are broken up so that the individual submicron-sized fibers can be seen. Transmission electron microscopy (TEM) can give the crystallographic structure of a fiber to distinguish asbestos from other fibers.

TEM is the definitive technique for measuring asbestos in ambient air but it costs \$300 to \$500 per sample. In addition, not many labs are set up to do that kind of analysis. "[Fewer] than 20 labs in the country have the combination of equipment and experience to do TEM," says Ian M. Stewart, vice president of McCrone Environmental Services, part of Walter C. McCrone Associates, a microscopy firm based in Chicago.

For that reason, scanning electron microscopy (SEM), which is cheaper and more accessible, is often suggested as a substitute for TEM. But Small and Stewart think the ability of SEM to distinguish chrysotile fibers is limited because of poor contrast.

In either electron microscopy technique, the number of fibers seen does not reflect the number in the original sample, because the sample preparation techniques break up the fibers. Therefore, the results are expressed as the mass of asbestos per volume of air.

Ambient air levels

Out in the country, away from man-made or natural sources of asbestos, there is less than 0.01 ng of asbestos per cubic meter of air, estimates William J. Nicholson, a physicist who is associate director of the environmental sciences laboratory at Mount Sinai School of Medicine. "But in a typical urban environment, there's about 3 ng per cu m over 24 hours," he adds. In the 1970s, concentrations of asbestos in New York City air ranged from 20 to 60 ng per cu m. Asbestos in outdoor air in cities probably stems from construction and remodeling or demolition work on buildings and from car brakes.

In 1978, Nicholson measured the levels of asbestos inside 10 schools that contained visibly damaged asbestos building materials. The concentration of chrysotile ranged from 9 to 1950 ng per cu m. Other studies have found asbestos air levels inside buildings with asbestos-containing materials ranging from 1 to more than 500 ng per cu m.

Judging whether these low concentrations of asbestos are a health risk requires relating them to the higher levels that epidemiologists found were hazardous to workers. Unfortunately, the occupational doses are measured in fibers per volume of air, whereas ambient air levels are measured in mass per volume of air. Accurately interconverting the two types of measurements is virtually impossible.

"The fibers suspended in ambient air are different from those in an occupational setting, not only in concentration but in size distribution," Lynch says. "Vir-



Asbestos abatement worker on the job last summer in Maplewood, N.J., elementary school

tually all of the fibers [in ambient air] are small." That means that a nanogram of asbestos from the workplace might contain 2000 relatively large fibers, but the same mass in ambient air might be made up of 70,000 smaller fibers, to use an example from the NRC report.

However, the NRC panel decided to interconvert the exposure measurements from the two environments by assuming that the mass of an asbestos fiber found in the ambient air was equivalent to the mass of a fiber, of a particular dimension, found in the workplace. That assumption underestimates the number of fibers in ambient air and overestimates their size.

And that assumption also introduces a huge uncertainty in the panel's risk assessment, because fiber size has been hypothesized to be related to asbestos's toxicity. "That's why the lower limit of our risk assessment is zero," says Lynch. "Longer fibers are definitely toxic, but some researchers say that short fibers have no activity."

Some animal experiments indicate that shorter-length particles have little carcinogenic effect, perhaps because they are small enough to be cleared by macrophages. "However, the majority of the NRC committee does not agree that small fibers are totally inactive, although they may be less toxic," Lynch says. "It just isn't known." In contrast, the Canadian report concluded that thin asbestos fibers longer than 5 μm are hazardous.

Qualitative risk assessment

Using all of these assumptions, the NRC committee calculated the risks of developing mesothelioma and lung cancer from breathing asbestos in the ambient air over a lifetime. The panel calculated that at an exposure level of 0.0004 fiber per cc—about the level of asbestos

Special Report

Underlying cause of asbestos's toxicity still unclear

"Everyone's got an interesting theory and there are data sets to support each and every one. But when you come down to the essentials—that is, what is it about asbestos that imparts its activity—your guess is as good as ours," Arthur M. Langer of Mount Sinai School of Medicine told federal officials last fall. The group was gathered for a briefing on the National Research Council's report on nonoccupational health risks of asbestiform fibers.

Although the state of scientific knowledge isn't quite so bad as Langer's remark implies, there's remarkably little that can be said with certainty about the root of asbestos' toxicity. Epidemiological studies indict asbestos as causing pulmonary fibrosis (asbestosis), lung cancer, mesothelioma (cancer of the lining of the lung and abdomen), and perhaps gastrointestinal cancer in workers exposed to large amounts in their jobs.

But only a few clues have yet been uncovered to link the physical and chemical properties of the various forms of asbestos to their biological activity. For example, it's not clear if the same properties trigger all the health effects or whether a different characteristic is responsible for asbestosis, say, than for lung cancer.

Important details that could help tie specific characteristics of asbestos fibers to disease are often missing from epidemiological studies that span several decades. Records of the exact types, origins, dimensions and fiber concentra-

tions of asbestos that workers were exposed to years ago may never have been kept or may have been lost. And inaccurate use of mineralogical terms in the scientific and medical literature prevents precise characterization of exposure.

More recent experiments in animals and in tissue culture—where conditions can be carefully controlled—overcome some of these difficulties. Interpreting such studies and extrapolating the conclusions to humans can be controversial, however.

The cellular mechanisms underlying asbestos's carcinogenicity are being explored. The multistage theory of cancer holds that two steps are necessary in the development of cancer. In the initiation step, DNA in a cell is damaged or mutated. In the promotion step, the altered cell is encouraged to divide and proliferate.

Although the evidence is contradictory, most laboratory studies show asbestos fibers don't damage DNA. Therefore, asbestos has not been shown experimentally to be an initiator of cancer.

Both laboratory and epidemiological studies point to asbestos's role as a promoter of lung cancer, however. For instance, asbestos exposure multiplies the risk of lung cancer from cigarette smoking. There also is evidence that asbestos may help carry certain carcinogenic hydrocarbons into cells. In addition, interaction of asbestos fibers with cell membranes favors the release of substances important to the carcinogenic process.

A key determinant of asbestos's tox-



Crocidolite fibers in hamster respiratory tract. Small spherical cells are macrophages

icity may be fiber size. The fiber has to reach the lung before it can do damage. "Fibers above a certain diameter are not even inhaled," says Brooke T. Mossman, associate professor of pathology at the University of Vermont and a member of the committee that prepared the NRC report. Those over about 3 μ m in diameter probably are screened out by nasal hairs or other protective mechanisms in the upper respiratory tract.

Some researchers think that very small asbestos fibers also may not be toxic, although the NRC panel concluded no minimum size of fiber could be declared not to have any effect on health. Short fi-

in New York City air, according to the conversion factor the panel chose—the risks of developing mesothelioma range from zero to 350 per million.

At any exposure level, the risk of developing lung cancer depends on an individual's sex and on whether he or she smokes. The greatest risk is to male smokers, ranging from zero to 290 per million. Female non-smokers were calculated to have the lowest risk, ranging from zero to 13 per million.

The committee also calculated the risk of a lifetime of exposure at a higher level, equivalent to the level that might be found in buildings with asbestos surfaces. Those risks ranged from zero to 1700 per million. The Canadian report, however, states that "asbestos in building air will almost never pose a health hazard to building occupants," unless elevated exposure is caused by disturbing the asbestos.

"There's an enormous amount of uncertainty" in as-

sessing the risks of asbestos fibers in ambient air, Nicholson says. "The fibers are measured in so many different ways. There's the possibility of differential toxicity. The fiber dimensions are different in different environments." Nicholson recently prepared assessments of asbestos health risks for EPA and OSHA. His quantitative risks findings are generally in the same ball park as the NRC panel's.

"In all of these decisions we state our assumptions," says panel member John Van Ryzin, professor of biostatistics at Columbia University. "I was very insistent that we report what our uncertainties are."

The NRC panel's charge was to assess the risk from nonoccupational exposures to asbestos, not to recommend what to do about them. Yet the uncertainties inherent in calculating risk mean policy makers have difficult decisions ahead in tackling how to manage asbestos exposure.

bers may be breathed in and out without settling to any great extent in the lungs. More important, however, is that the body's system of defense against foreign matter may cope with short fibers better.

"Macrophages can swallow short fibers and transport them out of the lung," Moesman says. The cilia of the cells lining the trachea can sweep the engulfed fibers up to eventually be coughed out, spit out, or swallowed. Some may stay in the body, traveling to the lymph nodes, but there is no direct evidence that this causes disease, Moesman says.

Fibers of intermediate size, thin enough to enter the lung but too long to be entirely surrounded by macrophages, may be a culprit. In fact, one theory holds that it is the long, thin dimensions of asbestos fibers, rather than any specific chemical property, that it is the key to their toxicity.

That notion, known as the Stanton hypothesis, grew out of experiments performed by the late Mearl F. Stanton and coworkers at the National Cancer Institute. They inserted fibers of different sizes and types—the major forms of asbestos as well as other, nonasbestos fibers—into the lining of the lungs of rats. They concluded that the factor most tied to mesothelioma in their experiments was a particular size of fiber (specifically, fibers less than 0.25 μm in diameter and longer than 8 μm), rather than a particular chemical composition. Besides the various types of asbestos, fibers of borosilicate glass, potassium titanate, and some aluminum compounds caused mesothe-

lioma in the rats when the fibers fit the key dimensions. Other researchers have found that silicon carbide fibers and some naturally occurring zeolite fibers cause mesothelioma in similar experiments.

If size and shape, rather than chemistry, control the carcinogenicity of fibers, any proposed substitutes for asbestos need to be studied very carefully. For example, epidemiological studies of workers exposed to fibrous glass have shown a small increase in respiratory cancer. Until about 10 years ago, however, most glass fibers were larger than the size implicated in Stanton's studies. It may be too soon for any adverse effects from the thinner, more recently introduced glass fibers to show up.

The Stanton hypothesis is not without its critics, however. For one thing, it is experimentally difficult to completely separate fibers by size. A batch of fibers nominally of one length can contain fibers of quite different sizes. And milling minerals to reduce their length also can profoundly change their crystallinity and surface characteristics, says Langer.

Other workers have statistically re-examined Stanton's work with different results. French researchers conclude that the ratio of length to width (known as the aspect ratio) is most important and that it is not possible to separate the effects of length and width. Langer recalculated the data for crocidolite and judged fibers 4 to 8 μm long were most toxic, rather than those longer than 8 μm .

"Fiber dimension may be very important," Langer says, "but other factors are at least as important. You cannot dismiss

surface chemistry." Langer and graduate student Robert P. Nolan have been studying how minerals communicate with cell membranes through information on the mineral surface.

"Morphology may be important in getting the fiber to the site where it does damage," Langer says. "But once at the target site, surface characteristics take over. The nature of the chemical functionalities, their spacing, number, and geometrical configuration on a mineral surface are all going to affect how that mineral communicates and therefore interacts with a cell," he adds.

The question is more than academic. If surface chemistry is the key, then there would be a rational basis for the argument that certain forms of asbestos are less toxic than others. Some scientists believe, on the basis of epidemiological studies, that chrysotile fibers produce far less mesothelioma than crocidolite or amosite, although the issue is hotly debated.

If certain chemical functionalities could be pinpointed as the bad actors in asbestos toxicity, in theory modifications to the surface could result in less hazardous forms of asbestos. For instance, a Canadian government-industry organization called Société Nationale de l'Amiante is supporting research in Langer's lab and elsewhere on a modified phosphorylated chrysotile. "So far, the phosphorylated fiber appears to have far less membrane activity as compared to untreated fibers," Langer says. "The implications of producing a safe fiber are of vast pragmatic importance. The concept and work are exciting."

For the government to regulate a substance, it must first determine that the material poses a hazard. Then federal agencies must decide if they can take steps to reduce or eliminate the risks.

In the case of asbestos, there is clearly an occupational hazard to workers. OSHA currently is trying to lower the permissible exposure level in the workplace to either 0.5 or 0.2 fiber per cc.

The Consumer Product Safety Commission banned the use of asbestos in spackling compounds and artificial embers for fireplaces in the mid-1970s. A few years later, manufacturers voluntarily removed asbestos insulation from hair dryers after CPSC began an investigation.

EPA has the authority to ban hazardous chemicals and mixtures under the Toxic Substances Control Act. In the 1970s, it forbade further use of sprayed-on asbestos materials as a hazard both to the workers applying the material and to people near the construction site. That

use of asbestos had become a popular method of fireproofing and insulating steel girders.

In 1983, EPA began drafting regulations to ban immediately some other uses of asbestos—including cement pipe and flooring and roofing products—and to phase out the rest over a 10-year period. But in early 1985, the agency said that, under TSCA, it must give other federal agencies a chance to regulate hazardous substances before it acts. So EPA has turned over its proposed ban on asbestos to OSHA and CPSC.

That move has angered critics in the environmental movement and trade unions and even within EPA itself, who suggest the action is simply an attempt by the Reagan Administration to stall further regulation of asbestos. However, if OSHA and CPSC don't move on the issue, the problem will end up back at EPA.

Yet some who are concerned about exposure to asbestos aren't sure that a ban on the material addresses the

Special Report

Asbestos abatement requires multidisciplinary teams

The costs of removing asbestos from buildings are enormous. Estimates for, say, taking ceiling insulation out of an average-sized elementary school can run from \$100,000 to more than \$1 million. The expense stems from the time and expertise needed from professionals in many different areas if the job is to be done properly.

When a building owner decides to have asbestos removed from a property, there often is only a potential hazard from asbestos that might be disturbed at a later date. But once the abatement project begins, there is an immediate hazard to the workers involved. And if the cleanup is not done with great care, there may be real danger to the occupants who return to a supposedly safe building.

"An asbestos removal project is really a demolition project that leaves the building standing," says Roger G. Morse, a Troy, N.Y., architect whose firm specializes in asbestos work. "At the same time, there's potential for contaminating the whole building. You need people who know what they are doing watching over the whole thing."

The asbestos abatement industry is growing by leaps and bounds and the potential for problems from shoddy work is growing with it. For example, many local

governments are required by law to award contracts to the lowest bidder. "It's sometimes difficult to eliminate guys who don't know what they're doing," says Morse. "All it takes for a contractor to set up is \$20,000 to buy equipment."

"It's a new industry evolving more quickly than government can regulate it," says Brent W. Schopf of Archway Contracting Co., Pennsauken, N.J. Schopf is a charter member of the National Association of Asbestos Abatement Contractors, a nonprofit trade association formed in January 1984 to try to set standards for the industry.

In addition to the contractor whose workers actually will take out the asbestos, a removal project requires, at a minimum, an architect or engineer to draw up specifications and coordinate the work as well as an analyst and air-sampling laboratory to monitor fiber levels. Every employee must be trained in safe work practices, and the Occupational Safety & Health Administration requires they be given physicals at regular intervals.

Before the work can start, the contractor must notify local and state agencies and the Environmental Protection Agency, Schopf says, and then wait the required period to give them time to respond. Next, the work site is sealed,

usually with plastic sheeting, to make a closed environment.

Decontamination facilities are built, including a shower and change room isolated by airlocks so employees don't carry fibers outside and home on their bodies or clothes. Another airlock is used to load the asbestos waste onto a truck for disposal.

Then, negative air pressure is established in the work area. That way, any air leaks will be from the outside into the contaminated area, rather than the other way around. Air is drawn in from the outside and exhausted through high-efficiency particulate air filters (HEPA) to remove asbestos fibers.

Workers dressed in hooded coveralls—called moon suits—and wearing respirators then remove the material. A number of techniques, such as scraping, are used and the material must always be kept wet to keep down dust levels. The waste, still wet, is double bagged and placed in containers to be taken to a landfill each day. No material is allowed to accumulate. Both the transporter that carries the sealed waste and the landfill that receives the asbestos must be certified. EPA requires that the asbestos be buried under at least 6 inches of dirt within the day. Finally, the area is carefully

real risks. Substitutes must be adequately tested, for example. "I'm concerned that if some material is not called asbestos, it is automatically exonerated from biological wrongdoing," says Langer.

Nicholson points out that asbestos in most products being manufactured today—cement pipe, for example—is tightly bound and not likely to become airborne easily. "The current hazard is from asbestos already in place—about a million tons of friable asbestos in insulation and pipe lagging that's going to have to be removed someday. That's a much greater problem than continued use of asbestos."

Asbestos abatement

A recent EPA report estimates that 15 million children attend schools where friable asbestos is present. An EPA survey of buildings other than schools estimates that 700,000 commercial, residential apartment, and federal buildings contain friable asbestos. The only current federal regulation that requires asbestos be removed from buildings is an EPA rule saying asbestos materials must be taken out of a building before it is demolished.

Two factors, however, are encouraging a growing

trend to rip asbestos materials out of buildings wherever these materials are found. One is EPA's asbestos-in-schools program, which requires school districts to inspect their buildings for crumbling asbestos. The second is building owners' fears that occupants may sue over future asbestos-related disease. Asbestos abatement—which includes both removal and sealing off asbestos in various ways—has become big business.

The asbestos-in-schools program has been lambasted from all sides for publicizing the presence of asbestos in schools but not giving school authorities enough help—either technical or financial—to deal with the problem rationally.

EPA publishes a booklet called "Guidance for Controlling Friable Asbestos-Containing Materials in Buildings" to help school authorities decide what to do when they find asbestos. It does not specify, however, that asbestos must be removed. Local officials must judge if that is necessary. Other options are to leave the asbestos-containing material alone, enclose it, or encapsulate it with a sealant that binds the fibers tightly. Many authorities in asbestos control agree that the problem is too complex to formulate general regulations that would fit every building situation.



Abatement worker scrapes asbestos-containing insulation from ceiling

cleaned by wet wiping and vacuuming with a HEPA-equipped vacuum.

"The moon suits are uncomfortable. They are hot and sweaty and it can be tough to work in a respirator," says Schopfel. "But in our company, productivity is pretty high. There's nothing else to do but work. It's hard to talk when you're wearing a respirator and you can't eat or drink. Any employee who takes off his respirator during work is fired."

Air samples are taken regularly throughout the entire operation to monitor fiber levels and check for leaks outside the work area. Also, contractors usually

are required to get the fiber levels—which are raised unavoidably during the removal work—down to a specified level before they can be released from the job, a procedure known as clearance monitoring.

"Clearance monitoring is a release mechanism saying the contractor has achieved certain levels under the best available technology," says Ian M. Stewart, vice president of McCrone Environmental Services. "It can't say you have a safe building. No one has told us what a safe level is."

Many contracts specify a final fiber level of 0.01 fiber per cc or less, as de-

termined by phase-contrast optical microscopy. However, that technique can pick up only large fibers and can't distinguish asbestos from other fibers.

EPA has been trying to draw up recommendations for final fiber levels and the best way to determine them, says Michael E. Beard, a chemist with the agency's R&D lab in Research Triangle Park, N.C. The agency is evaluating the three techniques—phase-contrast microscopy, scanning electron microscopy, and transmission electron microscopy (TEM)—that currently are used in determining postabatement asbestos air levels. The goal is to find an effective technique that's practical to use.

"For instance, some researchers think that the indoor asbestos air levels after abatement work ought to be as low as those outdoors. However, to measure such very low levels would require electron microscopy—and probably the very expensive and not widely available TEM technique. "If all jobs are required to use TEM," says Stewart, "the turn-around time for samples will go to months rather than days. What do you do, leave the plastic tents up and buildings empty while you wait?"

So, as seems the case with everything else concerning asbestos control, EPA is faced with some difficult judgment calls on asbestos air monitoring.

"You have to decide on a case-by-case basis whether to remove asbestos," Selikoff says. "Asbestos does not constitute a hazard unless it is inhaled. Unless it can become airborne, there's no urgency in removing it. If it can be sealed off or is inaccessible and in good condition, it doesn't need to come out unless it will be disturbed by repairs or renovation. This can be planned for."

However, local school boards often lack the expertise and are too short of funds to hire experts to help them make the right decisions. "EPA is going in the right direction, but [it doesn't] have enough qualified people to supply guidance," Nicholson says. "Right now, some school administrators are so frightened that they panic when they see a crack in the ceiling. Others have the stuff falling all over and are not doing anything."

Says Susan Mazzochi, cofounder of Parents Against Asbestos Hazards in Schools, based in Maplewood, N.J.: "We discovered asbestos in our children's school and were shocked that the school board wasn't acting. The school board didn't want to do anything because it would cost money. In absence of any law that states how the problem should be addressed, it becomes a power struggle between the parents and the school board."

Another group that thinks EPA should take a more active role in asbestos abatement policy is the Service Employees International Union (SEIU), which represents about 100,000 school workers. Maintenance workers such as SEIU members are often the individuals expected to remove or clean up damaged asbestos materials in school buildings, sometimes with inadequate training and protective gear.

SEIU petitioned EPA in late 1983 to require corrective action when hazardous asbestos is found in schools and to issue regulations to protect school workers, who are not covered under OSHA. When EPA refused to act on all of the union's requests, SEIU filed a lawsuit against the agency in September 1984.

EPA is in an awkward position because no one can say exactly what levels of asbestos are hazardous. In certain situations where damaged asbestos is flaking into work areas and circulating through air-conditioning systems, the decision to remove it is straightforward. But most cases are not that simple.

"The appropriate action should be determined by a complete building survey by a qualified individual," says William H. Spain of the environmental health and safety division of Georgia Institute of Technology. Spain

Special Report

NRC's estimated cancer risk has wide margin of uncertainty

Exposure group	Individual lifetime risk of developing cancer, per million ^a	
	Exposure at 0.0004 fiber/cc ^b	Exposure at 0.002 fiber/cc ^c
Male smoker	64 (0 to 290) ^d	320 (0 to 1500)
Female smoker	23 (0 to 110)	120 (0 to 530)
Male nonsmoker	6 (0 to 22)	29 (0 to 130)
Female nonsmoker	3 (0 to 13)	15 (0 to 66)
All	9 (0 to 350)	46 (0 to 1700)

Note: For example, the risk of developing lung cancer for a male smoker who is exposed throughout his lifetime to an asbestos concentration of 0.0004 fiber per cc probably is about 64 in 1 million, but may range from 0 to 290 in 1 million. ^a Lifetime assumed to be 73 years. Exposure occurs continually from birth. ^b Approximately equivalent to asbestos concentration in urban outside air. ^c Approximately equivalent to asbestos concentration in U.S. schoolrooms with asbestos surfaces. ^d Range of estimates. Source: "Asbestos: Fibers: Nonoccupational Health Risks," National Academy Press, 1984.

and his colleagues in Georgia Tech's asbestos programs group offer courses for building owners, architects, contractors, and others on managing asbestos. Their course on supervising asbestos abatement contracts is so popular that they have offered it 15 times since its inception in May 1982.

Georgia Tech is the site of one of three new asbestos information centers, funded by EPA and opening this year to answer questions about controlling asbestos. "Bill Ewing [William M. Ewing, also at Georgia Tech] and I could spend 10 hours a day on the phone talking about asbestos," Spain says.

Spain does not think air levels of asbestos should be the criteria for determining the need for abatement. "Air samples are like a photograph, they reflect only the

circumstances at that particular time. Air levels that are low during normal activities might be higher during certain maintenance procedures that might disturb the asbestos, like changing light fixtures or running telephone lines," he says.

Given the popular notion that even the smallest bit of asbestos is deadly, many school systems and building owners are rushing to take it out. Unfortunately, this can sometimes turn a potential risk into an actual one.

"If building surveys and abatement work are not done correctly, the hazard could be made many, many times worse than it was initially," Spain says. "A substantial, or at least a noticeable, portion of abatement projects are being done in such a way as to put people at risk." The Canadian report also points out that removal projects can increase the risks of asbestos-related disease.

The danger lies in not containing the asbestos as it is removed. Both abatement workers and bystanders then are exposed to loose fibers as the removal work is going on. In addition, asbestos fibers, which take a long time to settle out of the air, can become caught up in the air-circulation system of the building and subject the occupants to sizable doses once they return to a supposedly clean building.

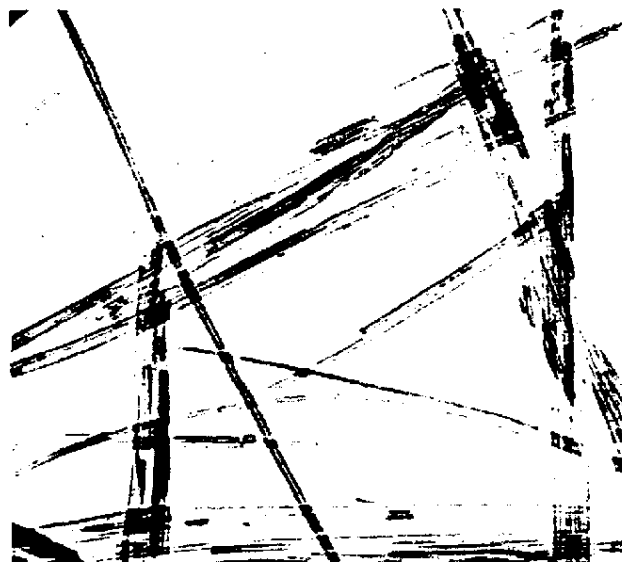
Indeed, tenants of the 17th floor of the Medical Towers building in Houston have filed a \$110 million suit against the building manager and a contractor who remodeled the 18th floor last summer. The plaintiffs charge they were exposed to asbestos dust and now have increased risk of getting cancer.

The consequences of acting too hastily to remove asbestos are also apparent in New Jersey, where about 300 schools were scheduled to have asbestos taken out last summer. As the opening of the fall school term approached, it became clear that many of the jobs had been done sloppily and with inadequate monitoring. Most of the schools opened on time anyway.

URL 03138



McCrone Environmental Services photo



Bureau of Mines photo

Magnified 148X under polarized light, chrysotile fiber bundles appear blue and purple. The characteristic hollow-tube structure of individual chrysotile fibrils is visible in the transmission electron microphotograph (35,000X)

Property liability lawsuits multiplying rapidly

When Manville Corp. (formerly Johns-Manville) filed a bankruptcy petition in August 1982, it was seeking protection from millions of dollars in claims by more than 16,000 people suffering from asbestos-related diseases. Now, however, other asbestos manufacturers are being deluged with lawsuits from building owners. These fast-multiplying property damage suits may turn out to be even more expensive than the health-related ones.

For example, last September the state of Maryland filed suit against 47 asbestos producers for the cost of cleaning asbestos out of 3000 buildings owned by the state. "The suit asks for \$500 million in compensatory damages," says Evelyn O. Cannon, assistant attorney general. "We also asked the court to require the defendants to come

into the buildings, identify the asbestos, remove it, and replace it with substitutes," she adds. The first hearing in the state's suit is scheduled for later this month.

If the size of Maryland's suit turns out to be typical, a crude extrapolation yields many billions of dollars at stake in suits from state governments alone. Businesses, local governments, and private homeowners also are potential plaintiffs in such suits. So is the federal government, but the Department of Justice indicates it probably won't sue. However, a Justice Department report encourages school systems to try to recover the costs of their abatement projects from asbestos manufacturers.

A decision last fall by a federal judge in Philadelphia cleared the way for a

class action suit by schools against asbestos producers. Judge James M. Kelly ruled that a combined suit would let thousands of small school districts sue to recover the money they've spent to remove asbestos without being burdened by prohibitively high legal costs. Districts may sue on their own for compensation, his ruling said, but all punitive damages will have to be part of the class action.

Because Manville is in bankruptcy, it can't be sued directly as the other asbestos producers can. Claimants against Manville instead must petition the bankruptcy court. When a deadline expired last Jan. 31, more than 3500 property damage claims had been filed. For other companies not under the protection of Chapter 11, the suits will continue to snowball.

"Most of the contractors who have been hired by the school boards to perform asbestos removal work have little experience in this specialized and sensitive field," states a report issued last August by New Jersey's Department of the Public Advocate. "Because many good contractors are overextended, there is a lack of qualified asbestos removal workers."

As a result, inspectors found workers tracking asbestos out of sealed areas, flushing asbestos down toilets, not wearing protective respirators or clothing, and hauling asbestos away in private cars, as well as numerous other abuses of good work practices.

To counter such abuses, there should be some way to demonstrate who's qualified to do asbestos abatement work. Some states already have contractor certification requirements. An incentive for the rest of the states to introduce certification procedures is built into the Asbestos School Hazard Abatement Act of 1984. That law, which gave EPA \$50 million in fiscal 1985 to assist states and local school districts with asbestos control, requires states to certify contractors.

The asbestos programs group at Georgia Tech is developing a model one-week training program for asbestos abatement supervision under an EPA contract. Another organization, the National Asbestos Council (NAC)—composed of contractors, building owners, architects, analysts, and other professionals concerned about proper asbestos abatement—is developing training materials for small contractors and maintenance personnel who have to deal with asbestos.

A different problem is starting to put even well-qualified contractors out of work, however. "We're starting to hear of contractors that can no longer get liability insurance," says McCrone Environmental Services' Stewart, who is past president of NAC.

"In the past two weeks I've heard from at least 15 contractors who are losing their insurance," echoes Brent W. Schopf, a contractor who is a charter member of the National Association of Asbestos Abatement Contractors. Insurance companies, burned by massive personal injury and property damage claims against asbestos manufacturers, are specifically excluding asbestos abatement work as contractors' general liability policies come up for renewal.

"If something isn't done, all of the abatement work is going to grind to a halt," says Stewart M. Huey, executive director of NAC. He suggests that state insurance commissioners may have to create an assigned risk pool, as is done for workmen's compensation. Or the federal government could start a reinsurance program, as is the case with flood and nuclear power plant insurance.

"It's a nasty problem and a lot of people are working on it," says Schopf. "It's going to be an interesting summer."

All of the problems with asbestos abatement are exacerbated by panicky, oversimplified responses to a complex issue. "I think we ought to control asbestos," says Langer. "We should not tear it out indiscriminately and then tax society \$20 billion. In some cases it may not have to be removed. Where it does, we don't have the trained people to remove it properly and we may increase risks by taking it out. We live in a chemical society. Let's learn to control and live with these materials." □

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Product-Safety Czars

The Consumer Product Safety Commission wants to ban formaldehyde-foam insulation. The White House wants to ban the CPSC.

by RICHARD I. KIRKLAND JR.

For eight years now the Consumer Product Safety Commission has been struggling to master its role as a combination imperial safety engineer and national nanny. Charged with the impossible task of overseeing the safety of practically everything the consumer buys—a few notable exceptions, such as cars, food, and drugs are handled by other agencies—the commission has churned out countless warnings and fact sheets and prompted the recall of millions of dangerous or defective products. It has also promulgated standards for items ranging from aspirin bottles to lawn mowers. By moving the slats on baby cribs closer together to prevent accidental strangulations, the CPSC has saved about 50 lives a year.

As if all that weren't enough, the CPSC has been branching out. In addition to identifying and policing the clear and present dangers posed by things like sharp-edged toys or faulty electric sockets, the commission has devoted increasing attention and resources to the infinitely more subtle chore of routing out so-called chronic hazards, products that may one day lead to cancer or birth defects. Two years ago, for example, the CPSC made headlines by urging the recall of 20 million hair dryers that gave off asbestos fibers, a known carcinogen. Last January, after two years of investigation, the agency proposed a ban on a type of insulation known as urea-formaldehyde foam, charging that the formaldehyde gas released by the foam was a potential cause of cancer. Currently, the CPSC is monitoring a number of other household items that contain asbestos and formaldehyde to determine whether they, too, might pose a cancer risk.

To Susan King, chairman of the CPSC from 1978 until last January, the commission's stepped-up program for regulating chronic hazards is "the most important initiative undertaken by the agency in the last few years." But to a number of business groups this initiative is evidence that the commission is getting too big for its britches. For months these groups, which include the National Association of Manufacturers, the Chamber of Commerce, the Chemical Specialties Manufacturers Association, and the Formaldehyde Institute, have been waging a vigorous campaign to persuade Congress to propose a ban of its own—one that would get the CPSC off its cancer crusade.

An ultimate solution

This idea has the firm endorsement of Budget Director David Stockman. In a recent letter to Senator Robert Kasten, who chairs a subcommittee overseeing the CPSC, Stockman charged that the commission had "adventured too far in some areas of regulation" and cited its chronic-hazards program as one of those areas. Stockman proposed a draconian remedy. Given its druthers, he said, the Reagan Administration would abolish the agency entirely. If Congress doesn't have the stomach for this ultimate solution, the budget director suggested that the five-member body should be dismantled as an independent commission and relocated, under a single administrator, in one of the executive departments, such as Commerce. There its activities could be more closely monitored and directed by the White House. To quash even a hint of expansionist tendencies, the Office of Management and Budget had already

slapped the CPSC with a 27% reduction in its original 1982 budget of \$45 million, entailing the loss of a quarter of its staff. The CPSC says this is the largest percentage cut of any regulatory agency.

In all likelihood, the new crowd at the White House would have proposed similar measures even if the CPSC had never moved to corral a single carcinogen. Practically from birth, the agency has carried the stigma of incompetence, a charge often leveled by business and consumer groups alike. Its first mandatory product standard was a year and a half in the making and consisted of warning labels for swimming-pool slides that instructed bathers to "look out for people and objects below" and cautioned: "Correct belly slide: head up, arms straight ahead, fingers pointing up." Almost every time the agency was challenged in court on a recall or a ruling, it lost.

The CPSC's operations (and its litigation record) have improved markedly since those early days, and the Reaganauts' distaste for the agency undoubtedly has far less to do with its management than with its mandate. That mandate assumes that a vigilant federal regulator, focusing primarily on product design and defects, can do much to reduce the annual total of 28,000 deaths and 33 million injuries associated with consumer products under the commission's purview. The problem is that only a fraction of those incidents are the result of faulty products. Most stem from human error or recklessness. Within the fairly narrow sphere where product standards can have some impact, the CPSC claims its actions will save some 300 lives a year. But critics, while acknowledging victories such as better baby cribs, argue that industry would have made most of the improvements anyway. According to Stockman's calculus, the CPSC's work either fails the cost/benefit test or could be done better by other agencies.

One clear area of overlap is regulating carcinogens. Under the provisions of the Toxic Substances Control Act of 1976, the Environmental Protection Agency has the

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Stuart M. Statler, 37, a Percy Republican and the CPSC's acting chairman, has been fighting to keep the agency in business, but he won't be heading it for long. If the White House can't abolish the CPSC, it will probably appoint a conservative who would keep it under tight reins.



primary authority to control dangerous chemicals in consumer and industrial products, as well as in the environment. But the CPSC can take the lead role in regulating a particular consumer product when it chooses. In its work on toxic substances, the EPA will spend more than \$100 million this year, 30 times the amount the CPSC dedicates to its chronic-hazards program. With vastly superior technical and financial resources, EPA, not the CPSC, seems the logical candidate to grapple with the hidden risks of cancer in homes and playgrounds.

Stuart Statler, a Republican and acting chairman of the CPSC, thinks otherwise. The commission, he argues, doesn't need EPA's kind of budget because its staff merely functions as a sophisticated clearinghouse, monitoring and evaluating the high-priced research done by other organizations. When more specific answers are needed, the CPSC hires outfits like the National Academy of Sciences or private research labs. Such a setup, says Statler, allows the CPSC to move with alacrity when problems materialize. Echoing a concern expressed by several public-interest groups, such as the Environmental Defense Fund, Statler worries that EPA, oriented toward "global" approaches to health issues, would "overlook the chronic health impacts of consumer products over the short term."

Industry prefers the EPA

But in most cases the problems posed by potential carcinogens are indeed "global," or at least very far reaching. For example, in tabbing the formaldehyde in foam insulation as a potential cause of human cancer, the CPSC immediately raised questions not only about one small industry, but about the formaldehyde used as an adhesive or preservative in hundreds of other products with billion-dollar markets—plastics, plywood, textiles, cosmetics, drugs, and food. To turn the argument around, there's some reason to wonder whether the CPSC, with its orientation toward specific products, is properly equipped to grapple with such

broad and complex health issues. Notes one spokesman for the Chamber of Commerce: "It's not like we're saying don't do anything about possible carcinogens. But when you see an industry saying give this authority to EPA—and you know the problems industry has had with EPA—then you realize they must be having some real questions about the competence of the CPSC to do this kind of work."

Knotty questions of competence and scientific judgment lie at the heart of the current furor over the CPSC's proposed ban on urea-formaldehyde foam, which can be pumped into the walls of existing homes to provide effective insulation. The furor revolves around two disputed points. First, should formaldehyde be considered a human carcinogen and, if so, at what level of exposure? Second, what evidence is there that the foam poses such a risk of exposure to formaldehyde that it must be banned?

Although formaldehyde has been widely used for over 90 years, to date no conclusive evidence has turned up that it is a human carcinogen. Morticians are routinely exposed to high levels of formaldehyde fumes, but one study of them showed no unusual pattern of cancer. A number of animal studies have also been negative. The CPSC's case for carcinogenicity rests primarily on a single laboratory study of rats and mice. In that study a significant number developed nasal cancer from sniffing dose levels of formaldehyde at 15 parts per million; a few rats developed cancers at six ppm. After studying preliminary reports from that exper-

iment and surveying other literature, a panel of government scientists, called together by the CPSC, advised the agency last fall that it was "prudent" to regard formaldehyde as a potential human carcinogen. They did not, however, recommend what a prudent course of action might be.

It stinks

At the moment there is no clear scientific consensus that the test results can be extrapolated to humans, especially at the lower levels that reflect "real world" exposures. Formaldehyde, as every high-school biology student knows, has a distinctly unpleasant odor—it stinks, in fact. In a room where the chemical was wafting through the air at six ppm, most people would be bolting for the door, noses and stomachs in hand. Since formaldehyde usually becomes noticeable at about 0.5 ppm, critics charge that the CPSC has prematurely frightened the populace by crying cancer at the drop of an overdosed rat. James Ramey, chairman of the Formaldehyde Institute, thinks that the logic behind the CPSC's proposed ban on formaldehyde foam is disturbing evidence of "a zero-risk philosophy."

CPSC staffers adamantly deny this charge, and Dr. Peter Preuss, chief of the agency's chronic-hazards program, declared to a Senate subcommittee that "we have no intention whatsoever of systematically banning every formaldehyde-containing product." Instead, the agency promises to work with industries like the particle-board and plywood manufacturers on developing product standards that will reduce the amounts of formaldehyde their products might release in the home.

Why, then, didn't the CPSC do something similar with the formaldehyde-foam industry? Because, say its staffers, unlike other products that contain formaldehyde, foam insulation isn't produced in a factory where it can be subjected to quality control and inspection. Instead, it is manufactured at the site by the installer, who mixes urea-formaldehyde resin with a foaming agent and air or nitrogen. If the

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A \$100-million industry has been wiped out by bad publicity.

mixture isn't accurately prepared or is put in hot places like attics, the house may reek of formaldehyde. The ultimate quality of the product depends on the individual skill of the installer. Since no product standards could control that variable, says the CPSC, an outright ban was the only alternative.

By taking this tack the CPSC managed to avoid the difficult question of determining an acceptable residential threshold for formaldehyde gas. Nor, charge its critics, did the agency commission adequate scientific work to establish whether houses properly insulated with the foam have significantly higher levels of formalde-

hyde gas than foamless homes. Some research indicates that they do, but a University of Iowa study came to the opposite conclusion. Natural gas and cigarettes give off formaldehyde when they burn, and it also seeps out from carpets, draperies, and wood paneling. In proposing its ban, the CPSC rejected an option developed by the Department of Energy, which had relied on a combination of strict quality specifications, certification of installers, and grievance procedures to protect consumers from "unreasonable risk." The Small Business Administration, which favors the DOE approach, has charged the CPSC staff with "unobjective

advocacy in support of a ban." And the CPSC's regulatory logic has done nothing to reassure other industries, which fear they may be next on the CPSC's chronic-hazards hit parade.

An academic question

There the matter rests, in limbo, until the commission meets again late this summer to decide whether or not to go through with its proposed ban. By now, however, the issue is more or less academic. The formaldehyde-foam industry, which once had sales of over \$100 million a year, has been wiped out by bad publicity. Most of the 1,500 small companies that installed the product have gone bankrupt or switched to other materials such as cellulose or blown fiberglass.

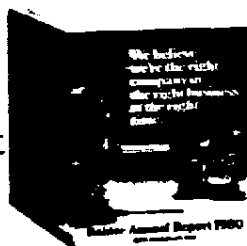
As for that proposed ban on the CPSC itself, just how far Congress will go remains to be seen. Judging from the bills already reported out by Senate and House subcommittees, the commission can expect to feel the full force of the Reagan budget cuts. These would slash its chronic-hazards program in half, dismantle eight of its 13 field offices, and sharply curb its compliance and enforcement activities. Congress also appears ready to restrict the CPSC's power to set mandatory standards unless the commission could first prove that voluntary measures or warning labels wouldn't adequately protect consumers.

So far, Congress has resisted more radical moves, such as transferring the agency to the executive branch or stripping away its power to regulate carcinogens, and no one has jumped up to endorse Stockman's suggestion that the agency simply be abolished. Even industries highly critical of CPSC's performance have come to like the idea of a consumer-products czar in Washington—at least as an alternative to the confusion that might be created by 50 such czars at the state level. Like the now prostrate formaldehyde-foam industry, the CPSC may well survive the threat of absolute banishment, but, in both cases, survival won't feel like much of a victory. E

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Environmental Regulation: What's Good and What's Bad About It

We Americans are, bit by bit, relinquishing our legacy of self reliance in favor of an ever-increasing dependence on bureaucracies.

Monte C. Throdahl, Group V.P., Monsanto Co., St. Louis, Mo.

Employees of the Environmental Protection Agency (EPA) responsible for administering its regulations have some of the toughest and most demanding jobs in government because the decisions they reach never seem to have enough information of the right kind to support them. Often these decisions satisfy no one—not the industry being regulated, not the special interest groups advocating reform, not Congress, not the public—and all for different reasons.

That regulators find themselves in this position reflects on a major phenomenon in our culture known as the psychology of entitlement, the belief that institutions owe people more while people owe institutions less. We Americans are, bit by bit, relinquishing our legacy of self reliance in favor of an ever-increasing dependence on bureaucracies. While, on the one hand, we see a growing awareness of "self" and "individual gratification," there is also a transference to institutions of obligations to provide what are seen as basic human rights—the right to a job, the right to clean air, the right to a living wage, the right to recreation time, the right to a healthy life.

While all of this may be interesting, what does it have to do with environmental, safety, and health regulations?

Item: Dr. Lewis Thomas, president of Sloan-

Kettering Cancer Center, recently took note of the public's tendency to demand simple answers to questions of health, longevity, and serious illness.

Item: It has gradually become a common belief that the environment needs to be changed and our lifestyles transformed if medicine is to become effective in dealing with disease.

Item: Because of the perceived public mandate to do something about halting pollution and insuring health, legislators have been turning increasingly to the regulatory process. The net result has been a growing number of complex environmental laws and regulations designed to minimize pollution and insure human health. These laws include such EPA-administered regulations as the Clean Air Act, the Water Pollution Control Act, the Resource Conservation and Recovery Act and the Toxic Substances Control Act.

Item: If the regulatory agencies are to be the means of assuring a clean and safe environment, then all of us must be interested in guaranteeing that the agencies work as they were intended.

Using the example of environmental regulation, there are five basic constituencies affecting the formulation of policy: academia, public (single) interest groups, government, business, and labor.

The most workable regulation occurs when all parties have appropriate input. There exists, then,

need for a balanced implementation agencies.

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need for a balanced approach in the actual implementation of regulations by the regulatory agencies.

I see three basic factors, single interest groups, compliance, and innovation, that are impacting on the chemical industry. In some ways they offer potential for industrial and social benefits, but, if they are allowed to get out of balance among each other, they could cause significant harm to industry and to the goals of the environmental movement.

Single interest groups

It may be useful to view these factors as three forces whose purposes are reasonably consistent. If one force dominates others destructively—for whatever reason, or by whatever means—then imbalance occurs and nobody benefits. That's what I believe is going on now with regard to single interest environmental groups.

The way such groups have thrust themselves into other points of the triangle can only be described as disruptive to the regulatory process. The regulators, and we, the regulated, have the responsibility, accountability and resources for providing an environment that is safe for the general public and provides healthy workplace conditions for our employees. If we can agree on the results we wish to achieve, then what is needed is a means of balancing the concerns and inputs and assuring reasoned compliance while using scarce resources wisely. That's what the regulations are meant to do.

I will examine the points of compliance and innovation, but as I said, superimposed over these other two factors of the regulatory process is the disproportionate influence of the single interest groups, supported by the media.

How can this relationship be described? The tactic frequently used by these groups is "exaggeration to the point of outrage." There is no public benefit to be derived from such an approach.

• Intervention by single interest groups has changed the character of the normal relationship between the regulated and the regulator. Like it or

"The tactic frequently used by single interest groups is 'exaggeration to the point of outrage.' No public benefit can be derived from such an approach."

not, a few thousand people today belonging to such groups have more influence over the EPA than either Congress or industry. Through third party litigation, regulation is being forced to levels far beyond the rule of reason.

• Single interest groups have a proper place in regulation, but their role should be one of "watch-dog" to observe and comment on the regulatory product. They should not inject themselves into the "nuts and bolts" of the process. This only serves to inhibit both the regulator and the regulated and to disrupt the process itself.

Let me cite a couple of recent examples.

The dust cover to Dr. Samuel Epstein's newly released book, "The Politics of Cancer," states "Most independent experts now agree that the overwhelm-

"The Toxic Substances Control Act can act as a catalyst. The law has the potential of improving profits and promoting progress."

ing majority of all human cancers are environmentally induced or related—and thus preventable." The jacket continues, "Dr. Epstein clearly demonstrates that the crucial problems of regulation and prevention stem not from a shortage of laws or of scientific information, but from a failure to implement laws and put knowledge into practice."

In the October 31 issue of *US Magazine*, Dr. David Reuben of "Everything You Always Wanted to Know About Sex" spoke about his new book, "Everything You Always Wanted to Know About Nutrition." "People of America," he said, "the greatest threat to the survival of you and your children is not some terrible nuclear weapon. It is what you are going to eat from your dinner plate tonight." He continues, "No one should eat an ingredient he doesn't understand."

Exaggeration to outrage. You and I should be outraged with such irresponsibility.

Of course, any group, any individual has the right to express views about any government actions, private agendas and personal desires notwithstanding. What is needed is a chance for the system to work—for the regulator and regulated to be allowed to complete their job.

Compliance with regulations

We in industry can recite the worst-possible-case scenarios with regard to environmental regulation. No profits, no growth, no progress—all the way from here to another Dark Ages.

The present regulatory climate—the philosophy and procedures—suggests a situation more serious than an adversary dilemma; the situation is best described by the word "distrust." Distrust of industry and of the science it creates.

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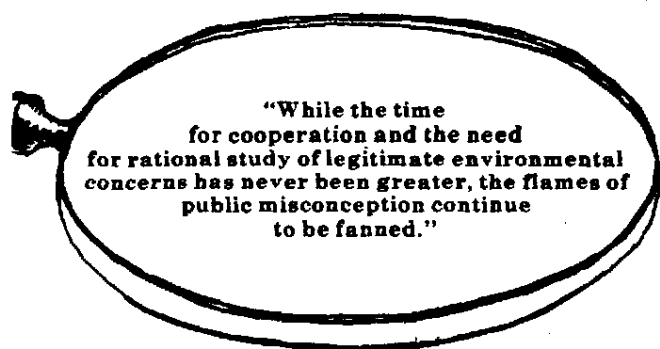
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The immediate cause of this problem is a misunderstanding of the regulatory agencies' role in which it is seen as the only bulwark between industrial villains and the people. This has led to such concepts as "zero risk" and to the misuse of data to



justify some noble end on the part of the agencies. Congress intended that the agencies be the arbiters between the public and private sectors and not knight errants protecting the people.

But there is also a positive side to environmental regulations. The Toxic Substances Control Act (TSCA) can act as a catalyst. The law has the potential of improving profits and promoting progress. How?

- Compliance with regulations can have the indirect benefit of influencing the way corporations plan. Compliance makes us pay stricter attention to what products are likely to survive and under what conditions.

- Compliance will require us to look further down the road with every product, both new and existing, to find out what the effects of that product are on society, on the environment, and on human health.

Because of TSCA and such acts as the Federal Insecticide, Fungicide & Rodenticide Act (FIFRA), the Food, Drug and Cosmetic Act, and changing social concerns, industry is learning more about new products long before they ever appear in the marketplace. Testing has been incorporated into the most basic levels of new product research; and while costly, it has the corollary benefit of forcing us to observe (and understand) potential risks and problems at a stage where they can be dealt with, rather than a dozen years and several million dollars later. Compliance can be beneficial to industry when handled with rule of reason. This means minimizing inconsistency, overlap, and just plain bad science in the formulation of regulations. Neither regulators or the regulated should be forced to make decisions about scientific issues they don't have the knowledge to resolve.

The chemical industry can't comply effectively under the handicap of four separate cancer policies—Occupational Safety & Health Administration, Environmental Protection Agency, Food & Drug Administration, and Consumer Products Safety Commission (OSHA, EPA, FDA, and CPSC). If everything must be quantified in parts per million,

or even less, then there just isn't enough time and the economic resources to do the job.

When chemical engineers are asked to design a plant it is only logical that they be given a fixed goal to attain in determining waste disposal levels and worker exposure. The necessity to meet *best available* technology places a tremendous burden on industry in light of the rapid rate of technological change.

But the standards are going to continue to change until the lines of communication between the researchers and regulator, between industry and individual, and between scientist and society are opened up.

The code is confusing

Standards of compliance are often dictated by a confusing code of expediency, activity, and immediacy and without reasonableness.

While the time for cooperation and the need for rational study of legitimate environmental concerns has never been greater, the flames of public misconception continue to be fanned. A recent example is the study prepared by three agencies within the Department of Health, Education and Welfare (HEW). The report suggests that at least 20% of cancer is associated with industrial exposure. In lieu of new data, the report criticizes previous studies which indicate that about 1 to 5% of cancer deaths are caused by occupational exposure.

This report, admitted to the OSHA carcinogen hearing *after* the expiration date of post-hearing briefs, ill serves the American public. For scientists and officials to publicly speculate that we are swimming in a sea of industrial carcinogens is irresponsible. This not only can cause fear and alarm, but can deceive people into thinking that regulatory compliance alone will control cancer.

Do not misunderstand. I do not suggest that regulators look the other way until science can discover the key to handling carcinogens. Regulations are necessary, and interim steps must be taken to safeguard health and safety.

What are some steps that are being taken? Let me cite three:

- Formation of Chemical Industry Institute of Toxicology (CIIT)—a research and testing organization, founded and supported by more than 30 companies and run as an independent institute.

- Fellowships for training toxicologists supported by private industry.

- Substantial increases in technical funds supporting corporate-owned, in-house toxicological and related health research laboratories to assure meticulous attention to generating highest quality data to support regulatory requirements for health safety.

We should not, however, try to overreach our current technology in setting standards of compliance. The name of this plea is consistency.

Innovation

Developing the technology to comply with environmental standards brings us to the third factor of the regulatory relationship—innovation. I doubt

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whether there is any more effective way to kill the innovative spirit than by scaring it to death.

The basic concepts here are not easily understood by most people—including Congress, and some regulators.

Regulatory agencies, in effect, are using regulation to "pull" innovation into the marketplace—often relying on unknown solutions to reach a given standard. Yet, at the same time, environmental regulations require America to speed up the rate of technological innovation, there are growing signs that the rate of innovation is, in fact, declining.

- The nation's total research and development expenditures in constant dollars have declined by about 5% since the late sixties, while expenditures for basic research are down more than 10%.

- Industrial R&D spending since the late sixties has risen a little faster than inflation, but expenditures for basic research have declined more than 20%.

- R&D spending here has slipped from 3% of the Gross National Product in 1965 to about 2% a decade later, while Japan and West Germany have made substantial increases, and the Soviet Union has pushed well above 3%.

- Foreign inventors now receive about twice as many U.S. patents each year as they did in 1968, while the number of foreign patents issued to American inventors has declined.

While there are a number of reasons for this apparent decline, when it comes to frustrating would-be innovators, nothing beats the federal regulatory process. For starters, there is the staggering drain on financial resources. Economist Murray Weidenbaum, director of Washington Univ.'s Center for the Study of American Business, calculates that regulatory compliance will cost business almost \$100 billion in 1979 alone.

Will the approval process cost so much that a useful innovation meant to serve a small market can never be profitable?

Will the fruits of innovation be lost entirely because of a needless product ban based on flimsy evidence?

These are not hypothetical situations. In the agricultural chemical industry, the fifties saw about 20 new pesticides enter the market. The sixties also produced about 20. But from 1971 to 1977, only three to four truly new products reached the market.

Sensitive to these facts, President Carter recently initiated a Cabinet-level review of how federal policies affect innovation. Also, a subcommittee of the Senate Commerce, Science, and Transportation Committee has begun exploring the connections among U.S. trade deficits, federal policies, and industrial innovation.

But we can't place all the blame on federal regulations. Some of our innovation decline occurred before the current regulatory climate existed.

If viewed in the right perspective, consistently managed regulations can benefit research and innovation. Regulations can enhance the development and understanding of manufacturing and testing procedures, providing that sophistication doesn't have to be arrived at yesterday.

Safeguarding technological pre-eminence

Again, the issue comes down to a need for balance. What can we do, then, to safeguard our technological preeminence before it is too late?

- We need to support the Carter Administration's effort to learn how federal policies help or hinder industrial innovation, and to identify positive steps toward encouraging innovation. The White House study, headed by Commerce Secretary Juanita Kreps, will include input from business and industry. This will be gathered through such groups as the Business Roundtable, the Conference Board, the Industrial Research Institute, and *ad hoc* advisory panels.

- John Hanley, president and chairman of Monsanto, has suggested that Congress establish a formal system of reviewing all regulatory agencies every three years. Congress should determine whether each agency is properly weighing the benefits of proposed regulations against the costs and the impact on industrial innovation.

"I doubt whether there is any more effective way to kill the innovative spirit than by scaring it to death."

- There is a need to rededicate the importance of innovation within industry. American innovation has earned us the title of the greatest problem-solving society ever. This is not the time to tarnish that reputation.

The foregoing was one of two plenary addresses delivered at the 71st Annual Meeting. The second, by Steven Jellinek of EPA, will appear in the March issue.



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For more than the past decade, the federal government, under mandate from Congress, has issued many regulations designed to protect you and me and the environment from further pollution by hazardous chemicals. So far, this has only been a beginning. More stringent regulations are coming.

The chemical industry, which produces the chemicals essential to the modern technology of rubber and plastics, is rapidly becoming encircled with regulations which govern what chemicals we can use, how we handle them and how we dispose of them. Hazardous chemicals will be regulated from their inception to their final disposal - from the cradle to the grave.

Unfortunately, industry did not fully recognize the dangerous effects of some of the chemicals we have used in great quantities over the years and we have been careless in protecting our workers, the air, the water and the land from the effects of these substances. In our defense, a lot of these effects have only been recognized recently. Now, as more and more instances of harm have been recognized and publicized, the government feels that industry must be regulated in order to correct the situation. Unfortunately, in all such situations, the pendulum is swinging far to the other side. As a result, we may find ourselves over regulated and fighting for our economic existence.

The key will be in which materials are classified as hazardous substances and on what basis. By broad definition, it is a substance which poses a present or potential threat to human health, living organisms or the environment (toxic, carcinogenic, corrosive, irritating or sensitizing, explosive or flammable).

There are over 33,000 chemicals (including 2415 suspected carcinogens) listed in the 1978 NIOSH publication, Registry of Toxic Effects of Chemical Substances. The current trend of government thinking is definitely on the conservative side and it would like most of these regulated. Carcinogen (cancer causing) is the sensitive word and this is the area which will cause us the most consternation, although all highly toxic substances such as lead, antimony oxide and cadmium will come in for more rigid regulations too.

How do you determine if a substance is a human carcinogen in the absence of a definite human link? Cancer can be the result of exposure 20 to 30 years back and no one dares wait that long today. Animal tests are the criteria being championed. Massive doses which produce cancer in animals are equated to producing cancer in humans. This can encompass a lot of chemicals we use in our industry today.

So far, regulations in the workplace have been promulgated on those substances such as vinyl chloride monomer, naphthylamine, acrylonitrile, asbestos, benzidine, lead and benzene, 24 in all with known human cancer links or long term toxic effects, and this gives the government a very good argument that regulations are necessary and for many more chemicals which are suspect.

Let us look at the various agencies and regulations which

will deeply affect the chemicals we use and the way we do business in the future. The following are the principal agencies and acts which concern us:

OSHA - Title 29 CFR - Occupational Safety and Health Act
administered under Dept. of Labor

EPA - Title 40 CFR - Environment Protection Act:

- a. PL91-604 Clean Air Act - National Emissions Standards
- b. PL92-500 Clean Water - Hazardous Substances, Toxic Pollutants, Organic and Inorganic Effluent Guidelines and Hazardous Spills.
- c. PL94-580 1976 Resource Conservation and Recovery Act.
- d. PL94-469 - TSCA Toxic Substance Control Act.

DOT - Title 49 - Hazardous Material Transportation

FDA - HEW - Title 21 CFR - Regulations on plastic and rubber products in contact with food.

NIOSH - National Institute of Occupational Safety and Health -
HEW

The act which will determine what chemicals will be allowed to even be born in the market place is the Toxic Substances Control Act administered by EPA.

The first phase of this act required the registration of all chemicals used in the United States. This caused the chemical manufacturers and importers a lot of paper work but did not really affect the usage of any chemical. The second phase, effective June 1, 1979, was the publication of the Initial Inventory list. All chemicals used must be registered. If they are not, a processor had until the end of December 1979 to still get them on the list. However, 30 days from publication of the initial list, no new chemical could be introduced into the market place unless approved by EPA through a prenotification procedure after the manufacturer has run some expensive tests to determine the possible harmful effects of the substance. Anything highly toxic or with a suspected carcinogenic effect will have a hard time reaching the market place. The revised Inventory, which is expected to be published in June, 1980, will include more than 52,000 substances and compounds. Once this Inventory List is published, you can only use chemicals on that list.

Rules for pre-manufacturing notification have been issued. As written, prenotification will involve both the manufacturer and customers who will use the product.

The dilemma will come in trying to invent a new substance to replace an existing one found to be carcinogenic and introducing it through the premanufacturing notification process.

You can be sure that the number of new chemicals introduced will be reduced. The testing alone required to determine if one chemical is harmful or not, can run from \$100,000 to \$800,000 and take up to three years. In April of this year, the first Section 5 (e) action on a premanufacturing notification was

taken by the EPA, delaying the manufacture of six new alkyl phthalate plasticizers until sufficient toxicological test data are obtained. The cost of complete testing for all six compounds could exceed \$4 million. The current cost of paper work to file can run from \$2500 to \$40,000. New forms for premanufacturing notification have now been proposed by EPA. These should substantially reduce the cost of the paper work and simplify the application procedure.

Another phase of TSCA requires that 50 chemicals/year from the inventory list be thoroughly tested for possible harmful effects because of their suspect nature and potential occupational exposure. Again, animal tests will be the determining factor. Among the items which were to be checked initially are: alkyl epoxides, alkyl phthalates, chlorinated benzenes, chlorinated paraffins, hexachloro-1,3-butadiene, 1,1,1-trichloroethane, toluene. Note some of these are whole classes of chemicals not just individual compounds. More recent additions include antimony trioxide, xylenes, methylethyl ketone, methyl isobutyl ketone, and 4,4' methylene dianiline.

There are a lot of chemicals already present in our economy which have been proven, or found to be suspect in causing harm to man or the environment. How will we be required to handle them? The Occupational Safety and Health Administration will determine the steps industry must take to provide protection to the people handling them. Title 29 CFR Sub-part Z, Toxic and Hazardous Substances, provides regulations for the handling of vinyl chloride monomer, alpha and beta naphthylamine, asbestos, benzidine, lead, benzene (which has been negated in the courts but is the subject of a soon to be released Supreme Court decision) and acrylonitrile. It did include MOCA but this was suspended on a technicality. Many of these are important to the plastics and colorants industries and this is close to what is in store for a lot more chemicals. Title 29 also includes limits on airborne contaminants which includes a multitude of fillers, pigments and solvents used in our industry. The TLV (Threshold Limit Value) used to be set to protect most workers. The trend is to reduce it now to protect all workers and in some cases to attempt to create a "zero risk" environment.

OSHA has been criticized for not moving fast enough in regulating other materials which are suspect. It has proposed to set up a system of classifying suspected carcinogenic materials into certain categories (I, II, III, IV) which automatically will govern their handling. These controversial regulations which have been in the making since mid 1978 were published in the Federal Register on January 22, 1980 and were scheduled to become effective on April 21, 1980. Several court actions have been initiated by various industry associations who contend that these proposed regulations are too stringent and by labor associations who contend that OSHA has not gone far enough to control these hazards.

As proposed, Category I will be used for those toxic substances which meet the definition of a potential occupational

carcinogen based on positive results in (1) humans or (2) a single mammalian test species where replication has been determined to be unnecessary or (3) a single mammalian species if results have been replicated in the same species. Category II is for Toxic Substances which may be carcinogenic based on unreplicated results in a single mammalian species or if the evidence is found to be only "suggestive". Categories III and IV will probably not be included.

To set priorities, OSHA will first establish a candidate list of potential occupational carcinogens. From the candidate list OSHA will establish one priority list of ten substances in each of the two categories. These priority lists will be published at least every six months in the Federal Register and it would be safe to assume that additional substances will be included with each publication. It has been reported that some 500 substances will eventually make the priority lists.

What will this mean to you, a manufacturer or processor, handling a Category I substance in your workplace? Some of the substances proposed for Category I by OSHA and by NIOSH are: asbestos, benzidine, benzene, cadmium, carbon tetrachloride, chromium, lead chromate, aniline derivatives, 2-naphthylamine and vinyl chloride monomer. Many of these materials are used in the plastics and colorants industries.

Let us examine what it will mean to handle a Category I or even Category II substance. Let us take vinyl chloride monomer as an example. This is a suspected carcinogen and NIOSH has classified it as "human positive". Exposure to vinyl chloride has been linked to liver disorders and indications are that it may be biochemically altered in the body to form cancer producing metabolites. Both OSHA and NIOSH have listed it as a Category I substance. OSHA has issued a vinyl chloride standard and anyone handling it will come under all the requirements outlined here. All other officially designated Category I substances will be placed under similar requirements.

PERMISSIBLE EXPOSURE LIMIT - Levels are to reflect the lowest levels feasible, or in certain cases, no occupational exposure. The PEL for vinyl chloride is 1 ppm averaged over any eight hour period and no exposure can be greater than 5 ppm per 15 minutes. The limit on inorganic lead is now .05 mg/m³ with an action level of .03 which is 50% below what industry expected.

EXPOSURE MONITORING - Air monitoring of individuals will be on a monthly basis if above the limit and quarterly if below. This can be an expensive procedure. Most small firms are not equipped to do this themselves. If the analysis procedure is sophisticated then the cost can be high for both large and small firms.

REGULATED AREAS - Under Category I a separate area must be maintained which totally segregates the material from other workers. This means partitioning of the area and installing separate air and dust systems. There is a question of what to do if you handle more than one substance in this category. You probably

can combine them in one area if they are not synergistic.

METHOD OF COMPLIANCE - The permanent standard requires control by engineering and work practices as far as feasible, however, the standard also allows protective devices such as respirators and clothing. Work practices can mean limiting exposure by restricting the hours of a worker in contact with the chemical. Rotation of workers may be necessary. You must also submit a compliance plan and time table.

RESPIRATORY PROTECTION - This leads to heavy expense for purchase, maintenance and fit tests. Air masks are more satisfactory. However, the cost of installation and maintenance is high. An air compressor with a CO monitor is required. Masks and accessories cost in the range of \$600.00 each. We feel that respiratory protection is necessary to supplement engineering controls.

EMERGENCY SITUATIONS - (Category I and II permanent.) A written plan is required to cover possible emergencies including major spillage.

PROTECTIVE CLOTHING AND EQUIPMENT - This can be either throw away type or washable and includes gloves, uniforms, coveralls, shoes or shoe covers.

This is a photo of one of our workers engaged in handling a suspected chemical. The helmet totally encloses the breathing area when the face piece is in place. Air is brought in from outside the plant through a compressor and monitoring system and reaches the worker through an umbilical air line. The coveralls are disposable type.....used for one shift.

It is our policy to require wearing this equipment when handling powder chemicals of known or suspected hazard including those which are merely mentioned as a suspect. I would presume that this respirator could be used in vinyl chloride exposure areas also.

HOUSEKEEPING - For chemical powders dry sweeping cannot be used. You will need filtered vacuum cleaners and a single good unit will cost around \$2,000.00.

WASTE DISPOSAL - This opens up a whole new vista of expense and problems. EPA regulates this area mainly through state EPA's under the 1976 Resource Conservation and Recovery Act. Manifest systems to transport waste have been drawn up and are already in effect in many states. The biggest problem is in finding facilities approved for disposal. There are not enough facilities to take all the hazardous waste being created now and as more substances come under this category, the situation will only worsen. It will be difficult to establish new facilities. No one wants a Love Canal in their area. The cost is high because much of the waste has to be transported over long distances. It has to be kept segregated and placed in sealed containers. Secured landfills or incineration are the approved methods of disposal. In New Jersey there are only two approved incinerators and no secured landfills. In the US there are reportedly only 15 secured

landfills. To move eighty 55-gallon drums of waste from New Jersey to a secured landfill in New York (Niagara Falls) can cost \$35/drum plus transportation. To incinerate a fibre drum of waste, can cost \$25-35 each plus transportation. Other states are in no better condition.

HYGIENE FACILITIES - This can require "dirty" rooms, "clean" rooms, showers and positive pressure lunch rooms. These rooms are designed so that dirty clothing is removed in one area. The worker then passes through a shower before entering the "clean" area to put on his street clothes.

MEDICAL SURVEILLANCE - Depending on the type of tests required, medical tests on a quarterly basis can run well over \$400/yr/man. You must maintain records. A new dimension - Medical Removal Protection has come forth in the New Lead Standard. Some chemicals such as lead require bi-monthly monitoring of blood or urine.

EMPLOYEE TRAINING AND EDUCATION - This is very important and requires trained personnel to do the job right. The workers have the legal right to know the hazards they are working with and what their protection is under the regulations.

PRECAUTIONARY LABELS AND SIGNS - Labels and signs will be required not only in the workplace, but on the products containing the material as well as on the incoming substance itself. This can lead to problems because many workers will not touch anything bearing a cancer suspect label. To keep your work force from revolving like a top, you will have to do an exceptional job of training and educating. OSHA is also proposing a separate labeling system for all toxic substances.

RECORD KEEPING - Medical and work records must be maintained for 30 years.

OBSERVATION OF MONITORING - You must provide for observers if requested.

It is going to be difficult handling any of the chemicals designated as hazardous. While you're handling them don't let any escape into the air or into the water for EPA has stringent regulations in these areas. Solvents require recovery systems and dusts require dust collectors and soon single systems will not be sufficient to meet new tight standards. Double systems will be required. Standards for lead are being drawn up now limiting the amount of lead in the air at the plant fence line at 1.5 microgram per cu. meter as an average over an extended period.

Water contamination is forbidden so water treatment facilities are required. This will affect the chemical manufacturer more than the user but what do you do with the wash water from contaminated work clothes? If you send them to a laundry then you have to advise them of the nature of the chemical and you are still responsible for proper disposal.

I would like to say a few more words concerning waste

disposal. The Federal Manifest System, was issued in February by D.O.T., since it has to do with the ignitable, corrosive, poisonous and reactive materials on the list of hazardous materials under Title 49. On May 5, 1980 EPA adopted hazardous waste management regulations which define and list hazardous wastes and which set standards for hazardous waste treatment, storage and disposal facilities. These rules will go into effect sometime in late 1980. A total of 501 hazardous wastes, processes and chemicals have been listed. In addition to the D.O.T. hazardous materials, it includes the carcinogens in OSHA-292 and any chemical substances which leach arsenic, barium, chromium, and cadmium and lead in a 5ph aqueous medium. Lubricating oils and chlorinated hydrocarbons are included. The generator is responsible for determining if his waste is hazardous. Waste may be the biggest problem facing the chemical industry in the 1980's and beyond.

What will be the consequence of all these regulations to the industry?

1. It will make our job harder and will cost us a lot of money- non profit returning money and the name of the American Business Game is still profit. Cost will have to be passed on and that name is inflation.
2. Some companies that cannot cope will disappear.
3. Those companies who can exercise ingenuity in eliminating waste and in compounding around the hazardous chemicals will survive.

Do not assume everything the government proposes is the gospel. Voice your objections if you have grounds to dispute their rulings. The agencies want to hear from you. Support your Trade Organizations - AIHC, CMA, SPE, SPI and others. We may be concentrating on regulating the wrong things. It is still ambiguous just how much cancer is caused by industrial pollution and chemical handling. Depending on which day you pick up the newspaper, estimates vary between 1%-5% and 20%-40%. The experts cannot agree on this. Quoting from Dr. Harry B. Demopoulos' paper "A Rational View of Cancer in the Workplace", the four leading causes of cancer are: cigarettes, alcohol, dietary fat and nitrites/nitrates in food, none of which are from industry. Cancer from vinyl chloride is only 0.001% of the total cancers and from asbestos 0.01%. (Dr. Demopoulos was director of the non-profit Cancer Institute of New Jersey.)

Some time ago, HEW announced a study made for the government which claims 20-40% of cancers is caused by industrial chemicals. Seventeen percent are attributed to asbestos alone. They claim 1.6 million out of 4 million workers heavily exposed to asbestos will die from cancer over the next 30-35 years.

Once they are in effect, the chemical manufacturers will have to go all out in meeting these regulations. Once on the books, rules are difficult to remove. How the exposure problems are solved will be up to their own ingenuity and engineering skill. Rest assured the cost will be reflected in the price of the chemical.

While there is a great controversy over how much industry contributes to today's cancer rate and we do not agree with the necessity for some of the regulations imposed, we do recognize that existing regulations must be met.

Failure to comply in any of these areas, TSCA, EPA regulations on the air, water and solid waste, OSHA and the D.O.T. Transportation Rules, can be costly not only to your company but even to individuals involved. The fines and penalties are stiff. With all the regulations being issued, almost daily in these areas, it is well nigh impossible for a single individual in a company to keep abreast. All regulations are published in the Federal Register which you can get from the government on a daily basis. You may find it easier to subscribe to a good service which will dig out the regulations as they are issued and will summarize what is happening regularly. There are several of these subscriber services available. The Bureau of National Affairs (BNA) does an excellent job summarizing the changes and providing copies of the regulations. Their OSHA Reporter, EPA Reporter and Chemical Regulation Reporter cover the areas we need to know about. You should also get on the NIOSH, OSHA and EPA - TSCA mailing lists. The agencies have done a good job in getting out information. Be sure someone in your company is responsible for keeping up with all the regulations. It would be well for all of you having anything to do with handling chemicals, from salesman to technical man, to also have some knowledge of these regulations. As individuals you should note that one of the latest regulations states that anyone who has any knowledge of hazard from a substance is required to report it immediately to EPA. -

Overall, the chemical industry is not a bad place to work from a health standpoint. We have had cases of harmful effects from overexposure to some chemicals; benzene, vinyl chloride monomer and beta-naphthylamine, but, considering the average life span today is 70 years as compared to 50 years as recently as 100 years ago, it is evident that considerable progress has been made in the safety and health fields.

I'll close with one last warning: these regulations may be hazardous to the health of those responsible for their implementation.

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CURRENT DEVELOPMENTS

It added that the two agencies limited both sampling frequencies and the range of their water quality analyses in order to keep costs down and support the maximum number of stations.

The geographic coverage provided by the networks, GAO continued, "is too sparse to represent water quality conditions either within individual river basins or nationwide."

Data Said 'Questionable'

Network data used by EPA, USGS, and CEQ in statistical comparisons of water quality "are highly questionable," according to the GAO report.

"The basic variability of water quality and complex causes of the variability, the limited frequency and locations of samples, and the inconsistency in field work and laboratory performance make it virtually impossible to meaningfully compare network data from month to month, season to season, and year to year," the report continued.

GAO criticized EPA and USGS for not studying the combined effect of all individual difficulties on the "credibility" of the data, despite the fact the two agencies "have known for years that network monitoring has many inherent weaknesses."

"A particularly notable problem" with network field and laboratory work, GAO said, is delays in getting samples analyzed. "Because many constituents of river water are unstable, stale samples cannot produce correct or valid measures," the report offered.

GAO said the national water quality assessments based on monthly network sampling are also "highly questionable," and added that "better assessments of progress toward cleaner water could be achieved through well-managed special studies."

Although EPA, the council, and USGS "agreed with some of GAO's concerns," the report said, "they disagreed strongly with the recommendation to stop using the national water quality networks."

The agencies told GAO that "statistical analysis will overcome the complexities of water quality" and that "changes in water quality can be meaningfully analyzed without understanding the reasons for the changes," the report said.

Up to five copies of the two-volume report, "Better Monitoring Techniques are Needed to Assess the Quality of Rivers and Streams" (CED-81-30), may be obtained free from GAO, Document Handling and Information Services Facility, Box 6015, Gaithersburg, Md. 20760; telephone (202) 275-6231. Additional copies are \$1 each.

Research

RESEARCH BILL ADOPTED BY SENATE PANEL MATCHES FUNDING LEVEL SOUGHT BY REAGAN

The Senate Environment and Public Works Committee May 15 approved a bill (S 1205) authorizing \$306.24 million for Environmental Protection Agency research and development in fiscal 1982.

The overall total and the totals of all categories of research within it are identical to the amounts requested by the Administration. The House Science and Technology Committee May 13 approved a bill (HR 3115) with the same overall total. However, several categories of that measure differed from the Administration's requests (Current Developments, May 15, p. 101).

The report accompanying S 1205 called groundwater contamination "one of the most acute contemporary environmental problems now facing the nation."

The \$29.71 million authorized in S 1205 for drinking water research included a new initiative in groundwater research.

The report suggested that EPA use aquifers under Spokane, Wash., Wood River Junction, R.I., and Suffolk County, N.Y., to study the transport and fate of groundwater contaminants.

A "thorough" solid and hazardous waste research program, the report continued, "is critically important both to the cleanup of past unregulated dumpsites and to appropriate regulation of future hazardous waste disposal."

The program should include, the report said, "both health and ecological effects and research into effective control technologies and demonstration of such technologies."

The report recommended that hazardous waste monitoring and demonstration projects be carried out in Coventry, Smithfield, and North Smithfield, R.I.

According to the report, EPA should evaluate the impact of tidal action on cleanup of hazardous waste sites near oceans.

General Policy

MITCHELL TO SPONSOR BILL TO HAVE SUPERFUND LAW COVER MEDICAL PAYMENTS

Sen. George J. Mitchell (D-Maine) May 14 said he will introduce legislation this year to provide compensation for individuals' out-of-pocket medical expenses for injuries and illnesses stemming from exposure to hazardous substances.

Mitchell, the ranking Democrat on the Senate Environment and Public Works Subcommittee on Environmental Pollution, told the Coalition for Health and the Environment that the absence of this type of compensation provision in the superfund law "is incredible."

Out-of-pocket medical expenses were included in the original Senate version of the 1980 Comprehensive Environmental Response, Compensation, and Liability Act, but were removed under threat of a filibuster by Sen. Jesse Helms (R-NC) and others.

"By what standard of decency and common sense do we say that damage to trees and grass" is more deserving of compensation than injury to human beings, Mitchell asked.

Precautions for Switching to Coal

He also promised to try to assure that any legislation introduced this year requiring utilities to switch from oil to coal also stipulate that these utilities comply with present nitrogen oxide and sulfur dioxide emission standards.

Mitchell, together with Sen. Robert T. Stafford (R-Vt), chairman of the Senate Environment and Public Works Committee, had introduced such an amendment to the utility oil backout legislation last year. The amendment was defeated, and oil backout legislation was not enacted.

The Maine Democrat sharply criticized environmentalists for not lobbying in support of the amendment. "Absolutely no effort was made by any environmental group to help get our amendment adopted," Mitchell said. "Not a single environmental lobbyist was in the halls."

Brutal Fight on Air Act Predicted

Mitchell also predicted that massive efforts will be made this year "to destroy the effectiveness, if not repeal, the Clean Air Act."

Congressman Henry Waxman (D-Calif), chairman of the House Energy and Commerce Subcommittee on Health and Environment, predicted "a brutal, knock-down, drag-out fight if the Administration comes in, as I fear it will, with a proposal to fine-tune the Air Act out of existence."

Waxman called "the big lie" the idea that "we have to give up clean air in order to accomplish our energy and economic goals. 'It's just not true,' he insisted.

Waxman also said the Reagan Administration has failed to submit any data to support its budget cuts in health and environmental programs.

General Policy

WATT MEMO SAYS INTERIOR SEEKS TO OPEN WILDERNESS AREAS, STREAMLINE EIS SYSTEM

The Sierra Club May 14 released a memorandum from Interior Secretary James G. Watt to department officials, which listed opening wilderness areas and "realigning" the environmental impact statement system as some of the department's "major goals" for the next four years.

The May 7 memorandum, entitled "Management by Objectives," stated four or five goals for each main Interior office.

In a cover letter, Watt said the department heads should focus on "clear, and quantifiable, if possible, accomplishments," and "specific tasks designed to show monthly progress." Disagreements should be brought directly to his attention, the secretary said.

Goals of the Secretary

Under the heading "Goals of the Secretary," Watt gave "realign the entire EIS [Environmental Impact Statement] system," and "develop strategic minerals policy," as two of his office's goals.

Streamlining the Outer Continental Shelf program and restoring and improving the parks also were stated as goals for the secretary's office.

For the "Goals of the Solicitor," Watt listed "open wilderness areas" and "settle pending lawsuits" as top priorities. Changing the federal reserve water rights doctrine and the "Winter's doctrine strategy" on Indian and federal water claims also were listed.

The opinion on federal reserve water rights, issued by the solicitor's office under the Carter Administration, "argued that the federal government had certain rights to unreserved water for the purposes of federal programs," according to Don Sant, director of Interior's Office of Policy Analysis.

Interior wants to reevaluate that policy, Sant told BNA May 18, to determine its effects on existing state water rights.

The "Winter's doctrine," Sant said, established that Indian tribes had been given certain water rights by treaty with the federal government. "These rights haven't been quantified and there's been a long history of litigation," he explained.

Interior "is trying to get the legal mechanism moving" to set out exactly what those Indian water rights are, in order to reduce future conflicts, Sant stated.

Other Interior Goals

Under the heading "Goals of the Assistant Secretary — Land and Water Resources," the Watt memorandum listed "1902 Reclamation Act Reform," "water policy," and "new public lands policy." The memorandum added that the department should "streamline EIS process," and "accelerate public lands leasing."

The "Goals of the Assistant Secretary for Fish and Wildlife and Parks" are to "formulate land acquisition policy," to "rebuild state and federal trust and relationship (Federalism)," to "improve refuge system utilization," to "balance use of fishery resources using scientific rationale," and to "efficiently manage national park system," according to the memorandum.

For the assistant secretary for energy and minerals, Watt's list said priorities should be to "develop and implement a public awareness program regarding land and resources so that Congress will act," to "remove regulatory restrictions," and to "increase production of energy and mineral resources."

Sierra Club Opposes Policies

John McComb, Washington office director for the Sierra Club, said Watt's memorandum "has a great deal in it that is disturbing, but this pledge to lay our wilderness areas open to exploitation is almost too arrogant to be believable."

"This memo clearly peels the mask from Watt's effort to portray himself as being in the mainstream of environmental thinking," McComb said. "Congress has created these wilderness areas, and any effort to subvert the will of Congress will be met by lawsuit after lawsuit after lawsuit."

'Bureaucratic Shorthand' Cited

The phrases in the memorandum, such as "open wilderness areas" are not what they appear to be, according to Douglas Baldwin, Interior's director of public affairs.

The language describing the goals is "bureaucratic shorthand," from flip charts used at a May 2 departmental meeting, Baldwin said. Expressed fully, he added, the phrases represent "a road map we can proudly publish and confidently work on."

Realigning the EIS system, Baldwin explained, will make the documents "serve scientific and environmental objectives," not social ones.

Opening wilderness areas, he continued, will mean allowing leaseholders to conduct exploratory work on lands being studied for possible inclusion in the wilderness preservation system.

Under the Wilderness Act of 1964, Sant explained, wilderness and study areas were left "open for exploration for 20 years." There is a non-impairment standard applied to such exploratory work, he added, and controversy exists over "what isn't impairment" to a wilderness environment.

However, according to Tim Mahoney, of the Sierra Club, Interior's objective on wilderness areas "is not a professional land-use decision."

"It's a point blank order, and a political one at that," Mahoney said.

General Policy

CEQ CHAIRMAN-DESIGNATE PLANS REVIEW OF ENVIRONMENTAL IMPACT STATEMENT RULES

The Council on Environmental Quality plans to undertake a review of the environmental impact statement (EIS) process required under the National Environmental Policy Act as part of the Administration's ongoing regulatory reform efforts, according to A. Alan Hill, CEQ chairman-designate.

"I have never felt that any regulations are sacred and chiseled in tablets of stone," Hill said in a May 19 interview with BNA. "But we won't open the whole box up."

Under NEPA, CEQ establishes guidelines for federal agencies to follow in preparing impact statements on federally funded projects.

The Federal Highway Administration is calling for a review of the impact statement process, the chairman-designate said, adding "they will want exemptions" from it.

"We will get a bunch of nibblers around the edges of NEPA to get exemptions. We will want to knock that off," Hill said. "We will want to keep it intact."

Living with the Resource
Conservation and Recovery Act

by

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URL 03159

No one in any sphere of the chemical industry can escape a common misfortune: we all know what the acronym RCRA means, and some of us have even examined its translation into a document that resembles in dimensions the Baltimore telephone directory.

I use the term 'misfortune' not because I am against the Resource Conservation and Recovery Act. On the contrary, Union Carbide called on Congress for its enactment back in 1974. But for those of us in the chemical industry, coming to grips with the reality of RCRA is somewhat like going on a stringent diet. It's good for you. It offers great promise and real rewards. But in the meantime it hurts like hell.

Over the past 3 years, the Environmental Protection Agency has attempted to interpret the will of Congress by producing a set a technically sound and administratively thorough regulations to control the movement of hazardous and toxic solid wastes through the cycle from generation to disposal. The Congressional mandate was broad: it empowered EPA to "establish performance standards ... as may be necessary to protect human health and the environment."

My purpose is to examine in general terms how well the EPA has carried out this mandate thus far, and what the agency's performance will mean to the chemical industry.

I want to focus particularly on the evolution of the EPA's thinking during the period of 16 months between the initial proposal of regulations of RCRA and the promulgation last May 19 of the first set of actual regulations binding under the law. As you are no doubt aware, these

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are only general standards. Technical guidelines for design, operation and performance will be issued in November, and actual technical standards will unfold over the next three to five years.

I think that both the regulators and the regulated are at an early point on a learning curve, and that there is some evidence that the EPA recognizes this. The control of hazardous and toxic wastes throughout a maze-like life cycle is an extremely complex problem, and one fraught with the peril of small loopholes. And even the smallest loophole when you are dealing with substances like dioxin are unacceptable, not only in terms of intrinsic risks to human health and the environment, but to the very credibility of the efforts of government and industry to manage the complexities of an industrial society. So the EPA has been exceedingly thorough. And in not a few instances, very exacting standards designed to enclose low-volume, low-toxicity materials in the same impermeable membrane needed to control really dangerous substances and concentrations will prove very costly.

And despite the EPA's exhaustive efforts in producing a very thorough set of documents, operations in the real world are less a matrix of procedures than a wriggling mass of contingencies. Over the next few months, companies subject to RCRA regulations will be forthcoming with a whole catalogue of "what ifs" and scenarios. They will be seeking clarifications from the EPA in order to provide plant operating managers with specific guidelines covering both routine and contingency situations.

I suspect this is what is meant by the term "techniques of compliance," because in large part there are no variables in technique other

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than to do precisely what the RCRA regulations tell us to do, abiding by the letter and spirit of the law. It is a good law, and I do not envy those who had to take on the task of interpreting it through complex regulation.

I think we must understand at the outset that the RCRA regulations are in part a political document. I do not mean this as a criticism, nor do I wish to imply that they have been tampered with for political gain. It is simply a fact of life that all federal regulations are in some way political, because they must reflect the values and goals transmitted through the political process.

Let me cite two cases in point. First, the RCRA regulations fail to come to terms with the abiding regulatory tension between renovation and innovation. In ways that will impose particularly heavy cost burdens on the chemical industry, and which will result in a less productive use of those funds, RCRA may demand that existing disposal processes and facilities be expensively retrofitted to meet the yet to be promulgated standards. Many of these facilities are perfectly acceptable in terms of performance standards for health, safety and environmental goals. But as is so often the case, the EPA may prescribe not just performance standards as directed by the Act but design and operating standards. These can be expected to result in a substantial misallocation of capital. And they can be expected to yield little of real value.

I realize that the Agency might find it easier, initially, to prescribe and enforce design rather than performance standards. But the easiest way is not necessarily the best. Mr. Costle has in the past recommended a cost-cutting policy to allow industries of all kinds to propose

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the best ways to clean up air pollution at individual plants, provided total environmental benefits are not reduced. He said -- and these are his own words, "This would mean less expensive pollution control, not less pollution control"

We feel Mr. Costle's own recommendation should be applied to RCRA too. This kind of approach has already worked effectively with the Clean Water Act. It will work equally well here.

EPA'S current proposals that existing waste-disposal facilities be judged on the same basis as new facilities is of major concern to us. Disposal sites which were constructed in the past without sufficient concern for their impact on the environment -- those which have been the source of pollution -- must, of course, either be retrofitted or closed. But many other facilities were built according to good engineering practices, and are environmentally sound. It would be unreasonable for EPA to require that these, too, be retrofitted or replaced simply because they are of a different design than that required for new facilities.

It would be far more productive if mandated expenditures were directed toward innovation -- toward the design and operation of new waste treatment facilities as they are needed. And it would be more fair and realistic if the costs of retroactive upgrading were borne at least in part by the government, since the economic benefits of older and less costly waste handling practices have long since flowed from the companies generating these wastes into the commonwealth.

Nonetheless, the political realities as seen from the vantage point of the EPA mitigate against this good sense. In fact, most Americans

know little about chemistry, and cannot differentiate between one degree or concentration of hazard and another, or between one effective waste handling process and another. At the same time, a recent public opinion survey by Union Carbide tells us that the great majority of Americans are extremely concerned about risks to health, safety and the environment, and advocate stringent government controls irrespective of the costs.

So the political reality is that the EPA is inclined to provide Congress and its constituencies with rigid and inflexible rules, even if they are less effective rules.

Another political reality is that the public understands that it is not eager to pay for health, safety and environmental controls out of tax revenues, and does not clearly understand that these costs will be paid anyway via higher prices and diminished economic growth and competitiveness.

So if we concede that the EPA has its own set of pressures to deal with, I think we can also concede that the RCRA regulations are on the whole intelligent and purposeful. It is a mature document, whatever its faults. And I think it tells us that we have come a long way since the passage of the Occupational Health and Safety Act in distilling rancor and zealotry out of the regulatory process. The process itself is maturing, and the regulators and regulated are getting better at their jobs. This offers great promise for the future.

There is some evidence of this trend if we contrast the actual RCRA regulations as promulgated with the regulations we in the chemical industry had anticipated.

The four characteristics of hazardous wastes as defined by the EPA remain unchanged. These are ignitability, corrosivity, toxicity and reactivity, which essentially defines substances that catch on fire, eat away metals, are poisonous, or undergo volatile changes when mixed with other substances like water. And I think we would all be quite unanimous in our desire to see to it that any substance with one of these characteristics be very carefully confined, transported and disposed of.

In defining toxicity, EPA could have chosen to stick with bio-assays, using the Ames test to gauge toxicity using bacteria. Instead, the EPA has issued lists of specific materials that are de jure either hazardous or toxic, including specific chemical products, intermediates and by-products. These lists presently name some 400 substances, and they are open-ended. But there is equally provision for having a substance removed from the list for a companies' specific waste either by demonstrating that it does not have the characteristics defining hazard in a specific process, for example, or by demonstrating that the substance generally does not have the hazardous properties ascribed to it.

Testing procedures to monitor the migration of toxic wastes from a disposal site have also been scaled down from initial proposals. The permissible levels of heavy metals in leachate from a landfill were initially pegged at 10 times the Safe Drinking Water Act's drinking water standards. This proposal was roundly criticized as unattainable and unnecessary, since it would normally apply to large volume, low-hazard wastes. The EPA has raised the permissible level to 100 times the drinking water standard.

The RCRA regulations also exempt a large number of small waste generators who were included in the original proposals -- with one important exception. And that is the generation of extremely dangerous substances even in very small amounts. Five pounds of dioxin is a lot of dioxin.

RCRA controls and compliance requirements were expected to be imposed on all generators of 100 kilograms per month of any of hazardous substances -- roughly half-a-barrel. In fact, the limits for exemption have been lifted to 1000 kilograms per month for most substances, except for those specific chemical products known to be acutely toxic or carcinogenic in even minute quantities. For generators of such substances, RCRA controls will apply at the level of one kilogram per month. An intelligent distinction has been made between substances that are low hazard or low density in the waste stream, and those which are categorically dangerous. On the other hand, wastes are deemed to be hazardous in perpetuity unless the generator or disposer can prove otherwise.

In expanding the small generator exemption, the EPA has extricated itself from an administrative nightmare, without really sacrificing anything much in the way of sound health and environmental practices. By excluding generators who produce less than 100 kilograms of waste a month, the EPA loses control of about one percent of the hazardous waste stream in the U.S., and eliminates overburdening the compliance system with thousands of small generators. In fact, about six percent of the hazardous waste generators in the nation account for nearly 98 percent of the waste.

The proposed requirement that cash bonds be posted as assurance of financial responsibility for each waste disposal facility has been dropped

in favor of surety instruments such as bank letters of credit or pledges of securities. The arbitrary liability figure of \$5 million for each waste disposal facility has also been abandoned, and replaced by a formula which ties liability to the estimated highest cost of closure of a site at any point in its useful life. What is not clear is whether the bonding requirements will be reduced after that highest-cost point in time has been passed. But here EPA has heeded industry's insistence that cash bonding at an arbitrarily high level for each disposal site would represent a massive tie-up of scarce capital for no productive purpose.

What one hand giveth, however, the other taketh away. In the apparent desire to maintain very tight reins of waste flows, the EPA has decided not to issue permits valid for the typical 30 year life of a landfill. Instead, EPA disposal permits will extend for only ten years, renewable subject to review. This little genuflection to bureaucracy promises to make it quite difficult for independent disposal contractors to get necessary long-term financing. This is certainly self-defeating from the EPA's own point of view, since an expansion of this activity is clearly needed.

The EPA has nonetheless defined the universe of hazardous waste in the United States, and designed a compliance system that will track these wastes from origin through all phases of use and transport to final disposal. The costs and paperwork are going to be enormous, but the system should assure that hazardous substances do not get lost or mislaid.

The particularly knotty problem in this system is the issue of recycling. One man's waste is another man's raw material, and the EPA does not intend to so burden the recycling process with compliance costs that

recycled materials are uncompetitive with valuable raw materials. At the same time, a hazardous waste in storage awaiting re-use is no less hazardous than hazardous wastes being discarded. The agency is still receiving comments on this issue, and evidently is striving to open a stream for efficient waste recycling without opening a loophole for evasion.

Another set of issues that will provide gainful employment to legions of lawyers will emerge from the potential conflicts between RCRA regulations and those promulgated under older environmental laws. So will the diversity of laws and procedures among the states, particularly regarding transport and siting.

Initially, EPA proposals intended to prohibit hazardous waste disposal sites in substantial areas of the country, including some coastal zones and inland waterways and geological fault regions. In the yet to come RCRA regulations, these prohibitions may have endured. One important proviso has been retained by the EPA, however. And that is that unreasonable interference by states with the intent of RCRA provisions -- for example, excessive stringency in disposal siting designed to shift the burden to other states and extend the waste transport risks -- will be construed by EPA as undue interference with interstate commerce.

The initial promulgation of RCRA regulations is only the beginning of a journey. The implementation of the regulations will in itself raise new environmental issues. Is it better, for example, to concentrate toxic substances now dispersed in low concentrations in air and water, and put them into the ground in high densities? It is not a novel question. We have achieved significant gains in air quality in the United States, but in the

process we have also begun to produce hundreds of millions of tons of wet flue gas sludge to be dispose of.

RCRA is a positive first step, but it will not prove sufficient for the long haul. Public expression of the very human desire to have safe disposal sites, but only in someone else's neighbor, is going to tangle the EPA's limited authority. And the massive costs of compliance may prove to be simply beyond the capabilities of some very essential participants in the system in industry.

Sooner or later, the federal government will have to confront our collective responsibility for solving our waste problems. The burden cannot be borne solely by industry, and neither can the costs.

Much will depend on the EPA's judgment and good faith. Reason tells us we can minimize, although we can't entirely eliminate, certain costs, delays, confusion, and — most important — risks to health and safety. There is no such thing as "zero" risk. If we were to operate on the premise that no risk-taking is permissible, we would never take a bath, ride in an automobile, or I might add, purchase a share of common stock. But reasonable people can agree reasonable precautions. That is what, I think, we all seek -- a reasoned approach.

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Deregulation gets some teeth

It is not quite four months since Ronald Reagan swept into office vowing to cut regulations and to revitalize industry. And it is little more than a week since the Senate approved Anne M. Gorsuch, his philosophical twin, to head the agency with perhaps the greatest amount of regulatory control over the chemical industry, the Environmental Protection Agency. But in recent days they have shown they mean business.

In three separate and significant developments, the Administration has either moved to ease existing regulations concerning toxic substances and hazardous wastes or has given notice that it intends not to support a regulation that would put additional burden on the chemical industry.

- EPA, under the prodding of Vice-President Bush's regulatory reform task force, has proposed changes in the Resource Conservation and Recovery Act in line with industry desires. The agency will meet this week to further develop a "degree of hazard" approach that would match regulation to the chemical involved. This exists to some degree in current rules, but not to the extent industry wants.

- During last week's hearings by a House Commerce subcommittee on the reauthorization of the Toxic Substances Control Act, EPA expressed a willingness to work with industry to correct some of the many problems industry has had in complying with the act. EPA agreed to industry's recommendation that the act be extended for just one

year to give Gorsuch sufficient time to make administrative changes, changes that the industry feels will be positive.

- Late last month, the Reagan Administration decided to block acceptance by the Organization for Economic Cooperation and Development of so-called Minimum Premarket Data (MPD), which would be required to evaluate new chemicals for toxic effects. The Carter Administration issued the MPD package as guidelines for the chemical industry, pending an OECD vote in May.

The current negotiations between EPA and OMB are indicative of just how loud and clear Reagan's call to arms has been

Environmentalists are suspicious over the way EPA is handling TSCA

heard by his administrative agencies. While the impetus for the agency's effort to change hazardous-waste rules was the formation of the Bush task force in March, EPA has seen fit to try to preempt the reformers and come up with its own set of reforms.

The agency presented its proposal to OMB about three weeks ago, at which time OMB officials decided to make some suggestions of their own. The two agencies will meet this week to continue their negotiations. High on the list is adopting a degree-of-hazard rule for wastes. But that will not be easy.

"People just don't understand that the degree of hazard must go beyond the inherent property of the waste," says John Lehman, director of EPA's solid waste office. "It's only part of the equation. The degree of hazard is a measure of the potential danger to human health and the environment." Thus, he says, the method of managing the waste, and the environmental setting into which it is disposed, must both be considered.

The agency is proposing that it classify wastes according to these factors. But an EPA spokesman says that risk, costs and implementation all have to be taken into account, too. "It becomes a huge matrix," he comments. "It is very, very, very complicated."

The current system is much simpler. The agency dictates, for example, that all hazardous wastes have to be incinerated at a specific temperature. And that, according to Blakeman Early, a Wash-

ington representative for the Sierra Club, is just the way it should be. As far as he is concerned, the degree-of-hazard approach is simply "not doable." Early explains: "EPA has had an awful time just defining what a hazardous waste is and defending that. I don't think that it can identify varying degrees of hazard that would survive industry challenge."

Environmentalists are also suspicious of the way EPA is approaching reauthorization of TSCA. Although the House subcommittee is recommending a two-year renewal of the act, EPA is willing to accept annual congressional review, recommended by industry, and the agency has requested operating authority only for fiscal 1982. This willingness to accept industry's position is taken as a sign of the times by many environmentalists. Indeed, the pressure on industry may ease up somewhat. And during the TSCA-reauthorization hearing, industry pointed out where it would like that easing to occur. A major focus of industry comment at the hearings was Section 5 of TSCA, which sets forth a system of premanufacturing notification (PMN).

"The PMN forms that EPA has proposed to date have been entirely too elaborate and require information beyond reasonable needs and statutory authority," says Ralph Engel, president of the Chemical Specialty Manufacturers Assn. even without final rules, he says, the average cost, excluding testing, to prepare a PMN is \$12,000—a figure he maintains is too high.

Safety director Etyl Blair of Dow

Bush is pushing EPA regulatory reform.



Chemical, testifying for the Chemical Manufacturers Assn., excoriated EPA, saying, "The short time period granted by Congress for review of PMNs is clear evidence that Congress did not intend EPA to use Section 5 [for] detailed analysis and final regulatory judgment."

Environmental groups tend to become unhappy at such statements and say that, if anything, the PMN system and TSCA in general have been largely ineffective. And they also maintain that EPA has been far too lenient in its dealings with industry. Jacqueline M. Warren, an attorney for the Natural Resources Defense Council, says, "If you were to look at the PMN notices they've received, you'd see none of [the filers] conducted long-range toxicity tests; more than 60% of the notices they had received [as of Mar. 24] had no toxicity information at all."

Warren also is incensed over the Administration's move to scuttle the

CMA: Congress expressly denied EPA authority to order mandatory testing

OECD's implementation of its Minimum Premarket Data rule. The move is a major policy shift for the Administration in the international effort to harmonize toxic substances laws. Last September, the EPA said it would adopt the MPD package, and the Carter Administration, in its last days, issued the MPD package as guidelines for companies preparing PMNs.

Leading the charge against the OECD's MPD package was CMA. In a 17-page letter to the State Dept.'s Assistant Secretary for International Environmental Affairs, James Malone, CMA said it agreed with the objective of harmonization but had "basic misgivings about the legal, policy and economic implications" of the proposed MPD package. CMA said Congress "expressly denied" EPA authority to prescribe such mandatory testing, that the effect on U.S. companies would be greater than on those of other OECD member countries, and that the testing required under MPD "is neither economically feasible nor scientifically justified for many new chemicals."

Warren, however, sees mandatory testing as a necessity. "The chemical companies aren't doing the testing now," she says. And she accuses CMA of "taking advantage of a leaderless EPA," by going straight to the State Dept. with its "parade of horrors" regarding the MPD issue. □

The Senate endorses Gorsuch as EPA head

The Senate confirmed Anne McG. Gorsuch last week as administrator of the Environmental Protection Agency. And those who expected lively controversy at the confirmation hearings over her background as a less-than-enthusiastic environmentalist were disappointed. Weeks before the hearings began, she had been doing her homework, visiting members of the Senate Environment and Public Works Committee, and by the end of the opening statements, it was clear that Gorsuch had the committee's support.

While confrontation may not have been the hearings' byword, the senators did share a number of the environmentalists' concerns. Bipartisan concern over exactly who would be in charge was reflected in statements made by Senators Max S. Baucus (D., Mont.) and Robert Stafford (R., Utah). Says Baucus: "My concern is that the EPA Administrator be, in fact, the primary policy-maker of the EPA . . . [and] that the EPA remain an independent agency."

Congressmen and environmentalists alike worry about a friend of Gorsuch, Interior Secretary James G. Watt. They fear that Watt, who heads the cabinet-level committee on natural resources and has actively sought to expand his power base in the Reagan Administration, will dominate decision-making at the agency. Stafford, who heads the Senate committee, warned Gorsuch in his opening statement that "there are laws which say that a decision to protect health is to be made by the occupant of the office of the Administrator, and no other. A person who relinquishes such a decision violates the law."

Decision-making. Gorsuch tried to convince the senators that agency decisions would be hers alone. Referring to Watt's natural resources committee and to Vice-President George Bush's task force on regulatory affairs, she said, "I don't feel bound by any vote taken anywhere." To impress upon the panel that she was not without recourse, Gorsuch noted that she had had two meetings with the President and one with the Vice-President.

On specific policy issues, however, Gorsuch avoided any firm commitments. She did concede that cost-benefit analysis should not be part of the process to set ambient air-quality standards. Environmentalists take some comfort from her statement, while industry groups want costs to be considered. Gorsuch would not say whether revisions to the



EPA's Gorsuch: Decisions will be hers.

Clean Air Act would have national deadlines or sanctions against states that don't meet air-quality standards. The most specific she got was to say that June 30 is the Administration's delivery date for recommendations.

Pollution control. On more general issues, however, Gorsuch was emphatic. A firm believer that states should be equal partners in pollution control, she said: "We shall restore the states to their rightful place as partners with the federal government in policy-making as well as policy implementation."

In addition, Gorsuch hopes to improve the scientific and technical basis for standards and regulations, as well as to introduce peer review into the regulatory process earlier and more frequently. She wants to streamline permit regulations to reduce delay and cost of compliance. And she repeatedly expressed the desire to make EPA regulations result-oriented, not process-oriented. □

More challenges, more trials for respirators

The National Institute for Occupational Safety and Health is raising still more questions about the effectiveness of respirators with a recent announcement that some models may give ten times less protection in the field than laboratory testing would indicate. The institute is in the midst of a controversy over further testing of the equipment, and the outcome of the debate may be crucial to

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the Reagan Administration's efforts to allow wider use of personal protective devices by employers.

On Apr. 24, following on-the-job tests of powered-air purifying respirators manufactured by MSA (Pittsburgh), NIOSH reported that the devices fall far short of "anticipated" protection during in-plant use. Those tests were conducted in a silica flour mill, and the institute wants to perform additional studies to see if the units may be a problem in other industries, such as lead smelting and coke ovens. The new tests are aimed at finding out how jostling or other movements during work conditions may affect respirator performance. In addition, both ethical and technical questions about the test methods themselves are being asked.

Before the tests can be conducted, some objections must be overcome. The United Steelworkers of America are opposing a NIOSH plan to test the MSA respirators in a lead smelter. In a May 1 letter to the institute, the union's safety and health director, Adolph Schwartz, said the USWA will not cooperate with testing of the current models unless some modifications are made to the units before the tests are conducted. If NIOSH insists on testing units on workers without further modifications, the union says, it will charge NIOSH with unethical experimental research on humans.

Meetings have been scheduled among the manufacturer, agency and union to agree on how the new tests should be conducted. The Steelworkers have asked both the company and the agency for all respirator-testing data.

The tests involve equipment that has already been modified once. In December 1980, NIOSH ordered MSA to retrofit the units because leakage from grommets connecting filters to the blower housing of some of the respirators allowed particulates to enter. What concerns officials from NIOSH, companies, and the unions is that the first fix, replacing the undersized grommets, may not have been effective.

Agency competence. The debate over MSA's respirators has also opened up NIOSH to new attacks on its competence. MSA, one of the largest respirator makers in the U.S., called NIOSH's Apr. 24 notice a case of "product assassination," and said the agency's testing showed that there have been "errors almost beyond comprehension."

Michael J. Wright, the Steelworkers' industrial hygienist, says that NIOSH should have halted the sale and use of the MSA respirators until further stud-

ies were completed, if the agency really believed the results of its own initial field studies. Further, Wright says confusion reigns over NIOSH's Apr. 24 notice. He adds, "If the respirators are defective, and at this point we don't know, the only thing to do with this notice is to tear it into pieces and stuff it in the cracks of the respirators."

NIOSH officials defend their actions concerning MSA's respirators. "We don't know the nature of the problem yet," says one official, "but we did want everybody to know what's going on." □

Superfund taxes hike the industry's bills

U.S. chemical companies are finding something new in their April invoices for feedstocks. Aside from the normal price changes, there is the superfund tax—a federal levy ranging from 0.02% to 4.92% and designed to help pay for cleanup of hazardous-waste dumps. The tax is paid by producers but, not surprisingly, most producers are passing it on to their customers.

The taxes apply to 42 chemicals (CW, Dec. 17, 1980, p. 38). And among those showing noticeably higher prices are such basic raw materials as benzene, propylene, and methane.

What remains unclear is how much of the charge chemical manufacturers can or will pass along as a hidden tax on derivatives, which are not subject to direct taxation. How to go about implementing and collecting the superfund tax has some baffled, partially because the Internal Revenue Service has yet to issue regulations on how it should be accomplished.

Over the next four years, taxes on the 42 chemicals are expected to finance 85% of the \$1.7-billion federal fund to clean up hazardous wastes and spills. In New York City last month, American Hoechst President John G. Brookhuis estimated that his company will contribute \$2.5 million this year in the form of "a surcharge that we receive from our suppliers." The company won't have to collect any taxes, but it has not determined how it will recoup its costs. Considering that in 1980 the company lost \$10 million on sales of \$1.3 billion, it is unlikely that it will attempt to absorb superfund costs.

Basically a synthetic resin manufacturer, Reichhold Chemicals will not be heavily involved in tax collection. And, most of the company's methane and ammonia sales are exempt from super-

fund taxes because the chemicals are used to manufacture plastics and fertilizers. Explains Chairman Edward E. Shea, "it's primarily a matter of monitoring the activities of feedstock suppliers."

Shell Chemical is not at all reticent about its intention to recover all of the \$25 million it expects to pay for superfund. Earlier this year, the company sent its customers letters notifying them of the tax, along with an outline of the act and copies of pertinent pages. As an integrated chemical manufacturer that produces both taxable feedstocks as well as intermediate products, Shell is caught in the middle, but it is taking it in stride.

Itemized bill. Shell produces 9 of the 42 chemicals that are subject to superfund taxes. Customers for these products receive an invoice that itemizes the superfund costs as "environmental excise tax, Public Law 96-510D." And on May 1, the company increased its prices for certain derivatives—plastics, styrene, elastomers and polybutylene—to reflect the amount of taxable chemicals used in their manufacture. Bills for these products note that the price increase includes superfund costs. Because Shell's petroleum operations are subject to a number of federal excise taxes, its accountants are not overwhelmed by the superfund, says a company spokesman, but "it's a difficult and time-consuming process to collect taxes and redistribute them."

Edwin A. Schneider, PPG Industries' marketing manager for the chemicals division, says his company follows a similar procedure in billing its chlorine and anhydrous ammonia customers. Its reasoning is that the taxes should be "disassociated from the price of the product

Chemicals will finance 85% of the \$1.7-billion fund for cleaning up hazards

because that method best clarifies the billing for our customers."

Different policies. But that philosophy is not consistent throughout the chemical industry. Hercules, for example, does not break out the superfund unless a customer requests it. On the other hand, says a spokesman, about 50% of the bills that Hercules receives from suppliers have the superfund taxes itemized. At Union Carbide, the divisions informally have decided to follow their respective industry operations.

Regulations covering how the tax should be implemented and collected are

FOUR YEARS UNDER
THE TOXIC SUBSTANCES CONTROL ACT

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URL 03173

Four Years Under the Toxic Substances Control Act

Speech given at 1980 Retech Meeting

Baltimore, Maryland

October 15, 1980

BACKGROUND

This October marks the 4th anniversary of the Toxic Substances Control Act, (TSCA) the landmark decision by Congress to minimize and control the adverse effects of hazardous chemicals on our nation and its people. The Act was welcomed by environmentalists and industrialists alike, at that time, as a major step toward curbing the possible adverse effects of certain chemicals. Implementation of this Act has moved slowly, but the real impact of TSCA is beginning to emerge as EPA concentrates its authority on careful scrutiny of new chemicals and regulation of manufacturing, importing and processing of specific chemical substances.

Most of you in the plastics industry now probably have become generally familiar with the law from your experience in reporting for the Chemical Substances Inventory. So, today I would like to amplify on your familiarity by covering the beginnings of this law, providing you an up-date of where we stand now, and suggesting where I think we are aiming in our regulatory efforts. Before delving into these areas of focus, however, I feel it is important for all of us to review the Congressional intent of the law.

Congressional policy indicated:

- * that industry should collect and maintain sufficient data on the health and environmental effects of all chemical substances;
- * that TSCA have the authority to control those chemicals that are deemed unreasonable risks or hazardous to health and the environment, and
- * that control and regulation must be as economically feasible as possible to ensure the continuation of technological innovations.

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EPA was given the responsibility for carrying out this policy. In 1977, when TSCA became effective, the first task was building an organizational framework. The Act itself authorized the Agency to have another Assistant Administrator to direct and supervise its implementation.

In late 1977 Mr. Steven D. Jellinek, was appointed to that position and he set about to build the framework, which divided the three areas of testing, chemical control and program integration among three Deputy Assistant Administrators. The next step was recruiting scientific and managerial staff, followed by developing basic plans and procedures for the implementation of TSCA.

The structure has recently been amended with only one central Deputy Assistant Administrator under Mr. Jellinek and other key individuals working along with the AA on his staff to provide a new thrust towards the international scope of TSCA as well as stronger cross-agency integration.

In 1977, the Toxics staff numbered 45 persons. Today OPTS employs over 600 people with expectations surpassing 700 for the end of 1981. And the initial budget for OPTS was \$7.4 M compared to today's budget of close to \$63 million.

As the organization began to take shape, five areas of focus came into being.

These included:

- (1) establishing systems for effective assembly, storage, retrieval, dissemination, and use of chemical information;
- (2) systematic selection of chemical substances for assessment and control;
- (3) Section 4 testing and data-gathering to understand human and environmental exposure to toxic substances and the risks involved;
- (4) A program for premanufacture review of new chemical substances manufactured or imported;
- (5) Regulation and control of manufacturing; processing, use, disposal of chemicals or classes of chemicals that may be hazardous or imply risk.

While TSCA's short regulatory life has been impeded by controversy over such matters as confidentiality, regulatory timing, economic impact, and testing of new and old chemicals, substantial headway has still been achieved in each of the five areas of focus.

UPL 03175

INFORMATION GATHERING

Let's begin with a discussion about obtaining chemical information. Information for the Initial Inventory of Chemical Substances was compiled beginning in 1977 and the first Inventory was published on June 1, 1979. Over 43,000 chemical substances were listed based on the reporting efforts of 7,400 chemical producers and importers. The reporters provided information not only on what they manufactured, but also where and in what quantity the chemicals were manufactured. Most of you may now be familiar with this 6-volume set, its first supplement published in October 1979 and the cumulative supplement which came out in July 1980 adding over 11,000 substances to the first Inventory. For your information, the Inventory is now available in printed, microfiche, and computer-readable tape forms. A check against the Inventory may be made from any one of EPA's regional offices through a computerized system.

Although initial reporting took place in early 1978 a second reporting phase took place from June 1, 1979 to December 31, 1979. This period provided processors and users of chemical substances and mixtures opportunity to report any chemicals that were not on the Initial Inventory due to original omission.

During this period, about 6,000 processor reports were received including, unfortunately, hundreds in which only the trade name was provided. This fact, together with a large number of substances reported under confidentiality considerations has hampered EPA's efforts in identifying such chemicals in order to determine what substances should be included on the Inventory. Thus, even with publication of the Cumulative Supplement, there are about 3,000 substances not in the printed Inventory. They are, however, in the Master Inventory File.

Publication of the Cumulative Supplement when added to the Initial Inventory is considered the Revised Inventory. Thus, thirty days after publication of the Revised Inventory in July 1981, it became unlawful under TSCA to manufacture, import, process or use any chemical substance either in its bulk form or as part of a mixture if it does not appear on the Inventory.

The inventory file provides us an excellent reference for the name and number of chemicals in commerce. However, it does not provide information on their characteristics. Therefore, other courses must be used to determine possibly hazardous qualities.

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Chemical and groups of chemicals which require investigation and attention, testing and possibly regulation, come from three reliable sources. These include: 1) the recommendations of the Interagency Testing Committee (known as ITC) which was established by section 4(e) of the Act; industry's voluntary reporting under section 8(e)'s substantial risk requirement; and EPA's own chemical selection process through Section 8.

SELECTION OF CHEMICALS

Let's briefly focus on these three sources.. The ITC made its first report to EPA in October 1977 centering on ten chemicals and categories of chemicals. This has been followed by successive reports every six months.

The 5th ITC Report, published on December 7, 1979, brought the total for five reports to 23 individual chemicals and 15 categories of chemicals to be considered for testing. [June ITC recommendations not available at this writing]. Although unable to rule assertively on each of the earlier reports because of lack of testing Protocols and Standards, EPA has moved ahead by publishing at the end of 1979, a proposed section 8(d) rule requiring manufacturers, processors, distributors and others with access to data, to submit any unpublished reports relating to chemical substances and mixtures on the list. This testing information would aid in determining what further testing may be needed.

It is important again to note that this proposed rule affects those who process and distribute the chemicals as well as those who manufacture them. The comment period for this proposed rule ended February 29, 1980. I feel sure that there are chemicals involved here that could mean changes in certain plastics developments.

The second vital source from which the Agency can select possibly hazardous chemicals, comes from the substantial risk notices voluntarily submitted under section 8(e). This brief section compels any person or firm with knowledge of or information concerning a chemical that poses substantial risk, to report that information to EPA. Congress provided for this part of Section 8(e) believing that industry and others could make a substantial contribution to TSCA's growing library of information and ultimately aid in preventing injury.

There have been over 330 substantial risk notices submitted to date. Not all of these, in fact, project a strong risk factor, but they do provide worthwhile information. A published summary and evaluation of those substantial risk notices submitted up to June 30, 1979 is available in a Chemical Assessment Series Volume.

The life cycle of a chemical spans the time from manufacture to disposal. It is TSCA's duty to identify and evaluate the health and environmental exposures that occur during this entire time. Part of the third source then, for selecting chemicals for assessment is a set of 15-20 use-exposure categories that EPA is developing to identify chemicals with significant exposure. A plan under Section 8(a) has been proposed for early data-gathering which would facilitate TSCA's screening and ranking of potential risk chemicals.

This first Section 8(a) Level A proposal for gathering information appeared in the February 29, 1980 Federal Register and applied to 2300 named chemicals. This information, along with data available to EPA from scientific literature, other cooperating agencies, and chemical information publications, will be used to rank the chemicals. The chemicals in the proposed rule are known for high exposure potential and some have previously-obtained toxicity information. Once the information becomes available and ranking is complete, EPA will then be in a position to make further in-depth evaluations on the chemicals ranking highest on the list, i.e. having the greatest potential for risk.

UPL 03178

TESTING

Moving on now to the third element of TSCA's strategy, I would like to discuss test requirements. In order to determine whether a chemical may cause adverse effects to health or the environment, it follows that EPA must assess its risk.

The known chemical, physical and biological properties of a chemical and its potential for injuring health or the environment make up the first stage of hazard assessment. Secondly, the total effect of risk to the general population must be assessed. Particularly, to what extent is the population exposed, and under what conditions does the exposure occur.

In Section 4, TSCA states that where there is an insufficiency of data and experience relating to a chemical's health and environmental effects, testing must be conducted to provide this needed information. This aids in determining whether the manufacturing, processing, use or disposal of such substances or mixtures do, in fact, present substantial risks. Standards for the development of such test data are to be developed under Section 4(a).

Testing standards under Section 4 would determine such risk-related, health effects characteristics as oncogenicity, teratogenicity, mutagenicity, and others. Testing for the environmental fate, persistence and ecological effects also would be standardized.

EPA plans to develop testing standards that would be compatible with the needs of the five Interagency Regulatory Liaison Group (IRLG) Agencies. These agencies include the Consumer Product Safety Commission; the Food and Drug Administration of the Department of Health, Education and Welfare; and the Food Safety and Quality Service of the Department of Agriculture; also, the Occupational Safety and Health Administration of the Department of Labor; and EPA.

Rules for good laboratory practice will be included in the standards to assure quality test data. In May 1979, the first standards for these good lab procedures were proposed along with testing standards for oncogenicity and other chronic effects. Standards for mutagenicity, teratogenicity, reproductive effects, metabolism studies and acute and subchronic toxicity were proposed on July 26, 1979.

When the Standards become final, they will be separated and applied according to individual chemicals and classes of chemicals. It is presently planned that EPA will publish health effects testing rules for some of the chemicals recommended by the ITC in mid 1980 and additional rules at six month intervals thereafter.

PRE-MANUFACTURE REVIEW

Premanufacture review, the vital provision of Section 5, deals with the introduction of new chemicals into commerce. This is our next field of discussion.

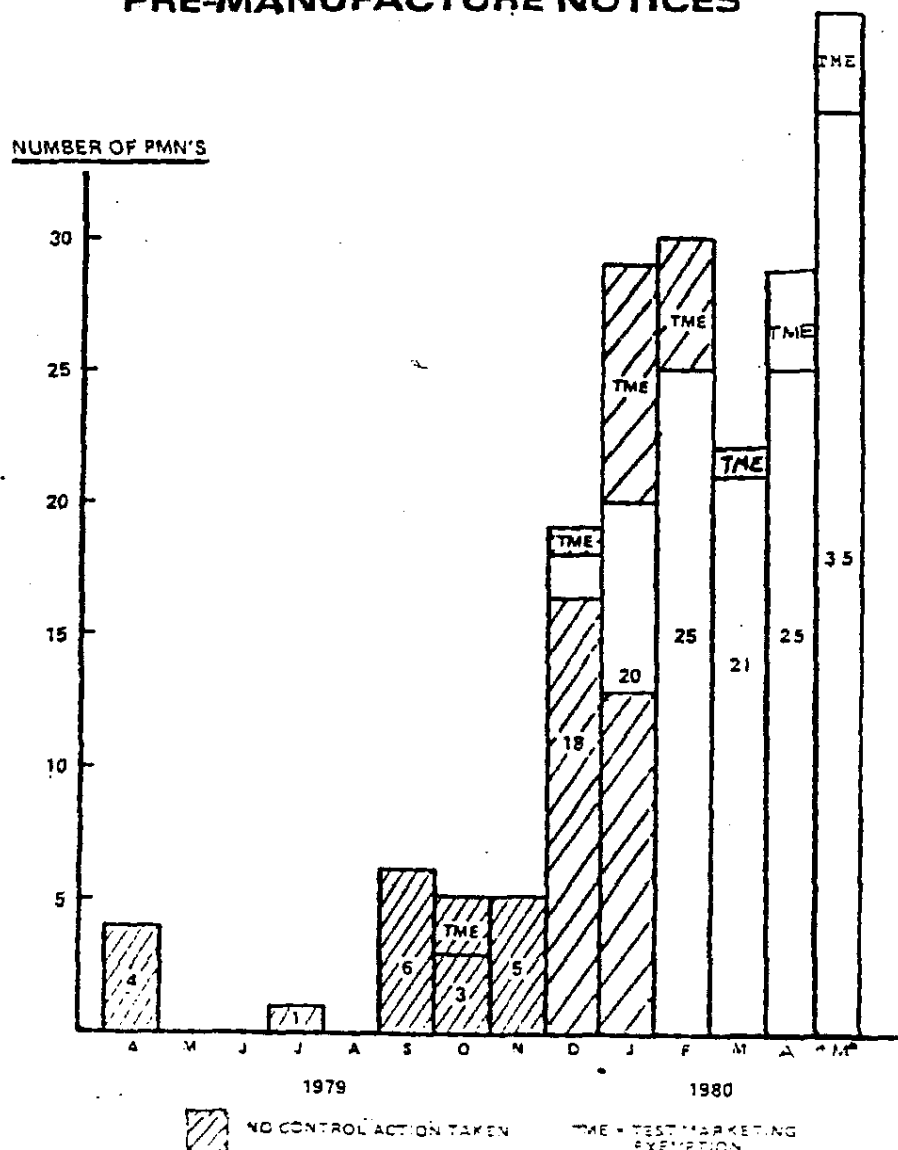
EPA can act to assess a chemical's potential for harm even before it is marketed. This is a possible result of premanufacture notification. Any chemical not in the Inventory file is designated a "new" chemical and becomes

subject to premanufacture notification. EPA must be notified at least 90 days in advance of an individual's or firm's intent to manufacture, process or import a chemical.

This TSCA Proposal took effect on July 1, 1979, even though the final rules have not as yet been promulgated.

Premanufacture Notification is enlisting a great deal of time and a large portion of OPTS's resources. The Office is constantly learning more about this process and is endeavoring to handle the PMNs, as they are called, as efficiently as possible. It has been determined that the number of new chemicals introduced into commerce each year corresponds with innovation in the chemical industry. This explains our interest and industry's interest in devoting much time and attention to the study of PMNs. The bar chart shows you the number of PMNs received since April 1979.

PRE-MANUFACTURE NOTICES



URL 03180

Because EPA must review each notice it receives within 90 days, we must assess and evaluate any necessary regulatory actions within a very short period of time. Important to note is the fact that EPA does not have the authority to require testing of a new chemical unless it is covered by a Section 4 testing rule. Section 5 Testing, guidelines are being developed but they will be just that, guidance not mandatory rules.

As of this date, the first 18 PMN notices received have not experienced regulatory action. Although industry has been compliant with the law, mostly limited data has been provided on potential effects of new chemicals on health and the environment. There has been acute toxicity information submitted, such as skin sensitivity, or eye irritation, but little information on chronic health effects or environmental test data. Increased cooperation between EPA and industry should aid in modifying some of the more difficult areas in this regulatory process.

I would like to mention two areas that OPTS recognizes as needing attention. The first is simplification of the rules to quickly dispose of PMNs generally accepted as innocuous substances. Examples could be certain structural polymers in which the substance is new only because of a change in composition involving different combinations of monomers or even no change in polymer composition, because simply, an alternative manufacturing process employing different raw materials is used.

Simplifying the rules or even exemption from certain classes of chemicals would greatly reduce the reporting burdens on industry. It would also allow EPA to use its resources and manpower more efficiently.

The second area needing attention is the mandatory 90 day period between notification and manufacture. It has been determined this time period can cause severe problems for producers of new chemicals which were developed to solve urgent trade processing problems. In most cases, the new chemical may involve just a modest change in composition. Yet, technically it is possible that the resulting new material may produce seriously toxic effects. We have to find a way to expedite these special situations.

CONTROL ACTIONS

Regulatory Action is our last area of focus. It follows that this area would come last since we cannot take action until information has been gathered and the risks assessed. Control action has been taken to date on three chemicals P-polychlorinated Biphenyls, known as PCBs, Chlorofluorocarbons or CFCs, and asbestos. In February

URL 03181

1978, under Section 6, we published marking and disposal rules for PCBs and in June 1979, rules that banned their manufacture, processing, distribution and non-totally-enclosed uses. In March 1978, in a joint action with the Food & Drug Administration (FDA) and the Consumer Product Safety Commission (CPSC), we issued aerosol uses of CFCs. This was also the result of an assessment by the National Academy of Sciences. EPA is currently exploring other ways to effectively reduce CFC emissions by controlling their uses in air conditioners, refrigerators and solvents.

Our asbestos program has received a good deal of attention. We established a national compliance program for states and school districts to identify schools containing friable asbestos in ceilings which should be sealed or removed. To assist local officials in this voluntary program, a guidance package was published and thousands of copies were distributed to schools across the country. Due to the urging of citizens and environmental groups, EPA responded with a decision to establish rules for regulation of asbestos. An advanced notice of proposed rulemaking for the school asbestos program was then published in September and October 1979. This was followed by a second notice of proposed rulemaking concerning hazardous exposures to commercial and industrial uses of asbestos fibers.

Also under the authority of Section 6, a proposal has been issued to require hazard warning labels on certain chemicals. This proposal is divided into parts: labels for chemicals having acute hazard, and labels for chemicals involving possible carcinogens. As the year progresses, other chemicals will be added to labeling program as we continue to evaluate for risk.

That sums up the strategic areas of focus and gives you an overview of what has been done. We have been quite busy the past four years, but much remains ahead.

In 1981 members of the plastics industry will feel TSCA's impact as it ripples from chemical manufacturers to processors. Although many of you manufacture and import chemical substances, most of you in the plastic industry fall into the processor category.

That being the case, let's take a moment to define just what a processor is and distinguish a processor from a chemical user. This is important, in one sense, because any time there is a regulatory action with regard to a specific chemical, whether it be obtaining test data or restricting use in some fashion, the responsibilities for carrying out the action are equally applicable to the processors as to the manufacturers of the substance.

URL 03182

TSCA refers to the processing of chemicals as preparation of a chemical or mixture, after its manufacture for distribution in commerce ---

- (a) "in either the same or different form or physical state in which it was received by the person so preparing such substance or mixture, or
- (b) as part of an article, containing the chemical substance or mixture."

Examples of chemical processing in plastics industries would be blending of chemicals to provide a solution or mixture with definite properties such as color, flexibility, or fire retardancy, and of course molding or extruding substances into shapes as articles.

TSCA defines a "user" as a business concern which uses a chemical to perform a specific task after which either --

- (1) the chemical remains essentially the same, meaning no permanent damage or chemical change occurred

or

- (2) the chemical is consumed and neither reacted or processed.

Examples of industrial uses include use of solvents to degrease metal parts before painting, bonding or assembly; use of lubricants; use of fluids or gases for heating or cooling; and use of solvents, soaps and detergents to clean equipment.

Because there may be an overlapping of definition and possibly arbitrary situations, we at OPTS feel it is necessary to provide a strict interpretation of the law. Therefore, I have detailed these definitions because those of you in the plastics industry will be greatly affected by TSCA as processors and users of chemicals, more so than as manufacturers.

In closing, I'd like to show you a list of additional rules under TSCA, some of which were promulgated in 1980, others still ahead.

- (a) Significant new use for a chemical
- * (b) Reporting of use and exposure information on about 2300 chemicals
- (c) Testing standards for additional health effects and environmental fate

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- * (d) Testing rules for health effects of certain specific chemicals or groups of chemicals
 - * (e) Record keeping and reporting of allegations of significant adverse reaction of specific chemicals to health and environment
 - (f) Control of Asbestos in schools and industry
 - * (g) Hazard warnings on chemical labelling
 - (h) Testing guidelines for PMNs
 - (i) Standards for exemption of small businesses from reporting requirements.

I call your attention to four specific proposals marked here on the chart by an asterisk. Earlier I mentioned the 8(a) proposal to develop the use and exposure information on 2300 chemicals.

The 8(d) proposal requires that some persons submit information on any or all health and safety studies that they have conducted at any time. These may include

epidemiological, occupational exposure, toxicological, ecological and clinical studies. These studies will affect the development of testing rules.

Under Section 8(c) of TSCA, manufacturers, processors, or distributors are required to maintain records and report allegations of substantial adverse reactions to health and the environment. EPA plans to propose rules requiring this record keeping and reporting.

The last pointed proposal requires labeling of hazard warnings on chemicals. A hazard is defined to include substances, to name a few, which are carcinogenic, toxic, corrosive, irritants and flammable. Our two proposals will be in two parts: one covering acute hazards, the other carcinogens.

It appears that some manufacturers, particularly small manufacturers, will voluntarily stop manufacturing or elect not to use suspect chemicals rather than wait for results of chemical testing. This could affect the plastics of the future. There is no question that where there is a threat of unreasonable risk to the environment, TSCA will be involved and it will affect innovation.

Yet when faced with adversity, humans have proved to have a great facility for adapting to necessary change. We are an inventive species, applying our ingenuity to come up

with alternatives and substitutes. I feel certain that in years to come the chemicals industry and industries reliant on the chemical industry will realize that TSCA was largely instrumental in initiating a dynamic period of growth in the industry through new and varied processes and relationships between manufacturers and processors.

At EPA we recognize that cooperation among all the divergent interests in our country is the key to a successful national regulatory process.

The Office of Industry Assistance, which I represent, is your source for information and direct contact with EPA personnel specializing in all aspects of TSCA. Call us at our toll-free number 800-424-9065, for any assistance needed.

I expect the 80's will be just as innovative as previous decades. I look forward to sharing with you the excitement and creative energy yet to come.

Thank you.

URL 03185