Where science is uncertain, cooperation is needed

The Supreme Court struggled with the so-called benzene case for a long time, almost its entire 1979-1980 term, before deciding finally to avoid the real issue.

Actually, there are several issues involved in this case at that vague front where legal considerations confront scientific evidence or lack of scientific evidence. But the prime issue that was to have been resolved in the case of the Industrial Union Department (AFL-CIO) versus American Petroleum Institute was how much regulatory agencies must consider cost-benefit factors in making rules. The court chose to ignore that issue. It must now wait, apparently, until the coke ovens emissions case later this term to deal with cost-benefits and regulatory rules.

Implicit in that question is the relative importance of benzene. It is a basic chemical. Should that be a consideration in a regulatory agency's attitude toward it? It is clear, for example, that vinyl chloride would never have reached the market place had the Toxic Substances Control Act (TSCA) been in place those many years ago. Instead, industry and the regulators reached a working understanding that allows the huge industry to continue, while workers appear to be adequately protected.

That is not to say that the same questions arise over benzene that were confronted in the vinyl chloride regulation. For one thing there is the evidence of the effects of the chemical. For another, there are the apparent inconsistencies in the Occupational Safety and Health Administration (OSHA) benzene exposure rules. For example, why are service station attendants excluded?

A benzene exposure limit of 10 ppm had been long accepted despite evidence that benzene at higher exposures was linked to leukemia. But when a study at an Ohio Pliofilm plant indicated an excessive number of leukemia cases at what were reported to be lower exposures, OSHA issued an emergency standard.

That emergency standard, challenged in court, never saw the light of day. And the data from the Pliofilm plant subsequently revealed much higher exposures to benzene. Nevertheless, the agency went ahead with a permanent standard of 1 ppm maximum exposure.

That standard was overturned by a Federal court in New Orleans, which held that the agency must weigh the costs of meeting its proposed rules against the benefits derived.

OSHA argues that its Congressional mandate is solely to protect the worker, not to be involved in economic balancing acts. They have a point.

The problem is that there is no check and balance against that position. That is, who looks out for the other side. Our form of government has prospered on a system of checks and balances. But the only immediate check on regulators is the Administration itself.

This is a dilemma for the regulated as well as the regulators. The result has been confrontation in courts. And the courts have been ill-equipped or reluctant to deal with the real issues.

In the benzene case, the Supreme Court did not really confront the scientific issues. Four justices held that OSHA was perfectly within its rights to enforce a lowered exposure standard. Four others argued that the agency didn't have enough evidence to lower the standard. And Justice Rehnquist held the judiciously unique position that the Occupational Safety and Health Act was unconstitutional.

That still leaves open the question of how much evidence is enough to mark an agent carcinogenic. No one wants to have to count dead bodies, which, in essence, is what happened in the vinyl chloride case.

The truth is that many questions remain about carcinogenicity and testing for carcinogens. Short-term tests, such as the Ames Salmonella tests, remain limited, despite the fact that a battery of such tests is now available. Moreover, bioassays on animals are dependent on the protocols and the care with which such tests are performed. Some tests are proven more valid than others. In addition, some basic questions about carcinogenicity remain unanswered. For example, why, and how, and is there a threshold, and what about cumulative factors?

The truth is that science has a lot more to do before it can let the courts make these kinds of decisions. Meanwhile we must have effective controls against exposure to carcinogenic agents. Such controls can only come about through cooperative efforts of industry, unions, scientists and the regulators.—Irvin Schwartz

Readers Respond

Salary compression

Editor:
An associate of mine gave me a copy of your first issue of *Industrial Chemical News*. I read it with interest and filed for a subscription.

Now then, being a subscriber may I be allowed to be critical? Your first article, Salary Survey, was both informative and interesting. One big question did arise. A graph plotting plant workers against chemists (with B.S.) is shown. I find no explanation of this graph within the article, however. I believe the graph depicts salary increases or track record of these two groups relative to the consumer price index. If in fact this is the case I think you may have missed an excellent opportunity to publicize a matter of great concern to many engineers and other scientific workers. This concern is commonly called salary compression or salary erosion. It is evident in the loss of real salary gains (and subsequent buying power) by these professionals when compared to employees primarily covered by the cost-of-living-allowance (COLA) provisions of bargained-for contracts. Salary compression is a major, real concern of your specified readership, the industrial chemist.

At the end of the article is a block item giving some of the details of how your survey was conducted and what you hope to do with it in the future. I am impressed and eager to see more. I do, however, feel that in addition to this type of information, similar data gathered from industrial chemists is pertinent and valuable. If in fact you do "want the companies to give more thought to issues that concern (your) readers' employment conditions" it seems imperative that you survey your readers.

I am looking forward to more of your publication. Please continue to perform this service for us.

John R. Katzfey
Western Electric, Chicago

Chemicals on computer

Editor:
I have just reviewed Vol. 1, No. 1 of *Industrial Chemical News* and find it to be an outstanding publication. Its mix of articles and advertisements makes it worth my while to examine each and every page. I would like to congratulate you on your efforts.

With regard to the article "How to plug into a computer listing of chemical information," I would like more information on this system. Would you give me the name and address of the person whom I should contact to get hooked up and where to get a copy of the 307-page book about the data base?

James R. Grant
Northwest Indiana Criminal and Toxicology Laboratory, Gary, Ind.

(Editor's Note: For further information on the Chemical Information System, contact Stephen R. Heller, CIS Coordinator, MIDSD, PM-218, Environmental Protection Agency, 401 M Street SW, Washington, DC 20460.)

Correction

Editor:
A correction on the Washington Wire page of the October issue—less than 10 parts per billion (ppb) of nitrosamines is the USDA tolerance for meats—not 10 parts per million (ppm).

This new publication will be well received and read by numerous industrial chemists throughout the U.S. I'm glad to have received your first issue.

Martin E. Winston
Winston Laboratories, Ridgefield Park, N.J.

for the fourth quarter of 83% to $80.9 million over the fourth quarter of 1979. Sales for the company rose 28.8% to $284 million from the same period in 1979.

For the full year, sales at Texasgulf increased 38.1% and earnings shot up 137.8%. The company had 1980 earnings of $326 million on sales of $1.1 billion compared with 1979 earnings of $137 million on sales of $789 million.

Ethyl Corp. had a good fourth quarter, but did not do so well for the full year. Fourth-quarter earnings totaled $24.7 million, an increase of 12.3% over fourth-quarter 1979. Sales were essentially flat—$432 million last quarter against $431 million the year before.

But full-year earnings at Ethyl fell 8% to $89.7 million from the year before, whereas sales were increasing 5% to $1.74 billion from 1979. □

Automated DNA/RNA synthesizers debut

A new competitor has appeared in the race to develop automated machines to synthesize deoxyribonucleic acid (DNA) sequences for genetic engineering. The introduction of such a machine by Bio Logicals, Toronto, Ont., last week has come hot on the heels of the commercial appearance of another such machine by Vega Biochemicals, Tucson, Ariz., in the last week of 1980. A third entrant, Genetic Instruments Co., may bring a machine to market at the end of 1981.

Bio Logicals spokesmen say their machine can add a nucleotide to a growing DNA chain on a solid support every 30 minutes. Their scientists have constructed chains greater than 20 nucleotides long and are exploring the upper limit. When ready for delivery at the end of April 1981, the machine will cost $19,500.

Ogilvie: developed chemistry for Bio Logicals' DNA synthesizer

The Vega Biochemicals machine, which is already available at $49,500, is currently wedded to chemistry that still takes three hours to add a nucleotide. Vega spokesmen say, however, that their machine has flexibility in programing, and design that can be adapted to any chemistry developed in the future.

The Bio Logicals and the forthcoming Genetic Instruments machines carry out reactions by passing reagents and solvents in sequence over a solid support in a column. Solid supports may be functionalized silica gel or controlled-pore glass. Chemistry for both is based on the phosphite method. In this method, a protecting group such as di-*p*-anisylphenylmethyl is removed from the 5′-hydroxy group of a nucleotide already on the solid support and the hydroxyl group couples with a 3′-phosphinylnucleoside bearing a very reactive leaving group on phosphorus. An oxidizing agent converts the resulting phosphite to a phosphate.

Bio Logicals' chemistry was developed by organic chemistry professor Kelvin K. Ogilvie, McGill University, Montreal, and the machine was designed with assistance from Waters Associates, Milford, Mass. Genetic Instruments' chemistry was developed by organic chemistry professor Marvin Caruthers, University of Colorado, Boulder, and the machine was designed by molecular biologist Leroy Hood, California Institute of Technology, Pasadena.

Vega Biochemicals uses a 10-ml glass reaction flask, formed by joining top and bottom by a standard taper joint. Reagents and solvents enter in sequence through the fritted glass top and are removed through a fritted glass bottom. Chemistry is based on the phosphotriester method, in which a deprotected 5′-hydroxyl of a nucleotide already on the chain couples with a nucleotide whose phosphate is esterified with one protecting and one reactive leaving group. Vega's chemistry was developed by biochemist Keiichi Itakura, City of Hope Research Institute, Duarte, Calif., and Vega's engineers designed the machine. □

Report probes chemical reproductive hazards

Some chemicals pose a real hazard to human reproduction, both for men and women, and the task of identifying which chemicals these are and how best to protect people from them is going to be incredibly difficult. That, in essence, is the conclusion of the just-released report of the Council on Environmental Quality, "Chemical Hazards to Human Reproduction."

The report, which was prepared under contract by Clement Associates, is a comprehensive literature review of the subject, and its conclusions are not likely to provoke any surprise among workers in the field. But they are not intended to. It was prepared, according to CEQ staffers, to pull together what is known about the reproductive hazards of chemical substances so that the council can assess whether there is something it should do about the problem.

The present state of scientific knowledge about reproductive hazards is roughly comparable to what was known about carcinogens in the early 1960's, the report says. Here are some of its findings.

There are clear examples of chemicals interfering with normal reproduction for both men and women. And evidence derived from geographical patterns, time trends, and specific environmental factors suggest that chemicals may be involved in other cases where the specific cause of difficulty has not been pinpointed.

Animal studies are promising and probably essential for pinpointing the specific agents responsible for adverse effects. In an analysis of 21 chemicals that affect both animals and humans, there is "a reasonably close concordance between effects reported in humans and in one or more experimental animal." With one exception, humans were affected at doses similar to or smaller than those that affected the most sensitive test animal. However, there is no consistent pattern as to which animal will be the most sensitive. Thus, useful animal testing must involve studying many species to find the most sensitive—a lengthy and expensive process, and one likely to give many "false positives" since there seem to be many agents that affect animals but not humans. A really useful in-vitro prescreening test—analogous to the Ames test for carcinogenicity—has not been found yet for reproductive hazards. □

Casarett and Doull's TOXICOLOGY

The Basic Science of Poisons

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Letters

Industrial chemistry course

SIR: Your recent discussion (C&EN, Feb. 9, page 43) regarding academic vs. industrial or chemical engineering thinking and preparation of students was read with much interest. I have been concerned with the matter for some time, and have spent many an hour with my industrial friends in discussion regarding graduates and how much training was necessary to "fit" them for their new job.

Our department has begun to attack the problem by implementing a new "industrial chemistry" major. This program has been met with much enthusiasm and cooperation from our local industry, and is apparently being met with equal enthusiasm by our students and administration. We expect to share some of our costs, ideas, and personnel—through seminars, laboratory interaction, guest (industry) lectures, and internships.

I know that others have had successful experiences along similar lines, and would not be a bit surprised to see that the traditional "standoffishness" (on both sides) will soon give way to a spirit of cooperation. After all, whenever I have discussed the matter one-on-one I have found that we are not so far from our brothers after all; it is the larger group meeting which leads to arguments—perhaps that is the nature of the human being.

Thomas Neil
Associate Professor of Chemistry, Keene State College, N.H.

On studying cancer causes

SIR: I read with interest the report called Science Update—Biochemistry in the March 2 issue. On page 29 the subject of research into causes for cancer is discussed.

I wonder if the reason our nation has failed to find the means by which cancer is started is because most of the effort, such as that of the National Cancer Institute, has been directed towards finding a "chemicals" cause instead of a natural biological cause, as discussed in the article?

As a result of Congress and the Delaney clause of the Food & Drug Act, we have been in a position of their having predetermined that there are indeed sinister causes for cancer. Too bad research cannot be conducted in the proper atmosphere instead of being directed by people with no knowledge of science.

Consultant, Orinda, Calif. R. W. Lillie

More on nuclear arms race

SIR: You will no doubt receive several letters which state that the article on the nuclear arms race does not belong in C&EN. As a reason the writers will state that it is not chemical or scientific in nature, and thus has no connection with the American Chemical Society.

Let me suggest to these people, and others, another point of view, another way of thinking. As a chemist (or other scientist) you are practicing a science which is of great interest to you, of great value to you, other than as a mere means of livelihood. Most of you think that it is important that chemistry (and all science) continue to exist and continue to progress. The existence of science and the progress of science are something to which you attach a high valuation.

Those who have studied the nuclear war situation agree that the degree of probability of a nuclear war is pretty much a random phenomenon: The chance of nuclear catastrophe increases as the number of weapons increases, as the proliferation increases, and as time goes on. The chance of nuclear catastrophe is now high and constantly increasing: it is now "four minutes to midnight."

A major nuclear war will not destroy mankind, but will demolish the technologically advanced nations. Chaos will reign. Transportation will come virtually to a standstill. Energy supplies, including electricity, will almost vanish. When you flip the switch the NMR instrument will not come on, the centrifuge will not spin, the accelerator will not bombard nuclei. Most science libraries will disappear in smoke, because most are located in or near cities. *Chemical Abstracts* will not get the information to abstract, and its computers will not alphabetize. A large percentage of chemists will be dead, because they too are located in or near cities. The science of chemistry will come virtually to a standstill.

Please, if you have any love of chemistry (and science in general), and a desire for its continued development, then join in the efforts to reduce the possibility of nuclear catastrophe.

Kent State University R. Thomas Myers

TCDD in hexachlorophene

SIR: I have previously called attention to the 2,3,7,8-tetrachlorodibenzodioxin (TCDD, dioxin) contamination of 2,4,5-T and its "effects" on Vietnam veterans exposed to agent orange as being insignificant owing to the low and brief exposures involved (C&EN, Nov. 12, 1979, page 50). In particular I pointed out that the Seveso, Italy, accident with TCDD involved a factory making hexachlorophene, which was and still is used by many doctors and nurses and which was removed from general use in antiseptic soaps in the early seventies after being implicated in the deaths of newborns (C&EN, July 7, 1980, page 50). However, I could not find any literature references to show hexachlorophene being analyzed for TCDD, although Whiteside, in his *New Yorker* article "The Pendulum and the Toxic Cloud," July 25, 1977, page 30, mentions the association of contaminated 2,4,5-trichlorophenol being common to both 2,4,5-T and hexachlorophene, and the detection of very low levels of TCDD in hexachlorophene in 1976.

I now have found mention in an analytical procedure for hexachlorophene residues (Van Auken, O. W., Hulse, M., "Hexachlorophene,"

Continued on page 58

International Regulatory Aspects For Pesticide Chemicals

VOLUME I
TOXICITY PROFILES

Author

Gaston Vettorazzi, M.D., M.S., Ph.D.

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Edited by Marshall Sittig

P. Kipper
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Park Ridge, New Jersey, U.S.A.
1980

Technically Speaking

Legislation imposing strictures on substances that might harm the environment often limit discharges to a few parts per million. For a fresh look at what a small figure this is, consider that *one* part per million is equal to:

—One inch in 16 miles;
—One minute in two years;
—A one-gram needle in a ton of hay;
—One penny in $10,000;
—One ounce of salt in 62,500 pounds (of food);
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TOXICOLOGY OF PESTICIDES

Wayland J. Hayes, Jr., M.D., Ph.D.

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U.S. Public Health Service

The Williams & Wilkins Company/*Baltimore*

vation—not the casual result of a test with some other purpose. Any study designed to reveal a dosage producing no effect should contain, in addition to a control group receiving no toxicant, one or more groups of subjects given larger dosages fully expected to produce measurable effects of the compound. Since such tests are almost always prolonged, particular attention must be given to the number of subjects assigned to each group so that the number available at the end of the study will be adequate to reach a statistically significant result (see Section 2.2.7.1).

There are several reasons for placing the expression, "no effect" in quotation marks. First, many studies reveal effects that are obvious, reproducible, and highly significant from a statistical standpoint but of questionable biological significance. Depending on circumstances, an example might be partial inhibition of an easily regenerated enzyme. There is no substitute for judgment in toxicology. Second, as discussed in one of the following sections, the effects of small dosages of toxic compounds may be beneficial and thus qualitatively different from the effects of larger dosages. Third, failure to detect any effect by an elaborate scheme of testing does not exclude the possibility that an effect would have been detected if some other scheme had been used. Rapid progress has been made recently in chemical detection of toxicants or their metabolites. Analytical chemists have already achieved such skill that they easily measure biologically unimportant traces of several pesticides. Biochemists and physiologists are not far behind.

For these reasons, it is generally recognized that what is needed is a "no significant effect" or "no adverse effect" level, that is, a level that causes no detectable injurious effect. There is no complete substitute for long-term tests, but increasing attention must be given to evaluating the biological significance of observed effects that involve no demonstrable injury to health. A toxicologist may do as much harm by unnecessarily condemning a compound as by failing to detect and to prevent a real toxic hazard.

The Lowest Effect Level as a Practical Toxicological Measurement. As already mentioned, it usually is impractical to use such a large number of subjects per group that the possibility of a rare (<1%) but highly undesirable effect, such as neurotoxicity or carcinogenesis, can be excluded in the lower dosage range. This problem is not of such importance as may appear at first because the frequency of an effect can be increased by increasing the dosage—just one reason for using injurious dosages in long-term studies. Thus, the existence of a highly undesirable effect of a particular compound can be taken into account in the selection of a safety factor. A more serious objection from a purely scientific standpoint is the imprecision of finding the highest "no significant effect" level. From a statistical point of view, it would be preferable to employ for safety evaluation the lowest effect level, that is the smallest one at which a meaningful, injurious effect or even a relevant, harmless effect is detected. This implies: (*a*) that the "no significant effect" is determined in order to put a limit on what is meant by the smallest effect level; but (*b*) the more objective, positive finding is used for safety evaluation; and (*c*) the nature of any injurious effect observed will be taken into account in choosing a safety factor.

The matter of safety factors based either on the "no significant effect" dosage level or on effective dosage levels is discussed in Section 9.1.4.1

Threshold Levels as Biological Facts. The practical difficulty in establishing a "no effect" level for a particular compound using a manageable number of experimental animals and the more complex problem of extrapolating a safe level for man must not be permitted to obscure the fact that thresholds do exist. The toxicologist faced with a single limited experiment would be wise to recall the impossibility of proving a negative. The logician faced with a complete lack of supporting evidence would be wise not to press pure logic too far and conclude that no threshold exists so that even a single molecule may represent a hazard. As pointed out by Friedman (1973), the question of the existence of a threshold is a problem of biology, not of mathematics or of probability. In not a single instance has the absence of a threshold been demonstrated. On the contrary, concentrations are known at which compounds with the highest biological activity are inactive.

For example, as described by Friedman (1973), limitation of vitamin A intake to 10% of the minimal required dosage leads to severe deficiency disease and yet it constitutes a dosage of 3.6×10^{15} molecules per kilogram of body weight or a concentration of 6×10^{-9} M in the body. In a similar way, ineffective levels of vitamin D and vitamin B_{12} (where the daily requirements are only 10 μg/day and 1 μg/day, respectively) are 4×10^{-11} M and 1×10^{-12} M. By conservative estimates, postmenopausal women and adult men have 1.5×10^{21} molecules of estradiol per kilogram of body weight or the equivalent of 2.6×10^{-12} M.

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have an LD 50 value of 0.0006 mg/kg in guinea pigs, a harmless dose would still produce a concentration of 1.9×10^{-10} M in guinea pigs. For botulinum toxin, where talk of activity in terms of molecules has long been common, an amount of toxin that would produce absolutely no effect in mice would represent a dosage of 4.2×10^{7} molecules per kilogram or a concentration in the mouse of 7×10^{-17} M, assuming a molecular weight of 900,000.

Values of the same orders of magnitude apply to some carcinogens. An ineffective amount of aflatoxin in the rat determines a dosage of 9.6×10^{12} molecules per kilogram and a concentration of 1.6×10^{-11} M. However, many strong carcinogens are less potent. For 1,2,5,6-dibenzanthracene, methylcholanthrene, and 3,4-benzpyrene administered by different routes, the ineffective concentration in the body ranges from 1×10^{-8} to 1×10^{-7} M.

Of course, the limiting level is even higher for compounds that are not inherently very active. For example, an ineffective amount of Aramite® as a carcinogen involves a concentration of 3×10^{-4} M.

Hutchinson (1964) and later Dinman (1972) suggested that 10^{6} molecules per cell is the limiting concentration for biological activity, whether pharmacological or injurious. As pointed out by Friedman (1973), there are *about* 6×10^{13} *cells in a 70-kg human body,* from which it follows that the suggested limiting level for activity is 8.6×10^{15} molecules per kilogram or about 1×10^{-8} M. The demonstrated no effect levels for vitamin D, vitamin B_{12}, and estradiol (10^{-11} to 10^{-12} M) are so low that the corresponding thresholds may be somewhat lower than the limiting level of 1×10^{-7} just discussed. The same reasoning applies to the thresholds of toxic action of tetrachlorodibenzdioxin and botulinum toxin *and the threshold of carcinogenic action of* aflatoxin. Further evidence that the limiting concentration for the activity of a few highly active compounds is less than 10^{-8} M is the report that certain pheromones have thresholds of the order of 1×10^{-12} M. Of course, these values do not prove that the limiting concentration is ever less than 10^{-8} M in susceptible cells, since some compounds, such as botulinum toxin, have an extremely high affinity for the cells on which they act, and *their* distribution in the body at critical dosage may be very uneven.

However, exactly what concentration is limiting is far less important than the fact that thresholds do exist even for the most active compounds. No one doubts that the existence of deficiency conditions proves that minimal or threshold concentrations of vitamins, hormones, and other beneficial compounds are required for proper action. There is no chemical or other scientific reason to suppose that there is an inherent difference in the dosage-response relation of injurious compounds.

Beneficial Effects of Small Dosages. Schulz (1888) may have been the first to observe stimulation from very low concentrations of poisons. He investigated the effect of mercuric chloride, iodine, bromine, arsenous acid, chromic acid, formic acid, and salicylic acid on yeast and concluded that, when sufficiently diluted, all of them can increase the vitality of yeast over a longer or shorter period of time. Only a few years later the bacteriologist, Hueppe (1896), stated the rule that has come to bear his name: "Every substance that kills and destroys protoplasm in certain concentrations, inhibits development in lower concentrations, but acts as a stimulus and increases the potential of life at even lower concentrations beyond a point of neutrality." In stating this principle, Hueppe mentioned certain apparent exceptions. He also acknowledged the independent discovery of the rule by Arndt and Schulz.

A special, universally accepted instance of the beneficial effects of small dosages involves the reactions of plants to what are now called essential trace elements. A plant cannot live if even a single one of these metals or metaloids is completely absent from the medium in which the plant is grown, but an excess of any one or them is injurious. This is the law of optimal nutritive concentration. Recognition of it must be credited to Gabriel Bertrand even though he may never have stated it concisely in publication. The relationship of beneficial and harmful effects of trace elements was implied in the discussion that followed his presentation on "complementary nutrients" at the Fifth International Congress of Applied Chemistry held in 1903 in Berlin (Bertrand, 1903). Personal communications from his son, Dr. Didier Bertrand, and one of his students, Dr. Rene Truhaut, establish that Gabriel Bertrand presented the law of optimal nutritive concentration in his courses at the Sorbonne from 1908 through 1930. Later, Didier Bertrand (1962a, 1962b, 1969) generalized the law and expressed it in mathematical form.

As reviewed by Townsend and Luckey (1960) and in a very different way by Smyth (1967), evidence has continued to accumulate that small dosages of many compounds are beneficial even though larger dosages of the same compounds are injurious. Townsend and Luckey tabulated many examples from the

David, you've knocked off Goliath. Now what?

When Ralph Nader first took to the field in the mid-60s with publication of his "Unsafe At Any Speed," he saw himself as jousting with corporate giants. Even a firm the size of General Motors was not so big that it did not feel the steel of his lance, take pause, even stumble. It was an appealing picture in some ways. As Irving Kristol noted at a meeting of the Chemical Manufacturers Association several years ago, Americans have never been really anti-business. But they certainly have had a large streak of anti-big-business in them—in fact, anti-bigness, period. Dragon-slaying was part of this nation's mystique long before Teddy Roosevelt made a sport of busting trusts. And the country has benefited, for the most part.

But as we enter the 1980s, perhaps we should ask ourselves some questions. Have those Goliaths we used to fear become an endangered species that we may one day miss? Have those Davids we used to cheer bred too fast and gone too far? Have they assumed some of the trappings of Goliaths? Has the slaying of Goliaths upset the political "ecology" of this country to such an extent that the field is being left to the biggest predator of them all—Big Government? Perhaps those Goliaths had been playing a critical role in decentralizing and defusing governmental powers, in helping maintain a certain balance of power between government and the individual.

The questions are not as far-fetched as they seem. The track record of Goliaths these past few years has not been impressive. Nader, with one slim volume, humbled one of the country's largest corporations and helped set in motion legislation that has hobbled a major industry. The tiny snail darter, whose existence wasn't even known a short time ago, with the help of environmental friends, held up construction of a major dam. Two obscure city reporters played a key role in ousting a President. And one of those same reporters, with the help of a fifth column of court clerks, has taken on the U.S. Supreme Court in a book called *The Brethren*. On TV, Mike Wallace, master of his medium, has little trouble cowing normally powerful adversaries. And now we have the spectacle of the once-mighty Chrysler going hat in hand to Washington, victim not only of its own frailties but of an increasingly costly and complex matrix of rules and regulations. Ford could be next. And if multi-billion dollar Chrysler and Ford are having problems, what hope is there for little XYZ Chemical Co.?

In little more than a decade, the U.S. chemical industry has been smothered with upwards of 30 health and environmental enactments. At least eight, including the Toxic Substances Control Act, are major acts passed by Congress only since 1969. Indeed, one expert observer of the chemical industry, whose views we respect, sees an industry virtually run—not just regulated, but *run*—from Washington and state agencies before the end of the decade.

Those who fear the alleged bigness of business and concentration of corporate power like to hold Big Oil up as their prime example. But it's a poor choice, at least nowadays, as even a casual look at our third-quarter CW 300 review shows (*Nov. 21, 1979, page 38*). The table lists the 34 largest U.S. oil and gas companies. The largest—Exxon—posted sales of $77 billion for the latest 12 months. That's a lot of money, to be sure. But it represents only 21% of the total 12-month figure for the entire group. Other such "large" firms as Mobil and Texaco accounted for about 10-11% of the total. And such "large" companies as Shell, Conoco, Sun and ARCO are in the 2-4% range. Concentration? Nonsense. And bigness in this context has little meaning. The table listing chemical companies on page 34 of the Nov. 21 issue presents a similar picture.

These figures tend to pale beside those contained in the government's budget. Moreover, it took chemical "giant" Du Pont some 200 years to top $10 billion in sales. The Department of Energy cleared that mark at birth without production.

The power in this country has moved from the board rooms to a cancerous complex of regulatory agencies and organizations in the Federal City and state capitals—to the alphabet soup of EPA, OSHA, DOT, EEOC, FTC, SEC, IRS. . . .(Note that none of the first five existed when Nader first published his book.)

When all the Goliaths are slain, who will protect the little Davids—and the rest of us—from the biggest Goliath of them all?

Patrick P. McCurdy

chemicalweek

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In terms of regulation, you ain't seen nuttin yet

"Well, how do you think the '80s will look?" I asked, passing the butter.

"Look," he said, munching on a luncheon roll. "We cannot paint a picture of what the chemical industry will look like in 1990. But we can try to identify the half dozen most important factors that will gradually change it."

"Sounds reasonable," said I, sagely.

"Just using the cancer issue as an example, in the next few years the government is going to be identifying a whole list of things that are suspected of causing cancer. Some will be found sufficiently hazardous that efforts will be made to take them off the market. But just the fact that they're on a list . . . For example, the OSHA regulations will provide for 20 of them on a priority list with another 300 right behind those 20 as suspected human carcinogens for regulatory purposes . . . As soon as those lists come out, people will design away from those materials, whatever they happen to be."

Recalling the speed with which "contains no chlorofluorocarbons" emblazoned aerosol cans at the first hint of a problem, I had to agree.

The man across the table continued. "As a consequence, the actions of OSHA and a couple of other agencies in developing a list of carcinogens is going to directly impact on materials that are going to be available. So purchasing is going to be a different game in the future . . . as to what to buy, how to buy it and how much it's going to cost. . . .

"Or take production. The government is moving very heavily into the process area. Under TSCA, they are going to be deciding some things as to *how* you make products. So even in the production process, government regulations that are being developed under TSCA and a couple of other laws will to some degree determine how you produce things."

"But. . . ." I found myself mumbling.

"And not only that, but you've got the life-cycle concept, which they're pushing now with asbestos. They are proposing now that they will decide what uses are reasonable for asbestos, or where there are substitutes. And they'll allow the substitutes on the market, but you phase out of asbestos. And they will now begin to set a total poundage of asbestos for all uses. And they will gradually reduce that every year."

"Maybe that's not such a bad idea for a product like asbestos."

"Maybe. But how do you administer it? How do they decide who gets it in terms of use, who makes it . . . etc.? Do you allow 12% in hair dryers, or 2%, as against, say, 35% in brake lining? Once you get into the question of the government saying you can have a million pounds a year, you're faced with who's allowed to make and sell that million pounds and who is allowed to use it."

"I see what you mean. The government would become the allocator."

"Right. You're also faced with their ultimate objective, which, in effect, is to phase it down to an irreducible minimum. Work it down, and say there are only 12,000 pounds that can be used, and at the end of the life-cycle process, that will be all that is permitted. And it gets into very, very complicated decisions by management as to their share of this and how it's going to be worked out to customers . . . It's a quota system. The question will be whether or not there will be a quota for your product and whether you'll have access to it."

"Sounds like George Orwell's 1984," I muttered over coffee.

"So what are you going to do?" he continued. "You'll phase away from it *now*. That's the whole objective—to phase you out of it. So you'll be faced with an allocation system . . . a quota system. The thinking—even with big quotas—is that in 10 years, you literally won't know how you're going to get it . . ."

"Maybe it's not such a good idea after all."

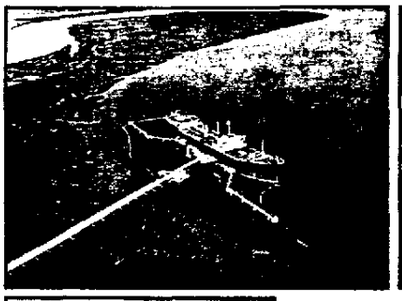
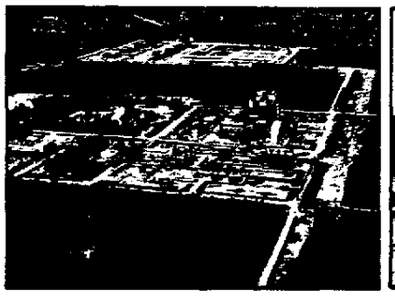
"I'm not saying it's good or bad. But it will be a whole different set of rules, a new game, sort of like war. Furthermore, there's the compliance problem. Everyone's complaining about government regulation. But the burden of regulation isn't even here yet. Take the whole mass of regulation that the chemical industry will live under in the '80s—none of it, effectively, has been put into place yet."

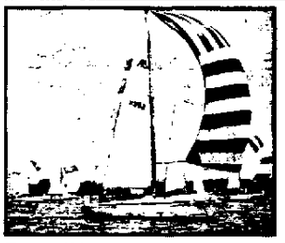
"You mean, this is just the beginning?"

"You ain't seen nuttin yet."

"I think I'll have another drink."

Patrick P. McCurdy



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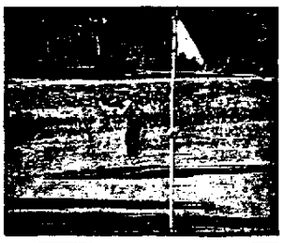


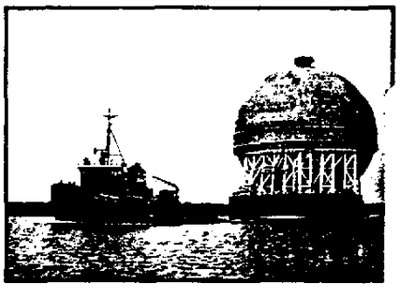

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Brain tumor risk in petrochemical workers

Epidemiologists struggle to sort out tenuous evidence that points to elevated incidence of brain tumors among petrochemical workers

Jeffrey L. Fox
C&EN, Washington

The current effort to show a link between exposures to petrochemicals and the incidence of brain tumors among workers in the petrochemical industry is stretching epidemiology to its limits.

Some critics even argue that epidemiologists risk a tumble by leaning somewhat beyond the reasonable limits of their science. This possibility was apparent at the recent workshop sponsored by the New York Academy of Sciences at which was assembled a blue-ribbon group of epidemiologists and other authorities familiar with brain tumor incidence in humans and in experimental animals (C&EN, Nov. 3, page 6). Some observers at the workshop could not help concluding that establishing a firm link between brain tumor incidence and employment in the petrochemical industry may prove very difficult. Moreover, even if established, that link may represent the result of practices long since outmoded. Many naive and dangerously sloppy procedures of several decades ago have been eliminated.

C&EN staff photos

Robbins: bring the best minds together

But sloppy procedures still exist, and other procedures that are genuinely thought to be safe well might be otherwise. Thus, the petrochemical industry—and any other industry, for that matter—must rely on imperfect early warning systems, such as those mustered by epidemiologists, to ferret out potential health hazards in the workplace.

Epidemiologists often refer to their preliminary surveys as "hypothesis generating" devices. The current hypothesis, being voiced by epidemiologists working for the Occupational Safety & Health Administration, for the National Institute for Occupational Safety & Health, and for the National Cancer Institute, is that the incidence of brain tumors among petrochemical employees is anywhere from 1.5 to 2.5 times higher than the incidence in the general population. Several other epidemiologists, some of them employed by the petrochemical industry but others without such ties, do not find evidence for elevated incidence. These disagreements were by no means reconciled during the New York Academy of Sciences workshop.

"Polarizations came to mind during preparation of this meeting," says workshop organizer and epidemiologist Irving P. Selikoff. "We're conscious of this. But we were taught it was good to find causes of disease. Now, when causes in industry are found, there's no automatic pat on the back." There are also no automatic pats on the back when someone finds the obverse, no evidence for causes, he could have added.

Epidemiologic evidence regarding brain tumors is anything but straightforward. Many factors could serve to show the intense analytic efforts under way at the Texas petrochemical plants, including facilities run by Union Carbide in Texas City and Dow Chemical in Freeport but also at other installations owned by Texaco, Mobil, and Gulf Oil.

For instance, the incidence of brain tumors in the general population in the U.S. is on the rise, according to

Maltoni: dosage and route are important

Lawrence Garfinkel of the American Cancer Society. The rise is not a sharp one; it applies more to men than women; and it follows no immediately obvious pattern. Also, the apparent rise in incidence might be due, in part, to improved diagnostic procedures and to better reporting of cancers.

Quibbling about statistics and how to analyze them is just the sort of activity that preoccupies many of the epidemiologists now scrutinizing the petrochemical industry. There are plenty of good reasons for the quibbling—scarce data, reliance on old records of questionable validity, and sharp differences on how to approach an issue are all factors.

"It is clear there is a rise in the risk of brain cancer," asserted NIOSH's Anthony Robbins at the beginning of the workshop. "From the point of view of the workers, we've been too slow in recognizing that risk. We are attracting attention to this issue [by having a public workshop]—not to blame anyone. But until you bring the best minds together, you don't solve the problem."

What Robbins said was echoed often during the three-day meeting, particularly by his colleagues from NIOSH and OSHA. Their concerns, quite properly, revolve around the principle of ensuring the health of workers. But those concerns can act like a centripetal force, continually drawing one's attentions back to

Animal studies provide troublesome hints

Ideally, the results of carefully controlled animal studies of carcinogens will complement epidemiology, confirming suspicions about humans by referring to systematic data about mice and rats.

But a good case may be made that animal studies are sometimes misleading and can be prejudicial to the epidemiologist. For example, humans might be more, less, or altogether insensitive to a particular chemical that induces cancer in rats and mice. How often such discrepancies crop up is not so important here. The point is that the existence of bad or even good animal studies can send epidemiologists off on an oriented search, but a wild goose chase nevertheless.

To anyone who is strict about the conduct of scientific investigations, the question of initial biases—of whatever nature—is bound to be troublesome. Thus, conscientious epidemiologists are likely to find themselves trapped in a paradox: wanting and needing helpful clues about enigmatic human health problems, but also wishing to avoid one of the worst pitfalls in science—namely, relying on false premises.

There is plentiful animal data for the epidemiologists searching for causes of human brain tumors to review. Scientists have identified several dozen chemical compounds that can cause brain tumors in various animals, including mice, rats, hamsters, rabbits, and nonhuman primates. When tested, however, many of these chemicals do not cause cancer consistently from one type of animal to another. Moreover, the anatomic site of tumors caused by a particular agent can vary from one species of animal to another. This lack of consistency is fairly commonplace in animal testing programs. It's a complicating factor that helps to muddy otherwise limpid clues now available.

Not all brain tumors are alike. The major kind of tumor being followed in the epidemiologic studies is called a glioma. The spontaneous incidence of gliomas in mice is "exceedingly low," according to Italian toxicologist, Cesare Maltoni of the University of Bologna. Thus, the incidence of gliomas arising after exposure to various chemicals is a relatively reliable test system, he says. Nonetheless, that incidence also varies according to how the chemicals are administered to the animals—by feeding, injection, implantation, or inhalation. "It is important to know the dosage and route by which a carcinogen gains entrance," Maltoni emphasizes.

Other observations of animals undoubtedly will complicate the assessment of the human health question. For example, there is the matter of varying susceptibility to particular cancer-causing agents during an animal's life span. "Embryos and newborn animals are far more sensitive to many agents than are adult animals," Maltoni notes, referring to the incidence of central nervous system tumors.

This age-dependent variation in susceptibility is pronounced in *Erythrocebus patas*, a species of reddish, African monkey being studied by Jerry M. Rice and colleagues at the National Cancer Institute in Bethesda, Md. "We cannot get central nervous system tumors by injection of carcinogens into adults," he says about such animals. "They need to have very early exposure during gestation to develop tumors later, two to three years after birth."

To Rice, these results suggest that there may be periods in life when humans are particularly or peculiarly susceptible to developing certain kinds of tumors. Thus, induction of brain tumors in adults "might have occurred very much longer in the past," he notes.

What all this means regarding workplace exposures to putative carcinogens and the incidence of brain tumors is difficult to say. And when these observations are tied into a widely held view of how cancer develops, the story looks even more complex.

Many scientists believe that cancer develops in two phases, called initiation and promotion. An early event, initiation, caused by one type of chemical, may not cause a tumor unless followed by exposure to (usually) other types of chemicals, called promoters. Thus, the search for a single type of workplace exposure to explain brain cancer incidence might be misguided.

Imagine the following situation. One group of adults, when children, either had a particular disease, took a certain medicine, or was exposed to some other "initiating agent," whereas another group of adults avoided that agent. Then during adulthood, members from both groups were met with an onslaught of many "promoting agents." Some such promoting agents might be found in the workplace, particularly when that workplace is a petrochemical facility. But other kinds of workplaces and altogether different kinds of environments also might provide some of the adults with deleterious promoting agents. Sorting through all these possibilities to identify the culprit agents could prove a formidable challenge.

Studies of animals are introducing further complications. For example, some scientists contend that virus particles are associated with chemically induced brain tumors in mice. Other scientists dispute the importance and even the existence of such particles. Their importance to human brain tumors is unknown.

Other observations are puzzling. Why, for instance, does a particular chemical produce primarily brain tumors without affecting other organs? Access of the chemical to such organs partly accounts for their differing sensitivity. But other metabolic influences, including either different activation or detoxification in various organs, also could be important, according to Paul Kleihus of the University of Frieburg in West Germany. Thus, for instance, enzymes in the brain cells of rats are slow to rid DNA there of certain kinds of damage. Long-lived damage might lead to brain tumors during the later life of such animals.

By far, the most puzzling phenomenon is one noted by Maltoni and his colleagues. Varying the dose and the means by which it's administered for some carcinogens can cause systematic fluctuations in brain tumor incidence in animals. Thus, an elevated dose of vinyl chloride, for example, induces few (or no) brain tumors, whereas a lower dose may induce many such tumors. This "masking" phenomenon departs significantly from the typical observation that tumor incidence rises directly in proportion to the dose of carcinogen an animal receives. If such a phenomenon pertains to human brain cancer, the search for pertinent workplace hazards may be tortuous indeed. □

workers and their environment. Thus, well-intentioned beliefs can predispose one to look for clues more zealously in one place than in another. This is not meant to say that OSHA or NIOSH officials are tailoring their investigations to distort the truth. But these epidemiologists clearly are instilled with the belief that the workplace, particularly a modern petrochemical facility, can and must be safeguarded.

That committment, which was on clear display among many of the federal officials at the workshop, is naturally even stronger among officials of unions representing the petrochemical workforce. "We must identify the job places where cases of brain cancer have appeared to see if there's a common denominator," says Raphael Moure of the Oil, Chemical & Atomic Workers International Union. "What are the locations in the plant?" Once that's known, he says, "conditions can be improved and exposures minimized." Like Moure, Sheldon Samuels of AFL-CIO now *assumes* that the risk for brain tumors is elevated for workers in pet-

Thomas: analyses suggest elevated risk

rochemical plants. "The failure to identify specific agents is a disappointment, but not an insurmountable difficulty," he says.

Although a fear about elevated brain cancer incidence certainly is justifiable, the statements of the two union officials indicate they have already gone from fear, to belief, to plan of action. Here again, their professional commitments more or less make that course inevitable. But it comes when many of the epidemiologists are arguing over whether there is any elevated risk. If the risk is the same as that faced by the general population, it seems a rather striking challenge to the petrochemical industry to improve the workplace.

"I'm puzzled by the widespread nature of the problem [of brain tumor incidence]," says H. Michael Utidjian of Union Carbide. "It seems widespread over many populations and work classes, sometimes extending to white collar workers. I don't know of any other case of occupationally related cancer where it's appeared over such a wide range of workplaces." It is "oversimplistic," he adds, to say conclusively that brain tumors are due to exposures in the chemical industry.

Several epidemiologists have concluded that brain tumor incidence, at least among some petrochemical workers, is not elevated. For example, one such study was conducted by Chi-Pang Wen of Gulf Oil's medical and health resources division of the company's oil refinery in Texas—the same installation included in an NCI survey. Wen says his study "represents the largest retrospective cohort study of refinery workers to date in North America in terms of length of observation (44 years of employment experience) and person-years of observation." And he concludes that "the results indicate no increased risk of brain tumors among workers at this Texas refinery."

He and NCI's Terry L. Thomas (and her collaborators) differ sharply in their conclusions. "Our analyses suggest that refinery workers have an elevated risk of brain cancer," Thomas says. And it's possible that current studies "underestimate" that risk, she adds.

Eventually, their differing conclusions have to be reconciled: They are, after all, looking at overlapping (albeit not identical) populations. Hence, it seems that discrepancies in analytic methods and in deciding what information to include stand in the way of reconciliation.

Yet other epidemiologists, looking at different workplaces, come up with all kinds of puzzling clues. Michael R. Alderson of the Institute of Cancer Research in the U.K. has surveyed eight refineries there and concludes there is no increased risk for brain cancer, although preliminary evidence for increases in malignant melanoma (skin cancer) is being followed up, he says. "But even if you accept some of the U.S. data, the problem of brain cancer is in no way like other hazards."

Hints from other surveys provide a kaleidoscope of incongruent observations. Women more than men employed in the Swedish chemical industry might be at greater than normal risk for brain cancer. Workers in the rubber tire building industry in the U.S. are also at greater than normal risk, says Thomas Mancuso of the University of Pittsburgh School of Public Health. But so are workers in the electrical machinery and also paper (and allied products) industries. And so also are workers in certain segments of the transportation industry, according to epidemiologists at the University of Southern California in Los Angeles.

Epidemiology is very much an outgrowth of clinical medicine. According to one wag, epidemiologic surveys are often really "hunches, shored up with statistics."

However, the fact is that many clinicians have hit upon important medical treatments by following up their hunches. The same phenomenon may be at work among the epidemiologists scrutinizing brain cancer incidence. Hence, the possibility that they are onto something means that their surveys, no matter how preliminary, cannot be disregarded.

All of this close scrutiny also may serve a broader purpose. For example, Selikoff and his colleague William J. Nicholson at Mount Sinai School of Medicine in New York City find evidence of higher incidence for other kinds of cancer besides brain tumors among several groups of industrial workers. "Brain tumors may be 'the canary' for locating other cancer risks," Nicholson says. Thus elevated risks of diseases, such as lung cancer and malignant melanoma, cited by several of the epidemiologists at the New York Academy of Sciences workshop well could prove to be a more significant public health problem than brain cancer. □

Wen: results indicate no increased risk

Many chemicals induce brain tumors in animals

- 2-Acetylaminofluorene
- Acrylonitrile
- 1-Aryl-3,3-dialkyltriazenes
- Azoethane*
- Azoxyethane*
- Azoxymethane
- Butylnitrosourea
- Cycasin
- 1,2-Diethylhydrazine
- Diethylnitrosamine*
- Diethyl sulfate*
- Dimethylbenzanthracene
- Dimethyl sulfate*
- Elaiomycin
- Ethyl methanesulphonate
- Ethylnitrosobiuret*
- Ethylnitrosourea*
- 1-Methyl-2-benzyl-hydrazine*
- Methyl methanesulphonate
- Methylnitrosourea*
- Methylnitrosourethane (intraplacental)
- Procarbazine*
- Propane sultone
- Propylene imine
- Pyrrolizidine alkaloids
- Vinyl chloride

* These chemicals can cross the placenta to induce brain tumors in offspring. Source: Victor Alexander at al. NIOSH

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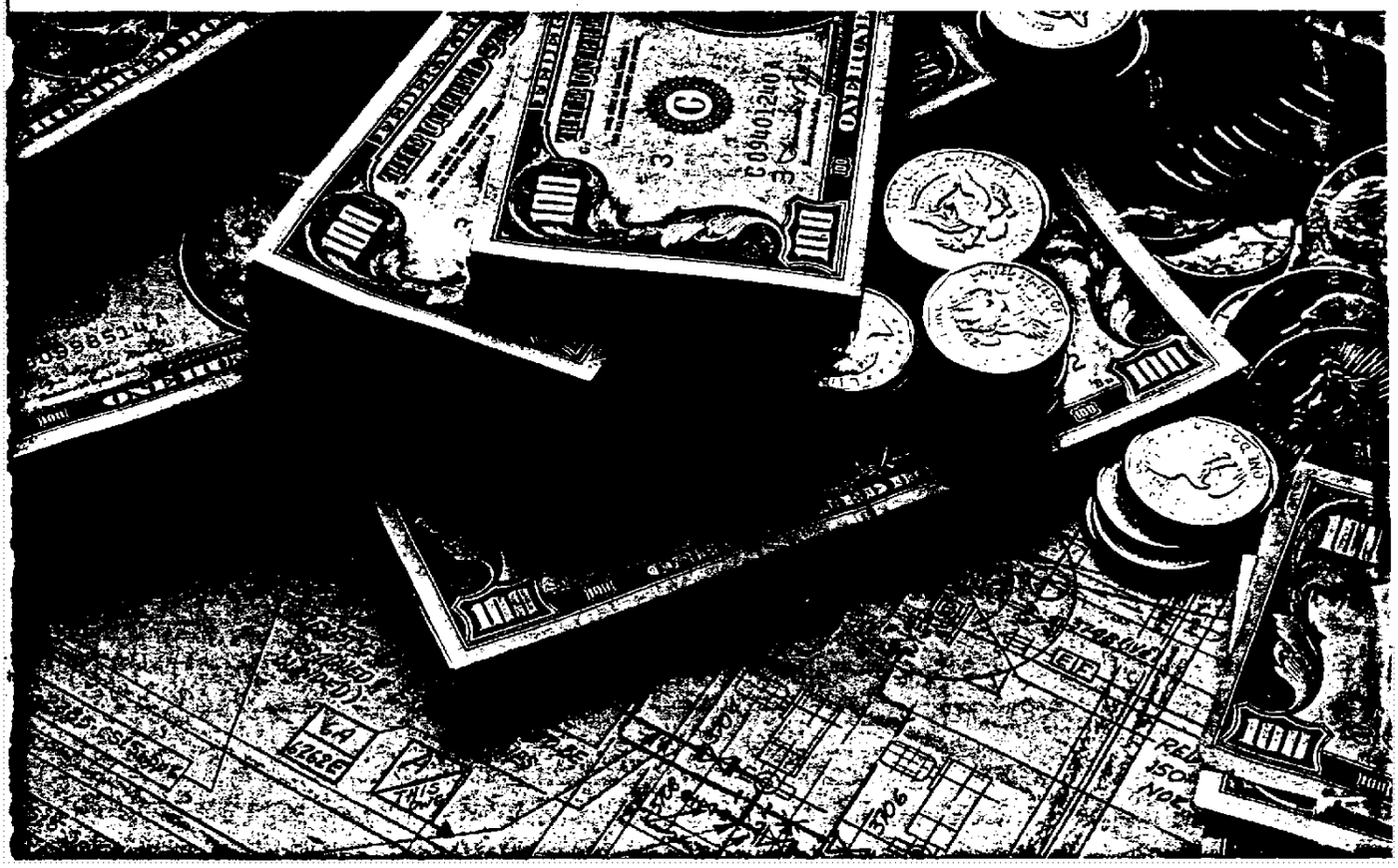

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environment

CPI weighs in with costly toxicology labs

Mobay's new toxicological testing laboratory in Stilwell, Kan., was dubbed a "palace of science" by company board member Karl Buechel at the plant dedication last November. The $6-million, 60,000-sq.ft. facility at Mobay's test farm is only one of a series of "palaces" that chemical companies have been building lately to meet the expanding needs for toxicological testing under developing government regulations.

New labs built by Stauffer, Allied, Monsanto and Shell during the past year have been even more costly. Only very expensive, highly automated precision equipment can turn out reliable, reproducible data from a variety of toxicological tests.

But that hasn't stopped companies like Dow and Du Pont, pioneers in toxic testing, from expanding their facilities. Du Pont is enlarging its Haskell Labs by 30%, at a cost of some $8 million. And Dow is adding 28,000 sq.ft. to the laboratory at its Midland, Mich., plant.

Under Strain: "The rapid escalation of requirements for toxicology data has placed a strain on private and public facilities that conduct toxicology research," explains Konrad Weiss, president of Mobay. "This made it obvious that, from a practical and scientific standpoint, the corporation's requirement in this area could be met only with a new facility."

Why did Shell build a 60,000-sq.ft. toxicological testing lab at its suburban Houston research complex? The company, first among petroleum companies to build such a unit, rattles off a series of reasons: The need for space for long-term animal studies, the improved quality and better scheduling it would provide, the possible opportunity to improve procedures and follow up on testing experiences, and Shell's significant increase in spending for toxic testing made a new lab necessary. Donald Stevenson, director of the Shell lab, says, "Building our own lab was a good business decision."

Stauffer, with its emphasis on agricultural chemicals, had some experience with toxic testing before it built its new 60,000-sq.ft. lab at Farmington, Conn. The company has two labs in California (at Mountain View and Richmond) to do metabolism and acute toxicity testing. "The quality issue was the main reason we built our own lab," says Wayne C. Jaeschke, vice-president for environmental services.

Animal testing at new labs include equipment like this computerized scale at Monsanto.

Going Outside: Having its own toxicological-testing facilities doesn't mean a company does all of its own testing. The range of work done by outside labs runs from 70% by Allied to an "overflow of about 10%" for Dow.

In April 1979 Allied completed a $1.4 million, 17,000-sq.ft. animal laboratory.

'The more in-house work done the more expertise developed at a company'

Another 25,000-sq.ft. lab has been requested from the board. "With the addition, we could take on much of the longer-term studies," says Harry J. Robinson, Allied's vice-president for medical affairs.

Both Monsanto and Shell hope to keep 70% of the testing work in-house. In fact, Monsanto already is studying an addition to its new 47,000-sq.ft. lab in order to stay with that percentage. The $12-million lab, dedicated in the fall of 1978, is expected to reach the 70-30 ratio in the third quarter of this year. Shell will reach it by 1983. Its lab has just started to receive test animals.

"The more in-house work done, the more expertise is developed within the organization and the better understanding a company has of its products," says Roger Folk, director of Monsanto's Environmental Health lab.

Growth Pattern: Charles Reinhardt, director of Du Pont's 113,000-sq.ft. Haskell labs, says that only 20% of the company's toxic work goes to outside labs.

Ground has been broken for the expansion that will increase lab space to 150,000 sq.ft. and staff to 265. The expansion will be completed by the summer of 1981.

Dow, with its $12.4-million/year environmental science and health-data-gathering budget, has decided that its 138,000-sq.ft. toxicology-testing lab at Midland has gotten big enough. The company will be expanding new toxicology-test labs at its Freeport, Tex. plant.

Looking Back: Several of the labs, notably those of Monsanto and Stauffer, were located near universities so that they could overcome expected staffing problems by attracting people to a "learning environment."

Stauffer's Jaeschke says the company has had "good success" attracting scientists. But Monsanto's Folk says staffing has been a major problem. "It's hard to build up the expertise within a group and the communications that make a lab work."

Monsanto also had some major air-handling and temperature-control problems during startup of the laboratory. "The state-of-the-art of humidity control is not there yet," Folk says.

Stauffer's Jaeschke says its lab also had some initial operating problems, but "nothing major." Looking back, Jaeschke would like to have built in more storage and staff space. But he asserts that he is pleased with the decision not to go with a "clean-dirty spaces," as many labs did. He says such a layout is not cost-efficient. Dow's Perry Gehring agrees, saying that a clean-dirty area is a "waste of money."

Stauffer uses limited access as a control. Monsanto's lab is also limited-access, but Folk says any expansion would include a clean-dirty area for long-term testing.

There will probably be more differing views as more chemical companies develop their own toxicological testing labs. It seems to be the wave of the future for the chemical industry. □