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TESTIMONY FILED BY OSHA IN PROCEEDINGS ON GENERIC CARCINOGEN PROPOSAL

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Testimony Filed by OSHA in Proceedings
on Generic Carcinogen Proposal

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SUMMARIES

4/6/78

Patrick J. Lawther and
Robert E. Waller

Title:

Patrick J. Lawther -- Professor of Environmental and Preventive Medicine and Director of the Medical Research Council Air Pollution Unit, St. Bartholomew's Medical College, University of London.

Robert E. Waller -- Staff, Medical Research Council Air Pollution Unit, St. Bartholomew's Medical College, University of London.

Number of Pages:

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Main Points Addressed:

(1) Consideration of dose-response in extrapolating animal test results to man.

(2) Accounting for interactions between agents in assessing carcinogenic risk.

(3) Retrospective epidemiological studies may be helpful in identifying potential carcinogens.

Summary:

The testimony begins with an admission that not much time was spent considering OSHA's proposal.

The testimony implicitly criticizes OSHA's proposal for not considering dose-response effects in classifying substances on the basis of animal experiments:

> "Many substances may yield tumours in animal experiments if applied in massive quantities, but it does not necessarily follow that these pose detectable risks to humans in the circumstances in which they may be exposed occupationally."

4/6/78

David G. Hoel

Title:

Acting Scientific Director, National Institute of Environmental Health Sciences.

Number of Pages:

10

Main Points Addressed:

The need to use animal tests and quantitative risk assessment in identifying human carcinogens.

Summary:

The thrust of the testimony deals with the rationale for using both laboratory animal experimentation and quantitative risk assessment in identifying human carcinogens. Quantitative risk assessment is necessary because there are some cancers which result from somatic mutation of a single cell and there is a broad range of potencies among carcinogens. Thus, risk must be assessed "at low exposure levels in order to have a rational standard setting and methodology."

The testimony continues by examining in-depth the theoretical basis of various models for quantitative risk assessment. A discussion of Cornfield's recent work is included.

The testimony concludes by stating, "In gathering empirical evidence for the qualitative predictability of animal studies for man careful use of epidemiological evidence is needed."

One of the most difficult problems in assessing carcinogenic risk of a substance is the substance's interaction with other agents. For example, there is evidence that risk of lung cancer from exposure to asbestos is much greater for cigarette smokers. Thus, "risks within a large industry can often be most effectively assessed by making comparisons within the work-force between groups with graded exposures to a suspect agent, and these comparisons may be more revealing than those made with control populations outside the industry."

Although for most substances there is little or no human evidence upon which to base an assessment of carcinogenesis, the testimony indicates support for retrospective epidemiological studies where sufficient data is available.

4. Specific comments on OSHA proposal:

(i) Category I. Single long term test relevant if "unambiguously" indicates induction of malignancy. Position on short term tests in Category I should be clarified. Good screening device but no consensus as to whether they validate or replace long term tests. If positive result strengthens long term test, does negative result weaken it?

(ii) OSHA should not ignore injection site sarcomas and should not insist on exposure by same route as humans.

(iii) Category II. "Suggestive evidence" should be clarified.

(iv) Category III. "Meager evidence" should be clarified.

(v) Category IV should be eliminated. Put a carcinogenic substance in Category I whether or not found in U.S.

Lorenzo Tomatis

Title: Chief Unit of Chemical Carcinogenesis, International Agency for Research on Cancer
Lyon, France.

No. of Pages: Statement 6 pages. Extensive attachments.

Main Points:

1. Environmental factors and human cancer.

2. Contribution of experimental data for implementation of primary prevention of cancer.

3. Implementation of primary prevention of cancer.

Position: Although OSHA proposal needs refinement and clarification, it represents "an extremely valuable contribution to the implementation of primary prevention of cancer."

Summary

1. Percentages of cancer attributable to environmental factors intended to show:

(1) variations in different countries which suggest environmental risk factor although species not identified.

(ii) risk factors identified.

Most important are those substances identified as carcinogenic because intervention possible.

Survey of 368 selected chemicals revealed positive association of exposure with 26 chemicals or processes. In the majority of cases exposure occupational. Risk may extend beyond the 26.

Reasonable to conclude the "maximum precaution should be taken where risk greatest." However, survey of laws of 14 countries showed widely varying degree of regulation.

2. Generally agreed exposure "to recognized human carcinogens should be avoided or drastically reduced." Differences in regulation reflect differences in extrapolating human risk from animal data. Experimental data per se can contribute to primary prevention of cancer.

3. Primary prevention of cancer can be implemented on human epidemiology without waiting for experimental confirmation of specific chemical. Experimental data also valid for regulation.

4/6/78

Anders Englund, M.D.

Title:

Director, Bygghalsan, The Foundation for Industrial Safety and Health in the Construction Industry, Sweden.

Number of Pages:

8

Main Points Addressed:

(1) The necessity of relying upon animal studies for determining carcinogenesis.

(2) Exposure limits should be set as low as technologically feasible.

(3) Use of engineering controls should be given preference.

(4) A general discussion of the environmental and medical monitoring requirements.

Summary:

While admitting a lack of expertise regarding extrapolation of animal data to man, the testimony supports the general use of such data because of the inherent difficulties and time delays associated with epidemiological studies.

Exposure to carcinogens should be as low as feasible. Although the testimony lists economic considerations as part of the "feasibility" equation, it speaks approvingly of Sweden's experience with limiting exposure to asbestos to such an extent that asbestos use is currently negligible.

The use of engineering controls should be preferred by OSHA and is in accordance with the ILO Convention and Recommendation on Prevention of Occupational Cancer adopted in 1974.

The medical surveillance and recordkeeping requirements in OSHA's proposal are necessary to provide human data for epidemiological studies. In addition the medical surveillance requirements may aid in early detection of cancers, although the significance of this benefit is questionable.

4/6/78

John W. Berg

Title:

Associate Director for Epidemiology and Statistics, Colorado Regional Cancer Center

Number of Pages:

27

Main Points Addressed:

(1) Epidemiologic studies justify a serious concern for occupationally-related cancer.

(2) Scientific as well as ethical considerations demonstrate the impropriety of relying upon human data for initiating controls over exposure or for setting PELs.

(3) The requirements for an "adequate" negative epidemiological study.

(4) The need for specifying uses for the information generated under the recordkeeping requirements.

Summary:

Death rates are a poor basis for evaluating cancer incidence due to erroneous diagnosis by physicians signing death certificates, and improvements in treating cancers. Data from the Third National Cancer survey demonstrates that there have been "important increases in cancer risk in many sites, especially in men," and apparently increases in occupational risk is one cause.

If consideration is limited mostly to mortality statistics, there remains substantial evidence of special cancer risks for many kinds of workers.

The testimony provides a lengthy review of the evidence that the causes of many cancers are multiple. One study is said to indicate that the higher incidence of urban lung cancer is due to occupational exposure. The point of the discussion is that there are "many ways industrial exposure can act to increase cancer risk in vulnerable people and vulnerable tissues."

Trained epidemiologists with significant experience are few and sources of data are poor. Therefore, even for substances in long use, animal tests must be relied upon for predicting carcinogenesis.

OSHA should recognize and act upon any adequate negative epidemiological studies. However, the studies being reported or relied upon by industry are not adequate. The studies tend to rely upon improper or insufficient data, such as accounting only for deaths of workers who are on the payroll at the time of death. The criteria for a proper negative study is provided.

It makes much greater sense for OSHA to plan analyses of data obtained through recordkeeping requirements before the accumulation of masses of data begin. Numerous recommendations are made regarding the collection and use of data, including creation of "an area registry" or "a highly structured care system reaching retired workers and day workers."

4/5/78

Elizabeth K. Weisburger

Title:

Chief, Carcinogen Metabolism and Toxicology Branch, Carcinogenesis, Division of Cancer Cause and Prevention, National Cancer Institute

Number of Pages:

4

Main Points Addressed:

Metabolization of carcinogens by humans as compared with experimental animals.

Summary:

The testimony begins by noting the differences in types of exposure to carcinogens (quantity/duration/frequency) to which chemists are subjected, to that of industrial workers. For both groups, greater than normal cancer incidence is indicated.

After a very brief and disjointed review of several studies, the testimony states that the "data suggest that humans can metabolize and thus activate chemical carcinogens by similar mechanisms as experimental animals".

The testimomy concludes with the following recommendation:

> Because of the heterogeneous background of humans, one should assume that individuals belong to the most sensitive group, in order to insure an adequate margin of safety. Thus, assuming one is dealing with very sensitive individuals, exposure to foreign compounds such as carcinogens or other noxious agents should be kept as low as technologically possible.

4/5/78

Darrel D. Douglas

Title:

Leader, Respirator Research and Development Section, Los Alamos Scientific Laboratory

Number of Pages:

8

Main Points Addressed:

The use of respirators for protection from carcinogens where engineering controls are not sufficient.

Summary:

The testimony begins by emphasizing that respirators are generally a secondary means of control. The use of respirators present many problems; particularly proper facial fitting due to the variation in face shapes, shape changes caused by facial movements, and interference from facial hair. Respirators have been designed for male facial configuration and, therefore, fitting women is particularly difficult. In addition, use of respirators creates communication, vision, hearing and efficiency problems.

Although use of respirators may be required regardless, at least for some employees, engineering controls should be used to reduce exposure to lowest levels feasible:

(i) reduce number of employees using respirators;

(ii) lower exposure levels allow use of less confining and easier to use respirators; and

(iii) lower exposure levels reduces potential exposure for employees not properly fitted.

Where respirators must be used, they should be chosen from a respirator selection table to be published with each standard. A discussion of the analysis necessary to compose and use such a table is provided. Modifications are proposed for one component of this analysis, the Protection Factors for Respirators developed by E.C. Hyatt.

Finally, the testimony recommends that OSHA require the isoamyl acetate test as part of the procedure for testing the respirator face seal during fitting.

4/5/78

S. John Bvington

Title:

Chairman, Consumer Product Safety Commission

Number of Pages:

1

Summary:

OSHA is praised for its "pioneering effort" and supported for its efforts in establishing a generic regulation. The CPSC is developing a similar set of regulations for carcinogens in consumer products. The CPSC pledges to continue working through the Interagency Regulatory Liaison Group to develop a uniform federal policy.

4/5/78

Duncan A. Holaday

Title:

Sanitary Engineer Director, Public Health Service

Number of Pages:

13

Main Points Addressed:

(1) The need for reducing exposures through use of engineering controls.

(2) The need for monitoring at least as frequently as required in OSHA's proposals.

(3) The need to fully regulate all mixtures.

Summary:

The testimony is unusually general in discussing the need for regulation, appropriate controls, monitoring, employee education and training, and the posting of signs. Brief references to practical experience is used frequently as support for the positions proffered.

Depending on the work to be performed and the hazard presented, engineering, work practice and protective clothing controls should be utilized. However, it is "standard industrial hygiene doctrine" to reduce exposure below PELs by use of engineering and work practice controls, with preference to engineering controls.

All workers exposed to the possibility of skin contact with a Category I substance should be provided special clothing by the employer designed to protect against the particular substance. Where protection against skin contact is necessary, protection against eye contact is necessary. Gas and vapor tight goggles are not yet perfected.

The requirement for monthly monitoring where the PEL is exceeded is supported in the testimony. In fact, "standard industrial hygiene practice would be to conduct even more frequent monitoring" in order to determine what measures need be taken to reduce exposure below PEL.

The requirement for quarterly monitoring where PEL is not exceeded is a "minimum" requirement. Statistical data developed by NIOSH indicates that the predictability of employee exposures based on one day's monitoring extends only for 30 days. Also, seasonal changes such as prevailing winds and rain patterns may increase exposure above PEL.

Periodic re-training of workers is necessary to assure that workers are aware of dangers, follow proper procedures, and understand the need to report any breaches of procedures or other unusual dangers.

A percentage exemption from the proposed regulations for mixtures should not be allowed. "[N]o practical way exists to determine the atmosphere concentration of a substance when it volatizes other than by taking air samples and analyzing them".

4/5/78

Robert L. Harris

Title:

Professor of Environmental Engineering, School of Public Health, University of North Carolina

Number of Pages:

27

Main Points Addressed:

(1) The uses of monitoring results.

(2) Analytical techniques for monitoring and the need for an "action level" concept.

(3) The need for recordkeeping regarding environmental monitoring to aid physicians treating workers and to establish or disprove causal links between exposures and illnesses.

Summary: The statement discusses the short and long-term uses of monitoring results. The short-term uses are (1) determining the need for continued monitoring, (2) assessing the adequacy of engineering controls and work practices, (3) judging the need for respiratory equipment and selecting such equipment, and (4) advising employees regarding their exposures. The long-term uses include assessing the health consequences of various work situations.

The statement does not discuss specific equipment, sampling techniques or laboratory analytic techniques or procedures.

The monitoring frequency provisions in OSHA's proposal are described as "reasonable". The requirement for quarterly monitoring where initial monitoring demonstrates exposure below the PEL is supported as a "minimum, [which] has the desirable characteristic of at least one series of measurements during each season of the year thus accommodating different comfort ventilation regimes and any seasonal changes in processes or production rates".

In conducting any monitoring, efforts "should be made" to specifically monitor individual workers judged to have the highest exposure.

The testimony provides an extended explanation of the methods for analyzing sampling results for determining compliance with exposure limits set forth in "Statistical Methods for the Determination of Noncompliance with Occupational Health Standards", a NIOSH Technical Information Document, and a comparison publication by Bar-Shalom, Segall, and Budenars, "Decision and Estimation Procedures for Air Contaminants". It is recognized that exposure levels fluctuate during a day and from day to day" and the ramifications of this fact upon regulatory monitoring requirements is discussed:

> Recognition that there are excursions in concentrations in workplaces suggests the setting of ceiling values with some specified frequency (for example 1 short time sample in 20) for which it is permissible for that level to be exceeded. This approach has been taken for determining whether compliance with, or violation of, community air quality standards occurs. Statistical methods are available for dealing with extreme values in defined frequency distributions in such cases. Such ceiling values along with daily mean permissible limits can define and limit high intermittent exposures as well as average exposures, and can be set to be protective of health in the same way as are absolute ceiling values. They have the additional merit of permitting design of rational monitoring programs for determination of compliance and have the capability of compliance with some specified level of confidence.

The greater the amount of reliable data, i.e., the greater the frequency of monitoring, the greater will be the statistical confidence regarding average levels of exposure. Thus, exposure levels near the PEL require more sampling to demonstrate compliance than do exposure levels well below the PEL. Many substances may be present in the workplace only in trace amounts. Thus, the monitoring provisions in OSHA's proposal should be modified to provide for an "action level" concept for determining when a monitoring program should be instituted or relaxed. Specific operation of the "action

level" concept is explained.

The requirements for detailed recordkeeping of monitoring results in OSHA's proposal will aid physicians treating workers and will help establish or disprove causal links between exposures and illnesses.

For various reasons, the testimony supports the recommendation for employer education in the June, 1977, National Research Council Report, "Informing Workers and Employers about Occupational Cancer".

4/5/78

Robert D. Soule

Title:

Associate Professor of Industrial Hygiene,
Indiana University of Pennsylvania

Number of Pages:

14

Main Points Addressed:

(1) The inability of science to provide any method for setting safe exposure levels.

(2) The need to set PELs at the lowest engineering or technologically feasible level.

(3) The control of exposure through engineering controls, including substitutes.

(4) The need for detailed recordkeeping regarding environmental and medical monitoring.

Summary:

The statement begins by stating that, although the industrial hygiene profession has adopted "Threshold Limit Values" for substances based on dose-response data, even where an apparent dose-response relationship has been established for a substance, "the extrapolation of data to threshold or no effect levels is virtually impossible because of the lack of credible mechanisms for predicting them". On this basis zero exposure of workers is recommended as a goal. Presently, PELs should, where necessary, be technology-forcing. Also, recommendations are made regarding the use of, and relationship between, time weighted averages and ceiling exposure limits in setting PELs.

The statement recognizes that PELs are somewhat controlled by monitoring capabilities. However, with few exceptions, e.g., asbestos, the engineering or technological feasibility of controls, and not the

sampling/analytical feasibility, will be the determining factor in setting PELs.

The current state of monitoring technology and preferred monitoring methodology is briefly reviewed.

Three different types of sampling methods are ranked, with preference given to "sampling conducted in the individual's breathing zone". The statement fully supports the monitoring frequency provisions in OSHA's proposal upon the grounds they will provide an adequate record of workers' exposure and will detect abnormal exposure resulting from equipment or procedural failures.

The statement ranks in order of preference engineering controls (preventing release of contaminants), work practice controls (designed to minimize exposure), and personal protective equipment (prevention of exposure). Different types of controls within these classifications are also discussed and ranked, particularly for engineering controls. Thus, the use of a substitute substance is ranked as the best engineering control since it eliminates exposure to the carcinogen.

The criteria for determining the feasibility of substitutes is also discussed. Generally, where use of a substitute will allow production of a "reasonably comparable product", exposure to the more hazardous substance should not be allowed. No economic factors were stated as criteria used in reaching such a conclusion.

The statement recommends detailed recordkeeping of environmental and medical monitoring as an aid in assessing individual workers' exposures and whether there are any ill-effects from such exposures; and for evaluating the effectiveness of engineering controls and judging compliance with applicable occupational safety and health standards.

4/5/78

Bruce J. Held

Title:

Group Leader, Safety Science Group, Lawrence Livermore Laboratory, University of California

Number of Pages:

13

Main Points Addressed:

The use of respirators; their limitations, selection and cleaning.

Summary:

The statement begins by emphasizing "the desirability of controlling exposures to carcinogins or any toxic material by means of engineering methods". Respiratory protective devices are stated to be limited in value due to fitting, communications and vision problems; the increase in worker fatigue and reduction of efficiency with their use; the inability of some persons due to health to wear a respirator; the inability to monitor effectiveness until after use; the short effective life and common failure of sorbent-type canisters to prevent exposure from gas or vapor-type carcinogens; and the difficulty with having employees use respirators properly.

The statement fully supports the provisons in OSHA's proposal governing selection of respirators in those circumstances where respirators must be used. Specifically, respirators should be chosen according to "protection factors" ("a quantitative measurement of the leakage of an air contaminant into the facepiece of a man performing certain exercises"), corresponding to the level of air contaminant from which the worker is to be protected. The statement supports OSHA's development of a Protection Factor Table and Respirator Decision Logic Table for directing employers in selecting respirators. A statement of the respirator decision logic is provided.

The statement describes the respirator program requirements currently provided in OSHA regulations as "minimum" requirements. Recommendations to employers regarding the best procedures for operating

a respirator program consume several pages of the statement. Quantitative fitting is said to be "by far the most accurate and satisfactory", and it is suggested that this be required.

4/5/78

WILLIAM LIJINSKY

Title:

Director, Chemical Carcinogenesis Program,
Frederick Cancer Research Center

Number of Pages:

33

Main Points Addressed:

(1) Science's lack of knowledge about cancer etiology.

(2) The necessity of erring on the side of caution and safety.

(3) The necessity for government action based on industry's past failures to act responsibly.

Summary:

The thrust of this testimony is that there are so many unknowns with respect to cancer that we must err, if at all, on the side of caution.

As a starting point, the testimony points out industry's past failures to act (e.g., vinyl chloride, kepone, pbb) as justifying government action.

The testimony notes that while there are difficulties with animal experiments, there is no alternative but to rely heavily on them. Past experience with animal and human carcinogens provides no reason to assume man is exceptional or different from animals in his response to carcinogens.

Since animal experiments can't be designed precisely enough to extrapolate from the effects of relatively high doses to the effects of low doses, the shape of the dose response curve must be assumed to be that which affords the greatest protection to man.

Animal tests may, in fact, understate the risk since variations in human response are probably greater than in genetically-related animals. Further, man is exposed to multitudes of carcinogens while an animal is exposed to only a single carcinogen.

There are many unknowns in addition to those noted earlier. Science knows little about the role of promoters or initiators in man. We don't know how many molecules are necessary to cause a cancer. Further, we know little about species and organ specificity. While specificity differences may be due to metabolism and physiology, we don't know enough to make assumptions with regard to man.

All of the foregoing demonstrates the impossibility of predicting anything from positive animal tests other than that the substance poses a carcinogenic risk to man. There is no way in which the risk can be quantified even imprecisely. Where, therefore, the substance is of little or no value, it should be banned; where there is value, exposure should be reduced to the lowest level feasible. (There is a brief reference later in the testimony to risk benefit analysis.)

The testimony then discusses bioassay testing guidelines. Quality variations in all types of testing are recognized. The use of the mouse is defended as is the use of maximum tolerated doses. The limited number of animals which can practicably be used and their relatively short lifetimes is again cited as one of the statistical insensitivities of animal tests. The testimony notes that two species should be used because one may be refractory to the substance under test.

With respect to short-term tests, the testimony states:

> "Recently there has been a demand for development of a variety of short term tests which could be used for screening of substances for carcinogenic potential, so that those with the highest potential could be allocated to the expensive animal test. Many of these tests, most notably the bacterial mutagenicity test developed by Ames, appear promising until subjected to validation against large numbers of compounds of known carcinogenicity, when discrepancies appear which make the tests less reliable as an indicator of carcinogenicity and quite useless as a predictor of risk. While the correlation of the 'Ames' test with carcinogenicity is qualitatively fairly good, al-

though there is a disturbing number of carcinogens which are negative in the test (non-carcinogens which are positive are not worriesome except that they add confusion), there is no convincing correlation between carcinogenicity in animals and mutagenicity in bacteria. However, a correlation between the two biological activities would hardly be expected."

4/5/78

BENJAMIN VAN DUUREN

Title:

Professor, Environmental Medicine, New York University Medical Center

Number of Pages:

11

Main Points Addressed:

(1) The use of structural similarity to known carcinogens.

(2) The routes of exposure in animal experiments.

(3) "Safe" or "no-effect" levels.

Summary:

Evidence of a structural similarity between a known carcinogen and a substance in combination with positive results in a single mammalian species or in several short-term tests should be sufficient to place the substance into Category I. CMME, BCME, and TCE are cited and discussed as classical examples of the utility of structural information.

Positive results following subcutaneous implantation in the absence of local tissue damage or other toxic effects should not be ignored by OSHA.

There is no method for accurately determining a safe or no-effect level for a carcinogen. Certain evidence indicates that even a single small dose can irreversibly damage cells, making them cancer prone.

The two-step process of initiation and promotion may be triggered by man's continuous exposure to cigarette smoke, a complex mixture of organics which contains both initiators and promoters.

4/5/78

M. ADRIAN GROSS

Title:

Associate Director for Pre-clinical Investigations, Division of Scientific Investigations, Bureau of Drugs, Food and Drug Administration

Number of Pages:

16

Main Points Addressed:

(1) Proper approach to measurement of statistical significance and risk assessment.

Summary:

This testimony suggests that OSHA adopt the Mantel/Bryan approach to measurement of statistical significance and risk assessment. This approach is particularly to be preferred to the more conservative approach offered by Crump which OSHA cites in its preamble.

In addition to being sounder and based on hard data, the Mantel/Bryan approach will encourage better animal tests. Indeed, the testimony suggests industry be permitted and encouraged to conduct animal tests utilizing its own protocols.

OSHA should build in quality control provisions for testing, particularly insofar as contract laboratories are concerned.

Finally, the testimony expresses support for OSHA's position on benign tumors and its use of decreased latency period as a classification criterion.

4/5/78

RICHARD BATES

Title:

Associate Commissioner for Science, Food and Drug Administration

Number of Pages:

26

Main Points Addressed:

(1) Unknowns with respect to cancer.

(2) Value of animal tests and meaning for man.

(3) Thresholds

Summary:

The thrust of the testimony is that while much is not known, there are few certainties and the debate will continue, responsible government must move forward, and if it must err, err on the side of caution.

It is often necessary to control exposure for which there is some evidence of hazard before that evidence has reached the point scientists would universally regard as conclusive.

Development of disease in an individual is the result of many factors, including heredity, environment, nutrition, age, and health over which we have varying degress of control.

The incidence of disease can be reduced either by reducing exposure to causative agents or through measures that reduce the level of susceptibility. We, unfortunately, have little control over the latter.

Animal tests are a useful indication of carcinogenic potential. Unfortunately, we can't yet use the results of animal experiments to precisely predict the effect on man. Although we are aware of the variables, we can't yet precisely measure them. Maximum tolerated doses are necessary to

enhance bioassay sensitivity. Scientific debate continues on the relevance of benign tumors, but prudence suggests one err, if at all, on the side of caution.

Although a variety of mechanisms may exist for cancer and there may be a basis for sorting out mechanisms having differing levels of risk, this is a most difficult process given our present knowledge.

There may be evidence to suggest that risks are lower at lower doses but there is no convincing evidence for the general concept of thresholds.

4/5/78

DONALD KENNEDY

Title:

U.S. Commissioner of Food and Drugs

Number of Pages:

13

Main Points Addressed:

(1) Extrapolation of animal data to man.

(2) Thresholds

(3) Quantitative risk assessments

Summary:

The OSHA proposal is commendable because it spells out how the agency intends to deal with carcinogenic substances and because it provides a consistency to regulatory decision-making. The FDA is incorporating similar systems into its regulations.

OSHA and the Interagency Regulatory Liaison Group are coordinating their activities.

The general policy of limiting worker exposure to the extent technically feasible and, where possible, elimination of exposure are endorsed by FDA.

Animal data present a sound basis on which to make decisions, but the data must be adequate and of good quality. One can't rely on poorly designed or conducted animal experiments. Quotations are taken from several FDA decisions and other sources to support some of the following positions.

(1) Single species results are sufficient to indict a substance.

(2) Use of maximum tolerated dose is appropriate.

(3) Replication of positive carcinogenic responses reduces the likelihood of false positives.

(4) Human epidemiology studies suffer from a lack of sensitivity in detecting associations and thus must be viewed cautiously.

At present it is not possible to ascertain safe levels. The problem is further complicated by synergism and the multitude of carcinogens to which the population is exposed.

Because of differences in potency and exposure, OSHA should use quantification of risk as a component of decision-making. No particular method is suggested.

4/5/78

CURTIS HARRIS

Title:

Head of the Human Tissue Studies Section, Experimental Pathology Branch, Carcinogenesis Research Program, Division of Cancer Cause and Prevention, National Cancer Institute

Number of Pages:

7

Main Points Addressed:

(1) Extrapolation of carcinogenesis data to humans from short-term bioassays of carcinogens in cultured human cells and tissues.

Summary:

This testimony describes on-going work at NCI which is directed at a better understanding of the interaction of chemicals with cultured human tissues and cells. This kind of work will aid in the qualitative assessment of the carcinogenicity of chemicals. Among the possibilities of such studies is a comparison of human and animal models. One of the lessons already learned is the wide interindividual variation in oncogenic susceptibility of human tissue. Certain similarities in human and animal tissue effects have also been detected.

4/5/78

ARTHUR UPTON

Title:

Director, National Cancer Institute

Number of Pages:

18

Main Points Addressed:

(1) Multi-causal nature of cancer.

(2) Need for reduced worker exposure to carcinogens.

(3) The necessary role of animal tests.

(4) Principles which guide the NCI Bioassay Program.

(5) Criteria for assessing human carcinogenic risks from animal test results -- single species criterion.

Summary:

Cancer has many causes, many of which are cited in the testimony.

Because no single chemical has yet been identified as a cause of cancer in the general population does not mean chemical pollutants are a minor cause of cancer. Long latency periods and the lack of records make analysis difficult.

Despite difficulties with epidemiology studies, a few dozen chemicals have been identified as posing a carcinogenic risk.

The degree of protection warranted to reduce occupational carcinogenic risks depends on economic and social considerations (which the testimony does not address).

The following four principles utilized for radiation hazards should be equally applicable to hazards from chemicals.

"1. Any exposure to ionizing radiation is considered to pose some risk of increased cancer incidence.

2. At low exposures, the excess risk is considered likely to be proportional to the increase in exposure (relative to background).

3. 'Permissible' exposures to radiation are to be set as low as is readily achievable (reflecting a judgment that no increase in radiation exposure that is unnecessary or does not involve a benefit is socially acceptable).

4. Stricter standards are to be set for 'involuntary' exposure (e.g., general population exposure to radiation) than for deliberate exposures (e.g., diagnostic or therapeutic uses of radiation) where tangible benefits accrue to the person assuming the risk."

Animal tests must be used to assess risks because of the difficulties of studying man.

The principles which guide the NCI bioassay program, developed following recommendations of the Panel on Carcinogenicity of the International Union of Cancer, are discussed.

Compromises between cost and sensitivity are noted in discussions of the two species criterion (rat and mouse) and the design of the experiment. The use of maximum tolerated dose is vigorously defended as essentially a "screening procedure" to identify those chemicals with the potential to cause cancer not to measure the frequency of cancer at a particular level. There is no evidence that a chemical which is carcinogenic at high doses would not also be carcinogenic at lower doses. Interpretation of bioassay test results often raises difficult problems which require evaluation by experienced professionals in several disciplines. A "formula" for such interpretation will not do.

There is general agreement on the methods for conducting carcinogen bioassays in rodents. Even the

best-designed tests are, however, statistically insensitive and hence may fail to detect weak carcinogens.

A substance (or mixture) which is found to be carcinogenic in animals should be assumed to at least have the potential to induce cancer in humans also. This is a widely accepted view premised on the following:

"1. All the chemicals demonstrated to cause cancer in humans, with the probable exception of arsenic, are known to cause cancer in animals, although they often act at different sites.

2. Most chemicals shown to induce cancer in one mammalian species also induce cancer in other mammalian species when properly tested. Although there is often much variation in susceptibility from one species to another, there are few, if any, adequately-documented cases of species-specific carcinogens.

3. The pathological development of tumors in various species of animals, including man, is similar; there are laboratory animal models for most types of human cancer.

4. There is evidence that the mechanisms of molecular interactions of many carcinogens with target cell macro-molecules are the same in several animal species and in humans. At this fundamental level of biological organization, there is no reason to expect qualitative differences in response between species."

The use of the mouse as a test animal is defended. It has been universally endorsed by experts and regulators; it is a good model for at least certain types of human cancers; several agents known to be carcinogens in man also induce mouse tumors; a great deal is known about the mouse, particular mouse strains and their differing characteristics.

The argument that less weight should be placed on results obtained in strains with high spontaneous tumor incidence is rejected. Although causation may

logically not be "proven" between the carcinogen and the tumors in such situations, we should not await such "causation" evidence (which may be unobtainable at present) to act.

Distinctions between carcinogens, enhancing agents, causation agents, and co-carcinogens are not relevant when ascertaining hazards to human health.

A reproducible carcinogenic response in any single species is sufficient to describe the compound as a carcinogen and a potential threat to humans. A positive second species finding is not necessary. Negative results in second or third species do not establish the agent is not a potential threat for humans.

4/5/78

LAWRENCE FISHBEIN

Title:

Assistant to the Director for Environmental Surveillance, National Center for Toxicological Research, Food and Drug Administration

Number of Pages:

8

Main Points Addressed:

(1) Structure-activity similarity to known human carcinogens.

Summary:

OSHA should not foreclose consideration of the growing body of structural and metabolic similarity information. Other agencies, such as EPA, have stated at least their intent to use structural similarity as a priority-setting tool.

Positive results in a single animal species coupled with structural similarity to a known carcinogen or group of carcinogens should be sufficient to place a substance in Category I. Multiple short-term tests and structural similarity should place a substance in Category II.

4/5/78

BERNARD GOLDSTEIN

Title:

Associate Professor, Departments of Medicine and Environmental Medicine, New York University Medical Center

Number of Pages:

5

Main Points Addressed:

(1) Validity of use of animal test systems.

(2) The role of short-term tests.

(3) Dose-related risk assessment and varying potency.

(4) The costs of cancer care.

Summary:

There is a sound basis for testing in animal models to assess risk to man. With the possible exception of arsenic and benzene, all human carcinogens are animal carcinogens. These two exceptions do not discredit animal tests. Indeed, there is some evidence suggesting even these two substances may be animal carcinogens.

There is a strong conceptual basis supporting OSHA's use of short-term tests to support animal test results.

OSHA should make greater use of dose-related risk assessment. The regulatory response should not be identical for substances found to cause cancer in species at significantly different doses.

The costs of cancer care and treatment are very high and getting higher.

4/5/78

JOYCE McCANN

Title:

Professor, Biochemistry Department, University of California (Berkeley) (?)

Number of Pages:

32

Main Points Addressed:

(1) The role of short-term tests.

(2) Quantitative human risk extrapolations from animal carcinogenicity tests.

Summary:

(1) Current knowledge amply justifies using short-term tests within a regulatory framework aimed at identifying and regulating potential human carcinogens.

(a) The scientific evidence available strongly supports OSHA's proposed use of short-term tests.

(b) Potential errors can be minimized, and the usefulness of short-term tests maximized by using appropriate batteries of tests.

(c) In certain cases some kind of interim regulation (unspecified) based solely on short-term test data might be justified.

(2) Quantitative human risk extrapolations from animal carcinogenicity tests can be useful within the lowest feasible level framework proposed by OSHA.

(a) There may be examples where "feasibility" and acceptable risk are quire incompatible.

(b) Risk estimates can be wrong by an order of magnitude, or even more, and still be useful as rough estimates in determining if the lowest feasible level is compatible with acceptable risk.

(c) Although the data are not extensive, they indicate that carcinogenic potencies of chemicals in rodents and in humans are roughly similar.

(d) For use in low dose extrapolations, a linear dose response, even though uncertain, is the most reasonable assumption consistent with the use of risk assessment calculations for the purpose of determining upper limit estimates.

(e) Although risk estimates can be useful within the context of the lowest feasible level approach, they should not be used to set exposure levels higher than the lowest levels feasible.

(3) The degree of uncertainty associated with results of carcinogenicity tests varies widely, and this should be considered in designating substances Category I or II. Additional criteria for categorization might include the number of dose levels administered and the commonness of the tumor. Positive results involving several dose levels and rare tumors might not need confirmation to be deemed Category I whereas a single dose level result might need confirmation by short-term tests.

Melvin D. Reuber

Title: Employed NCI Cancer Research Center
Frederick, Maryland

No. of Pages: 2 plus attachments

Main Point:

Criticism of "Mouse Hepatic Neoplasia" as biased and inaccurate report of 1974 conference.

Position: Mouse is a good test animal.

Summary

1. The conference on which "Mouse Hepatic Neoplasia" is based was biased in two ways: failure to invite experts on mouse and publication without clearing editing with authors.

2. Based on my experience neoplastic lessions of the liver can be reliably diagnosed and provide a valid index of human carcinogenic risk.

3. This view shared by "specialists" at NCI and IARC.

David G. Kaufman

Title: Associate Professor of Pathology and of Biochemistry and Nutrition, N.C. School of Medicine. Attending associate Pathologist, N.C. Memorial Hospital, Chapel Hill, N.C.

No. of Pages: 24 plus attachments.

Main Points:

1. Synergistic effects, co-carcinogenesis and modulating factors in chemical carcinogenesis.

2. Individual variability in susceptibility.

3. There should be separate regulations for labs.

Position:

Summary

1. Kaufman describes at length experiments he has conducted and reported experiments in which exposure to two substances, one of which may not be carcinogenic or to two carcinogenic substances increases the yield of tumors and shortens the latency period. Thus the dose of the carcinogen itself may not serve to characterize the risk to which the organism is susceptible. The actual risk may be influenced by factors that need not be carcinogenic.

2. Kaufman describes his and other experiments which demonstrate Vitamin A deficiency permitted more extensive binding of Benzo-a-Pyrene (BaP) and other chemicals to DNA in hamster cells.

Human genetic inheritance has role in determining risk:
xeroderma pigmentosa
atoxia telagiectasia
Fanconi's anemia
familial polypsos of the colon

Inbred animal species also show greater susceptibility to binding BaP to tracheal DNA. Experiments with human cells show variation in susceptibility.

3. Kaufman describes different kinds of labs and lab techniques. He favors separate regulation for labs.

Harold L. Stewart

Title: Scientist Emeritus of National Institute of Health.

No. of Pages: 5 (single space) plus many attachments.

Main Points:

1. No threshold: exposure to carcinogens should be zero.

2. Long extracts from report of ad hoc committee on testing for environmental chemicals (NCI 1973) of which Stewart was chairman.

Position: The general principles of chemical carcinogenesis recited in OSHA proposal are scientifically sound and rationally based.

Summary

1. Because of long latent period, variations in individual susceptibility and exposure to many agents, it is not possible on the basis of animal data to determine a threshold level.

Animal experiments should be conducted at different dose levels. Doses can be lowered to point where latent period exceeds life span at levels that are carcinogenic to equally susceptible longer lived species.

MTD should be used to override genetic or experimental variations.

Because of individual variations, and exposure to many chemicals cannot assess human hazard on basis quantitative animal data.

2. In two chapters of books (attached) he discusses:

(i) false distinction benign and malignant tumors. Benign may be intermediate stage to malignancy.

(ii) futility of relying on epidemiology and need for animal data "I do not know of any circumstance in which a positive result in a single species would not be sufficient to classify a compound as a carcinogen."

(iii) unfounded attacks on mouse.

(iv) Att. C. p. 311. Any exposure to a carcinogen adds to burden of exposure therefore exposure level should be zero.

Richard A. Griesemer

Title: Acting Director, Bioassay Program, Division of Cancer Cause and Prevention, NCI

No. of Pages. 14 plus very extensive attachments. A very large part of the attachments deal with cyclamates and saccharine.

Main Points:

1. Animal experiments are appropriate for detecting human carcinogens.

2. Defends MTD, but such experiments should not be used for risk assessment.

3. Route of exposure. To determine if a chemical is a carcinogen the route should reach all parts of the body. For quantitative risk evaluation, the route of exposure relevant.

4. Defends use of tumor prone inbred species.

5. Need for replication.

6. Tests on single chemicals and mixtures of chemicals.

Position: OSHA proposal reflects current understanding of the mechanisms of carcinogenesis and of the relationship between the carcinogenic process in animals and in man.

Summary

1. Epidemiology is useful when cancer is unusual, otherwise not sufficiently sensitive. Moreover, cannot wait for results.

Animal data should be used in two steps:

(a) test to see if substance carcinogenic.

(b) further tests for evaluating risk.

In the interval exposure should be measured and steps taken to prevent further exposure until risk analysis complete.

2. Defends MTD but such experiments should not be used for risk analysis.

It has not been demonstrated that the "principles" of toxicology apply to carcinogens. Evidence of irreversible changes from small exposures indicates great caution in predicting thresholds.

3. In first stage of testing (1(a) above) exposure route should be to whole body. In second state (1(b) above) the human route of exposure is relevant.

4. Defends using tumor prone inbred species and calculates probability of false positive where spontaneous tumor at that site is less than 1%. Defends use of mouse liver in detecting carcinogenesis of TCE.

5. OSHA is very conservative in requiring replication. Strong positive in a single test should be enough.

If results of test were weak would still be "suspicious" of combined result if replication also weak.

Judgment essential.

6. Exposure to single chemicals gives different results than exposure to two or more which act synergistically. OSHA proposal fails to take this into account.

4/6/78

MARVIN SCHNEIDERMAN

Title:

Associate Director, Field Studies and Statistics Program, Division of Cancer Cause and Prevention, National Cancer Institute

Number of Pages:

33

Main Points Addressed:

(1) U.S. cancer incidence and relationship to industrial causes.

(2) Difficulties of epidemiology studies and value of negative epidemiology.

(3) The role of short-term tests.

(4) The value of extrapolation models.

Summary:

U.S. cancer incidence and mortality have gone up even after one takes into account the aging of the population and changing racial and sex compositions.

Going through several computations and manipulations of figures, the testimony concludes that at a minimum the cancer rate has increased 9-10% for certain types of cancer over the last 30 years which increase is most likely to be industrially-related. By arguing as some have done that for some of these increasing cancers, such as lung and bladder, the increases are completely attributable to cigarette smoking is throwing away the baby with the bath water.

Interaction between the multitudes of carcinogens to which we are exposed means many of our animal and mathematical risk extrapolation models are not sufficiently sensitive.

The problems and drawbacks of human epidemiology studies are extensively discussed. The testimony

notes that there are very few substances for which there are adequate epidemiology studies for which it is claimed that the evidence is firm, that the animal studies show the material to be a carcinogen and the data on humans show it not to be a carcinogen. Three such cases of "putative proofs" of non-carcinogenicity in man and carcinogenicity in animals are dissected. These include sodium penicillin, saccharin, and phenobarbitone.

Placing himself in the chemical manufacturers' role, Dr. Schneiderman discusses how he would react to positive and negative short-term tests for a product which his company was considering developing.

The testimony quotes from and discusses at some length studies on various extrapolation models. The testimony notes that what is necessary but not yet available is a biologically meaningful model of the distribution of times to death which answers the question how many cancers or what proportion of the population will develop cancers before a certain age, such as 70 or 80. Finally, the testimony criticizes Cornfield's recent approach to modeling and quotes from a letter to the editor thereon written by Schneiderman.

Richard Peto M.D.

Title: Reader in Cancer Studies
Oxford University, Oxford, England

No. of Pages: 21 pages with attachments

Main Points:

"Parts I and II of my testimony give some general background considerations; Part I (on pages 5-10) argues that one should not suppose that very low doses of carcinogen are completely without risk, while Part II (on pages 11-16) argues that, although industrial carcinogens should be controlled, one should not suppose that we are currently suffering an epidemic of cancer due to chemical pollution other than from smoking. (Both Part I and Part II could be skipped by someone already in agreement with these propositions.)"

"Parts III and IV, which are briefer, then give some particular recommendations; Part III (on pages 16-17) recommends particular statistical methods for deriving P-values from animal experiments, and emphasises that, in such experiments, very extreme P-values may sometimes be needed in order to be convincing, while Part IV (on pages 18-21) says that it might be wise not to make blanket rules covering both mutagenic carcinogens and non-mutagenic carcinogens, and covering both weak and strong animal carcinogens."

Position: Not wise to make blanket rules covering both mutagenic carcinogens and non-mutagenic carcinogens and covering both weak and strong animal carcinogens.

Summary

"Various annexes are appended to fill out claims made in Parts I-IV; Annex B examines in more detail the reasons for expecting cancer risks to be proportional to carcinogen dose-rates at low dose-levels, while Annexes C, D, E, and F are reprints or preprints of published papers.

Annex A (pages 22-23) Curriculum Vitae.

Annex B (pages 24-35) "The carcinogenic effects of chronic exposure to very low levels of toxic substances" (modified from a paper which is to appear shortly in Environmental Health Perspectives). Annex B argues that what should in general be expected from chronic low exposure levels is that, because of the (frequently ignored) effects of the general background of carcinogens, no safe threshold doses will exist. The number of cancers to be expected will, then, at low doses, simply be proportional to the dose-rate, while the average age at which the induced

cancers appear will not exhibit any material dependence on the dose-rate.

Annex C consists of copies of two published papers which pursue the likely effects of chronic exposure to very low doses with more mathematical and biological details, and which explore the statistical confidence intervals associated with the risks of cancer in the species studied at very low doses. (No quantitative cross-species comparisons follow from such considerations, unfortunately.)

(a) Crump, K.S., Hoel, D.G., Langley, C.H. and Peto, R. (1976). Fundamental carcinogenic processes and their implications for low-dose risk assessment. Cancer Research, 36, 2973-2979.

(b) Guess, H.A., Crump, K.S. and Peto, R. (1977). Uncertainty estimates for low-dose-rate extrapolations of animal carcinogenicity data. Cancer Research 38, 3475-3483.

Annex D is a reprint of a paper in which I describe multistage models for human cancer induction, and infer that, although the sort of mutagenic carcinogens currently being identified by short-term tests and animal tests probably constitute one class of human carcinogens, there probably exists another class of rate-determining causes of human cancer which we do not yet understand and which act synergistically with these mutagens.

Peto, R. (1977). Epidemiology, multistage models and short-term mutagenicity tests. In: Origins of Human Cancer, 2, 1403. Cold Spring Harbor Publications, New York.

Annex E consists of two recent papers by Richard Doll, which are important because they give a readable but scientifically sound overview.

(a) Doll. R. (1977). Strategy for detection of cancer hazards to man. Nature, 265, 589-596. This is not, in fact, a very detailed strategy for the detection of cancer hazards to man, but it is a very good brief review of what is known about cancer epidemiology, compiled by one of the best judges in the world of what is trustworthy and what is still open to reasonable doubt.

(b) Preprint of Doll, R. (1978). The pattern of disease in the post-infection era: national trends. To be published in the Proceedings of the Royal Society of London. As well as the general epidemiological perspectives in (a), people concerned with the regulation of carcinogens should have some idea of which cancers are common and which are rare, and which are increasing and which are decreasing. This paper, which Doll presented to the Royal Society in December 1977, is excellent because it bypasses, almost without the reader noticing them, almost all the errors of interpretation that unsophisticated epidemiology can generate. Most of the age-specific British cancer trends are either downwards (e.g. stomach or colorectal) or are due to drinking, to sunbathing or, most important of all, to smoking (e.g. oesophagus, melanoma, or female lung cancer). Unexplained increases are taking place in the incidence of myeloma and non-Hodgkin's lymphoma, but neither of these is at present a common neoplasm and there is no trace of the general catastrophic increase of cancer which many people fear - rather the opposite, in fact. US trends have not been as well analysed, but appear generally similar.

Annex F consists of a reprint of an editorial which appeared in 1974 describing how animal carcinogenicity studies should be analysed in order to avoid the results being misleading due to the early deaths of animals from toxicity either preventing tumors of old age developing or making internal tumors be detected (at post mortem) much earlier than they would otherwise have been. In my testimony, I recommend the routine use of these methods.

Peto, R. (1974). Editorial: Guidelines on the analysis of tumor rates and death rates in experimental animals. British Journal of Cancer, 29, 101-105.

As with the main testimony, so with the Annexes; Annex A is only of interest to me; Annexes B, C, D, and E relate only to Parts I and II of my testimony, and so may be skipped by any incurious reader who is already in agreement with the points being argued in Parts I and II of my testimony (thresholds should not usually be expected, and there is no epidemic of cancer in progress in Britain or America except due to smoking); While Annex F gives details which will be of interest chiefly to statisticians. I reserve the right to add further supporting documentation to my testimony, particularly further statistical details concerning the estimation of the TD_{50} from animal carcinogenicity studies."

4/6/78

ROBERT HOOVER

Title:

Head of the Environmental Studies Section of the Environmental Epidemiology Branch, National Cancer Institute

Number of Pages:

21

Main Points Addressed:

(1) Relationship of industrial chemicals to cancer.

(2) Strengths and weaknesses of epidemiology.

(3) Interpretation of significance of negative studies.

Summary:

The evidence suggests that a substantial amount of cancer may be related to industrial chemicals and occupational exposure. Occupational cancer associations are, in effect, found as often as one looks for them.

The strengths and weaknesses of epidemiology are discussed. Five weaknesses are noted: (1) epidemiology is weak at identifying low levels of risk, (2) there is a long latency period for most carcinogens, (3) multiple exposures are the rule, (4) the inability to control unknown risk factors for the disease in question, and (5) numerous practical problems such as finding a statistically significant population.

In general, because of the stated weaknesses, positive studies should supercede negative studies.

Isadore Nathan Dubin

Title: Professor of Pathology Medical College of Pennsylvania (Philadelphia)

No. of Pages: 21

Main Points:

Significance of hepatic neoplasms in mice.

Histopathological diagnosis of malignant neoplasms in the absence of metastases.

Use of rats and mice in tests.

Risk to man.

Position:

Summary

1. Definition of terms.

2. Long discussion of various liver tumors without specific reference to the mouse.

3. Tumors that don't metastasize treated as carcinomas - non-metastasizing gliomas, ceruminous brain tumors of cats, squamous cell carcinoma of the cornea.

NCI workshop decided metastases not essential to diagnosis of heptacellular carcinoma.

Pathologist uses objective criteria to determine malignancy.

Reference to discussion at 1975 Workshop on Mouse Hepatic Neoplasia where heptacellular tumors divided into Type A which metastisize and Type B which metastasize in a few cases. Dubin believes there is a correlation between histopathologic structure and malignancy.

4. Doubts have been expressed concerning the mouse as a test animal, but use of these rodents has been established by eminent scientists and authoritative scientific bodies. IARC(1975) recognizes mouse and rats. In NCI studies control assures only one agent affects animal. The balance of the paper quotes various statements about use of animals but no specific discussion of the mouse.

4/5/78

CHARLES BILLINGS

Title:

Consultant (?)

Number of Pages:

25

Main Points Addressed:

(1) Proposed regulatory controls

Summary:

This testimony is a general review of the provisions of OSHA's proposed regulations from the perspective of an industrial hygienist. A detailed practical example of how problems are diagnosed and corrected by industrial hygienists is includes. There is a heavy emphasis in the testimony on engineering controls and the preference therefore over respirators. The proposed regulation is described as innovation-forcing.

4/6/78

NICHOLAS ASHFORD

Title:

Senior Research Associate, Center for Policy Alternatives, Massachusetts Institute of Technology

Number of Pages:

11

Main Points Addressed:

(1) Necessity for and wisdom of generic approach.

(2) Relevance of scientific issues raised to regulatory action.

(3) Proper role of economic issues in OSHA decision-making.

Summary:

Weaving legal and scientific arguments, the testimony endorses OSHA's generic approach and the need therefore.

The present opposition to the OSHA proposal represents misguided efforts to force social policy to conform to economic and scientific paradigms which are inappropriate and contrary to the Congressional intent.

The issues raised in this proceeding are not new and there is little new evidence to be brought to bear. Controversies continue and will continue but government policy must move forward.

The testimony rejects a significant role for economic considerations in OSHA decision-making processes based principally on interpretations of Congressional intent.

Establishing and publicizing a strategy that prioritizes agency activity by hazard creates a license for industry to neglect areas that it might otherwise improve.

The OSHA proposal will be technology-forcing.

Beyond the obvious direct effects of the OSHA proposal are less obvious but nonetheless valuable indirect effects -- e.g., simplification of liability standards in private tort litigation, incorporation of these provisions in collective bargaining agreements.

Benjamin F. Trump M.D.

Title: Professor of Pathology and Oncology,
Chairman of the Department of Pathology
University of Maryland School of Medicine

No. of Pages: 13 with numerous attachments.

Main Points:

Extrapolation of animal data to man as regards normal, premalignant and malignant epithelin.

Use of in vitro human organ and cell culture.

Comparison of metabolism and production of mutagens in animals and man.

Criteria for neoplasia in rat kidney and mouse liver.

Summary

Introduction

Epidemiologic studies have been important in uncovering carcinogens and changing patterns of cancer incidence.

Most carcinogens require metabolism to be effective. Differences between human and animal metabolism complicate extrapolation. Thus of utmost importance to develop tests to study interaction of carcinogens and human tissue. In vitro ways of such tests are being developed.

Related goal is of these tests to correlate information derived by various methods such as morphological response, histopathologic tumor types, production of mutagens by target tissue and carcinogen metabolism and mutagen production by cells such as peripheral blood monocytes. The study has focussed on several important target organs. Human tissues (normal and abnormal) are studied as received and parallel in vitro tests are run. Parallel experimental animal models are used.

1. The purpose of the study is to characterize epithelia in normal, pre-malignant and malignant state and to compare experimental models with changes in human tissues. Farthest advanced in benzo-a-pyrene Fe_2O_2 model in hamster with human broncogenic carcinomas. This has lead to a new proposed classification of broncogenic carcinomas.

A similar study has been done on rat kidney.

Further studies involve dieldrin, DDT and saffrole.

2. Have established ways to transport and maintain human organs *in vitro* for months.

3. Xenotransplantation of target organ tissue to nude mouse creates new powerful tool. Exposure of BaP to transplants shows results comparable to specimens from human lung cancer.

4. Maintenance of the human bronchus *in vitro* provides good basis for studying exposure to carcinogens including smoke. Cultured bronchi can metabolize several classes of human carcinogens.

Metabolism of BaP by human bronchi and pulmonary alucolar microphages (PAM) were studied to see if PAM is useful as an indicator cell.

5. Mutagenesis can be observed on transplant bronchus.

6. Significance of these studies. Strong support for need of animal data

(a) There is close correspondence between certain types of human cancer and cancers induced in animals by chemical carcinogens.

(b) Early lesions in rat kidney previously termed adenomas are transplantable and presumably represent adenocarcinomas *in situ*.

(c) Exposure of xenographt (lung tissue) show same sequential development of lesions as shown in human specimens and in hamsters.

(d) Both human and animal tissues metabolize carcinogens to mutagenic metabolites which bind to DNA.

(e) There is great individual variability (up to 75 fold) in ability of tissues to bind mutagenic metabolite to DNA.

Edward J. Baier

Title: Deputy Director of NIOSH
(accompanied by a panel which
does not include Kraybill).

No. of pages: 12 pages plus an appendix of 31 questions from OSHA and NIOSH's answers.

Main Points:

Terminology
Classification
Collection and evaluation of data
Determination of exposure limits
Model standard

Position: NIOSH supports the overall concepts in the OSHA proposal. NIOSH will offer several technical points, modifications and comments.

Summary

1. Suggests that OSHA not equate "toxic" and "carcinogenic". Proposes to rename categories

I. Probable [or Confirmed] Occupational Carcinogen
II. Suspect Occupational Carcinogen
III. Carcinogenic Evidence Inconclusive

NIOSH opposes Category IV.

NIOSH agreed with Category I criteria and agreed with OSHA on short term tests.

2. NIOSH believes OSHA should establish priorities and proposes use of NIOSH list and NIOSH's National Occupational Hazard Survey.

Believe chemicals should be reviewed case-by-case to assess soundness of data for classification.

Although NIOSH has no proposals, they believe OSHA should deal with co-carcinogens.

NIOSH proposes that statistical significance be at the 95% confidence level.

Agree with requirement for replication (unless very strong positive) but hope that replication will not be rote but will be done in another lab using different strain, additional dose levels and different route of administration.

3. NIOSH believes that scientifically sound judgments can be made only by review of all data. NIOSH offers to lead in setting up a government review panel made up of experts from NCI, FDA, EPA, CPSC and NIEHS.

4. NIOSH believes that "lowest feasible level" should be based on health risk and if engineering, etc. controls cannot bring exposure doses below concentrations which cause cancer in animals, no exposure should be permitted.

Vinyl chloride cited as case where industry said control impossible, but control achieved.

5. Model Standards. NIOSH favors more flexibility in certain parts of model standards: prevention of dermal and eye exposures; protective clothing and equipment; hygiene facilities and lunchroom facilities. Suggests approach comparable to the standards completion project.

Emergency notification requirements in standards burdensome and OSHA should consider whether such extensive reporting required.

NIOSH favors warning signs when there are process control failures and periodic measurements to assure effectiveness of ventilation and control devices.

Controls must be evaluated when there is a process change and the standard should deal with protection to repairmen.

NIOSH favors quantitative fit for respirators.

No smoking should be permitted where carcinogens may be released into the work place air.

NIOSH favors extending medical exam in certain way.

OSHA submitted 32 questions to NIOSH some of which are answered in Appendix C. NIOSH's answers cover:

1. Animal studies are appropriate to identify potential human carcinogens. Species should be those consistently positive when tested with human carcinogens. Rodents fit this criteria.

NIOSH rejects the criticism of mice as test animals.

2. Don't know how valid 1-5% estimate for occupational cancers. The dose relationship shown by carcinogens lead to expectation of fewer cases at low doses.

OSHA is directed by its statute to determine socially acceptable value of risk and the establishment of absolute risk, not relative risk.

3(a). OSHA sets out tables showing agents identified as occupational hazards by epidemiology and confirmed and suspect carcinogens by target organ (6 pages).

(b). No one study can provide all needed health information. Epidemiological studies have potential to determining effect of long-term low level exposure, but difficult to determine past exposure and dose-response. Animal data present problem of extrapolation. Both studies should be used.

(c). Epidemiology uncovered smoking risk, benzene and arsenic.

More weight must be given to positive epidemiological studies than negative.

(d). Efforts should be made to identify high risk individuals in epidemiological studies.

4. Animal data can be relied on in the absence of human data. Inhalation and percentaneous routes of exposure are satisfactory. Oral route also satisfactory.

Inhalation preferred route; topical applications also give useful information.

Injection site sarcomas by themselves probably do not indicate carcinogenicity.

Support MTD.

5. Present information is not sufficient for development of a consistent basis for decisions on additive and synergistic effects.

6. Not clear whether cancer caused by first exposure or repeated exposure. Latency is an imprecise term.

7. Short term tests which are being validated should be used as originally intended as screening device. They cannot be substituted for long term animal studies.

8. Discussion of various factors involving extrapolation:

(a) failure of rodent tumors to metastasize not critical.

(b) differences in target organ not critical.

(c) route of administration important for health purposes.

(d) OSHA should also consider physical agents - ultraviolet and infra red.

4/5/78

ROBERT A. SQUIRE

Title:

Associate Professor of Comparative Medicine and of Pathology, Johns Hopkins University School of Medicine (Consultant to Clement Associates)

Number of Pages:

38

Main Points Addressed:

(1) Relevance of animal and short-term tests.

(2) Benign tumors

(3) Mouse liver tumors

(4) Thresholds

(5) The concept of maximum tolerated dose.

(6) Alternatve classification scheme

Summary:

It is appropriate and valid to base assessments of potential human cancer risks on animal studies.

Carcinogenesis is dose-dependent. Risk often correlates with levels and duration of exposure. There may also be a cumulative effect of exposure to a carcinogen due to the irreversible nature of carcinogenic toxicity.

It is probably true that all substances are toxic at some level and that most are safe at another since metabolic, pharmacokinetic and detoxification, or repair processes are dose-dependent.

Many substances are not carcinogenic. Over one-half of the substances in the NCI Bioassay program are negative.

Carcinogenesis is a specific and perhaps unique toxic manifestation.

Because of the many variables inherent in them, epidemiologic and case studies are considered relatively insensitive. Similar difficulties can, however, arise in animal studies.

Short-term tests contribute to the assessment of the hazards of substances. Such tests, however, cannot be used as "definitive" tools for human cancer risk assessment. Some may have greater predictive value than others. At a minimum, a battery of mutagenesis and transformation tests seems the best short-term test approach.

There may be problems of interpretation where there is a high spontaneous tumor incidence and where the carcinogen under test is a weak one. Evaluation of data must be done carefully and expertly. Any clearly positive animal study, however, must be considered as the best qualitative evidence for human carcinogenic risk assessment.

After an extended discussion, the testimony concludes that benign and malignant tumors must generally be considered equally.

The use of the mouse and its susceptability to liver tumors is defended.

The OSHA position on thresholds is supported. The testimony notes, however, that levels of risk can be estimated by use of mathematical models and that where such models are used the curve should be derived from observed multiple positive end points.

OSHA's concept of maximum tolerated dose testing is generally endorsed except where prior studies have shown for a particular chemical that no electrophillic or toxic moieties are produced by the chemical.

Concerning OSHA's categorization scheme, the testimony states that OSHA wrongly proposes to treat substances of varying potency alike. OSHA's failure to utilize chemical structure similarity and its rejection of injection site tumors is criticized. The categories are deemed to be too restrictive and ones which do not allow for consideration of all pertinent data. Finally, it is noted that the scheme limits the degree of judgment necessary for properly evaluating data.

The following classification scheme is offered as an alternative:

"Category I Toxic Substances

Meets the definition of a potential occupational carcinogen in at least one of the following:

1. Humans

2. Two mammalian test species, if supported by one or more of the following:

   a) Two or more different short-term tests for unscheduled DNA mutagenicity, or cell transformation (at least one of these must involve a mammalian cell system)

   b) One or more positive studies demonstrating tumor induction at the site of injection of the test substance

3. One mammalian species, if the positive findings are dose-related at two or more dosage levels and supported by criteria 2(a) or 2(b) above

4. One mammalian species, if rare tumor types are induced (that is tumors with spontaneous rates in matched or historic controls of no more than 5%) and supported by criteria 2(a) or 2(b) above.

Category II Toxic Substance

1. Meets the definition of a potential occupational carcinogen in one mammalian species, but does not meet other criteria recommended for Category I

2. Positive results in two or more different short-term tests for either unscheduled DNA synthesis, mutagenicity, or cell transformation (at least one of these must involve a mammalian cell system)

3. Positive results in local (injection) tumor tests in two or more mammalian species.

Category III Toxic Substance

Definition remains unchanged."

Replication should be defined to mean a second experiment conducted at a different laboratory by a different investigator or one conducted at a different time.

Detailed review of experiments may be necessary prior to classification and an outside panel of experts in such cases may be the best means for doing so.

OSHA needs to deal more fully with the questions of contaminants and metabolites. Hormone carcinogenesis must be treated differently.

Laboratories should be exempted from the regulation.

4/7/78

Mathew S. Meselson

Title:

Thomas Dudley Cabot Professor of the Natural Sciencies, Harvard University

Number of Pages:

8

Main Points Addressed:

(1) The use of data on human cancer mortality and incidence for determining carcinogenesis.

(2) The use of animal tests for determining carcinogenesis.

(3) The use of short-term tests, particularly the Ames test, for determining carcinogenesis.

Summary:

The testimony downgrades the use of epidemiological studies. Although epidemiological studies are valuable for identifying industrial carcinogens, as demonstrated with asbestos, BCME, benzidine and vinyl chloride, reliance upon such studies could incur a "great toll" in human cancers. Epidemiological studies are "particularly uninformative" for substances only recently introduced into the environment.

In discussing the use of animal tests, the testimony begins by noting that "only a small proportion of chemicals subjected to standard animal carcinogenicity tests are found to be carcinogenic." However, almost all known human carcinogens produce positive animal test results.

Animal tests may also be used for quantitative risk assessment. A 1975 NAS study concluded, "it appears reasonable to assume that the lifetime cancer incidence induced by chronic exposure in man can be approximated by the lifetime incidence induced by similar exposure in laboratory animals at the same total dose per body weight."

The Ames test, although not conclusive, has been shown to produce results approximately 90 percent consistent with animal bioassays. The Ames test, especially for substances with results indicating high potency, "should be used both to signal the need for particular caution in the workplace and to establish priorities for intensive long-term and epidemiological investigations."

4/7/78

Emmanuel Farber

Title:

Professor of Pathology, Chairman of the Department of Pathology, University of Toronto.

Number of Pages:

5

Main Points Addressed:

(1) The need to classify substances based on the weight of evidence for carcinogenicity.

(2) The need to recognize the complexity of the carcinogenesis process for identifying and classifying carcinogens.

(3) The difficulty with using animal tests to predict quantitative risk to man.

Summary:

The testimony begins by supporting the use of animal tests for identifying substances as potentially carcinogenic to man. However, animal tests "vary greatly in quality, and for statistical, biological, and methodological reasons often give results which are not fully conclusive." Category II classification is "reasonable" for substances for which there is suggestive evidence of carcinogenicity.

The remainder of the testimony cites liberally to the appendices (3 papers discussing the carcinogenic process and 1 paper describing a promising experimental short-term test), but adopts specific positions. OSHA's proposed classification is described as "somewhat too rigid" in light of the complexity of the carcinogenesis process. Based primarily upon work done with liver cancer, the testimony continues with a description of the current state of knowledge regarding the carcinogenesis process. It is indicated

admittedly, there is much waste that might be eliminated. The idea seems to be that the total bill should be cut at the expense of the physicians, the pharmacists, the drug industry, and the hospitals. Indeed one proposal being floated is that the number of physicians should be reduced and so medical schools should be cut rather than expanded. Other proposals are simply that physician's fees should be reduced. The New York State Workman's Compensation Board has tried this approach and the system is in a shambles, since physicians will not undertake to treat patients when they are paid 50–70% less than their usual fees.

If indeed new health schemes are to be put forward, far more facts will have to be impressed on the public, the laws will have to be altered, and ideas of individual responsibility will have to be enhanced—for maintenance of health, as well as other things. Meanwhile, the A.M.A. is right to concern itself with its members' interests.

VENTURES OVERSEAS

It has become so difficult to gain admission to medical schools in this country (though for some a large parental cash contribution is said to help) that students have long looked elsewhere for a medical degree. Pressure on the medical schools in Canada seems as great as in the U.S. The U.K. is closed, and medical schools elsewhere in Europe (Paris and Brussels, for example) are gradually curtailing the admission of U.S. students to medical courses. New medical schools are therefore being opened, schools in which there is not the assurance of the backing of the medical school by a university of known high standards; and people are certainly worrying about standards, though there is a lot of humbug on this issue. No-one who has taught medical students in other countries and now teaches in the U.S. can be very happy with the standards here. But any deficiency does not necessarily lie with the students, for those who are unable to gain admission and go overseas are closely comparable with those admitted. But now new fears are emerging, for when a shortage of anything arises someone can be relied on to try to fill the gap. New medical schools have been opening, of questionable quality and staffing, in foreign countries and in Puerto Rico. There is no doubt that some of these are simply fraudulent schemes to attract money from unsuspecting students and parents. Others are of higher quality and with more reputable backing, but they are equally concerned to attract students. The advertisements, referring to recognition by various national or international bodies, may give the incorrect impression that the schools are accredited in U.S. terms.

The American Association of Medical Colleges has issued a statement warning teachers at recognised medical faculties in the U.S. against association with such schools or in any way lending their names to be used to exploit American students. Before associating with such a foreign institution, teachers are advised to familarise themselves with the educational quality of the instruction offered, though it is not clear just how this is to be done. This drawing away of cautious skirts from such places may be a proper action for the individual who wishes neither to exploit nor to be exploited, but whether it is a wise move by the A.A.M.C. seems more doubtful. There is no question that the establishment of an adequate medical school and the influx of staff to run it can have a remarkable effect in an area where medical services are scanty; and if, on some Carribean island or in a poor area of South America, enterprise develops a new medical school, the A.A.M.C. might do better to help, advise, caution, and encourage its launching. It may not approve the facilities, the teachers, the programmes, or the students, but at least it would have some information to give inquirers. It might even see some ways in which medical education in the U.S. could be improved. After all, there was a time when none of the medical schools of the U.S. had any standing at all in the world; and in earlier times still this was true of Europe's most famous medical centres.

WHEN IS A CARCINOGEN?

The Occupational Safety and Health Administration (O.S.H.A.) is proposing new regulations to control all carcinogens which, if adopted, will have a profound effect on U.S. industry. O.S.H.A. bases the need for new regulations "on a rising U.S. death rate due to cancer and a growing acceptance that 60 to 90% may be related to environmental factors." The arguments marshalled to support the latter contention rely heavily on the differing incidence of certain types of cancer in different countries. O.S.H.A. goes further by suggesting that the increasing incidence of certain cancers in the U.S. is a consequence of increasing exposure to industrial chemicals and other toxic substances, such as asbestos. O.S.H.A. is asking for a series of draconian measures which will regulate all carcinogens and potential carcinogens in a standard way from now to eternity, since the agency requests "that the proposed procedures, model standards, and classification criteria will be consistently applied and foreclosed from reconsideration in future regulatory activity." Such regulations represent a plea for extraordinary powers, and they might be interpreted as indicating that those who drafted them operate on the principle that their mind is already made up and that they do not wish to be confused with facts or new information.

O.S.H.A. goes on to define a carcinogen as any substance that has been validly shown to produce tumours, either benign or malignant, in animals or which decreases the latent period between exposure and the development of tumours. It might well be asked how a substance which leads to the development of a benign tumour can be classified as a carcinogen, since the term carcinogen implies malignancy. The production of tumours in any species is sufficient for the agent concerned to be labelled a carcinogen. Moreover, a substance which has been shown to be associated with non-replicated tumour development is to be regarded as a carcinogen if it has also been shown to be mutagenic by the Ames test. No allowance is to be made for the fact that differing species show widely different susceptibilities to carcinogens, and O.S.H.A. adheres to the view that positive studies in animals should be given more weight than negative studies in man. The implication in such a statement is that cancer epidemiology in man is worth nothing unless it demonstrates a positive association. When criticised for these generalisations, the O.S.H.A. experts assert that the incubation period for most cancers is 25–35 years, and only by these means can an epidemic of cancer be prevented. But, many people are saying, O.S.H.A.'s logic and facts are questionable. Has there in fact been a dramatic increase in cancer in the U.S., apart from lung cancer? Moreover, since carcinoma of the stomach and cervix have declined appreciably over the past 50 years, it *could* be argued that the decrease is the consequence of increased use of chemicals! It is clear that the environment—using the term in the broadest sense to include cigarette smoking, diet, and other factors—is responsible for the development of certain cancers, but industrial chemicals certainly play a far lesser role than do dietary habits, cigarette smoking, and family size.

The thorny issue of carcinogens can be resolved only by calm deliberation, and the type of rhetoric that O.S.H.A. has been using to justify its proposed regulations has evoked a fierce reaction. In this context, O.S.H.A. published in support of the regulations a fine piece of hyperbole: "Never before have massive quantities of asbestiform tailings been spewed into the water we drink, never before have industrial workers been occupationally exposed to vinyl chloride or to asbestos . . ." Many U.S. scientists are very uneasy about this type of demagoguery, when there are something like 40 or 50 recorded deaths in the whole world from polyvinyl-chloride-related angiosarcoma of the liver, while there will be around 90 000 deaths in the U.S. this year from lung cancer; and, of that 90 000, over 90% will be a direct consequence of cigarette smoking. Perhaps it is our behaviour we need to change, not our insecticides.

Bob 716 Golde

Jand/

There are three points in my written statement which I wish to comment on briefly.

RELATION OF RATE OF CHEMICAL MANUFACTURE TO CANCER MORTALITY

I have searched for a reasonable statistical indication, even a crude numerical association between the manufacture of chemicals and petrochemicals and the subsequent incidence of all cancer; that is to say, I have searched for any evidence of a cause-effect relationship. If such exists, all reasoning persons must agree that a comparison of the quantity of chemicals manufactured must correlate with the incidence of cancer over a long period of time, allowing to be sure for any delay in onset of cancer from the exposure. OSHA prefers to call this delay the "latent" period, and repeatedly describes it as varying from 5 to 40 years. I should have been happier if they had described it as <u>one</u> to 40 years for they would then have been more inclusive. The fact is that <u>4 to 20</u> years covers the vast majority of cases.

I invite you now to examine three of the eleven graphs in my prepared statement. The graph marked "Figure 10" shows in black circles the number of <u>billions</u> of pounds of chemicals produced annually in the United States between 1930 and 1976. The figures are taken from United States International Trade Commission reports. Also shown on the graph are figures representing age- (and sex-) adjusted

annual mortality from cancer for the period from 1935 to 1975, 40 years. These figures, which are denoted by the black triangles, are from publications of the U.S. National Center for Health Statistics and the U.S. Bureau of the Census. If we look at chemical production, we see that the first periods of rapid, steady growth were in the '30s and that during the was years, 1940 to 1945, the rate of growth was extraordinarily fast. Also, the war years represented a period notable for its lack of attention to good industrial hygiene. In fact, it was purposeful and written policy of the Public Health Service during the war years to loosen existing industrial hygiene standards in order to expedite production. I invite your attention to the fact that cancer mortality remains unchanged during the 40 years for which we have accurate figures.

Now I should like to invite your attention to the second graph, marked "10A", in which I have plotted the measure of chemical production which is most relevant to potential health hazards: formulated index figures, published by the Federal Reserve Board, which take into account not only quantity of production, but the number of employees and production works involved, the number and size of manufacturing establishments involved, the standardized dollar value, the quantity sold and distributed, and some other factors as well, all standardized on this graph to the year 1947.

Nineteen forty-seven was, for purposes of calculation, a good year to serve as a standard and, fortuitously, it lies close to 1950, which is the year to which the estimated death rates [in 1970 to 1978] have been standardized. These index points include all sub-categories of all synthetic organic chemicals and this is of fundamental importance in assessing any possible relationships between the extent of chemical production, and exposure, and incidence of cancer. You see on this graph 10B, the rapid, nearly explosive, increase in the output of manmade chemicals of all kinds, and especially during the war years. And once again, I invite you to note that cancer mortality did not change during this period of forty years. I might add, also, that had I excluded 80% of the deaths from lung cancer in males, (deaths presumably due to cigarette smoking) the triangles showing mortality would have fallen on a line with a downward slope.

Surely enough time has elapsed between the period of the greatest expansion in chemical manufacturing to allow for the various so-called "latent" periods. It is clear that no measurable relationship exists between rate of chemical manufacture or of the attending exposures involved and the subsequent incidence of cancer.

Next, I should like to invite your attention to the third of the graphs which you have in your hand. It is the one marked "10C". On this graph I have plotted the index

EXTRAPOLATION FROM RODENTS TO MAN

It is inexcusable for definitive carcinogen assessment to be made in inbred strains of mice, which have spontaneous development of cancers as a consequence of genetic defects in cancer resistance. They are a long way from humans!

Of the nearly 250 strains or substrains available, an investigator can select a particular strain "appropriate" for making tumors in a particular organ. The selection is simplified by the availability of lists of strains - continuously updated in the Mouse Newsletter, according to their cancer predeliction. The Newsletter is a virtual "bad seed catalogue."

To produce breast tumors, look for C3H: though, BALB/c will also give breast tumors when "milk agent" is used, and will also provide lung tumors in 26 to 29% as an "extra." For liver nodules, benign or malignant, choose male C3H, or male C3He.

There are strains for lung tumors, leukemia, lymphomatous cancers, skin cancer, adrenal and pituitary gland tumors, ovarian and testicular tumors, etc. The list is long.

Inbred rat strains, similarly prone to develop spontaneous tumors, are also inherently sick and have short lives.

These rodents are disease prone, making them highly sensitive to changes in environment; they commonly have chronic kidney, lung and brain diseases, etc. They are not only deficient in resistance to carcinogenesis - that is, have defects of DNA repair, detoxifying mechanisms, etc., but may be unable to excrete, metabolize, and demonstrate normal proliferative responses - non-specific defects which increase susceptibility to cancer. (Humans who resemble inbred mice are those with xeroderma pigmentosum, where adequate DNA repair mechanisms are lacking so that a few rays of sunshine cause skin cancers).

Furthermore, rodents have the instinctive habit of eating their own feces, so that they ingest carcinogens manufactured from otherwise harmless substances by their unique intestinal bacteria. Nature has apparently provided the rodent with this habit to keep him alive in times of famine. The rat and mouse in the natural state are hearty, adaptable beasts.

But, for the inbred strains there is another feature that makes them undesirable for cancer testing: stress or illness, chemically or non-chemically caused will increase the number of spontaneous tumors. As for chemical "stress", they are given doses which on a weight basis are equivalent to hundreds or thousands or tens of thousands times more than the exposures of occupational personnel.

It is possible to induce cancers in these fragile, rodents by such non-chemical means as increasing their caloric intakes slightly by feeding them ad libitum, by varying the number in a cage, varying the kind of shavings on the cage floor, handling, making noise, etc. Doctor Roe has stated in his written testimony that any experienced experimental pathologist, given adequate resources, could show that any agent is "carcinogenic" in inbred mice.

It is inconceivable to me that tumorigenicity in these animals should be more than a preliminary screening test to signal for testing in non-inbred rodents and in higher species. If observations indict a substance in several species, the substance should surely be classified as potentially carcinogenic to man.

"NO-THRESHOLD" - A MISCONCEPTION

Finally, I should like to speak of the grossly mistaken concept that "no threshold" exists for carcinogens. OSHA's prejudice on this is clear from the statement made on page 54165 of its Proposed Rules, where it states that "there is no means of predicting an individual threshold, even if they do indeed exist."

The biological effects of all chemicals are subject to thermodynamic requirements. The dose of a chemical required to produce any specified effect is governed by the laws of quantum chemistry, meaning that all chemical reactions, including those responsible for alterations in cellular genetic materials, require a change in the quantity of free energy among the reactants. In cellular reactions, the energy change almost always involves multiple reactants. A basic reaction in chemical carcinogenesis is the binding of a substance (the carcinogen) by electrons to DNA. Most carcinogens are inert until rendered water soluble, cell-permeable, and have undergone one or more chemical modifications. The sequence leading to binding to DNA involves multiple, quantal steps.

After binding has occurred, one or more of several DNA repair mechanisms are set in motion. Any cell in which DNA has been altered is equipped with a complex sequence of

enzymic steps known as "excision repair", a four- (and possibly five) step response which is normally 100% effective. Normal human cells can repair common DNA aberrations at the rate of over 100,000 base-pair combinations per cell per hour! There are also other DNA repair mechanisms which can be activated. These are also multi-stage processes which are not, however, 100% effective, but they are repeated on each division of the cell, and are normally backed up by "excision repair."

A third quantum barrier is immunologic. For example, inadvertently transplanted cancers - cancers in kidneys transplanted into immunosuppressed subjects - flourish and spread to other organs in the recipient. Discontinuance of immunosuppressive therapy causes rejection (cure) of the cancer. Also, several heritable immunodeficiency orders are accompanied by very high rates of early-onset cancers, usually multiple.

The term "non-threshold" has no basic meaning, significance or example. Although it may seem to be a convenient colloquialism, there is nothing in all of nature to which the phrase "non-threshold effect" is applicable!

SUMMARY OF STATEMENT OF TESTIMONY

My name is Henry van Raalte. I am a physician with a doctorate in Medicine from Leyden Univeristy where I also received a post-graduate specialized training in internal medicine. For more than the last twenty years of my professional life, I have been increasingly and later almost exclusively involved in occupational medicine and toxicology. From 1959 to 1971, when I retired, I was head of the Toxicology Division in the Shell International Research Company for the Royal Dutch/Shell Group of companies.

Since 1971 I have been a consultant in occupational medicine and toxicology, consulting for Government, Industry and a Labor Union. I am an appointed member of the Netherlands' National Health Council and do some teaching at Universities. I have been elected to membership in scientific societies in France, England, Argentina, Colombia and Mexico.

At the outset I would like to comment on OSHA's suggestion of a cancer epidemic. I should point out that my comments are based on study of published statements by authoritative scientists outside the adversary arena.

There is no cancer epidemic and there has not been an overall increase in cancer incidence. The cancer burden from occupational exposure is a small proportion of the overall incidence, clearly caused by factors in non-occupational lifestyle. This does not mean that we should not control occupational exposure, but the suggestion that the OSHA proposal would protect man from the mass of environmental cancer hazards and would significantly reduce the overall incidence of cancer, is not correct.

To avoid misunderstanding, I repeat that occupational exposure to real cancer hazards should be controlled. But there is not an epidemic, requiring exaggerated "overkill" regulations.

A regulatory approach to these relatively small numbers of real cancer hazards should not be mechanical and inflexible, according to bureaucratic formula, as OSHA proposes. The boundaries of Category I will include chemicals which should not be there and could possibly exclude a few which should be controlled as presenting a human cancer hazard.

OSHA's proposal "freezes" science by adopting "lumpcounting" and "time to tumor" philosophies. Science requires an evaluation and consideration of all available data rather than just that data allowed to be considered by the "generic rules." Attention should be paid to the advice of the subcommittee on carcinogenesis of the National Cancer Advisory Board. It warned that each case must be considered on its own, and the criteria appropriate for one agent may not necessarily apply to another and urged that evaluation of hazards also be individualized.

Chemicals which induce cancer in rodents vary enormously in their potency. They also vary in their mechanism of action. Similarly, the hazard to man varies from very high to practically none.

All available evidence should be considered before extrapolating positive results in one rodent species to man. Although lead induces renal tumors in rats, there is after 400 years of intensive use no evidence that lead induces cancer in man. Also, in this respect I refer particularly to certain specific mouse liver tumors — and this probably applies also to mouse lung adenomas — the relevance of which to man is in serious doubt. [Even Dr. Upton used the term "uncertain"]. This is not the case — to avoid misunderstanding — with some other tumors in the mouse, even with some other mouse livertumors like those caused by "butteryellow." In many cases the mouse may remain a useful study animal. Among all known human carcinogens there is none which is carcinogenic in the mouse liver only and not in other mammalian test species.

Now let us take dieldrin as an example and put all available data in a row:

1. The compound induces livertumors only in the mouse.

2. Negative results have been obtained in seven (or more) tests in rats, including four recent NCI studies (two with dieldrin, one with aldrin, and one with photo dieldrin.

3. Negative results were also obtained in hamsters.

4. No premonitory changes (biochemical or structural), such as occur early in the mouse, occur in the monkey.

5. All short-term tests for mutagenic activity (both in vitro and in vivo) are negative.

6. In man there is, after more than twenty years, no suggestion or indication of carcinogenic activity or of any premonitory liver injury (or any other injury) in highly exposed workers.

7. Similar phenomena (1, 2, 3 and 5) have been shown to occur with the "dieldrin-simulator" phenobarbital with which no carcinogenic activity could be demonstrated in about 9,000 patients using the drug over the greater part of their lifetime.

8. A similar situation also exists in the case of DDT.

The nature, type and cellular origin as well as the site of the tumor, are important factors in arriving at a conclusion of carcinogenic or co-carcinogenic activity of the compound under study. Simple "lumpcounting" is not good enough.

"Lumping together all benign tumors with malignant tumors flies in the face of medical science. All benign tumors do not progress to malignancies. It may or may not be so in rodents but it is certainly not true for man. Contemporary medical teaching and modern textbooks on human pathology and surgery abound with examples of consistently benign tumors.

OSHA's flat rule that a positive study supercedes all negative studies negates that science generally accepts the fact that in all examinations both

false nagatives and false positives always occur.

Much of the debate on thresholds hastended to obscure two facts:

1. proponents of the "no-threshold hypothesis" fail to consider the fact that not all cancer inducing agents have one and the same mechanism of action. Some of these inducers have a mechanism of action which has just as much of a threshold as exists in the case of other non-carcinogenic injuries.

2. The term "acceptable risk" does not mean that it is accepted that some people will contract cancer caused by the incriminated chemical, but it does mean that the risk to the exposed is not greater than the risk to those not so exposed.

that effects are reversible. Initiation is "quite rapid" and consists of "the induction of some one or more molecular alterations" followed by "a round of cell replication for 'fixation'". A delay in the occurrence of "fixation" "may favor the reversibility of the first step by repair processes." Also, [t]he fate of cells altered by exposure to an initiating dose of a carcinogen is largely environment dependent."

It is very difficult to predict the potency of substances as human carcinogens based upon animal tests:

(i) The human population is too genetically diverse and, therefore, susceptibility to carcinogens is more variable; and

(ii) The potency of carcinogens varies greatly between animal species.

4/7/78

UMBERTO SAFFIOTTI

Title:

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Number of Pages:

52

Main Points Addressed:

(1) Detailed analysis of OSHA's classification criteria.

Summary:

This testimony is a careful line-by-line analysis of OSHA's classification criteria organized by key phrases. This summary is, accordingly, similarly organized.

"Causes" -- The determination of causality requires professional judgment, expertise, and evaluation of all relevant data. The OSHA proposal accomplishes this end through the use of the word "cause" and the broad discretionary criteria (discussed below) which OSHA is to apply in classifying substances.

"At any level of exposure or dose" -- MTD dosing is necessary to ensure greater sensitivity (various sensitivity parameters are discussed).

There is no convincing evidence to support the argument that metabolic pathways for carcinogenic activation are qualitatively different in a critical manner at high and low levels of exposure so that the chemical becomes completely detoxified up to a certain level of exposure, while at high dose levels the detoxification machanism is overloaded and carcinogenic metabolites are produced and become effective.

"As the result of any oral, respiratory or dermal exposure or any other exposure which results in systemic distribution" -- All these routes of exposure are deemed relevant. Non-systemic injection-site tumors are not deemed relevant.

"An increased incidence" -- The link between an increased incidence of tumors and causality noted above again requires judgment and expertise. The OSHA proposal will ensure adequate professional analysis and the requisite causality.

"Of benign or malignant neoplasms or a combination thereof" -- Three cases are discussed. (1) Those where benign neoplasms are not known to progress to a malignant state, (2) those where benign neoplasms are known to progress to a malignant state, and (3) those where there is a combination of benign and malignant neoplasms. The OSHA policy is prudent with regard to all three cases. Insofar as the first case, there is no established body of evidence to show that certain chemical agents can induce exclusively benign neoplasms which will not progress to a malignant state without ever inducing any malignant tumors. The evidence is said to be even stronger for the latter two cases.

"In humans or one or more experimental mammalian species" -- The concept of extrapolation from mammalian test results is endorsed. A positive finding in a single species should be enough to indict a substance as a carcinogen. OSHA is therefore "reticent" not "radical" in requiring some sort of confirmation for a Category I finding.

"In a statistically significant manner decreases the latency period" -- The need for judgment and flexibility is again emphasized. It is suggested that the word "cause" be used in connection with this phrase so that the concept of judgment which the word "cause" embodies be included herein. A definition of latency period must be provided in the context of each bioassay.

"A presumption exists that a toxic substance shall be classified as a Category I substance" -- The presumption/rebuttal approach is sound and traditional in science. The OSHA proposal is a sound marriage of specific criteria with the necessary flexibility for scientific judgment.

"The toxic substance meets the definition of a potential occupational carcinogen in humans" -- The inadequacies of relying on human data alone and the pitfalls of epidemiology are briefly discussed.

"or two mammalian test species" -- This is a clearly sound criterion. The second species is merely confirmatory. No evidence exists that carcinogens are species specific.

"or in a single mammalian species if those results are replicated in the same species in another experiment" -- The relevance of mouse liver tumors is defended citing principally the work of Tomatis.

"Conclusive evidence of carcinogenicity in one species supercedes negative findings in another species" -- This proposition is defended citing a specific example where a contrary position would have been erroneous (beta-napthylamine).

"or a single mammalian test species if those results are supported by short-term tests" -- Several revisions of an editorial nature are suggested. The testimony is generally supportive of the use of short-term tests as confirmatory evidence. The discussion is principally focused on neoplastic transformation of mammalian cells in culture by chemical substances. Again, the need for judgment is articulated and the OSHA proposal is endorsed as embodying sufficient flexibility to accommodate such necessary judgments.

"The Secretary finds any other evidence is sufficient to convince him that the toxic substance should be classified as Category I" -- This provision is necessary for unusual situations where, for example, a single positive animal test result might require action. This provision stresses the judgmental nature of the process of determining causality.

"Rebuttal of Category I Presumption" -- (1) The definition of "physical induction" should be clarified (three areas of clarification are discussed). (2) The criterion which permits rebuttal based on a finding that the positive results in animals are not "scientifically relevant to man" is endorsed as providing necessary flexibility and permitting the exercise of professional judgment.

4/7/78

SAMUEL EPSTEIN

Title:

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Number of Pages:

109

Main Points Addressed:

(1) Increasing incidence of cancer.

(2) Community cancer due to industrial chemicals.

(3) The extension of the Delaney Clause concept to OSHA.

(4) Transplacental carcinogenesis.

(5) The need for a generic approach.

(6) The costs of the OSHA proposal.

(7) The track record of the chemical industry.

Summary:

There is a significant increase in cancers even after age adjustment. The AIHC arguments to the contrary are misleading. Most of the decrease in cancer cited by the AIHC is due to better detection and treatment of cancer.

Carcinogens found in the workplace impact the health of surrounding communities. Numerous examples and statistics are cited. The impact on community cancer rates are likely to be substantial.

The Delaney Clause concept should be adopted by OSHA. A single positive result should result in a Category I finding. Where such a finding has been made, OSHA should impose a zero exposure requirement as measured by the most sensitive analytical methodology then available.

The following frequent criticisms of the Delaney Clause are cited and rebutted:

(1) Any chemical can be carcinogenic by testing in various routes;

(2) Most chemicals are carcinogenic when tested at high doses;

(3) Animals are much more sensitive to toxic and carcinogenic effects of chemicals than humans;

(4) Safe levels can be predicted from animal experiments;

(5) The Delaney Clause precludes scientific judgments and discretion; and

(6) Advances in analytic technology have made the zero concept intolerable.

OSHA's reliance on short-term tests for regulatory purposes appears ill-advised and invites legal challenge.

The criterion which permits rebuttal of a Category I presumption because the data are not "scientifically relevant to man" gives the Secretary too much discretion and may create political pressures and a possible return to individual rulemaking.

The AIHC Alternative is attacked as being, in effect, a covert attempt to avoid generic rulemaking and undermine the OSHA proposal. AIHC's classification criteria are also critically examined. (There are many misstatements of the AIHC position in this discussion and a failure to correlate AIHC regulatory responses to classifications.)

The following "myths" fostered by the chemical industry and their yielding scientists (examples are cited) are discussed:

(1) Tumorigens are less dangerous than carcinogens;

(2) Animal carcinogens are less dangerous than human carcinogens;

(3) Most chemicals are carcinogenic when tested at high doses;

(4) Safe levels of exposure can be determined; and

(5) Human experience has demonstrated the safety of occupational exposure to animal carcinogens or to low levels of human carcinogens.

The problem of transplacental carcinogenesis is added reason to require a generic approach.

There is a great need for a generic approach because of (1) increases in the number of chemicals, (2) past regulatory activities have been few, slow and have only come after the fact, (3) the protracted nature of individual substance rulemakings, (4) inconsistencies between approaches to environmental and occupational hazards by federal agencies, and (5) the inadequate scientific basis for current regulatory practices.

Risk benefit analysis is rejected as a sound tool for decision-making. It hasn't worked in the past and is generally used as a camouflage to maximize short-term benefits to industry at the expense of workers.

Industry forecasts of economic problems are discounted. The chemical industry is viable and healthy. This is only more of the same (e.g., vinyl chloride and TSCA compliance cost claims).

The economic costs of cancer are substantial.

The track record of the chemical industry is poor. Among the "strategies" used by the industry are (1) mimimizing the risks involved, (2) diversionary tactics (e.g., requiring impossible proofs of carcinogenicity), (3) propagandizing the public through public relations campaigns, (4) blaming the victim (e.g., (e.g., hypersusceptible individuals, tobacco), (5) controlling information, (6) influencing policy (lobbying), (7) exhausting the regulatory agencies, and (8) industry, particularly multi-national, flight to foreign countries with less stringent controls.

Industry manipulates, suppresses and destroys much critical data. A cadre of "consultants" and "scientists" assist them in these practices. Numerous examples are cited.

4/7/78

David H. Wegman, M.D.

Title:

Assistant Professor of Occupational Health, Harvard School of Public Health; Assistant Professor of Community and Family Medicine, University of Massachusetts Medical School; Occupational Hygiene Physician for the Commonwealth of Massachusetts.

Number of Pages:

9

Main Points Addressed:

(1) The reasonableness of generic regulation.

(2) The scope of the occupational cancer problem.

(3) The uses and limits of epidemiological studies.

Summary:

Ideally, the regulation of a substance as a carcinogen should be based upon epidemiological studies, replicated results in animal tests involving several species and short-term tests, but this would be "cumbersome" and "foolish":

(i) Relatively little is known about the process of carcinogenesis;

(ii) Too little is known about workplace exposure. There is a limited number of well-documented occupational carcinogens despite the first being noted 200 years ago;

(iii) Collection of such data prior to allowing use of a new substance would stifle commerce.

Other than cigarette smoke, "almost all the examples of substances specifically associated with human cancer risk are from occupational settings." In fact, interaction or synergism of cigarette smoke with exposure to asbestos and radon doughters has been shown to cause a greater risk of cancer than would cigarette smoke alone. Much of respiratory tract cancer risk is probably due to the interaction of substances found in the workplace with cigarette smoke. The estimate by John Higginson that only 1-3 percent of cancers are "definitely" a result of industrial exposure is not inconsistent with this proposition.

Epidemiological studies have been underutilized, but there are serious difficulties in evaluating work-place risks because industry's failure to keep adequate records makes determinations regarding exposure very difficult. Duration of employment is an inadequate measure of exposure. Also, retrospective studies normally must rely upon death certificates, rather than incidence data, and accuracy is not great. Finally, mixtures of substances are often used in industry and it is "unlikely" that the agent primarily responsible for cancer could be isolated.

Renate D. Kimbrough

Title: Research Medical Officer, Center for Disease Control, U. S. Public Health Service

No. of Pages: 7 plus very extensive attachments

Main Points:
1. The regulation of carcinogen and toxic chemicals has been inadequate.
2. Animal data is sound basis for extrapolation to man.
3. Female workers.

Position: Endorses regulation of carcinogens. Did not have enough time to comment on proposal as a whole.

Summary

1(a). Little progress has been made in regulating carcinogens.

(b). Insufficient information is available for fixing exposure levels for Category II and III substances. Workers should be regularly examined and standards revised.

(c). TSCA ignores intermediates formed in production process.

(d) Although there are good plants, many plants have primitive housekeeping.

2. Many cases have shown animal data are predictive of human hazard. Most substances adequately tested produce tumors in a number of species. The mouse is a good test animal.

3. Because of transplacental carcinogens, the exposure of women in reproductive years should receive speedy attention. Tumors in children are especially tragic and mortality in 11-15 age range very high and in Germany is increasing.

David Baltimore, Ph.D.

Title: Professor MIT, course in cancer biology, Consultant to NCI

No. of Pages: 4

Main Points: Statement is precis of presentation

Position: OSHA proposal provide a reasonable framework for avoiding exposure to potential carcinogens, however, because of expected developments, there should be a mechanism for flexibility and review of decisions.

Summary

1. Cancer is cellular disease. Functioning of whole organism may affect occurance of tumor, however a defect "in a single cell is a necessary event before any cancer can be manifest."

2. Gross principles of carcinogenesis in animals relevant to man. Test systems cannot provide clear potency indications so results should be used qualitatively not quantitavely.

3. Because of problems with both animal and short term tests, regulating chemicals by categories is appropriate.

4. There is little data to show viruses play role in human cancer.

5. Cancer research filled with uncertainty and fluctuation so necessary to attain flexibility in regulations.

William J. Nicholson, Ph.D.

Title: Mt. Sinai School of Medicine

No. of Pages: 4 plus extensive attachments

Main Points: Threshold.

Position: Since a threshold cannot be determined exposure to carcinogens should be reduced "to maximum degree commensurate with existing technology."

Summary

1. The task of identifying a threshold for exposure to a carcinogen is virtually impossible.

Epidemiology cannot identify no effect level because of unfulfilled requirements

(a) a large enough population for observation

(b) knowledge of the concentrations of exposure

(c) observation for sufficient time for malignant effect to be observed.

Animal experiments subject to similar difficulties plus possibility substance is species specific, and problems of extrapolation.

2. Inability to establish threshold does not negate dose response relationship for carcinogens. Reduced exposure reduces risk but a risk (in probablistic terms) remains for any exposure. Lung cancer mortality data indicates that even if time to tumor increases, there is still finite risk of tumor at times shorter than average.

3. These points illustrated by asbestos data. Only prudent course is to regard it as carcinogen for which we have no knowledge of a threshold. Worker exposures should be reduced to the maximum degree consistent with existing technology. Same rule should apply to other carcinogens more easily controlled or having more limited use.

Bernard Weinstein M.D.

Title: Professor of Medicine and Director of Environmental Sciences and a member of the Institute of Cancer Research at the College of Physicians and Surgeons at Columbia University

No. of Pages: 9 plus extensive attachments.

Main Points: 1. rodents in carcinogenic assays.

2. Site specificity.

3. Multiple exposures and tumor promotion.

4. Chemical structure and short term tests.

Position: I find that the scientific background detailed in the OSHA proposal is generally excellent, and provides a factual and critical summary of our current knowledge and state of the art.

Summary

The OSHA proposal closely follows the recommendations of National Cancer Board on Environmental Carcinogenesis.

1. Rodents are good test animals. Agree no distinction between induction of tumors and enhancement of tumors in rodent bioassays.

Disagree with OSHA: would not put as much weight on test which induced only benign tumors as when both benign and malignant observed. If benign only: classify as suspect carcinogen with high priority for testing.

High doses needed. However, this presents problem of extrapolating to low dose.

Another problem species differences in sensitivity to compound which can be as high as 5×10^5.

2. No conclusions as to safety can be drawn on basis of site specificity.

3. Distinguishes

initiating agents (solitary carcinogens)
tumor promoter (syncarcinogenesis)
cigarette smoking and asbestos

It is important to identify promoting agents.

4. Knowledge at present does not enable one to forecast carcinogenicity based on chemical structure, but structure can supply clues. Structure alone cannot be relied on for classification.

Agrees with OSHA's use of short term tests in classifying in Category I.

4/7/78

SOUTHWEST ECONOMETRICS, INC.

Title:

Consulting Firm

Number of Pages:

3

Main Points Addressed:

Snell Economic Analysis

Summary:

Evaluating a "policy" as opposed to a specific program is highly unusual and most difficult.

The present proposal will not itself generate any economic costs. The cost to be generated by individual rulemakings is now speculative at best.

Because of unknown variables such as the quantities of substances in respective categories, the permissible exposure limits to be set and the actual standards to be applied the Snell study can only be considered speculative.

The failure to include or make available the primary data used to develop the report insulates it from important critical review.

The study is replete with "judgments".

The study is compromised by a lack of sufficient baseline data such as present plant exposure levels.

Concerning methodology, Snell is criticized for its use of "percent of dollar value of product" as a cost calculation factor; its failure to adequately deal with compliance economies where multiple carcinogens are in a workplace; and its use of certain NOHS data relating to downstream user industries.

4/11/78

STEVEN JELLINEK
(EPA Comments Attached)

Title:

Assistant Administrator for Toxic Substances,
Environmental Protection Agency

Number of Pages:

Jellinek Testimony - 6
EPA Comments - 30

Main Points Addressed:

(1) Generic approach to identifying carcinogens.

(2) Confirmation of positive animal tests.

(3) Priorities

(4) The regulatory response

(5) Quantification of risk

(6) Procedural problems

Summary of Jellinek Testimony:

The EPA regulatory process is briefly described. The first decision is whether a substance poses a carcinogenic risk. The second is what regulatory action, if any, should be taken.

EPA endorses OSHA's generic approach to identifying carcinogens. The weight of the evidence supports OSHA's positions that animal studies can be relied on to indicate potential human cancer risk, it is not possible to establish safe threshold levels, and statistically significant increases in benign tumors provide a basis for determining that a substance poses a carcinogenic risk.

EPA policy is that an unreplicated test alone can be an adequate basis for concluding that a chemical poses a carcinogenic risk. OSHA's policy is thus overly conservative in requiring replication or other confirmation.

Other differences between EPA and OSHA approaches to regulatory decision-making (none of which are questions of science) are (1) OSHA's proposed categorical classification scheme automatically requires (not permits) regulation on the basis of evidence of carcinogenicity, (2) OSHA's proposal does not explicitly estimate the magnitude of risk in the regulatory process, and (3) OSHA's proposed regulations include no mechanism for setting priorities for substances within categories.

With respect to the second point, OSHA should use estimation of risk to help establish priorities and to help determine the "feasibility" of various levels of control. The greater the degree of risk the tighter the control should be.

Summary of EPA Comments (Appended to Jellinek Testimony):

OSHA's approach to identifying carcinogens is generally endorsed and is consistent with the EPA approach with the exception of OSHA's position on confirmation or replication data. Specifically mentioned are the use of high dose, the non-existence of thresholds and relevance of benign tumors.

The criterion which permits rebuttal of a Category I presumption based on positive results which are "not scientifically relevant to man" needs to be tightened up to avoid opening up generic issues unnecessarily. Rebuttals should be limited to "new" evidence on generic issues.

OSHA should embrace risk assessment and quantification as EPA has done.

OSHA assigns too minor a role to potency and exposure factors -- this may be due to differing statutory responsibilities.

It is not sound to attach critical significance, as does the OSHA proposal, to confirmation or replication prior to making a Category I finding.

The OSHA proposal allows some discretion in classification criteria for determining whether a substance should be in Category I or II. This is good. OSHA, however, should spell out whether it expects

to exercise that discretion often or rarely and, if so, on what basis -- e.g., potency, exposure.

A serious problem in OSHA's procedures is a failure to build in any prioritization system. The filing of a citizen petition automatically triggers the process without regard to priorities. EPA suggests that a petition create only a "candidate substance" for regulation with the agency then considering priority matters such as exposure potential and available data on potency.

The process of presumption and rebuttal should be separated out procedurally. In the present proposal it is not. It could be another separate step in the regulatory process and, if so, should come early in the process to assure full public participation.

OSHA's procedural deadlines may be too ambitious. EPA's required timetable is compared.

Given OSHA's limited resources, the concept of setting standards for Category II substances based on acute or chronic non-carcinogenic effects will seriously compromise OSHA's objectives of streamlining the regulatory process for carcinogens. By doing so, OSHA introduces an illogical element into its system.

The "feasibility" concept needs to be explained in detail. Under the rubric of determining feasibility, OSHA may engage in a decision-making process not unlike EPA's assessment of risks and benefits under the Acts it administers, but OSHA's procedures must be spelled out. While it may not be possible to establish a precise formula for feasibility determinations, it should be possible to indicate some key issues and factors in determining economic and technical feasibility.

4/11/78

ROY E. ALBERT

Title:

Chairman, Carcinogen Assessment Group,
Environmental Protection Agency

Number of Pages:

6

Main Points Addressed:

(1) Need for flexibility in categorization criteria and regulatory responses.

(2) Proper role of risk assessment and risk quantification.

Summary:

The testimony begins by a description of the EPA process for regulating carcinogens. The EPA process is viewed a more "flexible," "weight of the evidence" approach.

The rigidity of OSHA's classification scheme is criticized by way of hypothetical examples.

The following recommendations for improving the OSHA proposal are offered:

"(1) The risk assessment should be completely independent of the regulatory decision-making process, i.e., it should involve only an objective assessment of the available scientific evidence. (2) The classification of agents into categories should be done separately from the risk assessment and use the proposed OSHA criteria only as guidelines rather than as rigid specifications. (3) The OSHA categories should be regarded as 'categories of regulatory action' and be based not only on the weight of evidence that an agent is a human carcinogen but also on consideration of the socio-economic consequences of regulation. The necessary additional flexibility is already provided within the OSHA categories by the re-

quirement for 'feasible' levels of regulation, assuming the determination of what is feasible will take into account the degree of risk.

* * *

". . .[B]ecause carcinogens can vary in potency by as much as a million fold, OSHA should strongly consider using quantitative risk assessment to the extent possible for prioritization of chemicals and as a factor in judging feasibility of regulatory control."

4/10/78

BO HOLMBERG

Title:

Associate Professor, Occupational Toxicology,
Department of Occupational Safety and Health,
National Board of Occupational Safety and Health,
Stockholm, Sweden

Also associated with Stockholm University.

Number of Pages:

31

Main Points Addressed:

(1) Cancer incidence

(2) Irreversibility, latency

(3) Insensitivities of animal tests and human studies

(4) Extrapolation

(5) Thresholds, dose response

Summary:

Over the last ten years, there has been an increased age-adjusted incidence of cancer for certain sites. The increase is due to causative environmental factors (implication is industrial chemicals).

All chemicals will not prove to be carcinogenic if given at high enough doses. There are only a few classes of chemicals for which some of the substances appear to be carcinogenic.

Cancer is an irreversible effect. Although there exists a dose-response relationship for chemical carcinogens, no threshold can be observed. Cancer can be produced by a single administration of carcinogens. The growth rate of tumors is independent of the dose of the initiator. Neoplastic changes will not be intensified or changed into more fatal effects upon increases in dose.

Weakness of epidemiology studies are discussed at length.

We presently underestimate the fraction of occupationally-induced cancers.

It is easier to control occupational carcinogens than other carcinogens.

It is unfair to compare voluntary risks such as tobacco smoking with involuntary workplace risks.

Even if it were possible to extrapolate down to a dose which is low enough to give a mean latency period longer than the expected lifetime of the population, individual latency periods will vary from the mean.

Insensitivities of animal tests are discussed. These insensitivities make extrapolation of dose response data from animals to humans in quantifiable terms very difficult.

The dose response curve in the low dose area seems to be linear.

Although there exists a conventional relationship between dose and response as far as the frequency of all tumors is concerned, small doses of a carcinogen may be more effective in producing certain cancers as compared to high doses.

Evidence indicates that exposures to low doses of a carcinogen over a long period of time are more effective than high doses over a short period of time.

Transplacental carcinogenesis is a particular insensitivity of animal tests.

There can be no "zero" risk and no "safe" level in the workplace but rather the level ought to be set at accepted low risk levels. Levels should be established in accordance with technical feasibility and socio-economic factors.

OSHA's position on benign/malignant tumors, particularly in the context of the mouse is defended.

OSHA should not ignore subcutaneous injection site tumors.

Decisions as to the carcinogenesis of chemicals are difficult and should be reserved for experts.

Positive results in a single species are sufficient to raise a Category I presumption. The OSHA position on positive/negative results is endorsed.

Category I controls should also apply to Category II substances.

4/10/78

DAVID RALL

Title:

Director, National Institute of Environmental Health Sciences, National Institute of Health

Number of Pages:

15

Main Points Addressed:

(1) Significance of occupational exposure in cancer incidence.

(2) The importance of animal experimentation in predicting human risks.

(3) Thresholds

(4) Degrees of confidence that can be placed in extrapolating from animal tests to humans.

Summary:

All responsible persons agree worker exposure to carcinogens should be reduced to the lowest level feasible. What is judged to be feasible depends on technical factors and costs of control.

Statements that chemicals are a minor contributor to cancers are somewhat misleading. Assuming a role of 1-5% for chemicals, the range would still be 3,800 to 19,000 cancer deaths per year. Further, these figures may be inaccurate because of the difficulties associated with epidemiology studies. In addition, very few epidemiology studies have been conducted. Of the 368 compounds reviewed in IARC monographs, less than 8% have received adequate investigation. Since cancer is a multi-phased process whose progression is influenced by many factors, it makes little sense to say only 1-5% of cancers are attributable to occupational exposures. Cigarette smoking and diet, being matters of personal preference, are much more difficult to control than exposure to chemicals.

The process of interpreting animal and human data is very complex. It is difficult to reduce this to a formula. There may be a case where a single positive experiment is conclusive or where three positive results are inconclusive.

> "Division of this spectrum [of possibilities] into discrete categories may be necessary for regulatory purposes, but it is necessarily arbitrary from a scientific point of view. Thus the recommendation of a scientist would be to make the criteria for categorization flexible, and to apply as much scientific judgment to each case as is compatible with legal and regulatory requirements."

The undertone of the concluding paragraphs seems to express some discomfort with the rigidity of OSHA's classification scheme.

A revised preamble to appear in subsequent IARC monographs will distinguish between chemicals for which there is "strong" evidence of carcinogenicity (chemicals shown unequivocally to produce malignant neoplasms) and "weak" evidence of carcinogenicity (evidence based solely on the appearance of such neoplastic lesions as lung adenomas and hepatomas in mice). This dichotomy, however, should not lead to rigidity with respect to data interpretation.