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Testimony to DOL

Statement of

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I am Edward J. Baier, Deputy Director of NIOSH. With me today are: Richard F. Boggs, Ph.D., Division of Criteria Documentation and Standards Development; David H. Groth, M.D. and Richard W. Niemeier, Ph.D., Division of Biomedical and Behavioral Science; Robert H. Hill, Jr., Ph.D. and Robert T. Hughes, Division of Physical Sciences and Engineering; Robert H. Schutz, Testing and Certification Branch, Division of Safety Research; Richard J. Waxweiler, Division of Surveillance, Hazard Evaluations, and Field Studies; and Howard A. Walderman, Office of General Counc~~il,~~ HEW. Our resumes are provided as Appendix A.

We welcome the opportunity to appear today to discuss the Notice of Proposed Rulemaking by the Department of Labor, Occupational Safety and Health Administration, entitled: "Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk."

The OSHA proposal to establish a generic regulation for control of occupational carcinogens is, to date, one of the most complete compilations of major scientific opinions, judicial decisions, and Federal agency policy statements concerning occupational carcinogenesis. NIOSH shares OSHA's concern to develop new procedures for the regulation of occupational carcinogens. Our concern starts with the fact that approximately 2,000 substances have been identified by NIOSH as being "suspect carcinogens." By definition, this means that NIOSH has found some scientific evidence, based on observations in human populations or on results from experimentation with laboratory test animals, of varying degrees of quality and quantity,

identifying those substances as having potential carcinogenic activity. Our concern is heightened by the fact that the list is expected to grow larger as 1) new evidence is obtained on existing chemicals, 2) published data on unlisted chemicals are reviewed, or 3) new chemicals are manufactured and tested.

NIOSH supports the overall concepts contained in the OSHA proposal. There are, however, several technical points, modifications and comments that we wish to offer for consideration. The proposed standard has been reviewed by a number of NIOSH occupational safety and health professionals. While it is difficult to formulate a concensus statement on such a broad issue as the regulation of carcinogens, we have attempted to bring forward the best thinking of our staff on what we consider to be the critical issues of the proposal. The issues we wish to address concern:

a) Terminology
b) Classification of Chemicals
c) Collection and Evaluation of Data
d) Determination of Exposure Limits, and
e) Model Standards

a) Terminology

Throughout the proposal the term "Toxic Substance" is equated with carcinogen and consists of substances for which a report of carcinogenicity

is available. To use the term "toxic substance" in this manner is likely to lead to future confusion, since carcinogens constitute only a subset of toxic substances. The Toxic Substances Control Act (TSCA) considers toxic substances to include all aspects of toxicity--not only carcinogenicity. We recommend terminology consistent with TSCA. In order to obviate this potential confusion, we recommend that the term "toxic substance" be deleted from the proposed category nomenclature and propose the following terms:

| | | |
|---|---|---|
| Category I | - | Probable [or Confirmed] Occupational Carcinogen |
| Category II | - | Suspect Occupational Carcinogen |
| Category III | - | Carcinogenic Evidence Inconclusive |

Such a descriptive title system would identify our present understanding of the seriousness of the carcinogenic potential. We do not recommend a Category IV in this classification system since U.S. workers would not have the potential for exposure to these agents and hence they would fall beyond the regulatory responsibility of OSHA as we understand it. Should these substances enter the U.S. workplace, they would automatically become eligible for classification into Categories I, II, or III.

We are in general agreement with the definition of "Potential Occupational Carcinogens." We also generally agree with the definition of short-term tests and their use in the initial assessment of carcinogenic potential.

b) Classification of Chemicals

There are a series of steps by which chemicals are classified into the

categories of carcinogens. Initially chemicals are identified as "Potential Occupational Carcinogens" based upon some evidence for carcinogenicity and/or mutagenicity.

Our concern is with Part III. "Classification and Regulation: The Proposal", subpart A. "General", regarding OSHA's approach for the orderly handling of the large list of potential carcinogens, e.g., those already identified by NIOSH. One option proposed by OSHA for accomplishing this is to establish a separate schedule of substances for handling on an alphabetical basis. We think a preferable alternative is to set priorities for evaluation of the substances based on an estimate of the degree of potential occupational hazard. This might be accomplished by cross referencing the NIOSH suspect carcinogen subfile with data from NIOSH's National Occupational Hazard Survey. This method for orderly handling of the large number of potential carcinogens could be done either prior to evaluating the data and making category assignments or after categorization but prior to initiating any rulemaking effort.

Another concern is the adequacy and soundness of animal and human data which indicate the substance may be carcinogenic. As classification can be "on the basis of other scientific evidence," due consideration of the scientific adequacy of test results can be properly incorporated into the decision-making process. If chemicals are reviewed on a case-by-case basis, NIOSH is satisfied that the procedures are sufficiently flexible to provide due consideration of the adequacy of the data.

Another concern in this section relates to issues of carcinogenic potency. We considered this issue in addition to the importance of co-carcinogens and promoters in the development of this testimony. However, as these are difficult issues to resolve, no conclusions have yet been reached which would enable us to make a definitive recommendation as to how they should be dealt with in OSHA's proposed standard. We feel that these are important issues and warrant further evaluation in subsequent refinements of the generic standard and policy statement. Perhaps this is an area where we might discuss in some depth the issue and attempt to identify prudent actions in the absence of clearcut recommendations.

A criterion for "Potential Occupational Carcinogen" is a "statistically significant decrease in latency period between exposure and onset of neoplasms." We recommend that the term "statistically significant" be defined as "at the 95% confidence level." Further, because many exposures may be continuous, we recommend that the words "onset of" precede the word "exposure" in the criterion text.

A criterion for assigning chemicals to an OSHA Category I Toxic Substance is the necessity for replicated results. Replication may be achieved by obtaining a similar significant increase in tumor incidence in the same species where the experiments were performed with at least an independent set of control animals. Although we agree with the need for "replicating" animal experiments in order to include the substance in Category I (an exception might be made when highly significant results are obtained in an adequately conducted and biologically-appropriate test), we believe that

simple replication using the exact study design may not be particularly definitive. We would hope that where researchers have the option, such confirming experiments would be performed in a different laboratory, perhaps using a different sex or strain of test animal, additional dose levels, or a different route of administration so as to provide for a more comprehensive and accurate assessment of the substance.

The concepts expressed in the proposal (1990.111) on the rebuttal of a Category I classification are well-founded but sufficiently general as to provide wide latitude for disagreement. A review mechanism as suggested in the following section on Collection and Evaluation of Data, which includes experts from various agencies should 1) minimize conflicting treatment of substance by various enforcement agencies; 2) assist in the convergence of the evaluation process; and 3) minimize controversy during regulatory exercises undertaken with this proposal.

c) Collection and Evaluation of Data

We believe that the determination of carcinogenic hazard and the appropriate control recommendations should be arrived at by a thorough analysis of all available data, plus a review by scientists including occupational health experts, and with the conclusions documented. Only by such an in-depth evaluation can scientifically sound judgments be made as to the potential hazards and the control necessary to protect U.S. workers

Section 1990.103 provides for the review of data submitted to OSHA from "interested persons" or obtained by OSHA's own "cognizance."

We believe that there should be a systematic method to obtain and evaluate data in order to assure that appropriate data are secured and that all occupationally significant potential carcinogens are identified. Such a system could include the assembly and review of all relevant human and animal data bearing on the potential for carcinogenicity, including that contained in the NIOSH Registry of Toxic Effects of Chemical Substances, and the analysis of data based on comparisons of pharmacokinetics, metabolism, and other factors such as dose levels, route of administration, lesions induced, and statistical considerations. One way to evaluate these data is for OSHA to institute a procedure which would utilize the expertise available within other Federal agencies. NIOSH could take the lead in assuming primary responsibility for this evaluation including drawing upon the scientific expertise of other agencies such as NCI, FDA, EPA, CPSC, and NIEHS.

d) Determination of Exposure Limits

It is important that the "lowest feasible level" be determined by incorporating a sufficient concern for health effects. The proposal does not indicate how and the criteria by which "feasibility" will be determined. The lowest feasible limit is likely to be a function of engineering controls, and/or monitoring and analytical methodology, and/or

economic factors. We believe that good public health policy dictates that the health risk be the primary consideration in this process.

It has to be recognized that if the lowest feasible level cannot be set so that it is lower than that concentration which has been found to cause cancer in humans and/or animals, then exposure in the workplace should not be permitted.

An example of a real situation to illustrate these points is the experience of industry to comply with proposed environmental limits for vinyl chloride. Initially the producers of vinyl chloride claimed that it would be impossible to comply and that the industry would be virtually destroyed if the standard were enforced. Serious negotiation and a positive stance by OSHA, based on health effects data, encouraged reevaluation of the feasibility of reducing the permissible exposure limit of vinyl chloride to below 50 ppm and compliance at a much lower level was achieved. We believe that demonstrated health effects and safety factors should have a "technology forcing" effect in the direction of reducing risk and increasing protection of worker health. In this regard, we feel that new source performance standards should be considered in the OSHA model regulations so that new facilities would automatically incorporate the best available control technology.

e) Model Standards

In our opinion, certain requirements of the Model Standards are not

sufficiently flexible to account for differences in properties of the various substances to which they will be applied. Specifically, requirements for (1) prevention of dermal and eye exposures; (2) protective clothing and equipment; (3) hygiene facilities and practices; and (4) lunchroom facilities, should be tailored to the chemical and physical properties of the substance rather than standardized for all substances. Instead of developing different requirements for every substance considered, we believe that basic requirements for large groups of substances, e.g., gases, vapors, dusts, etc., can be developed and applied as appropriate. A similar approach was used in the NIOSH/OSHA Standards Completion Program and could have application in this standard.

The reporting requirements under "Notification of Use and Emergencies" may present an excessive burden on both employers and OSHA compared to the benefits to be derived. We believe OSHA should carefully consider whether, in order to adequately develop an effective compliance program, such extensive reporting is required. Perhaps as a minimum it might only be necessary to report the carcinogens being used in the workplace and the approximate number of workers employed in the area; appropriate use records could then be maintained only at each employer's worksite or other recordkeeping location. They could be submitted to OSHA Area Offices only in "emergency situations." NIOSH believes this should significantly reduce reporting requirements and still provide adequate information to enable protection of workers.

Under the "methods of compliance" requirements, the proposal does not require warning signals when process control failures occur nor periodic measurements that demonstrate the continued effectiveness of ventilation systems or other control technologies where they are used. NIOSH recommends that the standard include both requirements.

If controls are "feasible" and utilized, they must be evaluated if there is a process change. In addition, a maintenance program for the control systems is essential. The OSHA proposal does not address such requirements. Work practices preventing exposure of maintenance personnel during maintenance procedures or system repair should also be required.

The proposal also requires that the employer institute a respiratory protection program in accordance with 29 CFR 1910.134(e). However, 29 CFR 1910.134(e) (5) allows the use of qualitative fit tests to meet the requirements for having the respirator "fitted properly." We recommend the required use of quantitative fit tests in all respirator programs, especially those used for protection against potential occupational carcinogens. Test equipment for this type of quantitative testing is commercially available, and NIOSH will work with OSHA to develop uniform guidelines for this type of testing.

We recommend that Table 1 of each standard that contains a listing of the appropriate type of respirator for various conditions of use be generated with a standardized method for determination, such as the Joint NIOSH/OSHA Standards Completion Program Respirator Decision Logic.

We also recommend that where any potential occupational carcinogen may be released into the workplace air, smoking by employees be prohibited.

We agree that a work history, medical history, and physical examination are essential to maintain effective medical surveillance. For the sake of clarity, however, we think the proposal should be so stated as to specify the entire urinary tract and not just the renal system. We also feel strongly that medical exams must assess toxicity for all target organs and not just those shown to be positive for cancer in animal and/or epidemiologic studies. A chemical shown to cause cancer in animals at one site may cause cancer in humans at another site. Furthermore, carcinogens may also produce toxic effects other than cancer. The physician providing medical examinations should be urged to consider all toxic effects.

Under the recordkeeping availability requirement, the proposed wording "The employer shall assure that employee medical records required to be maintained by this section, be made available, upon request, for examination and copying, to the affected employee or former employee, or to a physician designated by the affected employee, former employee, or designated representative" should be changed to conform with the recent wording proposed by OSHA (42 FR 55623) under "Access to the Log of Occupational Injuries and Illnesses to Employees and their Representatives." That wording as proposed in the Federal Register on October 18, 1977, allows record accessibility to "the employee, former employee, and their representative."

In conclusion, we reaffirm the commitment of NIOSH to continue working closely with OSHA in further identifying and controlling occupational hazards, including carcinogens. We look forward to cooperating with OSHA in developing and applying this generic standard for potential occupational carcinogens in order to arrive at regulations which provide the best attainable protection of workers.

That concludes our formal statement. However, after submission of this statement, for the record, we received a series of questions from OSHA. We have attempted to answer these questions to the best of our ability in the allowable time-frame. The questions from OSHA are attached as APPENDIX B. Our responses to these questions are attached as APPENDIX C.

# APPENDIX C

The following are responses to some of those questions received from OSHA. Responses to some questions have not been furnished in this appendix either because they have been discussed in the prepared statement or because of the complexity of the issues and the short amount of time available to gather and evaluate the data, prepare an appropriate response and meet the April 4, 1978 due date for submissions to the OSHA Docket Office.

Questions 1, 2 & 21

The proposal recommends that animal studies be used to identify potential human carcinogens. This is quite appropriate. In fact, the purpose of the Proposal is to decrease human experimentation, i.e., decrease occupational exposures to carcinogens. Although there might not be 100% correlation between the effects of chemicals on animals and humans, that is not surprising nor should it discourage us from pursuing our goal. It should be noted that of the chemicals and/or classes of chemicals that have been found to cause cancer in humans, including: benzidine; 2-naphthylamine; bischloromethylether; chloromethyl methyl ether; 4-aminodiphenyl; N,N-bis(2-chloroethyl)2-naphthylamine; chrysotile; crocidolite; amosite; cadmium compounds; chromium compounds; nickel compounds; arsenic compounds; beryllium compounds; benzene; auramine; diethylstilboestrol; and vinyl chloride, all except possibly benzene have been found to cause tumors in animals (Tomatis, 1976; Newberne, 1975; Bayliss and Wagoner, 1977; Infante, et al., 1977; Oswald and Goerttler, 1971). Thousands of workers have developed cancer as a result of exposures to these agents. They have unwittingly provided scientists with the information needed to make the correlation between animal and human responses to carcinogens.

Another important consideration is the animal species and strain that should be used in the test systems. The degree of correlation between each species and humans as well as the relative cost in performing the studies must be considered before recommendations can be made. Obviously, those species which have been consistently positive when tested with known human

carcinogens are acceptable. Of the human carcinogens mentioned above, almost all have been shown to be positive in rats and several of them are positive in mice. Fortunately, these are the mammalian species which are least costly to process, and, therefore, their use can be recommended with very few or no qualifications.

Some scientists believe, however, that the mouse is too sensitive to carcinogens, and, therefore, the rat is a better model. Implied in this opinion is that mice will respond to lower doses of carcinogens than will humans. Since quantitative data on carcinogen exposures to humans is almost non-existent, that comparison is impossible to make. The fact that the mouse is slightly more sensitive to carcinogens than the rat is well-known (Tomatis, 1973), however, the model should be designed to protect humans, not rats. Another argument that has been frequently used to exclude mice is that they have a high frequency of spontaneous tumors which might be induced by hormones and/or viruses, and that tumor promotion, but not induction, is measured when that model is used. What the proponents of that argument fail to recognize is that whatever variables are present in mice might also be present in humans. Human tumors might also be induced by yet unrecognized viruses, and hormones certainly play a role in human carcinogenesis (Furth, 1975). It is not unreasonable to expect that the mechanisms of carcinogenesis operative in mice might be identical to those in humans, for example, humans have no zymbal gland. It is certainly possible that many carcinogens in humans are in fact co-carcinogens. There is no method to determine this with any degree of certainty in humans.

Question 4

It has been estimated that occupational cancer represents about one to five percent of the cancer cases reported annually in the United States. We don't know how valid the estimates are of the total incidence of occupational cancer. We know that there are a significant number of occupational cancer cases e.g., from 2-naphthylamine, asbestos, arsenic, vinyl chloride and this alone justifies vigorous preventive action.

Since numerous studies (vinyl chloride - B(a)P, Maltoni and Lefemine, 1975; Bingham and Falk, 1969) etc., have proven that a dose-response relationship is evident in the area of carcinogenesis just as in other areas of toxicology, it is readily apparent that positive results obtained at high doses indicate that lower risks are to be expected at lower doses. The specific limitations in estimating the lower risk factors are inherent in the specific limitations of the data gathering system. Such factors as animal numbers, number of dose levels, confidence limits and other factors must be considered in properly evaluating the dose-response relationship. In addition to a socially acceptable value of risk, the establishment of an absolute value of risk, rather than a relative value of risk (Subcommittee on Environmental Mutagenesis, 1977) is mandated by the OSHAct in regard to occupational carcinogenesis.

Question 5

a. The first direct connection between an occupational exposure and risk of a specific cancer was that of chimney sweeping and cancer of the scrotum pointed out by Pott in 1775. He recognized this association because he saw several affected chimney sweeps but little or none of the disease in persons with other occupations. The disease was exceedingly rare in the general population, and the risk ratio for chimney sweeps was quite high.

About 1880 Hirting and Hesse showed that "mountain disease" was a lung neoplasm. This condition was recognized as an entity in the Middle Ages because of its frequent occurrence among young miners despite the rarity in the general population. In 1895 the German surgeon, Rehn, published on the hazard of bladder cancer among dye workers. Rehn's association was based not on an exceedingly high risk ratio but rather on the absolute high frequency of the disease among exposed persons.

During the past several decades instances of occupational carcinogens have continued to be recognized both on the basis of an extremely high risk ratio and a high incidence rate among exposed persons.

The following tables show various agents which have been identified as occupational carcinogens on the basis of epidemiologic studies and confirmed and suspected carcinogens by target organ.

* TABLE I

Classification of Occupational Carcinogens

A. Organic agents

1. Aromatic hydrocarbons

| Agents | Affected organ(s) | Incubation period (years) | Risk ratio | Occupation |
|---|---|---|---|---|
| Coal soot<br>Coal tar<br>Other products of coal combustion | Lung, larynx, skin, scrotum, urinary bladder | 9-23 | 2-6 | Gashouse workers, stokers, and producers; asphalt, coal tar, and pitch workers; coke-oven workers; miners; still cleaners; chimney sweeps |
| Petroleum<br>Petroleum coke<br>Wax<br>Creosote<br>Anthracene<br>Paraffin<br>Shale<br>Mineral oils | Nasal cavity, larynx, lung, skin, scrotum | 12-30 | 2-4 | Contact with lubricating, cooling, paraffin or wax fuel oils, or coke; rubber fillers; retortmen; textile weavers; diesel jet testers |
| Benzene | Bone marrow (leukemia) | 6-14 | 2-3 | Explosives, benzene, or rubber cement workers; distillers; dye users; painters; shoemakers |

* Philip Cole and Marlene Goldman, Chapter 8-0

"Persons at High Risk of Cancer", edited by J. Fraumenic, National Cancer Institute

A. Organic agents (continued)

1. Aromatic hydrocarbons (continued)

| Agents | Affected organ(s) | Incubation period (years) | Risk ratio | Occupation |
|---|---|---|---|---|
| Auramine<br>Benzidine<br>α-naphthylamine<br>β-naphthylamine<br>Magenta<br>4-aminodiphenyl<br>4-nitrodiphenyl | Urinary bladder | 13–30 | 2–90 | Dyestuffs manufacturers and users; rubber workers (pressmen, filtermen, laborers); textile dyers; paint manufacturers |

2. Alkylating agents

| | | | | |
|---|---|---|---|---|
| Mustard gas | Larynx, lung trachea, bronchi | 10–25 | 2–36 | Mustard gas workers |

3. Others

| | | | | |
|---|---|---|---|---|
| Isopropyl oil | Nasal cavity | 10+ | 21 | Producers |
| Vinyl chloride | Liver (angiosarcoma), brain | 20–30 | 200 (liver)<br>4 (brain) | Plastic workers |

A. Organic agents (continued)

3. Others (continued)

| Agents | Affected organ(s) | Incubation period (years) | Risk ratio | Occupation |
|---|---|---|---|---|
| Bis(chloromethyl) ether<br>Chloromethyl methyl ether | Lung (oat cell carcinoma) | 5+ | 7–45 | Chemical workers |

B. Inorganic agents

1. Metals

| | | | | |
|---|---|---|---|---|
| Arsenic | Skin, lung, liver | 10+ | 3–8 | Miners; smelters; insecticide makers and sprayers; tanners; chemical workers; oil refiners; vintners |
| Chromium | Nasal cavity and sinuses, lung, larynx | 15–25 | 3–40 | Producers, processors, and users; acetylene and aniline workers; bleachers; glass, pottery and linoleum workers; battery makers |

B. Inorganic agents (continued)

1. Metals (continued)

| Agents | Affected organ(s) | Incubation period (years) | Risk ratio | Occupation |
|---|---|---|---|---|
| Iron oxide | Lung, larynx | – | 2–5 | Iron ore (hematite) miners; metal grinders and polishers; silver finishers; iron foundry workers |
| Nickel | Nasal sinuses, lung | 3–30 | 5–10 (lung)<br>100+ (nasal sinuses) | Nickel smelters, mixers, and roasters; electrolysis workers |

2. Fibers

| | | | | |
|---|---|---|---|---|
| Asbestos | Lung, pleural and peritoneal mesothelioma | 4–50 | 1.5–12 | Miners; millers; textile, insulation, and shipyard workers |

3. Dusts

| | | | | |
|---|---|---|---|---|
| Wood | Nasal cavity and sinuses | 30–40 | – | Woodworkers |
| Leather | Nasal cavity and sinuses, urinary bladder | 40–50 | 50 (nasal sinuses)<br>2.5 (bladder) | Leather and shoe workers |

C. Physical agents

1. Nonionizing radiation

| Agents | Affected organ(s) | Incubation period (years) | Risk ratio | Occupation |
|---|---|---|---|---|
| Ultraviolet rays | Skin | varies with skin pigment and texture | – | Farmers; sailors |

2. Ionizing radiation

| | | | | |
|---|---|---|---|---|
| X-rays | Skin, bone marrow (leukemia) | 10–25 | 3–9 | Radiologists; medical personnel |
| Uranium<br>Radon<br>Radium<br>Mesothorium | Skin, lung, bone, bone marrow (leukemia) | 10–15 | 3–10 | Radiologists; miners; radium dial painters; radium chemists |

3. Other

| | | | | |
|---|---|---|---|---|
| Hypoxia | Bone | – | – | Caisson workers |

**Table 2 Confirmed and suspected occupational carcinogens* by target organ.**

| Target Organ/Tissue | Occupational Carcinogen: Confirmed | Occupational Carcinogen: Suspected |
|---|---|---|
| Bone | | Beryllium |
| Brain | Vinyl Chloride | |
| Gastroenteric Tract | Asbestos | |
| Hematopoietic Tissue (leukemia) | Benzene<br>Styrene Butadiene and other Rubber Manufacture Substances | |
| Kidney | Coke Oven Emissions | Lead |
| Larynx | Asbestos, Chromium | |
| Liver | Vinyl Chloride | Aldrin<br>Carbon Tetrachloride<br>Chloroform<br>DDT<br>Dieldrin<br>Heptachlor<br>PCB's<br>Trichloroethylene |
| Lung | Arsenic<br>Asbestos<br>Bis (chloromethyl) ether<br>Chloromethyl methyl ether<br>Chromates<br>Coke Oven Emissions<br>Mustard Gas<br>Nickel<br>Soots and Tars<br>Uranium<br>Vinyl Chloride | Beryllium<br>Cadmium<br>Chloroprene<br>Lead |
| Lymphatic Tissue | | Arsenic<br>Benzene |
| Nasal Cavity | Chromium, Isopropyl Oil, Nickel, Wood Dusts | |
| Pancreas | | Benzidine<br>PCB's |
| Pleural Cavity | Asbestos | |
| Prostate | | Cadmium |
| Scrotum | Soots and Tars | |
| Skin | Arsenic<br>Coke Oven Emissions<br>Cutting Oils<br>Soots and Tars | Chloroprene |
| Urinary Bladder | 4-Aminobiphenyl<br>Benzidine<br>B-Naphthylamine | Auramine<br>4-Nitrodiphenyl<br>Magenta |

*Occupational Diseases - A Guide to their Recognition - U.S. Department of Health, Education and Welfare - NIOSH

Table 3 Suspected carcinogens based upon structural similarity to vinyl chloride.

| Suspected Carcinogen | Structure |
|---|---|
| Vinyl Chloride | $H_2C=CH$<br>$Cl$ |
| Bromoprene | $H_2C=CHCH_2Br$ |
| Chloroprene | $H_2C=CHCH_2Cl$ |
| Epibromohydrin | $H_2C-CH-CH_2Br$<br>$\diagdown O \diagup$ |
| Epichlorohydrin | $H_2C-CH-CH_2Cl$<br>$\diagdown O \diagup$ |
| Perbromoethylene | $Br_2C=CBr_2$ |
| Perchloroethylene | $Cl_2C=CCl_2$ |
| Tribromoethylene | $Br_2C=CH$<br>$Br$ |
| Trichloroethylene | $Cl_2C=CH$<br>$Cl$ |
| Styrene (Vinyl Benzene) | $H_2C=CH$<br>$\vert$<br>$\hexagon$ |
| Vinyl Bromide | $H_2C=CH$<br>$Br$ |
| Vinylidene Bromide | $H_2C=CBr$<br>$Br$ |
| Vinylidene Chloride | $H_2C=CCl$<br>$Cl$ |

b. No one study approach can provide all or even most of the needed health information. While epidemiologic studies in the occupational setting have the potential to determine effects of long term low level exposures, the difficulty in making quantitative estimates of present exposures and the even greater problem in determining past exposures makes it hard to obtain accurate dose response data. On the other hand, while more accurate dose response data can be derived from toxicological studies using experimental animals, one is always faced with the difficulty of extrapolating results from experimental animals to humans and often with the additional problem of extrapolating from observed higher dose levels to lower dose levels. However, when the two study approaches are utilized in a coordinated way, benefits of each approach can be maintained and many of the individual methodological weaknesses can be overcome.

The following table shows these strengths and weaknesses.

Table 4*

DISCIPLINARY APPROACHS TO HEALTH EFFECTS OF AIR POLLUTION

| Discipline | Population studied | Strengths | Weaknesses |
|---|---|---|---|
| Epidemiology | Communities<br>Diseased groups | Natural exposures<br>Observation in man<br>No extrapolations<br>Vulnerable groups included<br>Long term, low-level effects evaluated<br>Study many people | Quantifying exposure difficult<br>Many covariates<br>Minimal dose response data<br>Association vs. causation<br>Can only make few health measurements<br>Long latent periods for disease a problem |
| Toxicology | Animals<br>Biochemical systems<br>Cells | Easy to obtain dose-response data<br>Rapid data-acquisition<br>Cause-effect more definite<br>Mechanisms of response<br>Predict shapes of dose response curves<br>Administer toxic materials<br>Study acute and chronic effects | Realistic models of human disease?<br>Extrapolation from animals to man<br>Threshold of human response?<br>Artificial exposures |

*Dr. Carl Shy, "Strengths and Weaknesses of Epidemiological, Clinical and Toxicological Study Approaches," Chemist/Meteorologist Workshop 1975, U.S. Energy Research and Development Administration

c. The impact of epidemiologic studies in cancer research, such as the studies on cigarette smoking and lung cancer, prompted a recent Nobel Laureate to proclaim these studies as the major scientific finding of the 20th century.

It is doubtful that the impact of smoking on lung cancer incidence would have been known if research had been limited solely to cellular and whole animal studies. Although agents contained in cigarette smoke have been shown to induce cancer in laboratory animals, the sum of the carcinogenic effects of the known agents does not equal that of the cigarette smoke condensate. Particular difficulty has been encountered in inhalation studies of cigarette smoke on laboratory animals because the animals, particularly smaller species such as the rat, frequently die from the acute toxic effects of the nicotine and carbon monoxide in tobacco smoke. Another problem stems from the fact that the upper respiratory tract of experimental animals, particularly the nose, is much different from analogous human structures resulting in a more efficient filtration of smoke in the upper respiratory tract of these animals.

There is mounting epidemiologic evidence from a series of occupational health studies incriminating benzene as a possible leukemogenic agent. Thus far, no animal studies have been able to demonstrate this effect. Similarly, the carcinogenic activity of

arsenic has been demonstrated through epidemiologic but not by toxicologic studies. If reliance were placed solely on cellular and animal tests, then the importance of benzene and arsenic as carcinogenic agents would presently be unrecognized.

According to Sir Austin Bradford Hill, more weight must be given to positive as opposed to negative studies. Negative epidemiologic studies, particularly in cancer, cannot be construed as providing firm evidence of safety. This is because of the problems of latency and the small number of people often observed in epidemiologic carcinogenic studies which often preclude demonstration of statistically significant differences.

d. If the appropriate steps are used in epidemiologic research, then descriptive studies have the potential to identify unusual clusters and high risk individuals for subsequent study which should then limit the number of negative studies.

Question 6

It has been customary to rely upon animal studies in the absence of human evidence for a carcinogenic assessment of chemicals. An examination of the literature and of the experience in this method of approach reveals that animal data can be satisfactorily used as a predictor of human response.

The development of the vinyl chloride study, the coal tar/coke oven emission studies and various other examples illustrate the predictive value of animal bioassay methods.

In addition, the correlation between species with certain carcinogens such as benzo(a)pyrene, bischloromethylether, aminodiphenyl, benzidine, vinyl chloride, etc., have been in excellent agreement, even though the target tissue may differ among the species tested. In the case of benzo(a)pyrene, nine species of animals have been tested and all found to respond to this widely tested ubiquitous carcinogen. (Survey of Compounds Which Have Been Tested for Carcinogenic Activity - NCI).

If the responses of animals to known human carcinogens are examined it becomes obvious that all human carcinogenic chemicals, with the possible exception of arsenic and benzene, are also carcinogenic for animals.

The inhalation and percutaneous routes of exposure are the obvious routes of choice in experimental carcinogenesis studies when considering occupational exposure to chemical carcinogens. These routes are also the

choice when considering experimental design of studies to investigate oth toxic agents. However, it is well known that clearance from both the upper airways and the deep lung involves the mucociliary escalator in which materials are cleansed from these areas and usually find their way into the alimentary tract, in lieu of expectoration. Therefore, the oral route of administration via either stomach intubation, for purposes of exact quantitation of dose, or through consumption of food or water containing contaminants, is a perfectly adequate route of administration to test the carcinogencity of chemicals and complex mixtures found in the occupational environment.

Inhalation is usually the preferred route of a adminstration in animal studies for judging the carcinogenicity of airborne substances. Because of the expense of this type of study and methodologic difficulties, other routes, especially per oral, are used. In the usual case, this route gives valid, extrapolatable information, but each case has to be considered individually. Similarly, other routes, e.g., topical application, give useful information. Injection site sarcomas by themselves, probably do not indicate carcinogenicity by other exposure routes. They may indicate specific hazards in the event of accidental implantation of the substances.

The validity of using the maximum tolerated dose in rodent bioassays has been discussed and debated for a number of years. It is appropriate to mention that the National Cancer Institute as well as other agencies such as NIOSH, FDA and EPA continue to consider this as an appropriate approach in experimental bioassays. The reasons for this choice are obvious when considering economics and the probability of response.

Question 10

Present knowledge does not permit development of a consistent and rational basis for decisions on additive and synergistic effects. Complicating this problem is the question of promoting agents and co-carcinogens, widely and variously used terms without the same meanings to everyone.

Additive effects should be assumed when two agents cause cancer at the same site, especially when the two agents also have chemical similaries, such as PN's or aromatic amines. Synergistic effects should be assumed only when there are data or principles suggesting in the specific case that potentiation is likely. Similarly, co-carcinogenicity and promotion should not be assumed except in a specific case where there are data or principles that apply. In clearcut areas involving personal habits such as smoking, counseling of workers should be called for. Other areas of personal habits, such as diet or lifestyle, should not be considered in this proposed standard, at least until the issues are clearer.

Questions 15 & 16

Questions 15 and 16 are closely related and will be answered together. The problem of additive and synergistic effects is extremely difficult to assess with available scientific methodologies, either toxicology or epidemiology. To date, the scientific community has not adequately dealt with this problem. Toxicology and epidemiology both provide valuable information about carcinogenic risk. The problems of additive (or antagonistic) and synergistic effects do not make dose-response data in test animals irrelevant. Epidemiology and toxicology have both strengths and weaknesses. However, by combining two methodologies, in this case toxicology and epidemiology, it is often possible to overcome some of the weaknesses of each individual methodology, yet retaining their strengths. From this point of view, corroborating data on carcinogenic risk from both epidemiology and toxicology provides the most defensible data as to carcinogenic risk. Most toxicology studies assess effects of single exposures. It is virtually impossible to artificially generate an exact replica of the complex workplace environment in any toxicologic experiment. One of the greatest strengths of the epidemiology approach is to observe the effects of this complex environment directly in man. However, unless the possible synergistic or additive effect is specifically tested either epidemiologically or toxicologically, it is impossible to assess the importance of such interactions. In the final analysis, though, health may still be protected even if precise information on interactions is not available. This is because a given compound in a complex mixture may often serve as an index, which when controlled, will also result in decreased exposure to all compounds in the complex mixture. The situation with coke oven emissions is an excellent example in this regard.

Question 19

Latency refers to the long period of cancer induction. Because of the uncertainties in identifying the specific time or event in the genesis of the cancer and the uncertainties in identifying the cancer itself, the term latency is not precise. It usually is taken to be that interval between the first known exposure to the cancer-causing substance and the first evidence of the consequent cancer, which is often at autopsy.

Whether the cancer process is initiated by the first exposure is not known; it is generally thought that the process is initiated by the effect of repeated exposures, but there are rational bases for suggesting that any one of these repeated exposures may have been the initiating event. It is conceivable that both ideas are correct, for example, it might be that the cancer is initiated by one exposure and is enhanced sufficiently by subsequent exposures to progress to enough overt cases to constitute a statistically significant excess (whether in an epidemiologic survey or an experimental animal investigation). However, this speculation should not obscure the point that latency is an imprecise term referring to the many years required for the development of most cancers to the point they are observed and is defined more precisely in specific investigations or surveys for the purpose of that study.

Question 28

According to a report from the DHEW Subcommittee on Environmental Mutagenesis (1977), mutagenesis (short-term or in vitro) testing, in addition to providing valuable information on the risk to future generations, can provide valuable information regarding other toxicological manifestations. Examples are cited stating that there is an "apparent relationship between carcinogenicity and mutagenicity" (McCann, et al., 1975; McCann and Ames, 1976). However, the predictive value of short-term mutagenicity tests for carcinogenicity is currently under investigation, involving numerous efforts to assess the use of short-term mutagenicity tests.

The Subcommittee Report goes on further to state that the utility of mutagenicity test procedures for screening of chemicals for somatic effect, for example, carcinogenicity is not predicated on the assumption that the effect is due to mutations in somatic cells; but "the empirical demonstration of a high correlation between mutagenicity and the effect of concern (carcinogenesis) is a sufficient basis for establishing a role for mutagenicity testing as a predictive tool regardless of the mechanism involved."

There is widespread belief among investigators in the cancer area that DNA damage is involved in the induction of cancer. This is the basis for the supposition that carcinogens might be detected by the consequences of DNA damage in simple systems (Bridges, 1976).

Short term or *in vitro* tests that have had some testing for validation purposes included those referenced by Bridges (1976). Many other validation tests are ongoing (DeSerres, 1977; Dunkel, 1978). Reports are available commenting on the state of the art status of *in vitro* testing for carcinogenesis (Casto, 1977; Kouri and Schechtman, 1977; Conservation Foundation, 1977).

For scientific purposes, justification of the use of short-term tests for the purpose of screening thousands of chemicals for their suspected carcinogenic activity and for the purpose of prioritizing these chemicals for long-term animal bioassay, appears to be adequate. However, the original intent for utilization of these tests was only for these two objectives and not for use as a confirmational test for long-term animal bioassay.

It is inappropriate at this time to attempt to substitute a short-term test for a long-term animal bioassay for at least two reasons:

(1) Validation procedures are not complete and correlations between the test systems have not been adequately performed; and

(2) The outcome of the short-term tests as compared to the long-term bioassay are not biological equivalents. In one case the end point is mutagenesis, in the other case, carcinogenesis. However, one (mutagenesis) may often cause the other (carcinogenesis).

Question 31

In the attempts to develop models for predicting human carcinogens prolonged debates have centered around the type of lesion in animals that must be induced before a chemical can be called a carcinogen. Particular attention has been given to the mouse hepatoma (Butler and Newberne, 1975). Some scientists believe that most mouse hepatomas are not cancers because they do not metastasize, and imply that the mouse hepatoma is, therefore, not predictive. This argument is illogical. In the first place, not all hepatocellular carcinomas metastasize in any species studied, yet they are frequently responsible for the death of the hosts. Of 33 mice that died subsequent to chronic exposures to 4-dimethylaminoazobenzene, 71% died as a result of hepatocellular carcinoma (with ascites and/or anemia) yet pulmonary metastases were infrequently observed (Gellatly, 1975). Metastases are observed in humans in only approximately one-half of patients with hepatocellular carcinomas (Robbins, 1975). In the second place, even the spontaneous hepatocellular carcinomas in mice seldom metastasize. In fact, very few of any of the spontaneous neoplasms in mice or rats ever metastasize. In this way, rodents are more resistant than humans and possibly are <u>not</u> sensitive enough to the induction of cancer as we know it in humans. The reasons for that might also be explained on various factors that modify the ability of tumors to metastasize (Fidler, 1975). Thirdly, for predictive purposes there is no reason why the rodent tumors need metastasize. There need only be a correlation between cancer in man and a neoplasm in animals, and this has already been demonstrated many times.

It has also been observed that a carcinogen does not always produce tumors in the same organs in all species. The mouse liver responds more readily than most other tissues with most of the carcinogens that have been tested. Yet it is still predictive for cancer at other sites in other species, including man (Tomatis, 1973; Newberne, 1975).

Another consideration in evaluating a predictive model for human carcinogens is the route of administration. Although the route of administration might not be important in determining whether or not an agent is carcinogenic for research purposes, it is important from a preventive health standpoint. To properly evaluate carcinogenicity, the suspect agents should be administered to animals by the same routes as humans are exposed, namely, via the lungs, gastrointestinal tract, dermally and in some cases intramuscularly, intradermally and subcutaneously. The latter conditions would apply, for example, to those agents such as metal fragments that might become embedded in skin or muscles. In industrial exposures to particulates, oral exposures are frequently as important as pulmonary exposures in as much as the particulates that are trapped in the upper respiratory tract are usually swallowed.

Although in the above discussions chemicals have been given primary consideration as carcinogens, some consideration should also be given to physical agents, e.g., ultraviolet and infrared irradiation and heat. To exclude physical agents from consideration in the regulatory process is unwarranted. To exclude any agent on the basis of its proposed mechanism of action is also unwarranted, since the mechanism is not being regulated, but instead the agent. It is, therefore, recommended that paragraph (1) in section 1990.111 be deleted from the Proposal.