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AOMA Position Statement on OSHA's Generic Approach to Carcinogen Rulemaking

Editor's Note: The following statement, which was unanimously endorsed by the Board of Directors of the American Occupational Medical Association, was prepared by Robert E. Eckardt, M.D., Director of Research and Environmental Health for Exxon Corporation, and a former President of the Association. Dr. Eckardt is scheduled to present the statement at the hearings on the Occupational Safety and Health Administration's proposed regulation entitled "Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk," which will begin May 16 in Washington, D.C.

My name is Robert Eckardt. I am delighted for the opportunity to testify on behalf of the American Occupational Medical Association (AOMA) on OSHA's proposal. I was President of AOMA in 1960-1961 and have spent the last thirty years in occupational medicine and toxicology, including occupational cancer and carcinogenesis, so that this topic is not a new one to me. An abbreviated curriculum vitae is attached which gives further details of my training and background.

The OSHA proposal, "Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk," is a useful concept in rulemaking. However, in establishing this three-category approach, OSHA has made a number of simplifying assumptions which affect the scientific or technical validity of the proposal and hence its suitability. In this presentation, six of these issues will be addressed and a counterproposal made. These issues are as follow:

1. Relative potency of carcinogens.
2. Extrapolation from animal data to an assessment of hazard in man.
3. The "Everything is Carcinogenic" fallacy.
4. Significance of benign neoplasms in experimental animals.
5. Single-hit theory vs. multiple causation of cancer.
6. Medical tests — choice and interpretation.

Timeliness of Opinion

At the outset, it is important to recognize that much of the basis for the OSHA proposal comes not from the established, referenced scientific literature but from reports or opinions of individual scientists and agency committees. These opinions, offered in support of a litigated issue before one of the regulatory agencies, are reintroduced in subsequent proceedings as having the weight of established fact. Moreover, the rapid pace of development of new knowledge in this field can often eclipse judgments offered only three to five years previously. Examples of such new knowledge are the role of detoxification pathways in the carcinogenic process as illustrated by studies on vinyl chloride; the demonstration through elegant *in vitro* tests of DNA repair and the consequences of errors in the repair mechanism; the existence of retinoids and other chemical agents which may protect against carcinogens (Nutrition and Cancer Symposium, Federation Proceedings **35**:1307-1338, 1976) and others. The established experts in chemical carcinogenesis such as J. H. Weisburger, J. A. and E. Miller, J. Higginson, as well as senior officials of regulatory agencies like A. Kolbye are beginning to reevaluate their own thinking on the possibility of thresholds in carcinogenesis. Any regulation which forecloses the possibility of an open examination of the principles involved in the recognition, evaluation and control of potential occupational cancer hazards is a dangerous and inappropriate precedent. Mechanisms must be developed to assure regulatory agencies of timely scientific advice.

Relative Potency of Carcinogens

That there are differences in potency between carcinogens is a well-established fact. This is illustrated in accompanying Table 1 from the literature or from government study reports. It is evident from this table that the effective dose for various cancer-producing agents in animals (that is, their potency) ranges from over 1% in the diet to as little as a few micrograms per day. Further, as stated recently by Boyland (*J Soc Occup Med* **27**:98, 1977), "Thus there is a million-fold variation in the activity of carcinogenic substances when expressed on the basis of dose required."

I do not disagree with the statement (page 54162, FR, October 4, 1977*) that "a substance that will induce cancer in *any* dose, no matter how high or low, should be treated with great caution." However, this statement does not thereby support the concept of putting such a substance in Category I, with all the regulatory consequences that this implies. As I stated in 1962 ("Environmental Carcinogenesis," *Cancer Research* **22**:395-397, May, 1962), "The total available animal data must be *evaluated* in terms of significance including technological contribution, and not simply *listed* or *enumerated*."

Extrapolation from Animal Data to an Assessment of Hazard in Man

OSHA, in its proposal published in the Federal Register on October 4, 1977, recognized that in interpreting hazards to man from data available only in animals, sound judgmental decisions are required which take into account all available data and which cannot be done by simple categorization and standardized regulations. Throughout the OSHA document itself are multiple references to the need for sound judgments and the difficulties in making such judgments.

* "The correct interpretation of hazards to human health is sometimes extraordinarily difficult." (Page 54158)

*Wherever a five-digit page reference appears in this presentation, it refers to the Federal Register of Tuesday, October 4, 1977, Part VI.

Table 1. — Relative Potency of Carcinogens in Animal Tests.

Organ	Chemical	Potency	Dose	Reference
1. Liver	Trichloroethylene	Weak	869-2339 mg/kg/day — oral	(1)
2. Urinary tract	Nitrilotriacetic acid	Weak	15,000 ppm — oral	(2)
3. Urinary tract	Trisodium salt of nitrilotriacetic acid	Weak	15,000 ppm — oral	(2)
4. Liver	Chlordecone (kepone)	Moderate	30-60 ppm — oral	(4)
5. Liver and kidney	Chloroform	Moderate	600 mg/kg — oral	(8)
6. Lung	Bis-chloromethyl ether	Potent	1.0 ppm — inhalation	(5)
7. Liver	Carbon tetrachloride	Weak	1250-2500 mg/kg — oral	(9)
8. Liver - human Stomach, kidney and liver - rat	Aflatoxins	Potent	500 μ g/kg — oral	(6a)
9. Liver	Nitrosamines	Potent	milligrams — oral	(7)
10. Skin	Benzo(a)pyrene	Potent	0.3% solution — dermal	(3)
11. Skin	1,2-Benzanthracene	Weak	dermal	(3)
12. Bladder	2-Naphthylamine	Potent	oral	(6b)

* "The evaluation of carcinogenic hazards for man is based on a judgment of *all* available information: on bioassay, on toxicologic, metabolic and pharmacologic studies, *on the extent and route of exposure of man,* and on epidemiologic studies . . . ." (emphasis supplied) (Page 54166)

* "Any factor or combination of factors which *increases* the *risk* of cancer in humans is of concern regardless of its mechanism of action." (emphasis supplied) (Page 54164)

* "The particular characteristics of these animals and the results obtained may require *additional evaluation.*" (emphasis supplied) (Page 54164)

* "The *assessment of the carcinogenic activity* of a chemical depends on a *variety* of parameters. These include not only the total number of tumors induced but also their *multiplicity,* latent period, morphologic type, and *degree of malignancy.*" (emphasis supplied) (Page 54163)

* "In the assessment of the *carcinogenic risk.*" (emphasis supplied) (Page 54163)

* ". . . or where the route of administration is shown to be grossly inappropriate in terms of human exposure." (Page 54159)

In some instances, OSHA recognized the issue of complexity but chose to ignore it. For example, on page 54150 there appears "about one-third are skin cancers: troublesome, sometimes painful, usually treatable, and with little significant impact on life expectancy." Such cancers could hardly be called a "grave danger" (page 54173). Another example involves the number of species to be tested. Repeatedly throughout the document, scientists are quoted as recommending "adequate number of animals of at least two species" (page 54158), yet OSHA subsequently chooses to ignore their own quoted scientists and opts for a carcinogenic determination in one species if confirmed in another laboratory. The simple replication of an experiment in a second laboratory is in no way comparable to the demonstration of carcinogenicity in a second series unless metabolic pathway understandings *explain why only* one species gets tumors.

In yet another discussion of the value of animal studies to predict potential human effects, the OSHA document on page 54152 summarized a portion of a National Research Council Committee report by noting "They found an approximate correspondence between the sensitivities of humans and rodents when they were compared *on the basis of cumulative lifetime exposure*" (emphasis supplied). This would suggest that weak carcinogens in animals will be weak carcinogens in humans and that a sufficient intensity will be required in both animals and man for weak carcinogens. If such a sufficient intensity does not exist in the occupational setting, there will be no hazard to man.

All of the above comments suggest that OSHA should make provision for the availability of an expert scientific advisory committee. The function of this committee would be to review all of the available data, both animal experimental and human epidemiological, and render a judgment as to whether a particular compound constitutes a risk to man, and if so what the degree of that risk is.

The "Everything is Carcinogenic" Fallacy

OSHA quotes another regulatory agency (page 54151) on this topic. "The 'everything is cancerous' argument fails because it ignores the fact that not all chemicals fed to animals in equally concentrated doses have produced the same tumorigenic results." This supports the idea of a non-carcinogenic category. Experimentally, this cannot be *proven* so it is necessary to make *judgments* that materials are non-carcinogenic based on limited but adequate data.

Significance of Benign Neoplasms in Experimental Animals

On the question of benign versus malignant tumors, I agree with OSHA that too much time has already been wasted on this topic. However, since tumor is such an all-inclusive term, medically simply indicating a swelling, it might be possible to circumvent the problem by using the terms benign neoplasm and malignant neoplasm as is done in the quote on page 54163. Certainly there are many benign tumors that are not neoplasms. Additionally because it has been suggested that 41% of untreated

B6C3F1 mice, used by NCI in its carcinogenesis testing program, may develop neoplasms of the liver, this whole situation needs reevaluation. In some experiments we have conducted, the C3H mice that were being used in a contract laboratory in skin painting experiments, after two years or more without liver neoplasms, suddenly began to show, both in treated and controls, a high incidence (over 50%) of liver (hepatic cell) neoplasms. A cursory review of the literature conducted by a toxicologist in our laboratories revealed that the C3H mouse apparently goes through cyclical changes in incidence of such neoplasms, the incidence waxing and waning with time without apparent relationship to treatment or other identifiable environmental changes. If this is the case with C3H, and possibly also B6C3F1 mice, it will seriously impair our ability to demonstrate statistical significance of results without using inordinately large numbers of test and control animals. Therefore, it is important that OSHA clarify this situation with NCI and outside oncology specialists before locking themselves into a regulatory position which may be indefensible.

In a recent paper by Scribner (*Medical and Pediatric Oncology* **3**:151-157, 1977) there appear some most interesting statements which are pertinent to this discussion. These are:

Page 154, "However, the Environmental Protection Agency (EPA) and the Health, Education and Welfare Toxicology Subcommittee for Carcinogen Standards have decided to consider as a carcinogen any substance which induces an increased incidence of a tumor-type normally seen, or causes such tumors to appear at an earlier time than would be otherwise expected. However, this is a definition of a *cocarcinogen, and only of a cocarcinogen.*" (emphasis added)

Page 155, "Expressed differently, a person has far less probability of getting cancer from exposure to a cocarcinogen than from exposure to the same dose of a carcinogen."

Page 156, "Known human carcinogens should be removed from traffic if possible, or reduced to the lowest exposure if not. Compounds which qualify only as experimental cocarcinogens fall into an entirely separate class, and should probably be considered on a case-by-case basis. . . . With this approach, regulatory agencies should, in the long run, have a better record of professional and public support for their actions than would be the case if they were to attempt to impose uneconomic, and unpopular regulations on the use of carcinogens and cocarcinogens alike."

Single Hit Theory vs. Multiple Causation of Cancer

On page 54152, the statement is made: "Thus a single biological event produced by a very small number of molecules of the carcinogen *may* be sufficient to initiate the irreversible development of a tumor" (emphasis supplied). This statement would be just as acceptable if expressed in the negative, i.e. (the) event produced . . . may *not* be sufficient to initiate the irreversible development. . . . In fact, it is likely that this is the case, since many studies suggest that a series of stepwise events must occur in appropriate sequence before the development of a neoplasm. Most oncologists are now convinced of this and are beginning to examine critically with various experimental methods whether interference with mechanisms other than initiation may be a more fruitful avenue to cancer prevention. It is thus again potentially dangerous to base regulatory decisions on something that only *may* be true when the weight of evidence on mechanisms suggests it is more likely that it *may not* be true (see Dinman, "Non-Concept" of "No-Threshold": Chemicals in the Environment, B. D. Dinman, *Science* **175**:495, 1972).

Medical Tests — Choice and Interpretation

Finally, mention is made in the model standards (pages 54188, 54191 and 54194) of medical examinations according to a protocol to be provided. It is obvious that tests designed to screen for liver disorders which may be associated with liver carcinogens are useless with pulmonary, bladder, or skin carcinogens, and, therefore, should not be mandatory for anything but a liver carcinogen. Likewise urinalysis to include microscopic examination and cytologic examination for neoplastic cells is designed to detect bladder carcinogens and would be useless for liver, pulmonary or skin carcinogens. Thus, all laboratory tests should be optional, and delineated only after the nature of the carcinogen has been defined. It should further be recognized that about 25% of people will have one or more abnormal liver function tests even though never exposed to a liver carcinogen, so that these tests are highly nonspecific. Thus, they must be administered only after a definite set of action criteria have been developed for them. Action cannot and should not be instituted on the basis of a single abnormal test, since otherwise 25% of the work force could be excluded. It must be recognized that the average physician has no knowledge or experience with such tests in relationship to carcinogens. Therefore, it will be necessary to delineate action criteria for him or many false decisions and inappropriate actions may be taken by him. Dr. Hans Popper and/or other liver disease specialists might be helpful to OSHA in developing appropriate action criteria.

Also on pages 54188, 54191 and 54194, it is stated, "The employer shall obtain a written opinion from the examining physician which shall include:

(a) The results of the medical examination

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(ii) The employer shall instruct the physician not to reveal in the written opinion specific findings or diagnoses unrelated to exposure to *XXXX*." These two statements are contradictory. "The results of the medical examination" to a physician means the history, physical examination and all laboratory results, with a diagnostic conclusion. For instance if the employee were a chronic alcoholic all of his liver function tests discussed in the preceding paragraph might be positive and could well have pertinence in relation to a potential exposure to a liver carcinogen. In not reporting such results to the employer the physician could well be derelict in his responsibility to the employer and employee alike. Some rewording of these two phrases so they are consistent with each other seems to be in order.

An Alternate Proposal

Any attempt to place carcinogens into three simple classes or categories as proposed by OSHA highly oversimplifies an admittedly extremely complex problem. In the book by H. F. Kraybill and M. A. Mehlman, *Environmental Cancer* (John Wiley and Sons, New York, 1977, page 42 et. seq.), two other approaches are listed. The first is attributed to Maltoni (1973) and "describes the medical and legal terminology for the evaluation of risks of occupational carcinogens: (1) definite carcinogens where epidemiological evidence exists; (2) highly suspect carcinogens where strong experimental and/or some epidemiological evidence is present; and (3) potential carcinogens where experimental data give some indication of carcinogenic action of a compound on an

experimental animal." The second approach is offered by Kraybill and lists four classes of materials. His suggested classification is outlined below.

> *"Recognized or proven carcinogens.* An enumeration of carcinogens in the environment is, from an interpretative viewpoint, difficult. Some chemicals and materials are *recognized carcinogens* in animals or humans because they meet certain criteria, which are as follows: (1) epidemiological observations and surveys have established them as human carcinogens; (2) they appear on lists generally accepted by scientists as chemical or physical agents that have demonstrated a carcinogenic response in humans and experimental animals; (3) they are recognized as potent carcinogens because they evoke a response at low dose in one or more organ sites; (4) a dose response is confirmed in several or many species, strains, and several laboratories; and (5) the chemical or substance has been conclusively demonstrated to cause tumors, sometimes of a type frequently seen or sometimes appearing in an earlier time frame than otherwise expected. Implicit in such requirements is the statistical significance of tumor incidence, reproducibility of the tumorigenesis, and relevancy of route of exposure. Final confirmation is the observation that the tumors are transplantable.
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> *"Suspect carcinogens.* Another classification assigned to certain chemicals tested experimentally for carcinogenesis is that of *suspect carcinogens.* In this case, no conclusive relationship to cancer production has been shown, but there is some inference based on (1) an association of increased tumor incidence with known exposures; (2) other biological indications such as malignant transformation in *in vitro* systems (cell cultures) and (3) a positive response, either in only one species or in a strain, but not a consistent response by both sexes or in accordance with a dose-response pattern that parallels nonoccupational and occupational exposure levels. However, with carcinogens categorized as suspect, there is no epidemiological evidence.
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> *"Potential carcinogens.* A class of potential carcinogens can be separated out of the suspect carcinogen class. In this group are chemicals that have a structural similarity to proven carcinogens but have not yet been tested or on which there is suggestive evidence from mutagenicity data.
>
> *"Inadequate data for classification.* For many chemicals that may be inappropriately classified as carcinogens, there is either inadequate testing by prescribed protocols or there is insufficient data. Several kinds of deficiencies may be noted here, such as tests limited in time, inadequate dose schedule, insufficient test animals, nonrelevant exposure routes, improper species or strain, strong overlay of toxicity, and failure to recognize the role of a cocarcinogenic effect of contaminants."

A third proposal for categorization of carcinogens has been or will be proposed by the American Industrial Health Council.

Although I agree that utmost caution must be exhibited by regulatory agencies when assessing the hazards of direct, intentional food additives, the occupational situation presents an entirely different picture. I would propose that several categories of carcinogens be defined as follows:

Category I: (1) Compounds which are known to be carcinogenic in man; (2) compounds which have been demonstrated conclusively (statistically) to be carcinogenic in two species; (3) compounds which induce lung cancer by inhalation in animals; (4) compounds like 2-AAF and aflatoxins which produce a multiplicity of cancers in animals at small dosage.

Category II: (1) Compounds which produce neoplasms in only one of several species tested, unless the metabolism has been characterized in each species and the species producing tumors has a metabolism similar to that in man; (2) compounds which in man are associated with skin tumors only; (3) compounds which produce a barely statistically significant result at very large dosage.

Category III: Same as proposed Category II in OSHA document.

Category IV: Same as proposed Category III in OSHA document.

Category V: Noncarcinogenic.

All four of these alternative suggestions take full account of the complexity of the problem and do not attempt to oversimplify it. Rather they allow for full evaluation of all relevant data and the subsequent scientific judgments rather than simply trying to categorize in three simple groups. Perhaps some blending and consolidation of the four alternatives proposed would be an even more effective approach. If carcinogens are to be categorized it is imperative that it be done by knowledgeable experts. Some provision should be made to insure that experts in carcinogenesis are available for the task. It should not be left to an administrator to make such complex judgments without expert advice of the kind indicated. For instance, under the proposed rulemaking, placing a material in Category I would lead to severe and costly regulatory implications, so that a material wrongly placed in this category would unnecessarily have to meet all these restrictions.

Summary

Although I am sympathetic to what OSHA is trying to accomplish with their proposal, I think they have grossly oversimplified the extremely complex question of occupational carcinogenesis. I would urge, therefore, that OSHA seriously reconsider their proposal in the light of the comments that have been made in this presentation. I would urge that modifications be made in their proposal which more accurately reflect the present state of our scientific knowledge concerning carcinogenic mechanisms and the *risks* of cancer development in the workplace as a result of occupational exposures. Provisions should also be made to take cognizance of scientific advances which will be made in the future. Finally, required medical monitoring of employees potentially exposed to carcinogens should remain optional until the nature of the carcinogenic response to be monitored has been carefully defined.

References for Table 1

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