NIOSH Comments to DOL

NIOSH Comments on OSHA

Identification, Classification and Regulation of

Potential Occupational Carcinogens

Advance Notice of Proposed Rulemaking (ANPR)

5 April 1982

These comments address the specific issues requested by OSHA in its January 5, 1982 Identification, Classification and Regulation of Potential Occupational Carcinogens ANPR (29 CFR Part 1990). It may be necessary to expand or modify this response, after the April 5, 1982 deadline established by the ANPR, particularly with reference to new data that may become available between April 5, 1982 and public hearings on the proposed changes. NIOSH will specifically respond to those points in the ANPR relevant to NIOSH's role as the scientific component of the Occupational Safety and Health Act. In addition, NIOSH refers you to its previous submission of April 4, 1978 to the Docket Officer on its "Testimony for the OSHA Hearing on Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk," as a supplement to the current comments that follow.

Issue 1: How should OSHA consider the cost-effectiveness of provisions which are incorporated into a standard regulating carcinogens under the policy?

Answer: NIOSH believes that the final OSHA policy concerning carcinogens should also comply with the District of Columbia Circuit Court of Appeals decision on the cotton dust standard and not include cost-effectiveness provisions.

NIOSH maintains that the most effective means of controlling workplace exposures are engineering controls and design standards. Work practices, personal protective equipment and medical surveillance are all supplementary to engineering controls and should not preclude the requirement to eliminate hazards from the workplace environment. Respirators and other personal protective equipment should only be required as a secondary means of compliance. Medical surveillance is not a method to be used for compliance, or as a sole means of worker protection, it can, however, serve as an appropriate adjunct to environmental monitoring to determine if workers have been adversely exposed.

NIOSH's position is consistent with the decision of the District of Columbia Circuit Court of Appeals in American Textile Manufacturing Institute vs. Donovan concerning the proposed cotton dust standard. The Court ruled that the word "feasible" in Section 6(b)(5) of the Occupational Safety and Health Act meant "capable of being done" and that the intent of this Section is that no employee will suffer material impairment of health. NIOSH agrees with the Court that it

was the intent of Congress that the benefit of worker health must be placed above all other considerations and that any standard, that attempts to balance costs and benefits, violates Section 6(b)(5).

Although NIOSH recommendations typically contain a variety of elements including work practices and medical surveillance, they are not intended to be used in place of engineering controls even if they are more cost effective.

Issue 2: Is it proper or appropriate for OSHA to retain the requirement for setting a no-exposure level where a suitable substitute exists for a use or a process of a potential occupational carcinogen?

Answer: NIOSH maintains that discussions of safe levels of exposure should be limited to only those situations for which no substitute exists or the substitute is itself a carcinogen.

Prudent public health policy mandates cessation of worker exposure to occupational carcinogens by either substitution of a safe alternate, or by controlling the carcinogen to a level believed to provide the greatest protection to workers. Substitution has merit since it eliminates the possibility of exposure to the carcinogen. However, substitution may require major process changes and it is

possible that the substitute agent may itself be a carcinogen. Controlling exposure to a carcinogen is often difficult because of our limited ability to accurately estimate a safe level. The question posed is whether it is proper to require a no-exposure level where a substitute exists. Rejection of this requirement would imply that, even when a substitute exists, the level of exposure to a carcinogen would be based on risk assessment and choices between the level of exposure and substitution would become an economic and not a public health decision.

The history of bladder cancer in the dye industry is an excellent example of the potential costs of the proposed policy change. Beta-napthylamine, a synthetic dye, was recognized to be a bladder carcinogen in the first half of this century. The British banned its use in the 1950's. In the United States, on the other hand, we developed over the years a series of increasingly rigorous standards but exposure was not eliminated until the 1970's. Each new recommended level of exposure thought to provide protection was ultimately demonstrated to be ineffective. The ultimate cost of that approach to regulation can only be counted in cases of bladder cancer that resulted from exposure, but because of the latency between exposure and clinical manifestation of disease, we do not yet know the total number of bladder cancers that will result because of this stepwise approach.

Setting a level of acceptable exposure by risk assessment basically means a well educated guess of the effects of lowered exposure. NIOSH contends that when we reject substitution as a viable alternative we are gambling on future outcomes, as demonstrated in the case of beta-napthylamine induced bladder cancer. A more prudent policy is to minimize risk by eliminating exposure or through substitution.

Issue 3: Should OSHA amend the provisions for the review and utilization of negative (non-positive) animal and human data?

Answer: It is the NIOSH position that negative (non-positive) studies should be considered only when they have met the following criteria as specified in 29 CFR 1990.144:

> "(i) The epidemiological study involved at least 20 years' exposure of a group of subjects to the substance and at least 30 years' observation of the subjects after initial exposure;
>
> (ii) Documented reasons are provided for predicting the site(s) at which the substance would induce cancer if it were carcinogenic in humans; and

(iii) The group of exposed subjects was large enough for an increase in cancer incidence of 50 percent above that in unexposed controls to have been detected at any of the predicted sites."

29 CFR 1990.144 additionally states:

"...non-positive results obtained in human epidemiological studies should be used to establish numerical upper limits on potential risks to humans exposed to specific levels of a substance will be considered only if criteria (i) and (ii) are met and, in addition:

(iv) Specific data on the level of exposure of the group of workers are provided, based either on direct measurements made periodically throughout the period of exposure, or upon other data which provide reliable evidence of the magnitude of exposure."

NIOSH contends that the present policy is scientifically credible and that modification is not necessary. We have several suggestions that may help to clarify some of the important concepts. First, the terms "positive" and

"negative" need to be defined, because the distinction is a central issue. Second, the concept of an ability to "detect" an increased cancer risk should be defined or quantified, because it is stated that negative studies must have this ability before they are considered. Third, while truly negative studies (as opposed to those having insufficient sample size or other problems) should be given consideration equal to that given to positive studies, a definition must be established as to what constitutes a "truly negative" study.

In the following paragraphs we will define the terms "positive," "negative," and "detection of excess risk" and show that negative studies can be segregated into those that are likely to be truly negative and those that have little ability to be positive, and that when both positive and negative studies exist, there are methods for resolving the apparent conflict between their results.

Defining "positive" studies

There are many interpretations of the term "positive" when applied to health risk studies. For example, a very liberal interpretation would be that studies showing any increase in cancer rates are positive, regardless of the magnitude of the increase or the sample size.

Because of chance variation, it is prudent to consider the probability that a positive result is a false positive. This probability is commonly called "the level of statistical significance." The choice of a cutoff value for determining whether a positive result is statistically significant is somewhat arbitrary, but a generally accepted value is a probability of 5 percent. In other words, if there is less than a 5 percent probability that an observation is due to chance, then conversely, there is a 95 percent probability that the study is truly positive. We recommend that tests of statistical significance be used as a criterion for determining "positive" or "negative," with a positive outcome defined as having a probability of less than 5 percent attributable to chance.

Defining "negative" studies

There are two kinds of "negative" studies, those that provide truly negative results and those that have little ability to be positive possibly because of poor experimental design. Studies likely to be truly negative are those that have sufficient sample size (assuming sufficient, exposure study design, and length of observation) to detect an excess risk if one exists. Such studies should be given as much consideration as positive studies. Determination of a truly negative outcome requires the setting of a statistical probability level for acceptance. A study with a statistical power of 90 percent is generally accepted as being able to demonstrate excess risk. We recommend, therefore, that the criterion for determining

that a negative study has the ability to "detect" excess risk be defined as statistical power of 90 percent or more, for a 50 percent increase in a site-specific cancer rate, assuming statistical significance at the 5 percent level.

Resolving conflicting evidence

When both positive and negative studies exist for a given substance and cancer site, there are several approaches that can be taken to resolve the apparent conflict. One approach is to consider the study results with respect to statistical power. If the substance is a carcinogen, then a pattern should become apparent; in general, the studies with greater power should be positive, and those of lesser power should be negative. This approach was recently used to support the hypothesis that although vinyl chloride is carcinogenic in the brain, it may not be carcinogenic in the lung.

Another approach, which is useful when examining studies of similar design, is to calculate their combined relative risk. The overall significance of the association can then be assessed and tests of homogeneity can indicate which studies contained unusual results. Close examination of individual studies can be helpful in resolving different results. Variations in extent of exposure, length of observation, and control groups may provide insight.

In summary, we have proposed definitions of positive and negative results, and discussed methods for detecting excess risk. In addition, NIOSH reaffirms support of the criteria set forth in 29 CFR 1990.144.

Issue 4: Should OSHA alter or continue its process for reviewing data on the substantial number of substances for which there is some evidence of carcinogenicity, and for setting priorities?

Answer: NIOSH views the present policy concerning the review process to be very reasonable and is not in need of major modifications. In addition, we view the intent of publishing both the Candidate and Priority Lists as one which will solicit comments from the public sector and is therefore beneficial since public scientific debate is the result. Such debate is beneficial to protecting the public health and far outweighs any concern over "cancer scares."

The Federal Government employs highly qualified personnel who are quite capable to evaluate the evidence of carcinogenicity in the three-stage review process. Use of an outside panel to perform these scientific evaluations is both time and cost ineffective.

We suggest that a liberal interpretation in defining positive studies should be used during the initial screening procedure since a stricter screening may unnecessarily limit the scope of

the initial review. In contrast, we recommend that statistical significance be used as one of the criteria at the second stage of the OSHA review process, to provide "a more searching scientific review."

Issue 5: How should OSHA incorporate the provisions of Executive Order 12291, including cost/benefit analysis, in its priority setting process?

Answer: NIOSH has no comment on this issue.

Issue 6: Should the policy specify methods or techniques of quantitative risk assessment and significant risk determinations?

Answer: As stated in the ANPR, the Policy Preamble contains a lengthy discussion of risk assessment techniques and uncertainties. It is necessary to realize that the basis for this discussion is the scientific community's lack of understanding of the precise mechanism of carcinogenesis. This lack of understanding is clearly reflected in that discussion and these comments. While some of the participants argued that only one biological event is required to induce carcinogenic mechanisms; others argued that

many events, perhaps occurring sequentially, are required. There are, of course, shades of difference between these two theories and, as a result, numerous mathematical and biological models have been offered to explain, despite the absence of precise knowledge, the carcinogenic mechanism.

Because our understanding of the mechanism of carcinogenicity is incomplete, our use of mathematical models to predict its outcome must be employed with extreme caution. To select a model or models from among the many choices and to have them incorporated into Administration policy will not resolve those issues.

Since there is no single model that will satisfy all the requirements for performing risk assessments, NIOSH believes that any attempt to mandate use of specific models or techniques of risk assessment for regulatory purposes will only prolong the controversy and will detract from the goal of public health protection.

In order to further define the role of risk assessment as a method for recommending standards for worker protection, a review of the NIOSH approach that addresses the complexities of these techniques follows.

Historically, NIOSH recommendations for workplace standards employed a variety of methods to establish conditions that NIOSH believed would best prevent adverse effects. In most cases a safety factor was applied to further ensure that even the most susceptible individual would realize a degree of safety. When addressing issues of carcinogenicity, NIOSH typically assumed that no exposure could be considered safe. This assumption is not unique to NIOSH. The 1958 Delaney Amendment imposed a zero tolerance for carcinogenic food additives. This position was supported in 1970 by the Ad Hoc Committee Report to the Surgeon General:[1]

"The principle of a zero tolerance for carcinogenic exposure should be retained in all areas of legislation presently covered by it and should be extended to cover other exposures as well. Only...where contamination of an environmental source by a carcinogen has been proved to be unavoidable should exception be made (and then) only after the most extraordinary justification is presented...Periodic review...should be made mandatory."

This concept continues to guide NIOSH.

On July 2, 1980, the Supreme Court stated that OSHA had exceeded its statutory authority by failing to show that the benzene standard was "reasonable, necessary or appropriate." The Court ruled that Section 3(8) of the Occupational Safety and Health Act required OSHA to produce "substantial evidence" which demonstrates that the regulated substance poses a significant risk of material impairment of health and that the new standard would reduce that risk. The Court stated, however, that "substantial evidence" does not necessarily mean scientific certainty. The Court cited Section 6(b)5 of the Act to stress that regulation cannot attempt to produce a risk free workplace by regulating "insignificant" or "acceptable" risks, but it left to OSHA the determination of what "significant" or "unacceptable" means.

The District of Columbia Circuit Court of Appeals decision on August 15, 1980, upheld the lead standard, in which an acceptable risk was estimated for a material that is not known to be a carcinogen. These two decisions provided the impetus for the inclusion of a quantitative risk assessment effort in NIOSH's standards recommending program.

Other federal agencies have had experience with quantitative risk assessment. Many of those agencies provided testimony before the House of Representatives Subcommittee on Science, Research and Technology hearings on "How Risk Comparison Can Become a Valuable Instrument of the U.S. Regulatory Policy." The prevailing opinion appeared to be that quantitative risk assessment can be useful in establishing priorities and in estimating the anticipated reduction in risk as a result of regulatory actions. However, the testimony indicates that quantitative risk assessment should not be used as the sole basis for regulations because of the uncertainties inherent in the process. NIOSH analysis of the utility of quantitative risk assessment reinforces this opinion.

Certain regulatory statutes provide some guidance regarding the uses of risk assessments. This guidance differs not only from one statute to another, but often from one section to another within the same statute. Quantitative risk assessment techniques have been used extensively by EPA, USDA, and CPSC. EPA uses risk assessment techniques to determine acceptable risk with respect to its National Water Quality Standards. USDA, on the other hand, does not employ risk assessment techniques for the same purpose as

EPA. The Meat and Poultry Inspection Acts explicitly states that no substance, whatever its commercial benefits, may be added to meat and poultry if it poses any risk to human health. CPSC has had experience with both carcinogenic and acute non-carcinogenic quantitative risk assessments.

Although NIOSH has had only limited experience with theories and techniques of quantitative risk assessment, we do recognize the necessity to consider at least the following general concepts. Generally any quantitative risk assessment must consider:

1. biological reversibility or irreversibility of the process,

2. potential cumulative nature of the process,

3. possibility for a progressive nature of the process,

4. rates of absorption, metabolism, de-toxification, and excretion,

5. biochemical processes such as receptor occupation, alkylation, repair, and enzyme induction,

6. changes in homeostatic mechanisms such as hormonal balances and cellular immunity,

7. genetic and non-genetic variation among individuals, and

8. temporal variables such as aging.

Since we are concerned with workplace hazards, any quantitative risk assessment must, whenever possible, be based on human epidemiological data. When there is insufficient data of this kind to employ techniques of quantitative risk assessment, extrapolation of data from other species, must be performed. To make such extrapolations requires the adoption of sets of assumptions concerning the quantitative and qualitative biological relationships between species. Because of this assumed interspecies continuity, great uncertainty is introduced into the risk assessment process. In order to minimize this uncertainty, objective criteria must be applied whenever possible. The most appropriate mathematical models should be sought for each analysis. The scientific assumptions must be clearly stated and implications of those models must be carefully examined to make certain

that accepted principles of biology are not violated. The results obtained from any such mathematical treatment must also be carefully scrutinized for consistency with observed human outcomes.

At least three different types of extrapolations may be necessary to estimate human risk using animal data. These are: (1) extrapolation of known outcomes at high doses to anticipated outcomes at low doses, (2) extrapolation of observed effects in lower species to anticipated effects in man, and (3) extrapolation from controlled laboratory conditions to the diverse human environment.

Extrapolation from effects observed at high doses to anticipated effects at much lower doses assumes that all involved systems operate in identical fashion over the dose range. Vast experience with chemical and biological kinetics has demonstrated that this is not always true.

Species to species extrapolations assume that the biology and, therefore, the mechanism of toxicological response, is uniform across species. If it is determined that the signs and symptoms of toxicity in the test species are consistent with observed human effects, the persuasiveness of this

argument would be greatly strengthened, but in many instances that is not true. For example, arsenic is accepted to be a human carcinogen, but a parallel effect has not been observed in experimental animals.

Quantitative risk assessment, in the absence of complete human data, also requires extrapolation or at least normalization of data from well defined laboratory conditions to ill defined human workplace exposure conditions, in which a precise understanding of the extent of exposure is often impossible, and is additionally complicated by a variety of lifestyle and workplace variables. Among these lifestyle variables are use of alcohol, tobacco, and drugs. Workplace complications may include heat or cold stress, mental stress, physical stress such as noise or vibration, and multiple chemical exposures. A basic understanding of interactions of these kinds is implicit to performance of a meaningful quantitative risk assessment. At the present time our knowledge of such interactions is quite elementary.

The modeling of irreversible effects such as cancer, is currently the subject of much debate. Two general classes of mathematical treatment have been proposed for performing

assessments to estimate the risk of developing cancer. These models are both mathematically and biologically different.

In 1950, Iversen and Anley[2] proposed a quantitative model of carcinogenesis based on the occurrence of a single irreversible biological event (the one-hit theory). The one-hit theory is the simplest possible model that relates dose to response. A "hit," the fundamental process, is believed to transform a normal cell into a malignant cell. The expected number of "hits," or transformations is assumed to be directly proportional to the dose.

However, a number of investigators noted that the death rate from many forms of human cancer increased proportionately with the fifth or sixth power of age.[3,4,5] Because the data were considered consistent with an incidence rate proportional to the fifth or sixth power of duration of exposure, at a constant concentration, two plausible explanations of this phenomenon were offered. Fisher and Holloman[3] proposed that five or six different cells were transformed as a result of a toxic exposure into an organized single tissue and subsequently formed a tumor. Alternatively, multiple changes in a

single cell that occurred in discreet steps was proposed by Nordling.[4] These multi-hit or multi-stage models are consistent with both the biological irreversibility and the cumulative nature of the process.

Another mathematical approach to modeling carcinogenesis is application of the log-probit model. The basis of the log-probit model is the assumption that biological responses are distributed log-normally; a reflection of the heterogeneity and sensitivity of the exposed population. This model tends to predict lower degrees of risk than the one-hit or multi-stage models.

Several types of biochemical mechanisms have been proposed as the biological basis for risk estimation. Ehrenberg[6] suggested that risk estimates should be derived from the amount of covalent binding to DNA. Cornfield[7] suggested that competing chemical processes such as damage and repair, and activation and inactivation, be considered. Gehring, et al.,[8] have combined pharmacokinetic principles with knowledge of covalent binding to predict the dose-response characteristics of the metabolically activated carcinogen, vinyl chloride. Modeling, based on these principles, is advancing rapidly because of a more

comprehensive data base. On the other hand, the unavailability of data frequently limits their use.

NIOSH's emphasis on the reliability of quantitative risk assessment will be only as great as the adequacy of the information base available. The information base must include data on exposure patterns, chemical and biological relationships, and epidemiological studies. Animal studies should be used only when similarities to human biology cn be demonstrated. The evaluation should: trace the agent through its manufacture, transport, storage and use to understand conditions of exposure; identify unusual uses or worker practices that could subject workers to dangerous exposures; determine if the agent being evaluated is used as a component in another product and consider the potential for antagonistic, additive, or synergistic actions that may occur; identify additional exposures to the agent outside the occupational environment; and discuss gaps in knowledge that require additional research.

Chemical and biological aspects of the assessment should summarize information on transport, metabolic fate biotransformation products, and the excretion of the agent. When possible, structure activity relationship

analogies to related compounds should be included. The discussion should also compare, when there is sufficient data, the toxic mechanisms of action in the various species and strains of animals for which similar data exists.

Relevant toxicity studies should be summarized and presented with a critical evaluation of the merit of each study and must consider the adequacy of the experimental design, the quality of the experimental data, the suitability of the controls, the interpretation of the data, and the reliability of the conclusions.

Similarly, epidemiological studies must be critically evaluated in terms of the criteria contained in the IRLG Guidelines for Documentation of Epidemiologic Studies.[9] These guidelines recommend that the following topics be discussed: scientific background and objectives of the study; study design, with a description of the population from which the study subjects were selected and methods of selection; detailed description of comparison subjects and methods of selection; data collection procedures used, and description of the analytical methods and statistical procedures employed including the power of the study and the confidence intervals of the risk estimates. The

limitations of each study, with respect to risk assessment, should be explicitly stated.

In summary, NIOSH believes that regardless of the source of the data used, epidemiological or animal, doubts concerning the "real world" significance of the outcome are certain. Because of these uncertainties and the public health consequences, NIOSH, as well as the IRLG Working Group on Risk Assessment, favored the policy of making cautious assumptions whenever they are needed to conduct a risk assessment. For example, the IRLG has stated that use of the linear, non-threshold dose response model to evaluate the risk of cancer provides a conservative estimate that is consistent with this policy. It was concluded that this model has an adequate scientific basis and is less likely to understate risk than other plausible models. However, NIOSH also believes that comparative risk analysis using several mathematical and biological models should be performed.

It is expected that the data required for a risk assessment will usually be a subset of the total data collected for a given project. When the data are sufficiently strong, risk assessments may be used to support NIOSH recommendations.

However, less complete data sets, unsuitable for risk assessment, can often provide sufficient cause for concern about the effects of exposure. For instance, various in vitro bioassay techniques have been used to successfully screen chemicals for potential carcinogenicity. Often the positive results of such tests have later been corroborated by in vivo studies. By themselves, results from in vitro bioassays are inappropriate for use in quantitative risk assessment and, at this time, are not sufficient to base a standard. However, the tests are based on well known scientific principles and, therefore, are sufficient to dictate caution concerning human exposure.

Quantitative risk assessment must be a value free, objective undertaking. In order to help ensure scientific objectivity and the public health advocacy role the results of any risk assessment must be evaluated in the absence of economic and political considerations.

It must be understood that the NIOSH risk assessment program is not being developed to provide justification for its recommendations, but rather to further define the health benefit to be anticipated if Institute recommendations are subsequently promulgated into a workplace standard.

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