AIHC

AMERICAN INDUSTRIAL HEALTH COUNCIL

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December 19, 1978

Re: Docket H-090

AIHC Comments on:

Regulatory Analysis of a Proposed Policy for the Identification, Classification and Regulation of Toxic Substances Posing a Potential Carcinogenic Risk. U. S. Department of Labor, Occupational Safety and Health Administration.

Regulatory Analysis Review Group Report on OSHA's Proposed Regulation for the Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk, submitted by the President's Council on Wage and Price Stability.

Letter from the Council on Environmental Quality dated October 24, 1978 to Assistant Secretary Bingham.

INTRODUCTION

When the Proposed Regulation for the "Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk" [hereinafter referred to as the "Proposed Regulation"] was originally published on October 4, 1977, OSHA stated that it would conduct neither an economic nor an environmental impact analysis. Instead, OSHA stated that the analyses would be made in rulemakings on individual substances. 43 Fed. Reg. 54180-182. The Regulatory Analysis required by Executive Order 12044 also was not undertaken.

On July 25, 1978, the day the hearings on the Proposed Regulation ended, the Office of Management and Budget ("OMB") notified the Organization Resource Counselors (which had questioned OSHA's failure to make a Regulatory Analysis) that OSHA had changed its position and would prepare a Regulatory Analysis of the Proposed Regulation. The most significant part of the OMB letter stated,

> "As Dr. Bingham has noted, it is difficult to conduct meaningful analyses for a generic standard when specific definitions have not been published. However, when generic standards will, upon promulgation preempt later regulatory decisions, then the economic effect of significant regulatory alternatives may never be analyzed." (AIHC P.H.)

The apparent turnaround in OSHA's position seemed to result from a recognition that generic standards which preempt later regulatory decisions will never be evaluated unless they are evaluated prior to adoption of the generic standards. Indeed,

in a memorandum to Assistant Secretary Bingham and Harrison Welford of OMB (AIHC P.H.), Messrs. Morris and Wrenn indicated the Regulatory Analysis would contain a discussion of a number of highly significant regulatory issues unique to the generic Proposed Regulation:

(1) An examination of realistic alternative approaches to regulation;

(2) An explanation of the specific issues which will be foreclosed by the generic Proposed Regulation from consideration in future rulemakings on individual substances;

(3) Consideration of alternative criteria for categorization of substances;

(4) Specification of the parameters which will be included in a determination of feasibility;

(5) An explanation of why an analysis of the total costs of the Proposed Regulation could not be undertaken.

AIHC agrees with OSHA that the first four objectives described above are those which should be achieved by a Regulatory Analysis. The fifth stated objective is a denial of the purpose of the Analysis. Unfortunately, the OSHA Regulatory Analysis, with the exception of the erroneous fifth objective, does not achieve the objectives which OSHA set out for itself.[1/] OSHA's

1/ The Regulatory Analysis was prepared on the assumption that
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analysis leaves many issues in doubt and opens new areas of confusion.

OSHA's failure to examine the significant alternative proposed by the President's Regulatory Analysis Review Group ("RARG")[1/] is a significant defect in the Regulatory Analysis. The proposed alternative and the RARG analysis in support of the alternative are a major contribution to the development of a reasonable regulation. Nor did OSHA weigh the AIHC alternative, which is similar in many respects to that proposed by RARG. The result is that OSHA did not achieve its objective of analyzing in the Regulatory Analysis the realistic alternatives to the Proposed Regulation.

The Regulatory Analysis is superficial and disregards the central issue pointed out to OSHA by OMB. Unless a generic standard which will preempt later regulatory decisions is assessed prior to its issuance, the economic effects of the generic standard and significant regulatory alternatives will

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it was written at the time the regulation was first proposed in 1977. OSHA states that it is reviewing the voluminous hearing record but concludes that the Regulatory Analysis should be based on the Proposed Regulation. (Analysis at 3*.) This may have been a reasonable way to proceed in Ocotber 1977 so that comment could be made in the course of the hearing. At this stage, the Regulatory Analysis leaves unassessed the many issues raised in the hearings.

1/ The Regulatory Analysis Review Group, created by Executive Order 12044, is chaired by the Council of Economic Advisers and has as members the principal economic and regulatory agencies of the Executive Branch.

never be analyzed. Instead of facing this core issue, the Regulatory Analysis is a systematic effort by OSHA to avoid assessing the issue. When will OSHA examine the economic effects of the generic determinations OSHA proposes to make?

AIHC agrees with the conclusion of the RARG Report:

> "Because both the potential costs and benefits are likely to be very large, and because of the proposals' inflexibility and lack of sensitivity to cost-effectiveness considerations, we recommend that OSHA complete a more comprehensive and analytical regulatory analysis and consider modifying its proposal along the lines outlined [in the Report]." (RARG Report at 8.)

SUMMARY OF COMMENTS

1. Because the OSHA Regulatory Analysis was based on the regulation as proposed, OSHA failed to consider or evaluate the constitutional and legal objections to the proposal.

2. OSHA's analysis of "realistic alternatives" fails to address the significant alternative proposal of the President's Regulatory Analysis Review Group. The RARG's proposal, similar to that proposed by AIHC, would separate the scientific function of data evaluation and determination of human risk from the regulatory function of setting standards based on a weighing of risks and benefits in the light of public policy considerations.

OSHA misunderstands the RARG proposal that risk quantification be an essential part of the regulatory process.

The scientific evaluation of human risk and the degree of potency provides OSHA with an essential element for OSHA's assessment of the workplace hazard and its decision whether a substance should be regulated. The scientific assessment of the degree of potency does not determine or control the regulatory process; potency is a factor, albeit an important factor, in setting regulatory priorities and in OSHA's evaluation of the hazard in a regulatory proceeding.

The scientific and regulatory functions should be separate but separation does not and should not hamper interaction necessary for determining priorities.

3. OSHA has failed to make the economic analysis required by law and by Executive Order 12044. OSHA makes no realistic attempt to assess benefits nor costs. OSHA made no attempt to show that the costs are reasonable in light of the projected benefits.

As RARG points out, the fact that there are uncertainties in the estimates of benefits and costs does not detract from the utility of such estimates in achieving cost-effective regulations. Cost effectiveness is the best way to achieve the maximum protection of worker health. Cost effectiveness is a tool in the regulatory process, not an end in itself.

4. The Snell study demonstrates that a genuine cost analysis is both possible and meaningful.[1/] The Snell study was

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1/ When OSHA refused to undertake a Regulatory Analysis, (footnote continued on next page)

limited by time and resource availability to a preliminary cost analysis designed to provide a scope or magnitude estimate of costs. Most of the criticisms relate to the problems of such a study which Snell itself had pointed out. The Snell study also provides a methodology for a broad scope study similar to the full regulatory analysis proposed by RARG and provides an outline for such a complete analysis. OSHA made no attempt to take advantage of the Snell outline.

5. There are basic faults with OSHA's conclusion that the cost of regulation under the proposal would be nominal since OSHA would regulate to the lowest feasible level in any case. Two of the four cases used by OSHA demonstrate the weakness of a generic method of control to the lowest feasible level without an adequate cost analysis. OSHA fails to distinguish between regulations which would be issued after full scientific evaluation and regulations based on arbitrary criteria selected for administrative convenience. OSHA fails to take into account that its four examples had exclusions for mixtures and action levels while the Proposed Regulation does not. Finally, the proposal would ban substances when substitutes are available, a regulatory alternative not considered in the four cases.

6. OSHA has recognized the importance of economic considerations in determining feasibility. However, OSHA merely

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AIHC commissioned the Foster D. Snell Division of Booz, Allen and Hamiltion Inc. to undertake an analysis to estimate compliance costs and other economic effects of the proposed regulation on producing and user industries.

lists factors which should be considered in an adequate economic analysis without pointing out how those factors would be taken into account. OSHA has made only a token analysis of economic feasibility and its proposed generic determinations would exclude an economic feasibility analysis in subsequent individual substance proceedings.

7. OSHA's discussion of foreclosure of issues generically determined has raised new questions. For example, OSHA reasserts the proposed determination that positive animal data supercede negative animal and human data; however, OSHA has proposed no standards for evaluating the relative validity of the data. Similarly OSHA's reasons for not taking potency into account are themselves a sound criticism of OSHA's intention to rely on tests in a single species. OSHA disregards the valid scientific significance of negative data and the limited value of tests at maximum tolerated doses. OSHA also repeats its reliance on unvalidated short term tests.

The scientific issues raised by the Regulatory Analysis and in the hearing underline the reasonableness of the AIHC proposal that a scientific panel be established to carry out what RARG called Stage I of the regulatory process -- the scientific evaluation of all of the data and the scientific assessment of human risk.

In view of the uncertainties created by the OSHA proposal, there is no basis for OSHA's conclusion that the Proposed Regulation would reduce uncertainties and costs.

8. OSHA failed to assess the alternative proposal

by RARG that OSHA should seek a cost effective combination of engineering controls and personal protective equipment. This proposal, which AIHC believes is sound, would provide the greatest worker health benefits.

9. OSHA should undertake an adequate regulatory and environmental analysis of all generic issues which will preempt consideration of issues in later regulatory proceedings on individual substances. The Regulatory Analysis prepared by OSHA does not accomplish that objective and cannot be said to meet OSHA's obligation, which is a precondition for issuance of the regulation.

I. OSHA HAS FAILED TO EVALUATE THE CONSTITUTIONAL AND LEGAL OBJECTIONS TO THE PROPOSED REGULATION

AIHC explained in its Post Hearing Brief the reasons why OSHA's Proposed Regulation is unduly broad. (AIHC Brief at 36-114.) For the reasons stated in the AIHC Brief, the Proposed Regulation should be modified to comply with the legal and statutory criteria for generic rules. Three points are worth emphasizing.

A. The Proposed Regulation Is Unreasonably Broad

The Proposed Regulation covers substances of widely varying physical characteristics -- solids, dusts, liquids, gases -- widely varying potency -- up to a million fold -- and workplaces of widely different characteristics -- general industry, construction, maritime, agriculture, transportation and

laboratories.

The Regulatory Analysis recognizes that historically different standards have been applied in the "construction, agriculture and maritime industries" to allow for the "unique situations" in these industries. (Analysis at 60.) Later in the Analysis OSHA states it is reevaluating the record with respect to laboratories and the construction industry. (Analysis at 67.) The Analysis concludes that exclusions for specific industries may be made in rulemakings on specific substances.

The Analysis leaves the record in a state of confusion. While recognizing that in the past the differences among industries led to separate standards for these various industries, OSHA now says it is reevaluating the record only with respect to laboratories and the construction industry.

Moreover, OSHA's suggested approach of dealing with the inappropriate inclusion of these industries within the Proposed Regulation by considering excluding specific industries in the course of rulemakings on individual substances demonstrates that there is no factual basis for applying a broad generic regulation across the board. In addition, this suggested resolution suffers from three defects: First, the exclusion from the Proposed Regulation of these industries should be part of a policy decision recognizing the need to establish special regulations for such industries. Second, OSHA's express purpose for promulgating the Proposed Regulation is to speed-up rulemaking proceedings. Surely a great deal of time in individual substance rulemakings now will be devoted to the introduction

and consideration of evidence concerning the exclusion of these industries. Third, nothing in the Proposed Regulation provides for the possible exclusions.

Construction, transportation, agriculture, maritime and laboratories should be separately regulated and should be excluded from the Proposed Regulation.

B. OSHA Has Failed to Recognize that Its Proposed Automatic Issuance of an ETS is Unauthorized by Law

The Proposed Regulation provides that an Emergency Temporary Standard ("ETS") will be automatically issued when the Secretary concludes, after a comment period, that a substance satisfies the criteria and is classified in Category I. We have pointed out in our brief that the proposed automatic issuance of an ETS without a soundly based finding of "grave danger" required by the statute is unauthorized. (AIHC Brief at 49-50, 234-237.)

C. OSHA Has Failed to Correct the Due Process Shortcomings of the Proposed Regulation

OSHA also fails to recognize that the presumption/rebuttal process embodied in the Proposed Regulation creates a serious due process issue. A substance will be "blacklisted" and regulated as a Category I carcinogen before an opportunity for a hearing to determine if the Secretary has correctly categorized the substance.

II. OSHA'S ANALYSIS OF ALTERNATIVES IS INADEQUATE AND INCOMPLETE

One of the important areas which OSHA promised to discuss in the Regulatory Analysis was "realistic alternative approaches for regulating the hazards." Unfortunately, OSHA has failed to consider the alternative proposed by the President's Regulatory Analysis Review Group and has misunderstood a very similar proposal in the AIHC Alternative.

A. Alternatives to the Proposed Regulation

The RARG Proposal. The RARG Report proposes that the regulatory procedure be divided into two stages:

Stage I: the Scientific Issues.

Stage II: the Regulatory Stage.

In Stage I there would be a scientific evaluation of the data and an evaluation of human carcinogenic risk. Carcinogenic substances would be identified and characterized "based solely on scientific appraisal of all available evidence." (RARG Report at 6 (emphasis in original).)

Stage II is the regulatory procedure for determining what regulation, if any, is appropriate after OSHA performs a "'feasibility' balancing between social costs and benefits." (RARG Report at 9.) In the RARG alternative, policy considerations would not enter the scientific evaluation in Stage I but would be explicitly considered in Stage II.

RARG points out that the proposed Regulation considers

neither potency nor quantification of risk. Recognizing that risk quantification may be on the "frontiers of science", RARG concludes that the quantification is important in regulatory decisions for "[o]therwise, society cannot hope to allocate its scarce resources rationally to all of the ills which it faces." (RARG Report at 20.) AIHC agrees fully with the RARG conclusion that risk assessments and cost-effective objectives are a solid foundation for the most rational regulatory decisions possible.

RARG concludes that the OSHA proposal, with its automatic regulatory responses, "would not ensure cost effectiveness (the greatest health protection for the resource expended) in the regulatory stage." (Id. at 6.) RARG urges OSHA to adopt a "more cost-effective" approach to setting standards since "only in this way can the highest level of health and safety be attained." (RARG Report at 30.) The OSHA criteria of "financial capability" will not, RARG warns, allow OSHA to attain the highest level of health and safety. In connection with a "more cost-effective" approach, RARG urges that the regulatory phase include estimations of human exposure, identification of benefits, risk/benefit analysis, review of technical means to reduce exposure and policy considerations which enter into the choice of regulatory actions. (Id. at 16-20.)

The AIHC Alternative. The AIHC alternative is broadly similar to that prepared by RARG. Unfortunately, OSHA appears to have a basic misunderstanding of the AIHC Alternative. All carcinogens, whether identified on the basis of human or animal data, are classified in Category I in the OSHA proposal.

AIHC distinguishes between substances for which there are human data (AIHC Category I) and substances for which there are animal data of carcinogenicity (AIHC Category II) and suggests the same regulatory response to both categories. In its analysis OSHA appears to misunderstand the AIHC Categories. (Analysis at 31, 34, 35.) In order to compare AIHC and OSHA categories correctly, AIHC Categories I and II must be compared to OSHA's Category I, and AIHC Category III must be compared to OSHA's Category II. Perhaps it would have been clearer if the AIHC had labelled its categories I and II as IA and IB.

OSHA's Consideration of These Alternatives Is Inadequate. OSHA never directly addresses the fundamental merits of the distinction between the scientific function of risk assessment and the governmental function of hazard evaluation and regulation which both the RARG and AIHC alternatives stress. OSHA does discuss briefly the proposal by RARG and AIHC that an independent scientific panel of experts be established to perform the scientific function of appraising and evaluating the scientific data of carcinogenicity. (Analysis at 37-29.) But OSHA summarily dismisses the suggestion as beyond the scope of the Regulatory Analysis, while stating that until the panel is established, it is not a "viable alternative approach." OSHA thereby ignores its ability to request the President to exercise his authority under the Reorganization Act of 1977, 5 U.S.C. § 901 et seq., to establish such a panel.[1/]

1/ Appendix C to the AIHC Post Hearing Brief contains a legal memorandum regarding the authority of the President to establish a panel.

OSHA also argues that Congress rejected the idea that an agency independent of OSHA should have authority "to issue health standards." This is a straw man argument and is a clear misunderstanding of the reasons underlying the distinction between the scientific and regulatory functions. AIHC has not proposed that the scientific panel issue health standards. To the contrary, the regulatory function is specifically reserved for OSHA. The scientific risk assessment is intended as an aid to the Agency in performing its regulatory function.

OSHA acknowledges that data evaluation requires the skill of experts (Analysis at 39) but does not really address the reasons why the scientific function should be separated from the regulatory function. The viability of the separation is demonstrated by Great Britain's use of a scientific panel in evaluating the carcinogenic potential of pesticides, and by the Environmental Protection Agency's separation of the scientific and regulatory functions in its FIFRA evaluations. The Risk Assessment Group of the Interagency Regulatory Liaison Group ("IRLG") and OSHA's own witnesses in the hearings also clearly distinguished between the scientific evaluation of risk and the societal or regulatory determination as to the nature and level of control necessary to deal with the hazard. (See references in AIHC Brief at 118-124, 197-233.) OSHA never addresses this issue.

B. OSHA's Failure to Distinguish Between the Scientific Assessment of Risk and the Regulatory Response to Deal with Hazard

OSHA appears to misunderstand what is meant by the

separation of the scientific function of evaluation of data and risk from the regulatory function of hazard assessment and control. In its discussion OSHA asserts that facts other than potency must be taken into account in deciding the societal benefits and allocation of resources for control, and concludes that while potency may be important in fixing priorities the number of employees at risk is the primary concern. (Analysis at 47-48.) Of course the number of workers involved is an important factor in the hazard analysis. OSHA, however, seems to assume that those who favor separation of the scientific and regulatory functions also are arguing that the regulatory function should be controlled by the scientific evaluation of risk and that the number of exposed workers is not important This is certainly not the position of RARG or AIHC. The scientific evaluation is one "fact" available to the regulator. The regulatory hazard assessment also includes appraisal of the social danger, level of exposure, and the number of workers exposed. On the basis of the hazard assessment, OSHA may choose to regulate first the less potent substance. This is in no way contradictory to the separation of risk assessment from hazard assessment and control.

C. The Functions of Risk Assessment and Hazard Assessment Are Separate But Complementary

CEQ in its comment on the RARG Report refers to the fact that the distinction between the scientific function of risk assessment (Stage I in the RARG Report) and the regulatory

function of hazard assessment (Stage II in the RARG Report) is "conceptual" and refers to interaction between the two functions or stages in setting priorities and in recommending further testing as though this interaction is inconsistent with the separation. This comment by CEQ incorrectly assumes that because the two functions are separate there should be no interaction between those performing the scientific risk assessment and those performing the hazard assessment. In fact, the functions, though separate, should be complementary.

Interaction between the scientists making the data evaluation and risk assessment and those in the agency making the hazard evaluation is essential. There will always be more than one substance being considered for regulatory evaluation. Information on the risk presented by exposure to such substances and with respect to the hazard presented by the substances will be necessarily incomplete. The fact that the data base will improve progressively as the scientific risk assessment and hazard evaluation proceeds makes the interaction essential.

In a paper prepared at OSHA's request, AIHC presented proposals for prioritizing substances on the NIOSH list. (AIHC Brief, Appendix H.) The process proposed by AIHC contemplates interaction between the scientists making the evaluation of risk and officials in the Agency performing the regulatory function.

The process of interaction proposed by AIHC envisions the beginning of the prioritizing process with those substances for which there is confirmed evidence of carcinogenicity based on epidemiological studies or positive animal data in two mammalian

species. Based on a preliminay screening of the scientific data and an evaluation of the hazard data available, OSHA and the Scientific Panel would select jointly the substances for priority detailed risk assessment.

Substances on this priority list would be under constant review as OSHA secured more complete hazard data. Thus priorities could be adjusted, either because on full evaluation the data were found to be inadequate for a vaild scientific risk assessment or because more complete hazard data led OSHA and the Scientific Panel to conclude that adjustments should be made in the priorities.

This complementary process does not in any manner jeopardize or interfere with the separation between the two functions. Interaction simply assures that, within the limits of the data, the detailed scientific appraisal will be addressed to those substances which appear to present the higher hazard. The risk assessment in no way interferes with the ultimate decision that regulatory action is, or is not, necessary. OSHA's failure to analyze the separation and interaction of the scientific and regulatory functions is a major gap in the Regulatory Analysis.

III. OSHA HAS FAILED TO MAKE THE ECONOMIC ANALYSIS REQUIRED BY LAW

The National Environmental Policy Act ("NEPA"), the Occupational Safety and Health Act (the "Act") and Executive Order 12044 establish a legal obligation for OSHA to conduct a thorough economic impact analysis of the Proposed Regulation.

The statutory law and the court decisions which create this obligation are discussed in detail in AIHC's Post Hearing Brief. (AIHC Brief at 82-114.) OSHA's obligation is twofold:

(1) OSHA must make an economic assessment of the Proposed Regulation and alternatives to it; and,

(2) OSHA must prepare an Environmental Impact Analysis of the regulation.

OSHA has failed to comply with these requirements.

The shortcomings of the Regulatory Analysis in this area can be demonstrated by reviewing the manner in which the agency deals with one of the most significant issues in this proceeding: The proposal to determine generically "that the appropriate exposure level for a carcinogen is the lowest feasible level." (Analysis at 7.) This proposed generic determination is a rejection of the use of a risk/benefit analysis, which RARG stated was an essential part of "an adequate regulatory analysis." (Ex. 45 at 4.)

OSHA rejects the use of risk assessments in determining the level of control for carcinogens due to the uncertainties and inaccuracies in risk assessment procedures. Yet two regulatory agencies, EPA and FDA, regularly make risk assessments and use them in the regulatory process. Dr. Rall, Director of the NIEHS, urged OSHA to make quantitative risk assessments and testified that animal and human data could be used for that purpose.

It is unfortunate that OSHA chose not to mention or

discuss the Benzene decision in the Regulatory Analysis.[1/] The unanimous Court of Appeals in that case added its voice to that of OSHA's witnesses, Dr. Rall, Dr. Kennedy, Mr. Jellinik and Dr. Albert, in calling for a risk assessment. As the court pointed out, the Act directs that the benefits from a standard be measured with the aid of a risk assessment so that a determination can be made whether the costs are reasonable in light of the projected benefits. The Benzene decision thus conflicts directly with the concept proposed by OSHA as the keystone of its cancer policy, that permissible exposure be set at the lowest level feasible without consideration of the benefits in relation to costs.

The position of OSHA is also a negation of the objective of the Risk Assessment Group of the IRLG. The stated objective of that Group is to develop procedures and criteria for risk assessment that can be applied by all agencies, since otherwise "conflicting views of risk will continue to cloud regulatory decision making."[2/] OSHA should recognize there is no substitute for the risk/benefit analysis recommended and practiced by other agencies and required as a matter of law.

OSHA is equally superficial in its treatment of the estimation of benefits, and the use of a risk/benefit analysis to assure the most effective allocation of scarce resources to

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1/ American Pertoleum Institute v. OSHA, _____F. 2d 80 (5th Cir. decided October 5, 1978).

2/ 43 Fed. Reg. 7195-7197 (February 17, 1978).

protect the health of workers. OSHA retreats to the position that any method of benefit assessment must quantify the value of human life. (Analysis at 57.) This is a basic misconception on OSHA's part, as RARG pointed out in its assessment of EPA's drinking water standards. The Agency is not dealing with certainty in assessing benefits or in assessing risks. When OSHA asserts that science cannot accurately predict the effects of exposure to low doses of carcinogens (Analysis at 47), it is also saying that it does not know what the effects of requiring control to low levels will achieve in terms of worker health.

In this situation, as RARG pointed out, the Agency should make calculations as to the health benefits under various alternatives. Then by comparing the cost for the least stringent with the more stringent alternative, estimates can be made of the incremental costs for the levels of control, and those costs can be compared to the estimates of benefits. The Agency thus would be dealing with an allocation of scarce resources in a cost effective manner. We fail to understand the CEQ criticism of this method of analysis since this is the use of cost effectiveness as a regulatory "tool" rather than an end, which CEQ itself proposes.

RARG concluded that the objectives of the OSHA Act will not be achieved "unless costs to society and the risk reduction (i.e., health benefits expected) are also considered." (RARG Report at 7.) CEQ criticizes this conclusion on the basis that a complete analysis of costs and benefits should include consumer and environmental benefits and that such an analysis

cannot be made without exhaustive tests of a substance.[1/]

CEQ is not on sound ground if it is asserting that a cost/benefit analysis should not be made because a complete analysis is not possible. Such a nihilistic approach argues that one can never utilize an estimate in the regulatory process because it is not complete. As Dr. Rall so eloquently pointed out in regard to scientific knowledge of carcinogenesis, we are not dealing with certainties in this area, we are dealing with probabilities. By its very nature an estimate on probabilities will be characterized by uncertainties and incompleteness. As the court in the Benzene case held, OSHA is not required to make an exhaustive cost/benefit analysis, but mere speculation as to costs and benefits is not a substitute for an analysis which may indeed be rough and incomplete. This does not mean that the Agency should not strive toward completeness. But failure to achieve completeness in the analysis does not prevent the use of the cost/benefit data available. To the extent that elements are quantified, the issues that must be decided on judgment alone are reduced.

IV. THE SNELL STUDY PROVIDES A VALID BASIS TO DEMONSTRATE THAT A COMPLETE COST BENEFIT ANALYSIS IS BOTH POSSIBLE AND MEANINGFUL

OSHA's ultimate conclusion that no meaningful cost/benefit analysis of the Proposed Regulation can be made is based

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1/ CEQ appears to overlook the fact that under NEPA, OSHA is required to assess the environmental impact of a standard.

on two conclusions: first, that a valid risk/benefit analysis cannot be made, a conclusion demonstrated above to be in error; and second, that there are such great uncertainties and variations concerning costs that no regulatory analysis is possible except in proceedings on individual substances. The flaws in the reasoning underlying the second conclusion are discussed in this section.

OSHA acknowledges that when a generic regulation preempts future regulatory decisions, the generic standard will never be economically evaluated unless it is evaluated at the time of its adoption. Yet OSHA takes the contradictory position that an economic evaluation is possible only in proceedings on individual substances because of uncertainties as to the costs of regulation. The net of OSHA's position is that, while an economic analysis of preemptive generic standards is required, the analysis will not be performed except in proceedings on individual substances <u>where the generic standard cannot be evaluated</u>. Thus OSHA has put itself in the position of agreeing that an economic analysis is called for, but refusing to make the analysis.

The preliminary economic study undertaken by Foster D. Snell for the AIHC demonstrates that an economic analysis is both possible and meaningful. The RARG points out a number of problems in this study (RARG Appendix A), many of which had been identified in the original report.[1/] Each of the four major

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1/ In two documents, one filed as post hearing evidence and (footnote continued on next page)

points described by RARG in the first section, Overall Scope and Methodology, would have resulted in much higher cost estimates if they had been considered. Of the rest of the problems cited, changes in the assumptions would have more frequently led to higher cost estimates than to lower ones. Many of the cost elements discussed, such as a different interest or depreciation rate or a different, but reasonable, cost basis for multisubstance engineering controls, would have a far smaller effect on the final cost estimates than a casual reviewer might expect. The admitted shortcomings of the Snell study are no justification for the position that a more definitive study is not possible. Indeed Snell provided a blueprint for the more thorough study which OSHA ignored.

Despite its criticisms of the Snell Study, RARG concluded that "available estimates [i.e., the Snell Report] clearly indicate the potential for very high costs, and a more careful study of the costs (and benefits) expected to be derived from the proposal is in order." (RARG Report at 12.) OSHA's Regulatory Analysis clearly does not qualify as such a study.

A. OSHA's Failure to Make a Cost Analysis Requires OSHA to Adopt Generic Regulations Which Do Not Preempt Subsequent Regulatory Decisions

If OSHA persists in its view that a cost/benefit

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one filed as post hearing comments, Snell has discussed a number of criticisms of the Snell study most of which were based either on error or on misunderstanding of the purpose or scope of the study.

analysis of the Proposed Regulation is not possible and that the analysis can be made only in proceedings on individual substances, then OSHA must adopt generic standards which do not preempt later regulatory decisions. OSHA can do this by incorporating into the proposed regulations the necessary requirements to enable OSHA to determine in proceedings on individual substances what controls are necessary, appropriate and feasible under the statutory criteria. (See discussion by the court in the Benzene decision.) If the generic regulations do not preempt the regulatory decisions on individual substances so a genuine cost/benefit analysis can be made in each case, OHSA's insistence that a cost/benefit analysis can be made only for individual substances may be valid. The indispensable predicate of that position is that no generic standards will be adopted which preclude or prevent a full cost/benefit analysis in a proceeding to regulate an individual substance.

OSHA can meet its obligations to make an economic and environmental impact analysis in two ways. Either OSHA makes a vaild regulatory and environmental analysis of the Proposed Regulation or, alternatively, the Proposed Regulation must be modified so it does not preempt subsequent regulatory decisions. OSHA cannot validly avoid a full regulatory and environmental impact analysis and at the same time preempt subsequent regulatory decisions.

V. OSHA INCORRECTLY ASSERTS THAT THE COST OF REGULATION UNDER THE PROPOSED STANDARD WOULD BE NOMINAL AND NO MORE THAN THE COST OF REGULATION UNDER EXISTING POLICIES

OSHA reviewed the standards for DBCP, coke oven emissions, acrylonitrile and benzene and concluded that regulation of these substances under the Proposed Regulation would not result in the issuance of different standards. From this OSHA concludes that there are no incremental costs or benefits from the Proposed Regulation apart from the increased costs or benefits resulting from more rapid promulgation of standards.

There are a number of basic faults in this conclusion.

- Data on four substances is an insufficient base to assess the cost of a regulation which may cover hundreds of substances. Moreover, two of the four examples chosen actually demonstrate the problems inherent in relying on a policy of control to the lowest feasible level without an adequate cost analysis or consideration of economic impact. The benzene standard was found invalid by the Fifth Circuit on the basis that benefits consistent with the costs had not been demonstrated. The DBCP standard, judged by OSHA to be "feasible," led to the closing of both United States manufacturing plants.

- This conclusion is based upon an assumption that the substances regulated under the Proposed Regulation would be the same as those that would be regulated in the normal course of events. But in the normal course substances would be judged to require regulation as a result of a scientific evaluation of the evidence. Under the Proposed Regulation substances would be designated for regulation on the basis of policy determinations. It is likely that a number

of substances will meet the proposed requirements for Category I classification which would not be designated for regulation based on a full scientific appraisal of the evidence.

- This conclusion does not consider the difference between a standard which would be issued after a cost effectiveness evaluation and a standard which would be issued under the Proposed Regulation which rejects risk/benefit assessment and cost effectiveness.

- This conclusion ignores the fact that the Proposed Regulation calls for automatic issuance of an emergency temporary standard upon classification of a substance in Category I.

- This conclusion ignores the fact that costs for complying with OSHA's Category II requirements are projected to be billions of dollars per year. The substances involved would not likely be regulated as potential carcinogens under existing OSHA policies and therefore this is an incremental cost directly related to the establishment of the generic policy.

- This conclusion ignores the fact that in the chosen examples, unlike in the Proposed Regulation, exclusions for mixtures and action levels were provided, which greatly limited the costs of the standards.

- This conclusion ignores the fact that the Proposed Regulation includes a provision for forced substitution, a regulatory approach not used in the past.

In analyzing the cost of the choosen examples in terms of annualized cost per exposed employee, OSHA figures presented in the Analysis (including most but not all of the cost elements) range from $2,870 to $9,681 (totaled from Analysis at 85). These figures are generally higher than the $3,000 per employee estimated in the Snell study for comparable single substance exposures regulated at the 1 ppm level.

VI. OSHA HAS INADEQUATELY CONSIDERED THE MEANING OF ECONOMIC FEASIBILITY AND HAS FAILED TO SHOW THE PROPOSED REGULATION IS REASONABLY NECESSARY OR APPROPRIATE

A. The Regulatory Analysis Contains Only a Token Analysis of Economic Feasibility

OSHA concludes that the incremental costs and benefits of the Proposed Regulation are a function of the degree to which the standard promulgation process is accelerated. OSHA reaches this conclusion on the assumption that control to the lowest feasible level is automatic. OSHA does acknowledge the importance of evaluating economic feasibility and lists various cost factors which could be considered in making such an evaluation. (Analysis at 54-55, 61.) OSHA makes no attempt to clarify how those cost factors would, in fact, be taken into account, except to state that it is "unlikely" that its regulations would lead to "significant price rises or economic disruption." Id. at 62.

AIHC applauds OSHA's recognition of relevant cost factors. However, in the absence of an indication as to how these factors will be taken into account, it is impossible to determine their effect in a regulatory analysis. This is particularly true when consideration of the factors is summarily and incorrectly reduced to the ultimate determination that significant price rises or economic disruption will not occur.

OSHA's apparent conclusion that a six percent price rise due to its regulation is not "significant" must

be judged by the President's determination that a price rise exceeding five and three-quarters percent is unduly inflationary. We do not suggest that true health considerations should give way to an economic or inflationary impact analysis. On the contrary, cost effectiveness will enhance worker health.

VII. OSHA'S DISCUSSION OF FORECLOSURE OF ISSUES GENERICALLY DETERMINED HAS FAILED TO REDUCE CONFUSION AND HAS RAISED NEW QUESTIONS

A significant area of confusion in these proceedings has been the identification of those issues to be determined generically and the character of the foreclosure of consideration of those issues in subsequent proceedings by reason of those generic determinations. In August, when OSHA described the regulatory analysis it had agreed to prepare, OSHA stated that the analysis would contain "an explanation of what specific issues would be foreclosed by the generic standards in future rulemakings for individual substances". Seven issues to be generically determined are listed on pages 6-7 of the Regulatory Analysis.[1/] The following brief discussion of several of these issues will demonstrate that the overly simplistic approach to OSHA's generic determinations and the related discussions in the Regulatory Analysis fail to remove confusion and uncertainty and, in fact, raise

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1/ The sixth generic determination, that the appropriate exposure level for an occupational carcinogen is the lowest feasible level, is discussed supra, at 17.

new questions.

A. OSHA's Discussion Demonstrates That The Proposed Regulation Fails to Recognize the Uncertainties in Animal Data on Which OSHA Intends to Rely Generically

The third generic determination which OSHA proposes to make relates to the weight to be given animal data and human data, particularly negative human epidemiology. The third policy determination states,

> "(3) that differences in routes of exposure, lack of evidence of species or organ specificity, or evidence of some negative as well as positive data will not negate positive animal tests."

This generic determination is enlarged by OSHA's position that in the proceedings on individual substances, one issue will be whether the substance was properly classified but "the proposed regulation [will] not permit an attack on the criteria themselves." (Analysis at 76.) Thus a Category I classification would be required on the basis of a positive test in one species if replicated or supported by unspecified positive short term tests or upon such other evidence satisfactory to the Secretary.

OSHA's determination to rely on positive animal data without regard to negative data on the substance will create serious scientific and policy questions concerning the validity of OSHA's actions.

1. OSHA's generic determination is based on a false assumption as to quality of tests. OSHA makes no distinction between tests depending on quality. Thus OSHA implicitly assumes all tests are of equal quality, an assumption completely un-

justified by the record.

2. OSHA has not excluded acting on false positive results. OSHA has established no criteria for evaluating tests although it announced its intention to do so. (AIHC Brief at 53-68.) Since OSHA has announced no standards of statistical significance, the positive test upon which classification rests could be a false positive as a matter of chance. (AIHC Brief at 141-144, 159-166.)

3. OSHA's error in relying on results in a single species. In its zeal to reject the recommendations of EPA, FDA, Dr. Rall and RARG that OSHA should take potency into account and make quantitative risk assessments (see AIHC Brief at 197-233), OSHA has set out reasons which demonstrate that OSHA's proposed reliance on positive results in a single species for regulatory purposes is highly questionable. Thus OSHA concludes:

> "[T]he biological nature of a lesion in one species is not predictive of what might occur in another species. One cannot predict the site of the neoplastic response from one species to the next, let alone the biologic behavior of the lesion.
>
> Although the criteria discussed above are useful for the assessment of potency within any given test animal population, there are rarely sufficient scientific data to extrapolate to other species, including humans. In qualitative terms, a substance which is carcinogenic in one mammalian species is probably also carcinogenic in other mammalian species under certain conditions. Although carcinogens exhibit a wide range of potency in experimental animals, the quantitative extrapolation of specific observations to humans is hindered by major interspecies differences in response to carcinogens. The occurrence, site and nature of tumor develop-

> ment cannot always be predicted in other species. Nor can a prediction of tumor incidence or latency be accurately made. Therefore, the potency of a chemical carcinogen in one species cannot be used to predict the level of carcinogenic effect in another." (Analysis at 43.)

The species variation and the problems of extrapolating across species discussed at length in AIHC's Brief (at pages 115-179) are specified by OSHA in the above quoted excerpt from the Analysis as grounds for rejecting evidence of potency and risk quantification. The very same reasons demonstrate that the qualitative extrapolation on which OSHA proposes to build a multibillion dollar regulatory structure is based only on the conclusion that a substance carcinogenic in one species is "probably" carcinogenic in other mammalian species "under certain conditions".

OSHA's discussion of metabolism, pharmacokinetics, detoxification and molecular repair adds further confusion. OSHA concludes that because these functions are not constant between species, risk quantification is not possible. (Analysis at 44.) OSHA later, in trying to escape from the conclusion that it is freezing science, asserts that comparative metabolic data may be rebuttal evidence. (Analysis at 75.) But this possibility has little utility since OSHA repeats its advance rejection of rebuttal data by asserting that such data cannot be used "to permit an attack on the criteria themselves". (Analysis at 76.)

Thus, the classifiction criteria and generic determinations will lock OSHA into automatic regulatory action on the

results in a single species despite the uncertainties of cross species extrapolation and differences between man and the test animal. (See discussion in AIHC Brief at 137-144.)

4. OSHA's treatment of negative epidemiology and animal data is unsatisfactory. The third generic determination quoted above requires rejection of negative human epidemiology if there are positive animal data. OSHA does not even acknowledge the points made forcibly by NIOSH: (1) the weight given to test results should be a function of the quality of the test; and (2) if the results of epidemiological studies are rejected out of hand generically, no one will have any incentive to conduct such studies. (See discussion in AIHC Brief at 124-128.) The CEQ comment expresses concern about the "disincentive to test for workplace carcinogens that the OSHA cancer proposal may establish for industry."

A more fundamental scientific criticism is that OSHA's simplistic criteria foreclose the role of human epidemiology which Dr. Rall and the National Cancer Advisory Board underlined:

> "Negative epidemiologic data may not establish the safety of suspected materials. Negative data on a given agent obtained from extensive epidemiologic studies of sufficient duration are useful for indicating upper limits for the rate at which a specific type of exposure to that agent could affect the incidence and/or mortality of specific human cancers." (Preamble Ex. 71.)

We have discussed at length in our brief the error of relying on a single positive study in the face of negative data. (See AIHC Brief at 128-131, 141-166.) In light of the evidence in the record, it is surprising that OSHA does not even indicate

that its proposed position is under review.

5. OSHA's proposed generic determination that MTD studies may be used to establish human risk is unsound. OSHA proposes as its second generic principle to rely on tests using maximum tolerate dose ("MTD") to establish human risk. (Analysis at 6.) This proposed generic determination is an unwarranted, significant extension of the conclusion of NCI that a MTD test merely demonstrates that the substance has the potential for human risk. NCI clearly states that other information is needed before it is possible to determine whether a human risk exists: dose response data; differences between man and the animal with respect to metabolism, detoxification, excretion, and route of exposure; mechanism of action and the way the substance is metabolized in human tissue; validity of test procedure; and adequacy of pathology. (See discussion in AIHC Brief at 121-124, 138-137.)

NCI has restated its position on MTD testing in the Forward to the recently released report on the bioassay of Oxinphosmethyl for possible carcinogenicity. (CAS No. 86-50-0, NCI-CG-TR-69.) In the Foreward to the report NCI states:

> "Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis." (At iii (emphasis added).)

If OSHA persists in its proposed generic declaration on MTD testing, its position is not supported by NCI.[1/]

6. OSHA's reliance on short term tests as confirmatory evidence is misplaced. OSHA's proposed fifth generic determination declares that short term tests ("STT") are not by themselves a sufficient basis to justify regulating a substance as a carcinogen. (Analysis at 7.) However, OSHA re-asserts the criteria for classification of a substance in Category I as being positive results in one species "supported" in an undefined way by STT.

We have discussed in our brief (at 168-178) the error in placing such reliance on STT. These tests are in the process of validation. The correlation between the two different biological phenomena, mutagenicity and carcinogenicity, has not been established. Moreover, there are no criteria for selection of STT, their performance or evaluation. Until STT are validated, the correlation with carcinogenicity established and the criteria for conducting the tests standardized, STT can perform only the function of screening for further testing.

OSHA cites the National Cancer Advisory Board in support of its view on STT. (Analysis at 26.) The report of that

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1/ The need to re-examine the OSHA position on MTD testing data is also indicated by re-assessment of test protocols for bionutrients such as selemun, vitamin C and calcium. See discussion in "Biological Intermediates as Research Probes in Carcinogenesis Methodology", H. F. Kraybill, PH.D., Division of Cancer Cause and Prevention, National Cancer Institute, presented at 10th Inter-America Conference on Toxicology and Occupational Medicine, October 22-25, 1978. (Attached as Appendix A.)

Board demonstrates that OSHA's proposed reliance on STT as confirmatory evidence is in error. The Board said,

> "At present, none of the short-term tests can be used to establish whether a compound will or will not be carcinogenic in humans or experimental animals. Positive results obtained in these systems suggest extensive testing of the agent in long-term animal bioassays, particularly if there are other reasons for testing. Negative results in a short-term test, however, do not establish the safety of the agent." (Preamble Ex. 71.)

B. The Invalidity of OSHA's Proposed Generic Determinations as Inflexible Standards Underscores the Need for a Scientific Evaluation of All the Data

OSHA's blind reliance on simplistic criteria and generic determinations leads to basic scientific errors. Thus, for example, OSHA using its criteria reaches the conclusion that "aflatoxin is a potent carcinogen in rats and man, but a relatively weak one in mice." (Analysis at 44.) Had OSHA made a risk assessment of the kind recommended by, among others, FDA, its error would have been apparent. The FDA made a careful analysis of animal data and human epidemiology and reached a conclusion with respect to human risk opposite from that reached by OSHA. (Ex. 38.) FDA concluded from an examination of all the data that humans are closer to aflatoxin resistant mice rather than aflatoxin susceptible rats.

The need felt by OSHA for administrative simplicity should not obscure the fact that scientific evaluation of data is a scientific process based on a review of all the data. OSHA asserts that its generic proposals and criteria represent "current" scientific views. (Analysis at 19.) We have shown this

to be in error but, in any case, in a field developing as rapidly as the study of carcinogenesis it is a mistake to exclude any facts or data from the scientists making the basic scientific evaluation. No supposed administrative convenience can justify handicapping the scientists by denying them access to all the facts.

Stating a "minority view" from the CEQ, Mr. Strohbehn takes the position that carcinogenic potency and quantitative estimates of risk should be used only for setting of priorities after classification and for determination of the "feasibility" of a standard. Yet in an almost contradictory way, Mr. Strohbehn argues that quantitative estimates are not appropriate for ascertaining if a risk exists. Mr. Strohbehn appears to agree with the small minority who support the notion that a risk-free society is feasible and that, therefore, any substance shown to be a carcinogen in any system or test -- whether the test is scientifically valid or not, whether the test is appropriate or not with regard to actual exposure -- should be regulated as a grave cancer risk. Clearly the majority of scientists, as the OSHA hearing record shows, support the fact that there is a distinct difference between cancer risk from a substance which, for example, through inhalation at low dose levels causes tumors in 90% of tests animals in a single mammalain species, and the cancer risk from a substance given by intraperitoneal injection which produces three tumors only at the highest dose level, with two spontaneous tumors in control animals. It is scientifically naive to suggest that this type

of evidence is irrelevant in terms of assessing "cancer risk". No scientifically competent panel in this country would ignore such evidence.

Mr. Strohbehn's reference to "consensus" of national and international expert opinion that the "qualitative determination that a risk of cancer exists can be made with much more confidence than any quantitative estimate of the risk posed" does not address the real problem posed by the President's RARG. Certainly, a qualitative estimate is easier to make than a quantitative one. However, Mr. Strohbehn appears to ignore the fact that these same experts have urged that even though quantitative assessment of risk is difficult, OSHA should still undertake such an analysis. To do less would be socially irresponsible.

C. OSHA's Unjustified Conjecture That Promulgation of the Proposed Regulation Will Create Certainty and Thus Reduce Costs

An underlying theme in the OSHA Analysis is that the publication of a final regulation similar to the Proposed Regulation would create a "certainty" as to regulatory approach that would lead to cost reductions. (Analysis at 22-23, 56, 73, 95.) The basis for this conjecture is never explained. In fact, this assertion is difficult to reconcile with other statements in the Analysis, such as that "[o]ther federal agencies . . . will continue to have increasing roles in OSHA rulemaking." (Analysis at 39.)

In addition, every advance in knowledge of the cause

and mechanism of cancer will trigger a new range of uncertainties. There will be no way to tell whether OSHA's generic determinations will be used to blind the scientists making the data evaluation or whether the data will in fact be used. This uncertainty alone would leave industry, labor and the public in doubt whether OSHA will act on outmoded, generic criteria or on the new information.

If there were assurances that OSHA's regulatory decisions were based on quantitative risk assessment and sound cost/benefit analysis as the statute requires, there would be more socially sound cost/effective health determinations:

(1) There would be a prioritization based on scientific opinion.

(2) Numerous materials would not be considered of sufficient risk to warrant any application of resources.

(3) There would be an excellent chance of achieving economic trade-offs so that society would get the most health protection for the dollars invested. There would be less chance of failure to regulate an important hazard because resources would not be overloaded by dealing with relatively unimportant risks and hazards.

VIII. OSHA ERRONEOUSLY REJECTS A COST EFFECTIVE COMBINATION OF ENGINEERING CONTROLS AND PERSONAL PROTECTIVE EQUIPMENT

Perhaps no subject matter better illustrates the circular reasoning in OSHA's Regulatory Analysis than its consideration of engineering controls.

Much of the discussion in the Regulatory Analysis relates to the proposed seventh generic determination that engineering controls will have priority over personal protective equipment in reducing exposure. (Analysis at 7, 48, 102, 112.) OSHA, however, never discusses this proposed generic determination except in terms of its justification or defense. In addition, OSHA never realistically addresses the proposal by RARG in its report on the acrylonitrile standard that OSHA permit all methods of compliance, including respirators, in a program designed to achieve higher health benefits by using cost effective means. (Ex. 45.)

Thus OSHA assumes its generic conclusion and finds that there is no incremental cost from the Proposed Regulation because OSHA will not consider and appraise the genuine alternative presented by RARG. Nor does OSHA discuss the somewhat comparable alternative proposal of AIHC.

OSHA's Regulatory Analysis makes no attempt to compare the costs and benefits of the suggested alternative to OSHA's inflexible determination to require engineering controls under all circumstances. The issue of alternative compliance approaches which RARG stated should be addressed by OSHA, was not addressed.

OSHA did not attempt to weigh the benefits or the costs of alternatives. OSHA describes only its reason for preferring engineering controls for routine exposure situations, ignoring the potential use of respirators for situations that involve short, periodic or intermittent exposure, or for other situations where engineering controls are relatively ineffective.

XI. THE REGULATORY ANALYSIS IS AN EVASION OF OSHA'S STATUTORY DUTY AND ITS OBLIGATION UNDER PRESIDENTIAL DIRECTIVE TO ASSESS COSTS IN RELATION TO BENEFITS AND TO ANALYZE ALTERNATIVES

When OMB reported that OSHA had agreed to undertake a Regulatory Analysis, OMB stated that if generic standards which preempt subsequent regulatory decisions are not examined at the time of promulgation, they will never be evaluated. By deciding with circular reasoning that the economic consequences of the proposed generic standards are merely a matter of timing, OSHA has side stepped completely an economic analysis of the proposal and its alternatives. Thus, the fear of the OMB has come to pass -- the proposed generic standards will never be evaluated economically since they cannot be questioned in subsequent proceedings.

Similarly, OSHA has made no attempt to prepare the Environmental Impact Statement ("EIS") for those generic standards. OSHA says it will prepare an EIS in subsequent proceedings but the prior generic determinations will forbid an analysis of alternatives as required for compliance with NEPA. Unless OSHA modifies its position, OSHA will be avoiding its legal obligation

to prepare an EIS for its generic determinations.

The Courts of Appeals for both the First and Fifth Circuits have decided that the statutory requirement that standards be necessary and appropriate means that benefits must be evaluated and must bear a reasonable relationship to costs. (See AIHC Brief at 7-15, 55-75, 215-233.) OSHA seems, on the contrary, to propose for reasons of administrative convenience that the classification of carcinogens must be based on arbitrary criteria rather than full scientific evaluation of the risk. OSHA is also seeking to avoid evaluating benefits in light of costs on the ground that, because of uncertainty in the risk analysis, it cannot measure benefits and, since there are uncertainties, the regulatory response will be control to the lowest feasible level.

CONCLUSION

The White Paper, dated October 24, 1978, which accompanied the President's anti-inflation program, discussed the President's regulatory policy to achieve regulatory goals in cost effective ways. (See 43 Fed. Reg. 1938 (November 7, 1978).) Speaking of Regulatory Analyses required under Executive Order 12044, the Paper stated,

> "These analyses must identify the benefits and the costs of the proposed regulation and examine the implication of alternatives."

OSHA has failed to make the analyses required by law and by order of the President.

We urge OSHA to reconsider its position. The Proposed

Regulation should be amended to remove the scientific flaws and legal errors. The regulation should be re-proposed for comment. We urge also that OSHA recommend to the President that the Scientific Panel recommended by AIHC be established.

APPENDIX

Appendix A

BIOLOGICAL INTERMEDIATES AS RESEARCH PROBES IN CARCINOGENESIS METHODOLOGY

by

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BIOLOGICAL INTERMEDIATES AS RESEARCH PROBES IN CARCINOGENESIS METHODOLOGY

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ABSTRACT

A reorientation of views in the area of carcinogenicity bioassay procedures has suggested new approaches for placing into proper perspective problems in dose response. Chemicals normally presumed negative because of their physiological significance but which can elicit a tumorigenic response at relatively high doses are candidates for critical evaluations on the effect of dose. Endogenous and exogenous chemicals which fall in the class of biochemical intermediates such as the micronutrients, vitamins and minerals and endogenous compounds such as citric, malic, succinic and fumaric acids, xylitol, tryptophan metabolites and others are proposed as research probes in this critical appraisal on carcinogenicity.

Some data and findings are presented on the above types of chemicals demonstrating the mechanism of action of physiologically/nutritionally essential chemicals which may elicit tumor response under adverse dose schedules. Applicability of these findings to other chemicals is suggested as a means for reorientation of perspectives and current concepts on carcinogenesis, specifically in the area of dose regimes.

INTRODUCTION

The neoplastic process may be a multistage event with chronic toxic effects as precursors in the manifestation of cancer. While carcinogenesis is a complex mechanism about which little is known, enough knowledge exists to appreciate the fact that in assessing activity by current methodology toxicological principles should be recognized. Such is not the case. Indeed, this toxic mechanism called carcinogenesis is cast in a special role that may appear as unique. In the multistage process which may eventuate in cancer, is it not conceivable that the chronic toxic response parallels the physiological/pharmacological and biochemical chain of events which proceed to non-carcinogenic events? The metabolic capabilities and the inherent defense mechanisms of the mammalian system provide means for detoxication of environmental insults. Are these capabilities operable more so in the region of low dosing or exposure? For noncarcinogenic lesions this would seem to be the case. Beyond the metabolic or pharmacological capability, when the administered dose or the exposure is excessive, a region of intoxication becomes evident. Are these intoxications the antecedents of a breakdown in

normal cellular resistance and is the milieu swamped with unmetabolizable compounds which may create the conditions for cellular proliferation and a disturbance in DNA and RNA function?

The questions are raised because, in acccordance with numerous principles relative to carcinogenicity, the neoplastic process is considered irreversible and for a chemical indicted as a carcinogen there is a no-threshold. These principles become dogma, yet to toxicologists there is the inevitable possibility that there may be opportunities for repair[1]. In recent years, various investigators have calculated threshold values for carcinogens[2]. An international committee of the World Health Organization has had the courage of considering the possibility of a threshold by using the phrase "an envisaged threshold"[3].

Druckrey[4], a renowned investigator in the carcinogenesis research field, has enunciated that there is a dose dependency relationship in carcinogenesis. This would imply that various toxic manifestations at different dose levels would need exploration. This concept can be examined through making observations on biochemical parameters such as occurrence of the chemical in the tissue, the appearance of metabolites in the tissue and the presence or disappearance of pathological lesions as one proceeds downward in the dose response curve.

The use of mathematical models is commonly resorted to in making these extrapolations from the region of the high dose response to the lower dose areas. The inadequacy of current experimental procedures including kilomouse experiments has left one with few alternatives unless, as indicated above, one secures more definitive biochemical/pathological information to make these extrapolations more appropriately from a biological viewpoint. The work of Gehring and coworkers represents a step in this direction[5].

To place these issues in a better perspective, namely to establish that chemicals invoking a tumorigenic response at very high doses may show a non-tumorigenic or non-toxic effect at physiological levels, we decided to advocate the testing of biological intermediates, otherwise characterized as "presumptive negative chemicals," vitamins and essential minerals and some endogenous chemicals such as those identified in the tricarboxylic acid cycle or other endogenous chemicals in metabolic pathways.

RATIONALE AND CRITERIA RELEVANT TO EXPLORATORY STUDIES UTILIZING BIOLOGICAL INTERMEDIATES AS RESEARCH PROBES IN DOSE RESPONSE STUDIES IN CARCINOGENESIS

To better understand the significance of dose dependency in these biological mechanisms, including carcinogenesis, some isolated examples of chemicals such as selenium, which may induce some tumors at levels

of intoxication and yet at very low doses demonstrate a physiologically essential role, gave us clues to look for other chemicals fulfilling this requirement. In our view, information of this type may help to provide a better perspective on the matter of generalizations and extrapolations which should take into account biochemical and pharmacological phenomena that are dose dependent. Some of the criteria that were considered in the planning of such exploratory studies are outlined in Table 1. These criteria are described in greater detail in the following discussion.

TABLE 1
CRITERIA FOR ADAPTATION OF BIOLOGICAL INTERMEDIATES AS RESEARCH PROBES IN CARCINOGENESIS ASSESSMENT METHODS

Criteria	Potential Adverse Effect Associated with Neoplasia
Exceeding physiological requirements	Intoxication Protective mechanism overcome
Metabolic overloading	Alternate pathway development, Neoplasia induced indirectly
Appearance of deficiency state	Inadequate protective mechanism that is dose-dependent
Formation of metabolites that swamp physiological capabilities	Intoxication evoked due to pile-up of excess metabolites. Neoplasia may be induced by aberrant cellular environment.
Excess of endogenous chemicals via malabsorption syndromes	Malabsorbed endogenous chemicals on dose-dependent basis may create condition for induction of neoplasia.

EXCEEDING PHYSIOLOGICAL REQUIREMENTS

Micronutrients (vitamins and minerals) are required at physiological levels to provide for essential biochemical and physiological functions and to maintain homeostasis. At high doses in the zone of intoxication hypervitaminosis is well documented in the literature (vitamins A & D) and clinical cases of overexposure to minerals have been reported. For example, iron overloading may produce, in susceptible members of the population, iron storage disease. Cartwright[6] has indicated that hemo-

chromatosis is observed in 1 in 20,000 hospital admissions and 1 in 7,000 hospital deaths, being more common in males than females. Exceeding the recommended allowances by many orders of magnitude will result in overt toxicity.

Vitamin C, or ascorbic acid, has been advocated by Cameron and Pauling[7] for prevention of the common cold and may control cancer in some patients. Pauling advocates doses of 5 grams of vitamin C per day. Cousins[8] administered to himself 25 grams of ascorbic acid per day for therapeutic control of ankylosing spondylitis and Klenner[9] administered as much as 150 grams of vitamin C per day for short periods of time in various treatments of patients.

Stich and coworkers[10], in their work with human cells of the gastric mucosa, found that large doses of vitamin C (equivalent to 10 gms daily in man) produced some chromosome aberrations. They believe that doses of 6-7 grams could be hazardous. Schegel and coworkers[11] point out, as does Stich, that high levels of ascorbic acid could be toxic because of oxalic acid excretion. Smith[12] in his clinical studies emphasizes the risk of oxalate stones in high dose administration of vitamin C. Beyond 4 gms there was a rise in oxalic acid excretion. These clinical studies revealed that megadoses of ascorbic acid evoked calcium urolithiasis with urinary excretions of oxalic acid of 55 to 74 mg per 24 hours. This clinician recommends a limit of 4 grams of this vitamin per day.

On the basis of our previous suspicions, corroborated by the above information, and with the possibility that vitamin C administered in high doses may produce, through oxalic acid excretion, an irritant on the bladder wall, vitamin C has become a candidate for testing by the National Cancer Institute in a carcinogenesis bioassay. Other selections have not been made but vitamin E and, perhaps, niacin may be good models for exploring the effects of high dose in relation to tumorigenesis.

METABOLIC OVERLOADING

The practice of using maximum tolerated doses in typical carcinogenesis bioassays is to increase the "power of the test." This procedure is intended to provide a higher degree of assurance that "false negatives" will not be encountered as a reported observation. Such practices, however, provide the opportunity to achieve overt toxicity or an intoxication, as previously mentioned. Indeed, many animals have been intoxicated to the degree that mortalities occur and no neoplasia was observed. Many of these experiments have had to be repeated at lower dose regimens.

There is a strong possibility that high doses may lead to tumors not seen at low doses because alternate pathways may be taken or there is a spillover to different metabolizing enzymes.

We know little about the overdosing or underdosing of many of the biological intermediates. In Figure 1 the probable fate of ethylene glycol in the body shows that at high dose oxalic acid can be the primary metabolite. At low dose or normal exposure this chemical is metabolized to formic acid and carbon dioxide, or, through conjugation of glyoxylic acid with glycine and benzoic acid, is excreted as hippuric acid.

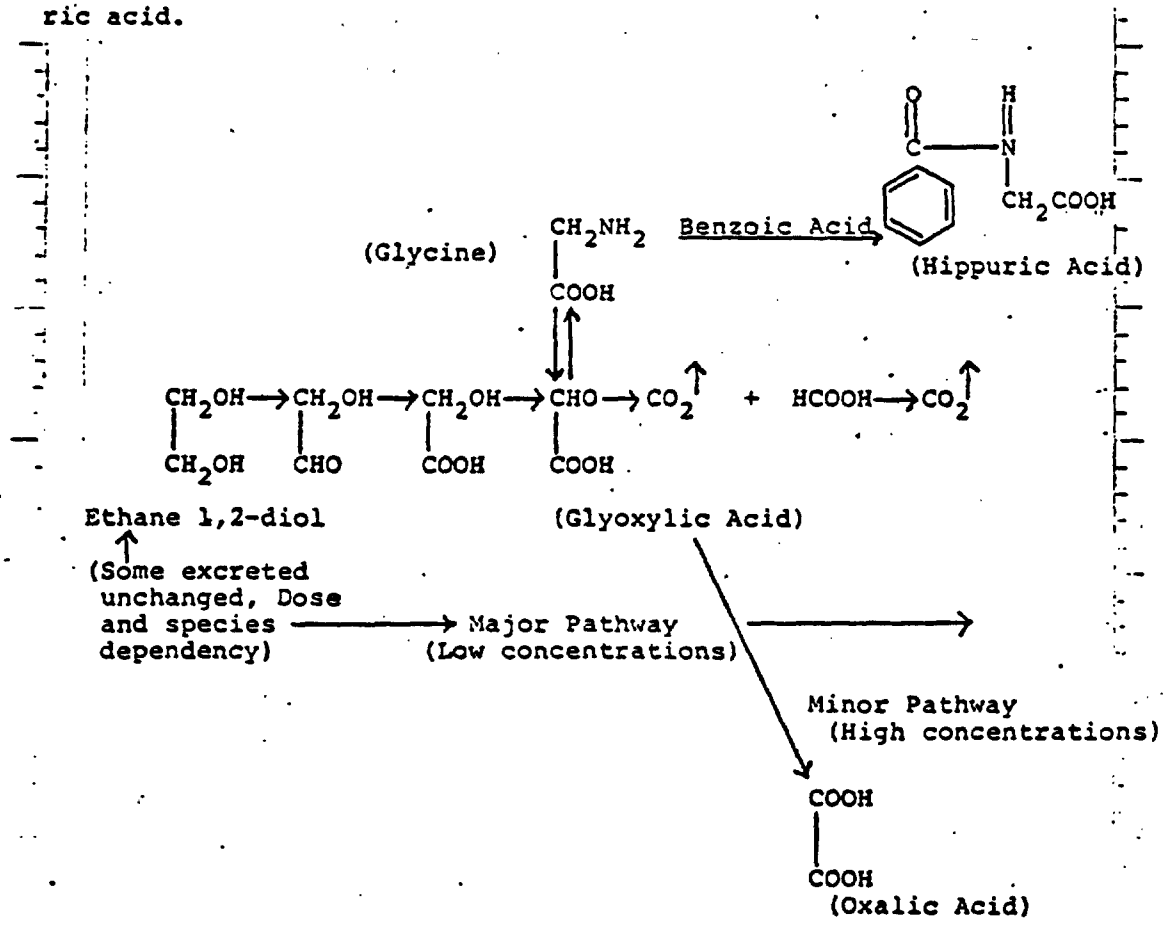
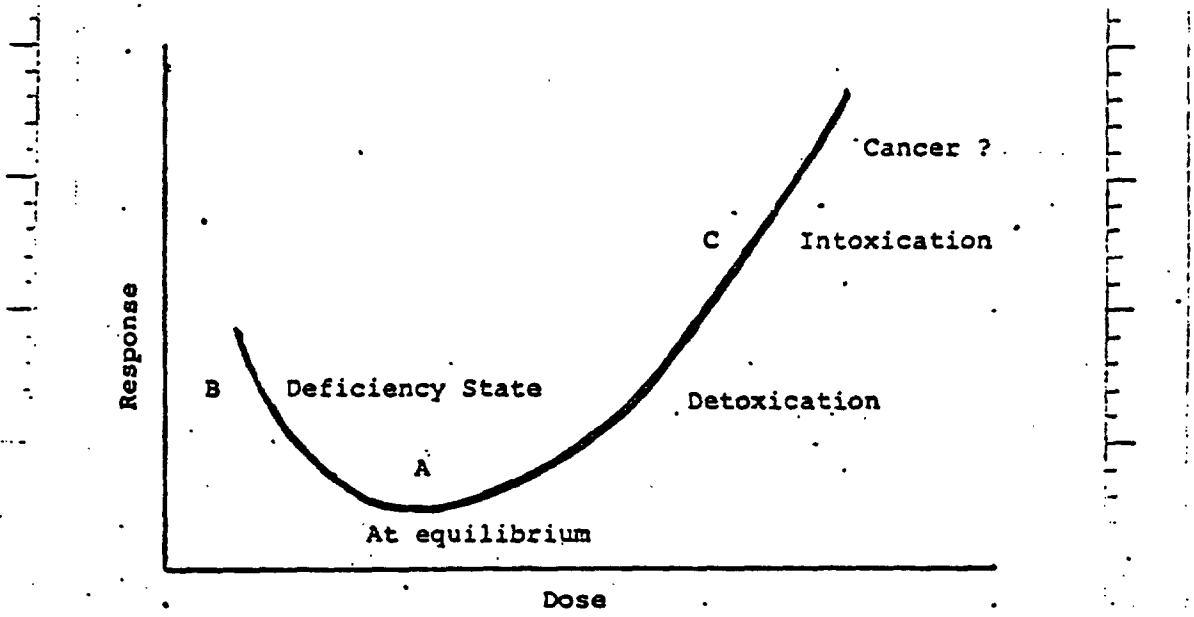


Fig. 1. Probable fate of ethylene glycol in the body. Influence of dose on metabolites formed and excreted. Source: Gessner et al (1961) Biochem. J. 79: 482-489.

Studies on calcium[26], selenium[13], arsenic[27], sucrose[24], and xylitol[24] are most instructive with regard to the dose effect and tumor induction. In Figure 2 the dose response curve for selenium illustrates the mechanism of action for this essential element. At the higher dose level of 5 ppm selenium has been reported to be a hepatocarcinogen[13]. This

adverse effect must be in the zone of intoxication while at lower doses selenium behaves as a scavenger taking up free radicals, substituting in cystine for sulfur as selenocystine, but at higher doses interferes with sulfur metabolism. There is an equilibrium point or, where homeostatic mechanisms occur, where there must be an envisaged threshold or a minimum risk level relative to cancer. Below this physiological level for selenium there is an apparent deficiency state where many physiological functions are hindered. Schrauzer[14] has suggested that a deficiency of selenium may give rise to a greater incidence of some cancers.



DOSE RESPONSE CURVE FOR SELENIUM

At A - Equilibrium - Homeostasis, Minimum Risk Level. Electron transport system in balance. Hydroperoxides, free radicals scavenged (detoxification), no hepatic necrosis, cellular respiration functioning.

At B - Absence - Deficiency - Noncompetitive action of selenium. Free radicals, hydroperoxides pile up. Disturbance of cellular respiration.

At C - "Intoxication" - Overdose of selenium (high protein diet affords some protection as does sulfate and arsenic), antagonist of sulfur metabolism. Inhibition succinic dehydrogenase, urease, choline oxidase, tyramine oxidase and proline oxidase. Inhibition of mitosis at metaphase. Abnormal bone and cartilage development. Cirrhosis of liver in cattle. Replacement of cystine by selenocystine in keratin.

Fig. 2. Probable biochemical events (multiphasic processes) in physiological response to selenium.

Previous reference has been made to vitamin E as a potential candidate for high dose studies. There is no evidence thus far that tocopherols are toxic[15]. However, since tocopherols, like vitamins A & D, are fat soluble and accumulate in the body, especially the liver and pancreas, cumulative untoward effects are hypothetically possible. Experimentally in rats, vitamin E deficiency is associated with lead toxicity erythrocyte deformability[16]. Vitamin E in higher than normal doses has been advocated for intermittent claudication, or calf pain, and clinically for retardation of mammary cysts. Roberts[17] in observing 46 patients where this vitamin was used for peripheral vascular disease, thrombophlebitis, and leg cramps, noted that vitamin E had the reverse effect in its association with thrombus formation.

DEFICIENCY STATES - AREA OF LOW DOSE

The opposite of overdosing would be a region of underdosing or a deficiency state for a physiological nutrient. The literature is replete with examples of the influence of deficiency states and the role of additions to the diet on tumorigenesis[18]. Lacking, of course, are systematic studies on dose response relationships relevant to these nutrients in terms of tumorigenesis and regression of tumorigenesis. Certain micronutrients, especially the vitamins, have been associated with increases and decreases in spontaneous tumor incidence. Vitamin A deficiency is associated with odontomas and salivary gland tumors[19]. Abnormalities in folate metabolism have been associated with acute and chronic leukemias[20] and in Vitamin B_6 and tryptophan metabolism with Hodgkin's disease and some with carcinoma of the breast and bladder[21]. Gluten enteropathy, a malabsorption syndrome, sets the stage for development of carcinomas[22].

Deficiencies in protein and riboflavin may depress the activities of metabolizing enzymes. As a result there is a persistency in carcinogenicity when drugs and chemicals are introduced into organs[23]. Antimetabolites and interactants with vitamins in the diet can lead to inadequate physiological levels of vitamins, setting the stage for tumor growth.

METABOLITES PRODUCED OR ENDOGENOUS CHEMICALS THAT MAY ENHANCE TUMORIGENESIS

Beyond the body's production of endogenous chemicals such as those in the tricarboxylic acid cycle (citric, malic, fumaric and succinic acid), these chemicals are introduced into the body as food additives and in drugs. Thus, the levels to be metabolized are increased from exogenous sources. An overload of any of these could lead to aberrant biochemical effects and pathological lesions.

Methyl methacrylate and xylitol are good examples of endogenous chemicals that warrant serious consideration. Recent studies from England have demonstrated that xylitol, a metabolite in the glucuronic acid pathway, produced adrenal gland and bladder tumors in rodents when fed at 20 percent in the diet[24]. This high level of xylitol, a polyhydric alcohol conversion product from xylose, probably produced bladder tumors by an irritant effect at this high concentration. Clinical observations reported by Schumer in 1970[25] have shown that normal human subjects infused with xylitol showed a marked decrease in serum phosphate and a marked increase in urates and bilirubin. This finding discouraged the use of this sugar alcohol in place of glucose to circumvent the hexose stimulation of insulin secretion.

SUSCEPTIBLE MEMBERS OF POPULATION - MALABSORPTION SYNDROMES - INBORN ERRORS OF METABOLISM

There is a wide spectrum of deficiency states because of malabsorption. These inborn errors in metabolism (pharmacokinetics) may evoke certain metabolic mechanisms that lead to an overload of certain chemicals. There are cases of faulty feedback mechanisms relevant to certain enzymes. Whether these malabsorbed nutrients or end products can lead to a buildup of such intermediates and neoplasia needs to be explored. Previous mention was made of gluten intolerance and malabsorption as setting the stage for development of carcinomas.

CONCLUSIONS

It is hoped that this brief account of the possible role of biological intermediates in the exploration of dose administration as an important variant even for physiologically essential chemicals in the induction of cancer may stimulate the development of this area of research. Failure to recognize the significance of certain toxicological principles in the conduct of carcinogenesis experiments has evoked some extensive critiques suggesting the lack of credibility of certain reported studies.

To place these issues into better perspective, it is maintained that dose response studies on biological intermediates, using wherever possible massive or maximum tolerated doses, may be quite useful. From studies on the essential vitamins and minerals and endogenous chemicals that may be demonstrated to evoke tumors at high doses it is assumed that such examples may cause a reexamination of the current studies which use a maximum tolerated dose for all chemicals indiscriminately.

A summing up of some of the relevant studies that might be envisioned in this important area of research is presented in Table 2.

TABLE 2

BIOCHEMICAL INTERMEDIATES IMPLICATED IN TUMORIGENESIS

Intermediate	Physiological level required for biological function	Observed toxic dose for response	Adverse effect	Reference
Selenium	0.1 - 0.5 ppm Prevents red blood cell damage	5 ppm in rat	Liver tumors	13
Calcium	Man 0.8 gms/day Bovine 15-19 gms/day	88 gms	Ultimobranchial tumors in bulls	26
Arsenic	Undetermined - Essential element Deficiency - effect on spleen and red blood cells	400-600 ug/l in water	Skin cancer	27
Sucrose	For energy, level ?	20% in diet of rodent	Kidney tumors	24
Xylitol	Nonessential but endogenous chemical in pentose metabolism - energy production	20% in diet of rodent	Tumors of adrenal glands - bladder	24
Vitamin D_2	400 I.U. - Ricketts prevention, Ca and P metabolism	1 ppm in diet of C3H tumor virus strain of mice	Mammary tumors	28
Orthoaminophenols (metabolites of tryptophan)	Dose ? in tryptophan metabolism	9-11 mg in 4 parts of cholesterol in bladder implants	Bladder tumors	29

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Box 3 - Alcoa Documents

1. OSHA Generic Cancer proposal (includes correspondence, articles and miscellaneous notes)