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MEMORANDUM FOR AIHC

Re: Final OSHA Generic Cancer Regulation as Distributed at the News Conference 1/16/80

The purpose of this memo is to summarize briefly the science and other issues OSHA addressed on the very lengthy preamble and final regulation (294 Fed. Reg. pages). The regulation will be signed and stamped into the Federal Register at 1 PM Friday, January 18th (the time fixed by OSHA for judicial review). The regulation will be published in final form in th Federal Register on Tuesday, January 22nd; it will become effective ninety days from that date.

The format of the preamble is to recite OSHA's original position on an issue; quote at some length from the record various views and contentions; and then select the position OSHA agrees to. The pattern of the regulation - categorization and draft standards - resemble the 1977 proposal with several major changes. Categories III and IV are dropped. Two model standards attached (an ETS and a model permanent standard) are described as guidelines; the headings in the models which represent "major industrial hygiene programs" must be included in all standards, but the Secretary has discretion to include, delete or change any specific provision in each heading. Three basic policy decisions, which will not be changed, are made concerning the standards (1) lowest feasible in all cases; (2) primary reliance on engineering controls and work practices, and (3) protective clothing and medical examinations to be free to the employees.

## I. Science Issues Decided by OSHA

1. Cancer is a multistage multi causal disease which can originate from the transformation of a single cell. OSHA will not distinguish for regulatory purposes between an initiator, promoter, co-carcinogen or enhancer; "carcinogen" for OSHA's purposes includes all.

Cancer is irreversible in the sense that a transformed cell will retain its potential to develop into a cancer for most of a lifetime. The transformed cell may not "inevitably" develop into a cancer; progression will depend on host and environmental factors.

Cancer is age dependent but OSHA cites and rejects Roe's "sexually effete" remark.

The latent period of the disease may be long and therefore it is imprudent to await human epidemiology.

Cancer is an environmental disease and can be reduced by reducing exposure.

Most substances are not carcinogenic.

2. Occupational Cancer. OSHA cites "industry" estimates of 1%-5% and the Estimates Paper (and Stallones Report). OSHA defends the Estimates Paper but concludes that it doesn't matter since reducing occupational exposure will reduce the cancer burden.

OSHA relies on Schneiderman for the conclusion that age adjusted incidence of cancer in white males rose 8% between 1970 and 1975 (7% if smoking is excluded) and that cancers at sites associated with occupational exposure rose 11% (Epstein) or 12% (Schneiderman with smoking excluded).

3. Epidemiology. There is a long discussion of the problems and limitations of human studies. OSHA will not list criteria for positive studies, but will rely on scientific judgment.

"Non positive" (negative) human studies will in general be superceded by positive animal studies and will not be consider d unless the human studies meet the following criteria

- involves the same substance being considered for regulation or a closely related substance;
- 20 years of exposure and 30 years of observation;
- documented reasons for predicting the site if the substance were a human carcinogen;
- study large enough to detect a 50% excess over controls.

If the non-positive study is to be used to fix upper limits of risk, it must meet the first three criteria, and must include exposure data based on actual measurement or "unequivocal evidence" of the magnitude of exposure.

4. Animal Studies. A substance shown to be carcinogenic in an animal study will be presumed to be a potential human carcinogen.

(a) Mammalian species. Tests with tumor prone animals will be used despite the difficulty of interpretation of results.

Evidence of "indirect mechanisms" e.g. virus induced cancer in the mouse or augmented caloric intake can be offered if it is "demonstrated" that the effect would not take place except for the virus or augmented caloric intake.

OSHA reviews and rejects the criticism of the use of hepatomas and adenomas in mice. The record shows mouse tumors, specifically liver tumors, are highly correlated with carcinogenicity in other organs or other species.

(b) Positive vs. negative studies: positive studies generally supercede negative studies, however, OSHA will examin on a case-by-case basis when there are positive and negative studies in the same species.

(c) MTD. There were contentions but no convincing evidence that testing at MTD is biologically inappropriate for qualitative evaluation. However, OSHA will consider "substantial scientific" data supporting metabolic overloading, secondary carcinogenesis or similar mechanisms if the evidence meets the following criteria:

- documented evidence that metabolites are produced in the animal at high doses which are not produced at low doses;
- metabolites at high doses are shown to be the ultimate carcinogen and metabolites at low doses have been tested and found to be non-carcinogenic;
- documented evidence that metabolites produced at high doses in animals are not produced in humans exposed to low doses.

For example, if it is argued that a substance produced bladder stones at high doses it must be shown that the cancers are associated individually with the stones; that stones are induced only at high doses; and that neither stones nor tumors are induced at low doses.

(d) Organ specificity. OSHA will not assume organ specificity, thus a non-positive human study cannot be limited to organs in which tumors have been induced in animals.

(e) Statistical significance. OSHA intends to use statistical evaluation of human and animal studies but the result will not be the only means for evaluation.

(f) Benign/malignant. Benign and malignant tumors will be equated unless evidence to be considered meets the following criteria:

- data from well conducted studies in two mammalian species;
- the studies are lifetime;
- the slides have been examined by a second pathologist;

- all tumors must be of type known not to progress to cancer and show no invasion or metastoses.

(g) Increase in spontaneous tumors will be evaluated scientifically, statistically and biologically. OSHA will consider good evidence on random variations in control range.

(h) Routes of administration. Any exposure which results in systemic distribution (cancer at sites other than site of administration) will be considered. Where tumor is induced at injection or implantation site because of the reactivity of the substance, it will be considered as suggestive or concordant data. OSHA will consider evidence of "solid state" carcinogenesis only when the evidence "establishes" that induction is related to physical characteristics and that the substance does not induce cancer in a different configuration or formulation.

(i) Confirmation of positive results. OSHA rejects the two species criterion. To avoid false positive OSHA will, as a guideline, require concordant evidence. OSHA, after scientific evaluation, may regulate on the basis of an "exceptionally well conducted" positive test including one which was terminated early because of an unexpectedly high cancer mortality.

(j) No-effect/safe levels. After a very extensive review of the record (20 Federal Register papers) OSHA concludes that no threshold has been demonstrated for a carcinogen and that there is presently no acceptable way to demonstrate a threshold or no-effect level. This conclusion is based on theoretical considerations and failure of evidence to support arguments for a threshold. Even if there are individual thresholds there is no way to set a population threshold.

(k) Protocols or criteria for animal studies. It is not feasible or desirable to establish criteria. OSHA will rely on scientific evaluation of bioassays in individual cases. OSHA notes that scientific review creates no new legal rights not inherent in §6(b).

(l) Promoters/Initiators. OSHA concludes that it is neither wise nor practical to make a regulatory distinction betw en initiators or promoters.

(m) Metabolic/pharmacokinetic data. The criteria for use of metabolic data are set out above. OSHA is changing its definition of occupational carcinogen to include a substance which is metabolized to a known carcinogen. Metabolic and pharmacokinetic data are not essential to evaluating past tests; those data can be used in planning tests.

## II. Short Term tests

After an extensive review of the record, OSHA concludes that STT results are meaningful and substances with positive results

in "well validated" systems are likely to be carcinogenic. On this basis OSHA will use results in STT as concordant evidence. The five systems described in the regulation (DNA damage/repair; bacteria, yeast neurospora or drosophila; mutagenesis in mammalian somatic cells; mutagenesis mammalian germinal cells; neoplastic transformation of mammalian cells in culture) are sufficiently validated to justify use of results as concordant evidence. To avoid false positives OSHA will require positives in two tests. (OSHA does not discuss NCI validation.) STT will not be used for classification or regulation but OSHA endorses CIIT conclusion that when there are positive results human exposure should be reduced as far as practicable without awaiting an animal bioassay.

## III. Structure Similarity

OSHA will, after scientific evaluation, use structure similarity in regulating a substance in a "well known class of carcinogens" while awaiting animal studies.

Structure will also be used in priority setting.

Structure similarity of inorganic substances will be used in a "judicious and appropriate manner, with careful exercise of scientific judgment." OSHA makes no generic determination which binds individual rule making on this matter.

## IV. Quantitative Risk Estimation

OSHA discusses risk quantification, methodology, extrapolation models at great length. Difficulties and uncertainties are discussed.

Potency, OSHA concludes, is valid only in relation to a specific test system. There is some correlation of relative potency in different test systems but the variation is wide.

There is empirical and theoretical reason for using Armitage/Doll multistage model or the linear one-hit model for making "best estimates of likely risk."

Pending validation, time-to-tumor models will not be used.

Mutagenic potency does not provide a basis for estimating carcinogenic potency but may in the future.

For prudent reasons, the most sensitive species should be used.

Uncertainties of low dose extrapolation are so great as to justify such estimates as a basis for a quantitative risk analysis.

Risk estimation will be used by OSHA:

(1) to establish priorities;

(2) to establish residual risk as a result of regulatory action. When used for this purpose, the "best estimate" from linear extrapolation and reasonable upper level of risk should be stated based on reasonable cautious assumptions as to uncertainties.

OSHA states an intention to include a risk estimate in the preamble to each final rule. Where data are available, a quantitative estimate of residual risk will be made.

## V. Scientific Review Panel

The Secretary acting alone may, or may request the Director of NCI, NIEHS or NIOSH to convene a science panel of government employees to provide recommendations on the identification classification or regulation of carcinogens. The panel report will be part of the record. While there will be time for public comment on the panel report, no provision is made for public input to the panel.

In addition, the Secretary may establish an advisory committee under §7(b).

## VI. Categories I & II

OSHA has accepted Rall's position that there are many factors which limit confidence in positive results. OSHA therefore will not have criteria to separate "conclusive" and "suggestive" evidence. OSHA intends to rely on scientific judgment and to classify on the basis of "full scientific review" which considers the limitations of each study.

## VII. Categories III & IV

These are eliminated. However, if OSHA initiates a proceeding on a Category I or II substance and concludes that it is not found in an U. S. workplace, OSHA will make a public statement.

## VIII. Candidate List and Priorities

To improve regulatory efficiency to assure that the "worse c ses" are considered first OSHA has established the following lists:

(1) Candidate List. Annually OSHA will publish a "candidate" list of substances based on review of available data. Substances on the list may be tentatively classified as Category I or II if the quantity and nature of the evidence permit such a "preliminary" designation. OSHA "emphasizes" that listing is not a "final scientific determination" that any listed substance is a potential occupational carcinogen nor is it intended even as a pre-classification warning.

Survey of data for the candidate list is described as a "brief scientific review."

The first candidate list which will contain 400-500 substances will be published in about 90 days.

OSHA addresses the "blacklisting" issue and concludes the tentative nature of the listing will overcome such objections.

(2) Priority list Category I and Category II. These two lists, each containing 10 substances, will be issued every six months. These lists are notification that OSHA intends to review the scientific and technological data on these substances.

Substances will be selected on the basis of: number exposed and level of exposure; reported levels causing tumors; the extent to which regulatory action can reduce the cancer risk; structure similarity to a carcinogen; whether substitutes exist; social and economic effects of regulation would be small; and regulation by other agencies.

Risk estimation will be used in setting priorities.

## IX. Suitable Substitutes

OSHA retains the no exposure level if a suitable substitute exists. Criteria of suitability include:

- evidence on the safety of the substance;
- technical feasibility;
- economic cost (only "moderately more" for a high or low volume chemical but "substantially more expensive" for a low volume chemical that is a small part of the cost);
- can producers of substance produce substitute;
- capital needed to switch.

OSHA discusses several examples of substitutes.

OSHA met criticism of no exposure by providing that:

- it would phase the requirement in leaving time for TSCA clearance and to install controls;
- it will be given a numerical value probably on the basis of analytical technology;
- the Secretary reserved discretion not to require no exposure.

## X. Emergency Temporary Standard

OSHA reaffirms its determination that exposure to a Category I substance is a "grave danger" within the meaning of §6(c)(1)(A).

However, the need for an ETS will be determined on a case-by-case basis. Thus an ETS may not be necessary if exposure has been reduced voluntarily as much as possible on a short term basis.

## XI. Regulation of a Category II Carcinogen

OSHA has departed from its proposal to regulate for toxic effects other than cancer. It will consider the weight of th evidence to determine whether it may be necessary to set the level on the basis of carcinogenic effects.

OSHA hopes Category II classification will stimulate data gathering and OSHA plans to use all possibilities under TOSCA to have the substance tested to determine whether it is I or not subject to this policy.

## XII. Economic and Environmental Considerations

There is a long discussion of the record and a discussion of economic considerations on particular issues. OSHA has responded in the following ways:

(1) it has provided for priorities;

(2) it has dropped the automatic ETS;

(3) it has introduced flexibility into the standards to promote more cost effective regulations. The standards are now guidelines. They are sufficiently flexible to permit performance orientation of regulatory provisions for individual substances;

(4) OSHA has provided for action levels and mixture exclusions on a case-by-case basis;

(5) the suitable substitutes provision has been changed to include technical and economic feasibility.

OSHA has not changed the primacy of engineering control and has not modified its stand on personal protective equipment. However, if there is a break through in technology, the policy is sufficiently flexible to accommodate it.

OSHA has not departed from lowest feasible control level.

OSHA has found serious methodological flaws in the Snell study. The total cost cannot be determined at the present time.

Qualitative and quantitative risk estimation will be made in setting priorities. Health assessments of a qualitative and quantitative nature are relevant in particular rule making, e.g. action level, monitoring frequency and assessing health effects of the rule.

OSHA adheres to its former position on assessing economic and technical feasibility. OSHA will not consider costs of alternative levels of control, because

- unreliability of risk estimates;
- ignores "equity" considerations;
- statute requires lowest feasible.

OSHA discusses at length the role of cost effectiveness or risk/benefit calculations in setting exposure levels and rejects those techniques.

OSHA details its criticism of Snell and concludes that it is not possible to assess costs of the regulation except in individual substance proceedings.

## XII. Environmental Impact Statement

OSHA published a final Environmental Impact Statement. Based on EPA's analysis of several OSHA standards, EPA concluded they reduced emissions. OSHA concludes that its regulation will have a good environmental impact. Environmental impacts will be examined case-by-case and will be considered in establishing priorities.

## XIII. Issues in Rule Making

The regulation limits the issues in a rule making but amended to include:

- whether a substance is properly classified including whether the studies were reliable;
- whether data warrants an exception or amendment;
- suitable substitutes.

## XIV. Standards

Labels. OSHA has retained the labelling requirements and contents, etc. will be decided case-by-case.

Medical records are available to OSHA or the employee or his representative. OSHA intends to apply general access regulations when they are final. Until then the decision will be made on a case-by-case basis.

Medical surveillance flexible; to be determined in each case. High risk procedures (e.g. x-ray) will be limited to high risk employees. OSHA has retained the requirement of no cost surveillance and has made no requirement which prevents use of company selected doctor.

## XV. Medical Removal

No provision in the regulation.

## XVI. Rule Making

OSHA indicates that if there is no requirement of an ETS, OSHA will normally begin the process with an ANPR setting forth the data it relies on for classification of a substance, after allowing a period of comment before proposing a standard.

## Laboratories/Construction

The regulation applies to all work places. However, OSHA will evaluate the guidelines on labs now being prepared in NIH.

Issues concerning the construction industry will be referred to the Advisory Committee created under the Contract Work Hours and Safety Standards Act.

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