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Organization Resources
Counselors, Inc.

Memorandum

February 27, 1978



To: ORC Clients

From: B. K. Kwon

This report is the result of the efforts of ORC and the task force on OSHA's carcinogen proposal.

The task force put a good deal of effort into developing the material, and it is felt that this approach contributes an adequate response to the proposal.

RESPONSE TO THE OSHA PROPOSAL

**"Identification, Classification and
Regulation of Toxic Substances
Posing a Potential Occupational
Carcinogenic Risk"**

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INTRODUCTION

This document has been prepared by Organization Resources Counselors, Inc. (ORC) as a constructive response to the proposal titled, "Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk," which was published by the Occupational Safety and Health Administration (OSHA).

ORC agrees with OSHA that there is a need to improve the standard-setting process. There is also a need to control serious health hazards, such as cancer. However, ORC does not agree with OSHA on two major policy issues related to the control of such hazards: (1) OSHA's contention that there is no safe level for carcinogens and that, therefore, the exposure must be limited to the lowest technically feasible level; and (2) OSHA's philosophy that if a substance is found to be carcinogenic in test animals, it automatically follows that it is a human carcinogen. We believe that these policies are arbitrary and inflexible, especially in the science of carcinogenesis, in which knowledge is incomplete but growing rapidly.

OSHA recognizes that we are at the frontier of scientific knowledge when dealing with carcinogens. Under these circumstances, simplistic policies on complex issues can only create confrontations. If we divert energies to unproductive debate and

litigation, we may seriously limit the availability of private and public talent that could be better used for developing practical measures to protect the health of the American working population.

ORC recognizes the seriousness of the problem and has developed alternate policies and proposals to help bring about effective results in occupational cancer control while avoiding wasteful confrontations.

A basic element of our alternate proposal is the separation of scientific and regulatory activities. Scientific evaluation of available data and direction for future research must be carried out by the best scientists in the world; society demands no less.

ORC recognizes that there are valid factors that the Secretary should utilize in determining the permissible exposure limits. These factors are: (1) utilization of dose-response data and practical threshold concepts; (2) economic and technical feasibility of compliance with such standards; (3) risk benefit analysis for such standards; and (4) enforceability of such standards. These factors should be jointly evaluated and placed into the record by the public and the regulator. Thus, any regulatory decision would be supported by information generated by both the regulator and regulated.

ORC recommends that the Secretary of Labor should have the sole responsibility for the regulatory process, while an independent scientific commission classifies substances into the various categories of carcinogens, based on available scientific data and professional judgment, and insulated from political pressures.

The effort in OSHA's proposal to prohibit or limit subsequent consideration of scientific and policy aspects of toxic substances standards promulgation raises fundamental questions concerning the Secretary's authority to alter the system of standards promulgation authorized in the Act.

Following is a discussion supporting the propriety and necessity of considering each of these issues as an integral element in effective regulatory policies for carcinogens.

Section I

THE LEGAL AUTHORITY AND THE RESPONSIBILITIES OF THE SECRETARY OF LABOR

LEGAL CONSIDERATIONS

The authority asserted by the Secretary of Labor, under the Occupational Safety and Health Act, to promulgate regulations such as those contained in the OSHA proposal should be reviewed. This review is necessary because this is a unique type of regulation providing for generic standards, and because there are realistic alternatives to the OSHA proposal that can better use public and private resources to protect the worker. Additionally, ORC believes that there are legal deficiencies in the OSHA proposal as it relates to: (1) the legal authority of the Secretary; and (2) the attempt to limit the opportunity of interested parties to build a complete record as provided for in the Act.

The OSHA proposal intends to amend Title 29 of the code of Federal Regulations by adding section 1990. OSHA asserts its authority to promulgate this amendment under sections 4(b), 6(b), 8(c), and 8(g) of the Act (42 F.R. 54183). An examination of these and other provisions of the Act leads us to conclude that the authority of the Secretary to promulgate this proposed rule does not exist.

ORC believes that those elements of OSHA's proposal that prohibit review of certain issues in future rulemaking activities are also outside the authority of the Secretary of Labor.

DEFINITION OF A STANDARD

Section 3(8) of the Act defines an "occupational safety and health standard" as a "standard which requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide safe and healthful employment or places of employment." The OSHA proposal does not fit this definition because it does not impose requirements on the employer to provide a safe and healthful workplace. It does, however, restrict the areas in which interested parties may present information concerning proposed standards.

The ORC alternate proposal recognizes the limitations of this type of rulemaking activity and the need for legislative or executive action that will separate the scientific and technical considerations from the policy considerations that may be within the authority of OSHA to promulgate. It should be noted that the ORC alternate proposal includes a model standard and an examination of the policy decisions that are needed to fulfill the mission of the Act. It should also be noted that a distinction in the ORC proposal is made between the reasonableness requirements of a policy decision and the substantial evidence rule which provides for the acceptance of scientific and technical information. In addition, the ORC proposal provides OSHA with the information necessary to develop a realistic rulemaking priority system.

LEGAL AUTHORITY OF THE SECRETARY OF LABOR

Section 4(b) of the Act essentially limits the authority of the Secretary to act in certain areas. Section 4(b)(1) restricts that authority in areas where other federal agencies have taken action. Additionally, section 4(b)(4) restricts the authority of the Secretary to promulgate standards that will "supersede or in any manner affect any workmen's compensation law or enlarge or diminish or affect in any other manner the common law or statutory rights, duties or liabilities of employers and employees under any law with respect to injuries, diseases or death of employees arising out of, or in the course of, employment." ORC does not believe that this section of the Act which limits the Secretary's authority can be the basis for greatly expanding it.

Under section 6(b) the Secretary can promulgate occupational safety and health standards. However, as mentioned earlier, the OSHA proposal does not present a standard as defined by section 3(8) and, therefore, a standard cannot be justified by reference to section 6(b).

Section 8(c) of the Act also is not relevant to the justification of authority for the OSHA proposal, as this section is limited to the promulgation of regulations regarding recordkeeping and reporting activities.

Section 8(g) of the Act must be examined closely for the authority claimed by the Secretary in the OSHA proposal. Section 8(g)(2) is broad in scope, stating that the Secretary shall "prescribe such rules and regulations as he may deem necessary to carry out . . . responsibilities under this Act, including rules and regulations dealing with the inspection of an employer's establishment." This section is clearly designed to deal with the subject matter of section 8 -- inspections, investigations, and recordkeeping. Rather than constituting a general grant of rulemaking authority, this section instructs the Secretary to exercise his authority, relating only to inspections, investigations, and recordkeeping, by issuing regulations informing the public of the requirements of section 8, and assuring that the Secretary's representatives act in accordance with the principles of due process. Additionally, this section cannot be read without reference to other sections of the Act, such as section 6(b)(5), that pertain to rulemaking.

Section 6(b)(5) requires that the Secretary take into account "the latest available scientific data in the field, the feasibility of the standards and the experience gained under this and other health and safety laws." The same section also requires that the Secretary "shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity . . ." It

is clear that the OSHA proposal, in its efforts to preclude the examination of certain issues in future rulemaking proceedings, will not permit the "best available evidence" and the "latest available scientific data" to be placed in the record or considered in the preparation of a standard concerning a particular toxic substance. Consequently, ORC believes that the OSHA proposal is without legal basis. In addition, OSHA's apparent argument that the requirements of 6(b)(5) may be disregarded at the time a particular toxic substance is placed in the rulemaking process, by asserting that those requirements can be met at the time this proposal is under consideration, is a misinterpretation of the section.

Additionally, because a major thrust of the Act is the provision for due process in the promulgation of occupational safety and health standards, the Act requires publication of proposals in the Federal Register, and provides opportunities for public comment. ORC believes that by expanding the clearly limited intent of section 8(g)(2), the Secretary has attempted to circumvent these due process provisions concerning toxic substances and has disregarded the specific due process requirements which Congress built into the Act in section 6. Specifically, the section 6(c)(1) requirement for temporary emergency standards, an exception to the normal due process for standards promulgation, requires that the Secretary determine "(A) that

employees are exposed to grave danger from exposure to substances or agents determined to be toxic or physically harmful or from new hazards, and (B) that such emergency standard is necessary to protect employees from such danger." Because of the automatic provision in the OSHA proposal concerning temporary emergency standards flowing from the classification method of a toxic substance, neither of the determinations required by section 6(c)(1) would be made and the resulting standard would have been promulgated in a manner contrary to both the intent and the clear language of that section.

ORC believes that the specifications contained in section 8(g)(2) cannot counter the inference in sections 6(b) and 3(8) that each substance should be dealt with individually and that a standard should be designed for each hazardous condition. The ORC alternate proposal, which also includes a model standard, takes this inference into account and recognizes that exceptions to any aspect of the model standard may be raised during the hearings on each toxic substance.

The only authority granted the Secretary by the Act to promulgate safety and health standards, whether "normal" or "emergency temporary," is contained in section 6. While this section grants the Secretary such authority, it also carefully circumscribes it. Departure from the clear limitations set forth in section 6 can only be brought about through Congressional action. Rulemaking cannot expand the authority that Congress has carefully circumscribed.

An additional consideration concerns whether or not an economic impact statement could be structured to cover this type of standard. It is the ORC view that an economic impact statement must be formulated for the OSHA proposal because of the substantial and widespread effect it will have on almost all industries and that the failure to provide this statement is by itself a valid reason for rejection of the OSHA proposal. Additionally, employers without the benefit of such a statement and without knowledge of the substances that may actually be included in future rulemaking procedures will be denied the opportunity to evaluate the environmental, inflationary, and feasibility aspects of the proposed regulation.

In its proposal, OSHA has foreclosed the reconsideration of certain issues in future rulemaking actions. Sections 6(b)(2) and 6(b)(3) of the Act, however, require OSHA to publish proposed rules and to "afford interested persons a period . . . to submit written data or comments" as well as to allow any interested person to request a hearing on the proposal. This foreclosure appears contrary to the requirements of sections 6(b)(2) and 6(b)(3) and would eliminate meaningful participation by the public in hearings. OSHA has justified this apparent abridgment of rights by citing a number of cases, including United States v. Storer Broadcasting Co. (351 U.S. 192 1955). In this case, the FCC refused to allow the issue of whether or

not a licensee could hold more than five VHF television licenses to be brought up for reconsideration during a hearing on the purchase of a station. However, there is a clear distinction between the complexity of issues facing the regulation of toxic substances and those of broadcasting stations. With broadcasting stations, the issues faced do not differ substantially from one purchase of a station to another. With toxic substances, however, the issues vary widely from one instance to another because of the diversity of the effects each substance has on humans, the extent of exposure and processes involved, and the countermeasures that must be taken to protect employees. Therefore, an attempt to apply the Storer Broadcasting rule to support the OSHA proposal is not valid.

Finally, it is beyond OSHA's authority to "ban" category I substances and insist on the use of a "suitable substitute" if one exists. The lack of a feasibility provision in the OSHA proposal concerning the use of a substitute ignores the provisions of section 6(b)(5) -- therefore, the "ban" is without legal basis. Also, section 13 of the Act specifically provides for a procedure for the removal of employees from imminent hazardous conditions or the elimination of imminent hazardous conditions. The OSHA proposal, in effect, ignores this provision of the Act and substitutes its own form of action for which no authority exists in the Act.

In attempting to justify its proposal, OSHA has not proven its case. It is ORC's view that the proposal does not contain the elements of a standard that can be properly promulgated under the Act. The following ORC proposal, however, recognizes the limitations of the Secretary's authority and has been drafted accordingly. This alternate proposal is not intended to be a standard and in fact could be adopted by OSHA without the use of section 6(b) rulemaking procedures. ORC, by presenting this alternative, intends to provide OSHA with a workable program that with appropriate legislation can most effectively provide for the protection of the worker from the various toxic substances.

PRACTICAL CONSIDERATIONS

The promulgation of standards and the priorities involved should not be based on reactions to outside pressures or some published event. On the contrary, the Secretary should evaluate the following critical issues prior to proposing and promulgating any standards or issuing any emergency temporary standards.

1. The Secretary should determine that a specific substance is presently causing material impairments, such as cancer, in the workplace and that ineffective efforts are being made by the employer to control such hazards. The question is not solely whether a substance is a carcinogen in animals or humans,

but whether an environmental condition exists in the workplace that could cause cancer, and whether the employer has instituted controls to protect the worker's health.

Most reported epidemiological studies evaluate the results of exposures to substances that occurred 30 to 40 years ago. These studies do not take into account the fact that production processes have changed significantly in the past 40 years, especially since the end of World War II. Therefore, it is arbitrary for the Secretary to assume that the workplace environment has remained unchanged without careful determination of current hazards. The decision to initiate a rulemaking must be based on prevailing facts rather than on assumptions.

2. The sole purpose of a health standard is to assure the protection of workers' health to the extent feasible. It has been an unbending policy of the Occupational Safety and Health Administration that "feasibility" in this case refers only to the technology involved. OSHA also goes further in that the technical "feasibility" is construed to mean utilization of technology which has not been developed at the present, that is, that the standard can be "technology-forcing." Such a policy can only make sense if the Secretary can assure that the technology to control hazards is easily available in the marketplace or can be developed. In the real world, however,

no technology, even if available, can assure the control of all hazards. Also, the successful application of a known technology in one plant does not necessarily assure the same degree of success in another -- many factors influence the application of technology, and evidence about difficulties in controlling hazards can be found in the files of every OSHA Area Office.

Since known technology does not provide practical assurance of success, it is difficult to envision the effectiveness of unknown technology. Such a policy may give workers a false sense of security if they think that utilization of technology will protect them. The existence of a standard is not what protects employees: it is implementation of a safety and health program, of which a standard, if appropriate to the work place, may be a part.

To institute a known technology to control hazards, an employer may have to invest significant amounts of capital and frequently sustain an interruption or decrease in production. This economic and production burden must be considered by the Secretary in his decision-making process. The Secretary must also recognize that the costs involved in implementing even known technology often result in no accountable return in terms of either the safety and health of employees or production. To invest in unknown technology is an arbitrary waste of the nation's resources and is likely to provide little increase in health protection for workers.

Consequently, if employee safety and health is to be promoted, the Secretary must determine the technical and economic feasibility prior to the proposal and promulgation of standards and evaluate alternative methods that would reduce the economic impact of compliance. The economic impact may be even more severe for small business establishments, which represent approximately 80 percent of all establishments in our country.

3. The companies included in the ORC Occupational Safety and Health Group recognize that employee safety and health programs are a major management responsibility. They plan their operations and utilize management talent to provide the maximum practicable protection of workers' health.

A standard that cannot be enforced by the Secretary or put into effect by industry should not be promulgated, for it would provide workers with a false sense of security by leading them to believe that their health is protected by the standard. It appears that the government may be liable if it promulgates a standard and subsequently fails to enforce it.

Therefore, the Secretary must determine, prior to the proposal of a standard, that it can be enforced and that employers, especially in small businesses, can comply with it.

The Secretary should make these determinations, as recognized in the proposed Executive Order on Regulatory Reform, prior to proposing a standard. The results of such determinations, which will help identify the need for proposing such a standard, should be published in the Federal Register and should be addressed during the hearing to assess the appropriateness of the Secretary's action.

Section II

A PROPOSED CARCINOGEN CLASSIFICATION COMMISSION

At the heart of ORC's alternate proposal is an independent commission of carefully selected prominent scientists whose sole function shall be the scientific classification of toxic materials with respect to their carcinogenic potential.

The correct and uniform classification of carcinogens is essential. It has been common practice for each federal or state regulatory agency to classify a substance as a carcinogen based on its own criteria, which often vary significantly. Recently, however, such federal regulatory agencies as the Food and Drug Administration, the Environmental Protection Agency, the Consumer Product Safety Commission, and the Occupational Safety and Health Administration, have moved toward consolidating these criteria. Although all of these agencies employ scientists, they are primarily used to support regulatory activities.

The classification of chemical substances as carcinogens should be performed by scientists whose primary expertise lies in the area of oncology and whose scientific judgment is removed from political or regulatory influences. To accomplish such an important task, it is recommended that Congress create a Carcinogen Classification Commission to provide all concerned regulatory agencies, including OSHA, with the means to determine

scientifically the classification of carcinogens. Subsequent to such classification and a possible judicial review, it should be the responsibility of such regulatory agencies as OSHA, to promulgate appropriate regulations to control carcinogens, taking into account the need for a standard and the adequacy of current protective measures.

The Commission should be composed of 15 prominent scientists with expertise in oncology and experience in cancer control. The Commission members should be subdivided into five groups: toxicologists, epidemiologists, pathologists (human and veterinary), industrial hygienists, and physicians. The toxicologists should evaluate the validity of all animal test data and determine the biological effects, including the oncogenicity of substances in the animals in question. The results of human epidemiological studies should be validated by the epidemiologists and industrial hygienists, the latter determining the relationship between exposure and extent of the resulting biological effects.

For both human and animal studies, the pathologists should examine and validate any tissue changes due to the biological action of the substance whose toxicity is in question. Whenever there is disagreement (for example, whether or not a lesion is truly cancerous), the Commission pathologists should obtain and examine the pertinent tissue preparations to arrive at a final decision. The physicians should determine if a

correct clinical diagnosis of cancer has been made in human case studies which are a part of any epidemiological work, for incorrect diagnoses may invalidate such studies. For instance, Infante, formerly of NIOSH, erroneously included a person with chronic leukemia in his cohort of rubber workers allegedly exposed to benzene. Since many epidemiologists are not physicians, they may be incapable of correctly associating clinical diagnoses with an exposure to a particular carcinogen. There are some physicians in the academic community without clinical experience in the diagnosis and management of cancer who profess to be experts in this field. Some have in the past made occasional but widely circulated, unfounded statements and opinions in connection with cancer cases in the name of worker or community health. Unfortunately, their comments have been accepted by regulatory agencies as authoritative and have profoundly influenced the agencies' policy decisions. The ultimate validity of the causal relationship between cancer and exposure to a substance can be best determined by a joint effort of these varied disciplines.

A precedent for this type of commission has been set by the National Council on Radiation Protection and Measurement, established by the Congress for the Nuclear Regulatory Commission (formerly the Atomic Energy Commission) to assess radiation hazards scientifically. This group of prominent scientists has performed eminently well; the proof of such performance can

be found in all activities associated with radiation exposure and control in both government and private sectors.

It is also recommended that the Commission provide opportunities for the public to present appropriate scientific data for evaluation and discussion. Any relevant scientific data, published or unpublished, should be evaluated by the Commission and acceptance of data should be based on the merits of the study. It is also important to evaluate objectively any negative data. It has been common practice for all federal regulatory agencies to ignore any negative data presented by the public, and especially by industry. The Commission should be able to arrive at independent conclusions concerning the importance of negative data, as well as poorly prepared positive data. The acceptance of poorly executed studies giving positive data has in the past led to regulatory decisions which created embarrassing situations. Examples include the FDA's decision on cyclamates and the EPA's decision against DDT.

To preserve the scientific integrity of the Commission, the members of the Commission should be subjected to confirmation by the Senate upon nomination by the National Academy of Sciences (NAS). The NAS should select the candidates from scientists recommended by professional societies, such as the American Occupational Medical Association, the Society of Toxicology, the American Association of Cancer Institutes, the

American Academy of Veterinary Pathologists, the Society of Epidemiology, the American Society of Clinical Pathologists, and the American Industrial Hygiene Association. Commission members could serve staggered three-year terms as full-time members. While in office, members should be prohibited from engaging in any contractual relationship with regulatory or public agencies, private industries, or labor unions. Congress would appropriate funds as a part of the budget of the NAS to provide for staff assistance. The Commission would be located within the Academy and serve all federal regulatory agencies for the classification of carcinogens.

Since Congressional passage of a bill to establish such a commission could take a long time, an interim classification unit could be appointed through an Executive Order issued pursuant to the Reorganization Act of 1977, 5 U.S.C. §901 et. seq. The interim unit could be established within the National Academy of Sciences and have the same numbers and qualifications as described above. Their duties and procedures for the discharge of such duties should be identical to the ones proposed for the permanent commission. The main purpose of establishing such an interim unit would be to provide the regulatory agencies with necessary classification decisions on carcinogens while the permanent commission is being established.

Section III

THE SIGNIFICANCE OF ANIMAL AND OTHER TEST RESULTS FOR HUMANS

GENERAL BACKGROUND

Aside from the legal issues associated with the proposed OSHA classification criteria for carcinogens, it is difficult to imagine that the Secretary could find scientific reason to assume that a substance found to be carcinogenic in animals should automatically be considered carcinogenic in humans. Although it is recognized that some such substances may in fact be human carcinogens, unless the preliminary animal data are confirmed by valid human epidemiological data, no substance can be categorized as a human carcinogen. It is essential that an arbitrary conclusion, such as that which led to OSHA's proposed policy, should be corrected to reflect facts rather than assumptions. It is not, however, that such animal carcinogens should not be controlled. It is urged that the classification of carcinogens be based on the best available scientific data; that is, a substance should be classified as an animal carcinogen if tests so indicate and no positive human data is available. ORC's alternate proposal shows a correct way to classify carcinogens.

An arbitrary policy such as the Secretary proposed is likely to lead to confrontations which might create situations

more detrimental than helpful, and might well delay the promulgation of carcinogen standards and their effective enforcement in the workplace.

DDT was banned by the EPA based on animal test data implicating it as a carcinogen in mice. However, these results could not be duplicated in other species of test animals, and there has been no evidence since then that the pesticide is a human carcinogen, despite the widespread and indiscriminate usage of this substance since 1940, a latency period of 37 years. Since the banning of DDT by the EPA, it has been replaced by many highly toxic pesticides for necessary pest control. In this instance, it is clear that, as a direct result of an arbitrary decision by a regulatory agency, more pesticides have been resorted to, all at substantial and considerable social costs.

It is, of course, prudent for an employer to control suspect human and confirmed animal carcinogens in the workplace. However, the potential consequences of treating an animal carcinogen as a confirmed human carcinogen when there is no good human scientific data to substantiate the claim can be costly in terms of jobs and wasted effort, and may not provide any additional protection for employees.

Anatomical and cellular dissimilarities exist between humans and the test animals, between species of animals, and

between strains within the same species. Therefore, it is recommended that such policy as that proposed by OSHA be removed from the regulatory scheme and be replaced by one which takes account of all scientific factors, including variability between mammalian species and humans. Since biochemical mechanisms and the pharmacodynamic system in animals such as rats or mice are not always identical with those systems in humans, it is not possible to justify any policy that arbitrarily equates humans and animals in respect to their susceptibility to the carcinogenic action of a given substance.

Chemicals found to be carcinogenic in one species may not be carcinogenic in other species of animals, making it essential that a chemical be tested and proven to be carcinogenic in at least two different mammalian species.

The proposal made by the Secretary fails to recognize the existence of varying degrees of carcinogenic potency in substances that might be classified as carcinogens. The results of governmental research on animal carcinogenicity are not accurately represented by OSHA's proposed policy that once a substance is found to be carcinogenic in animals at any level, regardless of dosage, it should be treated as a proven human carcinogen. There is no logical explanation for a policy decision that where dosages administered to test animals to achieve positive results differ by a factor of 100, both are to

be treated as having the same potency. If one substance is 100 times more potent than another, it should be treated differently for regulatory purposes.

Exclusion of such well-known and accepted scientific facts in developing agency policies constitutes an arbitrary action. It is urged that OSHA adopt the criteria regarding the potency of carcinogens set forth by the American Conference of Governmental Industrial Hygienists.

Some scientists consider results of some short-term tests, including Ames Salmonella mutagenesis, as valid scientific findings. It is, however, generally accepted that these short-term tests are considered screening tests useful as a guide to priorities in research, rather than confirmatory experiments.

The National Cancer Advisory Board has advised the National Cancer Institute that positive results obtained from short-term tests suggest extensive testing of the substances in long-term animal bioassays. Therefore, it is recommended that such short-term tests should not be considered at the present time in determining carcinogenicity of substances to be regulated.

Section IV

CRITERIA FOR CLASSIFICATION OF CARCINOGENS

While it is appropriate that outstanding scientists, such as those on the ORC proposed Carcinogen Classification Commission, undertake the classification of carcinogens, it is desirable that the Commission be guided by practical criteria which it would utilize in carrying forward its responsibilities, proposed minimum criteria are presented below:

A. Confirmed Human Carcinogen

A substance should be classified as a Confirmed Human Carcinogen if the substance, as the result of exposure, results in a statistically significant increased incidence of malignant neoplasms, or a combination of benign and malignant neoplasms in humans.

In classifying a substance as a Confirmed Human Carcinogen, the following factors should be considered as a minimum, in addition to the scientific validity of the epidemiological information: host factors, such as congenital and genetic diseases; immune deficiency diseases; acquired diseases and multiple primary neoplasms; and other environmental factors, such as tobacco, alcohol, radiation, drugs, diet, air, and water pollution; and viruses and other microbes.

A substance should be subclassified within the category of Confirmed Human Carcinogen based on its carcinogenic potency as follows:

1. Strong Confirmed Human Carcinogen, if the epidemiological data indicates the incidence of malignant neoplasms or a combination of benign and malignant neoplasms in humans is tenfold in excess of a valid control population; or

2. Mild Confirmed Human Carcinogen, if the epidemiological data indicate the incidence of neoplasms described above is less than tenfold, but in excess of two-and-a-half fold of a valid control population; or

3. Weak Confirmed Human Carcinogen, if the epidemiological data indicate the incidence of neoplasms described above is less than two-and-a-half fold but in excess of a valid control population when other environmental factors, such as smoking, were accounted for.

In subclassifying a substance, the following factors should be considered as a minimum: extent and intensity of exposure as it related to the increased incidence of neoplasms; statistical validity of the exposed population size; scientific validity of the control population; proper adjustment of age in both exposed and control population; and other environmental and host factors.

B. Suspect Human Carcinogen

A substance should be classified as a Suspect Human Carcinogen if the substance, as the result of exposure, results in a questionable increased incidence of malignant neoplasms in humans or revelation of a clinical case report, and if animal experimentation in two or more experimental mammalian species results in a statistically significant increased incidence of malignant neoplasms or a combination of benign and malignant neoplasms.

In classifying a substance into a Suspect Human Carcinogen, the following factors should be considered as a minimum, in addition to the scientific validity of the information:

- Factors listed under Confirmed Human Carcinogen;
- Specific exposure relationships described in clinical case reports;
- Randomization of test animals;
- Animal diet and drinking water;
- Extrapolated correlation between animal dose and human exposure;
- Impurities in the test substance;
- Stability of the test substance;
- Existence of a dose-dependent response;
- Bioassays employing inbred strains of animals which develop high spontaneous incidence of particular neoplasms in the treated and untreated animals;

- Bioassays in which, in addition to the test agent, animals are treated with a known carcinogen, some other agent which itself may be carcinogenic, or a cocarcinogen;
- Bioassays in which the test animals are subjected to grossly unphysiologic and inappropriate conditions, in addition to the administration of the test substance;
- Bioassays in which the test substance is administered by unusual routes of entry; and
- Metabolic similarity between humans and test animals.

A substance should be subclassified within Suspect Human Carcinogen based on its carcinogenic potency in test animals as follows:

1. Strong Suspect Human Carcinogen if test data indicate one of the three following results in two animal species:

- a. Respiratory. Neoplasm(s) from (1) dosages below 1 mg/m³ (or equivalent ppm) via the respiratory tract in 6- to 7-hour daily repeated inhalation exposures throughout lifetime; or (2) from a single intratracheally administered dose not exceeding 1 mg of particulate, or liquid, per 100 ml or less of animal minute respiratory volume;
- b. Dermal. Neoplasm(s) within 20 weeks by skin-painting, twice weekly at 2 mg/kg body weight or less per application for a total dose equal to or less than 1.5 mg, in a biologically inert vehicle;
- c. Gastrointestinal. Neoplasm(s) by daily intake via the gastrointestinal tract, within six months, with a six-month holding period, at a dosage below 1 mg/kg body weight per day; total dose, rat, $\leq$ 50 mg; mouse, $\leq$ 3.5 mg.

2. Mild Suspect Human Carcinogen if the test data indicate one of the three following results in two animal species;

- a. Respiratory. Neoplasm(s) from (1) dosages between 1 mg/m^3 and 10 mg/m^3 (or equivalent ppm) via the respiratory tract in 6- to 7-hour daily repeated inhalation exposures throughout lifetime; or (2) from a single intratracheally administered dose between 1 mg and 10 mg of particulate, or liquid, per 100 ml or less of animal minute respiratory volume;
- b. Dermal. Neoplasm(s) within 20 to 75 weeks by skin-painting, twice weekly at dosages between 2 mg/kg and 10 mg/kg body weight per application for a total dose equal to or less than 1.5 g, in a biologically inert vehicle; and
- c. Gastrointestinal. Neoplasm(s) by daily intake via the gastrointestinal tract, between six months and the lifetime of the animal, at a dosage between 1 mg/kg and 50 mg/kg body weight per day; total dose, rat, $\leq 2.5 \text{ g}$; mouse, $\leq 175 \text{ mg}$.

3. Weak Suspect Human Carcinogen if the test data indicate one of the three following results in two animal species;

- a. Respiratory. Neoplasm(s) from (1) dosages greater than 10 mg/m^3 (or equivalent ppm) via the respiratory tract in 6- to 7-hour daily repeated inhalation exposures, for 12 months' exposure and 12 months' observation period; or (2) from intratracheally administered dosages totaling more than 10 mg of particulate or liquid per 100 ml or more of animal minute respiratory volume;
- b. Dermal. Neoplasm(s) by skin-painting of mice in twice weekly dosages of $> 10 \text{ mg/kg}$ body weight in a biologically inert vehicle for at least 75 weeks, i.e., $\geq 1.5 \text{ g}$ total dose; and

- c. Gastrointestinal. Neoplasm(s) from daily oral dosages of 50 mg/kg/day or greater during the lifetime of the animal.

C. Confirmed Animal Carcinogen

A substance should be classified as a Confirmed Animal Carcinogen, if the substance, as the result of animal experimentation in two or more experimental mammalian species, results in statistically significant increased incidence of malignant neoplasms or a combination of benign and malignant neoplasms.

In classifying a substance into a Confirmed Animal Carcinogen, the factors described for Suspect Human Carcinogen concerning animal experimentation should be considered at minimum.

The subclassification of Confirmed Animal Carcinogen should be in accordance with the criteria set forth for Suspect Human Carcinogens.

D. Suspect Animal Carcinogen

A substance should be classified as Suspect Animal Carcinogen if the substance, as the result of animal experimentation in one or more experimental mammalian species, results in a questionable increased incidence of malignant neoplasms or a combination of benign and malignant neoplasms.

Section V

CRITERIA NECESSARY TO DETERMINE THE
PERMISSIBLE EXPOSURE LIMITS

THRESHOLDS

There are both practical and scientific bases for the conclusion, avoided by OSHA, that a true biological threshold does exist, is a practical fact in the daily life of every individual, and cannot be ignored in any attempt to control exposure to potentially toxic or carcinogenic chemicals. There are five basic reasons for the conviction that biological thresholds do exist:

1. Nature abounds in thresholds of many kinds;
2. There is much exposure to carcinogens and comparatively little cancer;
3. DNA excision repair mechanisms exist;
4. Post-replication DNA repair mechanisms exist;
and
5. Immunological surveillance mechanisms to protect against neoplastic cells exist.

In any discussion of threshold concepts, it is necessary to consider many thresholds, not just one. There are different kinds of thresholds built into biological systems, and they may function singly or in multiples. Cancer is a disease that affects the whole organism, and in its progress from induction through expression, many thresholds in many systems must be crossed before the defenses of the host are overcome.

The Meaning of Threshold

Perhaps one of the most difficult things to define is exactly what is meant by "threshold." In this presentation, threshold is the point below which no biological response to a toxicant can be measured. This point is expressed in terms of the concentration of the toxicant. Toxicity is usually expressed as a dose-response phenomenon, with a generally quantitative relationship existing between the concentration of the substance in question and the measurable response of the system being studied.

Most often, the observable response to a toxic substance is the result of a number of different thresholds having been crossed. When a threshold has been crossed, the physiological system involved changes in the way it responds to normal and abnormal challenges to the maintenance of system homeostasis.^{1, 2}

There are those who believe that the concept of a threshold is imposed by the existence of stochastic limits on the concentrations of molecules below which biologically significant reactions cannot be sustained.³ At present we lack the knowledge to construct a stochastic model which we can be sure represents reality within confidence limits of 99 percent. Granted the foregoing, however, the concept of a rate limit suggests that it would be imprudent to ignore the manifold possibilities for any given quantity of molecules to react with receptor sites other than

the ones with which we are immediately concerned. Any biological system that has the capacity to repair damage to its DNA, or in which post-replication repair might exist, "believes the concept that biological systems have exceedingly narrow ranges of response to environmental challenge."⁴

The Practical Significance of Thresholds

While there are many in the scientific community who have little doubt of the existence of a biological threshold for the carcinogenic response, there does not exist enough unequivocal evidence to say with complete confidence what a "no-effect" level would be for a specific chemical substance in a population as heterogeneous as the American working population. In spite of this, a very real and practical threshold can be shown to exist. It is not necessary to examine the literature on carcinogenesis too closely to find evidence that the urban population of the twentieth century has been exposed to many varied physiological insults from the many chemicals in the environment, some of which chemicals have been shown to be carcinogenic to one degree or another. However, the percentage of the population who have expressed cancer when they died from any cause is small when essentially 100 percent of the population has been exposed to multiple carcinogenic insults. If one were to accept the proposition that carcinogenesis is a "one-hit," "zero-tolerance,"

"no-threshold" affair, then all who reach the end of the statistically average life span should have identifiable cancer. The fact that this is not so is the most basic and irrefutable evidence for the existence of a practical threshold; that is, if the latent period necessary for the development of a cancer is equal to or greater than the life span of the average human being, then the risk is essentially zero. This does not deny that there are real threats from carcinogenic chemicals, for there are, but some perspective must be used when examining environmental causes of carcinogenesis.

The regulatory agencies, in responding to both real and perceived threats to the health of the American population, should be sure that they are in fact responding to real threats for a statistically significant percent of the population. The federal government must act on the basis of scientific facts instead of reacting to a barrage of mass media publicity, editorial comment, and federal agency one-upmanship. The points to be emphasized are that carcinogens can be dangerous substances, and that the human population should not be exposed to them at any level that has been proven to be dangerous. Preventing human exposure to chemical substances at levels shown to be hazardous is desirable, but spending large amounts of valuable talent and money preventing

exposure to levels of a chemical that are not dangerous is a waste. Also, diverting talent and money from real hazards to attain unnecessary reduction of exposure to substances identified as carcinogens affects the safety and health of employees. To assume that a biological threshold does not exist for potential or proven carcinogens is to ignore a wealth of scientific data to the contrary and, in the process, to cause the expenditure of public and private funds in ways that neither save lives nor prevent disease.

It must be repeated that it makes little difference whether or not an "actual threshold" as opposed to a "practical threshold" exists. What is important is to recognize that there are exposures possible that will not automatically result in cancer. Mantel⁵ has suggested that a risk of cancer in the range of one in 10^8 could be accepted as a "practical threshold." Jones,⁶ working with data on the relationship between dose and the latent period before expression of tumors, has suggested that if the latent period required for the expression of cancer is greater than an animal's lifespan it is, in fact, a "practical threshold."

When evaluating the risk of human cancer, what counts is the actual risk of individuals' developing cancer. If the latent period for the development of cancer extends well past the probable lifespan of the population at risk, then the

hazard is almost nonexistent. This is the kind of "threshold" that really counts in the evaluation of risk.

Two examples of existing differences between the perceived threat and that which in fact existed may be illustrative.

In the first case, workers ingested many small doses of radium while painting wristwatch dials in the 1920s and 1930s. Their exposure to radium received wide publicity over the years of perceived threat of cancer, and has been extensively studied by the scientific community. A recent review⁷ using information developed within the last ten years found that: "Even if the entire amount . . . were received in the first year of exposure (it never is, since radium persists in the bone) and that exposure occurred at the age of 17, the individual could expect to be about 100 years old before a malignant tumor might appear. This kind of data, showing the very long latent periods involved with such exposures, gives support to those who have postulated the existence of a 'practical threshold' for cancer caused by ingested alpha emitters in the human body."⁸

A second case involves nitrosamines in preserved meats that illustrates the need to examine available data before responding to perceived threats. It is thought that nitrosamines may originate from a reaction of sodium nitrite and the amines present in the meats as a result of cooking or digestion. Sodium nitrite is used as a preservative, a flavor enhancer, and an aid in maintaining the color of meat. Nitrosamines have been detected in commercially preserved food products at the level of a few

parts per billion (ppb), and in a few foods at levels around 100 ppb. In a study done in 1972,⁹ it was found that the several different nitrosamines found in cured preserved foods appear to have equivalent actions in the induction of cancer, and may well be additive. Since the range of each of the nitrosamines identified in this study was in the range of a few ppb, it was assumed that the average total nitrosamine content of nitrite-treated meat is about 10 ppb, and most likely does not exceed 100 ppb. Diethylnitrosamine, a well known, potent cancer inducer, when fed continuously to rats at a level of 75 parts per million (ppm), caused identifiable cancers in a significant portion of the rats after a period of time equal to approximately one-half the average life span of the rats. At a level of five ppm fed continuously, it caused a few cancers, but at a level of one part per million, fed under the same conditions, no cancers were observed.^{10, 11}

With the foregoing in mind then, it would appear that the dosage limit for the appearance of detectable cancers with diethylnitrosamine is close to one part per million of the entire average diet. Using these data, Jones and Grendon came to the conclusion that: "If the entire diet consisted of meat and all the meats eaten were nitrite-treated, the human dietary intake of nitrosamines would be from ten to one hundred times less than that of those laboratory animals that developed cancer (10-100 ppb compared with one ppm). There are the additional factors that man eats less food per

per unit of body weight than do rats or mice, and that only the cured and canned meat fraction of the diet is involved. These two factors contribute an additional reduction of at least 100 times in the comparison of man with the laboratory animals. Thus, the estimated magnitude of the risk to man from nitrates and nitrosamines in food is at least 1,000 times less (and probably 10,000 times less) than the minimum detectable level of cancer risk in laboratory mice and rats. In addition, the effect of the lower dose on the time of tumor development should cause the lag to stretch out far beyond the human lifespan to 10-20 times the human lifespan."¹² It should be noted that nitrosamine caused cancer has never been observed in humans.

Environmental Carcinogens and Cocarcinogens

It is difficult to control the many variables that can affect the development of cancer when assessing the incidence of cancer in the human population as opposed to test animals. The presence of many environmental carcinogens and cocarcinogens makes the existence of some kind of threshold phenomenon a necessity to account for the continued survival of the human race. Every individual is exposed from birth to substances that are now being implicated as at least potential carcinogens. When the presence of large numbers of known cocarcinogens is added in, the theoretical possibility of developing

cancer is so astronomically high that it is a wonder that anyone survives to maturity. The accuracy of theories and hypotheses that postulate an easy susceptibility to cancer among the population as a whole is questionable. If the "one-hit," "zero-tolerance" theories are valid, a substantial majority of the population should perish of cancer long before reaching their sixties. Since this has not come to pass and the average age of the population continues to increase, part of the reason must lie in the existence of many and varied biological thresholds, and the fact that, for much of the population, the latent period necessary for the development of identifiable cancer is longer than their life spans. It might be useful to examine a few of the potentially carcinogenic agents that the average individual might be exposed to. Perhaps the most serious and best known is tobacco in general and cigarette smoking in particular. It has been demonstrated in many studies^{13, 14, 15, 16, 17, 18} that smoking adds greatly to the risk of the development of many different kinds of cancers. Cigarette smoking increases the risk of lung cancer in particular, as well as the incidence of cancer in general. Indeed, Flamm¹⁹ indicates that even less than one-tenth of a puff of a cigarette in a lifetime could result in the development of lung cancer. Considering the number of people in the US who smoke, and the possibility of inhaling smoke from other individuals' cigarettes, pipes, and cigars, it

is evident that most of the population has received much more than one-tenth of a puff of tobacco smoke, yet most never develop lung cancer.

Alcohol is another agent that is widely consumed, and evidence identifies it as a cocarcinogen when combined with smoking.^{20, 21, 22} It has been demonstrated that alcohol and tobacco together have an effect on the induction of mouth and pharynx cancer that neither can produce alone.^{23, 24, 25} Although it is known that a large percentage of the population both smoke and drink, not all them succumb to cancer. Even with the inhalation of such a potent carcinogen as tobacco and the ingestion of a suspected cocarcinogen, alcohol, only a small percentage of the population who use these substances develop cancer of any kind.

Many people are exposed to ionizing radiation from periodic chest and dental X rays and from natural sources in the environment. Most people are exposed to some nonionizing radiation from sunlight; some bask in the sun for esthetic reasons. However, not all develop skin cancer.²⁶

Most people, at some time or another, take drugs that are at least potentially carcinogenic. Synthetic estrogens such as diethylstilbestrol (DES) have been used widely in the production of beef for human consumption, and while the risk is low,²⁷ it still must be considered. Other drugs include: androgenic-anabolic steroids,^{28, 29} phenacetin,^{30, 31, 32}

coal tars and creosote,³³ Dilantin,^{34, 35, 36} chlor-amphenicol,^{37, 38} amphetamine,³⁹ and reserpine.^{40, 41}

A large percentage of the population has been exposed to these and other drugs.

Another important source of exposure to potential carcinogens for the general population is the food we consume. Diet is an important factor in the overall picture of carcinogenesis, since most cancer in the United States is linked, in one way or another, with cultural and dietary patterns. One of the most ubiquitous carcinogens in the American diet, aflatoxin, comes from natural sources such as peanuts and cereal grains.^{42, 43} The polycyclic aromatic hydrocarbons^{44, 45, 46} have been considered the standard animal carcinogens and are found in many foods, but particularly smoked foods. Grilling a steak over charcoal can produce substantial amounts of polycyclic hydrocarbons, and many Americans are exposed to these potential cancer causing agents every summer.⁴⁷ In the United States, bowel cancer has been among the most common major cancers, and has been traced to beef consumption patterns. With the additional exposure from grilling beef over charcoal, this route of exposure could be serious. However, even with all the multiple exposures, only about 5 percent of those with cancer have developed bowel cancer.⁴⁸ Safrole, used as a flavoring agent, has been demonstrated to be a carcinogen in animals⁴⁹ but has not been

shown to cause cancer in man. Some medicinal teas may contain carcinogens,⁵⁰ and there is experimental evidence to link both coffee^{51, 52} and salt^{53, 54} to various forms of cancer. The list is potentially endless, and encompasses virtually every facet of life for all of us. Why, then, do we not all die of cancer? Again, the answer must be that nature has devised biological thresholds that function to protect most of us from casual exposure to potential carcinogens.

Controversies Over the Existence of Thresholds

Not all scientists agree to the existence of thresholds for those biological processes we call carcinogenic. Those who support the "one-hit" or "zero-tolerance" theory feel that there is not enough solid proof to accept the theory of thresholds. The "zero-tolerance" theory has been the backbone of a strongly held feeling among some cancer researchers that once a chemical has been demonstrated to have carcinogenic properties, it can no longer be considered to possess a biological threshold. A great deal of the background work that led to the development of this position came from work done with radiation carcinogenesis. Supporters of the "one-hit" theory have drawn an almost exact parallel between the damage done by radiation and that which might occur as a result of exposure to a chemical carcinogen.

Strong claims have been made by the partisans of this view for the lack of reversibility of this reaction, and for the possibility that this action may be aided by other chemicals in the environment.⁵⁵ There are several distinctions that can be drawn between the nature of the damage resulting from ionizing radiation, and that due to exposure to a chemical carcinogen. Perhaps the most important distinction is that the chemical, as it enters the system, is exposed to a host of competing receptors, membranes, electrochemical gradients, and other potential interferences. Ionizing radiation⁵⁶ readily penetrates the body and is inhibited only by the mass of the tissue being penetrated. Tritium (chemically) easily passes through almost all physiological membranes that will also admit water, and, it as most of the test systems supporting this work have been in-vitro, only one membrane had to be penetrated. In living animals, most chemical carcinogens have a more difficult time reaching the target cells than does ionizing radiation.

The "one-hit" model developed by Iverson and Arley⁵⁷ operates on the assumption that carcinogenesis is essentially a one-step event occurring in a single cell, with that cell becoming the focus of a clone of altered cells. This model assumes that the number of tumors developing within the lifetime of the host organism is a function of the total dose and nothing else. This theory came to be considered too restrictive, and

modifications of it were soon published. One modification of the basic "one-hit" theory assumed that a single cell must have undergone a series of changes or alterations before the cell could begin to grow independently of host controls.⁵⁸

All of these "zero tolerance" theories assumed that the incidence of cancer in an exposed population would be proportional to the powers of the level of the carcinogen. This assumption, however, did not fit with the observed results of experiments with animals or with human epidemiological data and led to the development of what has come to be known as the multi-event model, which postulates that there must be a certain number of cells affected or altered for a tumor to develop. These later theories also incorporated accommodations for the death of the individual foci or clones, and accounted for the fact that not all altered cells can be assumed to grow at the same rate.

In the search for evidence of the existence of a threshold for cancer, one must examine the basic dynamics of the process that brings about an altered function by one or more cells in an organism. In the process, one can gain a clearer understanding of the interrelated nature of the many biological thresholds operant in living creatures and the observed latent period between exposure to a carcinogen and the development of clinical cancer.

If we assume that any carcinogenic agent must in one way or another bring about some change in the target cells that renders them potentially cancerous, and that the number of such cells is likely to be proportional to the concentration of the agent,⁵⁹ then a minimum number of altered cells must not only survive, but must expand their numbers for a cancerous lesion to develop. Assuming that only those altered cells survive that are fortuitously situated in such a way that they may coalesce with other similar cells before the natural limits of growth and death overtake them, then there must be a severe mortality rate among the newly altered cells. If it is reasonable to assume that only those coalescences that can expand their size fast enough to resist the defense mechanisms of the host will survive, then it follows that only those coalescences that start with a large enough number of altered foci will be able to increase their size quickly enough to survive. Therefore: "Whether tumor development depends on the junction of two or many foci the time relation still holds. If, for example, it takes at least four foci to constitute a self-defending tumor colony, death would overtake any focal clone that did not happen to have at least three neighboring foci making contact with it before one of the group died. The average time required for pairs to meet is the average time required for such groups to form. This model, then affords a biological basis for

the observed phenomenon that the latent period is inversely proportional to a fractional power of the dose of various carcinogens, with a value close to 0.33 for the exponent -- but not necessarily precisely that value." This supports the view that the latent period in humans may be described as varying with the inverse cube root of the dose administered.⁶⁰

This evidence supports the existence of a practical threshold or a latent period. It is our belief that it also demonstrates the probable existence of actual thresholds, for the critical event in the development of cancer is the modification of a large enough fraction of the cells in the organ to cause a failure in the tissue organizational functions of the host. If this critical number is not reached, the host defense mechanisms will destroy the altered cells, and no cancer will develop from that exposure no matter how long the latent period is. This shows again the intricate relationship that prevails between the various operating thresholds present in living organisms and the lowest concentration of a carcinogen that will produce a tumor.

Host Defense Mechanisms and Carcinogenesis

Many people in the scientific world recognize that the theories developed by the advocates of "zero-tolerance" do not take into account the many difficulties a chemical carcinogen faces before it gains access to a target cell. Brown⁶¹

feels that the implicit assumption that the probabilities of the cellular transition events initiated by the carcinogen go forward proportional to the concentration of the carcinogen present has not been proven. The actual exposure is almost certainly modified by processes such as adsorption to nontarget receptors, metabolic alteration, excretion of the carcinogen, membrane permeability, enzyme binding, and tissue distribution. For all of these reasons, then, the alteration of a single cell, or even several, would not necessarily lead to expressed cancer.

There are a variety of defense mechanisms, both passive and active, that the newly altered cell or clone must overcome before it can reach the size necessary to sustain its multiplication in the host.

DNA Repair Mechanisms

In recent years there has been increasing evidence of the existence of repair mechanisms for DNA damaged by alkylating carcinogens.^{62, 63} The existence of these mechanisms in mammalian systems could have a significant impact on our understanding of the way the process of carcinogenesis operates. The existence of some of the DNA repair mechanisms that have been found in bacteria and in-vitro experiments with mammalian cells have been verified in rats and humans. For instance, Nicholl⁶⁴ showed that O-methylguanine produced

by the administration of a single high dose of dimethylnitrosamine is not removed from the kidneys of adult rats by repair mechanisms nearly so rapidly as it is from their livers. This evidence correlates with work showing that dimethylnitrosamine, in single dose experiments, selectively produces tumors in the rat kidney, not the liver.

Kleihues and Cooper,⁶⁵ examining the accumulation of DNA damage in the rat brain following repeated small doses of N-methyl-n-nitrosoureas, found that over the course of the experiment the accumulation of the test compound in the liver of the rat was less than 1 percent of that which had accumulated in the brain. These experiments provided support for the hypothesis that it is a deficiency of the excision repair system of the rat nervous system that is a possible determining factor in the selective induction of nervous system tumors by alkylnitrosoureas and related compounds.

The ability of the rat liver to excise enzymatically O-alkylguanine from DNA is higher than that of any other rat organ, but only for single, relatively low doses. This work supplies some further understanding of the fact that liver carcinogens, in general, must be administered daily for the most efficient action. The evidence is that multiple doses given at short intervals may overcome the existing repair mechanism in the liver.

Studies on the mechanism of Xeroderma Pigmentosum, where exposure to the ultraviolet component of sunlight results in extensive damage to the skin and an increased susceptibility to the development of skin cancers, have shown that these excessive skin cancers are due to a deficiency in the DNA repair mechanisms of those with this disease.^{66, 67} This indicates the existence of a very strong and active DNA repair mechanism, for in the majority of the population, skin cancer due to casual exposure to the sun is not common. The very marked increase in susceptibility to the development of skin cancers by those with a deficiency in this vital repair mechanism indicates the strength of this particular system. It seems reasonable to conclude that the presence of a mechanism for DNA repair that can be shown to operate so efficiently in the normal human must be considered an important piece of evidence for the existence of very real and practical biological thresholds.

One of the main tenets of the "one-hit" theory is the irreversibility of the damage caused by a carcinogenic chemical. Roe⁶⁸ has found, however, that animals exposed to very low intermittent doses of carcinogens did not respond with the expected development of tumors when the initial application of the inducer was not closely followed by the promoter. If the application of the promoter was delayed for a few months, the

development of tumors did not follow the schedule established for applications much closer together in time. Jandl,⁶⁹ examining the epidemiological data on benzene, which is considered by some to be a human carcinogen, found early blood cell changes that can be easily detected, are reversible and nonrecurring, and always precede by months or years any significant damage to the bone marrow or any injury that progresses to aplastic anemia or to leukemia. Tabershaw,⁷⁰ reviewing work done with benzene and leukemia, found that leukemia, if indeed it is caused by benzene, is likely to be dose-related and to be preceded by cytopenia which is reversible. It should be noted that cytopenia has not been demonstrated with concentrations of benzene below 25 parts per million.

These studies can be interpreted as evidence that injury to a cell by a mutagen or carcinogen cannot always be considered an irreversible process. Rather, the process of the development of cancer is a multi-event, multi-threshold progression, subject to many influences far beyond the initial presumed interaction of a carcinogen and cellular or somatic DNA.

Immunological Defense Mechanisms

An important part of the defense mechanisms of the host organism is the degree of immunological competence present. There is evidence in the literature on this subject to show

that some chemically induced tumors possess immunological properties and that they are capable of stimulating the immune system to produce strong tumor-associated rejection reactions. Other workers⁷¹ have shown that similar rejection reactions occur with autochthonous tumors in man. It is our belief that the degree of immunological competence of the host is an important part of the concept of thresholds.

Studies done on animals treated with agents that depress the activity of the immunological defense system⁷² have shown that these animals are much more susceptible to the development of tumors after treatment with inducing chemicals. The evidence raises questions about the state of immunological competence in animals made extremely sick by the administration of very large doses of potential carcinogens. Experimental work with animals,^{73, 74} and epidemiological studies in humans⁷⁵ have demonstrated that cell-mediated immunity plays an important part in the host organism's resistance to the development of tumors. It has also been shown that in animals treated with anti-lymphocyte serum, the incidence of "spontaneous" neoplasms increases. Thus, if the chemical under evaluation has the property, when administered at very high concentrations, of causing immunosuppression, the incidence of tumors developing in the tests could be quite unrealistic when compared to possible exposure in humans.

Immuno-suppression therapy practiced as a part of organ transplant activities in humans has resulted in much higher than normal incidences of some kinds of cancers. The mechanism is as yet not entirely clear, but the feeling is that it probably involves some alteration of the immunological processes, rather than chemical induction of cancer.⁷⁶ Work done with the recipients of renal transplants has demonstrated lymphoma incidences of up to 35 times higher than normal.⁷⁷ In this same group skin and lip cancers were up to four times more frequent than expected, and the overall incidence of cancer of all kinds was 2.5 times normal.

Working with diethylstilbestrol (DES), Gass⁷⁸ found that mice treated with DES developed mammary cancer only at those levels that also caused physiological disturbances; cancer did not develop at lower levels. The latent period for the development of mammary tumors in these test animals could be shortened only by the administration of doses of DES in excess of 30 parts per billion, which was the same level that produced an increase in the incidence of these cancers. The implication is that there is a threshold operating, and that the induction of physiological disturbances plays a role in the increase of tumors. It must be asked if studies that use test dosages of potential carcinogens high enough to cause physiological disturbances in test animals are really relevant to

possible or probable human exposures. The dosages seem to be rather poor indicators of the exposures likely to take place in the "real" world.

Correlation of Animal Testing With Actual Human Exposures

One of the largest problems in carcinogenesis threshold research is the relevancy and accuracy of animal testing. Most of the testing of potential carcinogens in animal systems is carried out using very large test doses that exceed the highest actual human exposures a hundred or thousand fold. This procedure is justified by the rationale that by this method the effects of long lag periods can be eliminated, and the use of very large numbers of test animals avoided. This is a statistical approach, and represents a serious compromise between correct scientific procedure and economic necessity.⁷⁹

Another popular argument for the use of large doses is that the test systems in use are not sensitive enough to detect statistically significant differences between the control and test animals because of statistical validity considerations. Some critics have said that because of the foregoing factors it would be necessary to test 50,000 animals to be able to detect a small difference. These criticisms have some validity, particularly when the carcinogen being tested happens to be very weak. One solution that has been proposed to this problem⁸⁰ is to pay more attention to those substances that are strong

carcinogens and give unequivocal results at moderate dose levels. The philosophy of shortening the latent period by using very large dose tests has resulted in experiments that, when related to possible human exposures, seem ridiculous. For instance, to ingest the same amount of cyclamate (2.18 grams per day or 5 percent of diet) that was fed to experimental animals, a human would have to consume 552 bottles per day of soft drinks containing cyclamates.⁸¹ Work done with trichloroethylene remaining in decaffeinated coffee resulted in male experimental animals receiving a dose of 1200 milligrams per kilogram of body weight of this substance. For a human to ingest this much trichloroethylene by drinking decaffeinated coffee (150 milliliters per cup with 9×10^{-4} milligrams of TCE per cup), it would be necessary to consume 10×10^7 cups of decaffeinated coffee per day.⁸²

Metabolic Alterations Due to High Test Doses

Beyond the lack of relevancy of experimental exposures to those experienced in the real world, the fact is that these very high dose levels are introducing error into the experiments. The assumption made in carcinogenesis testing is that the animals are to approximate the exposure of reasonably healthy human beings. Yet in most of the high dose experiments, the actual overt toxicity of the chemical being tested is ignored. The results of this policy are that a high percentage of animals

become sick or die from toxic effects⁸³ and seriously disturbed homeostatic mechanisms. As discussed previously, there is good evidence to indicate that it is indeed the overwhelming of the homeostatic mechanisms of the host organism that is the key event⁸⁴ in the expression of tumors.

With high enough doses, the ingestion of common sugar (sucrose) can have serious consequences for rat or human. A review of these studies⁸⁵ shows that excess sucrose in the diet can induce hypertriglyceridemia, hypercholesterolemia, hypertension, and kidney lesions. Many individuals in the scientific world question the validity of experiments in which test animals were overdosed: "For one to analyze, statistically, toxicity data obtained from experimental studies in animals where large doses of a chemical were given, and then predict what percent of humans may be adversely affected by a challenge at a lower dose, is not valid, biochemically or pharmacologically."⁸⁶

Studies⁸⁷ with 2, 4, 5-trichlorophenoxyacetic acid (2, 4, 5-T) support the view that metabolic systems which account for the detoxification of chemicals are seriously altered. Another study⁸⁸ has demonstrated that the metabolic systems that account for the conversion of glyoxylic acid to oxalate in rat liver homogenates are dependent on dose.

At the lower end of the dose scale the end product is carbon dioxide, but at higher levels there is a partial oxidation to oxalate. There are data now available to support the view that statistical calculations of thresholds, or conclusions as to the carcinogenicity of a substance, that depend on experimental studies done with animals administered very high doses of the substance in question, must be reevaluated.^{89, 90, 91}

Enzyme System and Metabolic Pathways

The practice of administering large doses of suspect carcinogens to animal test systems is generating serious criticism. One of the many problems related to high dose rates has to do with the alteration of the normal metabolic pathways, and the production thereby of secondary metabolic products not usually formed at lower doses. It has been suggested⁹² that in a number of cases the secondary metabolite formed is the actual active carcinogen, and not the chemical administered.

It is important to recognize that with increasing dose levels any chemical, carcinogen or not, is subject to differing excretion, storage, and biotransformation rates. The biological processes by which a living organism removes or detoxifies a substance are chemical reactions, and as such obey the general physical laws that have been found to control all chemical reactions. Therefore, when we examine the fate of a chemical

once inside a living organism, we must look at reaction rates. The rate at which a chemical reaction proceeds is generally understood to imply the rate at which the concentrations of reacting substances vary with time. The law of mass action indicates that the rate of any reaction is proportional to the concentration of the reactants present at any given time. An enzymatic reaction, then, should proceed at a rate proportional to the concentrations of enzyme and substrate. It has been demonstrated that when the concentration of the substrate is held constant, the velocity with which the reaction proceeds is proportional to the enzyme concentration.⁹³

This proportional relationship holds only for those cases in which the substrate concentration is held constant at low and intermediate levels. When substrate (carcinogen) and enzyme combine, there is, at the molecular level, an interval before the enzyme-substrate complex dissociates and the reaction products are released. After this dissociation, the enzyme molecule is again ready to react with substrate. By the law of mass action, therefore, the more molecules of substrate that are then ready to combine with the enzyme, the faster the reaction will proceed -- up to a certain point. The limiting factor in this reaction is the rate of dissociation of the enzyme-substrate complex. This dissociation rate is independent of the substrate concentration and will be the same for all substrate

concentrations. What this means is that at or above a certain concentration of the substrate, the velocity of the reaction is determined by the rate of dissociation, because the intervals during which it is not reacting are negligible. Therefore, any additional increase in the concentration of the substrate will not result in an increase in the reaction rate.

An enzyme reaction is said to be monomolecular or first order when only one substance is reacting and the velocity of this reaction is proportional to the concentration of this substance. In the healthy animal, enzyme concentration will usually remain at a constant characteristic level so that the only factor influencing the rate of reaction is the changing level of substrate. Therefore, when the concentration of the substrate is such that there are more active sites available on the enzyme than there are molecules of substrate for them to react with, then the enzyme reaction is first-order. At high levels of substrate concentration, the enzyme is saturated, and the reaction becomes almost constant in rate. When the reaction is no longer dependent on the concentration of substrate, it is said to be zero-order.⁹⁴

If the elimination processes are all first-order, the biologic half-life of the substance does not change with dose. That is, it will always take the same amount of time to eliminate one half of the substance present in the system.

Doubling the dose under these conditions does not double the duration of action of a drug, but increases it only by one biologic half-life. When a zero-order process is involved (as with very high doses of carcinogen administered to test animals), the time to eliminate one-half of the substance grows progressively longer as the dose increases. To put it another way, the quantity of drug eliminated from the animal per given unit of time ceases to be a constant fraction of that remaining in the body and approaches a constant figure.

When the elimination processes in an experimental animal are proceeding at a zero-order rate because of massive doses of a test substance, the concentration of that substance rises rather rapidly. Thus, depending on whether it is lipophilic or hydrophilic, a chemical can accumulate in various body tissues reaching very high levels. This chemical present in the body tissues, not being removed by the normal processes that would be effective at lower dose levels, is then available to react in ways and with enzymes that it normally might not, and certainly at concentrations that would never be reached in the "real" world.

At low levels, furosamide, a diuretic chemical, is for the most part excreted intact in the urine. With high doses, however, the first-order reactions are overwhelmed, leaving a high concentration available to form toxic metabolites⁹⁵

which can react covalently with macro-molecules. A situation illustrative of the problems that can occur with high-dose administration came about when a group of researchers administered a maximum tolerated dose (MTD) and one-half MTD during an experiment designed to assess the carcinogenicity of some pesticides. The levels given were too high, and many animals died, resulting in incomplete experiments.⁹⁶ Over the course of this study, a total of 175 dose changes had to be made because of metabolic overload on the animals.

It is significant that in discussing the existence of thresholds for the induction of cancer one should discuss first-order and zero-order enzymatic reactions, for these very terms imply, in the conversion from one to another, the existence of a threshold, one that in this case is both widespread and quantifiable. It is significant also because it is a graphic example that biological systems have efficient means to deal with toxic insults from the environment. To imply that there is no such thing as a "safe level" or "threshold" or that the human organism has "zero-tolerance" for exposure to carcinogenic substances is contrary to nature. The assumption, based on high-dose testing, that there is no threshold for carcinogenic substances is to ignore the existence of a variety of discrete thresholds that are being violated by the very design of the study. Thresholds do exist in nature; they are an implicit

part of the design of every part of the biological systems that function in this world. Thresholds, ranging from the stimulus required for a nerve cell to "fire" to those which regulate the amount of circulating thyroxin, are a fundamental concept in the homeostasis we call life. To deny the existence of this concept is to deny the existence of life. Science has not to this moment discovered the absolute threshold for every substance in question, nor is it likely to do so in the near future. What science does know collectively, however, is that nature has incorporated thresholds of many kinds into her creations, that they are not all of equal strength, that they can be overwhelmed, and that they cannot be ignored.

It is unscientific to proceed on the assumption that there is no threshold so far as carcinogens are concerned. It is unwarranted to assume that there is no threshold for regulatory purposes, since such an assumption, in light of the evidence cited above, can only be regarded as arbitrary and capricious. It is even more arbitrary to assume that no threshold can be identified, and therefore to foreclose future evidence to the contrary. Such a decision would also be a denial of due process and a violation of that provision of section 6(b)(5) of the Act which requires that development of standards relating to toxic materials or harmful physical agents must be based on "the latest available scientific data in the field and experience gained under this and other health and safety laws."

FOOTNOTES

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Section VI
RISK BENEFIT ANALYSIS

When Congress wrote the Occupational Safety and Health Act of 1970, the lawmakers recognized that absolute protection of all workers from all hazards was not possible. Therefore, in section 6(b)(5) of the Act, the lawmakers wrote: "in promulgating standards dealing with toxic materials or harmful physical agents under this subsection, (The Secretary) shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity."

Some degree of risk may remain in the workplace, even when an optimum effort has been made to control hazards. This optimum effort should be based on the feasibility of implementing controls and the acceptance of a certain amount of risk. The general public assumes willingly many risks every day. Many of us utilize public or personal transportation although thousands of drivers and riders die each year. Such risk cannot be reduced to zero level. No matter how extensive the controls are that employers institute in the workplace, some risk will inevitably remain.

There is also the risk of having cancer due to nonoccupational environmental factors, such as smoking. In

evaluating risk versus benefit, one must consider these non-occupational factors -- another reason why it is not possible to maintain "zero-risk" in the workplace.

An important issue the regulator must face in relation to every regulation -- but especially in relation to unrealistically low levels of the permissible exposure limits of toxic substances -- is whether employee health is best protected by available resources being expended in accordance with the requirements of OSHA's proposal, or whether more life or health would be saved by a different allocation of resources.

Risk benefit analysis is not a matter of weighing dollars versus life or health; rather, risk benefit analysis is a mechanism by which available resources are directed by a rational evaluation of priorities to determine how employee health can be best promoted and protected.

It is urged that the Secretary should consider this important factor in determining the permissible exposure limits.

Section VII

PROPOSED REGULATION AND STANDARD

ORC has developed and included in this statement a proposed procedural regulation and a model standard. The procedural regulation reflects the preceeding discussion of regulatory policies and the responsibilities of the Secretary of Labor. Contrary to OSHA's proposed model standards, ORC recommends that the requirement portion of any health standard should be in accordance with section 6(b)(5) of the Act, that "whenever practicable, the standard promulgated shall be expressed in terms of objective criteria and of the performance desired," and that OSHA adopt ORC's simplified and performance-oriented model standard. ORC's recommended model standard also meets the expressed policy of the President of the United States, which emphasizes simplicity and conciseness of any federal standards.

A. PROCEDURAL REGULATION

Subpart A - General

1990.1 Scope

This part provides for the regulation of toxic materials, pursuant to the Occupational Safety and Health Act of 1970 (the Act), as set forth in the various subparts below.

1990.2 Purpose

It is the purpose of the regulations of this part to provide standards dealing with carcinogens, which must adequately assure to the extent feasible, on the basis of the best available scientific evidence and experience, that no employee will suffer material impairment of health or functional capacity.

Subpart B - Regulation of Carcinogens

1990.101 Scope

This subpart provides for the regulation of carcinogens.

1990.102 Definitions

Terms used in this subpart shall have the meanings set forth in the Act. In addition, as used in this subpart, the following terms shall have the meanings set forth below.

"Act" means the Occupational Safety and Health Act of 1970 (Pub. L. 91-596, 84 Stat. 1590, et seq.).

"Carcinogen Classification Commission" (the Commission) means the Commission under a Congressional mandate to classify substances into an appropriate carcinogen category based on science and experience.

"Secretary" means the Secretary of Labor or a designee.

"Director of NIOSH" means the Director of the National Institute of Occupational Safety and Health or a designee.

"Feasibility or feasible" means capable of being accomplished in a manner which takes account; (1) technical capability of obtaining the desired results, and (2) costs in relation to the benefits gained.

1990.103 Classification of Carcinogens

(a) General. (1) Whenever the Secretary receives scientific information, petitions, or recommendations in writing by an interested person, or the Director of NIOSH, or upon his own cognizance, he shall transmit within thirty (30) days such information to the Commission and publish in the Federal Register the receipt and the transmission of such information.

(b) Rulemaking. The Secretary shall publish the Commission's decision in the Federal Register within fifteen (15) days of the receipt of the decision. The Secretary shall determine, within sixty (60) days from the publication of the Commission's decision, the need for a standard. He shall consider, among other things, whether such danger currently exists in the workplace, whether ineffective remedial action has been taken by employers, whether compliance with proposed standard is feasible, and whether such standard could be enforced.

The Secretary shall publish a proposal in the Federal Register within fifteen (15) days of the completion of such determinations, together with an appropriate indication of actions required by this subpart.

(c) **Reclassification.** Whenever the Secretary receives new scientific information, petitions or recommendations requiring reclassification in writing by any interested person, or the Director of NIOSH, or upon his own cognizance, he shall deliver such information to the Commission along the procedure set forth in 1990.103(a)(1).

1990.104 - 109 Reserved

1990.110 - Consequences of Carcinogen Classification

In the event the Commission determines that a substance shall be classified into a specific classification, the Secretary shall initiate the following actions:

(a) He shall at the time he publishes in the Federal Register a Strong Confirmed Human Carcinogen, issue an Emergency Temporary Standard, pursuant to section 6(c) of the Act, if:

(1) He determined that such grave danger currently exists in the Workplace and ineffective remedial action has been taken by the employers.

(2) He determined that an attainment of such standard is feasible.

(3) He determined that he can enforce such standard.

(b) He shall, within seventy five (75) days from publication of the Commission's decision, propose a permanent standard for a carcinogen and its subclassification, pursuant to section 6(b)

of the Act, which shall follow the format and content of the model standard set forth in 1990.150. Any deviation, addition or change from that format or content shall be explained, together with the reasons therefore. The determination of the permissible exposure limits shall be based on the technical information but shall also include, among other things:

- (1) Dose-response data and practical threshold concepts,
- (2) The feasibility of compliance with such standards,
- (3) Risk-benefit analysis for such standards, and
- (4) Enforcibility of such standards.

1990.111 Major Issues to be Raised in the Rulemaking

At any time after a request for a public hearing is made or upon the Secretary's initiative, subsequent to the publication of the proposal, the public shall be provided with an opportunity to participate in the rulemaking in accordance with section 6(b) of the Act, the regulation thereunder and 29 CFR Part 1911. The major issues in the hearing or in comment shall be the following: (a) whether the Secretary correctly determined the permissible exposure limits as required in 1990.110(b); (b) any deviation, addition or changes from the format or content set forth in 1990.150; (c) the environmental and the economic impacts arising from regulation of the substance; (d) whether the Secretary complied with the requirement set forth in 1990.103(b).

1990.112 Final Action

At the conclusion of the rulemaking, based on the record as a whole, the Secretary shall issue a standard which follows the format and content of the model standard contained in 1990.150. Any deviation, addition or change from the format or content shall be explained, together with the reasons and evidence therefore. The final determination of the permissible exposure limits shall be based on the record, including the records obtained on the items required in 1990.110(b).

B. MODEL STANDARD

1990.150 MODEL STANDARD FOR A SUBSTANCE WHICH MAY POSE A CARCINOGENIC RISK TO HUMANS

(a) Scope and application

(1) This section includes requirements for the control of employee exposure to substances which may pose a carcinogenic risk to humans.

(2) This section applies to the manufacture, reaction, packaging, repackaging, storage, or use of the substances.

(3) This section applies to the transportation of such substances except to the extent that the Department of Transportation or other Federal agencies may regulate the hazards covered by this section.

(b) Definitions

"Confirmed Human Carcinogen" means any substance which, as the result of any occupational exposure, results in a statistically significant increased incidence of malignant neoplasm, or a combination of benign and malignant neoplasms in humans.

"Suspect Human Carcinogen" means any substance which, as a result of any occupational exposure, results in statistically questionable increased incidence of malignant neoplasms or a combination of benign and malignant neoplasms in humans or is implicated in a publication of a particularly plausible clinical case report, and, as the results of animal experimentation in two or more experimental mammalian species, results in a statistically significant increased incidence of malignant neoplasms or a combination of benign and malignant neoplasms.

"Confirmed Animal Carcinogen" means any substance which, as the result of animal experimentation in two or more experimental mammalian species, results in a statistically significant increased incidence of malignant neoplasms or a combination of benign and malignant neoplasms.

"Suspect Animal Carcinogen" means any substance which, as the result of animal experimentation in one or more experimental mammalian species, results in questionable significant increased incidence of malignant neoplasms or a combination of benign and malignant neoplasms.

"Malignant neoplasm" means a population of cells displaying progressive growth and varying degrees of autonomy and cellular atypia. It displays, or has the capacity for, invasion of normal tissues and metastases.

"Benign neoplasm" means a less autonomous population of cells, exhibiting little or no cellular atypia, invasion of normal tissues, or metastases.

"Assistant Secretary" means the Assistant Secretary of Labor for Occupational Safety and Health, US Department of Labor, or a designee.

"OSHA Area Office" means the Area Office of the Occupational Safety and Health Administration having jurisdiction over the geographic area where the affected workplace is located.

"Exposure" means employee exposure that is determined to be in excess of the permissible exposure limits.

"Work practices" means all control methods other than engineering controls including the proper usage of protective devices.

"Feasibility or feasible" means capable of being accomplished in a manner which takes account; (1) technical capability of obtaining the desired results, and (2) costs in relation to the benefits gained.

(c) Permissible exposure limits

(1) Inhalation exposure limits

No employee may be exposed to an airborne concentration of xxxxxxxx in excess of the permissible exposure limits.

(i) Time-weighted average limit (TWA). No employee may be exposed to an airborne eight hour time weighted concentration of xxxxxxxx in excess of xxxxxxxx ppm (or mg/m^3).

(ii) Ceiling limit. No employee may be exposed to an airborne concentration of xxxxxxxx in excess of xxxxxxxx ppm (or mg/m^3) sampled for xxxxxxxx minutes.

(2) Skin and eye contact limits.

No employee's skin and eye may be exposed to xxxxxxxx by direct contact, when such contact will result in injury to eye and/or skin, or will result in biologically detrimental absorption of xxxxxxxx through the skin.

(d) Exposure evaluation

A program of exposure evaluation shall be established to identify the hazards, to assess the extent of employee exposures, and to determine the effectiveness of the control measures.

(1) Initial assessment

The employer shall make an initial assessment of the workplace for the hazards associated with xxxxxxx. Such assessment may consist of observation, calculation involving an estimation of airborne concentrations or actual measurement related to the employee exposure.

When the results of such assessment indicate the employee exposures to xxxxxxx are below the permissible exposure limits, a periodic exposure determination may not be required.

(2) Reassessment

Whenever there has been a significant production, process or control change which may result in new, increased or reduced exposure to the hazards, or whenever the employer has any other reason to suspect a change which may result in new, increased or reduced exposure to the hazards, the employer shall reassess the extent of employee exposure as described for the initial assessment.

(3) Periodic exposure measurement

When the results of the initial assessment indicate the employee exposure to xxxxxxx are in excess of the permissible exposure limits, a program shall be implemented to control the hazard(s). The employer shall repeat such determination at a frequency set forth below, until at least two consecutive measurements show employee exposures to xxxxxxx below the permissible exposure limits.

The frequency of the measurement of the concentration of xxxxxxxx or determinations of the effectiveness of the engineering controls shall be:

- (i) Monthly for Strong Confirmed Human Carcinogen,
- (ii) Quarterly for Mild Confirmed Human Carcinogen,
Strong Suspect Human Carcinogen,
Strong Confirmed Animal Carcinogen.
- (iii) Semiannually for Weak Confirmed Human Carcinogen,
Mild Suspect Human Carcinogen,
Mild Confirmed Animal Carcinogen.
- (iv) Annually for Weak Suspect Human Carcinogen,
Weak Confirmed Animal Carcinogen.

The frequency of such measurement may be altered if employee protection is assured.

(4) Methods of Measurement

The employer shall utilize methods recommended by OSHA or equivalent, for the measurement of employee exposure.

(5) Notification of Use. (In case of an
Emergency Temporary Standard)

Within xxxxxxxx the time of the effective date of this section, or within thirty (30) working days following the introduction of xxxxxxxx into the workplace, every employer shall report the following information to the nearest OSHA Area Office for each such workplace:

(i) The address and location of each workplace in which xxxxxxxx is present;

(ii) The number of employees who may be exposed to xxxxxxxx and an estimate of the frequency and degree of exposure that may occur; and

(iii) A brief description of the employer's safety and health program as it relates to control of employee exposure to xxxxxxxx.

(6) Employee observation

Employees or their designated representatives shall be afforded reasonable opportunity to observe the exposure determination required by this paragraph.

(7) Notification of overexposure

The employer shall promptly notify any employee who has been or is being exposed to xxxxxxxx in excess of the permissible exposure limits, and shall inform him or her of the corrective action being taken and the employee's responsibility for utilizing personal protective devices.

(e) Protective Equipment

The employer shall provide appropriate protective devices in accordance with the requirements set forth in 1910.132, .133, and .134.

(Provide an appropriate respiratory protection table.)

(f) Medical Surveillance

A medical surveillance program shall be instituted for each employee with potential exposure to xxxxxxx. The program shall provide such employee with an opportunity for examinations and tests in accordance with this paragraph. All such examinations and tests shall be performed by or under the supervision of a licensed physician, and shall be provided without cost to the employee.

(OSHA should develop a medical protocol with active assistance of occupational physicians and frequency of medical surveillance.)

(g) Signs and labels

The requirements for signs and labels shall be in accordance with labelling standards.

(h) Training

The employer shall institute a training program for employees engaged in operations associated with potential exposure to xxxxxxx. Such program shall include:

(1) The nature of the health effect(s) from exposure to xxxxxxx.

(2) The specific nature of operations which could result in exposure to the xxxxxxx and appropriate protective steps.

(3) The purpose for and explanation of the exposure evaluations.

(4) The purpose for and explanation of the medical surveillance.

(5) The engineering controls and use of the personal protective equipment.

(6) The proper work practices.

(7) Emergency procedures

(i) Methods of Compliance

The employer shall institute engineering and work-practice controls to reduce and maintain employee exposures to xxxx to or below the permissible exposure limits.

(j) Record keeping

The employer shall preserve the records of the medical surveillance and the exposure determination for 40 years or employment plus 20 years, whichever is longer. All other records shall be kept until they are replaced with the most recent records.

The employer shall provide employees, upon request, records that indicate their own exposures.

The records of the medical surveillance shall only be made available to employee's personal physicians.

(k) Effective date

This portion shall become effective (insert date of publication in the Federal Register).

(1) Appendices

The information contained in the appendices is not intended, by itself, to create any additional obligations not otherwise imposed or to detract from any existing obligation.

APPENDIX A

Substance Safety Data Sheet

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APPENDIX B

Substance Technical Guidelines

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APPENDIX C

Medical Surveillance Guidelines

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