

PLAINTIFF'S EXHIBIT

SH-3647

Comments of
JOHNS-MANVILLE CORPORATION
with respect to
NOTICE OF PROPOSED RULEMAKING
OCCUPATIONAL EXPOSURE TO ASBESTOS
(Federal Register - October 9, 1975)

To:
Occupational Safety and Health Administration
U.S. Department of Labor

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CONSIDERATIONS CONCERNING CARCINOGENICITY

On 9 October 1975 the Department of Labor, Occupational Safety and Health Administration (OSHA), issued a "Notice of Proposed Rulemaking -- Occupational Exposure to Asbestos" (the "Proposal") in the Federal Register. Among other things the Proposal would reduce the 8-hour time-weighted average (TWA) exposure limit from 2 fibers per cubic centimeter (cc), scheduled to go into effect on July 1, 1976, to 0.5 fiber/cc, on the rationale that:

Since the promulgation of the U.S. permanent asbestos standard, considerable new information has been forthcoming on the toxic effects of asbestos. This has been in two areas: In the widening spectrum of cancers associated with asbestos exposure, and in various manifestations of asbestos disease in individuals exposed to relatively low concentrations of dust.

The "considerable new information" alluded to above is reviewed and evaluated in Exhibit B, which is part of this response. Exhibit B also sets forth in detail the basis for rejecting OSHA's analysis and interpretation of the data and the conclusions which OSHA has derived from this "new information."

The Proposal further states in Section III, CERTAIN CONSIDERATIONS CONCERNING CARCINOGENICITY, that "in considering the controversial issue of carcinogenicity, OSHA is relying upon not only the new data reviewed above, but the leading scientific principles and opinions believed to reflect the research conclusions of international cancer experts, which were developed since or not known to OSHA at the time that the original standard was promulgated."

The specific elements addressed by OSHA and the principles set forth in Section III are:

- A. The Latency of Carcinogenic Effects
"Prudent policy would therefore seem to indicate that every reasonable measure should be taken to eliminate human exposure to chemical compounds as soon as their carcinogenic nature is identified."
- B. Variability in Individual Susceptibility in Relation to the Concept of a Threshold
"Thus, in the working population, certain groups, such as those already biologically compromised, may be more susceptible than other groups."
- C. A Threshold Limit
"Because of the variability of individual response to carcinogens and other factors, the concept of a 'no effect' or 'threshold level' may have little real significance on the basis of existing knowledge . . . the threshold concept for carcinogens is, at present,

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more a matter of responsible regulatory policy than a precise, scientific determination.

The proposed rule further states: "These theoretical concepts have a bearing on the asbestos issue, particularly as to the question of the existence, or nonexistence, of a threshold level of carcinogenic effect. A 'no effect' level theoretically may exist, but it has not been demonstrated." These theoretical concepts, as well as other practical aspects, indeed bear on the establishment of a standard for occupational exposure to asbestos, and it is for this reason that the totality of existing information, rather than arbitrarily selected segments, must be considered for use in support of a proposed regulation. It is well to reemphasize that the intent of the Proposal -- the protection of the worker -- is not at issue, but rather the validity of the bases on which the proposed regulation is promulgated.

This discussion is specifically addressed to the issues of dose response, threshold, and leading scientific principles and opinions, etc., as noted immediately above. The problem is clearly divisible into two components: the first involves the evidence supporting or negating the principles of dose response and a threshold level of carcinogenic effect, with their subsections of latency and individual variation; and the second, the applicability and usefulness of this information to a regulatory agency in fulfilling its responsibility.

A Dose Must Exist Below Which a Carcinogen Is Ineffective

CHEMICAL CARCINOGENS OF EVERY KNOWN CATEGORY, CHEMICAL COMPOSITION, AND STERIC CONFIGURATION PRODUCE MORE CANCERS WHEN ADMINISTERED IN LARGE DOSES THAN SMALLER ONES, AND A DOSE RESPONSE CURVE CAN BE DEMONSTRATED FOR GRADUATED DOSES (1,2,3,4).

Carcinogens are like all biologically active substances; they owe their effect to the manner in which they react with the chemical constituents of living organisms. For active substances in general, the greater the extent of reaction, the greater the magnitude of effect. Moreover, the response of a biological system (both animal and human) to a physiologically active agent is proportional, over some range of concentrations, to the concentration of the active agent within the system.

In the scientific community there are investigators who maintain that the evaluation of the effects and responses of a carcinogenic substance should be different from the evaluation of the effects and responses of toxic chemical substances which are not carcinogens. Disregarding established principles of dose response and biological thresholds, they believe that the effect of a carcinogen is all or none, that a single molecule is sufficient of itself to be the ultimate agent of harm; whereas they believe a biological system can tolerate certain concentrations of a noncarcinogenic toxic chemical without any demonstrable adverse

effect. There are convincing theoretical arguments as well as data to show that a dose must exist below which a carcinogen is ineffective.

Carcinogenesis is universally recognized as a complex multistage process in which each stage is composed of several steps (5):

Step I. The initial exposure of the target host to the carcinogen, with the sequential steps of host entry, anatomic distribution and localization, cell entry, metabolic conversion, and biologic availability.

Step II. Interaction with critical receptor sites (macromolecules), formation of new macromolecules or products, survival of such products (nonrepair).

Step III. Alteration (transformation) of cell(s) with persistence and proliferation of transformed cells to form clinical cancer.

This sequence of events can, under laboratory conditions, clearly be shown to be related to the dose (concentrations of the agent x time) of the carcinogen to which the biological system is exposed. Furthermore, under laboratory conditions, levels of exposure exist at which the various stages of carcinogenesis can be predictably altered by a variety of influences to inhibit or enhance the carcinogenic response. There are a plethora of data to show that all stages are governed by universally accepted principles of pharmacology, toxicology, and pathologic physiology (6).

A Threshold Level Exists Below Which a Biological System Will Not Exhibit Any Adverse Effects from Exposure to a Carcinogenic Agent

CHEMICAL CARCINOGENS CAN BE ADMINISTERED AT DOSE LEVELS WHICH YIELD NO CANCERS IN LABORATORY ANIMAL MODELS AND WHICH NEITHER SHORTEN THE ANIMALS' LIFE SPAN NOR RESULT IN DEMONSTRABLE ABNORMALITIES IN METABOLIC AND PHYSIOLOGICAL CAPABILITIES. THIS IS CLEARLY A NO-EFFECT (THRESHOLD) LEVEL (7).

A clinical (human) counterpart can readily be demonstrated in several areas. Wagoner (8) in his keynote address to the New York Academy of Sciences Conference on Occupational Carcinogenesis, repeatedly refers to the percentage of those exposed to an array of high-risk environments, who either had developed cancer or were expected to develop cancer eventually. This nonuniform pattern of cancer occurrence reflects the dose-dependent nature of the response in the worker population and this response in turn is capable of further modification by the biological variability that exists in man. This variability, as can be demonstrated in the laboratory, is fully in accord with dose-response concepts. There can be little doubt that all factors may be operative. Workers failing to develop cancer have not achieved an exposure that has transgressed their threshold as defined by Rall (9).

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Elucidation of the biochemical pathways for the metabolism of chemicals including carcinogens increasingly demonstrates that detoxification is a dose-dependent process. Studies by Gehring et al (10) on 1,4-dioxane and vinyl chloride clearly demonstrate the need for considering dose-dependent fate of chemicals in assessing their carcinogenic hazard. They further note that other compounds for which evidence indicates that their fate may be dose dependent include the carcinogens 2-naphthylamine and benzo(a)pyrene.

THERE EXIST AN ARRAY OF GENERAL ENVIRONMENTAL AND WORKPLACE SITUATIONS IN WHICH EXPOSURE TO CHEMICAL CARCINOGENS HAS FAILED TO RESULT IN AN INCREASED INCIDENCE OF CANCER (E.G. CARCINOGENIC PESTICIDES IN THE WORKPLACE AND CARCINOGENIC AROMATIC HYDROCARBONS IN AMBIENT AIR). THE CLEAR IMPLICATION IS THAT INDEED A SUBTHRESHOLD LEVEL OF EXPOSURE EXISTS IN ACTUALITY.

Suggestions have been made that with the passage of sufficient time (up to multiples of the existing life span), environmentally induced cancer might occur from subthreshold doses, particularly in experimental laboratory situations. This premise has questionable relevance with regard to the promulgation of occupational health standards. The two-stage concept of carcinogenesis is in fact crucially dependent on the demonstration and proof of subthreshold doses of carcinogen administered to an animal (11,12). Rall (9) readily admits that "most scientists would agree that a highly potent carcinogen such as an aflatoxin, nitrosamine, or a chloromethyl ether is probably perfectly safe at an exposure level of one molecule, ten molecules, a hundred molecules, or maybe even a thousand molecules per mouse or rat or dog or man; but we all believe that it is totally unsafe to be exposed to ten to the twentieth, ten to the twenty-first, ten to the twenty-second, or ten to the twenty-third molecules of this same compound."

This finds expression when, for example, the potent carcinogen benzo(a)pyrene is administered at dose levels resulting in a zero yield of cancers. The addition of promoting agents can transform the zero yield to a measurable yield of cancers clearly in concert with dose-response concepts. At microquantitative levels, the combination of initiator and promoter similarly can fail to produce tumors during the life span of the animal.

There are two instances of biological circumstances which unequivocally dramatize the concept of a threshold level of carcinogenic effect. The first relates to the carcinogenicity of certain steroid hormones. Estrogens and androgens are carcinogenic for experimental species, and in the case of estrogens, the occurrence of disease in humans has been documented (13). In the case of the synthetic estrogen stilbesterol and the naturally occurring estrone, cancer has been observed only after the administration of large doses of these agents. Estrogenic hormones are ever-present at subthreshold levels in the earth's population.

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The second instance relates to the universal occurrence of certain trace metals, such as nickel and chromium, in the bodies of man (14,15). In both animals and man these elements have been shown to be carcinogenic at high dose levels. Their physiologic presence, however, is unaccompanied by any demonstrable abnormalities.

The principle of a threshold, once accepted for carcinogens, as the foregoing establishes, then appropriately directs our attention to the accumulation of both experimental and clinical data to observe where, indeed, such levels may reside.

The Cancer-Producing Potency of Chemical Carcinogens Can Be Profoundly Altered

THE CANCER-PRODUCING POTENCY OF CHEMICAL CARCINOGENS CAN BE PROFOUNDLY ALTERED BY MODIFYING THE HOST, THE COMPLEXITY OF THE ENVIRONMENT, AND THE PHYSICAL PROPERTIES OF THE CHEMICAL AGENT.

Changes can be accomplished through: (a) pretreatment with chemical agents (both carcinogenic and noncarcinogenic) which can either stimulate or depress drug-metabolizing enzyme systems; (b) diet modification; (c) hormonal modification by endocrine gland removal or artificial administration of hormones; (d) varying population size (density) in laboratory animal cages (16). Significant induced as well as spontaneous differences exist in the human response to carcinogens. When, for example, the site and patterns of cancer occurrence in the nonsmoker and smoker or the alcohol user and nonuser are compared, the "shifting" levels of cancer induction bespeak a response to carcinogens that is dependent upon achieving a level of interaction (threshold) that is not fixed, but quite liable to change.

Spontaneous or physiologic variations, still cryptic as to mechanism, are routinely observed in clinical as well as experimental settings. This individual variability is at the suprathreshold level and is essentially irrelevant to the regulatory process.

The concept that one molecule of a carcinogen interacting with one intracellular macromolecule will result in a mandatory nonthreshold response, inevitably resulting in cancer development, precludes both naturally occurring and induced modifications of response to carcinogens.

The multiplicity of cofactors both exogenous and endogenous critical to the response to a carcinogen and the development of cancer is reflected in greater qualitative and quantitative variations in the human response to carcinogens than all other environmental agents. The paucity of knowledge of the mechanisms of cell initiation and their progression to clinical cancer has generated a mystique, as a frequent substitute for data, when interpreting diverse pathological expressions of the group of

diseases designated cancer. For example, each organ or organ system can develop an array of different types of cancer, often with important differences in natural history, in response to exogenous carcinogens. As shown in Table 1, a variety of cancers develop from environmental agents, and one wonders whether the various histological patterns and types (a) reflect qualitative or quantitative differences in intracellular genetic events; (b) are manifestations of response at the tissue level; or (c) are expressions of host factors operating at the systemic level. Critical to the above is the continuing opportunity for carcinogen-exposed tissue to express any one of its multipotential capabilities. While the factors concerned with the ultimate path are for the most part unknown, clearly dose and its corollary threshold can be shown to be involved.

Evidence Exists to Indicate That There is a Subthreshold Level for Exposure to Carcinogenic Substances

CONTROLLED LABORATORY STUDIES USING CHEMICALLY PURE CARCINOGENS CAN YIELD PREDICTABLE INCIDENCE RATES OF CANCERS IN DEFINED TIME PERIODS. PROGRESSIVE DILUTION OF CARCINOGENIC CONCENTRATION IS POSSIBLE TO THE EXTENT OF OBLITERATING CARCINOGENIC RESPONSE.

The reluctance to accept the existence of thresholds for the action of carcinogenic agents merits investigation. The reasons appear to be scientific, social, economic, cultural, and ethical in varying proportions. What are the unique chemical and physical properties of carcinogenic agents? What is unusual in their anatomic and metabolic fate that could be expected to isolate them from "dose response" and "threshold"? Most important, what might be the characteristics of the development and natural history of the group of diseases we call cancer, which, when viewed as a continuum, might erroneously generate the position that cancer originates in a nonthreshold event and progresses in a nondose-response manner?

The evolution and natural history of a cancer are only partially understood, and empirical observations relating to the biology of clinical cancer, with its inexorable fate, have generated a mystique that the answers to these three questions reside beyond the recognized boundaries of pharmacology, biochemistry, and physiology. Gillette (17,18), Levy (19), and Hefner et al (20), in discussions of pharmacokinetics, clearly provide for the inclusion of chemical carcinogens along with other toxic chemicals.

The complexity of the carcinogenic process is clearly manifest by the following factors which critically affect cancer incidence. First, the true nature of the critical target is not known in any instance of chemical carcinogenesis. Second, with few highly speculative exceptions, no specific biochemical markers can be identified in either tissues, body fluids, or excretory products, indicating the initiation of cancer even in high-risk human

TABLE 1. HUMAN ENVIRONMENTAL CANCER--ETIOLOGY, SITE, AND HISTOLOGY

<u>AGENT</u>	<u>SITE</u>	<u>HISTOLOGY</u>
Cigarette Smoke	Lung	Epidermoid
	Mouth and Throat	Squamous Cell
	Larynx	Squamous Cell
	Esophagus	Squamous Cell
	Bladder	Transitional
BisChE, Chromates, & Aromatic Polycyclic Hydrocarbons	Lung	Squamous Cell
Alcohol (excess use)	Mouth and Throat	Squamous Cell
	Esophagus	Squamous Cell
Ionizing Radiation	Bone	Osteosarcoma
	Skin	Squamous Cell
	Lung	Oat Cell
	Lymphoid Tissue	Leukemia/Lymphosarcoma
Vinyl Chloride	Liver	Angiosarcoma
Thorotrast	Liver	Angiosarcoma
Azo Dye	Liver	Hepatocellular Carcinoma
*Aflatoxin	Liver	Hepatocellular Carcinoma
Mustard Gas	Lung	Oat Cell
Nickel--Nickel Carbonyl	Nasal Sinus	Undifferentiated
	Lung	Squamous Cell
Asbestos	Lung	Bronchiolar
	Pleura/Peritoneum	Mesothelioma
Aromatic Amines	Urinary Bladder	Transitional

*Multispecies, probably including man.

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populations or controlled laboratory studies. Third, initial responses when detectable are nonspecific, and the earliest signs and symptoms are nonpathognomic. Fourth, cancer usually develops only after long-term exposure, a long latent period, and frequently after cessation of exposure. Fifth, factors other than carcinogenic agents per se (age, sex, nutrition, genetic abnormalities, hormonal state, or antecedent or concomitant disease in target organs) may be critical in the timing and site of cancer appearance. Sixth, dose response is quantifiable at the higher levels of exposure, and extrapolation of biological response to a "single molecule" or "zero" is contingent on the mathematical model one wishes to select. The crucial question with its critical reflection on environmental regulation and control is whether there is, in fact, a "no effect" dose of a carcinogen. Yager and Potter (21) recently summarized their views on carcinogenesis by observing that:

Carcinogenesis appears to consist of at least two separable stages, initiation and promotion. Initiation is an irreversible process that can be produced by sufficient treatment with a subcarcinogenic dose of a physical or chemical carcinogen, while promotion is a reversible process requiring repeated application of a promoting agent that ultimately stimulates the initiated cells to give rise to a tumor. . . . Since most, if not all, chemical carcinogens interact with DNA . . . it seems reasonable to assume that alterations in DNA (somatic mutations) may give rise to an initiated cell. However, epigenetic mechanisms cannot be discounted....The mechanisms responsible for promotion are also unknown and, while stimulation of cell replication is required, this does not in itself appear to be sufficient. . . . The effect of promoters on gene expression and other cellular metabolic processes may be indispensable. (emphasis added)

The requirement, as noted by Yager and Potter, for sufficient treatment and the recognition of a subcarcinogenic dose merit special attention. The failure to induce cancer at subcarcinogenic doses has been viewed by some as being compatible with the no-threshold concept. The assumption is made that any level of interaction between carcinogen and nucleotide results in an initiated cell with its potential for transformation and, perhaps ultimately, cancer. Actually as can be seen, even the subcarcinogenic dose requires sufficient treatment with a physical or chemical carcinogen for initiation to occur.

Despite OSHA's contention that scientific principles and opinions of major moment were developed since or not known to OSHA at the time of the promulgation of the 1972 standard, this statement must be regarded as unsupportable rhetoric since there is an absence of any bibliographic references as a basis for this position. A critical review of carcinogenesis literature through 1975 does not reveal a single conceptual advance in mechanisms of carcinogenesis

over the past decade.

While our knowledge of the mechanisms of carcinogenesis is limited, it is possible in dissecting the sequences of carcinogenesis to identify a series of scientific observations clearly consistent with the concept of dose response and threshold in cancer induction.

1. Exposure by animal and man to carcinogens has repeatedly demonstrated the existence of a "subcarcinogenic" or "noncarcinogenic" dose of chemical carcinogens. Independent of whether the basis for noncancer production is (a) inadequate numbers of molecules of the carcinogenic agent, (b) insufficient numbers of target cells, or (c) a host spectrum hostile to cancer development even after target cell transformation is operative, in none of the instances has the threshold for the production of cancer been breached.

2. Molecular biological studies with carcinogens alone, or with cofactors (synergists, promoting agents, or anticarcinogens), have all demonstrated that carcinogenesis is a stepwise process, and the tumor induction and/or progression can be significantly modified. The ability to manipulate the action of chemical carcinogens, as measured by time of appearance of neoplasm or rate of tumor yield, clearly reflects dose response and a threshold for effect.

3. A significant alteration in tumor yield has been demonstrated when a fixed dose of a carcinogen is administered in a single application, as compared to administrations in divided doses. In the latter situation, tumor yield is markedly increased. This observation is compatible with the concept of dose response and threshold, dependent upon whether it is a reflection of (a) size of cell population at risk, (b) the distribution of cells in various stages of cell division, or (c) manifestation of a threshold number of cells that must be exposed to the carcinogen. Rather than as heretofore assumed that threshold alone applies to the quantity of administered carcinogen, it is imperative to recognize that the protocol for application is also of major importance. The interaction of a carcinogen and receptor site does not have as an inevitable corollary the development of cancer.

4. The permanently altered cell concept is the basis for the difficulty that many scientists have in accepting the principle of threshold. Several investigators feel that the permanently altered cells may in fact be quasi-permanently altered; however, there is nothing in the "permanent" concept that is incompatible with threshold and dose response.

5. Enzymatic mechanisms for the repair of DNA have been identified following exposure to carcinogenic stimuli (22). Repair integrity is related to dose of carcinogen and may be the fundamental mechanism for threshold manifestation.

In view of the foregoing, independent of the varied interpretations that one might suggest for the spectrum of response to carcinogenic agents -- from "no effect" to maximum tumor yield -- this spectrum is a reality, and generates fundamental questions concerning the levels of interaction, mechanisms in efficiency of repair, and reversibility of lesions.

There are no consistent relationships between specific carcinogenic agents and the pathological and natural history characteristics of experimental environmental cancer. Certainly at low dose levels in experimental animals papillomas are produced which can and do regress. In man the same appears to be true in the case of keratoacanthoma (self-healing epithelioma). Occupational exposure to certain hydrocarbons results in early lesions which disappear following removal from the hydrocarbon environment. The progression from benign to malignant lesions in experimental models is, at the very least, dose dependent. Progression from benign to malignant in man is a rarity, as emphasized originally by Ewing (23) and by two generations of pathologists since. Reduced to the most simplistic of terms, exposure to a carcinogen can be at a nontumor production level, at a "subthreshold" dose as used in the studies on initiation and promotion, or at a level related to the natural history of the tumor (benign or malignant). One must clearly distinguish between the response at the molecular and the cellular level and overtly at the level of appearance of clinical cancer.

Relevance of Dose Response and Threshold to the Promulgation of a Standard for Occupational Exposure to Asbestos

DOSE RESPONSE WITH ITS COROLLARY THRESHOLD AND RISK/BENEFIT ANALYSIS ARE TWO INDISPENSABLE CONSIDERATIONS IN THE PROMULGATION OF A STANDARD

A synthesis of laboratory and clinical findings, in the case of dose response, and socioeconomic factors, in the case of risk/benefit analyses, provides the substance on which a standard is based. This invokes such issues as "risk/benefit ratios," as recently reviewed by Falk (24). The risk/benefit ratio, at best an elusive attainment, must clearly delineate the "cost to whom" and "benefit to whom." The quantitative contribution to this equation must virtually entirely be derived from data involving man. The concept of "risk" -- the summation of threshold and dose response -- when applied to population, is indispensably, but not exclusively, based on human as well as experimental data. Laboratory contribution to "risk" encompasses the concept of threshold as well as dose response when applied to environmental cancer.

In Summary

The biology of carcinogenesis and the natural history of cancer as investigated in the experimental laboratory yield the following undeniable principles:

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1. Chemical carcinogens are metabolized in accordance with acceptable principles of pharmacology and pharmacokinetics.

2. The effect of chemical carcinogens is dose dependent.

3. Chemical carcinogens can be administered at levels yielding no cancers in test populations, thus confirming the existence of threshold.

References

1. Druckrey, H.: Quantitative aspects in chemical carcinogenesis. In Truhaut, R. (ed.): Potential Carcinogenic Hazards from Drugs. Springer-Verlag, Berlin, 1967.
2. Saffiotti, U.; Montesano, R.; Sellakumar, A. R.; Cefis, F.; and Kaufman, D.: Respiratory tract carcinogenesis in hamsters induced by different numbers of administrations of benzo(a)pyrene and ferric oxide. Cancer Res. 32:1073-1081, 1972.
3. Saffiotti, U.; Montesano, R.; Sellakumar, A.; and Kaufman, D. G.: Respiratory tract carcinogenesis induced in hamsters by different dose levels of benzo(a)pyrene and ferric oxide. J. Natl. Cancer Inst. 49:1199-1204, 1972.
4. Wynder, E. L., and Mabuchi, K.: Etiological and preventive aspects of human cancer. Prev. Med. 1:300-334, 1972.
5. Farber, E.: Criteria for carcinogenesis. In Proceedings of the New York Academy of Sciences Conference on Occupational Carcinogenesis. In Press.
6. Miller, E. C., and Miller, J.A.: Biochemical mechanisms of chemical carcinogenesis. In The Molecular Biology of Cancer. Academic Press, New York, 1974.
7. Boutwell, R.: The function and mechanism of promoters of carcinogenesis. CRC Critical Reviews in Toxicology, Vol. 2, No. 2, 419-443, 1974.
8. Wagoner, J. K.: Occupational Carcinogenesis -- The two hundred years since Percival Pott. In Proceedings of the New York Academy of Sciences Conference on Occupational Carcinogenesis. In Press.
9. Rall, D. P.: Thresholds. Presentation to NIEHS Conference on Problems of Extrapolating the Results of Laboratory Animal Data to Man and of Extrapolating the Results from High Dose Level Experiments to Low Dose Level Exposures, Pinehurst, North Carolina, March 10-12, 1976.
10. Gehring, P. J.; Watanabe, P.G.; Young, J.D.; and LeBeau, J.

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E.: Metabolic thresholds must be considered in assessing the carcinogenic hazard of chemicals. Presentation to SOCHA Seminar on Chemicals and Cancer, Atlanta, Georgia, March 9-10, 1976.

11. Berenblum, I.: Sequential aspects of skin carcinogenesis. In Becker, F. F. (ed.): Cancer I, A Comprehensive Treatise -- Etiology. Plenum Press, New York, 1975, pp. 323-344.
12. Berenblum, I., and Shubik, P.: A new, quantitative approach to the study of the stages of chemical carcinogenesis of mouse skin. Brit. J. Cancer 1:383-391, 1947.
13. Furth, J.: Hormones as etiological agents in neoplasia. In Becker, F. F. (ed.): Cancer I, A Comprehensive Treatise -- Etiology. Plenum Press, New York, 1975, pp. 75-120.
14. Furth, A., and Haro, R. T.: A survey of metal carcinogenesis. In Homburger, F. (ed.): Progress in Experimental Tumor Research, Vol. 12. Karger, Basel, 1969, p. 102.
15. Sunderman, F. W., Jr.: Metal carcinogenesis in experimental animals. Food Cosmet. Toxicol. 9:105-120, 1971.
16. Weisburger, J. H.: Chemical carcinogenesis. In Casarett, L. J., and Doull, J. (eds.): Toxicology. Macmillan, New York, 1975, pp. 354-360.
17. Gillette, J. R.: A perspective on the role of the chemically reactive metabolites of foreign compounds in toxicity -- I. Correlation of changes in covalent binding of reactive metabolites with changes in the incidence and severity of toxicity. Biochem. Pharmacol. 23:2785-2794, 1974A.
18. Gillette, J. R.: A perspective on the role of chemically reactive metabolites of foreign compounds in toxicity -- II. Alterations in the kinetics of covalent binding. Biochem. Pharmacol. 23:2927-2938, 1974B.
19. Levy, G.: Dose-dependent effects in pharmacokinetics. In Tedeschi, D. H., and Tedeschi, R. E. (eds.): Importance of Fundamental Principles in Drug Evaluation. Raven Press, New York, 1968.
20. Hefner, R. E.; Watanabe, P.G.; and Gehring, P. J.: Preliminary studies of the fate of inhaled vinyl chloride in rats. Ann. N.Y. Acad. Sci. 246:135-148, 1975.
21. Yager, J. D., Jr., and Potter, V. R.: A comparison of the effects of 3'-methyl-4-dimethylaminoazobenzene, 2-methyl-4-dimethylaminoazobenzene, and 2-acetylaminofluorene on rat liver DNA stability and new synthesis. Cancer Res. 35:1225-1234, 1975.

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22. Lieberman, M. W., and Forbes, P. D.: Demonstration of DNA repair in normal and neoplastic tissues after treatment with proximate chemical carcinogens and UV radiation. *Nature, New Biol.* 241:199-201, 1973.
23. Ewing, J.: *Neoplastic Diseases -- A Treatise on Tumors.* W.B. Saunders, Philadelphia, 1928, p. 66.
24. Falk, H. L.: Considerations of risks versus benefits. *Environ. Health Perspec.* 11:1-5, 1975.

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