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Concepts of Thresholds in Standards Setting

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Concepts of Thresholds in Standards Setting

An Analysis of the Concept and Its Application to Industrial Air Limits (TLVs)

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The premises on which the concept of thresholds of toxicologic response rest are presented and discussed in light of recent, seemingly conflicting evidence from nontoxicologic quarters. Review of the metabolic factors governing toxicologic response, particularly homeostasis and adaptation, makes a good case for the existence of thresholds for chemical substances generally. Possible exceptions are certain natural body metabolities and long-wave ionizing radiation. Finally, the procedures that have to be taken to modify thresholds for the development of appropriate industrial air standards are presented.

The term "threshold limits" for industrial air originated more than a quarter century ago with the late Lawrence T. Fairhall, PhD, my predecessor and Chief Toxicologist for the US Public Health Service in the Division of Industrial Hygiene. He regarded "threshold limits" as a preferred alternative to "maximal allowable concentrations," which, as a term, was increasingly realized to be inexactly descriptive.

I shall present what I believe formed the basis of the Fairhall threshold limits concept as interpreted in terms of present-day usage, the evidence for the general validity of the concept, and how thresholds are incorporated into industrial air standards.

The discussion that follows is confined to the threshold limits for chemical substances in the air of work places.

The Threshold Concept.—The premise on which the concept of thresholds rests is that, although all chemical substances produce a response (toxicity, irritation, sensitization, narcosis, etc.) at some concentration, if experienced for a sufficient period of time, it is equally true that a concentration exists for all substances from which no response of any kind may be expected no matter how long the exposure, on an eight-hour daily, 40-hour workweek basis. Stated mathematically, the threshold concept is a *nonlinear* relationship between dose and response at the initiation of the response, the lower end of the curve in Fig 1, as opposed to a wholly linear nonthreshold response relationship that passes through the origin. The threshold concept seemed at the time (1948; the first list of air limits was published under the title, "1946 M.A.C. Values") entirely reasonable and sound scientifically. But it

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must be remembered that in the early 1940s no great depth of understanding existed in toxicology, and radiation biology was in its infancy; mechanisms of carcinogenesis consisted of crude hypotheses.

Of late, two factors have done much to throw doubt on the threshold concept; (1) the development of increasingly sensitive indicators of response, and (2) a general concern that highly injurious agents at high dosages may still be injurious at any concentration, however small, either per se or as a factor in diseases of multiple causation. Examples of the former are tests of behavioral responses; of the latter, fluoride, a recognized rat poison, cannot be envisaged by many as safe at any level. Respiratory irritants usually considered systemically benign at low concentration may have the potential of accelerating the induction of lung cancer. Similar findings have been noted by S. Laskin (unpublished data). Both of these factors act to move the threshold (for chemical substances) closer toward the origin. For extremely toxic substances with their small dose, large response characteristics, this serves to make the two thresholds difficult to distinguish, and is undoubtedly a major reason for the continuing controversy.

Doubt of the validity of the threshold concept has arisen chiefly from two areas, radiation biology and carcinogenesis. In an effort to provide a better understanding of the nature of thresholds and possibly resolve the question of their existence or nonexistence, a symposium was held in 1970 on the subject, Thresholds—Do They Exist? Despite discussions on many aspects of thresholds, the question of their existence in carcinogenesis and radiation biology was unresolved; and moreover, the subject basic to the threshold concept, adaptation, was not discussed.

Homeostasis and Adaptation.—In the thinking of the Threshold Limit Value (TLV) Committee, adaptation represents the most cogent and convincing basis for the existence of thresholds, first through homeostatic mechanisms which commonly find their ultimate expression in tolerance and development against noxious stimuli. Stated in more mechanistic terms, toxicity is the net result of two competing reactions, as diagrammed in Fig 2: Reaction 1, the toxic substance acts on the body, represented by the upward rising arrow at left; and reaction 2, the body reacts to the substance, represented by the downward pointing arrow at right. These reactions are the general basis for the attempt of the body to maintain normality (homeostasis) in the face of noxious stimuli, resulting in the utilization of a certain finite amount (dose) of a toxic agent without production of a toxic effect, hence a threshold.

Evidence for these adaptive mechanisms being operative (and hence, the existence of thresholds) is seen among all types of injurious agents and among all types of injurious responses. Possible exceptions are long-wave ionizing radiation and certain natural body metabolites, such as carbon monoxide and carbon dioxide where no amount above normal, however small, is not attended by some decrement in performance (CO) or cost to body function (CO_2). Certainly there is a recognized threshold for nerve stimulation; the induction of narcosis requires a definite concentration of the narcotizing agents. Thresholds for sensory irritation of the eyes, nose, and throat are well-established for many irritants; sensitization even in hypersensitive individuals requires a finite dose well above zero; and inhibition of carcinogenic action is a recognized phenomenon. A striking instance of the body's capacity to adapt to toxic elements has recently been reported.[2]

Tolerance and crosstolerance developed to those elements (arsenic, cadmium, mercury, indium, manganese, lead, silver, and tin) foreign to the mammalian body, whereas, tolerance did not develop to the so-called essential nutrients, copper and selenium. Manganese, an essential nutrient, was the exception.

In short, the entire body physiology is based on stimulating and inhibiting systems. This can only spell one thing, the existence of thresholds, because inhibition is synonymous with dose wastage. Accordingly, with these indisputable facts, the TLV Committee has perpetuated for now more than 25 years the original concept of Dr. Fairhall as a basic premise of the TLVs.

Application of Thresholds in Setting Industrial Air Standards.—In most instances

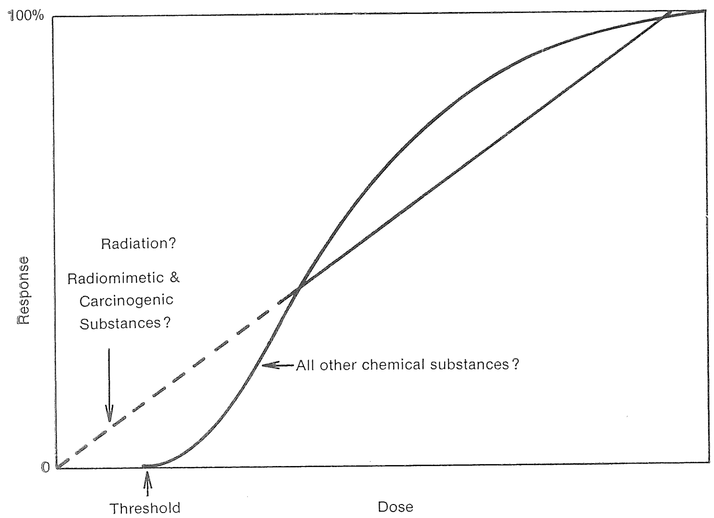
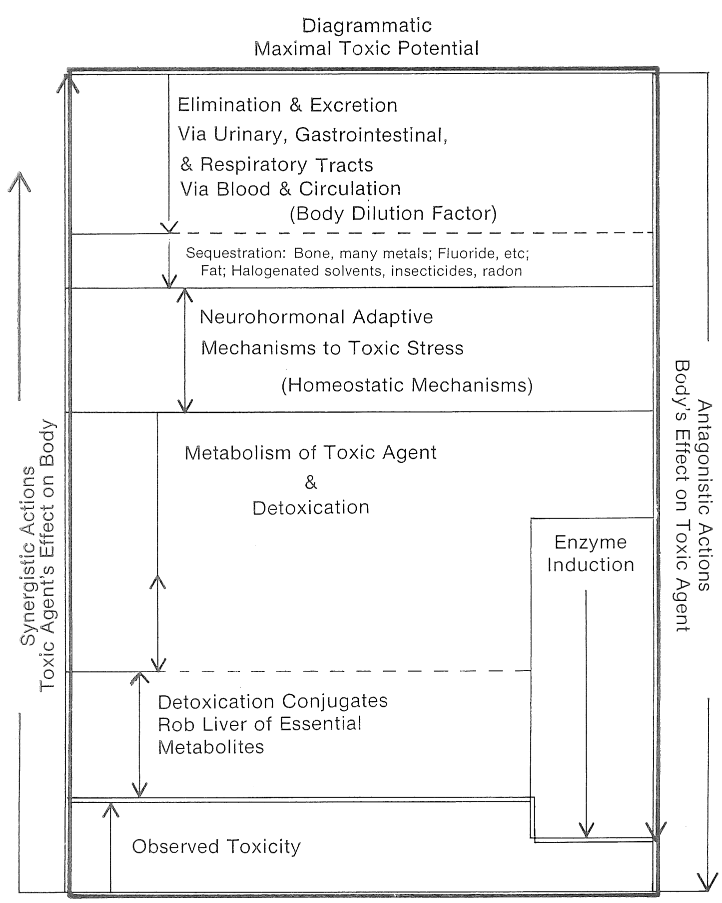


Fig 1.—Thresholds; do they exist?

Fig 2.—Concept of toxicity.



the thresholds cannot be used without modification for establishing the appropriate threshold limit value for the following reasons. First, the thresholds that have been determined for *toxic* injury (more often than not derived from animals) represent an average response value on a genetically more homogeneous species than man; second, the relative sensitivity of the animal species to the toxic agent to that of man is rarely known; third, if the threshold determination has been made on animals, the animals were presumably healthy, generally vigorous young adults, eating a standard diet differing considerably from that of man, and studied under standard conditions of temperature and humidity; all conditions, not met in all industrial situations. It obviously follows, however, that if the threshold determination is made with man as the subject as it is for determination of the thresholds for irritation and odor, then little or no adjustment in the threshold is required. Although here again usually normal, healthy nondrinking and nonsmoking human volunteers are used as subjects; this indicates the need of an added safety factor. Moreover, it is well recognized that industrial workers differ widely, not only in their nutritional needs and habits, from the animals on which the threshold was determined; but also in their personal habits of smoking, drinking, and eating. Among the pneumoconiosis-producing dusts (eg, asbestos and coal), smoking can cause such a profound shift in the threshold of response as to make the threshold of the particular dust irrelevant. Alcohol drinking causes a similar profound threshold shift in susceptibility to hepatotoxic agents (eg, halogenated hydrocarbon solvents). Dietary factors are recognized to influence the threshold of response to probably most of those industrial chemicals that are systemically absorbed (eg, carbon disulfide and vanadium, to name just two on which such evidence exists).[3] Similar findings have been noted by this author (unpublished data).

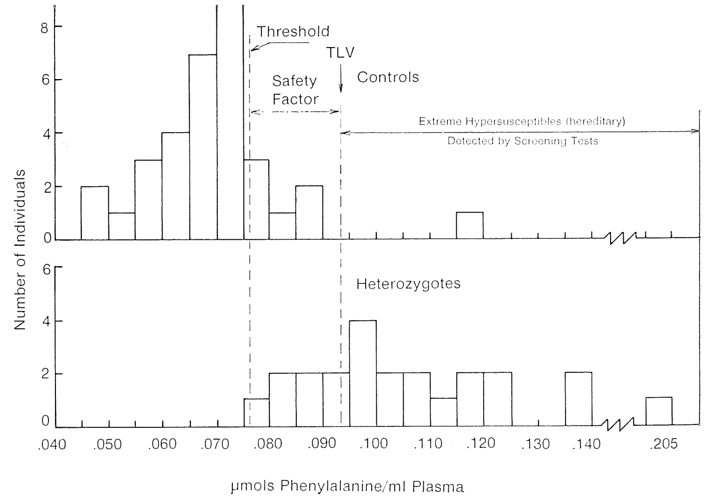


Fig 3.—Distribution of plasma phenylalanine level in 33 controls and 23 heterozygous individuals.

To the above threshold modifiers must be added preexisting systemic diseases in all their forms and degrees. Tuberculosis has been long known to predispose to silicosis; pneumonia, to berylliosis; asthma, and other respiratory tract sensitivities, to industrial asthmagens, such as the industrial isocyanates used in foam plastics; preexisting liver and kidney disease, to their respective toxicants.

Clearly, there are a multiplicity of "personal" factors that require consideration before each response threshold can be incorporated into a threshold limit value. Great in number and magnitude as these personal factors may be, procedures, described below, have been devised which make allowance for these threshold shifts before incorporation into standards. These procedures, however, fail to make allowance for major threshold shifts as a result of genetic abnormalities that express themselves as extreme hypersusceptibilities or hypersensitivities to industrial substances. Individuals with such hereditary traits can, however, be protected from adverse effects of exposures by means other than modification of thresholds as described below.

Procedure for Developing Air Standards With Modified Thresholds.—As indicated above, experimentally determined thresholds are rarely, if ever, used in the final TLV without adjustment. This is true whether the determination was made in animals or man, or derived from industrial experience. The reason is simply that the human species is genetically diffuse and heterogeneous with widely differing capacities to respond to toxic insult; and its extent is seldom known. Accordingly, a factor of safety is invariably added to the determined threshold to provide a cushion of protection for the more susceptible individuals. The magnitude of the safety factor depends upon the seriousness of the response. For example, the safety factor incorporated in the TLV for cyanide, which has lethal potential, is far larger (by at least tenfold) than that for trichloroethylene, in which the initial reaction is narcosis, or for sulfur dioxide, which produces irritation. The safety factor for narcotizing agents such as trichloroethylene is small for the average worker, but may be nonexistent for the beer drinker. For upper respiratory tract irritants, such as sulfur dioxide, the TLV provides no safety factor for the uninitiated, but for the insured worker the TLV provides a factor of at least five.

The safety factors are all judgmental values derived from the long experience of the TLV Committee members; no values predetermined according to category and degree of action are used. Substances with sensitizing potential pose a particularly difficult problem for the choice of a safety factor because of their varying potencies, ranging from the highly potent industrial, organic isocyanates through the intermediate poly-amine-methylene resins to substances of lower potency such as formaldehyde gas. However desirable it might be to incorporate a safety factor sufficiently large to protect the most sensitive individuals, the safety factor cannot be infinitely large but must be within the bounds of analytic and engineering practicality.

Protecting the Genetically Hypersusceptible Worker.—This limitation on the magnitude of the safety factor excludes protection by means of the TLVs those workers, who because of inborn errors in metabolism, are hypersusceptible to certain industrial chemicals. Figure 3 illustrates in terms of the plasma content of the identifying biochemical constituent, phenylalanine, of the hereditary defect phenyl ketonuria, the extreme variation expressed by a genetic deviate, even in the heterozygous form (one allele defective). Greater variation from normal occurs in the homozygous individual in whom both alleles are defective. For these genetically defective individuals for whom the TLVs afford little if any protection against certain groups of industrial chemicals, the procedure is to detect such individuals in the preplacement job examination, in much the same way as proper job placement is accomplished in the ordinary medical management programs by detecting prospective workers who may represent an undesirable health risk, if exposed to certain of the company's products during manufacture. Simple tests are now available[4,5] that may be used to detect individuals hypersusceptible to one or another group of industrial chemicals. The serum antitrypsin deficiency test, for example, is available for the detection of those individuals prone to acquire the familial form of pulmonary emphysema from inhaling respiratory irritants; the glucose-6-phosphate dehydrogenase test for those highly susceptible to hemolytic chemicals; immunologic tests for detecting hypersensitivity to the industrial isocyanates and related sensitizing agents. In this way, the individual is kept from unnecessary exposure to substances to which he is peculiarly susceptible and the TLVs are, in effect, made more inclusive.

A similar article by B. D. Dinman, MD, reaching similar conclusions that thresholds actually exist, has appeared in *Science* (175:495, 1972).

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