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A Toxicologist's View of Threshold Limits

HENRY F. SMYTH, JR., Ph.D.
Mellon Institute, 4400 Fifth Avenue, Pittsburgh, Pennsylvania

Conformance with a threshold limit may lead to more absorption of vapor than does conformance with a numerically identical maximal acceptable concentration, because the former is a time-weighted average concentration, while the latter is a limit below which all measurements should fall. The adverse effects which threshold limits are expected to guard against may not include cortical reflexes. Whether or not such reflex effects are of any importance to the well-being of the industrial worker is not completely clear.

I AM on record[1] as concluding that experimental study of the effects of repeated inhalation by animals has been as sound a basis for setting threshold limits as any other basis which has been used for the values of the American Conference of Governmental Industrial Hygienists (ACGIH). A considerable proportion of the values set on any basis has been modified later as experience has accumulated, and the proportion has been no greater for those based on experimental toxicology than for other bases. It is the collection of experience through industrial hygienists and industrial physicians, with annual reconsideration of values, which has made the threshold limits lists dependable.

However, some details are suggested by toxicological considerations. All that I have to say is related to the paragraph which has been used for several years as part of the foreword to the annual tables of threshold limits issued by the American Conference of Governmental Industrial Hygienists.[2] I quote:

> "Threshold limits should be used as guides in the control of health hazards and should not be regarded as fine lines between safe and dangerous concentrations. They represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day, without adverse effect. The values listed refer to time-weighted average concentrations for a normal workday. The amount by which these figures may be exceeded for short periods without injury to health depends upon a number of factors, such as the nature of the contaminant, whether very high concentrations even for short periods produce acute poisoning, whether the effects are cumulative, the frequency with which high concentrations occur, and the duration of such periods. All must be taken into consideration in arriving at a decision as to whether a hazardous situation exists. Special consideration should be given to the application of these values in the evaluation of the health hazards which may be associated with exposure to combinations of two or more substances."

I shall discuss points suggested by three phrases from the quoted paragraph:

> "The time-weighted average concentration,"
> "The amount by which these figures may be exceeded," and
> "Without adverse effect,"

and follow with a brief summary of our own exploration of the conditioned reflex, which leads out of my discussion of the third phase.

"Time-Weighted Average Concentrations"

The Maximal Acceptable Concentrations (MAC's) of the American Standards Association Z-37 Committee, are authoritative opinions, which are not widely referred to.

In the mid 1950's the Z-37 Committee

This paper was presented at the Tenth Annual Conference of the Pennsylvania Department of Health, University Park, Pennsylvania, on August 23, 1961.

undertook to review and to revise earlier standards which it had issued, and to extend the rather brief list to include additional industrial materials. This large Committee, operating under the awkward rule of consensus, with some members unable to vote until official action of their societies has instructed them, has made less than moderate progress. Since 1957 four standards have been issued, Carbon Tetrachloride,[3] Benzene,[4] Toluene[5] and Xylene.[6] The numerical values of these MAC's are identical with the 1960 Threshold Limits Values of the ACGIH, namely 25, 25, 200, and 200 parts per million by volume (ppm) respectively.[2]

The agreement is much less than one would think from the correspondence of the numerical values. This is an illustration of the weakness of quoting numbers divorced from their context. The threshold limit values refer to time-weighted average concentration for a normal work day, as explained in the paragraph I quoted.

On the other hand, the maximal acceptable concentrations of the Z-37 Committee refer to that concentration which should not be exceeded at any time during a normal work day. MAC's are peak concentrations, not averages. The Carbon Tetrachloride standard reads 25 ppm, "with the understanding that variations should fluctuate around 10 ppm."[3] If this standard is followed literally, the time-weighted average will be in the neighborhood of 10 ppm, only 40% of the threshold limit. The Xylene standard reads 200 ppm, "with the understanding that variations in concentration should fluctuate below this level."[5] Here again, a person working in the MAC conceivably could absorb about half as much as if he were working in the threshold limit concentration.

Thus the numerical identity of the standards of MAC and TL for four vapors, actually mean that the Z-37 Committee concludes that the exposures of workmen should be considerably less than those which the ACGIH Committee concludes are unlikely to cause adverse effect.

The question of which concept is sound, average, or maximum, requires some consideration of the type of injuries against which the standards guard, and of the toxicological mechanisms which cause these injuries. I made a special study of this subject in 1956,[7] and concluded that the injuries guarded against varied widely. I urged that some clue to the type of injury be included in tabulations of standards. Injuries are explicitly described in ASA Standards and in American Industrial Hygiene Association Hygienic Guides, but not in any tabulations I have seen published. Indeed, ASA has set the precedent of naming two standards for inhalation of one substance, to guard against two kinds of injury. In effect, the Xylene Standard[5] says, "To guard against discomfort to workmen, keep concentrations below 50 ppm, and to guard against narcosis and anemia, keep concentrations below 200 ppm."

My 1956 paper[7] concluded that the 238 ACGIH threshold limits and tentative threshold limits then extant guarded against nine different adverse effects.

1. Twelve per cent guarded against acute systemic toxicity. With these, the total amount absorbed in one day usually determines whether injury results, and the time-weighted average concentration is an appropriate guide to safe working conditions. Among the exceptions may be the cyanides, whose detoxication in the body is so rapid that the average during a briefer period, or even the instantaneous peak, is more important.

2. Thirty-three per cent guarded against chronic toxicity. With these, the total amount absorbed during several days or even weeks determines whether injury results, and the time-weighted average concentration is an appropriate guide to safety.

3. Twenty-three per cent guarded against narcosis. The degree of narcosis in a subject varies with the concentration in the fluid bathing certain cells in the central nervous system, and this is quickly responsive to the concentration being inhaled. The time-weighted average concentration is useless to judge safety. The concentration being breathed should never exceed some particular value, regardless of the day's average.

4. Twenty-six per cent guarded against

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uncomfortable but not harmful irritation of the eye, nose, or throat. Clearly, for these, the instantaneous concentration is useful for guarding comfort; the daily average is not useful; and neither has much bearing on safety.

5. Six standards are for asphyxiants, but these threshold limits are standards of good practice, so far below a truly injurious concentration that there is no need to debate which form of standard is the more sound.

6. Three standards guarded against fume fever. The total amount in the lung at any one time is the significant quantity. Lung clearance seems to proceed so quickly that the average concentration in an hour is more significant than that in a day, and a standard based on a maximum in the air seems a sounder index of safety.

7. Two standards guarded against eye pigmentation, more a cosmetic defect than an interference with vision. This condition develops slowly over a very long period, and the time-weighted average seems a sound control.

8. Two standards guarded against allergic sensitization. With these it is possible that no concentration can be set to which some previously sensitized person will not react. Hence, the standards could well be a form of zero, the smallest amount which can be analytically estimated. The nature of the most sensitive practical analytical method should determine which form of standard is the better.

9. One standard guarded against cancer. We know so little about the causation of cancer by most substances that it may be prudent to limit the concentration to a form of zero, the smallest amount which can be analytically estimated. The nature of the most sensitive practical analytical method should determine which form of standard is better.

For fifty per cent of the substances listed in 1956, I found that the ASA Maximal Acceptable Concentration concept of an instantaneous or peak concentration was the sounder protection against adverse effect, while the ACGIH Threshold Limit concept of a maximum time-weighted-average concentration over one working day was adequate protection in forty-six per cent of the standards. Since an excessive time-weighted average is impossible if a well-chosen maximum instantaneous concentration is never exceeded, I see no need for the concept of an average to protect health. However, I recognize that the requirements of many sampling and analtyical methods make it more practical to determine conformance with an average over an appreciable period than to determine conformance with a maximum. Developments in analytical instrumentation are reducing the relative convenience of a standard for average concentrations, and in some instances make the average very cumbersome to determine.

In summary, when Z-37 and ACGIH standards for inhalation are numerically identical, conformance with the Z-37 standard results in absorption of less toxicant than does conformance with the ACGIH standard. For about half the substances listed the ACGIH concept is physiologically wrong. The Z-37 concept, while likewise physiologically wrong for half the substances in the ACGIH list, errs on the side of safety. Health would be more consistently protected if all standards were written in terms of maximum peak concentration during a working day, rather than in terms of the time-weighted average throughout the day.

"The Amount by Which These Figures May Be Exceeded"

The ACGIH Committee contemplates that some operations will be conducted in concentrations above the threshold limit for brief periods, for they devote an entire sentence to suggesting the pertinent factors to be considered. Many industrial hygienists are qualified to interpret these pertinent factors for specific substances. Many others, including even lawyers, may blindly rely upon the threshold limits as averages of exposures to unlimited peak concentrations, and this reliance may result in harm to those exposed. How can the Threshold Limits Committee better guard against such misinterpretation?

It seems to be practically impossible to

conduct some industrial operations without exposing workmen to concentrations above the threshold limit. When the particular substance has a threshold limit which guards against acute toxicity, such as that for arsine, workmen may be seriously injured by relatively brief peak exposures. The operation should be fully automated, or if a workman must be present, adequate personal protection must be provided, maintained, and consistently used. When the substance has a threshold limit which guards against eye, nose, and throat irritation and is far below an injurious concentration, such as acetaldehyde, exposures well above the threshold limit can have no effect except to produce complaints from workmen, and some workmen will perceive no discomfort.

It ought to be possible to agree upon the penalty to health which may be exacted if a threshold limit is exceeded, even continually, and to indicate this in tabulations, as a guide to the solution of problems where operations under the limit are impractical. It is very difficult to find this information in the literature, partly because the bases for threshold limit values have not been explicitly stated by the ACGIH Committee until very recently.

"Without Adverse Effect"

The threshold limits values are stated to be guides to conditions under which it is believed that nearly all workers may be repeatedly exposed without adverse effects, and they are not fine lines between safe and dangerous conditions. Hence most industrial hygienists do not lose faith in the soundness of the values when they learn that every year a few are changed, usually downwards, as a result of industrial experience which comes to the attention of the Committee. However, serious uncertainty was evoked several years ago when it was rumored that values enforced in Russia are in some instances one-tenth or less of the ACGIH values. It was obvious that such a difference could be due only to a difference in concept of what the values should accomplish, because it is thoroughly demonstrated in American industry that guidance by the ACGIH values results in safe working conditions. Nevertheless, lack of information fostered doubts.

In this country the Russian values for concentrations of contaminants in the working environment first became generally known and debated following the XII International Congress on Occupational Health in Helsinki in 1957. The paper by Smeljansky[8] was particularly noteworthy, stating that the concentrations considered safe, and enforced in Russian industry, are lower than in the United States for a number of vapors. The basis for the values was stated to be experimental studies using the Pavlov conditioned reflex technique.

Elkins[9] has recently compared the values used in Russia and in the United States, grouping the substances by nature of action, chemical structure, or physical form. In some categories he finds agreement to be good, in others the Russian values are slightly lower than ours, in still others they are one-tenth or less of ours. He states that where agreement is least, the Russian values are said to be based on conditioned reflex studies with animals.

It is now possible to scrutinize the details of the bases for some of the Russian values, and to infer something of the philosophy under which they have been set, through the translations by B. S. Levine, made available by a Public Health Service Research Grant.[10,11,12,13,14,15,16]

The experimental methods which form the bases for the few values I shall discuss, are described in Book 3, pages 102-128, which is the third (1957) report of the U.S.S.R. Committee on the Determination of Limits of Allowable Concentrations of Atmospheric Pollutants.[12] This Committee deals with atmospheres outside of work places, but the methods it describes seem to be the same as those relied upon for industrial exposures.

Apparently only six experimental methods are employed. Odor and mucous membrane (eyelid) irritation is a considerably refined method for an estimate of the aggressive characteristics of substances. Less accurate estimates of these characteristics have been much relied upon for setting ACGIH threshold limits.[7] The Russian method uses ten human subjects, analytically verified concentrations, and several days working time for

each substance. The Russians are not satisfied with the subjective evaluation of the "objectionable" characteristics of a concentration, as is done in this country. The lowest concentration which can be distinguished from pure air by any one of the ten subjects is used for setting a standard.

The other five methods depend on the thesis that substances have an initial effect on the sympathetic nervous system, producing in the cerebral cortex reflex processes whose actions can be most sensitively detected by phenomena not part of the direct action of the substance.

The pneumographic method depends on the thesis that the body tends to defend itself against objectionable substances, even when they are not consciously perceived. Sympathetic reflexes mediated by the cerebral cortex respond to odor and nasal irritation by causing changes in respiratory rate, volume, and rhythm. By means of a rubber cuff over the thorax, the respiration of a few human subjects is followed during a few minutes inhalation of a concentration of a substance, then of pure air. The lowest concentration which produces a difference in respiration is the threshold of effect to be considered in setting standards, whether or not the subject is conscious that the substance is being inhaled.

The plethysmographic method depends on the same thesis of a defense reflex. The reflex here is a change in blood vessel constriction, detected by changes in the volume of a finger.

The optical chronaxy method depends on the thesis that irritation of the olfactory centers, even when not consciously perceived, cause a sympathetic irritation in optic centers lying nearby in the cerebral cortex. The elapsed time is measured, in thousandths of a second, between electrical stimulation of a human eyelid, and perception of an illusion of luminosity. Irritation from inhaled material reduces this time. Several days are required for training three human subjects, and for tests of chronaxy resulting from five-minute periods of inhalation of various concentrations, to determine the least effective concentration.

The adaptometric test depends on the same thesis of irritation of the optic center, sympathetic to irritation of the olfactory center. It measures the sensitivity to light of trained human subjects, when breathing vapors for fifteen-minute periods after an hour of adaptation of the eye to darkness. The eye is more sensitive when a vapor is being inhaled, whether or not the subject is aware of the inhalation.

The sixth test is the conditioned reflex determination in rats. It is the only one which is designed to produce chronic toxic effects. It seems to depend on the thesis that activation of any sympathetic reflex decreases the ability of the cerebral cortex to carry out conditioned reflex actions. It requires several weeks for training. Rats are trained to reach for food as a reflex response to a bell and to a colored light, but to avoid reaching when a buzzer sounds. By a complex scheduling of these events, one classifies the central nervous activity of the trained rats as to strong and weak, balanced and unbalanced, and uses some of each type in each experimental group. The trained rats are subjected to six months of daily inhalations of a substance. Every day their reflexes are tested, recording the time lapse between the signal and the learned response. At the end of six months one can judge which of the concentrations tested resulted in no change in reflexes, and which produced minimum changes. Some rats are sacrificed at once for tissue study, others are kept for thirty days to judge recovery of their reflex behavior, then tissues are studied. The entire study on one substance requires almost a year.

By relying upon the results of these six tests, the Russians indicate their belief that people should not be subjected to inhalation of a substance at a concentration which results in any detectable physiological response. They may feel that if there is such a response, a lifetime of exposure may result in injury, impairment of function, disability. I have seen no evidence that experience in industry plays any part in setting their standards. Our feeling has been that people should not be subjected to inhalation which they find consciously objectionable, or which is likely to lead to disability or suffering. Since

the concepts of what the standards are expected to guard against are so widely different, it should not be surprising that values for specific substances may be widely different. Experience under standards based upon our concept, during almost twenty years, gives us confidence that we are protecting health.

A review of some of the few available publications of Russian experimental work may be informative. In 1956 Novikov published the experimental work on benzene, upon which the Russian standard seems to be based (Reference 14, p. 185). He considers that the blood-cell changes we see from benzene may be secondary effects of sympathetic disturbances in that part of the central nervous system which regulates the hemopoietic system. He appears to believe that disturbances in the central nervous system which he detects by behavioral changes in conditioned rats, parallel the disturbances which affect the hemopoietic system, and that the only way to prevent blood-cell changes is to keep concentrations too low to affect behavior. At 20 ppm benzene he finds changes in conditioned reflex behavior, most marked in rats of weak, and of unbalanced strong, higher nervous activity. At 4 ppm he finds no effect. Those who have utilized his results seem to feel that there is no difference between human and rat sensitivity to this central nervous system effect, for Elkins[9] reports that the Russian MAC for benzene is 6 ppm. This is to be compared with the ACGIH figure of 25 ppm,[2] based on long industrial experience.[7]

In 1957 Borisova published experimental work on dichloroethane, upon which the Russian standard seems to be based (Reference 15, p. 110). Using humans, he found that the threshold for increased sensitivity to light, respiratory changes, and constriction of capillaries was 1.5 ppm, below the odor threshold, while 1.0 ppm had none of these effects. Elkins[9] reports that the Russian MAC for dichloroethane is 2.5 ppm. This is to be compared with the ACGIH figure of 100 ppm,[2] based on animal experiment, human experience, and analogy with carbon tetrachloride, but not revised to allow for more recent views about the latter substance.[7]

In 1958 Melekhina published the experimental work on formaldehyde, upon which the Russian standard seems to be based (Reference 15, p. 135). Using humans, the time to perceive a sensation of light as a result of electrical stimulation of the eyelid, was reduced by 0.07 ppm formaldehyde, and not affected by 0.03 ppm, while the threshold of odor was 0.06 ppm. Elkins[9] reports that the Russian MAC for formaldehyde is 0.08 ppm. This is to be compared with the ACGIH figure of 5 ppm,[2] based on complaints of workmen in industry.[7]

Our Exploration of Conditioned Reflex

About eighteen months ago, my group set out to explore the utility of the conditioned reflex technique, with much less knowledge of the Russian methods than we now have. A manuscript describing our first results is in press,[17] and a research grant for further work in methodology has been authorized by the National Institutes of Health (OH-16).

There are American reports of one middle-aged woman[18] and two young adult males[19] who worked for several weeks in noticeably high, but unmeasured concentrations of mixed vapors containing the monomethyl ether of ethylene glycol (methyl cellosolve solvent). The three were incapacitated, with headache, drowsiness, forgetfulness, and disorientation, diagnosed as "toxic encephalopathy," and attributed to inhalation of methyl cellosolve. The workers returned to normal after a few weeks of rest in a hospital, without other therapy. A survey of one establishment using the same mixed solvent in the same way, found eight of nineteen workers with non-disabling symptoms suggesting the same injury.[20] Because of these observations, several attempts were made to produce such symptoms in animals.[21,22,23] The symptoms were not found, but no specialized behavioral techniques were used at that time.

This recorded experience suggested methyl cellosolve as a useful substance for exploratory studies of the utility of the conditioned reflex technique. We asked ourselves if such symptoms in over-exposed humans would have been predicted had behavioral studies been understood and applied before methyl

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With no knowledge of the Russian methods, we trained rats in a conditioned avoidance response. At the sound of a buzzer, they climbed a pole, because originally they had received an electric shock while standing on the floor when the buzzer sounded.

Inhalation of methyl cellosolve for four hours daily for several days reduced the number of rats which climbed the pole when they heard the buzzer, but up to a lethal concentration all rats were able to climb when given the electric shock. Inhalation of the vapors reduced the effect of conditioning, but left them able to climb to escape pain. The number of rats affected increased with the days of inhalation, but seemed to reach a maximum by fourteen days. The effect seemed minimal at 125 ppm, five times the ACGIH threshold limit.[2] Some rats, allowed to rest for fourteen days without inhalation, returned to the conditioned behavior without retraining.

Contrasted with the behavior of methyl cellosolve, ethyl alcohol produced no such behavioral change short of a concentration which caused frank depression and ataxia.

This exploratory work, by conditioned reflex methods possibly less sensitive than the Russian methods, does not show an effective concentration lower than the current ACGIH threshold limit, with a vapor to which has been attributed transient human disability arising in the central nervous system.

Summary

Experience in this country with threshold limits based upon toxicological experiment with animals has been good.

Despite the fact that the limits are used only as guides, and are not sharp lines separating safe from injurious atmospheres, more consideration should be given to the condition the numbers are meant to represent. In particular the time-weighted average concentration is physiologically wrong for about half of the limits, and can result in injurious exposures. If the threshold limits referred to a maximum concentration existing at any time during the working day, the substances for which this is physiologically wrong, would be controlled by a conservative standard.

Tables of threshold limits would be more useful if they indicated the injury which could result from a small excess, in order to guide the management of exposures where full conformance is impossible.

The philosophy of the Russian maximum allowable concentrations seems to be that workmen should not be exposed to any concentration which produces a detectable physiological response, with no consideration as to whether such a response is harmful.

An exploratory study of the conditioned reflex behavioral technique indicates that the method may detect effects which other toxicological methods do not suggest.

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Occupational Health Training

The Public Health Service, through its Division of Occupational Health, will conduct a series of four related courses April 23-May 18, 1962, at the Occupational Health Research and Training Facility, Cincinnati, Ohio. *Industrial Hygiene Engineering,* designed for industrial hygienists and engineers in the field of occupational health, and *Industrial Hygiene Chemistry,* for chemists and chemical engineers in this field, are given concurrently, April 23-May 4. Trainees in both courses meet together for the first week for instruction in industrial hygiene and medicine, toxicology, and principles pertaining to evaluation of the environment. Meeting separately the second week, work for the hygienists covers temperature and humidity measurements, illumination, noise measurement and control, and industrial ventilation; for the chemists, laboratory analyses for lead, free silica, and solvents; and spectroscopy, polarography, x-ray diffraction, electron microscopy, and gas chromatography. Much time in both courses is spent in the laboratory.

A related course for the industrial hygienists and engineers, *Heat Stress and Its Control,* May 7-11 (1 week), covers methods of measurement and control of industrial exposure to extreme physiological stress caused by temperature and humidity, with attention also on associated personnel problems. Course time is divided about equally between lectures and laboratory exercises.

A related course for the chemists and chemical engineers is *Solvent Analysis Techniques,* May 7-18 (2 weeks). Lectures and laboratory exercises cover distilling column fractionation and gas chromatographic separation of the components in binary and complex solvent mixtures, in the principles and application of simple physical and chemical tests, and in ultraviolet and infrared spectrophotometric procedures for identification and determination of separate components.

Full descriptions of these courses are given in the *Training Program Bulletin* which is available on request. Trainees may register in single or related courses. Applications or requests for information should be addressed to the Chief, Training Program, Robert A. Taft Sanitary Engineering Center, 4676 Columbia Parkway, Cincinnati 26, Ohio, or to a PHS Regional Office.