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EXPOSURE LIMITS: HISTORY, PHILOSOPHY, FUTURE DEVELOPMENTS

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INTRODUCTION

EXPOSURE limits of occupational toxicants constitute one of the most powerful instruments for control of occupational disease. Without such limits occupational health protective activities would be reduced to a state of uncertainty and chaos. Although any expert in the field is well aware of the fact that exposure limits are by no means perfect, people feel comfortable with the admittedly incalculable amount of imperfection because they are convinced that the harm resulting from that little inadequacy is small if not insignificant, or is at least tolerable, and that it may be easily and speedily corrected in the event of concern or emergency. The historical start of the business was rather simple, and the benefit achieved was obvious; this original ease of success has tended to lull those responsible into a state of security.

However, if we look back and make comparisons between then and now, we must realize that things have become more and more complicated. Not only is chemical and technological ingenuity, with its exponentially increasing innovation and introduction of new chemicals, overpowering our capacity to adequately evaluate the safety of all these novel compounds, but also the progress in modern toxicology and molecular biology is shaking our trust in the validity of our traditional concepts of safety and in the classical armamentarium of setting exposure standards. My discourse will aim at a critical appraisal of the present situation, rather than reporting just the credits of the past system, and will particularly focus on the perspectives as viewed from the standpoint of a toxicologist.

HISTORY

There may have been suggestions or occasional announcements of acceptable concentration limits for single compounds at a very early stage from different parts of the world, which may be claimed to represent the first occupational exposure limit(s).

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The first systematic approach, however, originated in Germany where a rapidly growing and prospering industry was active as early as the middle of the last century in the technical production of new synthetic dye-stuffs and other organic chemicals. Three of the major companies established emergency medical care units which were also charged with developing preventive measures against acute and chronic occupational poisonings. These activities were soon reinforced by more scientific approaches in some universities. K. B. Lehmann is credited with having established the first standards for some organic solvents and irritant gases, such as sulphur dioxide, the halogens and acid fumes. He introduced systematic chemical analysis into some working areas and compared the prevalent concentrations with the workers' health status. In addition, he performed controlled short-term exposure experiments with laboratory animals and volunteers. To quote one example:

Lehmann ordered his laboratory servant to stay enclosed for one hour in the housekeeper's laundry room, where he was to pour out a calculated amount of the volatile test fluid, to move a sheet of newspaper vigorously until complete vaporization and distribution were achieved, and to handle an analytical sampling device for determination of the concentration in the room air. The experimenter checked the condition of the test person by observing him occasionally from outside through a window. If the servant left the premises with significant signs of survival, the concentration was rated 'just tolerable for short-term exposure'.

The primitiveness of this test procedure should not detract from the principal achievement of K. B. Lehmann's work: quantitative evaluations based on chemical analysis.

The first report of a standard based on a quantitative approach appeared in 1886 (LEHMANN, 1886), initiating a long series over more than four decades. Many of the proposed limit values were included in HENDERSON and HAGGARD's famous monograph (1927, 1943) and later on expanded by FLURY and ZERNIK (1931); English and Russian translations of this compilation of early German work were made available.

In the United States, another system of standard setting was introduced in the early forties, the so-called Maximum Allowable Concentrations, and later on the Threshold Limit Values. This list of exposure limits grew rapidly and now is widely used in the English speaking world and in many other countries as well. The list has attained, in quantitative terms, a leading position since the fifties. In Germany, the TLV-List was copied until 1968; after that Germany initiated its own list. The U.S.S.R. also has developed its own list of standards (IZMEROV, 1974), which is based on completely different concepts. Other socialist countries oscillate considerably in their national lists between values derived from East and West. Holland and Sweden also began recently with elaborating national lists of their own (ZIELHUIS and NOTTEN, 1979; HOLMBERG and WESTLIN, 1979) with remarkable scientific validation and social philosophies.

Efforts towards an international unification of exposure limits have a long history. They were promulgated by scientists as well as by international organizations such as WHO (1980), ILO (1980), EEC (BERLIN, 1981) and others (VIGLIANI, 1977). All have been unsuccessful up to now for a variety of reasons, the major ones being differences in scientific concepts, and varying industrial conditions and requirements. Also, the comparability and reliability from experimental and medical experience differ widely from country to country.

SCIENTIFIC BASIS

It has long been known that toxic effects are dependent on dose and that with continuous decrease of dose a point will be reached at which no toxic effect will be detectable or will occur. The first unequivocal statement of this pragmatism, which is based on everyday empirical experience, can be found in PARACELSUS' famous work (1538) where he states that 'anything may be poison[ous] and nothing may be without poison[ing property]; it is the dose which makes a thing non-poisonous'.

The first experimentally based report on the existence of a dose which does not cause harm, as proof of non-toxic exposure levels, came rather late. It dealt with experiments to establish dose–response relationships with inhalation of hydrocyanic acid (FLURY and HEUBNER, 1919). It was found that a distinct toxic effect, in this case death, will not occur below a defined exposure concentration, no matter how long the exposure time may be. This result differed decisively from what had been found with phosgene gas, a deep lung irritant, which always produced the same amount of damage (E) (pulmonary edema), irrespective of the proportions of exposure concentration (c) and time (t), provided that the product of both factors remains constant (FLURY, 1921, Figs 1 and 2). Flury established from these results the following rule:

$$c \times t = E = \text{const.}$$

The typical hyperbolic curve characteristic of this equation implies that each fraction of the exposure effect adds to all the others; in other words, nothing is lost in the total balance and no threshold dose exists.

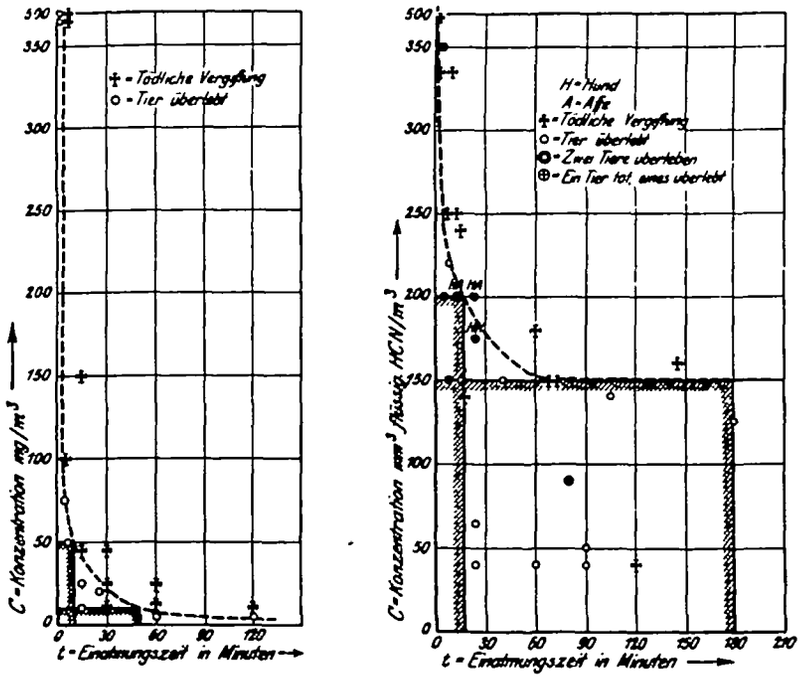

FIG. 1. Death or survival of experimental animals after exposure to phosgene (left) and hydrocyanic acid (right) at varying concentrations and time periods. Originals from FLURY, (1921).

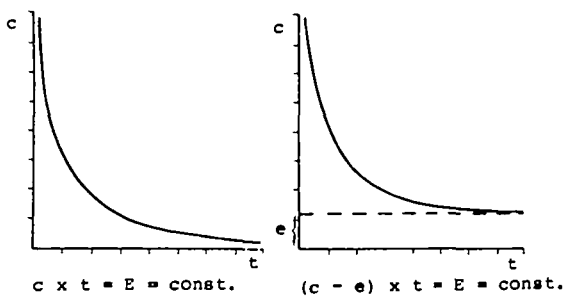

FIG. 2. Concentration × time curves as derived from Fig. 1, indicative of the existence or non-existence of a threshold. For explanation, see text.

In the case of hydrocyanic acid, however, a threshold can definitely be set for the criterion death or survival, and certainly for non-lethal as well as for minimal toxic reactions. Flury again phrased this in mathematical terms by subtracting a constant elimination factor (e) from the exposure concentration:

$$(c-e)\times t = E = \text{const.}$$

This equation (FLURY, 1921) provides a basis for setting threshold values and tolerance levels for unlimited exposure periods, the justification for the latter assumption being the asymptotic approach of the $c \times t$ curve to the abscissa e (constant value $c = e$). The reason for the constant elimination rate in the case of hydrocyanic acid was not clearly recognized until years later: it is the enzymatic detoxification of the cyanide ion by the binding to sulphur under the formation of thiocyanate (LANG, 1933). This reaction is governed by the limited availability of activated sulphur, which constitutes the rate limiting step, and makes the reaction proceed with zero order over a wide range of concentrations.

An exposure limit must be lower than an experimentally determined threshold of effect, because of the following factors:

(a) No experimental design can thoroughly eliminate some degree of imprecision of data, which can only be defined in biostatistic terms of variation; in other words, the $c \times t$ curve is a band rather than a precise line.

(b) These dose–effect relationships can, as a rule, only be determined in experimental animals which might be more or less sensitive than humans.

(c) Other factors which increase sensitivity may be taken into account, such as the interference of states of disease, concomitant drug intake, combined exposures to occupational toxicants, genetically determined hypersensitivities, etc.

The standard setting is bound to some very important prerequisites, i.e.

(1) The relevant toxic effect must be reversible; even fractional irreversibility, with accumulation of damage with time, cannot be tolerated.

(2) The elimination (reversion) characteristic of an induced alteration which tends to damage health with increasing dose must be zero order, which means the reaction is independent of concentration (or amount of damage), so that no fraction of the alteration from one exposure period (e.g. work shift) is carried into the next one.

(3) Alternatively, the alteration must reach, in the course of a work shift or one work week, a steady-state level which is regarded as tolerable ('safe').

(4) To fulfill conditions (2) and (3), sufficient knowledge about the mechanism of induction and reversion of the relevant alteration must be gained.

Once we acknowledge that adherence to these stringent criteria is obligatory for the setting of scientifically valid exposure standards, we soon realize that specific knowledge is lacking for most of the existing chemicals and values. The business is rather characterized by a variety of compromises which have to be made or already have been.

Compromise I: Relevance of effect(s) for workers' health

As a rule, an exposure limit is based on just one toxicological effect which can be determined precisely. It should, of course, be the most sensitive effect amongst a variety of induced alterations. The assessment of the significance of such a change from normal in terms of impairment of health is dependent on the definition of health. We do not have, or we avoid application of, global definitions of health. Rather, our societies rely on case by case decisions of the medical profession. These take into account the individual's constitution, living conditions of all sorts, competing environmental influences such as climate, state of present knowledge, national traditions of medical and social disciplines, and many other things.

It is obvious from this that one has to accept compromises in evaluating the medical significance of measurable alterations in the individual worker's body functions. One important issue in this respect is the inter-individual variation of susceptibility. It is common practice to take into account here those factors which can be predetermined or predicted, either by medical investigation of any kind in an individual, and/or by historical experience or knowledge of the mechanism of action of a given chemical. This philosophy accepts residual risks from the unknown. The validity of this concept depends, of course, on the intensity of efforts to elucidate the mode of toxic actions. Here we encounter the ever-moving frontiers of science.

The only reasonable way out of this dilemma is to accept the best possible compromise, to be aware of the inherent inadequacies, and to be willing to continually revise the general criteria for standard settings as well as the standard of a given compound. However, the dangers to future developments from this 'pragmatic' concept are obvious and will be dealt with later on.

Compromise II: Lack of knowledge of basic data

The basic requirements for setting exposure limits as outlined above constitute an ideal. If we look into the present list of some 500 chemicals with exposure limits, we realize that the prerequisites are really fulfilled in only a few cases, like that of hydrocyanic acid. In particular, difficulties may arise in deciding whether or not a toxic effect is completely reversible. Complex formation of carbon monoxide with hemoglobin, and of cyanide with cytochrome oxidase, are clearly reversible processes which leave the inactivated biochemical structures completely intact. But what about the action of typical irritants, such as the halogens or formaldehyde, which induce cell damage and necrosis of individual cells even in the range of concentrations which nowadays is accepted as within exposure limits? Certainly the structure and function of

the damaged mucous membranes rapidly are restored by new epithelial cells. But what is the significance of the induced cell proliferation? Which proliferation rate can be regarded as tolerable? Cell proliferation can, for instance, act as a promoting factor in chemical carcinogenesis. How far can we diverge from normal proliferation rates? This example, which is representative of many others, illustrates the predicament in trying to meet today's stringent scientific criteria.

Again, compromises are unavoidable. A review of the existing documents which were produced to explain or justify the setting of occupational exposure standards reveals that those who performed this work in the past argued rather generously, to say the least. With many limit values, just a single short-term animal exposure experiment, with an insufficient number of test animals and a superficial counting of deaths and survivals with no pathological investigation at all, provided the only basis for a standard. In other cases, a poorly designed field study without representative chemical determination of prevailing air concentrations was available. Only too often, the documentations close with phrases like 'in the Committee's view, a threshold limit value of such and such is regarded to protect sufficiently from harmful effects'.

A careful review of some 150 occupational chemicals in the German List of MAK-Values revealed that less than 10% of the respective exposure limits is based on appropriate and sufficient animal tests and/or field experience (HENSCHLER, 1972–1983). The other values must be taken as 'preliminary', and more studies of a well defined nature have to be carried out before these standards may serve as acceptable measures of protection of workers' health.

In a 'documentation', the reliability of an exposure limit should always be stated clearly; detailed information of the scientific data used to set the value at a certain level, and not at a fraction or a multiple thereof, should be provided.

In general, one should always keep in mind that all lists of exposure standards are extremely uneven regarding the validity of the single limit values, and that their compilation is the result of a broad compromise.

Compromise III: Lack of long-term experience

Occupational exposure limits differ from other types of tolerance levels, e.g. for food additives, pesticide residues, etc., in that no fixed 'safety margins' between experimental no-effect levels and standards are applied. Rather, full utilization is made of what is believed to be the whole zone of no-effects, provided that the most sensitive criteria for detecting harmful effects are used. In principle, the basic $c \times t$-rules are applicable for both short-term and long-term exposure. As mentioned above, many existing exposure limits are only derived from acute or subchronic exposure experiments or field studies. Extrapolation from short-term to long-term exposure is justified for the overwhelming majority of conventional toxic effects. However, there are exceptions with some particularly severe toxic manifestations, e.g. neurotoxic and carcinogenic effects which appear only after considerable latency periods. Also, susceptibility to a given exposure may increase with age, therefore the practice of using young experimental animals for short-term tests may result in missed toxic effects.

The same problem is encountered with experience from human exposure in the workplace. Many reports on field studies comprise only limited, or sometimes intermittent, exposure periods, whereas the exposure standard should cover con-

tinuous exposure over a worker's active employment for four to five decades. Here again, compromises have to be made in the procedure of standard setting.

Compromise IV: Lack of human data

The history of occupational exposure limits started with experiences from humans. Later on, animal experiments were introduced, in part for more profound research into the mechanism of toxic effects and in part for the purpose of prediction of toxicity and no-effect levels of new compounds in humans. Occupational health experience has for long enjoyed priority over animal experiments. The justification for this has mainly been species differences, and unrealistic exposure conditions in animal studies.

This has changed dramatically in the past few years, for two reasons:

(1) The ever-increasing discovery and introduction of novel chemicals to the workplace, combined with the sensitized health awareness of the population, have induced new legislation which makes toxicological pre-testing compulsory.

(2) Continuing improvements in protective measures and changes in technical production processes have diminished exposures decisively, both in prevailing concentrations of airborne occupational toxicants and in the number of persons exposed. Therefore, the opportunities for human studies to determine no-effect levels have been diminished.

As a consequence, predictive animal tests are now given priority over experience with humans in the procedure of setting exposure limits. Nevertheless, the limitations of animal experiments should be kept in mind. Their predictive value may be hampered by species differences in the pharmacokinetic and metabolic handling of the test compounds, in the sensitivities of the respective target tissues and receptors, in decisive divergencies in the physiological systems and their reactivities, such as thermoregulation, cardiovascular adaptation reactions, and many others, and particularly in the generally drastic dissimiliarity in the disposition of inhaled xenobiotics in the respiratory tract of the preponderantly used small rodent species with their highly efficient protective nasal filter. However, the more we learn about species differences from thorough testing of an increasing number of chemicals, the better our extrapolation from animals to humans will be, and the more reliable our predictions will become. The compromise to be made will never be substituted by perfect derivations, but its role will certainly become less important with scientific progress in the field of toxicological methodologies.

Compromise V: Time weighted average vs peak exposure

There are only a few workplaces where a more or less stable concentration is encountered. Fluctuations in the course of a work shift are the rule rather than the exception, yet exposure standards have been nominated for 8-h averages only. The reasons for this have been: (a) limitations of analytical techniques which until recently had to make use of sampling over extended periods; (b) reports on experiences from human exposure have only referred to analytically determined averages; (c) animal experiments with inhalation exposure, as well as laboratory exposure tests with volunteers, have almost exclusively applied constant concentrations. However, the need for limiting peak exposures is obvious from simple practical experience and consideration.

In some countries, proposals or regulations for this purpose have been put forward, one of these being the 'ceiling value' concept. Another concept suggests varying the allowable factors of excursions from the time weighted average with the order of magnitude of these, and still another recommends uniformly using fixed factors for all compounds and values. We found all these approaches unsatisfactory. On one hand, the analyst is left with the uncertainty of how to define, determine and evaluate a 'ceiling' or a factor. On the other, simple toxicologic and pharmacokinetic considerations reveal that with some compounds one need not regulate peak exposures at all, whilst with others the safety evaluation is almost exclusively based on a 'peak' concentration. We have therefore developed a system which tries to integrate the basic principles of dose–response relationships, pharmacokinetics, types of toxic effects and mechanisms, and applicability and statistical validation of analytical determinations. A unification of these variables can be achieved only by accepting a series of compromises. Details have been published elsewhere (HENSCHLER *et al.*, 1979).

The system again is based on the $c \times t$-concept, and subdivides the great variety of possible toxic reactions into four fundamental types:

(1) Strong local irritants, eliciting immediate response, where c equals constant so that the time factor may be neglected;

(2) Systemic activity, with a known elimination rate e;

(3) Mixed type, where effects start at lower concentrations with type (2) but switch with increasing concentration to type (1), requiring different handling;

(4) Irreversible effects, as with carcinogens where $c \times t = \text{constant}$.

From these basic types of activities, five categories have been established for admissible excursions from the 8-h time-weighted average in terms of factor, period of time, and frequency per shift (see Table 1). Categories I, IV and V are self-explanatory. Categories II and III comprise the majority of occupational toxicants with systemic activity. The determining factor for the classification is the elimination half-life of the compound or of its active metabolites. The magnitude of allowable excursion factors and times is set by compromises between pharmacokinetic principles and analytical applicability. Pilot studies with some model compounds revealed satisfactory compliance with the principles of best prevention of toxic effects. Details will be

TABLE 1. SYSTEM OF LIMITATION OF EXCURSIONS FROM THE 8 h TIME-WEIGHTED AVERAGE OF EXPOSURE LIMIT VALUES (abs. = absolute, av. = average)

Category	Type	Deviation factor	Deviation time	Frequency per shift
I	Local irritants	2	5 min, abs.	8
II	Systemic activity, latency of response > 2 h			
	II, 1 Half-life > 2 h	2	30 min, av.	4
	II, 2 Half-life 2 h–8 h	5	30 min, av.	2
III	Systemic activity, latency of response > 2 h, half-life > 8 h (highly cumulative)	10	30 min, av.	1
IV	Very weak toxic potential (expos. lim. > 500 ppm)	2	60 min, abs.	3
V	Strong odorants	2	10 min, abs.	4

published elsewhere (BOLT and DROPE, 1983). We hope that this sytem will contribute to a solution of this important practical problem.

Compromise VI: Mixed exposures not covered

One of the most conflicting fields in the business of setting exposure limits is the evaluation of exposure to more than one chemical. Up to now, fixed standards exist for single compounds only.

Recommendations for handling exposure limits for mixtures have been put forward, the simplest one being to add up the fractions of the proportions of the single components. The prerequisite for applying this arithmetic approach is that *all* components of the mixture elicit identical toxic effects and that their synergistic activities are of a simple additive nature. If one looks more carefully into the practically relevant mixed exposures, it becomes evident that these conditions are never fulfilled.

Many occupational toxicants pass through the organism concurrently and yet act independently from each other. There are, however, exceptions with spectacular magnification of the activity of one component or the other or of both in the case of interactions at the target tissue or at the sites of biotransformation. Dramatic increase of toxicity may result if a normally very potent pathway of detoxication is blocked by otherwise ineffective concentrations of a concomitant toxicant, as with some organophosphorus compounds (DU BOIS, 1972). It is this condition which deserves our utmost attention in order to prevent real harm. The likelihood prevails that this type of disastrous interaction will be disclosed by systematic studies of the mechanisms of action, rather than by chance.

Considering this, one can only recommend that case by case evaluations of mixed exposures be performed by the best scientific expertise. This compromise will certainly not be favoured by regulatory agencies, but it will foster relevant scientific work to build the foundations for a more satisfactory escape from a real dilemma.

Compromise VII: No exposure limits for carcinogens

The early lists of exposure limits included proven occupational carcinogens, with definite values regarded as 'safe'. These were based on some (very limited) human experience and on the speculation that thresholds will also exist for carcinogens. However, the past two decades have revealed that one encounters increasing difficulties if one tries to determine a no-effect level of a carcinogen. Four facts contradict this naive approach:

(1) The few existing really quantitative lifetime studies with chemical carcinogens in intact animals have all shown that the $c \times t = \text{constant}$ rule is strictly obeyed, which means that no ineffective dose can be defined. Certainly, if one continues to reduce the dose in a serial long-term study, one will find, for a given number of animals, a dose which produces no substance-related tumours. But if one increases the number of animals manifoldly, some tumours will again be found. Also, the argument that with some very low dose level, tumour manifestation will fall beyond the life span does not prove the opposite: stochastic rules postulate from the shape of the incidence-curve that there will always be a definable residual probability of tumour formation. At present, we must admit that we cannot derive definite no-effect doses of carcinogens from whole animal studies.

(2) Molecular biology teaches us that the primary genotoxic event, the covalent binding of ultimate electrophilic carcinogens to DNA, follows first order kinetics, as do the antagonistic reactions such as inactivation of electrophiles by tissue nucleophiles and enzymatically controlled repair processes. In other words, there will always be a fraction of noxious material which causes damage to DNA, and a fraction of damage will persist so that no threshold of genotoxic effect can be derived.

(3) Epidemiology cannot provide instruments to prove a zero tumour risk. It can only state that with a given exposure and time and in a given number of individuals there is no statistically significant increase in tumour formation. But this does not exclude the induction of tumour formation in the population under study; it may well be that the otherwise hidden increase will manifest itself in a statistically significant manner if more exposed individuals are available for such a study. In brief: epidemiology can neither provide evidence for threshold values of carcinogens nor render figures which would allow for setting a certain exposure limit for a single carcinogen.

(4) In recent studies, toxicologists have attempted to differentiate between genotoxic and non-genetic, or epigenetic, mechanisms of chemical carcinogenesis, with the idea that 'epigenetics' might follow the classic toxicologic rules of dose–response relationship and thus allow the identification of a threshold. The weakness of this concept lies in the definition: it is positive in the case of genotoxics, but negative for 'epigenetics'. According to the basic theories of natural science, it is easy to prove the positive case (e.g., covalent DNA-binding from genotoxic electrophiles), but it is impossible to prove definitely the negative case. The attempt to exclude a genotoxic interaction somewhat resembles the paradox of Zeno, where Zeno tried to overcome, in a step by step procedure, the ever-decreasing but never completely disappearing degree of uncertainty.

In practical terms: presently we understand quite well the mechanisms underlying the genotoxic alteration which is believed to be the initiation step of chemical carcinogenesis, but we know very little or nothing about the mechanisms of 'epigenetics', which are frequently identified with tumour promoters. As long as we know of very potent promoters which exceed well known initiators in potency and as long as we do not understand the dose–response relationships of 'epigenetics', we are not justified in differentiating between these two categories for the purpose of setting standards.

In the light of this state of knowledge, efforts to create a 'practical' threshold as opposed to 'theoretical' concepts are devoid of credit. In fact, the scientific community, notwithstanding its joint efforts to rate carcinogens according to their potency and to elucidate the dose–response relationships in the very low dose range, has abstained from acknowledging tolerance levels regarded as 'safe' for proven carcinogens. Irrespective of the scientific position, regulatory bodies are free to set their administrative levels in order to control exposure from carcinogens. For instance, in my country a different category of standards for occupational carcinogens has been introduced as 'technical guidance concentrations' (TRK) which are based on the political, socio-economic and technical decision-making processes, with the only scientific element in the argumentation being that adherence to the respective level might reduce risk as compared with a state of no regulation at all. But this type of

standard should by no means be confused with the conventional exposure limit (TLV, MAK etc.), which is based on a well definable philosophy of safety evaluation.

As long as no better means of quantifying risks from occupational carcinogens are at hand, we will have to live with this compromise; this has important implications for the measures to control exposures under practical work place conditions. Efforts to extend the compromise to integrating both categories into a single, undifferentiated exposure limit, as was used until a few decades ago, would ignore scientific progress and lack scientific and ethical credibility.

ASPECTS OF FUTURE DEVELOPMENT

As stated at the outset, the system of exposure limits has had its probation. At present, no preferable alternative is at hand, although the system obviously has inherent inadequacies with which we have to live and with which we will probably have to live for some part of the foreseeable future. The main reason for the existing insufficiencies is obviously the lack of systematic inclusion, testing and evaluation of existing occupational toxicants. Once the shortcomings have been recognized, they could be overcome by serious efforts to increase research activities, both at the quantitative and the qualitative level.

Some tendencies have developed in recent years, however, that cast a shadow on this positive outlook. If we look back on changes in exposure limits in the course of the past 10–15 yr, we see that the existing limits usually were lowered, often in a sequence of steps. With some compounds, these decreases have been dramatic; increases in figures are extremely rare exceptions. And if we review those values which have remained constant over more than 10–20 yr, it becomes clear that in most cases nobody has reassessed them. Therefore, lack of change is by no means indicative of a satisfactory probation.

The general public has become more and more aware of these facts and developments and an atmosphere of apprehension has arisen. Suspicion is supported by the tremendous improvement of analytical methodologies at the chemical, biochemical and biophysical level. The new techniques detect, with ever increasing sensitivity and specificity, even the slightest changes of biological functions from exposure to chemicals, but they cannot integrate them into real diagnostic procedures for separating states of disease from health. The sensitized layman is tempted to demand protection from any deviation from the normal. As a consequence, pressure is put on administrators and politicians to influence the procedure of setting exposure levels. One approach in this direction is not to keep exposure levels as high as tolerable, but as low as technically and economically possible; this is equivalent to the funeral of conventional standards.

There always has been unanimous agreement in the scientific community that the creation and evaluation of data relative to effects and thresholds are entirely scientific issues which have nothing to do with political or socio-economic parameters nor with technical feasibility. What differs from country to country is the degree to which scientists are ready to participate in the political decision process. Nourished by the above-mentioned inadequacies of the present system of standard setting and being further pressurized by the rapidly increasing numbers of newly introduced substances, a tendency for a steady strengthening of social and political influences can be foreseen.

Up to now, we have been successful in trying to keep the business clean. Whether and how long this position can be held will depend mostly upon the speed and extent with which scientific progress can fill the existing gaps and also on the natures of the persons engaged in these matters: persons who have to survive in a classical conflict situation between *Homo sapiens* and *Homo politicus*. Are our forces facing the compromise of unification?

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DISCUSSION

J. T. SANDERSON, President BOHS in the Chair (Esso Europe Inc.): In the U.K. we have established a tripartite system to cope with the problem of setting exposure limits with an implied level of acceptable residual risk associated with their implementation. However, it seems to me that in West Germany you have no such system for providing the 'social' input and I would be interested to hear from you how the matter is handled by your Commission.

Professor HENSCHLER: The Commission in Germany restricts itself to entirely scientific (medical, ethical) elements of evaluation and validation. Social, economic and technical parameters are expressly excluded, as is emphasized in the preface of the MAK-List. Therefore, MAKs represent medical standards, aiming at exclusion of impairment of health, rather than at compromise values at the socio-economic level. The Minister of Labour may, when publishing the annually revised List of MAK-values to make it compulsory for the inspectors, change this or that level in taking into account socio-economic elements; but up to now he has not.

The situation is different with occupational carcinogens where the Minister, by a 'tripartite' committee called AgA, sets standard levels which imply a residual risk. The MAK-Commission does not set tolerable levels for, but just identifies chemicals as, carcinogens.

R. G. SMITH (A.I.H.A.): How do you view the use of biological standards relative to air standards?

Professor HENSCHLER: Biological standards (BAT-values in the German List) are regarded as a useful additional instrument for workers' health protection, not as substitutes for air standards (MAK). They allow monitoring the uptake of toxicants and the correlation with toxic effects in an individual, and thus the identification and protection of individuals at greater than average risk. There are some disadvantages, e.g. that these biological standards cannot be used for evaluating new compounds or industrial processes, that they can only be established for a limited fraction of industrial chemicals (excluded are e.g. local irritants and

compounds with unsuitable pharmacokinetic properties such as the high vapour pressure fluorocarbons) and that ethical reasons and methodological risks, such as are incurred with blood sampling, hamper practicability. At present, no definite regulations as to the use of biological standards exists in Germany.

J. INGLE (M.O.D., Navy): Would you consider exposure limits for sensitizing agents to be a special case requiring special consideration?

Professor HENSCHLER: Yes, we do. Sensitizing properties of chemicals are characterized in our List by a special notification 'S'. This stands for a capacity to sensitize a considerable proportion of those at exposure in the working area. It does not indicate the setting of a specifically low level which could prevent or minimize sensitization, because relevant information about dose-response relationships in sensitizing effects is lacking. It must be admitted that rating compounds for 'S' has not been systematically accomplished up to now and not according to specified criteria but just as a result of practical experience.

S. J. SILK (H.S.E.): How are standards used in Germany for compliance with relevant legislation?

Professor HENSCHLER: I am not the right person to answer this question because we have a subdivision of activities between our Commission, which establishes standards, and the AgA, which establishes technical rules for practical application of the standards. This formulation of rules, and legislative enforcement, is an ongoing business. In general, inspectors are bound, in their orders and decisions, by existing standards and rules. Compliance in terms of complete control will probably, as in most countries, depend on available analytical methods and manpower, both of which are steadily increasing in Germany.

F. S. GILL (University of Birmingham): I would like to raise the question of setting a standard for an occupational carcinogen such as asbestos, where there is no safe level. It is necessary, nevertheless, to provide some guidance for the user. Do you support the notion that a standard should be set based upon some calculated degree of risk for that carcinogen that is comparable with some other hazard whose risk is known and has been generally accepted?

Professor HENSCHLER: We have two categories of standards in Germany: MAK-values for non-carcinogens which are entirely based on health criteria, and TRK-values (Technical Guidance Values) which take into account social and economic criteria and which accept a residual risk that in most cases cannot be quantified. This type of standard is based on consent of different groups of interest, such as trade unions, employers, consumers' organizations, governmental agencies, and others. This calculated risk may be compared to other types of risk. Personally, I would not favour comparison of risks from deliberate exposure, like tobacco smoking, with those from forced exposure, such as occupational. But discussion is going on in my country, as in many others, the results of which cannot be foreseen at present.

T. L. OGDEN (H.S.E.): I have heard that 'Action Levels' are set in the Federal Republic of Germany at a fraction of the exposure limits. Is this true, and can you explain how the Action Levels are used?

Professor HENSCHLER: Action levels have indeed been proposed by the governmental insurance system (Berufsgenossenschaften) in specific instructions for medical surveillance. For many of the existing instructions the action level is 2/3 of the respective MAK-value, for others more or less than that. This use of MAK-values has neither been intended nor recommended by the Commission which establishes the values.

A. T. GILLIES (Thomson Laboratories, Milton Keynes): How are community exposure standards set in the Federal Republic?

Professor HENSCHLER: Community exposure standards (MIK = Maximum Immission Concentration) are established by another organization (VDI, Verein Deutscher Ingenieure). They started with 1/20 of MAK but now elaborate independent and specific values which are based on evaluations of relevant literature. These values take into account (known or suspected) peculiar sensitivies of babies and the aged, states of disease, and exposure for 24 h per day.

J. J. TWISK (Labour Inspectorate, The Netherlands): Could you give some information on the policy which is being used for setting standards for substances with effects on reproduction?

Professor HENSCHLER: We are now introducing a new system which categorizes occupational toxicants as follows:

(A) Teratogenic risk proven. MAK-values not valid.
(B) Suspected teratogenic risk which cannot be excluded, even if MAK-values are obeyed.

(C) No teratogenic risk if MAK-values are obeyed.
(D) Data available but inadequate for rating according to (A), (B) and (C).

A position paper on this new system has been published and is under discussion in the scientific community (ASP 18, 181; 1983). In a year or two, those compounds in the MAK-List for which sufficient information is available will, in addition to their MAK-value, be characterized according to the new system.

J. T. SANDERSON: In this country we have not yet tackled the difficult problem of defining the level of compliance required for an exposure limit. Could you describe the situation in this respect in Germany?

Professor HENSCHLER: Unfortunately, I am not sufficiently familiar with this specific problem in my country. I am confident that at least in some sectors hard figures are available. This question should be addressed to officials of the labour inspectorates. I am sure that, in general, compliance will not be complete, as seems to be the situation in all countries.