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EXPOSURE LIMITS FOR OCCUPATIONAL AND ENVIRONMENTAL CHEMICAL POLLUTANTS

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THE CONCEPT OF OCCUPATIONAL EXPOSURE LIMITS

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ABSTRACT

Germany was the first country to introduce occupational exposure limits (OEL) in 1886. A theoretical consideration for the existence of toxicological thresholds has been provided. Prerequisites for OELs are seen in: reversibility, existence of a threshold, deviation of (physiological) functions from normal to be regarded as "safe", knowledge about mechanism of toxic effect; and for the decision process: complete transparency of decision making, and combination with intensive health surveillance in the workplace. A variety of additional provisions has been introduced into the German MAK-list: a system for limitation of peak exposures; notification of sensitization and skin absorption, and of reproductive hazards; no satisfactory regulation of exposure to mixtures has been established. Occupational carcinogens constitute a special case because the identification of a threshold and the establishment of health-based standards has not yet been demonstrated justifiably. At present, strategies are elaborated for the quantification of cancer risk from a given compound. Despite many shortcomings and criticism, OELs continue to be an important and valid instrument for the protection of workers' health.

HISTORY

Occupational Exposure Limits (OEL) are one of the most efficient instruments of protection of workers' health. They have a long tradition, much longer than any other exposure standard. The first initiatives were taken in Germany more than one century ago. Due to pressure by the socialists in the parliament, backed by the postulate of Karl Marx for the welfare of the working population, legislation was introduced which enforced, inter alia, the compensation of damage to health by occupational activities of the employees. Employers had to pay insurance fees into a compensatory fund. This fund was to be handled by a special organisation, "Berufsgenossenschaften". These organisations were also called upon to make provision for protection of workers' health.

As a consequence, people in academia initiated research work to improve protection from chemical exposure. The first proposals for occupational exposure limits were published by Karl Bernhard Lehmann in 1886 (1). He recommended adherence to "maximum tolerable concentrations in the workplace" for short-term as well as for long-term exposure. These recommendations were based on field studies, model exposures of volunteers and animal experiments. His quantitative approach involved determining the prevailing concentrations of occupational toxicants in the air breathed by employees, by virtue of appropriate chemical-analytical methods. Lehmann was also the first scientist to use a dynamic flow exposure device for experimental animals.

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These early efforts were fortified, from 1919 on at the University of Würzburg, by a collaboration of K. B. Lehmann with Ferdinand Flury. He introduced some basic dose-response-principles, derived from animal exposure studies with phosgene (2). With this compound, a hyperbolic relationship was found and expressed by the equation

$$c \times t = W = \text{const.},$$

which later was called Haber's Law. It indicates that identical products of exposure concentration and time will result in identical magnitudes of effect; or, in other words, high concentrations over short exposure periods will result in the same effect as low concentrations over extended exposure periods, provided the product of $c \times t$ remains constant. From this equation, when transformed into a conventional dose-response-diagram, no threshold of effect can be derived.

However, the same research group demonstrated the existence of a threshold with another toxicant, hydrocyanic acid (3). With this gas, a finite concentration value can be demonstrated below which no lethal intoxication will result, however long the exposure time may be. Flury derived from these data the equation

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

whereby e = factor of elimination (of effect). On transposing this relationship into the dose-response-diagram, a threshold can be identified. A mechanistic explanation of this phenomenon was provided some years later by the demonstration (4) of the detoxication of hydrocyanic acid through rhodanide formation by the enzyme rhodanese which works, under the given exposure concentrations, at zero order kinetics.

Based on these observations, Flury and Lehmann elaborated, in the course of almost two decades, exposure limits for almost one hundred chemicals (5).

PREREQUISITES FOR OEL SETTING

Ideally, OELs should fulfill the following criteria:

1. Complete reversibility of toxic effect(s) in the relevant exposure concentrations. This means that any accumulation of toxic effects from day-to-day exposure over long periods of time (even until a worker's retirement) should be ruled out.
2. There should be clear evidence, from field experience and/or proper animal experimentation, of the existence of a threshold of toxic effect(s), or:
3. In case of the development of steady-state levels of deviations from normal in the course of a work shift, these should be regarded as harmless to health, or as tolerable ("safe").
4. There should be sufficient knowledge about the mechanism(s) of toxic effect(s) to explain the existence of thresholds, the safety to health of (functional) deviations from normal, and for the determination of relevant endpoints of toxicity for the establishment of OELs.

In addition to this, modern OEL standard setting should include two other criteria:

5. Complete description of the decision process. This means a comprehensive docu-

mentation of existing scientific data (published and available to everybody) and a profound argumentation for an established standard, and why it has not been set higher or lower.

6. OELs should only be regarded as justified if an intensive health surveillance is provided.

ADDITIONAL PROVISIONS

OELs as maximum allowable concentrations in the air of the workplace do not cover all aspects of protection of workers' health. Some additional provisions are necessary and have found their place in the national lists of OELs in different countries. These are:

— *Limitation of peak exposure.* Depending on their mode of action, some compounds are better regulated by limitation of exposure peaks (e.g. local irritants), whereas others do not need such a limitation, provided the average concentration for a work shift or even longer periods of exposure is not exceeded (e.g. systemically acting compounds with a high tendency to accumulate). A simple "ceiling" regulation has been introduced in some countries, aiming at fixing a concentration which should not be exceeded at any time. This solution is unsatisfactory to analysts who are unable to characterize the peak concentration with the postulated precision. Rather, they need a short-term average as a limit value. An alternative system was introduced in the German MAK-list in 1983. It takes advantage of the mode of action of compounds and takes into consideration toxicokinetic parameters with systemically active compounds (6).

— *Regulation of exposure to mixtures.* In recent years, it has been stated that exposure to mixtures is the rule rather than the exception. This is certainly an overestimation of the situation in practice. Nevertheless, mixtures prevail at many workplaces, and a means for limiting exposure to such mixtures should be available. A simple rule was introduced into the TLV-list very early, on the assumption that the toxic effects of the components of a mixture will add up arithmetically and that the relative proportions of the components may be weighted in terms of their OELs, and add up to unity. Toxicologists are well aware that the majority of occupational toxicants will not act additively but interact, particularly at the level of enzymatic biotransformation, in a non-additive way. Thus, the simple additive formula lacks sound scientific backing. However, everyday experience tells us that for most purposes the simple rule may suffice in practice, except in those cases where one compound potentiates excessively the activity of another: it is these (rather rare) occasions that occupational hygienists should be especially aware of.

— *Sensitization.* Hypersensitivity as a consequence of previous exposure may occur with every occupational toxicant. There are, however, some compounds where this concerns considerable proportions of those exposed. It is necessary to indicate these "obligatory sensitizers" in a specific manner. The German list has introduced for this purpose the sign "S" (7), and this is now regularly found in most national lists. We are, however, lacking systematic criteria for allotting this specification, rather, pragmatism based on field experience has been operative up to now.

— *Skin absorption.* In many instances, routes of uptake other than inhalation may add considerably to the body burden of occupational toxicants, particularly through skin. The German MAK-list has assigned, from the very beginning, a specific note to those compounds ("H"), and this has been adopted by the TLV-list. At present, no convincing system for characterizing and quantifying skin absorption has been proposed. The reason for this may be seen in the fact that the extent of skin absorption not only depends on the physical-chemical characteristics of a compound, but also on operational details of the use of the compounds. Again, pragmatism prevails in allotting the specification for skin absorption.
— *Reproductive hazards.* This quality has only recently been taken into serious consideration in setting OELs. The general term is meant to describe disorders in male and female fertility, and any type of damage to the embryo with manifestations in the pre- and postnatal period. No systematic regulatory systems have been proposed till now to cover all these aspects of reproductive hazards. The German MAK-list introduced, in 1983, a new categorization of embryotoxic effects with differentiation according to the validity or non-validity of existing MAK-values for the state of pregnancy. Of course, the practical regulations should be oriented towards women in child-bearing age, rather than the state of (overt) pregnancy.

PROBATION AND VALIDITY OF OEL

There are only a few countries which have developed OELs of their own. Until now, Germany has registered more than 500 chemicals in the national MAK-list, the US TLV-list contains approximately 600 compounds, and even more are to be found in the list of the USSR. Holland and Sweden started their own national systems towards the end of the seventies, the United Kingdom is at the very beginning of a new system based on a tripartite decision process. Some other countries are adopting this or that major list of OELs for their own purposes, or keeping close to it, the selection being governed mostly by political issues. France is publishing, without commentary, the three main lists (Germany, U.S., U.S.S.R.) as a recommendation. Efforts towards a unification on the international level have been unsuccessful so far. The reasons for this failure can easily be identified as major differences in the magnitude and type of chemical production, development and innovation, in the economic structure, and in the experience in hazard management in the occupational areas.

CHALLENGES

However, the period of probation continues. The old concept of setting and applying occupational exposure limits has been challenged and continues to be challenged for a variety of reasons. These are:

— *Lack or scarcity of valid toxicological, epidemiological or other data.* Less than 10 percent of 150 carefully reviewed compounds in the German MAK-list have been found to be appropriately based on valid data (8). The majority of MAK-values was set long ago, when the standards of scientific publications and requirements were

less stringent, on an insufficient or unsatisfactory data base. The list of compounds which have been evaluated but for which no MAK-value can be established has increased steadily since the opening of this new category (IIb in the German list). Some "historical" MAK-values were set just on the basis of a few acute inhalation experiments with limited numbers of animals. Thus, the validity of OELs is very variable, and this should be kept in mind when making judgments for health protection measures. On the other hand, this obvious insufficiency of the validity of the data emphasizes the necessity of a permanent health surveillance in the workplace.

— *Legal fixation of standards.* OELs have been taken, from the very beginning, as recommendations. Legislators have, however, in some countries converted the recommendations into legally binding standards. There are several disadvantages associated with this conversion: the system is no longer flexible in that it takes extended periods of time to change a standard according to (rapidly) incoming new information; the legal character of standards persuades juridical people to take compliance with the standard as safe, and non-compliance as proof of impairment of health; legal fixation is inhibitory, rather than stimulating to scientific efforts to improve the data base for a given standard.

— *Changing definitions of and postulates for an improvement of the state of health.* Traditionally, OELs have been set according to a phycician's diagnosis of what is health, what is disease. More recent developments have, however, provided new instruments with ever-increasing precision to detect deviations from the normal. These chemical, biochemical or physical parameters can be established with ever-increasing sensitivity and reliability. This tempts formalists to assign to them a higher degreee of relevance and validity. However, in doing so we are in danger of replacing an integrated health surveillance system by automatism, and so to overlook more relevant signs and symptoms which may develop independently of isolated parameters, however sensitive these may be.

— *Health based or socio-economically feasibility.* The original concept of OELs focussed entirely on health as the only criterium for setting a standard. Some countries have, however, introduced technical and analytical feasibility, and social and economic acceptability as additional criteria. This may be one of the reasons for differences of OELs at the international level. The standard setting procedure then moves to a negotiation about how much health, or how much deduction from complete health a society is willing to accept. This, of course, is to the detriment of the consistency of scientific evaluation of impairment of health. In essence: the health criteria may shift from case to case, which no layman will understand. This conflicting situation is far from being resolved satisfactorily and needs vigorous efforts to reach a tolerable consensus at the international level.

— *Air and/or biological monitoring?* Biological monitoring has been introduced only recently as an additional instrument for controlling exposure and protecting workers' health. The reason for this was the experience that internal exposure or intoxications may in some instances be induced by uptake of xenobiotics through routes other than inhalation. Germany was the first country to introduce biological exposure limits in 1981 (9). Some enthusiasts have postulated that air monitoring be

substituted by biological monitoring because the latter is more indicative of a body's burden. This is unjustified: air monitoring is indispensable for the control of technical processes and protective devices whereas biological monitoring allows for the identification of individuals at higher than average risk. In fact, the optimal protection of workers' health needs both approaches of control.

OCCUPATIONAL CARCINOGENS: THE SPECIAL CASE

Although occupational cancer from exposure to chemicals has been known for more than two centuries (10), it has not been regarded as a disease much different from others. Only the rapid progress in the field of the molecular biology of cancer induction by chemicals, and quantitative investigations on the dose-response-relationships from the middle of this century on have raised concern about the special features of occupational cancer:

- The severity of clinical signs and symptoms including the autistic course of the disease, and limited success in treatment by knife, ray and cytostatic drugs;
- The long latency period between (start of) exposure and manifestation of cancer which complicates the establishment of cause-effect-relationships;
- Transplacental transfer of systemic carcinogens, which hits an embryonic organism, much more sensitive than the adult;
- The possibility of an interaction of carcinogens with the genetic material of germ cells resulting in a genetic change in future generations;
- The phenomenon of irreversibility of primary carcinogenic lesions resulting in the accumulation of genetic damage of every single hit over long periods of time.

These basic criteria render chemically induced cancer a special case which needs different consideration and handling from the "conventional" toxic materials. This is realized more and more now even by industrial hygienists who have long been resistant to differentiating between carcinogens and non-carcinogens. In addition, special activities in a variety of countries in testing more and more chemicals for carcinogenicity in animal experiments and in in vitro systems have resulted in a dramatic increase in the list of proven and suspected carcinogenic occupational chemicals. Also, epidemiology has added more and more compounds to these registers, and has provided figures which allow for the estimation of cancer risk for some compounds such as benzene, aromatic amines, vinyl chloride and asbestos. At present, scientific committees dealing with evaluating health risks from occupational toxicants are spending much more time dealing with carcinogens and mutagens, than establishing OELs.

THRESHOLD VALUES FOR CARCINOGENS: DO THEY EXIST?

By far the greatest challenge to the OEL concept originates from the question whether or not threshold values can be established for carcinogens. Due to general agreement within the scientific community, it is impossible to formulate a dose (or concentration over time) of a carcinogen (or mutagen) which is without a residual risk to health. Neither do large-scale animal experiments provide evidence for the existence of a no-

-effect-level, nor can epidemiology exclude a cancer risk by the lack of observations under the given conditions of a study. Rather, the present theory of chemical carcinogenesis indicates that even the lowest doses will produce some genotoxic damage irrespective of the observation or non-observation of tumor formation in finite experimental conditions.

This means that — contrary to "conventional" occupational toxicants — health based occupational exposure standards cannot be established for proven carcinogens. Irrespective of this scientifically backed situation, industrial hygienists argue that some limitation of exposure to carcinogens should be introduced, one reason for this being the expectation that a certain limit will always be better than if nothing is done at all. The conclusiveness of this argumentation may or may not be a matter of concern. An alternative solution could be a reduction of exposure to the lowest feasible level, or substitution of a hazardous compound by a safer alternative. Nevertheless, the introduction of OELs also for carcinogens has the advantage that the prevailing concentrations will be monitored, and excessive exposures will be identified and — hopefully — reduced below the OEL. The establishment of such an OEL can, however, no longer be based on health criteria. A way out of this dilemma is the involvement of technical feasibility and socio-economic acceptability in the standard-setting procedure. This system was introduced in the German OEL-system in 1976 by establishing "technical guidance concentrations" for occupational carcinogens (TRK-Werte). They admit some residual cancer risk but are principally based on technical, analytical and economic criteria. Some other countries however do not differentiate between OELs for non-carcinogens and carcinogens, and between health-based and non-health-based.

QUANTIFICATION OF CANCER RISK: AN UNAVOIDABLE NECESSITY

The number of identified or suspected carcinogens has dramatically increased since the early seventies. Most countries differentiate between human carcinogens, animal carcinogens and suspected carcinogens. The only difference between human and animal carcinogens is, at least for regulatory purposes, the origin of the relevant data. The more we perform animal carcinogenicity tests, the greater will be the proportion of animal carcinogens. All "human" carcinogens have been found positive in proper animal experiments, whereas only a few "animal" carcinogens have been found to produce tumors in humans. Based on this difference, some authors have questioned the value of animal experiments to protect workers from cancer hazards. This conclusion is unjustified for three reasons: cancer in humans can only be identified if exposure limits are sufficiently high, if populations with and without exposure are available in sufficiently high numbers, or if a tumor is very specific and normally not found ("exotic" tumor). Although epidemiology is improving its methodology and frequency of application, the chance of identifying new "human" occupational carcinogens is decreasing the more our protective measures become effective. It is wise, therefore, to regulate human and animal carcinogens in the same way.

Taking all three categories of carcinogens together, some national OEL-lists number more than 150 proven or suspected carcinogens, constituting almost 30% of all chemi-

cals listed, the tendency being an exponential increase. One can expect that the fifty percent mark will be exceeded soon. Thus, the conventional regulatory systems to protect workers' health lose credibility. Future efforts should therefore be directed toward a quantification of carcinogenic risk in order to set priorities in terms of reduction of exposure or elimination of carcinogenic compounds. In other words: protection and prevention should focus on the major risks and put aside bagatelles which, beyond any doubt, still fill the lists of occupational carcinogens to a considerable extent.

PERSPECTIVES

As shown above, many criticisms have been raised about occupational exposure limits. There is a tendency in some societies to increase the amount and power of this criticism. Some individuals postulate zero tolerance at workplaces. In view of this, the question arises whether the existing system of occupational exposure limits will survive. One may easily expect that it will persist as long as no better alternatives are at hand. But no such alternative can be envisaged at present. In my mind, the system of occupational exposure levels is the only and the most effective means to protect workers' health. However, we should always be prepared to improve the system, particularly with regard to compliance of standards and health surveillance. The best guarantee for a survival and improvement of the system is a permanent advancement of its scientific backing.

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