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Evaluation of adverse effects in the standard-setting process

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SUMMARY

Occupational exposure limits (OELs) were first introduced more than a century ago in Germany [1]. They were based on observations of people exposed at the workplace, and on experimental exposures of humans and animals, all accompanied by analytical determination of airborne occupational toxicants. The "acceptable concentrations for short-term and long-term exposure" were derived using crude subjective criteria (humans), or gross pathological alterations (animals). Over the years considerable refinement of these criteria has been achieved, both in their type and number, starting from overt histological derangements, going on to the physiological and biochemical level, and even to subtle psychological parameters. This development has taken place in parallel with, and has been considerably influenced by changes in the definition of health and the perception of effects detrimental to health. Differences in the elementary philosophy of health and in the activities aimed at preventing damage to health in different societies have complicated all the efforts to harmonize standard-setting processes at the international level.

DEFINITION OF HEALTH

OELs are set to protect workers' health. Therefore, any standard-setting procedure has to define health. In 1950, the WHO formulated a positive definition of health which included "complete mental and social well-being"; this has never been used for occupational standard-setting because it lacks operational criteria. Most national lists of OELs do not define explicitly what they regard as health-threatening effects. The Dutch list recently introduced a definition which is entirely based on epidemiologically discernable indications of impaired health [2], which rules out the special situation in individual cases. The German list [3] aims at the protection of

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the health of the employee (as an individual) and at avoidance of undue annoyance. The U.S. Threshold Limit Value list [4] indicates that "a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit". In essence, there is no internationally accepted uniform concept of health, of health-impairing effects, and of what should be aimed at in standard-setting procedures. Rather, a continuous progression towards more stringent criteria for health and higher expectations of protective and preventive measures is observed; this process demands flexibility in the mechanism for establishing OELs.

DEFINITION OF ADVERSE

A basic rule in toxicology states that effects increase, in number as well as in severity, with dose; that there is a lower limit for detection of effects; and that there is a continuum from slightest observable to most serious effects, ending with death. For operational purposes, some authors have categorized the continuum as follows: no effects < no observable effects < slight effects within the range of compensation < borderline effects with uncertain significance for health < early health impairment < overt disabling disease < death. Some investigators have based these categories on arbitrary dose–response curves (see, e.g., [5]), with vertical lines separating the categories. However, these lines actually delimit ranges reflecting inter-individual differences in sensitivity (biological variation) as well as imprecision of the methods of determination. Therefore, they are not suitable for use as yes or no decision points. Irrespective of these difficulties, crude approaches say that "adverse" may be placed on the transition from borderline to early health impairing effects.

The term "adverse" has found a wide range of interpretations. One common feature seems to be that "adverse" precedes overt disease, and that it includes subjective elements, such as perceived itching, burning and stinging sensations, malodour, nauseating effects, general discomfort, headaches, and others. The best definition for standard-setting procedures may be that proposed by Sherwin [6] in 1983: "the causation, promotion, facilitation and/or exacerbation of a structural and/or functional abnormality, with the implication that the abnormality has the potential of lowering the quality of life, causing a disabling illness, or leading to premature death". The most sensitive and unsatisfactory aspect in this wording again is that "quality of life" is not defined.

SENSORY IRRITATION TESTS: A TOOL FOR SETTING OELs?

The majority of OELs in different national lists are based on irritation of the respiratory tract and mucous membranes of the nose and eye. Estimations vary from 40% to 70% [7]. It therefore seems attractive to look for tests representative of irritative effects to standardize OEL-setting procedures. Alary [7] has introduced a formalized experimental system which registers reductions in the respiratory frequency in mice during single periods of airborne irritant inhalation [7]. On the basis of concentration–response curves, an RD_{50} value (50% reduction in respiratory rate) is calculated; the OEL should then be set at 0.03 x RD_{50}. This factor is based on a certain comparability with existing OELs. Alary postulated that a limit of 0.03 x RD_{50} will protect against any systemic effects of occupational toxicants. The method has been propagated as the best available approach and is widely used in several countries. It has also been introduced as a standard method in the U.S. [8].

The concept underlying this system and its use for standard-setting have, however, been seriously criticized by Bos et al. [9], who argue that:

– the latent period until a plateau of respiratory depression is reached differs widely from compound to compound; sometimes it is not reached at all;

– the slopes of the concentration–response curves spread over a wide range so that with flat curves the risk is underestimated;

– the significance of the phenomenon of "desensitization" decrease of the curve during continuing exposure is misinterpreted as a kind of adaptation; in fact, it may be the consequence of irreversible damage to nociceptors;

– concentration dependence holds only for some chemicals; with others, dose rather than concentration is the determinant factor;

– there are major differences in results from different laboratories indicating unsatisfactory reproducibility;

– there are large strain and species differences in sensitivity, which make extrapolation to humans a dubious procedure.

Two other serious arguments may be added:

– deep lung irritants such as phosgene, nitrogen dioxide and cadmium oxide exert only minimal acute irritant effects; in these cases the test grossly underestimates the toxic potency of these compounds. And yet these chemicals may cause, under practical workplace conditions, severe pulmonary edema, frequently with lethal outcome without any early warning by sensory irritation;

– many alkylating agents cause severe damage to mucous membranes and skin after latent periods of many hours. They destroy the sensory nerve-endings, eliminating any nociceptive response. The risk associated with this class of compounds, mostly carcinogens, would be entirely under-

estimated by the 0.03 x RD_{50} approach.

The sensory irritation test is too simplistic to be used reliably for setting OELs. It overlooks many deleterious health effects. At best, it may be useful for evaluating homologous and analogous classes of chemicals in which, on the basis of general structure–activity relationships, the irritant potency of congeners may be predicted. Without taking into consideration mechanistic and other relevant information on the toxicological properties of chemicals, the sensory irritation test can not be recommended as a tool in OELs setting processes.

ADVERSE EFFECTS — DEFINITION AND USAGE

It is clear from the above evaluation that more comprehensive approaches for standard-setting need to be applied. As long as toxicology lacks a conclusive database on the interrelationship of effects of different quality in a multitude of widely varying organs, tissues and cells, we will be bound to case-by-case evaluations using the best available information. In doing so, we should set minimal requirements, and set priorities for the criteria to be used in the evaluation of toxic effects. The minimal requirements for setting health based standards continue to be (a) reversibility of effects, (b) identification of the "critical" toxic effect(s) in the anticipated concentration range, (c) development of a representative analytical parameter to monitor effect(s), and (d) a minimum of knowledge about the type and mechanism of the critical effect. Regarding priorities, genotoxic effects should be treated differently because a OEL must be based on an acceptable number of additional cancer cases, which is a political rather than a scientific issue. Next comes a comparative evaluation of the severity of effects, including particularly the question of late effects. If mechanistic knowledge is insufficient, long-term exposure tests to exclude (or confirm) the possibility of accumulative effects are unavoidable.

At present, the decision about the acceptability of slight "adverse" effects is still a matter of medical evaluation. This has to consider all aspects of states of disease, such as onset, type, severity of effects, compensation and reparability, hierarchy of organ(s) involved, and the consequences for the quality of life. However, those evaluating these borderline effects, and their impact on well-being and health should be aware that their evaluations will not stand forever; they must be open to reevaluation in the line with scientific progress in the representativeness and sensitivity of methods of detection and the interpretation of effects, and changes in the impact on society of the definition of health and perception of risk as well as improvements in preventive measures.

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