Maximum Workplace Concentration Values and Carcinogenicity Classification for Mixtures

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In Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) generally sets maximum workplace concentration values (i.e., a proposed occupational exposure level [OEL]) for single substances, not for mixtures. For mixtures containing substances with a genotoxic and carcinogenic potential, the commission considered it scientifically inappropriate to establish a safe threshold. This approach is currently under discussion. Carcinogenic mixtures are categorized according to either the carcinogenicity of the mixture or the classification of the carcinogenic substances included. In regulating exposure to mixtures, an approach similar to that used by the American Conference of Governmental Hygienists is proposed: For components with the same target organ and mode of action or interfering metabolism, synergistic effects must be expected and the respective OELs must be lowered. However, if there is proof that the components act independently, the OELs of the individual compounds are not considered to be modified. In the view of the commission, calculating OELs for solvent mixtures according to their liquid phase composition is not justified, and the setting of scientifically based OELs for complex mixtures is not possible. — Environ Health Perspect 106(Suppl 6):1291–1293 (1998). http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-6/1291-1293bartsch/abstract.html

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Occupational exposure levels (OELs) are generally set for single compounds. However, workers are usually exposed to combinations of a wide variety of compounds. Thus, there is a need to assess health hazards and risks from exposure to mixtures and to design air control limits. Various scientific disciplines have investigated the biologic consequences of multiple chemical exposure. In toxicology most of the insights concerning mixtures have been accumulated by Cassee et al. (1), Groten et al. (2), Hasegawa et al. (3,4), Ito et al. (5), Jonker et al. (6,7), Mumat et al. (8), and Yang (9).

The resulting concepts to evaluate the toxicity of mixtures have been recently discussed during the Seventh Meeting of the International Union of Toxicology (10) and the European Conference on Combination Toxicology (11). The available information permits several conclusions (12–14):

- Analytical definition is the basic prerequisite for the evaluation of mixtures.
- Dose additivity is expected to occur even at low dose levels for chemicals with a similar mode of action.
- Effect additivity is expected to occur when exposure to the individual compounds of similar mode of action is in the range of their no observed effect levels.
- There is a special situation at the workplace because chemical compounds may be present at concentrations close to their effective threshold levels.

These conclusions became the basis of further discussions on the regulation of mixtures of chemicals at the workplace.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) defines the application of maximum workplace concentration (MAK) values to mixtures of substances in its List of MAK and BAT Values (15) as follows:

In general, the MAK value is only valid for exposure to a single, pure substance. It cannot be applied unconditionally to one component of a mixture in the workplace air or to a technical product which might contain more toxic impurities. Simultaneous or successive exposure to several substances may be much more or less dangerous than the exposure to one of the substances on its own. A MAK value for a mixture of substances cannot be satisfactorily determined by simple calculation because the components of the mixture generally have different kinds of effects; MAK values can presently be established for such mixtures only after specific toxicological examination or studies of the particular mixture of substances. Given the inadequacy of the current available data, the Commission decidedly refrains from calculating MAK values for mixtures, particularly for liquid solvent mixtures. However, it is willing, on the basis of its own investigations, to provide values for defined vapour mixtures of practical relevance.

Legally binding OELs in Germany are set by the Commission on Dangerous Substances of the German Federal Ministry of Labour (AGS), usually on the basis of proposals made by the MAK Commission. Exposure to multiple chemicals is regulated by the AGS as follows:

\[
\frac{c_1}{OEL_1} + \frac{c_2}{OEL_2} + \cdots + \frac{c_n}{OEL_n} \leq 1
\]

where \(c_1, c_2, \ldots, c_n\) = concentration of compound 1 to \(n\) and \(OEL_1, \ldots, OEL_n = OEL\) of compound 1 to \(n\).

This formula implies, in principle, that for exposure to mixtures, the OELs of the individual chemicals must be divided by the number of compounds present. A similar mode of action and additivity is generally assumed for all components.

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Abbreviations used: ACGIH, American Conference of Governmental Industrial Hygienists; AGS, Commission on Dangerous Substances of the German Federal Ministry of Labour; HCH, hexachlorocyclohexane; MAK, maximum workplace concentration; NOAEC, no observed adverse effect concentration; OEL, occupational exposure level; PAH, polycyclic aromatic hydrocarbon.
The American Conference of Governmental Industrial Hygienists (ACGIH) takes an approach that distinguishes whether compounds act additively or independently. In the former case, OELs do not have to be modified; in the latter case OELs have to be lowered according to the formula given above. OELs for solvents in a mixture are calculated according to the liquid phase composition, assuming gas phase composition to be the same (16).

Carcinogenic substances and mixtures have been categorized by the commission according to the evidence of their carcinogenic activity in one of three groups (A1, proven human carcinogen; A2, proven carcinogen in animals; B, suspected carcinogen). In contrast to the ACGIH, MAK values for substances or mixtures regarded as proven carcinogens were not set. For suspected carcinogens, a MAK value could be derived if it was shown that the tumors were not due to the genotoxic activity of the compound (15).

The rationale of the commission in evaluating noncarcinogenic and carcinogenic mixtures is outlined by some examples. Moreover, a proposal to regulate mixtures is briefly discussed.

Evaluation

Maximum Workplace Concentration Values for Noncarcinogenic Mixtures

Chemically related compounds may, in spite of their similarity, differ in their modes of action or toxicologic potency. Therefore, they should generally be evaluated individually. However, if they possess similar pharmacokinetics and metabolic pathways as well as the same mode of action and comparable toxicologic potencies, a MAK value for the sum of the components in a mixture may be established. Preconditions are that either toxicologic studies of the single components, animal studies with the mixture, or human experiences are available. Missing data on single components can be supplemented by considering structure–activity relationships on a case-by-case basis.

Most of the mixtures evaluated contain components of comparable toxicity, toxicokinetis, and common mode of action. MAK values for the sum of the components were set up for mixtures of isomers such as hexane isomers (except n-hexane), trichlorobenzenes, vinyltoluences, xylenes, for chlorinated biphenyls containing 42 and 54% chlorine, for 2-ethoxyethanol and 2-ethoxyethylacetate, and for the mixture of 75% 5-chloro-2-methyl-2,3-dihydroisothiazol-3-on and 25% 2-methyl-2,3-dihydroisothiazol-3-on (e.g., Kathon CG, Kathon MW, Rohm and Haas, Frankfurt, Germany).

Up to now, the commission has evaluated only one mixture in which the isomers have different toxicologic potencies but the same mode of action. In a study with α- and β-hexachlorocyclohexane (HCH), the β-isomer proved five times more active than the α-isomer in stimulating liver growth. The no observed adverse effect concentration (NOAEC) for the more active β-isomer was considered an adequate MAK value. Presuming an additive effect, a simple formula was set up to calculate the maximum tolerable concentrations of the α- and β-isomer in an HCH mixture (c = concentration):

$$c[A + HCH] + c[B + HCH]$$

$$\leq \text{NOAEC}(\beta + \text{HCH})$$

Complex Mixtures

The commission could not generally agree on setting MAK values for complex mixtures, which usually differ considerably in the number and proportion of their constituents, such as metal-working fluids or gasoline. Therefore, potency and even mode of action may vary with each specimen. In addition, calculating an allowable workplace concentration for a mixture like gasoline from the OELs of its respective components according to their proportion in the fluid may be misleading because the composition of the fluid may not be representative of that in the gas phase.

Interfering Metabolism

Interferences in metabolism are possible, e.g., for enzyme inhibitors or enzyme inducers leading to the toxification or detoxification of another compound present in a mixture. They are normally not considered when MAK values are set because it is impossible to account for all exposure scenarios. However, the MAK value for disulfiram was actually based on its interference with the metabolism of ethanol as the most sensitive endpoint. When determining the allowable concentration for a mixture containing a substance known to influence enzyme activities, possible effects on the toxification of other compounds should be considered.

Carcinogenic Mixtures and Mixtures Containing Carcinogens

A carcinogenic classification for mixtures can be based on study results with the mixture itself or on the classification of their respective carcinogenic compound(s). In the view of the commission, if a carcinogenic potential is proven for a mixture, even without knowledge of the carcinogenic compound, it must be categorized as a carcinogen.

For technical mixtures of α-chlorinated toluenes (benzyl mono-, di-, and trichloride and benzoyl chloride) a clear association between respiratory tract tumors and occupational exposure could be demonstrated, which led to a classification as A1 (proven carcinogen for humans). The mixture has not been tested in animal studies, but the single substances are classified as A2 (proven carcinogen in animals), except benzoyl chloride, for which no classification could be established.

For complex mixtures such as brown coal tar, coal tar, coal tar pitches, coal tar oils, and coke oven emissions, there is clear epidemiologic evidence of carcinogenicity. Therefore, these mixtures have been classified as A1.

Diesel engine emissions induce tumors in animals and are therefore classified as A2. The carcinogenic activity of these mixtures is suggested to be due to the presence of polycyclic aromatic hydrocarbons (PAHs). Other mixtures not studied in detail but known to contain PAHs (e.g., gasoline engine emissions, used motor oils, curing smoke, or used cutting oils) are also expected to have a carcinogenic potential and should be handled like A2 substances.

Conclusion and Perspectives

Maximum Workplace Concentration Values for Noncarcinogenic Mixtures

So far, the MAK Commission has established MAK values mainly for single compounds. However, there is a need to assess health hazards and risks from exposure to mixtures. This can be done either by using information from epidemiologic studies or animal experiments on mixtures or by evaluating the compounds of mixtures separately. Missing data for structurally related compounds of a mixture may be supplemented by structure–activity considerations. Current activities of the commission in this field include discussions on a common MAK value for trimethylbenzenes.
Regulation of Mixtures—Calculation of Maximum Workplace Concentration Values

The ACGIH concept of regulating mixtures according to whether their constituents act additively or independently is confirmed according to results of a recent symposium of the MAK Commission and The Netherlands Organization for Applied Scientific Research (14,17). Thus, it is not appropriate to generally divide the OELs of the different compounds by the number of chemicals present. Instead, the mechanisms of the chemicals must be evaluated and OELs must be lowered only if chemicals with similar modes of action or interfering metabolism are present.

Moreover, calculation of allowable air concentrations for complex mixtures from the composition of the liquid phase is considered difficult unless it is proven that the composition is the same for both phases. This may be true for mixtures with a narrow boiling range. In the view of the commission it is not possible to derive a scientifically based MAK value for complex mixtures with varying composition such as metal working fluids or gasoline.

Carcinogenicity Classification—Maximum Workplace Concentration Values for Carcinogenic Mixtures

A new classification concept of the commission allows the derivation of MAK values for carcinogens provided an adequate database is available. The concept has been published elsewhere (18) and is not discussed in detail here. Thus, in the future, MAK values for carcinogenic mixtures may be derived and carcinogens in mixtures may be regulated according to noncarcinogens.

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