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Occupational Exposure

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Abstract—Regarding the risk evaluation of mixtures in the workplace, the Working Group discussed whether there is a need to consider combination effects at the workplace and whether there is sufficient information on combination toxicology to suggest a scientific strategy for the evaluation of any mixture at the workplace. It was concluded that analytical definition of the mixture is a basic prerequisite for evaluation. The Working Group agreed that there is a special situation at the workplace because chemical compounds may be present at concentrations close to their effective threshold level; therefore, combination effects have to be taken into consideration, as shown by the data presented during the conference. Furthermore, observed-effect levels for individual substances have to be modified if the substances have the same mode of action or have the same target organs; no modification is necessary if the opposite has been shown. It was also concluded that the scientific database to date is insufficient for the proposal of a general approach. The assumption of additivity in all cases lacking data may more or less over-estimate the risk. Copyright © 1997 Elsevier Science Ltd

Introduction

Occupational exposure levels are set for single chemical substances, but exposure to a mixture of different components may often take place in the workplace. The Working Group started discussion with the following questions:

— Is it necessary to take combination effects into consideration at the workplace, or does the present way of setting occupational exposure limits (OELs) for single compounds afford enough protection?
—Is the information presented during the conference sufficient to suggest a scientific strategy?
—Which prerequisites enable a mixture to be evaluated?

Relevance of exposure to mixtures at the workplace

The participants agreed that there is a special situation at the workplace, as opposed to that in the environment. Exposure by means of ambient air, drinking water or food is usually much lower than that in the workplace atmosphere. OELs are close to no-observed-effect levels (NOELs), sometimes 50% of those in animal experiments. This also means that exposure at the workplace may be close to a NOEL. Furthermore, OELs are designed for single substances but not for a mixture of different components.

The results presented in the lectures and posters of the conference show—with some restrictions—that no effects occur if doses of the single compounds are considerably lower than the NOELs, that there might be some marginal effects if doses approximate the NOELs and that effects occur if doses are higher, for example in the range of lowest observed effect levels (LOELs).

Evaluation of the toxicological effects of mixtures at the workplace

There was intense discussion about which conditions allow evaluation of a mixture. First of all, the mixture has to be defined analytically. There are at present three possible scenarios as outlined below.

In the first case, there are different chemical substances in a mixture, but the same target organ or the same mode of action, as illustrated by the following examples. The study by Jonker *et al.* (1996), using different nephrotoxicants with either a similar or a dissimilar mechanism of action, showed an effect only if the different chemicals had been administered near effect levels. It was concluded, therefore, that (for example) carboxyhaemoglobin forming substances may combine their effects, resulting in an elevated carboxyhaemoglobin level, even when OELs are observed, if these OELs have been set up based on this effect, namely dichloromethane. Irritants such as aldehydes [described in a contribution from Cassee *et al.* (unpublished, 1996)] or CNS-affecting solvents may also combine. This is also true for organophospho-

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Abbreviations: LOEL = lowest observed effect level; NOEL = no-observed-effect level; OEL = occupational exposure limit.

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rous compounds, which act by inhibiting cholinesterase. Synergistic effects must be expected in all these cases. There is the possibility of an additive effect at least, or even of potentiation; nevertheless, it was agreed that potentiation will obviously be a very rare event, because only a very few examples have been described in the literature (e.g. the unique case of the interaction between malathion and EPN). In these cases of possible synergistic effects, the OELs given for the single substances must be lowered to prevent health effects from the mixture.

The second case to consider is that of different chemicals with different target organs and activities by means of an entirely different and independent mode of action. These results have to be clearly shown (i.e. a need exists for a comprehensive database). In this case, no synergistic effects are expected. Thus, the OELs valid for the individual compounds need no modification.

In all other cases, evaluation is not possible. From a scientific viewpoint, the present database on combination toxicology is not yet adequate to enable a general recommendation to be made for dealing with mixtures of chemical compounds; there must be a case-by-case evaluation. In addition, there was some debate about whether an assumption of additivity is preferable to a default position where there is insufficient information.

Different routes of exposure

In the poster from Elliott *et al.* (unpublished, 1996), presented to the Working Group, combined exposure to the pesticide propoxur and various solvents in human volunteers and *in vitro* in the perfused pig ear resulted in dermal absorption. The discussion on this paper concluded that routes of exposure other than inhalation, such as skin penetration, can contribute significantly to the toxicity of certain substances by means of a combination effect. Although this paper failed to show an effect of different solvent mixtures on the dermal absorption rate, there was consensus that routes of exposure other than inhalation should be considered when evaluating the possibility of exposure to several chemicals.

Combination effects of chemical compounds and physical parameters

The second contribution was a poster from Morata *et al.* (unpublished, 1996). Those authors have demonstrated hearing loss resulting from combined exposure to solvents such as benzene or toluene, and noise in an oil refinery. This result must be considered in conjunction with other contributions during the congress; these dealt with effects on the auditory system in animal experiments after combined exposure to solvents such as trichloroethylene or toluene and noise, although in very high concentrations compared with OELs (Johnson *et al.*, unpublished 1996; Muijser *et al.*, unpublished 1996). The conclusion was that consideration must be given not only to the effects of combined exposure to different chemical compounds, but also to those of combined exposure to substances and physical parameters such as noise, heat or irradiation.

Conclusions

The Working Group arrived at the conclusion that, in cases where chemical substances with the same target organ or the same mode of action are present at the workplace, synergistic effects must be expected. OELs given for single substances must be lowered to guarantee worker protection. On the other hand, if there is proof that the components of a mixture are acting in different and independent modes, OELs for individual compounds do not have to be modified. In all other cases, a general approach to the evaluation of a mixture is not possible to date. The assumption of additivity, however, seems to be better than a default position. From the data presented and discussed during the conference, this position may by no means under-estimate the risk.

REFERENCES

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