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Environment, Health and Safety Committee Note on: Why Do We Worry About Chemical Mixtures?

Concerns have been expressed about the exposure of humans and other organisms to mixtures of chemicals at work, in our food, in consumer products or in the environment. This Note outlines how chemicals in mixtures may interact and the types of effect that mixtures can have on living organisms, how their potential impacts are currently calculated and policy approaches to mitigate risk.

1. Introduction

In all aspects of life we are exposed to chemicals from many sources and in working out how toxic or harmful chemicals may be, we need to be able to make allowances for the complexity of these multiple exposures. This note contains a brief review of the approaches, procedures and methods available for assessing the toxicity of mixtures of chemicals, together with a consideration of the limitations of standard methodologies.

Uncertainties in assessment methodologies are compounded by the fact that experimental work may show an apparent association or correlation between the dose of a chemical and its effect, but this in itself does not prove that the chemicals cause the problem. It may that the quantitative data are not wholly relevant or that the cause of an observed effect is not totally attributable to the exposure to the chemical mixture.

Public misunderstandings, rooted largely in general in the language and vocabulary used, and in particular about the definitions and effects of chemicals, have resulted in the use of emotive language such as “a sea of chemicals“ or “...cocktails of chemicals”. These imply a mix of ingredients whose effects together are both unknown in degree, and which are suspected of having a far greater effect together than singly, especially in terms of ability to cause harm. This ability of some chemicals to have an enhancing effect on others is not an unfamiliar concept - for example most people will have seen cautions on medicines such as “Avoid alcoholic drink”. Therefore this enhancing effect is often considered an undesirable property, especially by those who are strongly opposed to the additions of any additives, natural or otherwise, to our food and environment.

2. The interactions of chemicals

Toxicity and exposure data are determined on the basis of the effects of a single chemical either arising from one or several exposures. This does not reflect the real life situation where in reality exposures may be multiple, mixed in composition and varying in frequency. What actually needs to be considered are the effects and interactions of:

- several chemicals together calculated on a purely additive basis
- chemicals which react together in the body to form different compounds
- chemicals which can influence the reaction of other chemicals in the body e.g. through inhibitory action of enzymic pathways
- chemicals which together have an effect which is greater than simply the sum of that expected from summation of the individual components

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Diagrammatically these modes of action could be represented as:

Additive: no interaction	**A&B = A+B**	Combined summed effect equal to total dose
Independent: no interaction	**A&B = A** and **B**	Combined effect equal to separate effect of each
Synergistic: interaction occurs	**A&B = AB**	Combined effect greater than summed effect of each
Antagonistic: interaction occurs	**A&B = AB**	Combined effect less than no interaction

Studies have shown that chemicals possessing a similar mode of toxic action have an additive effect and do not interact. However, this is not always the case. In some cases it may result in increased toxicity above the expected additive level. This is the basis of a synergistic effect. A particular form of synergistic action arises when one component of a mixture interferes with the metabolic fate of another resulting in enhanced toxicity. This is known as **potentiation** where enzymes exert a metabolic effect either through their activation or by blocking their action and hence impacting on the detoxification ability of metabolic pathways.

Aside from these combined effects of the chemicals themselves, there may, in the working environment, be other factors which affect the physiological response of the individual, e.g. heat or cold, pregnancy or nutritional status. The toxic effect experienced by individuals may thus be enhanced or diminished by environmental effects which are exerting an influence on the metabolic response and hence potentially the degree of toxic effect.
With this in mind it is hardly surprising therefore that the combined potential influence of synergistic or antagonistic effects coupled with environmental influences create difficulties in estimating the outcome of multiple exposures to chemicals either in combination or even singly.

3. How are effects calculated?

Traditional methods for calculating toxicity which involve making empirical experimental measurements have limitations because, as described above, mixtures of chemicals do not necessarily behave in the body as single compounds, but will combine, react, inhibit or potentiate. The same applies to calculations for Tolerable Daily Intake i.e. the daily amount of a chemical that has been assessed safe for humans.

Newer approaches make use of eco-toxicological approaches where multi-component mixtures with similar modes of action or with similar adverse outcomes are grouped in the experimental model and the experiments (i.e. concentration addition, independent action, synergistic or antagonistic action) are specifically designed to evaluate the complex effects of the different chemical modes of action.

4. Regulatory approaches

In assessing the toxic effects, the traditional approach when setting safe exposure levels for mixtures has been to take uncertainty into account by adding higher precautionary safety factors (often hundreds of times lower than the dose causing no observable adverse effect (NOAEL)). The risk-based approach requires that as much information as is practical about individual components of the mixture are compiled and evaluated. However, this approach has the limitation that it does not provide specific information about the overall toxicity of the mixture. Nevertheless, this approach has the advantages of flexibility, allowing a case-by-case analysis to be compiled. The US and Europe both use this approach, taking into consideration both the environment and effects on health in compiling the risk assessment.

The Health and Safety Executive (HSE) guidance provides methods for calculating the additive effects of multiple or mixed inhalational exposures. In the UK this is the recognised approach by which compliance with the Control of Substances Hazardous to Health (COSHH) Regulations would be judged. This approach is, however, readily adaptable to exposure routes other than inhalation. The general calculation methods are not considered directly applicable to materials causing skin sensitisation or cancer.

5. Looking forward, assessing and controlling risk

Robust methods are still needed to evaluate the toxicity of mixtures. These methods need to make adequate recognition of, *inter alia*

- the criteria used to “group” chemicals and their modes of action

- ethical considerations of the relevance of exposure levels and animal experimentation,
- the predictive basis of across-species extrapolation of effects
- the potential use of biomarkers and emergent biotechnologies.

Although our current methods are not without limitations, they have provided useful information as a starting point. Looking to the future, improved and more robust methods of estimation are needed so that a better assessment of risk from mixtures can be made. In the meantime, the principles of COSHH and the hierarchy of control measures will continue to define the legal framework for minimising exposure, primarily using engineering solutions in preference to Personal Protective Equipment.

The best assessment of risk that can presently be made is to assume an additive effect of chemicals This approach does at least allow a best estimate to be made of whether workplace exposure standards are being met and this is, at present, the best, and indeed the only, approach that can be adopted in the absence of specific test data on the mixture in question.

For further information see:

EHSC Note on the Pragmatic Approaches to Assessing the Toxicity of Chemical Mixtures 2012

Note was prepared by a Working Party of the RSC Environment, Health and Safety Committee.

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