Polish Journal of Occupational Medicine Vol. 3, No. 3, 333–336, 1990

SHORT COMMUNICATIONS

THE ADDITIVITY RULE IN THE EVALUATION OF HEALTH EFFECTS OF COMBINED EXPOSURE TO SOLVENTS – DOES IT HOLD?

JERZY A. SOKAL AND ZOFIA KORSAK

Department of Toxicity Evaluation, The Nofer Institute of Occupational Medicine, Lodz, Poland

Key words: Solvents, Combined exposure, Additivity rule

Abstract: On the basis of results obtained in experiments on animals exposed to mixtures of solvents the adequacy of additivity rule which is used in the evaluation of health effects of combined exposure to solvents is discussed. In the case of simultaneous exposure to mixture to toluen and xylene the modification of the additivity formula is proposed.

Combined exposure to various mixtures of organic solvents frequently occurs under industrial conditions whereas exposure limits are set saparately for single solvents. To overcome this inconsistency the well known additivity formula is often used for the evaluation of the total exposure.

$$\frac{C_1}{MAC_1} + \frac{C_2}{MAC_2} + \ldots \frac{C_n}{MAC_n} \leq 1$$

It is asumed that the toxic effects of combined exposure to two or more solvents are additive in nature due to similarities in their toxic effect and action mechanism. The additivity formula is also adopted in the appropriate requlations of the State Sanitary Inspector in Poland, and widely used in our hygienic practice. However, there are scientific and regulatory bodies which do not readily accept this formula. The West German MAC-Commission, for instance, takes the view that additivity rule is not based on any sufficient scientific grounds (1). We share this opinion, however, with the reservation that the application of MAC values for single solvents only could often lead to a considerable underestimation of actual exposure and consequently to adverse health effects. Under these circumstances it seems advisable to provide

Address reprints requests to Jerzy A. Sokal Department of Toxicity Evaluation, The Nofer Institute of Occupational Medicine, P.O. Box 199, 90-950 Lodz, Poland.

appropriate scientific data in order to verify the additivity rule for solvents. Three types of study may be considered: epidemiological studies, human volunteer studies, and animal studies. The first two types seem to be of rather limited value. It would be virtually impossible to obtain reliable epidemiological data on the intercation of solvents, due chiefly to difficulties with selecting the appropriate study populations.

Also, studies on human volunteers are limited to acute, threshold level exposure, in a small number of subjects, and their sensitivity in determining the type of interaction seems to be rather low. Therefore, only data from animal studies are a practical scientific basis for further regulatory actions concerning exposure to a mixture of solvents, if there is no evidence that animal data are not applicable to man. It must be remembered, however, that some methodological requirements should be fulfilled such as:

- CRITICAL EFFECTS DETERMINED BY APPROPRIATE METHODS
- LOW LEVELS OF SUBCHRONIC EXPOSURE INCLUDED IN EXPERIMENTAL DESIGN

to make extrapolation of animal data to man reliable.

Abiding by the principle mentioned, two combinations each of two solvents, were studied. The results of the study showed that the effects of combined exposure were not additive:

TABLE 1. Effect of combined exposure to toluene (50 Vol %) and xylene (50 Vol %) in animals

Exposure	Critical system (animal species)	Test	Extent of synergism, (%)
ACUTE (1000 – 4000 ppm)	NERVOUS SYSTEM (rat)	rota-rod performance	54
ACUTE (1000 – 5000 ppm)	RESPIRATORY SYSTEM (mice)	respiratory rate	52
SUBCHRONIC (1000 ppm, 3 months)	NERVOUS SYSTEM (rat)	rota-rod performance	40
SUBCHRONIC (100 ppm, 6 months)	NERVOUS SYSTEM (rat)	rota-rod performance, spontaneous motor activity	29 – 49

TABLE 2. Effect of combined exposure to xylene (50 Vol. %) and n-butanol (50 Vol %) in animals

Exposure	Critical system/organ (animal species)	Test	Extent of antagonism (%)
ACUTE (500 – 4000 ppm)	NERVOUS SYSTEM (rat)	roto-rod performance, spontaneous motor activity	30 – 84
ACUTE (1000 – 4000 ppm)	RESPIRATORY SYSTEM (mice)	respiratory rate	38
SUBCHRONIC (100, 200 ppm) 3 months	NERVOUS SYSTEM (rat)	roto-rod performance, spontaneous motor activity	58 – 74
	LIVER (rat)	lipid peroxidation, aniline p-hydroxylase activity	100

TOLUENE + XYLENE → SYNERGISTIC EFFECT

XYLENE + n-BUTANOL → ANTAGONISTIC EFFECT

Detailed results are presented elsewhere (2, 3). They are summarized in Table 1 and Table 2. We consider the results obtained to be sufficient evidence of interaction of the solvents studied, but there is still a question whether and how these results could be used in practice.

Evident antagonism was detected between xylene and n-butyl alcohol. It is not our intention, however, to increase the admissible level of exposure in the working environment, chiefly because some doubts in animal – man extrapolation still exist, and because there is no information on the combined effect of some other solvents. In addition, we must be aware that any permission concerning exposure limits should be carefully considered. There is, in our opinion, however, a sufficient scientific basis to suggest a decrease in the permissible level of exposure to a mixture of solvents in the case of simultaneous exposure to a mixture of toluene and xylene. The following modification of the additivity formula is proposed:

$$\left(\frac{C_{Toluene}}{MAC_{Toluene}} + \frac{C_{Xylene}}{MAC_{Xylene}}\right) \times 1.5 + \frac{C_3}{MAC_3} + \ldots \frac{C_n}{MAC_n} \leq 1$$

This modified formula is intended to assist industrial physicians, industrial hygienists and sanitary inspectors in the evaluation of exposure to a mixture of solvents and its possible health effects. Now, though changes to occupational

exposure limits for toluene and xylene, or establishing MAC value for the mixture of toluene and xylene, are not being planned, as more data on the interaction of the other solvents present in the mixtures occuring in practice are indispensable.

Studies on the interaction of solvents are time consuming and rather expensive: it seems to us that it would be advisable to encourage other countries to undertake and carry on the studies within a well designed and coordinated international project.

AKNOWLEDGEMENTS

The study was supported by the CPBR project 11.11 Occupational Medicineτ.

REFERENCES

1. Maximum Concentrations at the Workplace and Biological Tolerance Values for Working Materials 1989 – Report No XXV, Commission for Investigation of Health Hazards of Chemical Compounds in the Work Area, Verlag Chemic 1989

2. Korsak Z et al. Toxic effects of combined exposure to toluene and xylene in animals. I. Acute inhalation Study. Pol J Occup Med 1:45 – 50, 1988

3. Korsak Z, Sokal JA, Stetkiewicz J. Toxic effects of combined exposures to selected organic solvents in animals. Pol J Occup Med 3:216 – 221, 1990

Received for publication: 23rd August, 1990.
Accepted for publication: 28th September, 1990.