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LETTERS TO THE EDITOR

Re: "Mutagenic action of isocyanates used in the production of polyurethanes" by M Anderson, M-L Binderup, P Kiel, H Larson, J Maxild. Scand j work environ health 6 (1980) 221—226

Sir,

The above-named publication appears likely to cause unnecessary concern. In the interests of providing well-balanced information, I should like to point out that the authors of the article (a) withold important information, (b) make misleading statements, and (c) draw unfounded conclusions.

Notes on a

In the article no precise figures are provided for table 2. Therefore it is impossible to verify the dose-response effects or the validity of the discrimination limit.

The authors fail to mention that the positive Ames test results obtained for toluene diisocyanate (TDI) contradict the results of other authors. Foderaro (3) and Purchase et al (5) obtained negative Ames test results with TDI.

The authors also fail to mention that a positive Ames test is by no means new for 4,4'-methylenediphenylisocyanate (MDI). The US National Institute for Occupational Safety and Health pointed out corresponding findings by Foderaro (3) as early as 1978.

Notes on b

The statement that "correspondence" exists between the Ames test and carcinogenesis in animal experiments is also misleading. Rather, it is found that there is a purely mathematical correlation and that this correlation fluctuates from one substance group to the next, and it amounts to less than 50 % in some cases. Ames himself (1) and Weinberg (6) admit that even a number of substances encountered in our everyday environment can yield positive results in mutagenicity tests with bacteria, for example, beer and high oxygen concentrations.

It is also misleading to state that "Even when the present threshold limit values are observed, workers producing polyurethane will be exposed to quantities of isocyanates which are mutagenic in bacteria ... [p. 225]." It should rather be emphasized that, according to general scientific opinion, the results of mutagenicity tests on bacteria are by no means quantitatively transferable to humans. (Some of the reasons are mentioned briefly in *Notes on c.)* If this transfer is nonetheless to be attempted, the dose concept of "milligram per kilogram" (customary in toxicology) should at least be adhered to. The TDI situation then appears in a completely different light. According to the (generous) estimate of the authors, the Danish threshold limit value (TLV) permits the inhalation of a maximum of 1 mg of TDI per day. The smallest TDI concentration found by the authors to have a mutagenic effect was 125 μg of TDI per agar plate; this level corresponds to a concentration of roughly 3 mg per kilogram of substrate. In order for such a concentration to accumulate in a person weighing 75 kg, the person concerned would have to inhale more than 200 times the daily TLV dose of TDI — presupposing complete absorption and no metabolic processes (which, of course, does not apply).

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Notes on c

The conclusions of the article as to health hazards in the work environment are unfounded. From the fact that positive Ames test results were obtained for TDI, MDI and also for their amine analogues, the authors conclude that the isocyanates are hydrolyzed to form the corresponding diamines and that it is these diamines which are actually the mutagenic substances. This conclusion must remain pure speculation as long as the formation of the corresponding diamines from the isocyanates cannot be demonstrated under Ames test conditions. However, such proof has not yet been furnished. (It is also not to be expected since total hydrolysis of the isocyanates occurs only in the acid pH range, whereas the Ames test is carried out with a pH of 7.4).

It is a well known fact that it is particularly difficult to draw conclusions from the mutagenic action detected in the Ames test as to the possibility of carcinogenesis in animals or even in man. After all, the Ames test makes use of bacteria without nucleus walls, without protein membranes, and with artificially altered cell walls, and the bacteria are exposed to the test substances without their having suitable detoxication and elimination capabilities and without a DNA (deoxyribonucleic acid) repair mechanism. In vivo, on the other hand, the substances first affect cell walls, nucleus walls, and protein membranes of the skin cells or mucous membrane cells of the respiratory tract. In the case of the highly reactive isocyanates, conversions with NH_2- and OH- groups of proteins to adducts of higher molecular weight must be expected. It can, therefore, be assumed that no isocyanate at all reaches the nuclear material. According to general opinion [with which the authors have agreed in a different publication (2)] however, Ames-positive test substances have no effect on man if they are unable to reach the relevant target molecules (DNA).

In fact, TDI is a good example of the lacking correlation between mutagenicity in the Ames test, on one hand, and mutagenicity or carcinogenesis in animal experiments or on man, on the other. In vivo cytogenetic studies on numerous species of animals have failed to demonstrate any significant mutagenic effects after long-term exposure to TDI (4); even lifetime inhalation experiments carried out with rats breathing TDI concentrations of up to 15 times the Danish TLV value failed to show any carcinogenic effects (4). Finally, industrial medicine, over a period of observation of 40 a, has not recorded any increased occurrence of tumors, any teratogenic damage, or any fertility disorders in persons exposed to the effects of isocyanates.

Summary

The Ames test results published in Andersen et al's article can, at most, serve as encouragement to engage in more-detailed studies, for example, long-term animal experiments with MDI or epidemiologic studies on man. (Such studies are already in progress or are in the planning stage.)

At the moment, it is absolutely unjustifiable to suggest that isocyanates — provided that the customary TLV values are observed — represent a serious health hazard to man in the form of cancer or genetic damage.

References

1. Ames BN. Presented at the 8th international conference of occupational health in the chemical industry, Tokyo 1980.
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4. Hazelton Laboratories. Draft report to the International Isocyanate Institute 1981.
5. Purchase IFH et al. Br j cancer 37 (1978) 873.
6. Weinberg AM. Nature 279 (1979) 286.

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