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Authors` response to WF Diller`s Letter to the Editor - *Scand J Work Environ Health* 1981;7:237-238

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Authors' response to WF Diller's letter to the Editor — *Scand j work environ health* 7 (1981) 237—238

In his letter to the Editor of vol 7, no 3 of the *Scandinavian Journal of Work Environment & Health*, WF Diller presents a number of points of criticism of our article "Mutagenic Action of Isocyanates used in the Production of Polyurethanes" [*Scand j work environ health* 6 (1980) 221—226] which could lead to doubt about the scientific basis for our conclusions. We consider it therefore necessary to repeat the basis for our conclusions that "isocyanates must be considered to represent a serious health hazard [p 221]" (2).

We have shown that the two isocyanates toluene diisocyanate (TDI) and 4,4-methylenediphenylisocyanate (MDI) are mutagenic in three strains of *Salmonella typhimurium* in the presence of rat liver homogenate with co-factors (S-9 mix). Mutagenicity is only found when test conditions are such that volatile compounds are prevented from disappearing from the plates.

In his letter Diller refers to the work by Foderaro (3) and Purchase et al (6). They have found MDI to be mutagenic and TDI to be nonmutagenic. These references are not included in our article, since we do not consider reference to investigations which fail to meet normal scientific standards as being of scientific interest. The work by Foderaro (3) is a "written communication where details of the experimental procedure and quantitative results were not provided [p 59]." It is therefore not possible to compare these results with ours. In the case of the work of Purchase et al (6) the authors state that "the compounds were tested on only one occasion in each of the tests" and that "compounds which gave incorrect results were not re-tested; for example, the incorrect negative results on vinyl chloride, which is reproducibly positive in the Ames test when tested as a gas in this laboratory, was not altered during the validation study [p 875]." Since repeated experiments have not been made and the test procedures gave negative results with volatile compounds, we have not considered it relevant to compare the results of this investigation with ours.

McCann et al (5) have shown that there is a high correlation between carcinogenicity in animals and mutagenicity in the *Salmonella*/microsome test. Ninety percent (157 of 175) of the carcinogens were mutagenic in the Ames test, including almost all of the known human carcinogens that were tested. Despite the severe limitations inherent in defining noncarcinogenicity, few "noncarcinogens" showed any degree of mutagenicity. In the investigations of McCann et al 14 chemical compounds, which at this point had not been shown to be carcinogenic in animal tests, were found to be mutagenic.

In our opinion it is misleading to call these results "false positive," since we know that animal carcinogenicity tests are insensitive. This point can be illustrated by the fact that a number of the so-called "false positive" results have now been changed to "true positive" results after new carcinogenicity tests on animals. Six of the 14 compounds which McCann et al (5) considered to be noncarcinogenic in 1975 were considered by Sax (7) to be carcinogenic in 1981 (table 1). Another example is the one of aromatic epoxy resins. In 1978 they were shown to be mutagenic in the Ames test (1). As earlier animal tests had shown that they were not carcinogenic, the Ames test results could also in this case be called "false positive." In 1979 new animal experiments showed that aromatic epoxy resins were carcinogenic in mice (4). As it is not possible to find the true number of "false positive" results in the Ames test, it is not possible to estimate a true mathematical correlation between mutagenicity in the Ames test and carcinogenicity in animals. However, since about 90 % of the tested carcinogens are mutagens in the Ames test and only a few noncarcinogens are mutagens, there is only one thing to do if one wants to protect humans against harmful chemicals and that is to treat compounds which are mutagenic in the Ames test as if they were mutagenic and carcinogenic for humans.

Diller presents, in his letter, a number of completely speculative arguments for isocyanates not being able to reach human DNA (deoxyribonucleic acid), but does not present any documentation for his asser-

Table 1. Correlation between carcinogenic effect in animals and mutagenic effect in the Ames test.

Substance	Mutagenic in the Ames test	Carcinogenic	
		McCann et al (5) 1975	Sax (7) 1981
4-Acetylaminofluoren	+	—	+ (conclusive)
1-Naphthylamine	+	—	+ (human suspected)
Styrene oxide	+	—	+ (suggestive)
Glycidol	+	—	+ (suggestive)
1,2 Epoxybutane	+	—	—
5-Nitro-2 furamidoxime	+	—	—
5-Nitro-2 furoic acid	+	—	—
N-hydroxy-4 aminoazobenzene	+	—	—
Sodium nitrite	+	—	—
Folpet	+	—	+ (suggestive)
ICR-191	+	—	—
Nitrofurantoin	+	—	—
Dibenz(a,h)anthracene-5,6-oxide	+	—	+ (conclusive)
Sodium azide	+	—	—

tion. We are of the opinion that the only way to prove that mutagenic chemicals such as MDI and TDI are not dangerous to humans is to prove that the chemical cannot reach human DNA. Until there is proof of the opposite, we must assume that isocyanates are mutagenic and carcinogenic for humans and adopt appropriate measures.

We agree with Diller in his opinion that one cannot use quantitative results of the Ames test to predict cancer risk with respect to humans. The only way to be sure is to fix the hygienic standards for suspected carcinogens at 0.

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