CORRESPONDENCE

Biological effect monitoring of occupational exposure to 1,3-dichloropropene: effects on liver and renal function and on glutathione conjugation

Sir,—The report of Brouwer et al. (1991;48:167–72) states that in workers applying 1,3-dichloropropene (1,3-DCP) moderate induction of hepatic enzymes is indicated and subclinical nephrotoxic effects cannot be excluded.

In our opinion this study does not present evidence for a causal relation between exposure to 1,3-DCP and the reported effects for the following reasons.

(1) Study design
Significant shortcomings in the design of the study are:
(a) The absence of an adequate control group. A control group is necessary in a longitudinal study in which the results at the end of the season are compared with the results at the start of the season to compensate for intra-individual variations related to factors other than exposure to 1,3-DCP and for analytical variations.
(b) Insufficient exposure measurements to allow conclusions on a causal relation between exposure to 1,3-DCP and changes in liver and kidney function tests.

(2) Target organs
The authors state that “the primary target organs of DCP toxicity in experimental animals are the liver and the kidney.” This is based on studies of Torkelson and Oyen conducted about 30 years ago (published in 1977) using a sample of 1,3-DCP not representative of current commercial material, and a strain of the Wistar rat. The renal effects could not be reproduced in several subsequent inhalation and oral studies using well characterised commercially available samples of 1,3-DCP. No evidence of any significant renal or hepatic lesions related to treatment was found in studies of male and female rats, mice, rabbits, and dogs exposed to concentrations of up to 150 ppm for 13 weeks, or to 60 ppm for two years, or to dietary doses of a stable microencapsulated formulation of 30 mg/kg/day for 13 weeks.1 and W T Stott, personal communication.

The earlier findings have been attributed to an exacerbation of an endemic renal disease in the strain of rat used, or to unknown contaminants in the test material, or both, which are not representative of today’s material.

We conclude that the liver and the kidney are not primary target organs of 1,3-DCP toxicity in experimental animals.

(3) Liver enzyme induction
The authors’ reasoning for the moderate induction of liver enzymes by exposure to 1,3-DCP is based on the observations of a non-significant increase of serum γ-glutamyltranspeptidase (GGT) activity and a decrease in total bilirubin concentration, both within the normal range, at the end of the application season.

Indeed, changes in these parameters have been demonstrated in patients treated with enzyme inducing drugs, albeit much more pronounced.2

It should, however, be borne in mind that for quantification of enzyme induction more specific tests have to be used such as the determination of the half life of antipyrine in plasma or D-glucaric acid excretion in urine.

Also, the small changes in the study of Brouwer et al. may be caused by a change in lifestyle of the workers during the season—for example, an increase in use of alcohol and tobacco. Unfortunately this was not monitored by the authors. Therefore we are of the opinion that the conclusion of exposure related “moderate enzyme induction” is not justified.

(4) Subclinical nephrotoxicity
The authors claim of “subclinical nephrotoxicity” is based on three findings:
(a) A DECREASED EXCRETION OF CREATININE
In the abstract it is stated that creatinine excretion decreases from 93 to 87.5 μmol/l, which suggests a decrease in creatinine clearance—that is, a deterioration in glomerular function. What the authors want to say, however, is that there is a decrease in serum creatinine from 93 to 87.5 μmol/l (table 2 of the manuscript) which, by contrast, could be interpreted as an improved glomerular function at the end of the season.

(b) AN INCREASED EXCRETION OF URINARY ALBUMIN
The median concentration of urinary albumin increased from 5.2 to 7.6 mg/l. Apart from exposure to 1,3-DCP, this change could be attributed to intra-individual variation. This has been clearly shown by Stonard et al who found a similar change in a control group that was examined three times at monthly intervals.

We do not believe that a change from 5.2 to 7.6 mg/l may be interpreted as a “subclinical nephrotoxic effect.” This opinion is based on recently published geometric mean values of urinary albumin excretion in healthy subjects, ranging from 4.8 to 6.4 mg/g creatinine.10-13 The after season urinary albumin concentration in 1,3-DCP workers is in this range if it is accepted that 7.6 mg/l corrected for specific gravity is equivalent to 5.1 mg/g creatinine.

(c) AN INCREASED EXCRETION OF URINARY RETINOL BINDING PROTEIN (RBP)
The authors report an increase in median urinary RBP from 20 to 26.9 μg/l. Using similar methods other authors found geometric mean values of 82 and 71 μg/g creatinine.10,11 Therefore the statistically significant increase is in the lower normal range and not related to tubular dysfunction.

Our conclusion is that the changes of each parameter of renal function before and after the season were in the normal range and without (subclinical) significance for the workers. Furthermore, no evidence exists for a causal relation with exposure to 1,3-DCP.
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3 Lomax LG, Stott WT, Johnson KA, Calhoun LL, Yano BL, Quast JF. The chronic toxicity and oncogenicity of inhaled technical grade 1,3-dichloropropene in rats and mice. Fundam Appl Toxicol 1989;12:418-31.


6 Hanley TR, John-Greene JA, Young JT, Calhoun LL, Roz KS. Evaluation of the effects of inhalation exposure to 1,3-dichloropropene on fetal development in rats and rabbits. Fundam Appl Toxicol 1987;9:71-75.


The authors' reply

Sir,—Van Sittert et al are to be praised for their meticulous scrutiny of our article. The fact, however, that they dispute most of our conclusions is, in our view, based on the understandable fear for regulatory authorities who might misinterpret our findings rather than on purely scientific arguments.

(1) Study design

We have chosen a longitudinal study rather than a single observation compared with a control group. Intra-individual variation may play a part for some of the measured parameters and should, indeed, be checked by a control group. We may assume, however, that intra-individual variation is not likely to explain the observed changes which—with the exception of serum creatinine—all point towards liver enzyme induction, subclinical nephrotoxicity, and impairment of the erythrocyte glutathione system. Controls for analytical variation were included as part of our normal laboratory routine; in this respect the addition of a control group would not have improved the results.

We admit that exposure measurements did not take place in direct relation to the biological effect monitoring. Therefore, a dose-response relation could not be established. Exposure studies in the same group of workers and in the same period, however,12 supplied convincing evidence that the exposure of these workers to 1,3-DCP often exceeded the short term exposure limit of 2 × occupational exposure limit.

(2) Target organs

It was beyond the scope of our study1 to review all available animal data. We referred to Torkelson and Oyen4 because it was on this publication that the TLV was based. It is not clear what Van Sittert et al mean by referring to a possible difference between commercial and non-commercial 1,3-DCP.

(3) Liver enzyme induction

We see no reason to question our conclusion that exposure to 1,3-DCP leads to moderate enzyme induction. Both bilirubin and serum GGT are known as indirect indicators for enzyme induction,5 and we see no other explanation for the changes in these parameters than moderate enzyme induction. Average alcohol and tobacco consumption were monitored before the study and it is unlikely that this changed during the observation period to such an extent that it might explain the observed effects. It is known from clinical practice5 that the reaction of serum GGT activity even to potent enzyme inducers is most whetted, and that there is no dose-response relation.

The parameters for enzyme induction advocated by Van Sittert et al are either invasive and indirect (antipyrine half life) or obsolete (D-glucaric acid). Moreover, they should keep in mind that enzyme induction is an adaptive mechanism rather than an indicator for toxicity.

(4) Subclinical nephrotoxicity

Van Sittert et al are rightly confused by an error in the abstract of our article (creatinine excretion instead of concentration) which was corrected in the April issue of this journal. We do not agree, however, with their conclusion that the observed significant changes in urinary albumin and RBP are without (sub)clinical significance. Changes in renal parameters, even within the normal range, reflect an effect on renal function. It is a matter of semantics whether this effect should be referred to as either "subclinical nephrotoxicity" or "biological effect." In our view, any change in renal function in an adverse direction as a result of exposure to an occupational substance has to be considered an undesired effect. Therefore, we see no reason to review our conclusion that exposure to 1,3-DCP may result in subclinical nephrotoxicity.

In conclusion, we do not agree with Van Sittert et al that our study presents no evidence for effects of 1,3-DCP on the human liver and kidney. We believe that the reported findings are strong enough to justify further more detailed investigations into the effects of this important industrial substance on human liver and kidney functions.


4 Torkelson TR, Oyen F. The toxicity of 1,3-dichloropropene as determined by repeated exposure to laboratory animals. Am Ind Hyg Assoc J 1978;39:217-23.


6 De Wolff FA, Peters ACR, Van Kempen GMJ. Serum concentrations and