The Mutagenicity of Dichloroacetaldehyde

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Dichloroacetaldehyde, a presumed metabolite of the insecticides dichlorvos and trichlorphon, is mutagenic in the Salmonella/microsome test. Its mutagenic potency is higher than that of the established mutagen dichlorvos. It is possible that the bacterial mutagenicity test only or mainly detects the effect of methylation by dichlorvos.

2,2-Dichloroacetaldehyde is a presumed metabolite of the insecticides 0,0-dimethyl 1-hydroxy-2,2,2-trichloroethyl phosphonate (trichlorphon, dip-terex) [1] and 0,0-dimethyl 0,2,2-dichlorovinyl phosphate (dichlorvos, DDVP) [2] in the metabolism leading to dichloroethanol-glucuronide. The mutagenicity of dichlorvos has been detected in a number of test systems [3, 4] and the effect has largely been ascribed to the methylation of nucleophilic targets by dichlorvos [5–7]. It has been inferred that methylation of DNA cannot occur in vivo at practical use concentrations of dichlorvos due to its rapid metabolism [8]. It has also been suggested that the genotoxic effects of dichloroacetaldehyde should be investigated [9].

Mutagenicity tests were performed with the Salmonella/microsome test system using the plate incorporation assay [10]. The microsomal preparation (S-9) was from Aroclor 1254 treated male rats and the activation system (S-9 mix) was prepared as described by Ames et al. [10]. The Salmonella typhimurium strain TA 100 (hisG46, rfa, AuvrB, pKM101) has been used. Its spontaneous reversion frequency has been in the range 144–189 throughout the study.

Analytical standard dichlorvos was a gift from Shell Chemical Co. Dichloroacetaldehyde was prepared from dichloroaet (K & K Laboratories, Irvine, CA) as described by Paterno [11]. The chloroaet was the same as used by McCann et al. [12]. 2,2-Dichloroethanol and 2-chloroethanol were obtained from K & K Laboratories.

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the absence of S-9 and the possibility of a decreased mutagenicity to about 15 revertants/μmol in the presence of S-9.

A weak mutagenicity of chloroethanol has previously been reported [12] of which a part is detectable in the absence of S-9 and another part is dependent on the presence of S-9 but independent of NADP. This behavior has been confirmed (Fig. 3). Dichloroethanol gives under similar conditions no detectable mutagenicity.

The present study focuses the attention on the importance of evaluating the mutagenic effects of metabolites of a compound under study. It seems likely that — in the testing of dichlorvos — the Salmonella/microsome test system only or mainly detects the effects of methylation by dichlorvos. *In vitro* studies with liver fractions have indicated that these mainly metabolize dichlorvos by dealkylation to desmethyl-dichlorvos [1]. An *in vivo* mutagenicity study of dichlorvos using the host-mediated assay was negative [13], but it has been emphasized that this result is not in conflict with the positive *in vitro* results as the doses had to be kept relatively lower in the *in vivo* test [3].

A direct comparison between chloroacetaldehyde and dichloroacetaldehyde is not possible. The chloroacetaldehyde used in this study is, as pointed out by Elmore *et al.* [14], a mixture of the monomer hydrate and dimer hydrate forms of which the dimer has a lower mutagenicity than the monomer. The actual mutagenicity of chloroacetaldehyde is thus higher than that measured in the present study. Both chloroacetaldehyde and dichloroacetaldehyde are mainly hydrated in aqueous solution [15]. The order of the mutagenic potency, *i.e.* chloroacetaldehyde > dichloroacetaldehyde, is in agreement with the finding by Waskell [16] that trichloracetaldehyde (chiral) is a very weak mutagen for the TA 100 strain. Changes suggestive of a premalignant condition have been reported in a subacute toxicity test of chloroacetaldehyde [17]. Dichloroacetaldehyde has recently been shown to be mutagenic in mice in the dominant lethal test having a mutagenic activity comparable with that of trichlorphon [1].

Dichlorvos has been tested for carcinogenicity in two major assays. It was concluded from a 2-year inhalation study in rats that there was no dose-related increase in tumor risk [18]. It was concluded in the National Cancer Institute bioassay of dichlorvos that the compound was not demonstrated to be carcinogenic but that the possibility of tumorigenicity is not precluded [19]. Trichlorphon has been reported to be tumorigenic [20].

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