Methylation of Purines and Nicotinamide in the Rat by Dichlorvos

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Rats exposed to [^{14}C-methyl]-dichlorvos excrete labelled 7-methylguanine, 3-methyladenine, and 1-methylnicotinamide in the urine.

Dichlorvos (dimethyl 2,2-dichlorovinyl phosphate) is a methylating compound [1] and it has been shown to methylate nucleic acid *in vitro* [2, 3] and in bacteria [3, 4] as well as to yield 7-methylguanine in mice following i.p. injection and inhalation exposure [4].

In the present study two male R strain rats (240 and 260 g, 3 1/2 months old) were given 225 μCi of [^{14}C-methyl]-dichlorvos (3.2 mCi/mmol [4]) by i.p. injection. The animals were then placed in a metabolic cage with free access to food and water. Urine was collected for four consecutive 24 h periods during which resp. 53, 4.1, 1.2, and 0.7 per cent of the administered radioactivity was excreted by this route.

Analysis of the urinary excretion of 1-methylnicotinamide during the first 24 h period by the procedure given by Chu and Lawley [5] showed that 1.8 nCi was excreted as such. This indicates that dichlorvos behaves as methyl methanesulfonate which also yields 1-methylnicotinamide [5].

Urinary purines were isolated and chromatographed on a Dowex 50-X12 column with gradient hydrochloric acid and the radioactivity assayed as described previously [4]. The amounts of 7-methylguanine (7-meG) and 3-methyladenine (3-meA), which elute together in the system used, were resp. 5.8, 3.9, 2.8, and 1.9 nCi for the four 24 h periods. The relative amounts of 7-meG and 3-meA in the three first periods were determined by paper chromatographic separation as described by Löfroth *et al.* [6]. The per cent of 3-meA were resp. 7 – 8, 4 – 6, and 3 or slightly less.

It can be calculated from these data that the biological half-life for urinary excretion of the 7-meG formed is about 50 h (*cf.* Fig. 1). This is about the same as that which is being found for 7-meG formed from methyl methanesulfonate under the same experimental conditions [7], and it is intermediate to half-lifes reported for loss of 7-meG from rat liver DNA of 3.0 days [8], from rat liver RNA of 3.5 days [9], and from L-cell DNA of about 30 h [10]. An approximate half-life for excretion of 3-meA of 20 h can also be estimated (*cf.* Fig. 1). The faster excretion of 3-meA is in accordance with the fact that the rate of loss of 3-meA from DNA is faster than that of 7-meG [10, 11].

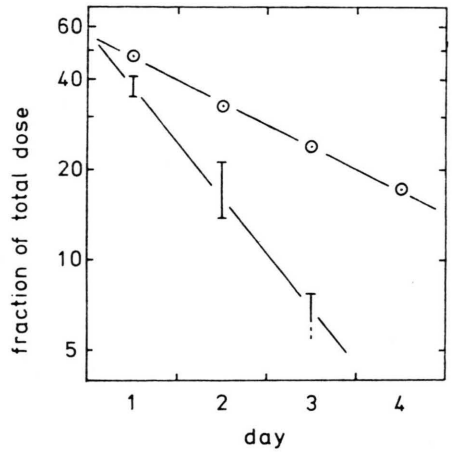

Fig. 1. The amounts of labeled 7-methylguanine ($\times 10^6$), ⊙, and 3-methyladenine ($\times 10^7$) I, excreted daily after i.p. injection of [^{14}C-methyl]-dichlorvos in rats. The amounts are expressed as fractions of the total dose (225 μCi) and corrected for isotope dilution assuming that both methyl groups in dichlorvos have contributed to the same extent.

These results indicate strongly that dichlorvos methylates nucleic acids in mammals.

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[1] G. Löfroth, Ch. Kim, and S. Hussain, Environmental Mutagen Society News Letter **2**, 21 [1969].
[2] G. Löfroth, Naturwissenschaften **57**, 393 [1970].
[3] P. D. Lawley, S. A. Shah, and D. J. Orr, Chem.-Biol. Interactions **8**, 171 [1974].
[4] R. Wennerberg and G. Löfroth, Chem.-Biol. Interactions **8**, 339 [1974].
[5] B. C. F. Chu and P. D. Lawley, Chem.-Biol. Interactions **8**, 65 [1974].
[6] G. Löfroth, S. Osterman-Golkar, and R. Wennerberg, Experientia, in press.
[7] G. Löfroth, unpublished data.
[8] G. P. Margison, M. J. Capps, P. J. O'Connor, and A. W. Craig, Chem.-Biol. Interactions **6**, 119 [1973].
[9] M. J. McElhone, P. J. O'Connor, and A. W. Craig, Biochem. J. **125**, 821 [1971].
[10] I. G. Walker and D. F. Ewart, Mutation Res. **19**, 331 [1973].
[11] P. J. O'Connor, M. J. Capps, and A. W. Craig, Brit. J. Cancer **27**, 153 [1973].