

## Methylation of Purines and Nicotinamide in the Rat by Dichlorvos

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

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

In the present study two male R strain rats (240 and 260 g, 3½ months old) were given 225  $\mu\text{Ci}$  of [ $^{14}\text{C}$ -methyl]-dichlorvos (3.2 mCi/mmol<sup>4</sup>) 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<sup>5</sup> showed that 1.8 nCi was excreted as such. This indicates that dichlorvos behaves as methyl methanesulfonate which also yields 1-methylnicotinamide<sup>5</sup>.

Urinary purines were isolated and chromatographed on a Dowex 50-X12 column with gradient hydrochloric acid and the radioactivity assayed as described previously<sup>4</sup>. 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.*<sup>6</sup>. 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

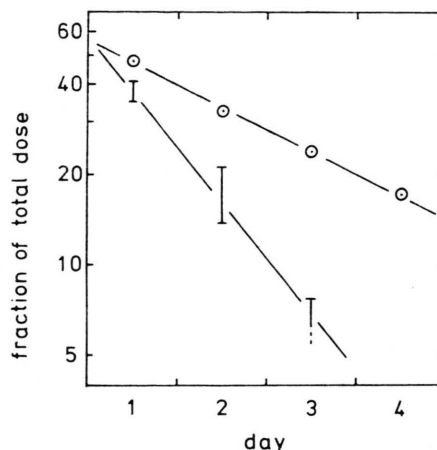


Fig. 1. The amounts of labeled 7-methylguanine ( $\times 10^6$ ),  $\odot$ , and 3-methyladenine ( $\times 10^7$ )  $\bullet$ , excreted daily after i.p. injection of [ $^{14}\text{C}$ -methyl]-dichlorvos in rats. The amounts are expressed as fractions of the total dose (225  $\mu\text{Ci}$ ) and corrected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

same as that which is being found for 7-meG formed from methyl methanesulfonate under the same experimental conditions<sup>7</sup>, and it is intermediate to half-lives reported for loss of 7-meG from rat liver DNA of 3.0 days<sup>8</sup>, from rat liver RNA of 3.5 days<sup>9</sup>, and from L-cell DNA of about 30 h<sup>10</sup>. 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<sup>10,11</sup>.

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

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