THE METABOLISM OF ^{14}C–ETHANEDIOL (Ethylene Glycol)

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During the last four years we have studied, in London, the metabolic fate of 22 diols, two of which are of considerable industrial importance. These two are ethanediol, which is used on a large scale as an anti-freeze in motor-cars, and hexanediol, which is used as a solvent for essences for soft drinks. In this paper, I wish to mention briefly some of our results on the metabolic fate of ethanediol.

This compound labelled with ^{14}C was made by hydroxylation of ^{14}C–ethylene with hydrogen peroxide and osmium tetroxide. The reaction is as shown and the recovery of ^{14}C was 43 per cent.

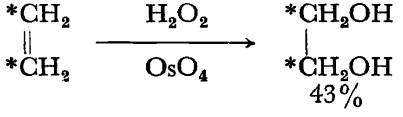


Table 1 shows the distribution of ^{14}C in rabbits, after a small oral dose of the diol. *Table 1* shows that a large proportion of the dose is eliminated in

Table 1. Fate of ^{14}C–ethanediol in rabbits; dose: 124 mg/kg

Exp.	*Time* (h)	% *of* ^{14}C *in*				
		Expired air	*Urine*	*Faeces*	*Body*	*Total*
1	26	42	21	—	—	—
2	74	60	23	1	11	95

the expired air as carbon dioxide. About $\frac{1}{5}$th of the dose is eliminated in the urine, largely as unchanged ethanediol. Some 10 per cent remains in the body after 3 days.

Table 2 shows some results obtained with rats. The diol is less readily oxidized to carbon dioxide in the rat than in the rabbit, and the percentage of the dose eliminated in the expired air decreases as the dose increases. More appears in the urine of rats than in that of rabbits.

We have not completely identified the urinary metabolites of ethanediol. *Table 3* shows the results of one experiment. The main metabolite is unchanged ethanediol. Urea is labelled, but at a dose of 124 mg/kg in the rabbit, no oxalate is excreted.

Table 2. Fate of ^{14}C–ethanediol in rats

Dose (g/kg)	% *of* ^{14}C *in 24 h in*	
	Expired air	*Urine*
0·1	23	35
0·6	19	55
1·0	14	58
5·0	6	32

Table 3. Fate of ^{14}C–ethanediol in the rabbit; dose: 124 mg/kg; ^{14}C: 80 μC

Compound sought	% *of dose in 24 h in urine*
Ethanediol	10·3
Urea	0·7
Glycolaldehyde, Glyoxal, Glycollic acid, Glyoxylic acid, Oxalic acid, Acetaldehyde, Acetic acid	0
Total radioactivity of urine	18

Figure 1 shows, graphically, the excretion of oxalate in four species given oral doses of ethanediol from 0·1 to 1·0 g/kg. It is to be noted that in all

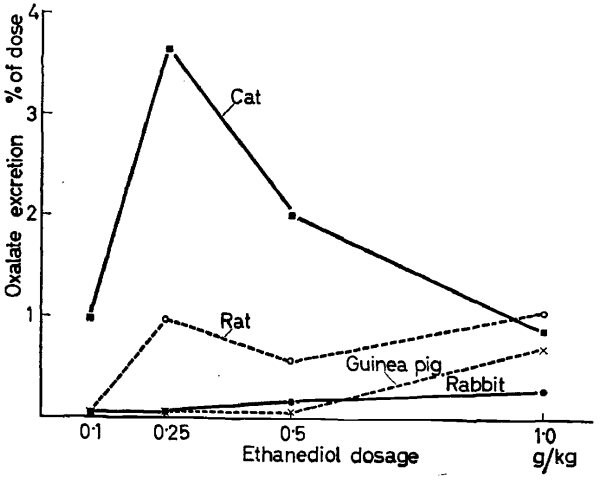


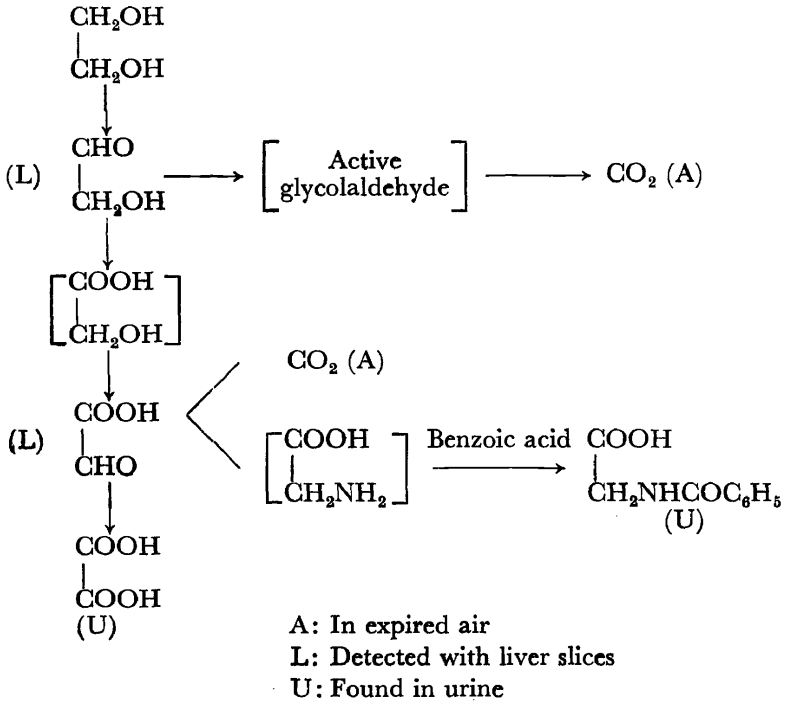
Figure 1. Species differences in urinary oxalate excretion following the oral administration of ^{14}C-ethanediol. Each point on the graphs is the percentage of the dose of ethanediol excreted as oxalate (by isotope dilution) in 48 hours after dosing, except the last point for the cat (1 g/kg) which is for 24 hours after dosing. The 1 g/kg dose was fatal to cats within 48 hours.

species except the cat, the output of oxalate is less than 1 per cent of the dose. Rabbits and guinea-pigs produce very little oxalate; rats produce rather

more, and cats, which are readily poisoned by ethanediol, produce much larger amounts—in one case nearly 4 per cent of the dose.

Figure 2 shows the probable paths of metabolism of ethanediol. The main path is to carbon dioxide, probably *via* glycolaldehyde and glyoxylic acid, both of which have been detected as metabolites of ethanediol in liver

Figure 2. Pathways of metabolism of ethanediol



slices. Further evidence for the formation of glyoxylic acid comes from the observation that the simultaneous administration of benzoic acid with ^{14}C–ethanediol leads to the excretion of ^{14}C–hippuric acid in rabbits.

The formation of oxalate is a minor metabolic reaction of ethanediol. In species not readily poisoned by ethanediol, such as rabbits and guinea-pigs, the oxalate output is low. In cats, which are more readily poisoned by the diol, oxalate formation is appreciable even with small doses.