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JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

SPECIFICATIONS FOR IDENTITY AND PURITY OF FOOD ADDITIVES AND THEIR TOXICOLOGICAL EVALUATION: SOME EXTRACTION SOLVENTS AND CERTAIN OTHER SUBSTANCES

AND

GENERAL CONSIDERATIONS ON ADDITIVES IN BABY FOOD

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# ETHANOL
## (Ethyl Alcohol)

by

Dr. P. S. Elias
(Consultant)

## Biological Data

### Biochemical aspects

Ethyl alcohol is rapidly and readily oxidized to $CO_2$ and water. The toxicity is diminished if substances which increase tissue oxidation are given beforehand. The pathway is generally agreed to be initial oxidation to acetaldehyde, conversion to acetyl co-enzyme A and acetic acid, final combustion in muscle and liver to $CO_2$ and water (Browning, 1965). Lung tissue can also convert ethanol to $CO_2$ (Masoro et al., 1953). Extrahepatic metabolism probably accounts for 50 per cent. of elimination (Larsen et al., 1961). Alcohol dehydrogenase controls the initial oxidation to acetaldehyde. The enzyme is found mainly in the liver and a little in the kidney. It probably requires the presence of NAD. The enzyme contains Zn which contributes to the binding of DPN with the enzyme. Acetaldehyde dehydrogenase controls the further oxidation of acetaldehyde to acetic acid (Vamps, 1965). Using $C^{14}$ labelled alcohol it has been shown that rats exhale 75 per cent. as $CO_2$ in 5 hours and 90 per cent. in 10 hours. Two per cent. is eliminated unchanged in the urine and expired air, while 0.5-2.0 per cent. is conjugated and excreted in the urine as ethylglucuronide (Bartlett & Barnett, 1949, Kamil et al., 1953).

Clearance of ethanol from blood depends on the amount of dosage. For low dosage it is proportional to the amount present, for larger doses it varies with time in the same animal (Williams, 1959). The rat metabolizes alcohol more slowly than the mouse and faster than the dog (Mull et al., 1956). In dogs alcohol passes

through the kidneys by simple diffusion. During absorption from the G.I. tract the concentration of ethyl alcohol was a little lower in peripheral veins compared with arterial levels. 2-4% of total ingested alcohol was eliminated by kidneys and 4% in the expired air (Treon, 1958). Recent evidence suggests that man metabolises alcohol at a rate depending upon the concentration present if catalase handles oxidation but independent of concentration in the human body if alcohol dehydrogenase handles oxidation. The action of tetraethylthiuram disulphide may increase the tissue concentration of acetaldehyde necessary to achieve metabolism to acetic acid. Other possibilities are prevention of the oxidation of ethanol and the production of disulphide metabolites. Any acetic acid formed joins the body acetate pool (Treon, 1958). Ethanol is distributed uniformly in body water (Camps, 1963). Ethanol has a direct effect on liver cells *in vitro*, decreases DPN and increases DPNH and therefore effects more acetate incorporation into fatty acids (Lieber & Schmid, 1961). Acute ethanol induced fatty liver differs from that induced by chronic small amounts in that the latter responds to choline but not the former. Hence hepatic fat may increase by a) increased mobilization of fat from depots, b) increased fat synthesis and esterification in the liver itself, c) including a relative choline deficiency, all leading to the picture of fatty infiltration and fibrosis (Klatskin, 1961). Decreased fat oxidation in the liver may contribute to the fat accumulation (Isselbacher & Greenberger, 1964). Ethanol produces a marked increase in serum cholesterol in the dog, while in man a small but significant increase occurs after large intakes. Hyperlipaemic subjects show greater rise (Grande & Amatuzio, 1960). Ethanol has a moderate short-lasting effect on adrenal medullary secretion producing a rise in urinary adrenalin and noradrenalin output. This is probably due to sympathetic stimulation (Perman, 1961). Alcohol is not absorbed through normal skin but can be absorbed through abraided areas (Camp, 1968).

Acute toxicity

| Animal | Route | $LD_{50}$ mg/kg body weight | $LD_{100}$ mg/kg body weight | References |
|---|---|---|---|---|
| Frog | s.c. | - | 7100-7900 | Spector, 1956 |
| Mouse | oral | 9488 | - | Spector, 1956 |
| | s.c. | 8235 | - | Spector, 1956 |
| | s.c. | - | 4700 | Browning, 1953 |
| | i.v. | 1973 | - | Spector, 1956 |
| | inhalation | - | 29300 ppm | Browning, 1965 |
| Rat | oral | 13660 | - | Spector, 1956 |
| | i.p. | 5000 | - | Spector, 1956 |
| | inhalation | - | 12700 ppm | Browning, 1965 |
| Guinea-pig | i.p. | 5560 | - | Spector, 1956 |
| | inhalation | - | 21900 ppm | Browning, 1965 |
| Rabbit | oral | 6300 | - | Spector, 1956 |
| | oral | 9500 | - | Spector, 1956 |
| | oral | - | 7390 | Spector, 1956 |
| | oral | - | 9000-10000 | Browning, 1953 |
| | i.p. | - | 3500 | Browning, 1953 |
| | i.v. | - | 9400 | Spector, 1956 |
| Cat | i.v. | - | 3945 | Spector, 1956 |
| Dog | oral | - | 5500-6500 | Spector, 1956 |
| | s.c. | - | 6000-8000 | Spector, 1956 |
| | i.v. | - | 5365 | Spector, 1956 |
| Man | oral | - | 6000-8000 | von Oettingen, 1943 |

Ethyl alcohol acts principally on the brain whether ingested or inhaled, by first inhibiting higher functions and then as anaesthetic. The lethal dose for man is 8-10 cc per kg body-weight or one quart-whiskey or a blood level of 0.5 per cent. or more (Haag et al., 1951, von Oettingen, 1943). Death occurs from severe and probably irreversible injury to the CNS. Acute intoxication affects visual acuity, fields of vision, eye coordination and distance judgement. The vapour is a minor irritant to the eye and respiratory tract mucosa. Animals as much as man develop tolerance. Dogs intoxicated by ingestion showed liver injury consisting of cellular oedema at the periphery of lobules and increase in lipid which regressed subsequently (MacNider, 1933). Inhalation of high concentrations caused reversible fatty infiltration of the liver (Weese, 1925). The TLV is 1000 ppm (Patty, 1958). However concentrations up to 3500 ppm do not produce irritation or any subjective symptoms nor any rise in blood alcohol concentration (Treon, 1958).

Short-term studies

Mouse. Groups of 10 mice were fed for 5 weeks on a control diet but drinking water was either normal water or 0.8 per cent., 4 per cent. and 20 per cent. ethyl alcohol. Mortality increased with dose but there was little effect on the mean weight of survivors (College Pharmaceutical Society, 1962).

Groups of male and female mice were given ethyl alcohol (unknown composition) i.p. for 6 months. No tumours were noted (Larsen & Heston, 1945).

Rat. Five female rats received orally 1 ml 40 per cent. aqueous alcohol 3 times per week for 41 days. No tumours were observed (Russell et al., 1941).

Nine groups of rats containing 5-25 animals received 20 per cent. alcohol in their drinking water and additional cystine with or without choline in their diet. Observation extended from 8 to 24 weeks. No tumours were observed (Wanscher, 1953).

15 rats received 15 per cent. alcohol in water for up to 14 weeks. No tumours were observed (Baumann et al., 1942).

Groups of male rats received 15 per cent. alcohol in their drinking water. After 177 days there were no tumours (Best et al., 1947).

24 rats were given 15 per cent. alcohol in their drinking water. After 120 days there were no tumours (Klatskin et al., 1951).

In another experiment rats were given ethyl alcohol in their food for 300 days without any pathological changes having been observed (Hamahara & Mori, 1939).

Rabbit. 64 rabbits were given 20 per cent. alcohol in water by stomach tube in quantities from 20-100 ml daily for 304 days. Thirteen died of infection but no tumours were seen in the rest (Connor, 1940).

Dog. Twenty-three dogs received a 40 per cent. aqueous solution at a rate of 10 ml/kg body-weight daily for 6 to 26 months without any signs of tumour development (MacNider & Donnelly, 1932).

Human observation

In man ethyl alcohol acts as a mental depressant; moderate doses stimulate the appetite and food absorption. Higher concentrations irritate the gastric mucosa (Jacobs, 1947). Ingestion of less than 0.5 g/kg does not effect the behaviour of man, 0.5-2.0 g/kg cause some disturbance and doses above 2 g/kg cause serious drunkenness (von Oettingen, 1943). The effect of inhalation depends on whether the person is accustomed to drinking alcohol. Absorption by the skin is rare. Some visual impairment is seen in chronic ingestion as well as some incoordination of voluntary muscles (Browning, 1965). Chronic intake of alcohol amounting to over 160 g pure alcohol per day for more than 10 years leads to hepatic cirrhosis in man (Thaler, 1969).

Long-term studies

Mouse. 16 mice received 0.1 ml of a 50 per cent. alcoholic solution every two days rectally for 547 days. Two animals developed tumours of which one was a sarcoma. In another experiment, 10 male and female mice received 0.1 ml of a 50 per cent. alcoholic solution every two days orally for 554 days. Two tumours of the back were observed (Krebs, 1926).

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