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TOXICOLOGICAL EVALUATION OF SOME EXTRACTION SOLVENTS AND CERTAIN OTHER SUBSTANCES

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BROMINATED VEGETABLE OILS

Biological data

Biochemical aspects

Brominated olive oil has been used for radiography in man and animals without apparent deleterious effects. Bromide ions may be very slowly released during metabolism of brominated oils (Cortell, 1941; 1956). Feeding of brominated maize oil appears to cause an accumulation of organically bound bromine in adipose tissues and organ fat of the rat, pig and man, and this lipid-bound bromine is released slowly. The exact chemical form in which this organically bound bromine is present in tissue fats is not yet known (BIBRA, 1970). Rats fed 0.8% brominated maize oil for 25 weeks accumulated bromine to a maximum of 10 000 ppm in their body fat after 8 weeks. This level

remained stationary during the remaining 17 weeks. Only 30% of the bromine disappeared in the following 8 weeks on a normal diet no change in level having been noted for the first two weeks. Starvation merely increased the bromine concentration in body fat without mobilisation of lipid-bound bromine (Gaunt et al., 1968).

Acute toxicity

Five groups of 2-4 rats each were fed brominated olive oil at levels of 15 000, 10 000, 5 000, 3 000 and 1 000 mg/kg bodyweight per day. All animals on the three highest doses died by the third or fourth day, those on 3 000 mg/kg died by the 8th day, but those on the lowest dose level survived 10 days. No significant pathological lesions were found at autopsy when compared with controls fed comparable amounts of olive oil (Cortell, 1941; 1956).

Brominated cottonseed oil was administered orally to groups of 5 male rats in doses of 2 500, 5 000 and 10 000 mg/kg/day. After 4 days of treatment all rats on the highest dose and 3 out of 5 on the middle dose had died. The survivors and those on the lowest dose were lethargic and had decreased body temperatures and respiration rates (Munro et al., 1969).

Short-term studies

Rat

Three groups of 16 young male and female rats were fed for 8 weeks either 0.5% brominated olive oil, plain olive oil or 0.22% sodium bromide (equivalent to the total bromine in oil) in their diet. There were no significant differences from controls regarding growth,

urine analysis, haematology and histological examination of liver and kidney (Cortell, 1941; 1956).

Five groups of 16 male and 16 female rats were fed for 90 days brominated maize oil in their diet at 0, 0.05%, 0.2% and 0.8% with 0.8% of plain maize oil as positive control. No significant effects on growth, haematological indices, renal function tests or serum chemistry were observed. Maize oil caused a mild degree of fat deposition randomly distributed within the liver lobules. At the 0.8% and 0.2% level there was enlargement and fatty infiltration of the liver and kidneys. Periportal fatty infiltration of the liver was also seen at the 0.05% level. At the 0.8% level the hepatocytes were enlarged and foamy. Lipid-bound bromine was found at all levels in adipose tissue after 13 weeks (Gaunt et al., 1968).

Three groups of 20 male rats were fed semi-purified diet containing 0, 0.5% or 2.5% of brominated cottonseed oil for 80 days. Growth and food utilization were impaired at the highest level and mild anaemia was noted. The liver, heart, kidneys and spleen were enlarged at the 2.5% level and the heart also at the 0.5% level. All rats had thyroid hyperplasia, myocarditis, fatty changes in the liver, arrested testicular development, renal tubular epithelial changes and reduced liver enzyme activities (Munro et al., 1969).

In another experiment groups of rats were fed 0, 0.02%, 0.1% and

0.5% of brominated cottonseed oil in the diet for 100 days. Enlargement of the heart appeared at the 0.5% level only, as well as accumulation of lipid in liver and heart. The activities of the hepatic drug metabolizing enzymes and isocitric dehydrogenase were normal but that of glucose 6 -phosphate dehydrogenase was reduced at the 0.1% and higher level. There was minimal liver pathology but the hearts of some animals even at the 0.1% level showed degenerative lesions (Munro et al., 1970).

In another experiment groups of 15 male and female rats were fed 0%, 0 0% or 0.5% brominated cottonseed, corn, olive and sesame oils for 105 days. Animals at the 0.5% levels showed degenerative heart lesions with interstitial oedema, swollen cells, hyaline degeneration and pyknotic nuclei. Lesions progressed to myocytolysis and mild infiltration with mononuclears. Lipid accumulated in the liver and microfollicular thyroid hyperplasia was seen. Only 2 animals at the 0.1% level showed mild myocardial changes. The heart weights of all animals at the 0.5% level were elevated except for brominated olive oil. All kidney and liver weights were increased at the 0.5% level. Hearts of animals on brominated cottonseed oil had reduced capacity to metabolize palmitic acid when fed 400 mg/kg bodyweight per day for 3 days (Munro et al., 1970).

Pigs

Groups of 2 miniature pigs were fed brominated maize oil for 42

days at 100 or 400 mg/kg/day. Tissue analysis showed the accumulation of lipid-bound bromide in adipose tissue, liver, spleen, adrenals, brain, kidney and lymph nodes. No organic bromine was detected in serum or urine. Histology showed no abnormalities apart from very slight fatty accumulation in the liver (Crampton, 1968).

In another experiment single pigs were given 0, 20, 40, 80 or 160 mg/kg/day brominated vegetable oil for 64 days, followed by 109-178 days on normal diet. Biopsy of subcutaneous adipose tissue showed dose related accumulation of bromine with a fall in the rate of accumulation after 20 days. When put on a control diet there was a very slow decrease in absolute amounts of lipid-bound bromine. All organs examined contained lipid-bound bromine (Crampton, 1968).

Long-term studies

None available.

Observations in man

Bromine estimation in human adipose tissue fat and other organ fats from Holland, Germany and U.K. revealed high levels of lipid-bound bromine only in that country which permitted the use of brominated vegetable oil as a food additive. High levels of lipid-bound bromine were found particularly in children up to the age of 15, the levels in adults being very much lower. Lipid-bound bromine increased in organ fat in an age-related manner and levels were much higher in the fat extracted from brain, liver and spleen than from adipose tissue. Body fat from countries not using brominated vegetable

oils contained only minimal lipid-bound bromine. Apparently no chemical abnormalities were associated with bromine storage (British Indust. Biol. Res., Assoc., 1970).

Comments

Brominated vegetable oils were considered at the Ninth FAO/WHO Expert Committee meeting of Food Additives (FAO/WHO, 1966) but not evaluated because of lack of suitable data. Attention was then drawn to the necessity for providing evidence on cumulation and subsequent release of bromine in body lipids. Recent evidence has demonstrated accumulation of bromine in the body lipids of the rat, pig and man (particularly children). Despite the absence of any definite pathological effects in man, it seems undesirable that lipid-bound bromine should accumulate in the tissues of man. Progressive cardiac lesions have been noted in the rat at comparatively high levels of intake. No long-term studies are available to define a no-effect level.

Evaluation

The absence of a no-effect level based on long-term studies precludes the establishment of any formal ADI.

Further work required

Long-term studies using various forms of brominated vegetable oil, commonly used commercially, with particular emphasis on bromine storage

in tissues and on cardiac pathology.

The significance of bromine deposition in body lipids should be determined and the possibility investigated of an epidemiological relationship to cardiac disease in man.

Identification of the brominated derivative(s) accumulated in the fat of animals and man as well as a study of their toxicological properties.

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