

activity with 2-butoxyethanol as substrate than rat ADH, and that it is expressed at much higher specific activity in areas of the mouse forestomach than in that of rats. These differences have been purported to result in higher local concentrations of toxic metabolites of 2-butoxyethanol in the forestomach of mice compared with that of rats (Green *et al.*, 2002).

It cannot be excluded that the continuous presence of the metabolite 2-butoxyacetaldehyde, which possibly exhibits weak clastogenic activity, can give rise to tumour formation in the regenerating forestomach tissue.

Anatomical and physiological differences between mice and humans limit, but do not entirely rule out, the relevance of mouse forestomach tumours to humans.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2-Butoxyethanol is a glycol ether that is widely used as a solvent in surface coatings (paints and varnishes), paint thinners, printing inks and glass- and surface-cleaning products (including those used in the printing and silk-screening industries), and as a chemical intermediate. It is also used in a variety of personal care and other consumer products. Occupational exposure occurs through dermal absorption or via inhalation during its manufacture and use as a chemical intermediate, and during the formulation and use of its products. Highest mean exposures have been measured for silk screeners. Exposure of the general population can occur through dermal contact or inhalation during the use of consumer products, particularly cleaning agents.

5.2 Human carcinogenicity data

A case-control study of acute myeloid leukaemia and myelodysplasia found no elevation of risk with exposure to a group of glycol ethers, including 2-butoxyethanol. However, the information provided by this study on 2-butoxyethanol specifically was limited.

5.3 Animal carcinogenicity data

2-Butoxyethanol was tested for carcinogenicity by inhalation exposure in male and female mice and rats. Clear increases in tumour incidence were observed in a single species. Exposure to 2-butoxyethanol induced a dose-related increase in the incidence of haemangiosarcomas of the liver in male mice and a dose-related increase in the incidences of combined forestomach squamous-cell papillomas or carcinomas (mainly papillomas) in female mice. In female rats, a positive trend was observed in the occurrence of combined benign or malignant pheochromocytomas (mainly benign) of the

adrenal medulla, but this equivocal result could not be attributed with confidence to exposure to 2-butoxyethanol. There was no increase in the incidence of tumours in male rats.

5.4 Other relevant data

Toxicokinetics and metabolism

2-Butoxyethanol is rapidly absorbed following ingestion, inhalation and dermal exposure in humans and experimental animals. Uptake and metabolism in rats are linear up to 400 ppm. The elimination half-life of 2-butoxyethanol from the blood is much longer in humans than in rats or mice. The principal pathway of metabolism in humans and experimental animals involves oxidation to butoxyacetaldehyde and butoxyacetic acid (the putatively active metabolite for 2-butoxyethanol-induced haematological effects) via alcohol and aldehyde dehydrogenases, respectively. Based on limited data and the results of a physiologically based pharmacokinetic model, humans appear to metabolize 2-butoxyethanol to butoxyacetic acid to a lesser extent than rats, which results in greater concentrations of butoxyacetic acid in the blood of rats than in that of humans. The elimination half-life of butoxyacetic acid in the urine is about 6 h in humans, and at least 15–55% of the inhaled dose of 2-butoxyethanol is excreted as free butoxyacetic acid. Although mice metabolize 2-butoxyethanol to butoxyacetic acid at a greater rate than rats, the metabolite is cleared much more slowly in rats, which is consistent with the greater sensitivity of rats to its effects in the blood. Similarly, slower clearance in female rats probably accounts for their greater sensitivity compared with male rats. Detoxification via conjugation of butoxyacetic acid with glutamine and excretion in the urine has been demonstrated in humans, but not to date in rats. The extent of glutamine conjugation varies within and between individuals, with a mean of around 70%. 2-Butoxyethanol may also be *O*-dealkylated to ethylene glycol, based on limited information in humans and more extensive evidence in rodents (conjugation of 2-butoxyethanol with glucuronide or sulfate has been observed in rats, but only tentatively in human hepatocytes *in vitro*).

Toxic effects

Several case reports that involved the consumption of up to several hundred millilitres of glass-cleaning liquid that contained various amounts of 2-butoxyethanol described a variety of effects (hypotension, coma, metabolic acidosis, renal impairment, haematuria, haemoglobinuria, hypochromic anaemia) in adults. In a survey of childhood poisonings, no symptoms were reported in children who had ingested comparable amounts of glass-cleaning liquids.

Incidental cutaneous exposures were not reported to produce adverse skin reactions or skin sensitization. Repeated dermal exposure produced increasing erythema. Exposure to 2-butoxyethanol vapour is irritating to the eyes, nose and throat.

In studies of occupational exposure to airborne 2-butoxyethanol (mean concentrations of 2–4 mg/m³), effects on blood parameters (lower haematocrit values), but no changes in

renal or hepatic function and no correlation with concentrations of 2-butoxyacetic acid in the urine of exposed workers were observed. In one study, airborne levels of 100–300 ppm [483–1450 mg/m³] 2-butoxyethanol caused acute and severe irritation of the eyes and respiratory tract and the appearance of cherry angiomas (benign cutaneous vascular lesions) after 3 months, which persisted and continued to develop.

Effects on the blood appear to be the most sensitive parameter in experimental animals following acute, short-term, subchronic or chronic exposure via oral, inhalation and dermal routes, based on an extensive database. Alterations in haematological parameters that are consistent with haemolytic anaemia have repeatedly been observed in multiple species, including mice and rats. There is substantial evidence from in-vivo and in-vitro investigations that rats are more sensitive to 2-butoxyethanol-induced haemolysis than other experimental species, and alterations in relevant parameters were observed following long-term exposure to concentrations as low as 31.2 ppm [151 mg/m³]. Female rats are more sensitive to the haematological effects associated with exposure to 2-butoxyethanol than male rats, which is consistent with sex-related differences in the clearance of the putatively active metabolite, butoxyacetic acid, and greater activity of the enzymes involved in its formation. On the basis of several in-vitro investigations in erythrocytes of humans and rats, humans appear to be much less sensitive. Although the physical–chemical pathway for haemolysis by 2-butoxyethanol has not been fully elucidated, it has been reported that haemolysis involves cell swelling, morphological changes and decreased deformability.

Haemolysis has been proposed to be linked mechanistically to the induction of liver neoplasia in male mice by 2-butoxyethanol. Damage to red blood cells results in the deposition of haemosiderin in Kupffer cells of both mice and rats which in turn apparently mediates the induction of hepatic oxidative stress that has been observed in both species *in vivo*. In mice, but not in rats, oxidative stress results in the formation of the oxidative, mutagenic DNA lesion, 8-hydroxydeoxyguanosine, as well as an increase in the proliferation of endothelial cells; both of these effects are assumed to contribute to the development of liver tumours. The apparent protection of rats against these consequences of oxidative stress, which is not observed in mice, has been attributed to a higher level of protective antioxidants in rat liver than in mouse liver. In view of the much lower sensitivity to haemolysis of human erythrocytes than those of mice and rats, and the fact that the concentration of the antioxidant, vitamin E, is approximately 100-fold higher in human liver than in mouse liver, the induction of liver tumours in humans is unlikely to occur through this pathway. Other potential mechanisms have not been investigated.

Toxic effects have been observed in the forestomach of mice and rats following both oral and inhalation exposure to 2-butoxyethanol; mice were more sensitive than rats. In a chronic inhalation study in mice, toxicity was observed at all concentrations investigated, i.e. at 62.5 ppm [302.5 mg/m³] and higher. The effects on the forestomach were increased in incidence and severity with increasing exposure concentration, and included irritation, inflammation, hyperplasia and ulceration. Increases in tumour incidences were observed in mice at the higher concentrations. The formation of forestomach tumours in mice is associated with high local exposure of the forestomach to 2-butoxyethanol, even during

inhalation exposure, and to high metabolic activity in certain areas of the forestomach, which results in high local concentrations of the toxic metabolite, 2-butoxyacetic acid.

Reproductive and developmental effects

In developmental toxicity studies in rats and mice that involved oral and inhalation exposure to 2-butoxyethanol, embryotoxic or fetotoxic effects were observed at doses or concentrations similar to or greater than those which induced toxicity (including haematological effects) in the dams. Alterations in haematological parameters were also observed in fetuses of exposed dams. Effects on reproductive ability and reproductive organs were also only observed at doses or concentrations of 2-butoxyethanol much greater than those associated with haematological effects.

Genetic and related effects

The available data on 2-butoxyethanol support the concept that the compound itself exhibits no appreciable genotoxicity. The oxidative metabolite, 2-butoxyacetaldehyde, appears to have a weak capacity to cause genotoxic effects *in vitro*, largely at the chromosomal level. The product of further oxidation, 2-butoxyacetic acid, does not appear to be genotoxic.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 2-butoxyethanol.

There is *limited evidence* in experimental animals for the carcinogenicity of 2-butoxyethanol.

Overall evaluation

2-Butoxyethanol is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6. References

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