5. Summary of Data Reported and Evaluation

5.1 Exposure data

1-*tert*-Butoxypropan-2-ol is a glycol ether that has been increasingly used since the 1980s as a solvent in coatings, glass-cleaning and surface-cleaning products, inks, adhesives and cosmetic products. No data are available on levels of occupational or consumer exposure to 1-*tert*-butoxypropan-2-ol.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1-*tert*-Butoxypropan-2-ol was tested for carcinogenicity by inhalation in mice and rats. In a single study, a dose-related increase in the combined incidences of liver tumours (hepatocellular adenomas and carcinomas), including hepatoblastomas, was observed in both male and female mice. A significant trend in the increase in malignant tumours was observed in females when hepatocellular carcinomas and hepatoblastomas were combined. In male rats, marginal, non-significant increases in the incidences of renal tubule adenomas (with one carcinoma at the highest dose) and hepatocellular adenomas were observed, but these findings were considered to be equivocal. In female rats, no dose-related increases in tumour incidence were found.

5.4 Other relevant data

No data were available to the Working Group on the kinetics, metabolism, toxic effects, reproductive effects or genetic and related effects of 1-*tert*-butoxypropan-2-ol in humans.

Kinetics and metabolism

1-*tert*-Butoxypropan-2-ol is rapidly absorbed and eliminated in rats and mice. It is eliminated from blood following concentration-dependent non-linear kinetics, with a half-life of approximately 16 and 10 min in rats and mice, respectively. Elimination kinetics were saturable following a single inhalation exposure to 1200 ppm, but saturation was less obvious following repeated exposures. Urinary excretion accounted for 48–67% of an orally administered dose of 1-*tert*-butoxypropan-2-ol; the principal urinary metabolites identified were glucuronide (23–52%) and sulfate (7–13%) conjugates, while expired carbon dioxide

accounted for up to 26%. Metabolites resulting from other potential pathways of metabolism have not been investigated experimentally. Biliary excretion of conjugated 1-*tert*-butoxypropan-2-ol may be significant (up to 40% following intravenous administration), although reabsorption may also occur, based on a recovery of only 4–11% of the administered dose in the faeces, which suggests enterohepatic circulation.

Toxic effects

1-*tert*-Butoxypropan-2-ol has low acute toxicity in experimental animals, although it may be irritating to the skin and eyes. Target organs following short-term, subchronic and chronic exposure include the kidneys and liver. Renal effects consistent with α_{2u}-globulin-associated nephropathy, including hyaline droplet accumulation, cell proliferation in the renal cortex and alterations in urinary parameters, were observed in male Fischer 344/N rats following exposure to 1-*tert*-butoxypropan-2-ol, but not in female Fischer 344/N or in male NBR rats, a strain that does not produce α_{2u}-globulin. However, effects on the kidneys were also observed in female Fischer 344/N rats in subchronic and chronic inhalation studies, including increased relative weights, altered urinary parameters and a concentration-related increase in age-related nephropathy, although generally to a lesser degree than that noted in similarly exposed male rats of this strain.

Toxic effects in the liver have also been observed in short-term, subchronic and chronic investigations in both male and female rats and mice, including increased weight and histopathological changes. However, these observations do not elucidate a potential mode of induction of the reported hepatic tumours in mice.

Reproductive and developmental effects

Although there is some evidence for a reproductive effect in female mice exposed to 1-*tert*-butoxypropan-2-ol (altered estrus cycle), this was only observed at concentrations greater than those associated with effects on the liver.

Based on the limited available data, 1-*tert*-butoxypropan-2-ol does not appear to induce developmental toxicity in experimental animals.

Genotoxicity

1-*tert*-Butoxypropan-2-ol, the structure of which does not carry any structural alert to genotoxicity, has been reported to be weakly mutagenic in *Salmonella* strain TA97 and to cause a statistically significant but very weak increase in the frequency of micronuclei in the peripheral blood of female but not male mice. No genotoxicity was observed in assays for the induction of sister chromatid exchange and chromosomal aberrations in the presence or absence of exogenous metabolic activation *in vitro*. In view of the scarcity of the data available, it is not possible to draw any meaningful conclusion regarding the potential genotoxic effects of 1-*tert*-butoxypropan-2-ol in mammalian cells or in mammals *in vivo*.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of 1-*tert*-butoxypropan-2-ol.

There is *limited evidence* in experimental animals for the carcinogenicity of 1-*tert*-butoxypropan-2-ol.

Overall evaluation

1-*tert*-Butoxypropan-2-ol is *not classifiable as to its carcinogenicity to humans (Group 3)*.

[1] After thorough discussion, several members of the Working Group favoured an evaluation of the evidence of carcinogenicity in experimental animals as *sufficient*. This view emphasizes the dose-related induction of hepatoblastomas in male and female mice, because hepatoblastoma is a rare neoplasm with a low spontaneous incidence in mice, especially in females. However, the majority of the Working Group considered the evidence to be *limited* for the reasons discussed in Section 5.3.