SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-92-2
Chemical Name	Butan-2-ol or *sec*-Butanol (sBA)
Structural Formula	CH_3-CH(-OH)-CH_2-CH_3

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Analog Justification

Data are available for sec-Butanol (sBA) on the following endpoints: acute toxicity (oral, inhalation, dermal), irritation studies (skin, eye and respiratory tract), reproductive toxicity, developmental toxicity and genotoxicity assays. Data on methyl ethyl ketone (MEK; 2-butanone), a major metabolite of sBA and structurally similar to sBA, will be used to address the repeated dose toxicity and supplement the genotoxicity endpoints.

Toxicokinetics and Metabolism

SBA is absorbed, distributed and excreted rapidly in urine, mainly as MEK, following oral administration. A small percentage of sBA is also excreted via urine and exhalation. Orally administered sBA is metabolized via alcohol dehydrogenase to MEK. The maximum concentration of MEK in blood was seen six hours after dosing. Further oxidation of MEK appeared to proceed by hydroxylation of the ω-1 carbon to form 3-hydroxy-2-butanone, which is further reduced to 2,3-butanediol. 2,3-butanediol was also detected in human urine following inhalation exposure to MEK. The main portion of the inhaled MEK is converted to acetate or acetoacetate via 3-hydroxy-2-butanone intermediate metabolite.

Human Health

sBA has a low order of acute toxicity to mammals. Oral LD_{50} values for sBA in laboratory animals range from approximately 2.2 to 6.5 g/kg body weight. The inhalation LC_{50} for sBA is between 8,000 (24 mg/L) and 16,000 ppm (49 mg/L) for a 4-hr exposure. sBA, like many other organic solvents, produces reversible depression of central nervous system (CNS) activity at high exposures. Laboratory animals that were exposed to acutely toxic doses of sBA exhibited clinical signs of CNS depression that were reversible in survivors upon termination of exposure. The dermal LD_{50} value for sBA in rats is greater than 2 g/kg body weight. In animal studies, sBA liquid is not irritating or sensitizing to the skin however, it is irritating to the rabbit eye. Vapors are weakly irritating to the respiratory tract of mice.

Limited repeated-dose, reproductive and developmental toxicity studies on sBA indicate a low potential for toxicity. Primary effects appear to be typical CNS depression associated with many aliphatic alcohols, and effects on liver associated with enzyme induction. sBA is quantitatively metabolized to methyl ethyl ketone (MEK); over 97% of an oral dose of sBA is converted to MEK in rats. Although there is no definitive repeated-dose study of sBA, information on repeated-dose toxicity of sBA can be deduced from reproductive toxicity studies, and from studies with MEK. A comprehensive subchronic toxicity study with the sBA metabolite MEK was conducted in rats; none of the exposure concentrations (1,250, 2,500, or 5,000 ppm—4, 8, or 15 mg/L, respectively—MEK vapor for 6

hours per day, 5 days per week, for 90 days) were lethal or even significantly harmful. There were no adverse effects on the clinical health or growth of male or female rats except a depression of mean body weight in the 5,000 ppm group. The female rats exposed to 5,000 ppm for 90 days showed only slightly increased liver weight, slightly decreased brain and spleen weights, and slightly altered blood chemistry in comparison with controls. Male rats that received this exposure exhibited only a slightly increased liver weight. At the lower concentrations (1,250 and 2,500 ppm), there was only slightly increased liver weight for female rats and no significant differences for males. The pathological examination did not reveal any histopathological lesions that could be attributed to MEK exposure. The NOAEL was determined to be 5000 ppm.

In a two-generation drinking water reproductive toxicity study of sBA, which included hematological and histopathological evaluations, mild changes in the kidney (non-reactive tubular degeneration, tubular casts, foci of tubular regeneration and microcysts) were observed in animals treated with 2.0% sBA. These effects were considered non-specific due to increased renal workload, possibly from an increased urine volume and pressure at the high doses. As a result, the authors concluded these results to not be a result of direct toxicity nor indicate a clear pathological significance. The only reproductive effect reported was a slight but not significant depression in growth of weanling rats in the second generation; the no-effect level for systemic and reproductive effects was 1.0% (estimated to be 1500 mg/kg/day by the authors and 1771 mg/kg/day by EPA/IRIS).

sBA is not a primary developmental toxicant; rats were exposed by inhalation to 0, 3,500, 5,000 or 7,000 ppm sBA—11, 15, or 21 mg/L, respectively—7 hours/day on days 1-19 of gestation and at 7,000 ppm, narcosis was observed in all animals. At 5000 ppm, the dams were partially narcotized with locomotion activity impaired. Maternal weight gain and food consumption was significantly reduced in all dose groups. The number of live fetuses was significantly reduced and resorptions were increased in the high exposure group only. Fetal body weights were significantly reduced in the mid- and high dose groups. There was no evidence of teratogenic effects in this study, and there was also no evidence of selective developmental toxicity. The NOELs were < 3,500 ppm for maternal toxicity and 3,500 ppm for developmental toxicity. During the two-generation reproductive toxicity study (see above) a teratogenic phase was incorporated in which the parents (28-30/group) were rebred to produce a second litter. The females were subjected to Caesarean section on day 20 of gestation (Cox *et al.*, 1975; Gallo *et al.*, 1977). At 2.0%, sBA caused a significant depression in fetal weight, with evidence of delayed skeletal maturation, but no skeletal and visceral malformations. The authors concluded that these changes represented mild toxicity and were reminiscent of stress lesions. All findings at 0.3 and 1.0% were negative. The no-effect level for developmental toxicity was 1.0% (estimated to be 1500 mg/kg/day by the authors and 1771 mg/kg/day by EPA/IRIS].

sBA was inactive in *in vitro* tests for mutagenicity in both bacteria and yeast in either the presence or absence of metabolic activation. There was no structural damage to chromosomes in cultured mammalian cells (Chinese hamster ovary) treated with sBA. MEK *in vivo* genotoxicity data provide additional supporting information on the potential for *in vivo* genotoxicity of sBA. MEK did not cause an increase in micronucleated polychromatic erythrocytes in two *in vivo* assays. MEK was also negative in the mouse lymphoma test, the chromosome aberration assay, and liver hepatocyte unscheduled DNA synthesis assay.

Like many other organic solvents, sBA produces reversible depression of central nervous system activity in laboratory animals at high exposure doses. sBA was found to produce intoxication effects with a slower recovery to normal behaviour than ethanol.

In humans, excessive exposure by inhalation may result in headache, dizziness, drowsiness and narcosis. No adverse systemic effects have been reported due to exposure to sBA.

Environment

The physical chemical properties of sBA are as follows: melting point, -114 to –115°C; Boiling point, 99.5°C; vapor pressure, 16 hPA at 20°C; water solubility, 125 g/l at 20°C and the Log Kow of 0.61 at 20°C. In air, sBA is calculated to contribute minimally to the formation of tropospheric ozone and can be degraded by reaction with photochemically produced hydroxyl radicals (OH^-). sBA has a calculated degradation half-life of approximately 24 hours. Degradation proceeds through the formation of MEK, acetaldehyde, and other intermediate oxidation species.

If released to water, biodegradation of sBA is likely to be the primary removal process. The volatilization half-life is 3.5 days and 30 days at 20ºC and 0ºC, respectively. Hydrolysis will not contribute to the transformation of sBA in aquatic environments because it is not susceptible to this reaction. sBA has a low potential to bioaccumulate in aquatic species based on a calculated BCF of 1.7. sBA is not expected to absorb significantly to organic matter in soil and sediment and therefore has potential to migrate through the soil horizon. Although volatilization can contribute to the loss of sBA from terrestrial habitats, biodegradation is likely to be the primary route of removal, with an estimated half-life of 1 to 7 days.

sBA was shown to be readily biodegraded by aerobic and rapidly biodegraded by anaerobic processes. Results of standard biodegradation tests suggest that sBA can be largely degraded in a few days. The biodegradation data also suggest that sBA can be rapidly degraded in wastewater treatment plants, which can prevent it from entering surface waters.

Experimental and SAR data indicate that sBA has a very low order of acute aquatic toxicity. The fish 96-hr LC50 of 3670, and the daphnid 48-hr EC50 of 4227 mg/L were reported for sBA based on measured and nominal concentrations, respectively. The SAR data using ECOSAR are in agreement with these results. A calculated algal 96-hr EC50 value of 625 mg/L using ECOSAR and a measured 7-day EC3 value of 95 mg/L for growth inhibition are reported. Chronic effects from sBA exposures are not expected based on reported short lifetime due to degradative processes.

In the terrestrial environment, sBA is expected to exhibit a low order of toxicity based on calculated data for earthworms.

There are adequate experimental and calculated data to support characterizing sBA as a low order environmental hazard based on the available data for acute and chronic aquatic toxicity, terrestrial toxicity, and low potential to persist in the aquatic and soil dwelling environments.

Exposure

Worldwide capacity of sBA is approximately 1,000 kt, and production 900 kt. Production volume in the U.S. is estimated to be between 500 million – 1 billion pounds (2.3- 4.5 kt). It can enter the environment from its production as well as application in the manufacture of MEK. sBA can also be released from its use as a solvent, paint remover, and industrial cleaning agent. Based on limited information, sBA also appears to be released to the atmosphere in some combustion processes. sBA enters the environment from several natural sources and has been detected in several environmental compartments (e.g., ambient air, edible plants, and wastewater) at low and variable concentrations.

The occupational exposure limit values for sBA vapors in different country's range between 50 and 150 ppm (150 - 450 mg/m^3) for the TWA values. Occupational exposure monitoring indicates that sBA may be found in the occupational setting up to 6.5 ppm.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation for further work because of the low hazard profile of the chemical.