SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-79-5
Chemical Name	1,3-Butadiene, 2-Methyl- (Isoprene)
Structural Formula	C_5H_8 (CH_2=C(CH_3)-CH=CH_2)

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,3-Butadiene, 2-methyl- (isoprene) is formed endogenously at the rate of 1.9 umol/kg per hour in both rats and mice and at the rate of 0.15 umol/kg per hour in humans. Isoprene is metabolized by microsomal cytochrome P-450 dependent monooxygenases to two monoepoxide metabolites, i.e., 3,4-epoxy-3-methyl-1-butene (EPOX-1) and 3,4-epoxy-2-methyl-1-butene (EPOX-2). These metabolites may then be hydrolyzed, conjugated with glutathione, or further oxidized to the isoprene diepoxide, i.e., 2-methyl-1,2:3,4-diepoxybutane. The intrinsic rates of formation of monoepoxides in human, rat and mouse liver microsomes are roughly similar, when epoxide hydrolase is inhibited, whereas the amount of monoepoxides at the end of incubation can be two to 15 times higher in mouse liver microsomes than in rat and human liver microsomes, respectively. A physiological toxicokinetic model has been developed for inhaled isoprene in mice, rats and humans, taking into account published or assumed kinetic parameters. On the basis of this model, at human exposure conditions (up to 50 ppm [140 mg/m^3]), rates of metabolism are about 14 times faster in mice and about eight times faster in rats than in humans. As the epoxide metabolites are likely responsible for the toxic effects of isoprene, this may explain why the mouse is more susceptible to isoprene toxicity than the rat.

Isoprene has a low potential for acute toxicity. In rats and mice, the oral LD_{50} of isoprene is in the range of 2,043 to 2,210 mg/kg. The 4-hour rat LC_{50} is 64,620 ppm (180,037 mg/m^3) and the 2-hour mouse LC_{50} is 56,363 ppm (157,033 mg/m^3). In humans, isoprene vapors are irritating to the eyes, nose and throat. Liquid isoprene is irritating to the eyes and skin. Data from a 13-week repeated dose study conducted in mice and rats found degeneration of the olfactory epithelium in male mice only at the highest concentration, i.e., 7,000 ppm (19,503 mg/m^3), but not at lower concentrations. IARC reports that in isoprene rubber production workers, subtrophic and atrophic processes in the upper respiratory tract, catarrhal inflammation, and degeneration of the olfactory tract were observed. Prevalence and degree were correlated with increasing length of service.

Repeated dose studies demonstrate clear species differences between rats and mice in susceptibility to isoprene. In a 2-week repeated dose inhalation study, the NOAEL for rats was 7,000 ppm (19,503 mg/m^3), the highest dose tested. However, in this same study, exposure of mice to isoprene produced changes in hematological parameters(decreased hematocrit, hemoglobin, erythrocytes), body and organ weights (increased liver weights, decreased thymus, spleen and testes weights) and also produced microscopic lesions in certain tissues (testes, thymus, liver, nasal cavity, forestomach) at levels as low as 438 ppm (1,220 mg/m^3). Thus, 438 ppm was the LOAEL for mice. Similarly, in the 13-week repeated dose inhalation study, the NOAEL for rats was 7,000 ppm (19,503 mg/m^3). In mice, however, hematological effects indicative of a nonresponsive macrocytic anemia and histopathological changes (forestomach, olfactory epithelium, liver) were observed at exposures of 700 ppm (1,950 mg/m^3) and higher. The NOAEL for mice in the 13- week repeated dose study was 220 ppm (613 mg/m^3). Isoprene was tested for mutagenicity in a series of *in vivo* and *in vitro* studies. Isoprene was not genotoxic in any of the *in vitro* assays conducted. However, when exposed by inhalation, isoprene was clearly genotoxic to mouse bone marrow *in vivo*.

Two-year inhalation carcinogenicity studies were conducted with isoprene in B6C3F1 mice and F344 rats. There is

clear evidence of carcinogenicity of isoprene in mice. Isoprene produced exposure-related increases in the incidence of malignant neoplasms in the liver, lung, Harderian gland and forestomach of mice, as well as increases in the number of hemangiosarcomas and histiocytic sarcomas. In rats, there were no significant increases in the incidence of malignant tumors. Isoprene exposures in rats were associated with increases in the rates of benign tumors in the testes and kidney (male) and mammary gland (male and female). Although single incidences of several rare brain neoplasms were observed in female rats, the fact that they were of several distinct cell types makes it difficult to determine if they are truly exposure related. Based on the carcinogenicity studies conducted in mice and rats, the NTP listed isoprene as reasonably anticipated to be a human carcinogen and IARC has classified it as 2B; possibly carcinogenic to humans.

Isoprene did not produce any maternal or developmental toxicity in rats following exposure to concentrations as high as 7000 ppm. However, both maternal and developmental toxicity were evident in mice. In mice, both maternal weight gain and uterine weight were significantly reduced at the highest dose (i.e., 7000 ppm). Significant reductions in fetal bodyweights were observed at the 280 ppm dose level for female fetuses and at the 1400 ppm level for male fetuses. Thus, in this study, 1400 ppm was the NOAEL for maternal toxicity. A NOAEL for developmental toxicity could not be determined as effects were observed at the lowest exposure concentration tested, i.e., 280 ppm.

Isoprene did not produce any significant effects on reproductive endpoints in rats. However, significant effects on reproductive endpoints were observed in male mice exposed to isoprene at concentrations of 700 ppm (1,950 mg/m^3) and higher. These effects included testicular atrophy as well as decreases in epididymal weight, sperm head count, sperm concentration, and sperm motility. In female mice exposed to 7,000 ppm (19,503 mg/m^3), the average estrous cycle length was significantly longer than that of the control group. Thus, in this study, 70 ppm (195 mg/m^3) is the NOAEL for reproductive effects in male mice and 700 ppm (1,950 mg/m^3) is the NOAEL for female mice.

Environment

Isoprene is a liquid at 25° C with a reported melting point of –145.9° C, a boiling point of 34.0° C, and vapour pressure of 733.3 hPa (25° C). Isoprene has a water solubility of 642 mg/l (25° C), a log K_{ow} of 2.42, and a density of 0.681 g/cm^3 (25° C).

In the air, isoprene has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals with a calculated degradation half-life of 1.2 hours depending on hydroxyl radical concentration. Aqueous photolysis and hydrolysis will not contribute to the transformation of isoprene in aquatic environments because it is either poorly or not susceptible to these reactions.

Results of Mackay Level I distribution modeling at steady state show that isoprene will partition primarily to the air compartment (99.9%), with a negligible amount partitioning to water (0.06%) and soil (0.02%). Level III modeling predicted greatest distribution (99.96%) to the primary compartment of release; when equal releases were assumed, the predicted distribution was: water (88%), soil (9.0%), air (3.1%), and sediment (0.21%).

Isoprene biodegraded to 61 % after 28 days in an OECD 301F study, but was not readily biodegradable because the replicate data exceeded the allowable range (53 to 75%). In an OECD 301D study, isoprene biodegraded to an extent of 2 and 58% in duplicate samples after 28 days, and showed no inhibitory effect in a supplementary study. The supplementary study resulted in 64% biodegradation on day 7, using the acclimated inoculum from the initial study. These data show that isoprene can exhibit high extents of biodegradation once acclimation has occurred. Bioaccumulation of isoprene is unlikely based on a low potential to bioconcentrate. The measured BCF is reported as 5 to approximately 20. The calculated BCF is 15.

Acute aquatic toxicity values for a fish and invertebrate are 7.4 (96hr-LC_{50}) and 5.8 (48hr-EC_{50}) mg/L, respectively. For algae, the 72- and 96-hr EC_{50} is 15 mg/L for biomass and >35 mg/L for growth rate. The algae 72- and 96-hr NOEC is 1.7 and 6.0 mg/L for biomass and growth rate, respectively.

Exposure

Isoprene is a petrochemical that is used as a chemical intermediate to manufacture primarily polymers, which occurs in closed production systems. Greater than 95% of high-purity isoprene is used as a monomer to manufacture elastomers such as polyisoprene, styrenic thermoplastic elastomer block copolymers (styrene-isoprene-styrene [SIS]), and butyl rubber. The remaining amount of isoprene is used to manufacture specialty chemicals, intermediates and derivatives which are then used in the production of vitamins, pharmaceuticals, flavorings and perfumes, and epoxy hardeners. The European Union has evaluated isoprene in the framework of Food Contact Material (CS/PM/3351/21640).

Total world isoprene consumption was reported as over 700,000 metric tons in 2004. Most isoprene production is consumed in the country of origin. Isoprene world consumption in 2000 was 579,000 metric tons, of which approximately 96% was consumed in the country of manufacture. In the United States, isoprene production in 1995 was approximately 619 million lb (281,000 metric tons).

Potential occupational exposure to isoprene through inhalation and dermal contact could occur at workplaces where isoprene or synthetic rubber is produced or used. A WEEL (Workplace Environmental Exposure Limit) of 2 ppm was established by AIHA in 2004. The WEEL was 50 ppm prior to the 2004 revision. Isoprene concentration in 426 workplace air samples (4-hr or greater) taken at 3 major isoprene or isoprene polymer producers in the United States from 1993 to 1998 showed that 81% were below 0.5 ppm, 91% were below 1 ppm, and 99% were below 10 ppm.

There are no direct sales to consumers. However, isoprene is used in production of polymers used in paint resins, tyres, footwear, moduled goods, adhesives, motor oil viscosity improvers. Isoprene monomer residual concentration was not detectable in isoprene-derived polymer samples at an analytical sensitivity of 0.1 ppm in work conducted prior to June 1998. Subsequent work in latter 1998, with an increased analytical sensitivity of 0.02 ppm, that evaluated polyisoprene samples demonstrated that 17 out of 19 samples had no detectable isoprene monomer residual, while 2 samples contained between 0.04 and 0.02 ppm. Consequently, potential for consumer exposure will be negligible.

The greatest potential for exposure to isoprene in the environment is in the air compartment because of its high vapor pressure. Partitioning to air from aquatic and terrestrial compartments would occur rapidly due to isoprene physico-chemical characteristics. As such, isoprene has an overall low potential for exposure in environmental compartments other than air. However, its persistence in air is short lived as a result of degradation processes, which suggests that exposure to isoprene will be limited in the environment.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (irritation, genotoxic, reproductive and developmental toxicity, carcinogenic) and the environment (fish, invertebrates, algae). Based on data presented by the Sponsor country, relating to production in one country which accounts for approximately 40% of global production and relating to the use pattern in one country, under normal manufacturing, formulation, industrial and consumer use of polymerized isoprene containing products, this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.