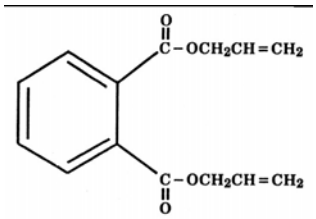
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	131-17-9
Chemical Name	Diallyl phthalate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Excretion, distribution and pharmacokinetic studies have been performed with rats and mice using ^{14}C-diallyl phthalate (DAP). In the excretion and distribution studies, ^{14}C-DAP was administered by gavage and $^{14}CO_2$, volatile metabolites, urine and faeces were collected for 24 hours. In rats, 25 – 30% of the DAP was excreted as CO_2, and 50 – 70% appeared in urine within 24 hours. In mice, 6 – 12% of the DAP was excreted as CO_2, and 80 – 90 % was excreted in the urine within 24 hours. Tissue distribution and pharmacokinetic studies were conducted in rats and mice dosed via the tail vein with ^{14}C-DAP. The DAP was found to clear rapidly from the blood of rats and mice, with a half-life of approximately 2 minutes in both species. No DAP was found in blood, liver, kidney, muscle, skin or small intestine 30 minutes after intravenous administration of DAP in both species. Monoallyl phthalate (MAP), allyl alcohol (AA), 3-hydroxypropylmercapturic acid (HPMA), and an unidentified polar metabolite were found in the urine of rats and mice dosed with ^{14}C-DAP. The polar metabolite was present in the urine of rats after administration of DAP or AA, indicating that this compound is a metabolite of AA.

DAP was more hepatotoxic to rats than to mice. The same species difference was observed in toxicity for AA. Because DAP was metabolized to AA, it was postulated that the differential hepatotoxicity of DAP was related to the toxicity of AA. AA is a potent periportal hepatotoxicant, and because mice produced more HPMA as a by-product of phase II metabolism than rats, it was postulated that the differential hepatotoxicity of DAP was related to the extent of glutathion conjugation with AA or acrolein (the active metabolite of AA). Oral LD_{50} values [NTP] were 891 mg/kg bw (males) and 656 mg/kg bw (females) in rats, and 1070 mg/kg bw (males) and 1690 mg/kg bw (females) in mice. Oral LD_{50} in dogs was ca. 800 mg/kg bw (combined). Dermal LD_{50} (rabbit) was 3300 mg/kg bw. Inhalation LC_{50} in rats (one hour) was 8300 mg/m^3 (combined), 10310 mg/m^3 (males) and 5200 mg/m^3 (females) [FIFRA Guidelines, 43FR 37336].

DAP is not irritating to rabbit skin [16 CFR 1500.41] or eyes [FSHA 16 CFR 1500]. DAP was sensitising in a local lymph node assay in mice [OECD TG 429].

In a repeated dose toxicity study [NTP], male and female rats (10 animals/sex/group) were dosed by gavage with DAP at 0, 25, 50, 100, 200 and 400 mg/kg bw/day on 5 days/week for a total of 13 weeks. Eight male rats that received 400 mg/kg bw/day either died during the study or were killed when found in moribund condition. Body weight gain for male rats at 400 mg/kg bw/day appeared to be depressed relative to that of the vehicle controls. Clinical signs in both sexes were observed at 400 mg/kg bw/day and less frequently at 200 mg/kg bw/day, but not at lower doses. The clinical signs consisted of diarrhoea, rough hair coat or alopecia around the head, hunched posture

and general emaciation. At necropsy, gross abnormalities of the liver were observed in all eight 400 mg/kg bw/day male rats that died early and three of these male rats also exhibited multifocal renal cortical tubular necrosis. The lungs in many of these male rats appeared darkened or bright red. Liver lesions were observed in the two surviving males and in most females at 400 mg/kg bw/day, and in 5/10 males at 200 mg/kg bw/day. The severity appeared to be dose related and greater in males than in females. Histopathological examination indicated that the liver was the primary target organ. Periportal lesions of hepatic lobules, necrosis, fibrosis, bile duct hyperplasia, and hepatocellular hyperplasia occurred in males and females at 200 and 400 mg/kg bw/day. Necrosis, fibrosis and biliary hyperplasia were not observed at doses lower than 200 mg/kg bw/day in both sexes, but hepatocellular alterations in the periportal region were observed with decreasing frequency and severity at doses as low as 50 mg/kg bw/day in males and 100 mg/kg bw/day in females. The NOAEL for females was 50 mg/kg bw/day. The NOAEL and the LOAEL for males were not determined because no histopathological examination at 25 mg/kg bw/day in the liver was performed.

DAP was weakly mutagenic in two strains of bacteria (WP2 with metabolic activation and TA 1535 without metabolic activation) [OECD TG 471 and 472]. Clear positive responses were observed in mouse lymphoma cells, both with and without metabolic activation *in vitro*. It also induced chromosomal aberrations in Chinese hamster cultured cells with and without metabolic activation [OECD TG 473] and an increase in sister chromatid exchanges and micronucleus formation with metabolic activation. DAP was not genotoxic *in vivo* in mouse micronucleus test [OECD TG 474]. It did induce a small number of chromosome aberrations in mice [OECD TG 475] although the biological significance of these data is not clear. Based on these data, DAP is considered to be genotoxic *in vitro*, however these findings were not clearly manifested when tested in good quality *in vivo* studies.

For carcinogenic potential of DAP, based on the NTP results in mice and rats, the observed evidence of lymphoma (mice) and mononuclear cell leukemia (rat) in aged animals is considered to be equivocal evidence of carcinogenicity.

In an oral study in rats by OECD reproduction/developmental toxicity screening test [OECD TG 421], rats (10 animals/sex/group) were dosed by gavage at 0, 16.7, 50 and 150 mg/kg bw/day from 14 days prior to mating to day 4 of lactation. At 150 mg/kg/day there were 3 mortalities, which were associated with possible dystocia. Effects on newborns and live newborns were not evaluated in these female rats. Histopathological changes in the liver of parental animals were observed at this dose. There were no treatment-related effects on the fertility of male or female rats. No treatment-related histopathological changes were found in the reproductive organs of parental animals. There were no treatment-related effects on offspring viability, growth and development from conception to early lactation. No morphological abnormalities were seen in offspring of rats given this chemical pre- and postnatally. The NOAELs for general toxicity in parent animals and for reproductive toxicity were 50 mg/kg bw/day.

Environment

DAP has a log Pow of 3.23 at 20°C, a vapour pressure of 0.000213 hPa at 25°C and a water solubility of 148 mg/L. Fugacity model Mackay level III calculations suggest that the majority of DAP would distribute to water if released into the water compartment, mainly to soil if released to the air or soil compartments. DAP is readily biodegradable (76 – 92% based on BOD, 28 days) [OECD TG 301C], and is hydrolytically stable at pH 4 and 7 ($t_{1/2}$ greater than 1 year). At pH 9 the half-life is 217 hours. The hydrolysis products are phthalic acid and AA. The estimated BCF is 61.25 and hence the potential for bioaccumulation is low. Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 2.3 hours.

In acute fish toxicity studies [OECD TG 203, 96 hours] LC_{50} values of 0.23 mg/L (measured, *Oncorhynchus mykiss*) and 0.44 mg/L (measured, *Orizias latipes*) were reported. In *Daphnia magna* [OECD TG 202], acute toxicity values of 48-h EC_{50} of 5.5 mg/L (measured) and 16.2 mg/L (measured) were reported. The results in algae [DIN 38412 L9 Part 9, *Scenesdesmus subspicatus* and OECD TG 201, *Selenastrum capricornutum*] were E_rC_{50} (72 hours) of 5.5 mg/L (nominal) and 14.9 mg/L (measured), respectively. The corresponding value for biomass was 15.1 mg/L (measured). The chronic toxicity values to *Daphnia magna* [OECD 211] were NOEC (21d, reproduction) of 1.16 mg/L (measured) and 3.2 mg/L (nominal). NOEC (72 hours) values from growth rate and biomass in algae were both 2.4 mg/L (measured) [OECD TG 201, *Selenastrum capricornutum*].

Exposure

Production of DAP during 2002 is estimated at 4400 tonnes worldwide. Annual production at the two manufacturing sites in Japan is estimated at 3900 tonnes. There are a wide variety of uses for this chemical, where DAP is covalently bound into a polymer matrix DAP is used in the production of polyvinyl chloride (PVC), unsaturated polyesters (UP), or polyDAP as a crosslinking agent, a dye carrier, an insulating agent, an agent for improving flowability and viscosity of compound mixtures (during chemical processing), or an agent which gives hardness to articles for goods such as ship bodies (sheet moulded compound, SMC), coil bobbins, window frames, UV curable inks, hot stamping foils, grindstones, impregnated paper-decorated particle boards for wall materials or furniture and so on.

The exposure of DAP may occur mainly according to the following three scenarios:
Occupational exposure: Limited exposure to workers through inhalation and dermal routes during operations at production and user sites is expected. A survey of occupational exposure in a Japanese factory producing DAP and polyDAP found that workers were exposed to DAP at concentrations of $\leq$0.11 mg/m^3 during manufacture of DAP itself and 0.02 – 0.96 mg/m^3 during manufacture of the polymer.

Consumer exposure: Based on the following information, exposure to consumer through inhalation and dermal routes is anticipated to be low. In studies performed in the residential indoor air environment, DAP was detected in the range of 0 – 134.5 ng/m^3, depending on the study. DAP is an intermediate and is used as a reactive plasticizer, which is covalently bound into the polymer matrix of products. One such application is the manufacture of decorative boards. A study performed to measure the amount of DAP emitted from decorative boards manufactured using DAP found that the amount was generally below the limit of detection of 0.05 µg/m^3 [JIS A1901: 2003].

Environmental exposure: Limited emission to the environment is expectedvia waste water at production and user sites, and evaporative emissions associated with its use in building and household materials, etc., and disposal of consumer products. No DAP was detected in either the sediment (Limit of detection 0.02 µg/g in dry sediment) or hydrosphere(Limit of detection 0.2 µg/L) of 27 monitoring points in Japan in 1985. Monitoring of wastewater from DAP manufacturing plant in Matsuyama, Japan found that levels of DAP were in the range of 0.003 – 0.005 mg/L. Sampling was conducted in the surface water of the settling pond, just downstream from the aerating facilities and leading to the outfall facing the bay in Seto Inland Sea in Matsuyama-shi, Ehime Prefecture. The annual estimated emission from the plant is considered to be 5.3 kg/year. Based on these monitoring surveys, use patterns and a nature of ready biodegradability it can be concluded that the environmental concentration of the substance is anticipated to be low in the Sponsor country.

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

Human Health: The chemical is a candidate for further work.The chemical possesses properties (sensitization, mutagenicity, liver and kidney toxicity, equivocal carcinogenicity and reproductive toxicity) indicating a hazard for human health. Based on data presented by the Sponsor country, worker exposure in sites manufacturing DAP and PolyDAP is controlled. No information is available for occupational exposure in industries using DAP or PolyDAP. It is therefore recommended that member countries perform an exposure assessment for workers and if then indicated, risk assessments.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties (acute toxicity) indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by two producers which accounts for approx. 89 % of global production and relating to the use pattern in one OECD country), exposure to the environment is anticipated to be low. Therefore, this chemical is currently of low priority for further work. Countries may wish to investigate any exposure scenarios that were not presented by the Sponsor country.