FOREWORD INTRODUCTION

DIALLYL PHTHALATE

CAS N°: 131-17-9

SIDS Initial Assessment Report

For

SIAM 19

Berlin, Germany, 19–22 October 2004

1.	**Chemical Name:**	Diallyl phthalate
2.	**CAS Number:**	131-17-9
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5.	**Roles/Responsibilities of the Partners:**	
•	Name of industry sponsor /consortium	DAP Consortium established for OECD HPV Program
•	Process used	Industry collected data, prepared the updated IUCLID dossier, and drafted versions of the SIAR and SIAP.
6.	**Sponsorship History**	
–	How was the chemical brought into the OECD HPV Chemicals Programme?	The substance is sponsored by Japan under the ICCA Initiative, and is submitted for first discussion at SIAM 19.
7.	**Review Process Prior to the SIAM:**	Japanese government peer-reviewed the documents and audited selected studies.
8.	**Quality check process:**	Japanese government peer-review committee performed spot checks on randomly selected endpoints and compared original

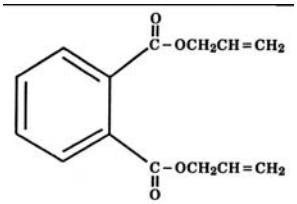
studies with data in the SIDS dossier

9. Date of Submission: 26 April 2004

10. Date of last Update: 23 December 2004

11. Comments: None

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 ≤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 $\mu g/m^3$ [JIS A1901: 2003].

Environmental exposure: Limited emission to the environment is expected via 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.

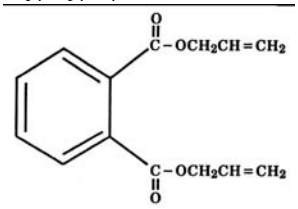
Environment: The chemical is currently of low priority for further work. The chemical possesses properties (acute toxicity) indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by two producers which accounts for approx. 89 % of global production 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.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 131-17-9
IUPAC Name: Diallyl phthalate
Molecular Formula: $C_{14}H_{14}O_4$
Structural Formula:



Molecular Weight: 246.27
Synonyms: (Chemical name)
1,2-Benzenedicarboxylic acid, di-2-propenyl ester
Allyl phthalate
Diallylester phthalic acid
o-Phthalic acid diallyl ester
DAP
(Trade name)
Dapon 35
Dapon R
NCI-C50657

1.2 Purity/Impurities/Additives

Purity ≥ 99% w/w

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Physical state	Colorless, transparent liquid	(DAISO, 2003a)
Melting point	–70 ºC	(Lewis, 1993)
Boiling point	157 ºC at 6.7 hPa*	(CITI, 1994)
Relative density	1.12	(Lewis, 2001)
Vapour pressure	2.13×10^{-4} hPa at 25 ºC	(Staples *et al.*, 1997)
Water solubility	148 mg/L at 20 ºC (pH 6.9–7.3)	(DAP consortium, 2003a)
Partition coefficient n-octanol/water (log value)	3.23 at 20 ºC	(Leyder *et al.*, 1983)
Henry's law constant	3.86×10^{-7} atm-m³/mole	Estimated by EPI WIN 3.11**
Flash point	166 ºC (closed cup)	(HSDB, 2002)

* Boiling point at 1013 hPa cannot be determined due to decomposition

** EPI WIN 3.11, developed by EPA, U.S.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Production of diallyl phthalate (DAP) during 2002 is estimated at 4400 tonnes worldwide. Annual production at the two manufacturing sites in Japan is estimated at 3900 tonnes.

DAP is produced either by the esterification reaction between allyl alcohol and phthalic anhydride, or by the condensation between allyl chloride and disodium phthalate.

DAP functions as a crosslinking agent. The functionality is ascribed to the two highly reactive allyl groups in the molecule. The allyl groups are able to react with other unsaturated organic chemicals to form C-C covalent bonds.

DAP also functions as a plasticizer. However, unlike other phthalate esters, such as di-butyl phthalate (DBP), di-(2-ethylhexyl) phthalate (DEHP), etc., DAP is used as a reactive plasticizer. It is added to polymer and prepolymer systems in order to make them softer and more easily moulded during the curing process and then it binds covalently into the polymer matrix to produce rigid thermoset plastics. The other phthalate esters, such as DBP and DEHP are normally added to the polymer in order to make the end products softer or more flexible. Due to their lack of functionality, these other phthalate esters do not bind chemically into the polymer matrix, and, therefore, there is the potential for them to leach out.

Whereas other phthalate esters are used at up to levels greater than 50% to plasticize final products, no use of DAP where it functions to plasticize the final product is known (therefore, DAP is an intermediate).

Approximately half of DAP produced is used as a monomer to form the DAP prepolymer. Prepolymers are semi-polymerised polymers before completing the polymerisation in the

succeeding process to manufacture the finished consumer products. The DAP prepolymer is used for impregnated paper-decorated particle boards for wall materials or furniture, printing in UV-curable ink, grindstone, coil bobbin, and hot stamping foil. The residual DAP in the prepolymer (< 2 wt%) reacts to be incorporated via covalent bonds into the polymer matrix during completion of the polymerisation to produce finished products.

DAP is also used as a crosslinking agent during the manufacture of other polymers such as polyvinyl chloride (PVC), unsaturated polyesters (UP), etc. Such polymers are used for finished consumer products such as window frames, insulating varnish for coil and wire, and sheet moulded compound for ship body. The DAP added to such polymers reacts, in the similar way to the DAP prepolymer, to be incorporated via covalent bonds into the polymer matrix of the finished consumer products.

During the chemical process, DAP functions as an agent for improving flowability and viscosity of compound mixture. DAP is consumed during the process and gives hardness to the finished consumer products.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

The environmental exposure to DAP may occur by emission to aquatic compartment from waste water at production and user sites and evaporative emissions associated with its use as building and household materials, etc., and disposal of consumer products. Environmental exposure is also expected from formulation and industrial use.

Monitoring of wastewater from the DAP manufacturing plant in Matsuyama, Japan found that levels of DAP were in the range of 0.3-0.5 µg/L (DAISO, 2003b). Sampling was conducted for the wastewater in 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 (equivalent to 2.7×10^{-3} kg/tonne DAP produced) (DAISO 2003b).

A Japanese study showed that no DAP was detected in either the sediment or hydrosphere of 27 monitoring points in Japan in 1985. The lower limits of detection were 0.0002 µg/mL in water (0.2 ppb) and 0.02 µg/g in dry sediment (0.02 ppm) (EA Japan, 1986).

2.2.2 Photodegradation

Indirect photo-oxidation by hydroxy radicals (1500000 molecule/cm^3) is predicted to occur with a half-life estimated at 2.3 hours (calculated using AOPWIN rate constant, 5.57×10^{11} cm^3/molecule-sec) (DAISO, 2003a).

2.2.3 Stability in Water

DAP was found to be stable to hydrolysis at pH 4 and 7 (a half-life greater than 1 year at 25°C) [OECD TG 111]. At pH 9 (at 25°C) the half-life was determined to be 217 hours, with degradation products of phthalic acid and allyl alcohol (DAP consortium, 2003a).

2.2.4 Transport between Environmental Compartments

Fugacity Model Mackay level III calculations (DAISO, 2003c) using EPI Suite v3.11 developed by Environment Protection Agency (EPA) indicates that DAP would distribute mainly to soil if released to the air or soil compartments and to water if released to the water compartment.

Table 2 Environmental distribution of DAP using Fugacity Model Mackay Level III

	1000 kg/h emission to these compartments separately		
	Air	**Water**	**Soil**
In air	19.9%	0.0%	0.0%
In water	8.6%	98.8%	0.5%
In soil	71.4%	0.0%	99.5%
In sediment	0.1%	1.2%	0.0%

2.2.5 Biodegradation

DAP is readily biodegradable [76–92% degradation based on BOD after 28 d, OECD TG 301 C] (CITI, 1990).

2.2.6 Bioaccumulation

An estimated BCF of 61.25 was calculated by EPI Suite v3.11 developed by EPA using the Log Pow value of 3.23 (DAISO, 2003c). However, as DAP is known to be metabolised in fish, there is low potential for bioaccumulation.

2.2.7 Other Information on Environmental Fate

No data available.

2.3 Human Exposure

2.3.1 Occupational Exposure

A limited exposure to workers through inhalation and dermal routes during operations at production and user sites is expected.

A US National Occupational Exposure Survey performed between 1981 and 1983 indicates that 8784 male and female employees were potentially exposed to DAP, mainly in the printing, polymer, electronics, and stone, clay and glass industries (NIOSH, 1983). However, no information is given on the potential level of exposure.

As a result of the concern about the potential risk of exposure to DAP, the Japanese Industrial Safety and Health Association has conducted an occupational exposure assessment of a factory in Japan (JISHA, 2004) producing DAP during operations such as sampling, analysis and drum filling and polyDAP during operations such as sampling, analysis and cleaning flexible containers (blowing off the dust). The survey found that workers were exposed to DAP at concentrations of

≤0.11 mg/m^3 during manufacture of DAP (maximum exposure occurred at sampling of the chemical for analysis) and 0.02-0.96 mg/m^3 during manufacture of the polymer (maximum exposure occurred during cleaning operations). In all cases, the exposure was below the following Occupational Exposure Limit, Time-Weighted Average (OEL-TWA) values.

The UK, German, Irish and New Zealand OEL-TWA values are 5 mg/m^3, and the Danish OEL-TWA is 3 mg/m^3.

Typically, as workers use PPE (protective gloves) and RPE (respiratory protective equipment-mask) during these operations and the workplace is equipped with local ventilators, DAP uptake is minimized and is practically negligible.

2.3.2 Consumer Exposure

Based on the following information, exposure to consumer through inhalation and dermal routes is anticipated to be low. Some of the typical applications of DAP in industrial and consumer products are shown in detail.

DAP is an intermediate. The chemical functions as a reactive plasticizer because of the allyl groups. Therefore, DAP is quite different in its use from other phthalate esters. Phthalate esters other than DAP are in general mixed with raw materials during production process and remain intact more than 50% in some case (Asahi-Kasei, 1999), functioning as plasticizers in the consumer products. By contrast, in every known use, DAP is mixed with raw materials and little remains intact in the consumer products because of chemical reaction .They can function either as a monomer, crosslinking agent or hardness-imparting substance to final consumer products.

Approximately half of DAP produced is used as a monomer for the preparation of DAP prepolymer, which is a partially polymerized soluble resin. The prepolymer contains up to 2% unreacted DAP monomer. The prepolymer is itself an intermediate and becomes covalently bound into the matrix of products. The DAP monomer content in the final product is expected to be much lower than in the prepolymer due to further reaction of the allyl groups.

A typical use of the DAP prepolymer is manufacturing pre-impregnated paper (paper prepreg) used in the manufacture of decorative board for house walls, furniture, etc. The paper prepreg is produced by impregnating paper with a solvent based solution of the DAP prepolymer. In this application, the paper contains less than 0.1-0.5% DAP monomer. After drying the paper to the desired moisture content, the pre-impregnated paper is applied to wood panels in a hot press to produce decorative boards. During the heating and curing process the DAP prepolymer resin flows into the board surface and is cured to a hard plastic finish that becomes an integral part of the surface. It should be noted that most of the residual DAP monomer present in the paper prepreg and the board are consumed by reaction with the prepolymer or itself during the heating and curing process. Therefore, the residual DAP monomer content in the finished product is expected to be very low.

Another typical use of the DAP prepolymer is UV curable ink used in printing processes. The potential dermal exposure to the chemical is expected to be very low. The amount of the UV-ink used in the printing paper is estimated to be 2 g/m^2 or less, the DAP prepolymer content in the ink is estimated to be 10 wt% or less, and the DAP content in the DAP prepolymer is 2 wt% or less. Therefore, at most 4 mg/m^2 of DAP is loaded in the paper printed with UV-ink including DAP prepolymer. Moreover, the paper loaded with the ink is irradiated by UV and dried. In the process, the DAP is expected to be consumed and incorporated via covalent bonds into the matrix. Therefore, the net content of DAP in the printed paper is expected to be reduced to a very low level prior to its use by consumers.

The rest of the DAP produced is also used as a reactive substance, mainly as cross-linking agents with other plastics such as polyvinyl chloride (PVC), unsaturated polyesters (UP), and so on to make the final products hard, insulative, weather-resistant, etc. In these cases, little DAP is expected to remain in the final consumer products.

Japanese Ministry of Health, Labor and Welfare (MHLW) established guidelines for 14 chemicals in Japanese residential indoor air environment such as di-(2-ethylhexyl) phthalate (DEHP, 0.12 mg/m^3), di-n-butyl phthalate (DBP, 0.22 mg/m^3), formaldehyde (0.10 mg/m^3) and other air pollutants although a value for DAP has not been established. Japanese implementation order for the building standard describes the allowable emission rate without reserve from the indoor building material below 0.005 mg/m^2 /h.

A study (DAISO, 2003d) showed that the DAP-emission rate from decorative laminate boards (DAISO DAP®) was less than 0.000011 mg/m^2 h, which is far below the formaldehyde allowable emission rate (0.005 mg/m^2 h) without reserve.

There are four studies available for DAP in residential indoor air environment. Every study focused on the growing concern for sick building syndrome and the indoor air for many phthalates including DAP and other air pollutants. Matsumura and Morita (2000) reported the concentrations of the DAP in indoor air of three houses in Japan were 79.3 (before repair of existing house), 25.8 (after repair of existing house), 7.1 (new house) and 134.5 (new house) ng/m^3. Matsumura *et al* (2004) also reported that the concentration of DAP in the air of four houses in Japan were 0 (existing house), 6.2 (existing house), 17.1 (new house), and 12.3 (existing house) ng/m^3. These monitoring studies demonstrated that indoor DAP levels and levels of other phthalate esters were more or less comparable. In contrast, no DAP was detected by the survey, which Saito *et al*. (2001 and 2002) conducted for 45 rooms (23 houses) and 12 offices (12 office building) between 1999 and 2001. (Hence, recently they have delisted DAP from the target chemicals list for the subsequent survey.).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Eigenburg (1986) performed excretion, distribution and pharmacokinetic studies in male Fischer-344 rats and male B6C3F1 mice using ^{14}C-DAP (labeled on the 2,3 position of the allyl alcohol moiety).

In the excretion and distribution studies, ^{14}C-DAP was administered by gavage to rats and mice at 1, 10 or 100 mg/kg. Following dosing, animals were placed in a metabolism cage 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 (ca. 150-200 g) and mice (ca. 20-25 g) dosed via the tail vein with 10 mg/kg bw of ^{14}C-DAP (40 or 120 µCi/kg bw, respectively). 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. In this study, the fate of phthalic acid moiety was not investigated, because [^{14}C]DAP was labelled on the 2, 3 position of the AA moiety.

DAP was more hepatotoxic to rats than to mice. The same species difference was observed in toxicity for allyl alcohol (AA). When AA was orally administered in mice and rats, histopathological evaluation after 24 hours revealed that the doses of AA (25, 50 and 75 mg/kg bw) were not hepato-toxic in mice, although in rats, periportal necrosis was evident in 9 of 12 animals in a dose-dependant manner. 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 the mouse 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 glutathione conjugation with AA or acrolein (the active metabolite of AA).

HPMA levels varied with dose and route of administration. Expressed as a percentage of the dose of ^{14}C administered, the values for rat were 13.2, 18.4, 16.5 and 20.6% at doses of 1, 10, 100 mg/kg bw orally and 10 mg/kg bw intravenously, respectively.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

Male and female SD rats (5 animals/dose in each sex) were exposed to DAP aerosols at concentrations of 940, 3090, 5390, 6660, 8080, 9170 and 9710 mg/m^3 for 1 hour under whole body exposure conditions (FMC Corp., 1982, FIFRA Guidelines, 43FR 37336). The purity of DAP used in the study is not mentioned in the report. Seven male animals (5930 mg/m^3 (one animal), 8030 and 9710 mg/m^3 (three animals each)) and eighteen female animals (3090 and 5930 mg/m^3 (two animals each), 6660 mg/m^3 (three animals), 8030 and 9170 mg/m^3 (four animals each) and 9710 mg/m^3 (three animals)) died during the study. Salivation, crusty nose, damp fur, poor coat quality, crusty eye, irregular breathing, crusty muzzle and yellow/brown stained fur were noted among the test rats. At necropsy, abnormalities were noted in the stomach, spleen, large intestines, kidney and eyes among the test rats. The LC50 was 10310mg/m^3 (males) and 5200 mg/m^3 (females). In another study, ten rats in both sexes were exposed to DAP at 4470 mg/m^3 (measured airborne concentration) for 4 hours. Exposure to the chemical produced immediate signs of irritation and 100 % mortality at Day 1. Necropsy revealed discoloration of the nasal turbinates and lungs (FMC Corp., 1980).

Dermal

There are five acute dermal toxicity studies. In the most reliable study, rabbits (10 animals/dose) were dosed with DAP at 200, 2000 and 5000 mg/kg bw (FMC Corporation, 1989a). On day 14 after dermal application of this chemical, deaths were found in 3, 4 and 6 rabbits of the 10 at 200, 2000 and 5000 mg/kg bw, respectively. The LD_{50} was calculated to be 3300 mg/kg bw. The LD_{50} observed in the other, less reliable, acute dermal toxicity studies are in general agreement with the reported LD_{50}.

Oral

Four reliable studies on acute toxicity are available.

In the most reliable study in rats (NTP, 1985), Fischer 344 rats (5 animals/dose in each sex) were dosed by gavage with DAP administered in corn oil at four doses ranging from 464-1470 mg/kg bw (males) and five doses ranging from 316-1470 mg/kg bw (females). All animals of both sexes dosed at 1470 mg/kg bw died during the study. Diarrhoea, inactivity, hunched posture, hyperpnoea and watery secretions around the nose and mouth were observed in almost all animals of both sexes at 1470 mg/kg bw before they died. These clinical signs occurred less frequently at 1000 mg/kg bw. Female rats receiving 681 mg/kg bw exhibited reduced activity on the day of dosing only. At necropsy, apparent haemorrhagic lesions were noted in the urinary bladder and the lungs appeared dark in animals receiving 1470 mg/kg bw (chemical induced deaths). The darkened appearance of the lungs was also noted frequently at 1000, 681 and 464 mg/kg bw. Fluid was found in the thoracic cavity and the intestines appeared to be reddened in two females in the 1000 mg/kg group that died early. The LD_{50} was 891 mg/kg bw (males) and 656 mg/kg bw (females).

In the most reliable study in mice (NTP, 1983), B6C3F1 mice (5 animals/dose in each sex) were dosed by gavage with DAP administered in corn oil at four doses ranging from 681-2150 mg/kg bw (males) and four doses ranging from 1000-3160 mg/kg bw (females). At least, one death occurred in all of the other dosed groups, except for females that received 1000 mg/kg bw. No chemically-related lesions were observed at necropsy. The LD_{50} was 1070 mg/kg bw (males) and 1690 mg/kg bw (females).

In an acute toxicity study in dogs (5 dogs, 3 males/2 females), LD50 was estimated as ca. 800 mg/kg bw (combined). Hematological analysis revealed that DAP caused hepatotoxicity in treated dogs.

Table 3 Acute oral toxicity in experimental animals

Species (Strain)	LD_{50}	Reference
Rat (Fischer 344)	891 mg/kg (male), 656 mg/kg (female)	(NTP, 1985)
Mouse (B6C3F1)	1070 (male), 1690 mg/kg (female)	(NTP, 1983)
Rat (Wistar)	896 mg/kg (combined)	(FMC Corp., 1989a)
Dog	Ca. 800 mg/kg (combined)	(FMC Corp., 1989b)

Conclusion

Oral LD_{50} values 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).

3.1.3 Irritation

Skin Irritation

Studies in Animals

Two reliable studies showed few or no signs of skin irritation by this chemical in rabbits (DAISO, 1998 and Ethyl Corp., 1979). In the more reliable study conducted under GLP [16 CFR 1500.41], 0.5 mL of undiluted DAP was applied to the shaved backs of 6 female New Zealand White rabbits (abraded and intact sites) and covered with an occlusive dressing for 24 hours (16 CFR 1500.41). The animals were examined 24 and 72 hours after removal of the chemical. There were no signs of

toxicity or ill health in any rabbit during the observation period. Some slight irritation was noted in the study but DAP is not classifiable as a skin irritant (DAISO, 1998). Two other studies of reasonable quality but not to current standards gave similar results.

Eye Irritation

Studies in Animals

DAP was found to be non-irritant to rabbit eyes in three studies, one of which was considered reliable. In this informative study (Ethyl Corp., 1979) 0.1mL of undiluted DAP was instilled into the right eye of 6 rabbits according to FSHA 16 CFR 1500. The animals were examined after 1 and 4 hours and then daily on days 1, 2, 3, 4 and 7. Examination did not reveal any positive grades of redness or chemosis in any rabbits indicating DAP was not an eye irritant.

Conclusion

DAP is considered to be non-irritant to skin and eyes.

3.1.4 Sensitisation

Studies in Animals

There is one report available for skin sensitisation.

Skin

In a mouse local lymph node assay [OECD TG 429], groups of 4 mice (CBA/Ca, female) were applied 25 µL of DAP solution on the surface of the ear at concentrations of 0, 0.5, 5 and 50 % w/v (acetone/olive oil 4:1 vehicle) on 3 consecutive days. There were no clinical signs of toxicity during the study. The Stimulation Index was 3.23 at 5 % w/v and 10.74 at 50 % w/v, DAP is considered to be a skin sensitizer (DAP Consortium, 2003b).

Conclusion

DAP is considered to be a skin sensitizer.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Oral

Five reliable studies on repeat dose oral toxicity studies are available. The key study is considered to be the 13-week study performed using Fischer 344 rats (NTP 1985) as this study was conducted under GLP conditions and well-reported.

In this study male and female Fischer 344 rats (10 animals of each sex/dose) were dosed by gavage with DAP in corn oil 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 at 400 mg/kg bw/day either died during the study or were killed when found in moribund condition. Body weight gain in male rats at 400 mg/kg bw/day was depressed 12 % relative to that of the vehicle controls. Clinical signs, such as diarrhoea, rough hair coat or alopecia around the head, hunched posture and general emaciation, were observed at 400mg/kg bw/day and less frequently at 200 mg/kg bw/day but not 100 mg/kg bw/day and lower in both sexes.

At necropsy, gross abnormalities with enlarged, mottled and pale rough, granular or pitted surface of the liver were observed in all eight male rats that died early at 400 mg/kg bw/day. In most rats, darkened or bright red lung was found. Liver lesions (enlarged, mottled with yellow blotches on the surface, and pale, rough, granular, or pitted) 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 was 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 less than 200 mg/kg bw/day in both sexes. 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 liver from the lowest dose group (25 mg/kg bw/day) were not examined by the authors because of the presence of only minimal hepatic changes at 50 mg/kg bw/day. Acute necrotizing colitis, characterised by loss of surface and glandular epithelium, varying degrees of mucosal and submucosal oedema, and acute inflammatory cell infiltration, was found in 7/8 early death males at 400 mg/kg bw/day. In addition, three of these male rats exhibited multifocal renal cortical tubular necrosis. Greenish-brown-kidney was observed in females at 400 mg/kg bw/day.

The NOAEL in this study was 50 mg/kg bw/day for females. The NOAEL and LOAEL for males were not determined because no histopathological examination at 25 mg/kg bw/day in the liver was performed. The liver was the primary target organ.

In a 14 day study using B6C3F1 mice (NTP, 1983), males and females (5 mice/dose/sex) were administered DAP in corn oil at 0, 50, 100, 200, 400 and 600 mg/kg bw daily. Deaths occurred in the 400 and 600 mg/kg bw/day groups, but not at lower doses. Mean body weight gains of all dosed mice were not depressed relative to the control group. No chemically related lesions were observed at necropsy.

In a 13 week study using B6C3F1 mice (NTP, 1983), males and females (10 mice/dose/sex) were administered DAP in corn oil at 0, 25, 50, 100, 200and 400 mg/kg bw for 5 days/week over the length of the study. Neither statistically significant body weight gains nor gross and microscopic alterations related DAP administration were observed in any of the high-dose group. The NOAEL for males and females was 400 mg/kg bw/day.

Table 4 Repeated dose oral toxicity studies

Species	Dose	NOAEL (LOAEL)	Principal toxic effect	Reference
Rat (F344/N)	0, 25, 50, 100, 200, 400 mg/kg bw/day by gavage, 5 days/week for 13 weeks	Females: NOAEL 50 mg/kg bw/day LOAEL 100 mg/kg bw/day Males: NOAEL Not determined. LOAEL 50 mg/kg bw/day	Liver was primary target (periportal lesions of hepatic lobules, necrosis, fibrosis, bile duct hyperplasia, hepatocellular hyperplasia and multifocal renal cortical tubular necrosis).	(NTP, 1985)
Rat (F344/N)	0. 50, 100, 200, 400, 600 mg/kg bw/day by gavage, 14 consecutive days	Females: NOAEL 50 mg/kg bw/day LOAEL 100mg/kg bw/day Males: NOAEL Not determined. LOAEL 50 mg/kg bw/day	Liver. Lung, stomach, cecum, spleen; no microscopy	(NTP, 1985)
Rat (Sprague-Dawley)	0, 16.7, 50, 150 mg/kg bw/day by gavage, up to 54 days	NOAEL 50 mg/kg bw/day (male and female)	Liver - periportal hepatocyte necrosis, enlargement and basophilia, bile duct proliferation and periportal fibrosis, stomach ulceration	(DAP Consortium, 2004)
Mouse (B6C3F1)	0, 25, 50, 100, 200, 400 mg/kg bw/day by gavage, 5 days/week for 13 weeks	NOAEL 400 mg/kg bw/day (male and female)	None	(NTP, 1983)
Mouse (B6C3F1)	0, 50, 100, 200, 400, 600 mg/kg bw/day by gavage, 14 consecutive days	NOAEL 200 mg/kg bw/day (male and female) LOAEL 400 mg/kg bw/day (male and female)	Death at 400, 600 mg/kg. No chemical induced lesions at necropsy	(NTP, 1983)

Conclusion

The repeated dose oral NOAEL in female rats was 50 mg/kg bw/day. The NOAEL and the LOAEL were not determined in males. The liver was the primary target organ. The NOAEL in male and female mice was 400 mg/kg bw/day.

3.1.6 Mutagenicity

Studies in Animals

There are nine *in vitro* studies and three *in vivo* mutagenicity studies.

In vitro Studies

In bacterial reverse mutation, the studies conducted by MOL, Japan (2000) and FMC Corp. (1986) are the key studies, as they were well conducted under GLP. In the MOL study, using four strains of *Salmonella typhimurium* and one strain of *Escherichia coli*, bacteria were exposed to DAP (0, 1.22, 4.88, 19.5, 78.1, 313, 1250 and 5000 µg/plate) both with and without exogenous metabolic activation (S9) [OECD TG 471 and 472]. Cytotoxicity was not observed up to 313 µg/plate (except *Escherichia coli*, where no cytotoxicity was shown over the whole concentration range applied) in

the presence of exogenous metabolic activation, and was not observed up to 78.1 µg/plate (five strains) in the absence of exogenous metabolic activation. Weak positive response was observed in *Escherichia coli* WP2 (1250 µg/plate and higher) with exogenous metabolic activation (MOL, Japan, 2000).

In a study (FMC Corp., 1986), using five strains of *Salmonella typhimurium,* the chemical was tested for reverse mutation at concentrations of 0, 25 or 50, 100, 250, 500 and 1000 µg/plate with exogenous metabolic activation and 0, 50, 100, 250, 500, 1000, 1500 and 3000 or 150, 300, 600, 1500, 3000 and 6000 µg/plate without exogenous metabolic activation by a method similar to OECD TG 471. Cytotoxicity was not observed at any dose with or without exogenous metabolic activation, except that TA100 was inhibitory from around 1000 µg/plate with and without exogenous metabolic activation. The test was weakly positive in strain TA100 (600 µg/plate and higher and around 1500 at the maximum) without metabolic activation and negative with metabolic activation. All other strains showed negative responses in all cases. The response seen in TA100 was observed at dose levels at or above the toxic limit. Interpretation of this study is complicated by dilution errors and differences between fresh and old samples. Final conclusive results were obtained with a freshly prepared sample without any experimental error.

However, other bacterial mutagenicity tests have been reported as negative with and without exogenous metabolic activation (Zeiger, 1985, Ethyl Corp., 1979, and FMC Corp., 1977).

In contrast to bacterial reverse mutation, clear positive responses were observed in each of three mammalian cell assays, particularly when exposed in the presence of exogenous metabolic activation, where the toxic effects were reduced and higher dose levels could be achieved.

In mouse lymphoma cells (L5178Y) (Mhyr, 1991), DAP produced concentration-dependant increases in mutation between 50-75 nL/mL (56-84 µg/mL, 46-49 % RTG) and 150 nL/mL (168 µg/mL, estimated from relative density = 1.12) which induced 6-9 fold increases in two experiments with and without exogenous metabolic activation. Gulati, et al (1989) reported that this chemical induced chromosomal aberrations in Chinese hamster ovary (CHO) cells with exogenous metabolic activation at the highest dose tested (200-300 µg/mL). The same authors also reported that a concentration-dependant increase in sister chromatid exchanges was observed in the presence of S9 between 160 and 250 µg/mL in Chinese hamster ovary (CHO) cells. In Chinese hamster lung (CHL/IU) cells with exogenous metabolic activation [OECD TG 473], DAP also induced micronucleus formation (20µg/mL) (MOL, Japan, 2002)

Table 5 Genotoxicity studies *in vitro*

Type of test	Test system	Dose	Result	Reference
Bacterial test (reverse mutation)	*S. typhimurium* TA98, TA100, TA1535, TA1537, *E.coli* WP2*uvr*A/pKM101	1.22-5000 µg/plate	Weakly positive with metabolic activation (WP2)	(Ministry of Labor, Japan, 2000)
Bacterial test (reverse mutation)	*S. typhimurium* TA98, TA100, TA1535, TA1537	1-10000 µg/plate	Negative, with and without metabolic activation	(Zeiger, 1985)
Bacterial test (reverse mutation)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.01-1µL/plate	Negative, with and without metabolic activation	(Ethyl Corp., 1979)
Bacterial test (reverse mutation)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	50-3000 µg/plate	Weakly positive without metabolic activation (TA1535)	(FMC Corp., 1986)
Bacterial test (reverse mutation)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.01-100 µL/plate	Negative	(FMC Corp., 1977)
Mammalian cell gene mutation test	L5178Y Mouse lymphoma cells	30-120 nL/mL (-S9) 12.5-200 nL/mL (+S9)	Positive, with and without metabolic activation	(Mhyr, 1991)
In vitro chromosome aberration assay	CHO	50-300 µg/mL (+S9) 50-500 µg/mL (-S9)	Positive, with metabolic activation	(Gulati *et al*, 1989)
In vitro Mammalian Micronucleus Test	CHL/IU	1.3 -40 µg/mL (+S9) 20 -120 µg/mL (-S9)	Positive with metabolic activation	(Ministry of Labor, Japan, 2002)
Sister chromatid exchange	CHO	5 -250 µg/mL (+S9) 1.6-125 µg/mL (-S9)	Positive with metabolic activation	(Gulati, 1989)

In vivo Studies

In a sex-linked recessive lethal test (SLRL) [OECD TG 477] (Valencia, 1985), Drosophila melanogaster were treated with feed containing DAP at doses of 100 and 140 ppm and injected with 500 ppm of the chemical 24 hours prior to mate with untreated females. No significant induction of mutation was observed in both tests.

In a mouse micronucleus assay [OECD TG 474], animals were injected intraperitoneally with DAP at 43.8, 87.5 and 175 mg/kg bw. There were no statistically significant increases in the frequency of micronucleated PCEs in any of the dose groups when compared to the concurrent vehicle control (Shelby, 1993).

In a chromosome aberration test [OECD TG 475], duplicate sets of male mice were injected intraperitoneally with DAP at 0, 75, 150 and 300 mg/kg bw (Shelby, 1995). In the first set of mice

there was a small but statistically significant increase in the number of chromosomal aberrations in bone marrow cells at the high dose (7.50±1.18%) when compared to the concurrent vehicle control (3.25±1.25%). The dose-response showed statistical significance but was modest in magnitude. The result of this study conflicts with the micronucleus study reported by the same authors although both study types investigate similar endpoints.

Table 6 Genotoxicity studies *in vivo*

Type of test	Test system	Dose	Result	Reference
Drosophila SLRL test	Drosphila melanogaster, Canton-S	0-140 ppm (feeding) 500 ppm (injection)	Negative	(Valencia, 1985)
Mouse micronucleus assay	Mouse, B6C3F1	43.8-175 mg/kg bw, 3 times at 24 h intervals	Negative	(Shelby, 1993)
Chromosome aberration test	Mouse, B6C3F1	75-300 mg/kg, single dose	Positive	(Shelby, 1995)

Conclusion

DAP was weakly mutagenic in two strains of bacteria (WP2 with exogenous metabolic activation and TA1535 without metabolic activation). Clear positive responses were observed in L5178Y mouse lymphoma assay with and without exogenous metabolic activation. It induced chromosomal aberrations in CHO cells with and without exogenous metabolic activation and sister chromatid exchanges in CHO cells with exogenous metabolic activation. In addition, DAP induced micronucleus formation in CHL/IU cells with exogenous metabolic activation.

DAP was not mutagenic in vivo in either a mouse micronucleus test or SLRL (Drosophila melanogaster). It did not induce micronuclei in mouse bone marrow cells. Although DAP induced in vivo chromosome aberrations in mouse bone marrow cells at the highest dose group, the biological significance of the data is not clear.

3.1.7 Carcinogenicity

In vivo Studies in Animals

In a NTP (1983) study, groups of 50 male and 50 female B6C3F1 mice were gavaged with DAP in corn oil at doses of 0, 150 and 300 mg/kg bw/day on 5 days/week for 103 weeks. Survival rates and mean body weights of DAP-treated mice were not different from those of the control mice. Pathological lesions unrelated to proliferative changes in the liver were not observed. Therefore, a maximally tolerated dose for the purposes of carcinogenicity testing may not have been achieved. The development of chronic inflammation and hyperplasia of the forestomach may have been related to the administration of DAP, but the available data are insufficient to indicate a clear cause and effect relationship. A dose response for forestomach chronic inflammation and hyperplasia, and lack of clear causality only for forestomach squamous papillomas were observed. An increase in the incidence of male mice with lymphomas was observed (12/50, 24%) in comparison with the concurrent controls. This increase was considered only to be equivocally related to administration of DAP as the incidence was not significantly greater than concurrent (6/50, 12%) or historical controls (18/120, 15%; 71/661, 11%) at the performing laboratory by pairwise comparisons.

In another NTP study (1985), groups of 50 male and 50 female Fischer 344 rats were gavaged with DAP in corn oil at doses of 0, 50 and 100 mg/kg bw/day on 5 days/week for 103 weeks. Mean body weights and survival of male and female rats in the DAP-treated groups were essentially the same as those in the control group throughout the study. DAP administration produced dose-dependant hepatotoxicity in both sexes characterised by periportal necrosis and fibrosis, pigment accumulation in periportal histiocytes and excessive bile duct hyperplasia. Male and female rats dosed at 100 mg/kg bw/day developed chronic liver disease characterised by periportal fibrosis, periportal accumulation of pigment and severe bile duct hyperplasia. Pigment accumulation also occurred at the 50 mg/kg bw/day dose in both sexes. Administration of DAP produced an increase in the occurrence of mononuclear cell leukaemia in female rats ($p<0.05$ by trend tests), and the incidence in the 100 mg/kg bw/day dose female rats was significantly greater ($p<0.05$) than in the vehicle controls by pairwise comparisons (vehicle control, 15/50, 30%; low dose, 15/43, 35%; high dose, 25/49, 51%). No increase of mononuclear cell leukaemia was observed in male rats. Because of the variability in the incidence of this neoplasm in aged Fischer 344 rats and the difficulty in definitively diagnosing this lesion in this strain, the authors of NTP 1985 considered the increase to be equivocal evidence of carcinogenicity (mononuclear cell leukaemia) in female rats. There was no evidence of carcinogenicity in male rats.

Mononuclear cell leukaemia is a disease that commonly arises in the spleen of the F344/N rat but is rare in other rat strains. Therefore, the carcinogenicity of DAP is unclear.

Conclusion

There is equivocal evidence of carcinogenic effect in male mice. The results, therefore, do not indicate that DAP is carcinogenic in B6C3F1 mice. In rats, there is equivocal evidence of carcinogenic effect in females, but no evidence of carcinogenic effect in males. In both rats and mice the neoplasms were of lympho-reticular tissues.

3.1.8 Toxicity for Reproduction

There is one report for reproduction/developmental toxicity.

Studies in Animals

Effects on Fertility

In a reproduction/developmental toxicity screening test [OECD TG 421], male and female SD rats (10 animals/dose in each sex) were gavaged with DAP at 16.7, 50 and 150 mg/kg bw/day from 14 days prior to mating to 4 days post partum (maximum 54 days) (DAP Consortium, 2004).

At 50 and 16.7 mg/kg bw/day, there were no mortalities through the study.

At 150 mg/kg bw/day, there were 3 female deaths. Two females were killed in extremis due to signs of distress around the expected time of parturition, including pilo-erection, pallor of the extremities and abdominal discomfort. One of the females was also bleeding from the vagina. These clinical signs are associated with possible dystocia.

Increases in histopathological findings (periportal hepatocyte necrosis, enlargement and basophilia, bile duct proliferation and periportal fibrosis) in the livers at 150 mg/kg bw/day were considered to be treatment-related.

There were no treatment-related effects seen on the fertility of male or female rats as shown by the high pregnancy rate for all DAP-treated groups and the lack of significant differences in the distribution of precoital intervals for all dose groups. Seven female animals gave normal parturition,

while three females failed to complete parturition possibly due to the test chemical. No effects of this chemical on number of corpora lutea, implantations and newborns and live newborns were found, although effects on new-borns and live new-borns were not evaluated in the three rats that died or were killed *in extremis* due to possible dystocia at this dose.

There were no treatment-related effects on offspring viability, growth and development from conception to early lactation. No morphological abnormalities due to this chemical were seen in offspring of rats given this chemical pre-and postnatally.

The NOAEL for general toxicity in parent animals was 50 mg/kg bw/day and the NOAEL for reproductive toxicity was 50 mg/kg bw/day.

Developmental Toxicity

See above.

Conclusion

There were no treatment-related effects seen on the fertility of male or female rats as shown by the high pregnancy rate for all treatment groups. There were no treatment-related effects on offspring viability, growth and development from conception to early lactation. No macroscopic abnormalities were seen in offspring. The NOAELs for general toxicity in parent animals and for reproductive toxicity were 50 mg/kg bw/day.

3.1. Initial Assessment for Human Health

Excretion, distribution and pharmacokinetic studies have been performed with rats and mice using ^{14}C-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.

MAP, AA, 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 dosed with 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 metabolised 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 the mouse 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 glutathione conjugation with AA or acrolein (the active metabolite of AA).

The acute oral LD_{50} was 891 mg/kg (males) and 656 mg/kg (females). The acute inhalation LC_{50} (1 hour) was 10310 mg/m^3 (males) and 5200 mg/ m^3 (females). The acute dermal LD_{50} was 3300 mg/kg. DAP is not a skin or eye irritant but it is a sensitizer in a local lymph node assay.

The NOAEL for the oral repeated dose toxicity was 50 mg/kg bw/day in female rats. The NOAEL and the LOAEL were not determined in male rats because no histopathological examination in the

liver at 25 mg/kg bw/day was performed. Histopathological examination indicated that the liver was the primary target organ. Gross abnormalities with enlarged, mottled and pale rough, granular or pitted surface of the liver were observed in affected animals for both sexes. Periportal lesions of hepatic lobules, necrosis, fibrosis, bile duct hyperplasia, and hepatocellular hyperplasia occurred in both sexes at 200 and 400 mg/kg bw/day, while necrosis, fibrosis and biliary hyperplasia were not observed at doses less than 200 mg/kg bw/day in both sexes.

DAP was weakly mutagenic in two strains of bacteria (WP2 with exogenous metabolic activation and TA1535 without metabolic activation), while other bacterial studies showed that DAP was negative in mutagenicity. In contrast, clear positive responses were observed in L5178Y mouse lymphoma assay with and without metabolic activation. DAP also induced chromosomal aberrations in CHO cells *in vitro* with and without exogenous metabolic activation and sister chromatid exchanges in CHO cells with metabolic activation. In addition, DAP induced micronucleus formation in CHL/IU cells *in vitro* with metabolic activation.

DAP was not mutagenic *in vivo* in either a mouse micronucleus test or SLRL (*Drosophila melanogaster)*. DAP did induce a small number of chromosome aberrations in mouse bone marrow cells at the highest dose group, although the biological significance of these data are not clear.

In two carcinogenicity studies, there is equivocal evidence of carcinogenic effect in male mice. In rats, there is equivocal evidence of carcinogenic effect in females, but no evidence of carcinogenic effect in males. In both rats and mice the neoplasms were of lympho-reticular tissues.

In a reproduction/developmental toxicity screening test, rats were dosed by gavage at 16.7, 50 and 150 mg/kg bw/day from 14 days prior to mating to 4 days post partum (maximum 54 days). Increases in histopathological findings (periportal hepatocyte necrosis, enlargement and basophilia, bile duct proliferation and periportal fibrosis) in the livers at 150 mg/kg bw/day were considered treatment-related. The clinical signs observed in females at 150 mg/kg bw/day were associated with possible dystocia. There were no treatment-related effects seen on the fertility of male or female rats as shown by the high pregnancy rate for all treatment groups and the lack of significant differences in the distribution of precoital intervals for all dose groups. There were no treatment-related effects on offspring viability, growth and development from conception to early lactation. No macroscopic abnormalities were seen at terminal necropsy.

The NOAELs for general toxicity in parent animals and for reproductive toxicity were 50 mg/kg bw/day.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The ecotoxicology of DAP to aquatic organisms has been investigated, and reliable test results are summarized in the Tables 7 and 8.

Acute Toxicity Test Results

In an acute fish toxicity study [OECD TG 203] (DAP Consortium 2003c), *Oncorhynchus mykiss* were exposed under semi-static conditions to DAP at measured concentrations of 0, 0.094, 0.18, 0.32, 0.54, and 0.87mg/L for 96 hours. Chemical analysis of the old or expired test concentrations at 24, 48, 72 and 96 hours showed a marked decline of DAP in the test solution of up to 55% of the nominal value. This decline was considered likely to be due to possible microbial degradation of the test material in the test medium in the presence of the test fish and/or possible metabolism of the

test material within the bodies of the fish. Because of the marked decline in the measured test concentrations, the LC_{50} (96 hour) of 0.23 mg/L (LC_{100} = 0.32 mg/L) was obtained based on the time-weighted mean measured concentrations.

In another acute fish toxicity study [OECD TG 203] (EA, Japan, 2000), *Oryzias latipes* were exposed under semi-static conditions to DAP at measured concentrations of 0, 0.02, 0.09, 0.16, 0.29, 0.53, and 1.08 mg/L for 96 hours. Chemical analysis of the old (expired) test solution 24 hours after renewal showed a marked decline of DAP up to 33.3% of the nominal value. This decline was considered likely to be due to the similar cause of the possible microbial degradation and or metabolism. The LC_{50} (96 hour) was 0.44 mg/L calculated on the geometric mean basis of 0 and 24 hours-measured concentrations.

In an acute aquatic invertebrate toxicity study [OECD TG 202] (DAP Consortium 2003d), *Daphnia magna* were exposed under static conditions to DAP at measured concentrations of 0, 0.0922, 0.181, 0.334, 0.559, 1.06, 1.90, 3.45, 6.04, and 10.70 mg/L for 48 hours. Chemical analysis of the test solutions throughout the test showed that the measured test concentrations to range from 92% to 108% of the nominal test concentrations. The EC_{50} was 5.5 mg/L.

In another acute aquatic invertebrate toxicity study [OECD TG 202] (EA, Japan, 2000), *Daphnia magna* were exposed under static conditions to DAP at measured concentrations of 0, 0.8, 2.6, 5.5, 12.6, 26.1, and 51.6 mg/L for 48 hours. Marked declines of DAP in the fresh media of from 22.5 to 93.7 % of nominal after 48 hours indicated that there was possible degradation of DAP by the test organisms. The EC_{50} (48 hour) (immobilisation) was calculated to 16.2 mg/L on the geometric mean basis of 0 and 48 hours-measured concentrations.

In an algal growth inhibition study [OECD TG 201], *Selenastrum capricornutum* were exposed to DAP at measured concentrations of 1.3 – 26.9 mg/L for 72 hours (EA, Japan, 2000). The marked declines of the test substance was recorded up to 67.7% of the nominal, it indicated that the substance is possible to degrade in the test condition. The ErC_{50} (0-72 hours) was 14.9 mg/L based on the geometric mean of the measured concentrations.

In another algal growth inhibition study [DIN 38412 L9 Part 9] (Kühn *et al*., 1990), *Scenedesmus subspicatus* were exposed DAP at nominal concentrations of 0 mg/L (control) and 0.63 to 80 mg/L for 72 hours (not reported for concentrations in detail). There was no marked decline over 20%. The ErC_{50} (0-72 hours) (growth rate) was calculated to 5.5 mg/L on the nominal concentration basis.

Table 7 Acute studies in aquatic organisms

Organism	Duration (h)	Result	Reference
Fish			
Oncorhynchus mykiss *Oryzias latipes*	96 (ss) 96 (ss)	LC_{50} 0.23 mg/L (measured) LC_{50} 0.44 mg/L (measured)	(DAP consortium, 2003c) (EA, Japan, 2000)
Invertebrates			
Water flea (*Daphnia magna)*	48 (s)	EC_{50} (48-h) 5.5 mg/L (measured)	(DAP consortium, 2003d)
Water flea (*Daphnia magna)*	48 (s)	EC_{50} (24-h) 22.3 mg/L (measured) EC_{50} (48-h) 16.2 mg/L (measured)	(EA, Japan, 2000)
Water flea (*Daphnia magna)*	24 (s)	EC_{50} (24h) 22 mg/L (nominal)	(Bringmann and Kühn, 1982)
Aquatic Plants			
Green algae (*Selenastrum capricornutum)*	72 (s)	ErC_{50} (72-h) 14.9 mg/L (measured) EbC_{50} (72-h) 8.5 mg/L (measured)	(EA, Japan, 2000)
Green algae (*Scenedesmus subspicatus)*	72 (s)	ErC_{50} (72-h) 5.5 mg/L (nominal) ErC_{10} (72-h) 3.8 mg/L (nominal)	(Kühn and Pattard , 1990)

(s): static, (ss): semi-static

Chronic Toxicity Test Results

In a chronic toxicity study [OECD TG 211] (MOE, Japan, 2002), *Daphnia magna* were exposed under semi-static conditions to DAP at measured concentrations of 0, 0.50, 1.16, 2.36, 4.27, 7.83, and 14.5 mg/L for 21 days. No reproductive inhibition was observed at the concentrations of 0.50 to 4.27 mg/L and all parent daphnia died at concentrations of 7.83 and 14.5 mg/L, although the EC_{50} (reproduction) was not determined. Therefore, a supplementary test with two concentrations of 6.18 and 7.72 mg/L was conducted. Chemical analysis of the test solutions at 0, 7 and 14 days showed that this chemical was not stable at the lowest concentration, at which the measured concentration was only 20 % of the nominal. The toxicity was calculated based on the time-weighted means ranging from 58.8-90.6 % of the nominal. The LC_{50} (21d) of 2.40 mg/L (on the mortality of parental daphnids), and on the effect on the reproduction the EC_{50} (21d) of 4.31 mg/L, the NOEC (21d) of 1.16 mg/L and the LOEC (21d) of 4.95 mg/L were available.

In a chronic toxicity study similar to OECD TG 211 (Kühn *et al*., 1989), *Daphnia magna* were exposed under semi-static conditions to DAP at nominal concentrations of 0.025-25 mg/L. The test substance was stable during the test (<20% loss of initial concentration of test substance). The NOEC (21d, reproduction) of 3.2 mg/L was reported.

For algae the 72-h NOEC of 2.4 mg/L [OECD TG 201, *Selenastrum capricornutum*] (EA, Japan, 2000) and the 8-day TGK (Toxic Threshold Value) of 0.65 mg/L (blue-green algae, Microcystis aeruginosa) (Bringmann and Kühn, 1978) were available.

Table 8 Chronic studies in aquatic organisms

Organism	Duration (h)	Result	Reference
Aquatic Plants			
Green algae (*Selenastrum capricornutum)*	72 (s)	NOEC (72-h) 2.4 mg/L (measured)	(EA, Japan, 2000)
Blue-green algae (*Microcystis aeruginosa*)	192 (8 days)	TGK (8 days) 0.65 mg/L	(Bringmann and Kühn, 1978)
Invertebrates			
Water flea (*Daphnia magna)*	21 days (ss)	(on the mortality of parental daphnids) LC_{50} (21d) 2.40 mg/L (on the reproduction) EC_{50} (21d) 4.31 mg/L NOEC (21d) 1.16 mg/L LOEC (21d) 4.95 mg/L	(MOE, Japan, 2002)
Water flea (*Daphnia magna)*	21 days (ss)	NOEC (21d, reproduction) 3.2 mg/L (nominal)	(Kühn *et al*., 1989)

(s): static, (ss): semi-static

Toxicity to Microorganisms

Bringmann (1978), Bringmann and Kühn (1977, 1980b, 1980c) and Bringmann *et al*. (1980a) have investigated the toxicity threshold of DAP against a range of aquatic microorganisms. In each test, culture media containing a dilution series of DAP were prepared in tubes and the test strain was inoculated into the media. The media was incubated for a period of time at 20-25°C, and then either the number of organisms counted using a cell counter (protozoa) or cell density measured using absorbance (bacteria) and the toxicity threshold (TGK, Toxischen Grenzkonzentration) was calculated. The table 9 summarises the results of these studies.

Table 9 Toxicities in aquatic microorganisms

Organism	Incubation period	TGK (mg/L)	Reference
Pseudomonas putida (Bacteria)	16 hours at 25°C	>100	(Bringmann *et al.* 1977)
Entosiphon sulcatum (Protozoa)	72 hours at 25°C	13	(Bringmann, 1978) (Bringmann *et al.*, 1980c)
Uronema parduzci (Protozoa)	20 hours at 25°C	22	(Bringmann *et al.*, 1980b)
Chilomonas paramaecium (Protozoa)	48 hours at 20°C	29	(Bringmann *et al.*, 1980a)

4.2 Terrestrial Effect

No information is available.

4.3 Other Environmental Effects

No information is available.

4.4 Initial Assessment for the Environment

DAP has a log P_{ow} of 3.23 at 20°C, a vapour pressure of 0.000213 hPa at 25ºC and a water solubility of 148 mg/L at 20°C. Fugacity model Mackay level III calculations suggest that the majority of the chemical would distribute mainly to soil if released to the air or soil compartments and to water if released to the water compartment.

The substance is readily biodegradable (76–92% degradation by BOD after 28 days) and is stable to hydrolysis at pH 4 and 7. At pH 9, the half-life is 217 hours at 25°C. The estimated BCF is 61.25 and DAP is known to metabolised in fish, hence the potential for bioaccumulation is low.

Reliable acute fish toxicity data are available for *Oncorhynchus mykiss*, LC_{50} = 0.23 mg/L (measured) and *Orizias latipes*, LC50 = 0.44 mg/L (measured). In *Daphnia magna*, an acute toxicity value of 48-h EC_{50} = 5.5 mg/L (nominal) and 48-h EC_{50} of 16.2 mg/L (measured) were reported. For aquatic algae acute toxicity, 72-h ErC_{50} = 5.5 mg/L (nominal) (DIN, *Selenastrum subspicatus*) and 14.9 mg/L (measured) (OECD TG 201, *Selenastrum capricornutum*) are available.

The chronic toxicity data for *Daphnia magna* of NOEC (21 days, reproduction) = 1.16 (measured) and 3.2 mg/L (measured) are available. For algae toxicity, NOEC (72 hours) = 2.4 mg/L (measured) (OECD TG 201, *Selenastrum capricornutum*) and TGK (8-days) = 0.65 mg/L (blue-green algae, Microcystis aeruginosa) are available.

Toxicity data to protozoa are available for *Entosiphon sulcatum,* Toxic Threshold value (TGK, 72 hours) = 13 mg/L; *Uronema parduzci,* TGK (20 hours) = 22 mg/L; *and Chilomonas paramaecium,* TGK (48 hours) = 29 mg/L. For bacterium (*Pseudomonas putida*), TGK (16 hours) is >100 mg/L.

5 RECOMMENDATIONS

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 the human health. Based on data presented by the Sponsor country, worker exposure in sties 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. 90% 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.

6 REFERENCES

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S I D S

D o s s i e r

Existing Chemical	ID: 131-17-9
CAS No.	131-17-9
EINECS Name	diallyl phthalate
EC No.	205-016-3
Molecular Formula	C14H14O4

Producer Related Part

Company:	Safepharm Laboratories
Creation date:	03-DEC-2004

Substance Related Part

Company:	Safepharm Laboratories
Creation date:	03-DEC-2004

Memo:	DAP Consortium ICCA HPV Diallyl Phthalate
Printing date:	23-DEC-2004
Revision date:	
Date of last Update:	**23-DEC-2004**
Number of Pages:	**221**
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: DAISO CO., LTD.
Contact Person: Hisaharu Shima **Date:**
Street: 10-8, Edobori 1-chome, Nishi-ku
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Telefax: +81-6-6445-8890
Email: hshima@daiso.co.jp
Homepage: http://www.daiso.co.jp/top-e.htm

03-DEC-2004

Type: cooperating company
Name: Daicel Chemical Industries, LTD.
Contact Person: Tsuneo BABA, Ph.D. **Date:** 12-AUG-2003
Street: 1, Teppo-cho
Town: 590-0905 Sakai-shi, Osaka
Country: Japan
Phone: +81-72-227-3243
Telefax: +81-72-227-3082
Email: ts_baba@daicel.co.jp
Homepage: http://www.daicel.co.jp/

03-DEC-2004

1.0.2 Location of Production Site, Importer or Formulator

Type: manufacturer
Town: NC 29045 Elgin
Country: United States

Remark:

Original Reference:
SRI. 1997 Directory of Chemical Producers - United States of America. Menlo Park, CA: SRI International 199
NIPA Hardwicke Inc., 3411 Silverside Rd., 104 Halsley Bldg., Wilmington, DE 19810, (302)478-1522.

Production site: Elgin, NC 2904
03-DEC-2004 (53)

Type: manufacturer
Town: TX 77530 Channelview
Country: United States

Remark: ARCO Chemical Co., 3801 West Vester Pike, Newton Square, PA 19073-2387, (610)359-2000.

Production site: Channelview, TX 77530
Original Reference:
SRI. 1997 Directory of Chemical Producers - United States of America. Menlo Park, CA: SRI International 1997. 535
03-DEC-2004 (53)

Type: manufacturer
Name of Plant: Matsuyama Plant of DAISO CO., LTD.

Street: 77, Kitayoshida-cho
Town: 791-8401 Matsuyama
Country: Japan
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Telefax: +81-89-973-9104

03-DEC-2004 (26)

Type: manufacturer
Name of Plant: Otake Plant
Street: 2-1-4 Higasihsakae
Town: 739-0695 Otake-city, Hirosima
Country: Japan
Phone: +81-0827-53-2151
Telefax: +81-0827-53-1839
Email: ts_baba@daicel.co.jp <Tsuneo BABA, Ph.D.>
Homepage: http://www.daicel.co.jp/kaisya/kaf.html

03-DEC-2004 (21)

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

IUPAC Name: 1,2-Benzenedicarboxylic acid, di-2-propenyl ester
Smiles Code: O=C(OCC=C)c(c(ccc1)C(=O)OCC=C)c1
Mol. Formula: C14H14O4
Mol. Weight: 246.27

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
03-DEC-2004 (42)

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: liquid
Purity: >= 99 % w/w
Colour: <= 50 Hazen unit

Remark: Acid Value (mg KOH/g): <= 0.2
Iodine Value (g I2/100 g): >= 200
Specific gravity: 1.105 - 1.115 at 30°C
Purity (GC): >= 99.0%
03-DEC-2004 (22)

1.1.2 Spectra

1.2 Synonyms and Tradenames

Diallyl phthalate

03-DEC-2004 (16)

1,2-Benzenedicarboxylic acid, di-2-propenyl ester

Source: DAISO CO., LTD. Osaka
19-JUL-2004 (81)

Allyl Phthalate

Source: DAISO CO., LTD. Osaka
19-JUL-2004 (81)

o-phthalic acid diallyl ester

Source: DAISO CO., LTD. Osaka
19-JUL-2004 (81)

diallylester phthalic acid

Source: DAISO CO., LTD. Osaka
19-JUL-2004 (81)

DAP

Source: DAISO CO., LTD. Osaka
19-JUL-2004 (81)

DAISO DAP Monomer

Source: DAISO CO., LTD. Osaka
19-JUL-2004 (32)

Dapon 35

Source: DAISO CO., LTD. Osaka
19-JUL-2004 (81)

Dapon R

Source: DAISO CO., LTD. Osaka
19-JUL-2004 (81)

NCI-C50657

Source: DAISO CO., LTD. Osaka
19-JUL-2004 (81)

1.3 Impurities

1.4 Additives

1.5 Total Quantity

Quantity: 4400 tonnes produced in 2002

Remark: The quantity is the estimated production in the world.

Reliability: (2) valid with restrictions
03-DEC-2004 (29)

Quantity: 3900 tonnes produced in 2002

Remark: The quantity is the estimated production in Japan.
Reliability: (2) valid with restrictions
03-DEC-2004 (29)

1.6.1 Labelling

Labelling: provisionally by manufacturer/importer
Symbols: (Xn) harmful
(N) dangerous for the environment
Specific limits: no
R-Phrases: (22) Harmful if swallowed
(50/53) Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-Phrases: (2) Keep out of reach of children
(24/25) Avoid contact with skin and eyes
(60) This material and/or its container must be disposed of as hazardous waste
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

03-DEC-2004 (38)

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: harmful
R-Phrases: (22) Harmful if swallowed
Specific limits: yes
Conc./Class. 1: >= 25 Xn; R22
%

Remark: Xn
03-DEC-2004 (38)

Classified: as in Directive 67/548/EEC
Class of danger: dangerous for the environment
R-Phrases: (50/53) Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Specific limits: no

03-DEC-2004 (38)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Use resulting in inclusion into or onto matrix

Remark: Approximately half of DAP produced is used as a monomer for the preparation of DAP prepolymer. Prepolymers are

semi-polymerised polymers before completing the polymerisation in succeeding process to manufacture the finished consumer products.

Almost all the residual DAP in the prepolymer (< 2wt%) is consumed during the reaction to produce the finished consumer products.

Almost all the rest of DAP produced is used and functions as a crosslinking agent during the reaction with the other polyemers such as poly(venyl chloride) and unsaturated polyester.

The use of DAP is not known to be intentionally added to the consumer products.

The concern of the consumer exposure is expected to be limited to the residual DAP containing the polymers used in the finished consumer products.

03-DEC-2004

Type: industrial
Category: Chemical industry: used in synthesis

Remark: DAP is the monomer for poly(diallyl phthalate).
03-DEC-2004

Type: industrial
Category: Electrical/electronic engineering industry

Remark: DAP is used as a constituent part of insulating varnish such as for a motor coil and of a resist ink such as for printed circuit boards.
03-DEC-2004

Type: industrial
Category: Polymers industry

Remark: DAP is used as carriers for adding catalysts and pigments to unsaturated polyesters. DAP can be mixed with PVC to improve the surface hardness of the products.
03-DEC-2004

Type: industrial
Category: Paper, pulp and board industry

Remark: DAP is monomer to produce poly diallyl phthalate used for impregnating paper with to make a tougher surface of decorated particle board used for such interior walls or furniture.
03-DEC-2004

Type: industrial
Category: Paints, lacquers and varnishes industry

Remark: DAP is used as a constituent part for insulating varnish used for such as motor coils. DAP is a monomer for the poly diallyl phthalate used for UV cure inks.
03-DEC-2004

Type: use
Category: Adhesive, binding agents

Remark: DAP is an intermediate of poly diallyl phthalate as a binder for grindstones.
03-DEC-2004

Type: use
Category: Construction materials additives

Remark: DAP is used as a constituent part of a varnish for impregnating the paper used for boards of interior walls or furniture.
03-DEC-2004

Type: use
Category: Impregnation agents

Remark: DAP is used as a constituent part of a varnish for impregnating the paper used for boards of interior walls or furniture.
03-DEC-2004

Type: use
Category: Intermediates

Remark: DAP is used as a monomers for poly (diallyl phthalate). DAP is also used as a crosslinking agent for polyvinyl chloride or unsaturated polyester.
03-DEC-2004

Type: use
Category: Semiconductors

Remark: DAP is used as a constitute of resist inks.
03-DEC-2004

Type: use
Category: Solvents

Remark: DAP is industrially used as a solvent for dissolve poly (diallyl phthalate) prepolymer before curing.
03-DEC-2004

Type: use
Category: Insulating materials

Remark: DAP is used as a constituent part of insulating varnishes for such as motor coils.
03-DEC-2004

Type: use
Category: Stabilizers

Remark: DAP is used as a crosslinking agent for stabilizing PVC against the cold weather or unsaturated polyester against heat or light.
03-DEC-2004

Type: use

Category: Viscosity adjustors

Remark: DAP is used as an agent for crosslinking and imparting appropriate flowability and viscosity of unsaturated polyester or polyvinyl chloride to mold.
03-DEC-2004

Type: use
Category: Colouring agents

Remark: DAP is used as a dye carrier, eg., in polyester dyeing.
03-DEC-2004

Type: use
Category: other: Peroxide diluent in polyester spray system

03-DEC-2004 (53)

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

Orig. of Subst.: Synthesis
Type: Production

Remark: Diallyl phthalate is manufacutured by either the esterification reaction of allyl alcohol and phthalic anhydride or the condensation of allyl chloride and sodium phthalate.
03-DEC-2004

1.8 Regulatory Measures

17-DEC-2004

1.8.1 Occupational Exposure Limit Values

Type of limit: other
Limit value: 5 mg/m3

Remark: Occupational Exposure Limit, UK, time-weighted average(TWA) 5 mg/m3, Sep. 2000
03-DEC-2004 (72)

Type of limit: other
Short term exposure
Limit value: 1 mg/m3

Remark: Exposure Limit - Rus
03-DEC-2004 (72)

Type of limit: other
Limit value: 5 mg/m3

Remark: Ireland - Occupational Exposure Limits - TWA

03-DEC-2004 (82)

Type of limit: MAK (DE)

Remark: No MAK established, Jan. 1999
03-DEC-2004 (72)

Type of limit: other
Limit value: 5 mg/m3

Remark: Germany - TRGS 900 - Occupational Exposure Limits - TWA
03-DEC-2004 (82)

Type of limit: other
Limit value: 5 mg/m3

Remark: New Zealand Work Place Exposure Limits - TWA
03-DEC-2004 (82)

Type of limit: other
Limit value: 3 mg/m3

Remark: Denmark Workplace Exposure Limits - TWA
03-DEC-2004 (82)

1.8.2 Acceptable Residues Levels

Maximum residues level: .01 mg/kg

Remark: DAP is listed in the Plastics Directive 2002/72/EC. Although it can be used, it should not be present above the limit of detection of 0.01 mg/kg. The EU Scientific Committee on Food (SCF) could not set a TDI for DAP because it was considered to be a genotoxic carcinogen.
17-DEC-2004

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

Type: TSCA
Additional Info: section 8(d) of TSCA

Remark: Pursuant to section 8(d) of TSCA, EPA promulgated a model Health and Safety Data Reporting Rule. The section 8(d) model rule requires manufacturers, importers, and processors of listed chemical substances and mixtures to submit to EPA copies and lists of unpublished health and safety studies. Diallyl phthalate is included on th
Original Reference:
40 CFR 716.120 (7/1/96)

17-DEC-2004 (53)

Type: other: Clean Water Act (US)
Additional Info: section 307(a)(1)

Remark:
Original Reference:
40 CFR 401.15 (7/1/
03-DEC-2004 (53)

Type: other: Clean Water Act (US)
Additional Info: section 307(a)(1)

Remark:
Original Reference:
40 CFR 401.15 (7/1/
03-DEC-2004 (53)

Type: other: Clean Water Act (US)
Additional Info: section 307(a)(1)

Remark:
Original Reference:
40 CFR 401.15 (7/1/
03-DEC-2004 (53)

Type: EINECS

03-DEC-2004

Type: DSL
Additional Info: Canadian Inventory

03-DEC-2004

Type: AICS
Additional Info: Australian Inventory

03-DEC-2004

Type: ECL
Additional Info: Korean Inventory

03-DEC-2004

Type: ENCS
Additional Info: Japanese Inventory

03-DEC-2004

Type: PICCS
Additional Info: PHilippine Inventory

03-DEC-2004

Type: CHINA
Additional Info: Inventory of Existing Chemical Substances in China

03-DEC-2004

17-DEC-2004

1.9.1 Degradation/Transformation Products

Type: degradation product
CAS-No: 88-99-3
EINECS-Name: phthalic acid

Remark: The test of hydrolysis as a function of pH was carried out based on the Method 111 of OECD Guidelines. Through the test, phthalic acid as a degradation product was detected experimentally using a combination of High Performance Liquid Chromatography with mass selective detection and Gas Chromatography with mass selective detection.

Result:

pH	Rate Constant (/s)	Estimated half lif at 25°C
4	-	> 1 year
7	-	> 1 year
9	8.88E-07	217 hours

Reliability: (1) valid without restriction
23-DEC-2004 (33)

Type: degradation product
CAS-No: 107-18-6
EC-No: 203-470-7
EINECS-Name: allyl alcohol

Remark: The test of hydrolysis as a function of pH was carried out based on the Method 111 of OECD Guidelines. Through the test, allyl alcohol as a degradation product was detected experimentally using a combination of High Performance Liquid Chromatograpy with mass selective detection and Gas Chromatography with mass selective detection.
Reliability: (1) valid without restriction
23-DEC-2004 (33)

Type: combustion products
CAS-No: 85-44-9
EC-No: 201-607-5
EINECS-Name: phthalic anhydride

Reliability: (2) valid with restrictions
03-DEC-2004

1.9.2 Components

1.10 Source of Exposure

Source of exposure: Human: exposure through intended use
Exposure to the: Substance

Method: Sampling was performed at a factory manufacturing diallyl phthalate and poly (diallyl phthalate). Sampling was performed during the working time that workers would be exposed to the chemical both indoors and outdoors. Samples

were taken from the air around workers' mouths. Workers performing extremely short duration tasks repeated the tasks 2-5 times for sampling. Samples were taken on both sides of the workers' mouths to take account of the effects of the air current.

Method of sampling:
Sample air was taken at an absorption rate of 2L/min using sampling tubes (glass fiber + XAD-7(270/140mg)).
Method of analysis:
HPLC: Hitachi L-7100 Series
Column: Inertsil ODS-80A (2.1 mm I.D. x 15 cm)
Mobile phase: ACN/H2O=1/1 (v/v%)
Column temperature: 40C
Flow rate: 0.2 mL/min
Wave length detected: 195nm
Extraction: Ultrasound extraction (15min.) - Centrifugation (300rpm x 10min.)
Extraction amount: 3 mL

Result: See Table Results of measurement of concentration in the air of diallyl phthalate for each task during diallyl phthlate monomer and diallyl phthalte prepolymer production.

The concentration of diallyl phthalate in the air during manufacture of the monomer (i.e. diallyl phthalate itself) was in a range of <0.015 - <0.111 mg/m3. Maximum exposure occurred during sampling of the chemical for analysis.
The concentration of diallyl phthalate in the air during manufacture of the diallyl phthalate prepolymer was in a range of 0.019 - 0.956 mg/m3. Maximum exposure occurred during cleaning operations.

Table: Result of measurement of concentration in the air of Diallyl phthalate for each task in MONOMER / POLYMER PRODUCTION

Work Frequency(Time)	n	range min. - max. (mg/m3)	mean Arithmatic (mg/m3)	Geometric (mg/m3)
MONOMER PRODUCTION				
[Filling into Drum / Rubber glove / No LV]				
72(5h)	2	<0.015 - <0.015	0.015	0.015
[Filling into 18L CAN / Rubber glove / No LV]				
72(5h)	2	<0.019 - <0.019	0.019	0.019
[Distillation sampling and analysis / Goggle+Rubber golve / No LV]				
3(0.08h)	2	<0.077 - <0.107	0.092	0.091
[Sampling of products / Glove+Goggle / No LV or LV]				
24(0.08h)	3	<0.111 - <0.111	0.111	0.111
[Inspection / Glasses / No LV]				
36(0.08-0.17h)	2	<0.026 - <0.026	0.026	0.026

POLYMER PRODUCTION

Work Frequency(Time)	n	range min. - max. (mg/m3)	mean Arithmatic (mg/m3)	mean Geometric (mg/m3)
[Filling into paper bags / Mask+Rubber glove / LV]				
300(5h)	4	0.019 - 0.055	0.034 ±0.017	0.031 ±1.675
[Sieving / Mask+Rubber Glove / LV]				
120(3h)	4	0.189 - 0.874	0.490 ±0.287	0.425 ±1.888
[Cleaning of flexible containers / Mask+Rubber globe+Protective cloth / No LV]				
24(1h)	2	0.211 - 0.956	0.584	0.449
[Sampling of polymerization liquid and analysis / Goggle+Glove / LV*]				
4500(0.2h)	4	<0.059 - <0.100	0.080 ±0.023	0.077 ±1.356
[Sampling of products and analysis / Google+Glove / No LV]				
600(0.2h)	2	0.092 - 0.205	0.149	0.137
[Inspection / Glasses / LV]				
84(0.4h)	2	<0.021 - <0.021	0.021	0.021

[//], [description of work / Protectives / Local Ventilator]
*, A local ventilator was furnished but not operated.
LV, Local Ventilator.

Reliability: (1) valid without restriction
03-DEC-2004 (55)

Source of exposure: Human: exposure of the operator by intended use
Exposure to the: Substance

Remark: The National Occupational Hazard Survey (1981-1983) indicates that 8,784 male and 2,027 female employees are potentially exposed to DAP in U.S.

Table Estimated Numbers of Employees Potentially Exposed to DAP by Occupation

Occupation Description	Total Male & Female	Total Male
Textile Mill Products	245	41
Printing and Publishing	1,175	
Rubber and Misc. Plastics Products	2,667	1,359
Stone, Clay and Glass Product	2,520	
Fabricated Metal Products	158	

	Machinary, Except Electrical	232	
	Electric and Electronic Equipment	1,095	606
	Transportation Equipment	692	21
	-Total	8,784	2,027

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
03-DEC-2004 (68)

Source of exposure: Human: exposure through intended use
Exposure to the: other: Emission from the Article

Method: This study was conducted according to the method in JIS A 1901:2003, Determination of the emission of volative organic compounds and aldehydes for building products - small chamber method, Japan Industrial Standards Committee, 2003.

Remark: Diallyl phthalate should not be classified into the so-called phthalate ester 'plasticizers'. The substance is often called a 'reactive plasticizer'. The expression is brief but often confusing.

There is less risk of the articles made from diallyl phthalate monomer such as DAP-decorative boards than those made from the other phthalate ester plasticizers. The reason for this lies mainly in the specific uses of diallyl phthalate due to its characteristic two reactive allyl groups.

Two allyl reactive groups readily react inter-molecularly between the monomers and/or prepolymers, produced beforehand or concurrently from the monomers, to form more rigid plastic resins by heating. The heating process incorporates the monomers covalently into the product polymers as a part of the polymers in the irreversible form in which the incorporated monomers cannot be retrieved and released during downstream uses including the decomposing process such as burning, aging, and hydrolysis. It is supported by the fact that the heat decomposition of diallyl phthalate prepolymer could not re-produce the diallyl phthalate monomer (Tsuge, Pyrolysis-gas chromatography of polymers -basic theory and data-, published by K.K. TechnoSystem, 1991 Japan). The reason of the impossibility of the re-production of diallyl phthalate monomer is that during the manufacturing process, heating process both or either C-C double bonds of two allyl
function groups open and make more tight C-C covalent cross-linkage to an opened bond in the other monomers or prepolymers.

The intentions of the addition of diallyl phthalate monomer are
1) to make the raw plastics softer to readily mold during the molding process, and 2) to react and make the raw plastic prepolymers turn thermosetting plastics during the heating process, so-called curing process.

On the other hand, the intentions of the addition of the other most phthalate ester plasticizers are to make the end user products softer or more flexible.

Diallyl phthalate ester is not intended to be stayed intact in the end user products. The reason for this is that in general diallyl phthalate is used not to make the end user products more flexible but more rigid and to make only processing plastics more flexible so as to readily mold. Therefore, the diallyl phthalate content in the end products may be trace.

On the other hand, the other most phthalate ester plasticizers must be intended to be stayed intact in high proportion in the end user products required softness or flexibility. The reason for this is that in general the more plasticizers plastics contain, the softer and the more flexible the plastics become. In some cases, the plasticizer content can exceed 50%.

Concerns about phthalate esters for sick building syndrome lie in the potential risk that humans and environment could be exposed by the esters with the adverse effects emitting from building materials or migrated into foods or drinks from the contacting wrapping materials or vessels for them. Therefore, this study was planned to determine the emission of the diallyl phthalate monomer from a building material, a DAP-decorative board as a representative example for the exposure assessment.

Result:

Determination of Emission of Diallyl Phthalate

Started Sample		Emission determined ($\mu g/m^3$)	Emission Rate ($\mu g/m^2h$)
1	sample	<0.05	< 0.011
2	sample	<0.05	< 0.011
3	sample	0.09	0.02 [2]
4	control	21	9.5 [1]
5	sample	<0.05	< 0.011
6	sample	<0.05	< 0.011

[1] Control sample (see Test Sample Section)
[2] The reason for the high value lie most likely in the contamination from the control sample; sample 5 was blind one identical to sample 2 and sample 6 was blind one identical to sample 3.
[3] < means that the determination did not exceed the lower limitation.

These data indicate that the emission of the diallyl phthalate from the DAISO DAP-decorative board tested is low, in view of the interim tolerance values in a room of di-n-butyl phthalate (220 $\mu g/m^3$)and di-2-ethylhexyl phthalate (120 ug/m^3) publised by the Ministry of Health and Welfare Japan (MHLW) on 22 January 20

Test condition: Laboratory: KN-Lab Analysis
Article: DAISO DAP-decorative board (Lot No.: 12092 -no additive-)

Chamber Temperature/Humidity: 28°C/50%
Chamber Volume: 20 L
Ventilation Volume: 10 L/h
Ventilation Rate: 0.5 times/h
Sample Surface Area: 432 cm^2
Gas Sample Volume: 1 m^3
Loading ratio of Sample: 2.2 m^2/m^3
minimum limit of determination: 0.05 μ/m^3
The duration time of the emission for the determination: 5 days.

Chamber: ADPAC System.

Test substance: Sample:
DAISO DAP-decorative board
Sampling: The sampling was conducted on 10 October 2003 at a DAISO factory manufacturing the boards. Three boards were extracted randomly in the Lot Number 031002 series. Two specimens (160 mm x 160 mm) per board were cut off. Two specimens from the same board was allocated to the one sample for the determination. Six specimens (Three samples) were prepared.

These specimens each were separately wrapped with aluminium foils and put in a polyethylene sack. Two samples are sent immediately to the Laboratory performing the determination on the same day. The rest of the samples were kept in the DAISO Labs at room temperature until the next determination date (Oct. 21, 2003).

A sample as a control was prepared as follows:
A wood board before pressing with the impregnated paper, the same size to the previous described specimens, glass filter (diameter: 55 mm, Toyo Roshi Kaisha, GA100, Lot 91291001), and diallyl phthalate (DAISO CO., Ltd. Lot No. 13061, purity >99.9(GC)) were prepared.

Diallyl phthalate (44.9 mg) was loaded on the center of the glass filter fixed on an aluminium foil folding its margin onto the filter. The aluminium foil with the glass filter was pinned on the wood board. This wood board with the glass filter loaded diallyl phthalate was allocated to sample 4. This sample is comprised by one specimen instead of two specimens in other case. (Therefore, sample loading ratio of this sample was 1.1 m^2/m^3.)

Sample 3 and 4 were sent to the Laboratory on 21 October 2003. The test for the determination started on 24 October 2003.

Sample 5 was comprised of the identical specimens to Sample 2; Sample 6 was comprised of the identical specimens to sample 3. Sample 5 and sample 6 were sent to the Laboratory on 11 November 20. The test started on 17 November 22.

Conclusion: The emission of the diallyl phthalate from the DAISO DAP-decorative board tested is low, in view of the interim

tolerance values in room of di-n-butyl phthalate (220 µg/m³) and di-2-ethylhexyl phthalate (120 µg/m³) published by the Ministry of Health and Welfare Japan (MHLW) on 22 January 2002, suggesting that there is likely low human risk of the diallyl phthala

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
17-DEC-2004 (31)

Source of exposure: Human: exposure of the consumer/bystander
Exposure to the: other: Emission from the article

Method: The survey was conducted from November 1999 to March 2001 (5 times/year, twice in summer and 3 times in winter). Thirty-four facilities such has houses or specific buildings in the metropolis were surveyed each time. Every facility examined in the first survey continued to be examined in the remainder of the study wherever possible. If necessary, new buildings were selected and examined.

The air was sampled for 24 hours at 2 indoor sites per facility and the concentration of the chemicals determined. Outdoor air was sampled at a facility in the same region. The sampling was performed using an active method where the air was collected by pumping using Empore C18 FF and quartz filter disk at the rate of 10 L/min. The sample was extracted with acetone and the concentration determined using GC/MS and GC/FPD.

Remark: Chemical substances, including those suspected of being endocrine disruptors, are widely used for building materials, household articles, insecticides, moss repellents, etc, both indoors or around the perimeter of residential properties and offices.

Especially in modern airtight residences there is a concern that a variety of chemicals may pollute the internal air and then pass into the body through the lungs, affecting the endocrine system and the immune system.

To address the growing concern for 'sick building' syndrome, the authors have surveyed homes and offices since 1999. based on their results, they expanded the survey to include semi-volatile organic chemicals (SVOC), including endocrine disruptors.

This report descirbes the results of the survey for formaldehyde, VOC and phthalate esters (19 chemicals).

Result: No diallyl phthalate was detected in the air during the study. The limit of detection was 5 ng/m3.
Reliability: (1) valid without restriction
03-DEC-2004 (14) (73) (74)

Source of exposure: Human: exposure of the consumer/bystander
Exposure to the: other: Emission from the article

Method: Apparatus:
Gas chromatography: Shimazu GC-17A, Flame photometric detector.
GC Injector with condenser for mass samples: Type OPTIC2-200

Ultrasonic cleaner: SHARP UT-205
High performance liquid chromatography: Shimazu LC-10ATVP

Reagents:
Commercial high grade reagents were used.
Quartz Filter: Pallflex 2500 QRT-UP. The filter was punched out and used in a circle with a diameter of 47mm. This punch-out filter was heated for 3 hours at 400°C in the electric furnace before use.
Empore Disk C18 filter (47 mm): 3M Octadecy (C18). This filter was cleaned with a ultrasonic cleaner in acetone before use.
Carbon Disk Filter: 3M, 47 mm. This filter was cleaned with a ultrasonic cleaner in dichloromethane.
DNPH Cartridge: Waters, Exposure Type.

Target Chemical Substances:

Organic phosphorous compounds: Tributyl phosphate (TBP), Tris(2-chloroethyl)phosphate (TCEP), Tris(ß-chloroisopropyl)phosphate (TCIPP), Tris(butoxyethyl)phosphate(TBHP), Tris(2-ethylhexyl)phosphate (TEHP), Tricresyl phosphate(TCP), Diazinon(DZ), Chlorpyrifos(CP), Chlorpyrifos-methyl(CPM), Fenitorothion(MEP), Pyridaphenthion(PF), Fenthion(MPP), Triphenyl phosphate(TFP)

Phthalate esters: Dimethyl phthalate (DMP), Diethyl phthalate (DEP), Diallyl phthalate (DAP), Di-iso-butyl phthalate, Di-n-butyl phthalate (DBP), Butyl benzyl phthalate (BBP), Di-n-hexyl phthalate (DHP), Dioctyl pthalate (DOP), Dinonyl phthalate (DNP)

Other Chemical Substances: VOCs (Volatile Oraganic Chemicals), formaldehyde, NOx (Nitrogen Oxides)

Sampling:

Phthalate Esters: A quartz filter (47 mm) and an Empore Disk C18 filter were set in piles in a Teflon filter holder. Air was collected at 5 L/min for 24 hours. Particulate substance was defined as substance trapped on the quartz filter; gaseous substance was defined as substance trapped on the Empore Disk C18 filter.

Outline of Target Residenses:

Target Residence No. 1: The house was built 23 years ago at Kashiwara-shi, Chiba prefecture with two-story, steel-frame building. Sampling was conducted in the living dining room in the ground floor before and after the repair of the room in Sep. 2000 and Oct. 2000.

Target Residence No.2: A newly built, two-story residence at Isezaki-shi, Kanagawa prefecture was investigated on July 2000. Sampling was conducted in a Japanese style room in the ground floor.
Target Residence No. 3: A newly built, steel-frame, and three-story residence with the ventilator on a steady basis. at Maebashi-shi, Gunma prefecture was investgated on Mar.

2001. Sampling was conducted in the child's room in the second floor.

Remark: In recent years, sick building syndrome (SBS) and chemical sensitivity (CS) have become big concerns socially. Although there are many factors for the development of these symptoms, it is pointed out that chemical substances which are emitted from building materials, furniture, household articles, etc. are involved greatly. However the generation sources are not only the chemical substances mentioned above but also smoking, heating appliances, etc. However, there are comparatively few examples of reports about the amount of generating chemical substances from these generation sources and the influence on the actual indoor air pollution of the substances.

This investigation of residential air pollution was conducted to clarify the relevance of chemical substance concentration to sick building syndrome and chemical sensitivity. The airborne concentrations of combustion products when smoking or using heating appliances in residential houses were experimentally measured.

For chemical substances, the single houses before and after rebuilding and newly built single houses were selected and investigated; For the combustion products by smoking or using heating appliances, the apartment house and collective housing were selected used for the experiments.

The investigated results showed that the concentrations of volatile organic chemicals (VOCs) such as toluene, xylene, ethylbenzene, and butyl acetate ester; semi-volatile organic chemicals (SVOC) such as tributylphosphate ester and dibutyl phthalate etc. were detected in higher concentration.

In the smoking experiment, carcinogenic substances such as Benzo(a) pyrene were detected.

In the heating apparatus experiment, the concentration of TVOC, VOCs, and NOx when using the open type of oil stove are more likely to be higher than those when using other types of stoves. Nonane, Decane, Xylene, Toluene, etc apparently increased in air after using the heating appliance.

Result: The results of the monitoring studies are shown in the table below. In residence No. 1 (the old residence) diallyl phthalate was detected at levels of 34.1 ng/m3 (particulate) and 45.2 ng/m3 (gasous) before repair and 2.9 ng/m3 (particulate) and 22.9 ng/m3 (gasous) after repair. In residence No. 2 (newly built, natural ventilation) diallyl phthalate was detected at levels of 8 ng/m3 (particulate) and 126.5 ng/m3 (gasous). In residence No. 3 (newly built, continuous ventilation) diallyl phthalate was detected at levels of 2 ng/m3 (particulate) and 5.1 ng/m3 (gaseous).

Table 1 Concentration of Phthalate Esters Indoors (unit ng/m3)

Chemicals	Residence		
	No.1	No.2	No.3

	Before repair		After repair		Newly Built		Newly Built	
	P	G	P	G	P	G	P	G
DAP	34.1	45.2	2.9	22.9	8	126.5	2	5.1
DMP	1.4	125.1	N.D.	57.7	1.4	66.9	1.6	3.4
DEP	26.3	123.8	0.7	65.2	3.9	160.4	1.5	4.2
DiBP	30.5	1.0	0.2	25.6	6.2	43.5	3.1	4.2
DBP	2632.7	68.7	94.1	1042.4	1459.4	1.4	6.5	2.6
BBP	8.2	N.D.	5.5	1.0	8.8	1.7	4.2	N.D.
DHP	30.5	N.D.	25.4	7.3	32.9	7.5	3.5	N.D.
DOP	540.6	N.D.	194.5	31.2	557.2	5.3	7.7	N.D.
DNP	2.6	N.D.	N.D.	1.0	3.3	0.3	N.D.	N.D.

DAP, diallyl phthalate; DMP, dimethyl phthalate; DEP, diethyl phthalate; DiBP, di-i-butyl phthalate; DBP, di-n-butyl phthalate; BBP, benzyl-n-butyl phthalate; DHP, dihexyl phthalate; DOP, dioctyl phthalate; DNP, dinonyl phthalate

Residence No. 1: Natural ventilation
Residence No. 2: Natural ventilation
Residence No. 3: Ventilator working on a steady basis

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
17-DEC-2004 (62)

Source of exposure: Human: exposure of the consumer/bystander
Exposure to the: other: Emission from the article

Method: Analytical Method:
Cleaning of Filter:
Quartz fiber filters are cleaned by heating at 350°C for 2 hours in a nitrogen atmosphere in an electric furnance.

Carbon Disk filters are cleaned by sonicating in an ultra sonicator , put into a dessicator with a screw cap, and dessicated in reduced pressure with a vacuum pump. Dessicated filters are put into a storing aluminium sack with a zipper and stored in a dessicator with active charcoal and silica gel.

Separate Trap in the Form:
In the case of trapping phthalate esters differently in the particular and gaseous forms, two filter were stacked (carbon disk filter onto quartz fiber filter), set in a paper filter holder made of teflon, and used to trap the sampling air at the flow rate of 5 L/min for 1 to 2 days (the duration depending on the concentration in the air).

Trap Separately in the Particular Size:
The Personal Cascade Impactor (PCI) is disassembled, washed with pure water, and dried in a nitrogen atmosphere. The PCI is assembled with the quartz filter weighed in advance. The PCI sampler and pump are connected with silicone tubes etc. The sampling air is trapped at the flow rate of 3 L/min at given time (1 - 7 days depending on the concentration in

the air).

Making weight and humidity of fiters constant:
In the case of weighing ariborne particulates, the filter is held in a dessicator at the relative humidity of 50% conditioned by using the solution saturated with sodium bisulfate, potassium nitrate etc for 24 hours to make the filter humidity constant.

Weighing filter:
The particulates trapped are weighed in the balance, which is able to weigh at less than 1µg. In winter, treatment to prevent weighing error due to static electricity is required.

Storage of Filter:
Filters are put into a aluminium sack labeled and stored in the dessicator with active charcol and silica gel. At the same time, a travel blank is stored as well.

Analysis:
The filter containing trapped substances is put into a tube with a ground-in stopper and extract by ultrasonicating with a mixture of acetone and toluene (7:3). The supernatant liquid is transferred to the centrifugation tube (10 ml) and centrifuged at 3000 rpm x 10 min at 0°C. An internal standard is added to the supernatant (1 ml) and mixed. One micro-liter of the solution is injected into the GC/MS.

Analytical Curve:
The analytical curve is made using 5 different concentrations of standard solution with an internal standard.

Analytical Method:
Cleaning of Filter:
Quartz fiber filters are cleaned by heating at 350°C for 2 hours in a nitrogen atmosphere in an electric furnance. Carbon Disk filters are cleaned by sonicating in an ultra sonicator , put into a dessicator with a screw cap, and dessicated in reduced pressure with a vacuum pump. Dessicated filters are put into a storing aluminium sack with a zipper and stored in a dessicator with active charcoal and silica gel.

Separate Trap in the Form:
In the case of trapping phthalate esters differently in the particular and gaseous forms, two filter were stacked (carbon disk filter onto quartz fiber filter), set in a paper filter holder made of teflon, and used to trap the sampling air at the flow rate of 5 L/min for 1 to 2 days (the duration depending on the concentration in the air).

Trap Separately in the Particular Size:
The Personal Cascade Impactor (PCI) is disassembled, washed with pure water, and dried in a nitrogen atmosphere. The PCI is assembled with the quartz filter weighed in advance. The PCI sampler and pump are connected with silicone tubes etc. The sampling air is trapped at the flow rate of 3 L/min at given time (1 - 7 days depending on the concentration in

the air).

Making weight and humidity of fiters constant:
In the case of weighing ariborne particulates, the filter is held in a dessicator at the relative humidity of 50% conditioned by using the solution saturated with sodium bisulfate, potassium nitrate etc for 24 hours to make the filter humidity constant.

Weighing filter:
The particulates trapped are weighed in the balance, which is able to weigh at less than 1µg. In winter, treatment to prevent weighing error due to static electricity is required.

Storage of Filter:
Filters are put into a aluminium sack labeled and stored in the dessicator with active charcol and silica gel. At the same time, a travel blank is stored as well.

Analysis:
The filter containing trapped substances is put into a tube with a ground-in stopper and extract by ultrasonicating with a mixture of acetone and toluene (7:3). The supernatant liquid is transferred to the centrifugation tube (10 ml) and centrifuged at 3000 rpm x 10 min at 0°C. An internal standard is added to the supernatant (1 ml) and mixed. One micro-liter of the solution is injected into the GC/MS.

Analytical Curve:
The analytical curve is made using 5 different concentrations of standard solution with an internal standard.

Calculation of Concentration:
The concentrations of the phthalate esters are calculated from the measurements and the air sampling volume of samples and blanks.

Limit of Measurement:
In the case of separate measurements in particulate or gaseous form, when the air was trapped at 5 L/min for 48 hours (14.4 m3) the limit of measurement of DHP was 3.8 ng/m3 and those of other phthalate esters were 1.7 ng/m3 or less.

In the case of the measurement of the particle distribution with the PCI when the air was trapped at 3 L/min for 1 week (30.24 m3), the limit of detection of DHP was 1.8 ng/m3 and those of the other phthalate esters were 0.8 ng/m3 or less.

Remark: Phthalate esters are widely used as plasticizers for polyvinylchloride (PVC), etc. In residential environments, a variety of domestic products contain phthalate esters. This has led to a concern that the air in residential environments may be polluted by the emission of the chemicals from the household goods.

Phthalate esters in the residential environment occur in the gaseous and/or particulate form. In this study, the authors developed an analytical method in order to investigate the

particle size distribution of phthalate esters and the levels present in particulate and gaseous form in residential properties. The analytical method was used to evaluate the levels of a range of phthalate esters in a variety of residential properties in Japan. The method was not only applicable to those phthalate esters used in household goods, but also to those used in building materials.

The following phthalate esters were examined in this investigation: Dimethylphthalate (DMP), Diethyl phthalate (PEP), Diallylphthalate (DAP), Di-n-propylphthalate (DPP), Di-iso-butylphthalate (DBF), Butylbenzylphthalate (BBP), Di-n-hexylphthalate (DHP), Dicyclohexylphthalate (DCHP), Di-(2-ethylhexyl)phthalate (DEHP, synonym: DOP), Di-nonylphthalate (DNP).

Result: Monitoring of four homes found levels of DAP in particulate form to range from below the limit of detection (£ 1.7 ng/m3) to 6.2 ng/m3. In gaseous form, levels ranged from below the limit of detection (£ 1.7 ng/m3) to 12.5 ng/m3, the highest level being found in a new home.

Table 1 Determination of phthalate esters in indoor air

-	Concentrations (ng/m3)									
	Collective housing		Stand-alone housing						Air outdoors	
	Existing house(1)		New home(2)		Existing home(3)		Existing home(4)			
	P	G	P	G	P	G	P	G	P	G
DAP	6.2	N.D.	4.6	12.5	N.D.	N.D.	4.1	8.2	N.D.	N.D.
DMP	177.2	1311.6	135	235	23.2	43.1	18.4	28.2	N.D.	5.1
DEP	25.9	70.5	120	450	55.2	60.4	170	310	N.D.	4.1
DPP	N.D.	50.7	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
DIBP	2.9	N.D.	3.4	N.D.	N.D.	N.D.	3.6	N.D.	N.D.	N.D.
DBP	1182	194	2400	58.2	760	16.3	2200	176	N.D.	N.D.
BBP	2.0	0.4	3.0	1.6	N.D.	N.D.	140	12.4	N.D.	N.D.
DHP	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	5.0	N.D.	N.D.	6.4
DCHP	N.D.	31.5	N.D.	N.D.	N.D.	N.D.	11.0	24.4	N.D.	N.D.
DEHP	464	27.1	784	11.2	710	18.8	2300	101	17.4	22.7
DNP	1.0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	4.1	1.7

P, Particle;G, Gass

(1) 24 Jun 2001 to 25th, Humidity 65%, Living Room, 14.4 m3
(2) 15 Aug 2001 to 16th, Humidity 62%, Living Room, 14.4 m3
(3) 12 Sep 2001 to 13th, Humidity 56%, Living Room, 14.4 m3
(4) 24 Aug 2001 to 25th, Humidity 68%, Living Room, 14.4 m3

DMP, Dimethyl phthalate; BBP, Butyl benzyl phthalate; DEP, Diethyl phthalate; DHP, Di-n-hexyl phthalate; DAP, Diallyl phthalate; DCHP, Dicyclohexyl phthalate;DPP, Di-n-propyl phthalate; DEHP, Di-(2-ethylhexyl)phthalate; DIBP, Di-isobutyl phthalate; DNP, Di-nonyl phthalate; DBP, Di-n-butyl phthalate

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint
17-DEC-2004 (63)

Source of exposure: Human: exposure through intended use
Exposure to the: Substance

Remark: Diallyl phthalate itself is not used in the UV-curable ink. Poly(diallyl phthalate) is used as an ingredient in the ink. Therefore, the concern of the exposure is limited to that from the diallyl phthalate remaining in the poly(diallyl phthalate).

According to our MSDS, the content of the diallyl phthalate in the poly(diallyl phthalate) is 2% or less. According to our another information, the content of the poly(diallyl phthalate) in the ink is expected to be 10% or less and the ink is used 2 g or less per 1 m² of paper in printing process.

During the printing process, the polymer in the UV-ink on the paper is dried, irradiated by UV, and cured. The process is expected to make a major part of residual diallyl phthalate incorporate via covalent bond into the polymer matrix.

The main consumer exposure route of DAP via the printed paper is expected to be skin. The consumer dermal exposure per day is expoected to be very low comparing to the NOAEL (50 mg/kg bw/day) of rat in the repeated dose test and therefore, the risk through the dermal exposure is expected to be low.

The inhalation exposure via papers printed using the UV-curable ink containing diallyl phthalate is also low because the inhalation exposure from the decorative board is supposed to be very low and the amount of poly(diallyl phthalate) loaded on the paper is even less than that of the decorative board. The amount of varnish in decorative board is used bout 10-fold than that in the printed paper (See decorative board data).

Reliability: (2) valid with restrictions
03-DEC-2004

1.11 Additional Remarks

1.12 Last Literature Search

Type of Search: Internal and External

Remark: Aquire (1992 - 2002)
Biodegradation Data (BIODEG) (1992 - 2002)
Biodegradation Bibliographic References (BIOLOG)(1992 - 2002)
Biological Abstracts - BIOSIS (1969 - present)
CA Search (1967 - present)
ECOTOX database
EMBASE (1974 - present)
EMBSINFO (1977 - present)

Enviroline (1970 - present)
Environmental Bibliography (1974 - present)
Gene-Tox (1992 - 2002)
HSELINE (1977 - present)
IRIS database
Medline (1966 - present)
National Technical Information Service (NTIS)(1964 - present)
NIOSH (1973 - present)
PASCAL (1984 - present)
TERRETOX (1992 - 2002)
TSCATS (1977 - present)
Toxfile (1965 - present)
NITE
Internet

Search terms:

CAS No. 131-17-9
Diallyl phthalate
Ecotoxicology
Toxicology
Environment

03-DEC-2004

1.13 Reviews

2.1 Melting Point

Value: -70 degree C

Remark: Original Reference:
Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 12th ed. New York, NY: Van Nostrand Rheinhold Co., 1993 361
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
03-DEC-2004 (60)

Value: < -10 degree C

Method: other: JIS K 0065
Year: 1990
GLP: yes
Test substance: other TS

Remark: Measured on Dec. 1990.
Test substance: Chemical name: diallyl phthalate (CAS No. 131-17-9)
Source: Tokyo kasei Kogyo Co., Ltd.
Grade: TCI-GR
Lot No.: AY01
Purity: 98.8%
Appearance: colorless, transparent, liquid
Reliability: (2) valid with restrictions
03-DEC-2004 (18)

2.2 Boiling Point

Value: 157 degree C at 6.7 hPa

Method: other: JIS K2254
Year: 1994
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: CITI reported that the boiing point could not be measured at 1013 hPa due to decomposition at 300°C.
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Lot 14082 (+Additive)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
17-JUL-2004 (19)

Value: 290 degree C

Remark: Original Reference:
FIRE PROTECTION GUIDE ON HAZARDOUS MATERIALS 11TH ED., QUINSY : NFPA, 1994.
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
Peer-Reviewed

03-DEC-2004 (3) (54)

Value: 158 - 165 degree C at 5.3 hPa
Decomposition: no

GLP: no data

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
Peer reviewed Literature data
03-DEC-2004 (59)

2.3 Density

Type: density
Value: 1.1206 g/cm³ at 20 degree C

Method: other
Year: 1945
GLP: no

Remark: Original Reference: Kardashev, D. A.; Leznov, N. S.; Nuzhdina, V. P. (1945); KHIM. PROM.; 2:5-6. (Rossian)
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
07-MAR-2004 (80)

Type: density
Value: 1.12

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
19-JUL-2004 (3)

Type: relative density
Value: 1.12 at 20 degree C

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
19-JUL-2004 (59)

Type: relative density
Value: 1.117 - 1.123 at 20 degree C

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (4) not assignable
03-DEC-2004 (49)

Type: density
Value: 1.118 g/cm³ at 20 degree C

Year: 1990

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Purity: 98.8%
Reliability: (4) not assignable

19-JUL-2004 (18)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: .000213 hPa at 25 degree C

Year: 1982
GLP: no data
Test substance: no data

Remark: Original Reference: Sears, JK, & Darby JR(1982) The Technology of Plasticizers, Wiley Publishers, New York. pp. 906-907
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
17-DEC-2004 (79)

Value: 3.2 hPa at 150 degree C

Year: 2004
GLP: no data
Test substance: no data

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
Peer Reviewed Literature Data
19-JUL-2004 (20)

Value: 3.999672 hPa at 154.5 degree C

Year: 1945
GLP: no
Test substance: no data

Remark: Original Reference: Kardashev, D. A.; Leznov, N. S.; Nuzhadina, V.P.(1945); New Tars on Basis of of Allyl Ehters of Two Basis Acids; KHIM. PROM. (USSR), 2:5-6
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
19-JUL-2004 (80)

Value: 3.2 hPa at 150 degree C

Test substance: other TS

Remark: Vapour pressure = 36 hPa at 200°C
Test substance: FMC Corporation (DAP, C8013-1)
Purity: 99 %
Moisture: 0.1%
Acidity (% acetic acid): 0.1%
Specific gravity 20°/20° 1.117-1.123
Reliability: (2) valid with restrictions
No information on test method
19-JUL-2004 (49)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: 3.23 at 20 degree C

Method: OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year: 1983
GLP: no data

Test substance: DAP (CEPEA)
Reliability: (2) valid with restrictions
Not reported detail test condition.
Flag: Critical study for SIDS endpoint
19-JUL-2004 (61)

Partition Coeff.: octanol-water
log Pow: 3.23

Year: 2002
GLP: no data

Remark: Peer reviewed literature.

Original Reference:
Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995. 122
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
19-JUL-2004 (53)

2.6.1 Solubility in different media

Solubility in: Water
Value: .148 g/l at 20 degree C
pH value: 6.9 - 7.3
Conc.: .148 g/l at 20 degree C
Descr.: moderately soluble (100-1000 mg/L)

Method: OECD Guide-line 105
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Deg. product: no
Stable: yes

Test condition: Preliminary test:
An aliquot (0.1195 g) of test material was diluted to 100 ml with glass double-distilled water. After shaking at 30°C for 20 hours and standing at 20°C for 3¼ hours, the solution was centrifuged and analysed.

Definitive test:
After addition of glass double-distilled water to the flasks, they were shaken at approximately 30°C and, after

standing at 20°C for a period of not less than 24 hours, the contents of the flasks were centrifuged at 10,000 rpm for 30 minutes and sampled with pipettes with the aid of vacuume suction.

Analytical Method:
- HPLC System: Agilent Technologies 1050, incorporating autosampler and workstation.
- Column: Prodigy ODS (2) 5 um (250 x 4.6 mm id)
- Column temperature: 40°C
- Mobile phase: acetonitrile: water (75:25 v/v)
- Flow-rate: 1 ml/min
- UV detector wavelength: 223 nm
- Injection volume: 5 ul
- Retention time: ca. 5 m

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Purity: >99%
Supplier: DAISO Co.

Conclusion: The solubility of the test material has been determined to be 0.148 g/l of solution at 20.0 ± 0.5°C.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

19-JUL-2004 (33)

Solubility in: Water
Value: 45.9 - 46.1 mg/l at 25 degree C
Conc.: 46 mg/l at 25 degree C
Descr.: slightly soluble (0.1-100 mg/L)

Method: OECD Guide-line 105
Year: 1990
GLP: yes
Test substance: other TS
Deg. product: yes

Test substance: Tokyo Kasei Kogyo Co., Ltd.
Lot Number: AY01
Grade: TCI-GR
Purity: 98.8%
Appearance: Transparent and colorless
Melting Point: < -10°C
Boiling Point: incapable measurement (browning at 300°C)
Density: 1.118 g/cm³ (20°C)

Reliability: (2) valid with restrictions

03-DEC-2004 (18)

Solubility in: Water
Value: 182 mg/l at 20 degree C
Descr.: moderately soluble (100-1000 mg/L)

Method: OECD Guide-line 105
Year: 1995

Test substance: CEPEA
Reliability: (2) valid with restrictions

07-MAR-2004 (61)

Solubility in: Water
Value: .6 other: % by weight at 25 degree C

Year: 1989
GLP: no data
Test substance: other TS

Test substance: FMC Corporation (DAP, C8013-1)
Purity: 99 %
Moisture: 0.1%
Acidity (% acetic acid): 0.1%
Specific gravity 20°/20° 1.117-1.123
Reliability: (4) not assignable
03-DEC-2004 (49)

2.6.2 Surface Tension

2.7 Flash Point

Value: 166 degree C
Type: closed cup

Year: 1997
GLP: no data
Test substance: no data

Remark: QC Reviewed Literature.
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
20-DEC-2004 (44)

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air
Light source: Sun light
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 1500000 molecule/cm³
Rate constant: .0000000000557313 cm³/(molecule * sec)
Degradation: 50 % after 2.3 hour(s)

Method: other (calculated)

Remark: SMILES : O=C(OCC=C)c(c(ccc1)C(=O)OCC=C)c1
CHEM : 1,2-Benzenedicarboxylic acid, di-2-propenyl ester
MOL FOR: C14 H14 O4
MOL WT : 246.27
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS
Hydrogen Abstraction = 2.9888 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 52.6000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.1425 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 55.7313 E-12 cm3/molecule-sec
HALF-LIFE = 0.192 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 2.303 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION
OVERALL OZONE Rate Constant = 2.400000 E-17 cm3/molecule-sec
HALF-LIFE = 0.477 Days (at 7E11 mol/cm3)
HALF-LIFE = 11.460 Hrs

Experimental Database: NO Structure Matches

Hydrogen Abstraction Calculation:
Ksec = 0.934 F(>C=C<)F(-OC(=O)R)=0.934(1.000)(1.600)= 1.494
Ksec = 0.934 F(>C=C<)F(-OC(=O)R)=0.934(1.000)(1.600)= 1.494
H Abstraction TOTAL = 2.989 E-12 cm3/molecule-sec

OH Addition to Olefinic Bonds Calculation:
Kd = K(CH2=CH-)
= 26.300 = 26.300 E-12 cm3/molecule-sec
Kd = K(CH2=CH-)
= 26.300 = 26.300 E-12 cm3/molecule-sec

Ozone Reaction with Olefins Calculation:
Ko = K(CH2=CH-R)Ox(-Alkyl)
= 1.200000 = 1.200000 E-17 cm3/molecule-sec
Ko = K(CH2=CH-R)Ox(-Alkyl)
= 1.200000 = 1.200000 E-17 cm3/molecule-sec

OH Addition to Aromatic Rings Calculation:
Es+ = sp+(-C(=O)-OCH2CH3) + sm+(-C(=O)-OCH2CH3) + = 0.848

Es+ = sm+(-C(=O)-OCH2CH3) + sp+(-C(=O)-OCH2CH3) + = 0.848
Es+ = sp+(-C(=O)-OCH2CH3) + sm+(-C(=O)-OCH2CH3) + = 0.848
Es+ = sm+(-C(=O)-OCH2CH3) + sp+(-C(=O)-OCH2CH3) + = 0.848
Most negative Es+ = 0.848
Log Kar = -11.71 - 1.34(Es+) cm3/molecule-sec
Ring #1 Kar = 0.1425 E-12 cm3/molecule-sec
TOTAL Kar = 0.1425 E-12 cm3/molecule-sec

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
03-DEC-2004 (28)

Type: air

Result: Atmospheric Photoxidation Half-Lives of DAP is 0.04-0.4 days by prediction of half-lives obtained by the Atmospheric Oxidation Program (Atkinson, 1988)

Atkinson, R. 1988. Estimation of Gas-Phase Hydroxyl Radical Rate Constants for Organic Chemicals. Environ. Toxicol. Chem. 7(6):435-442.

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (4) not assignable
03-DEC-2004 (79)

3.1.2 Stability in Water

Type: abiotic
t1/2 pH4: > 1 year at 25 degree C
t1/2 pH7: > 1 year at 25 degree C
t1/2 pH9: 217 hour(s) at 25 degree C
Degradation: 50 % after 217 hour(s)
at pH 9 and 25 degree C
Deg. products: yes
107-18-6 203-470-7 allyl alcohol
88-99-3 201-873-2 phthalic acid

Method: OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year: 1981
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result:

pH	Rate constant (/s)	Estimated half-life at 25°C
4	-	>1 year
7	-	>1 year
9	8.88E-07	217 hours

Test condition: TEST TYPE:
- Test medium:
Buffer solutions:
1) pH 4; 0.001 mol/dm3 Potassium hydrogen phthalate 0.01 mol/dm3
2)pH 7; 0.006 mol/dm3 Disodium hydrogen orthophosphate (anhydrous), 0.004 mol/dm3 Potassium dihydrogen orthophosphate, 0.004 mol/dm3 Sodium chloride
3) pH 9; 0.002 mol/dm3 Disodium tetraborate, 0.004 mol/dm3

Sodium chloride

- Test system:

- Concentration of test substance:
0.05 g/l in the buffer solutions with 1% co-solvent of acetonitrile.

DURATION:
pH4, pH 7; 120 Hours, 50 ± 0.5°C
pH9; 240 Hours, 25 ± 0.5°C

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
23-DEC-2004 (33)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

Type of measurement: background concentration
Medium: other: surface water and sediment

Remark: No DAP was detected in either the sediment or hydrosphere of 27 monitoring points in Japan in 1985. The lower limits of the monitoring are 0.0002 µg/ml water (0.2 ppb) and 0.02 µg/g dry sediment (0.02 ppm).
Result: Concentration: Below limit of detection.

Table: Summary of detection of diallyl phthalate

	Surface Water (µg/mL)	Sediment (µg/g dry)
Limit of detection	0.0002	0.02
Niigata East Harbour	0/3	0/3
Estuary of Shinano River	0/3	0/3
Nagoya Harbor	0/3	0/3
Offshore of Nagoya Harbor	0/3	0/3
Kinuura Harbor	0/3	0/3
Offshore of Mizushima 1	0/3	0/3
Offshore of Mizushima 2	0/3	0/3
Offshore of Ohmuta	0/3	0/3
Sea of Ariake	0/3	0/3

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
03-DEC-2004 (40)

Type of measurement: other: concentration in wastwater
Medium: surface water
Concentration: ca. .4 µg/l

Method: The Survey of Matsuyama Plant Drain:

The survey of Matsuyama plant drain was conducted on October 30, 2003.

The determination of DAP concentration in the waste water from the Matsuyama Plant was conducted on October 30, 2003 (sunny day). The area for sampling stations for water quality tests was a outfall leading to a bay in Seto Inland Sea in Matsuyama-shi , Ehime Prefecture.

Analitycal Method:

The determiation of the DAP concentration was carried out according to "Endocrine Disrupting Chemicals Interim Investigation Manual (Water, Sediment, and Aquatic Organisms)" (the Environment Agency, Japan, FY 1998).

Result: Table DAP concentration in the waste water.

Sample No.	Nominal Conc. µg/L	Determined Conc. µg/L		
Travel Blank	0	<0.2*		
Blank	0	<0.2*		
Control	0.28	0.3		
waste water	-	0.5	0.3	0.4

* below minimum limit of determination

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
03-DEC-2004 (24)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level III
Year: 2004

Result: 1000 kg/h emission to these compartments separately

	Air	Water	Soil
in air	19.9	0.0	0.0
in water	8.6	98.8	0.5
in soil	71.4	0.0	99.5
in sediment	0.1	1.2	0.0

Test condition: Data used for MacKay calculations
PHYSICO-CHEMICAL PARAMETERS:
- Temperature: 25°C
- Molecular weight: 246.27 g/mol
- Melting point: -70°C
- Vapor pressure: 0.0213 Pa
- Water solubility: 148 g/m3
- log Kow: 3.23

ENVIRONMENT:

Air	air	particles	total
volume[m3]	1.0E+13	2.0E+03	1.0E+13
depth[m]			1000
area[m2]			1E+10
organic carbon[%]			
lipid content[%]			
density[kg/m3]	1.2		
residence time [h]	100		

Water	water	particles	fish	total
volume[m3]	2.0E+10	1.0E+6	2.0E+05	2.0E+10
depth[m]				10
area[m2]				2E+9
organic carbon[%]		0.04		
lipid content[%]			0.05	
density[kg/m3]	1000	1500	1000	
residence time [h]	1000			

Soil	air	water	solid	total
volume[m3]	3.2E+08	4.8E+08	8.0E+08	1.6E+09
depth[m]				0.2
area[m2]				8E+09
organic carbon[%]			0.04	
lipid content[%]				
density[kg/m3]	1.2	1000	2400	
residence time [h]				

Sediment	water	solid	total
volume[m3]	8.0E+07	2.0E+07	1.0E+08
depth[m]			0.05
area[m2]			2E+9
organic carbon[%]		0.06	
lipid content[%]			
density[kg/m3]	1000	2400	
residence time [h]		50000	

INTERMEDIA TRANSPORT PARAMETERS:
air side air-water MTC: 5 m/h
water side air water MTC: 0.05 m/h
rain rate: 1E-04 m/h
aerosol deposition 6E-10 m/h
soil air phase diffusion MTC: 0.02 m/h
soil water phase diffusion MTC: 1E-05 m/h
soil air boundary layer MTC: 5 m/h
sediment-water MTC: 1E-04 m/h
sediment deposition: 5E-07 m/h
sediment resuspension: 2E-07 m/h
soil water runoff: 5E-05 m/h
soil solid runoff: 1E-08 m/h

HALF LIFE:
in air: 2.3 h (readily biodegradation)
in water 360 h

in soil 360 h
in sediment 1080 h

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
03-DEC-2004 (27)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg/l related to Test substance
Contact time: 28 day(s)
Degradation: 76 - 92 % after 28 day(s)
Result: readily biodegradable
Deg. product: not measured

Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year: 1992
GLP: yes
Test substance: other TS

Result: RESULT OF TEST EXPERIMENT:

The test substance did not dissolve in the water and the activated sludge.

Table measurement results after 28-days cultivation

sample	O2 uptake (mg)	test substance by GC (mg)
O2 uptake by test substance (mg):		Ss
a1	55.5	0.0
a2	47.5	3.4
a3	45.8	0.0
blank (water + test substance):		Sw
b	0.0	28.2
Corrected O2 uptake		Sw-Sc
a1-b	55.5	28.2
a2-b	47.5	24.8
a3-b	45.8	28.2
% degradation BOD/ThOD x 100		% (Sw-Sc)/Sw x 100
1	92	100
2	79	88
3	76	100

ThOD of test substance is 60.3 mg O2/l.

RESULT OF CONTROL EXPERIMENT:
reference substance: aniline

results: The degradation rate of BOD at 7 and 14 days after incubation were 64% and 81% respectively, which certified the validity of the experiment.

Test condition: INOCULUM/TEST ORGANISM

- Sampling site: Four sewage treatment works, three rivers, one lake, and two bays in Japan.

- Preparation of inoculum: Each 500 ml of the collect fresh samples from the ten sites and 5 l of the activated sludge which have been previously used were mixed. The mixture was adjust to pH 7.0 ± 1.0 and was aerated in a fill-and-draw activated sludge vessel. Thirty minutes after stopping aeration, discard about one third of the whole volume of supernatant and add an equal volume of a solution (pH 7.0 ± 1.0) containing 0.1 % each of glucose, peptone and potassium orthophosphate, to the settled material and recommence aeration. Thus procedure was repeated one per day.

- Pretreatment:

- Initial cell concentration:

TEST SYSTEM

- Culturing apparatus: closed system for measuring of oxygen demand with 300 ml culture medium bottles, CO2-absorbers, temperature controller, and respirometers.

- Number of culture flasks per concentration: 3

- Aeration device: magnetic stirrers

- Closed vessels used: Yes

INITIAL TEST SUBSTANCE CONCENTRATION: 100 mg/l

ANALYTICAL PARAMETER: BOD and degradation of test substance

SAMPLING:

TEST CONDITIONS

- Composition of medium:
the medium was prepared by the method described in the JIS K0102:1986 21.

- Additional substrate: no additional substrate

- Test temperature: 25 ± 1°C

- pH value: medium, test solution, and activated sludge were adjusted to pH 7.0.

- Concentration of suspended solids: 30 mg/L measured in the method described in the JIS K0102:1986 14.1.

CONTROLS:

The following three control experiments were carried out

with the test experiments (the activated sludge + test substance) at the same time:
1. water + test substance
2. activated sludge and aniline
3. activated sludge only (blank control)

REFERENCE SUBSTANCE: Aniline

Test substance: Source: Tokyo Kasei Kogyo Co., Ltd.
grade: TCI-GR
Lot No.: AY01
Purity: 98.8% (from the material of Tokyo Kasei Kogyo Co., Ltd.)
Identification: by IR, MS, NMR spectrometry.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

03-DEC-2004 (17)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

BCF: 61.25

Method: other
Year: 2003
GLP: no

Method: Estimated by BCFWIN v2.15 developed by U.S. Environmental Protection Agency

Result: Log BCF (v2.15 estimate): 1.79

SMILES : O=C(OCC=C)c(c(ccc1)C(=O)OCC=C)c1
CHEM : 1,2-Benzenedicarboxylic acid, di-2-propenyl ester
MOL FOR: C14 H14 O4
MOL WT : 246.27

---------- Bcfwin v2.15 ----------
Log Kow (estimated) : 3.36

Log Kow (experimental): 3.23
Log Kow used by BCF estimates: 3.23 (user entered)

Equation Used to Make BCF estimate:
Log BCF = 0.77 log Kow - 0.70 + Correction

Correction(s): Value
No Applicable Correction Factors

Estimated Log BCF = 1.787 (BCF = 61.25)

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)

Reliability: (2) valid with restrictions

03-DEC-2004 (25)

3.8 Additional Remarks

Memo: Henry's Law Constant

Result: Estimation of Henry's Law Constant by HENRY (v3.10) Program in EPI Suite:

Bond Est : 3.86E-007 atm-m3/mole
Group Est: 1.17E-007 atm-m3/mole

SMILES : O=C(OCC=C)c(c(ccc1)C(=O)OCC=C)c1
CHEM : 1,2-Benzenedicarboxylic acid, di-2-propenyl ester
MOL FOR: C14 H14 O4
MOL WT : 246.27

CLASS		BOND CONTRIBUTION DESCRIPTION	VALUE
HYDROGEN	4	Hydrogen to Carbon (aliphatic)	-0.4787
HYDROGEN	6	Hydrogen to Carbon (olefinic)	-0.6029
HYDROGEN	4	Hydrogen to Carbon (aromatic)	-0.6172
FRAGMENT	2	C-Cd	0.1269
FRAGMENT	2	C-O	2.1709
FRAGMENT	6	Car-Car	1.5828
FRAGMENT	2	Car-CO	2.4775
FRAGMENT	2	CO-O	0.1429
FRAGMENT	2	Cd=Cd	0.0000
RESULT		BOND ESTIMATION METHOD for LWAPC VALUE	4.802

HENRYs LAW CONSTANT at 25 deg C = 3.86E-007 atm-m3/mole
= 1.58E-005 unitless

		GROUP CONTRIBUTION DESCRIPTION	VALUE
	2	CH2 (Cd)(O)	-1.14
	2	Cd-H2	-0.82
	2	CdH (C)	0.44
	4	Car-H (Car)(Car)	0.44
	2	Car (Car)(Car)(CO)	-1.68
	2	CO (O)(Car)	9.14
	2	O (C)(CO)	-1.06
RESULT		GROUP ESTIMATION METHOD for LOG GAMMA VALUE	5.32

HENRYs LAW CONSTANT at 25 deg C = 1.17E-007 atm-m3/mole
= 4.79E-006 unitl

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
03-DEC-2004 (30)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Oncorhynchus mykiss (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: .18
LC0: .18
LC50: .23
LC100: .32
Limit Test: no

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: EXPOSED

- Nominal/measured concentrations:

0.10/0.094, 0.18/0.18, 0.32/0.32, 0.56/0.54, 1.0/0.87 mg/L

Chemical analysis of the fresh test preparations at 0, 24, 48 and 72 hours showed measured test concentrations to range from 103 - 127% of the nominal test concentrations. Chemical analysis of the old or expired test concentrations at 24, 48, 72 and 96 hours showed a marked decline in the measured test concentrations which were shown to range from 55% to 100% of the nominal values. This decline was considered likely to be
due to possible microbial degradation of the test material in the test medium in the presence of the test fish and/or possible metabolism of the test material within the bodies of the fish. Given the marked decline in the measured test concentrations results of the study were calculated based on the time-weighted mean measured concentrations.

Table 1 Verification of the test concentration: percent of measured concentration in the medium to nominal one after and before testing.

Sample		Nominal Concentration				
Hours	solution	mg/L				
		0.10	0.18	0.32	0.56	1.0
0	fresh	103	104	103	103	107
24	old	55	62	58	64	70
	fresh	113	114	115	120	-
48	old	74	83	74	102	-
	fresh	118	119	123	-	-
72	old	85	94	90	-	-
	fresh	122	124	-	-	-
96	old	92	99	-	-	-

old, fresh: 'old' solution was replaced with 'fresh'

solution for test every 24 hours.

- Effect data (Mortality):

LC0(96 hr) = 0.18 mg/L
LC50(96 hr) = 0.23 mg/L (0.18 - 0.32 mg/L)
LC100(96 hr) = 0.32 mg/L

Table 2. LC50

Time (h)	LC50 (mg/L)		95% Confidence Limits		
	nominal	measured	nominal	measured	S.M.
24	0.60	0.55	0.50 - 0.71	0.47 - 0.65	a
48	0.40	0.38	0.36 - 0.45	0.34 - 0.42	a
72	0.24	0.23	0.18 - 0.32*	0.18 - 0.30*	b
96	0.24	0.23	0.18 - 0.32*	0.18 - 0.30*	b

*, Test concentrations resulting in 0% and 100% mortality respectively.
S.M., Statistic Method for analysis of the mortality data
a, trimmed Sperman-Karber method (Hamilton et al., 1977)
b, geometric mean method

Table 2. Cumulative mortality

Nominal Test Conc. (mg/L)	Cumulative Mortality (Initial Population = 10)					
	3 hours	6 hours	23 hours	48 hours	72 hours	96 hours
Control	0	0	0	0	0	0
0.10	0	0	0	0	0	0
0.18	0	0	0	0	0	0
0.32	0	0	0	1*	10	10
0.56	0	0**	4***	10	10	10
1.0	0	0	10	10	10	10

* 6 fish moribund with swollen abdomens at ca. 70 hours were killed.
** 2 fish moribund with moribund with arched spines at ca. 23 hours were killed.
*** 5 fish moribund at ca. 24 hours, 27 hours, and 46 hours.
- Effect concentration vs. test substance solubility:

It does not seem likely that the concentration vs. solubility had any effect on the results, because the water solubility measured 148 mg/L (See Chapter 2.6.1), which was higher than the ceiling of the test concentration range (0-1.0 mg/L).

- Other effects:

After approximately 23 hours, 2 fish were observed to be moribund with arched spines. Due to the approach of substantial severity limit (Animals (Scientific Procedures) Act 1986) these fish were killed and classed as mortalities

for the 24-Hour time point.

After approximately 24 hours a moribund fish was observed, a further moribund fish was noted at 27 hours, and at 46 hours, 3 fish were were observed to be moribund with swollen abdomens.

After approximately 70 hours, 6 fish were observed to be moribund with swollen abdomens. Due to the approach of the substantial severity limit (Animal (Scientific Procedures) Act 1986) these fish were killed and classed as mortalities for the 72-Hour time point.

RESULTS: CONTROL

- Number/percentage of animals showing adverse effects:

no animals showing adverse effects.

- Nature of adverse effects:

no animals showing adverse effects.

RESULTS: TEST WITH REFERENCE SUBSTANCE

no reference substance

- Reference:
Hamilton et al. (1977) Trimmed Spearkman-Karber Method for Estimating Median Leathl Concentration in Toxicity Bioassays. Environ Sci Technol 11, 71

Test condition: TEST ORGANISMS

- Supplier:

Brow Well Fisheries Limited, Hebden, near Skipton, Yorkshire, UK

- size/weight/loading:

4.2 cm (sd=0.2), 0.86 g (sd=1.0) and 0.43 g bodyweight/liter at the end of the definitive test.

- Feeding:

The stock fish were fed commercial trout pellets which was discontinued 24 hours prior to the start of the definitive test.

- Pretreatment:

Fish were maintained in-house and in a glass fiber tank with a "single pass" water renewal system since 8 January 2003. Fish were acclimatised to test conditions from 15 January 2003 to 27 January 2003. The lighting cycle was controlled to give a 16 hours light and 8 hours darkness cycle with 20 minute dawn and dusk transition periods. The water temperature was controlled at 14.0°C with a dissolved oxygen content of greater than or equal to 9.6 mg O2/l.

- Feeding during test: No feeding

STOCK AND TEST SOLUTION AND THEIR PREPARATION

- Dispersion:

An amount of test material (5.50 g) was dispersed in 11 liters of dechlorinated tap water with the aid of a propeller stirrer set at approximately 2,000 rpm at ca. 25°C for ca. 24 hours. After that the mixture was cooled to 14°C. The mixture was filtered (0.2 µm Gelman SuporCap filter), initial 1 liter discarded to precondition the filter. The nominal value of the mixture i.e. saturated solution was 122 mg/l.

- Vehicle, solvent:

not used

STABILITY OF THE TEST CHEMICAL SOLUTIONS:

The test material was shown to be stable in the test medium after storage under light and dark conditions. The unsonicated test material was recovered after storage under dark, which showed no evidence of insolubility or adherence to glass.

DILUTION WATER

- Source:

Laboratory tap water (Water Supply Zone: Z0129 Sinfin Chellaston Shardlow)

- Alkalinity:

102 mg/L

- Hardness:

ca. 176 mg/L as CaCO3 (Adjusting ca. 100 mg/L with Elga Nimbus 1248D Duplex Water Softener before using.)

- pH:

mean 7.804 (minimum 7.700, maximum 7.900)

- Oxygen content:

not reported

- Conductance:

mean 413.267 µS/cm (minimum 335.000, maximum 558.000)

TEST SYSTEM

- Test type:

semi-static test

- Concentrations (mg/l, nominal concentrations):

0 (control), 0.10, 0.18, 0.32, 0.56, 1.0

- Renewal of test solution:

daily

- Exposure vessel type:

20 liter glass exposure vessels

- Number of replicates/fish per replicate:

1/10

- Test temperature:

13.8 - 14.0°C

- Dissolved oxygen: 9.6 - 9.9 mg O2/L.

The test vessels were aerated via narrow bore glass tubes.

- pH:

7.5 - 8.2

- Adjustment of pH:

Not adjusted.

- Photoperiod:

16 hours light and 8 hours darkness with 20 minute dawn and dusk transition periods.

DURATION OF THE TEST:

96 hours

TEST PARAMETER:

- Loading rate:

0.43 g bw/L at the end of the test.

SAMPLING:

MONITORING OF TEST SUBSTANCE CONCENTRATION:

Water samples were taken from the control and all surviving test groups at 0 (fresh media), 24, 48, 72(old and fresh media) and 96 hours (old media) for quantitative analysis.

STATISTICS:

The LC50 values and associated confidence limits at 24 and 48 hours were calculated by the trimmed Spearman-Karber

method using the ToxCalc computer software package (ToxCalc 1999) and at 72 and 96 hours the LC50 values were calculated using the geometric mean method.

- Reference:

Tox Calc Version 5.0.23C (1999), Tidepool Scientific Software, McKinleyville, CA 95519, USA.

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)

Conclusion: The acute toxicity of the test material to the freshwater fish rainbow trout (Oncorhynchus mykiss) gave LC50 value of 0.23 mg/L with 95% confidence limits of 0.18 - 0.30 mg/L based on mean measured test concentrations. The No observed Effect Concentration (NOEC) was 0.18 mg/L. The substance is toxic to fish under the conditions of this study.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

20-DEC-2004 (35)

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
LC50: .44 measured/nominal
Limit Test: no

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 2000
GLP: yes
Test substance: other TS

Result: RESULTS: EXPOSED

- Nominal/measured concentrations:

0/(not measured), 0.06/0.02, 0.12/0.09, 0.21/0.16, 0.38/0.29, 0.68/0.53, 1.22/1.08 mg/L.

- Effect data (Mortality):

Table 1. Mortality of Medaka (Oryzias latipes) Exposed to Diallyl phthalate under Semi-Static Test Conditions

Measured Conc. (mg/L)	Cumulative Number of Dead (Percent Mortality) 24 Hour	48 Hour	72 Hour	96 Hour
Control	0 (0)	0 (0)	0 (0)	0 (0)
0.02	0 (0)	0 (0)	0 (0)	0 (0)
0.09	0 (0)	0 (0)	0 (0)	0 (0)
0.16	0 (0)	0 (0)	0 (0)	0 (0)
0.29	0 (0)	0 (0)	0 (0)	0 (0)
0.53	1 (10)	2 (20)	5 (50)	8 (80)
1.08	9 (90)	10 (100)	--a(--a)	--a(--a)

a: No observation was made because all Medaka were dead at this observation time.

Table 2. LC50s of Medaka (Oryzias latipes) Exposed to Diallyl phthalate under Semi-Static Test Conditions

Time (h)	LC50 (mg/L)	95% Confidence Limits	S.M.
24	0.76	0.53 - 1.08	a
48	0.66	0.29 - 1.08	a
72	0.53	0.29 - 1.08	a
96	0.44	0.29 - 0.53	a

S.M., Statistic Method for analysis of the mortality data
a, Binominal

- Effect concentration vs. test substance solubility:

This test was conducted at the concentration under DAP solubility in water.

- Other effects

Loss of equilibrium or swimming ability at the maximum concentration group (1.08 mg/L) and abnormal swimming behavior at the 0.53 mg/L group were observed.

No abnormal syndromes were observed in the control group and at the group less than 0.29 mg/L concentration.

Table 3. Symptoms of Toxicity Observed in Medaka (Oryzias latipes) Exposed to Diallyl phthalate under Semi-Static Test Conditions

Measured Conc. (mg/L)	Cumulative Number of Dead (Percent Mortality)			
	24 Hour	48 Hour	72 Hour	96 Hour
Control	0	0	0	0
0.02	0	0	0	0
0.09	0	0	0	0
0.16	0	0	0	0
0.29	0	0	0	0
0.53	0	0	B(1)	0
1.08	C(1)	--a	--a	--a

0: normal
A: abnormal respiration (not observed)
B: abnormal swimming behavior
C: loss of equilibrium or swimming ability
D: other symptoms
(n): number of fish

a: No observation was made because all Medaka were dead at this observation time.

RESULTS: CONTROL

- Number/percentage of animals showing adverse effects:

No animals in control groups showed adverse effects.

RESULTS: TEST WITH REFERENCE SUBSTANCE

No test with reference substance was conducted.

Test condition: TEST ORGANISMS

- Strain:

Medaka (Oryzian Latipes)

- Supplier:

Kishida Chemical K.K.

- Age/size/weight/loading

Age: not reported
Size: 2.19 cm (2.01 to 2.40 cm)
Weight: 0.1622 g (0.0955 to 0.2349 g)

- Feeding:

The commercially available food, TETRAMIN was fed except for 24 hours before the exposure.

- Pretreatment:

The test animals were kept before the exposure under the same conditions (water quality, temperature, etc) to that in the test for at least 12 days

- Feeding during test:

Not feeding during test.

STOCK AND TEST SOLUTION AND THEIR PREPARATION

- Dispersion:

The test was conducted under the concentration of diallyl phthalate solubility in water.

- Vehicle, solvent:

No vehicle was used to dissolve the test substance into the test solution.

- Concentration of vehicle/ solvent:

No vehicle.

- Other procedures:

No other procedures specified.

STABILITY OF THE TEST CHEMICAL SOLUTIONS:

Diallyl phthalate was not stable in the test solutions. The DAP concentration in the test vessels decreased more than 20% during the initial 24 hours exposure.

REFERENCE SUBSTANCE:

No test with any reference substance was conducted.

DILUTION WATER

- Source:

The Nagoya city water was used as the dilution water after filtered through charcoal and dechlorinated.

Table 1. Water Quality of Dilution Water

Parameter	Concentration
BOD	<0.5 mg/L
COD	0.8 mg/L
pH	6.8
Coliform group bacteria	N.D.
Mercury	<0.003 mg/L
Copper	<0.005 mg/L
Cadmium	<0.02 mg/L
Zinc	<0.03 mg/L
Lead	<0.2 mg/L
Chromium	<0.05 mg/L
Iron	0.01 mg/L
Free chlorine	<0.05 mg/L
Fluoride	<0.05 mg/L
Ammonium ion	<0.1 mg/L
Arsenic	<0.001 mg/L
Evaporation residue	37 mg/L
Electric conductivity	7.1 mS/m
Total hardness (as CaCO3)	41.0 mg/L
Alkalinity	10.0 mg/L
Total organophosphorus compound	<0.001 mg/L
Simazin	<0.0003 mg/L
Herbicide Thiobencarb	<0.002 mg/L
Fungicide Thiuram	<0.0006 mg/L

- Aeration:

No aeration was conducted.

- Alkalinity:

10.0 mg/L

- Hardness:

41.0 mg/L as CaCO3

- Salinity:

Not reported.

- TOC:

Not reported.

- TSS:

Evaporation residue was 37 mg/L.

- pH:

The pH of the dilution water was 6.8.

- Oxygen content:

8.7-8.8 mg/L. (The values was reported as the oxygen contents of freshly prepared test solutions.)

- Conductance:

7.1 mS/m

- Holding water:

The dilution water was used as the holding water.

TEST SYSTEM

- Test type:

semistatic

- Testing Stock Solution:

The solution resulted from dissolving diallyl phthalate at the concentration (36.7 mg/L) in the dilution water was used as a testing stock solution.

- Test Solution:

The test solution where the animals were exposed to the test substance was prepared by diluting the testing stock solution with the dilution water.

- Concentrations

Nominal Concentration:

The the following nominal concentrations to expose the animals to the diallyl phthalate: 0.06, 0.12, 0.21 0.38, 0.68, 1.22 mg/L.

Measured Concentration:

The following measured concentrations were calculated as geometrical means of test solutions freshly prepared and after 24 hours exposure period: 0.02(0.06), 0.09(0.12),

0.16(0.21), 0.29(0.38), 0.53(0.68), and, 1.08(1.22), where the values in the parenthesis are the nominal concentrations.

- Dosing rate:

ca. 1.8

- Renewal of test solution:

Every test solution was renewed at 24, 48, 72, and 96 hours.

- Exposure vessel type:

3L beaker

- Number of replicates, fish per replicate:

1 replicates. 10 fish per 1 beaker.

- Test temperature:

24±1°C

- Dissolved oxygen:

The measured dissolved oxygen in the freshly prepared test solution: 8.7 - 9.1 mg/L.

The measured dissolved oxygen in the solution after 24 hours exposure period: 5.3 - 8.7 mg/L.

- pH:

6.8

- Adjustment of pH:

No adjustment of pH during test. The pH values during the exposure were reported but not conducting adjustment of ph during test.

- Intensity of irradiation:

Room light. The intensity of irradiation was not reported.

- Photoperiod:

16 hours light/ 8 hours dark.

DURATION OF THE TEST:

96 hours exposure.

TEST PARAMETER:

No other test parameters.

SAMPLING:

Every test solution (1.0 - 1.5 ml) was sampled to measure the concentration at 0 and 24 hours after the exposure initiation.

MONITORING OF TEST SUBSTANCE CONCENTRATION:

The monitoring of test substance concentration was conducted at 0 and 24 hour after the exposure initiation.

Table 2. Measured Concentrations of Diallyl phthalate During a 96-Hour Exposure of Medaka (Oryzias latipes) under Semi-Static Test Conditions.

Nominal Conc. (mg/L)	Measured Conc. (mg/L)			Percent of Nominal	
	0 Hour new	24 Hour old	Geometric Mean	0 Hour new	24 Hour old
Control	<0.003	<0.003	-	-	-
0.06	0.03	0.02	0.02	50.0	33.3
0.12	0.11	0.08	0.09	91.7	66.7
0.21	0.20	0.13	0.16	95.2	61.9
0.38	0.36	0.24	0.29	94.7	63.2
0.68	0.65	0.44	0.53	95.6	64.7
1.22	1.17	0.99	1.08	95.9	81.1

new: freshly prepared test conditions
old: test solutions after 24 hours exposure period

Test substance: diallyl phthalate

Purity: 99% or more
Lot Number: D43493F
Supplier: Kishida Chemical K.K.
Volume: 25 ml x 2
Date Obtained: 17 September 1999
Appearance: Colorless, transparent liquid

The following descriptions are excerpt from the reference document.
Name: diallyl phthalate
Formula: C14H14O4
Molecular Weight: 246.26
Melting Point: -70°C
Boiling Point: 305°C
Solubility in Water: 182 mg/L (25°C)
LogPow: 3.23
Vapor Pressure: 2.4 mmHg/L (150°C)

The values described above were excerpted form the following database:

TOXNET: National Library of Medicine (Toxicology Data Network)
WebKis-Plus: The Chemical Substances Database by Kanagawa Prefecture and National Institute of Environmental Science
ICSC: International Chemical Safety Cards

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
03-DEC-2004 (41)

Type: semistatic
Species: Leuciscus idus melanotus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC0: .3
LC50: .4

LC100: .6
Limit Test: no

Method: other
Year: 1975
GLP: no data

Method: Mann, H (1975), The Golden Orfe Test.
German Proposal about the Examination of the Effect of Chemical Substances on Fish; Vom Wasser; 44:1-13. (German)

H. Mann (1976); Fish Test with Gold Orfe to Compare Examination of the Acute Toxicity of Water Containing Material and Wastewater - Practical Experience from Three Ring Tests.; Z. f. Wasserß und AbwasserßForschung; 4:103-109. (German)(1976); Uniformed Procedure of Water, Wastewater and Sludge Test L15: Fish test. (Determination of the Effect of Water-containing Substances on Fish) ; Vorabdruck in Vom Wasser; 46:291-295. (German)
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (4) not assignable
03-DEC-2004 (56)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: 3.2
EC50: 5.5
Limit Test: no

Method: OECD Guide-line 202
Year: 1984
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS: EXPOSED

- Nominal/measured concentrations:

Chemical analysis of the test solutions during the exposure showed the measured test concentrations to range from 92% to 108% of the nominal test concentrations, therefore results were calculated based on the nominal test concentrations.

Sample Hours	Nominal Conc.[mg/L]	Measured Conc. [mg/L]	Nominal/Measured Conc. [%]
0	0 (control)	<0.10*	-
	0.10	0.0960	96
	0.18	0.183	102
	0.32	0.337	105
	0.56	0.548	98
	1.0	1.03	103
	1.8	1.87	104
	3.2	3.38	106

	5.6	5.96	106
	10	10.5	105
	135**	132	97
48	0 (control)	<0.10*	-
	0.10	0.0922	92
	0.18	0.181	101
	0.32	0.334	104
	0.56	0.559	100
	1.0	1.06	106
	1.8	1.90	106
	3.2	3.45	108
	5.6	6.04	108
	10	10.7	107

*, analytical limit
**, saturated solution

the test material was stable in the test medium for the duration of the test.

- Effect data (Immobilisation):

EC50(48h) 5.5 mg/L (4.8 - 6.4 mg/L, 95% confidence limits)
NOEC(48h) 3.2 mg/L

- Cumulative immobilisation:

Nominal Conc. [mg/L]	Cumulative Immobilized Daphnia (Initial Population: 10 Per Replicate)							
	24 Hours				48 Hours			
	R1	R2	Total	%	R1	R2	Total	%
Control	0	0	0	0	0	0	0	0
0.10	0	0	0	0	0	0	0	0
0.18	0	0	0	0	0	0	0	0
0.32	0	0	0	0	0	0	0	0
0.56	0	0	0	0	0	0	0	0
1.0	0	0	0	0	0	0	0	0
1.8	0	0	0	0	0	0	0	0
3.2	0	0	0	0	0	0	0	0
5.6	0	0	0	0	6	6	12	60
10	0	0	0	0	10	9	19	95

- Effect concentration vs. test substance solubility:

The maximum test concentration (10 mg/L) << solubility in water (148 mg/L)

RESULTS CONTROL:

No immobilized daphnia. See RESULTS EXPOSED.

Test condition: TEST ORGANISMS

- Source/supplier:

Derived from the laboratory, SafePharm Laboratories Limited which conducted this test.

- Breeding method:

Adult Daphnia were in polypropylene vessels containing approximately 2 liters of reconstituted water in a temperature controlled room at 21°C. The lighting cycle was controlled to give a 16 hours light and 8 hours darkness cycle with 20 minute dawn and dusk transition periods.

- Age:

1st instar

- Feeding:

Feeding a suspension of Chlorella sp. daily.

- Feeding during test:

no

- Control group:

Groups maintained under identical conditions but not exposed to the test material was used as the control groups.

STOCK AND TEST SOLUTION AND THEIR PREPARATION

- Dispersion:

Amounts of test material (250 mg) were each separately dispersed in 500 ml of the reconstituted water with the aid of shaking with an INFORS aerotron shaker set at 300 rpm at a temperature of 30°C for 24 hours. After 24 hours, shaking was stopped and the mixture pooled. Any undissolved test material was removed by filtration (0.2 µm Gelman AcroCap filter), initial 50 ml discarded to precondition the filter, to give a saturated solution of the test material. An aliquot (735 mL) of the saturated solution was diluted with reconstituted water and the volume adjusted to 1 liter to give 100 mg/L test concentration.

- Vehicle, solvent: no

STABILITY OF THE TEST CHEMICAL SOLUTIONS:

The substance was shown to be stable in the test medium. The unsonicated stability vessel showed no evidence of insolubility or adherence to glass.

DILUTION WATER

- Source: The following reconstituted water was used:

i) Stock Solution
   a) $CaCl_2.2H_2O$ 11.76 g/L
   b) $MgSO_4.7H_2O$ 4.93 g/L

c) NaHCO3 2.59 g/L
d) KCl 0.23 g/L

ii) Preparation

An aliquot (25 mL) of each of solution a-d was added to each liter (final volume) of deionized water with a conductivity

of <5 µS/cm and pH equal to 7.8 ± 0.2, adjusted (if necessary) with NaOH or HCl.

- Aeration:

The reconstituted water was aerated until the dissolved oxygen concentration was approximately air-saturation value.

- Hardness:

250 mg/L as CaCO3 theoretically

- pH:

7.8 ± 0.2

- Oxygen content:

saturation

- Conductance:

<5 µS/cm

TEST SYSTEM

- Test type:

semistatic

- Concentrations:

0, 0.10, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6, 10 mg/L, nominal test concentration.

- Renewal of test solution:

not renewed.

- Exposure vessel type:

250 mL glass jars containing approximately 200 mL of test solution

- Number of replicates/individuals per replicate:

2 / 10

- Test temperature:

20.9 - 21.0°C

- Dissolved oxygen:

8.8 - 8.9 mg O2/L (99 - 100% saturated)

- pH:

7.8 - 7.9

- Adjustment of pH:

not controlled for the duration of the test.

- Intensity of irradiation:

not described

- Photoperiod:

16 hours light and 8 hours darkness with 20 minute dawn and dusk transition periods.

DURATION OF THE TEST:

48 hours

TEST PARAMETER:

Mean cumulative numbers of immobilized Daphnia. The criterion of effect (immobilization) used was that Daphnia were considered to be immobilized if they were unable to swim for approximately 15 seconds after gentle agitation.

SAMPLING:

At 24 Hours and 48 Hours, the observations were performed.

MONITORING OF TEST SUBSTANCE CONCENTRATION:

Yes

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
20-DEC-2004 (36)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: 5.5 measured/nominal
EC50: 16.2 measured/nominal
Limit Test: no

Method: OECD Guide-line 202
Year: 2000
GLP: yes
Test substance: other TS

Result: RESULTS: EXPOSED

- Nominal/measured concentrations:

0 (control)/<0.1, 3.2/0.8, 5.7/2.6, 10.3/5.5, 18.5/12.6, 33.3/26.1, 60.0/51.5 mg/L.

The measured concentrations were geometric mean of the concentration measured at 0 hour and 48 hours after the exposure initiation.

- Cumulative immobilization:

Table 2 Mortality or Immobility of Daphnia magna Exposed to Diallyl phthalate under Static Test Conditions

Measured Conc. (mg/L)	Cumulative Number of Dead or Immobilized Daphnia (Percent Mortality or Immobility)	
	24 Hour	48 Hour
Control	0 (0)	0 (0)
0.8	0 (0)	0 (0)
2.6	0 (0)	0 (0)
5.5	0 (0)	0 (0)
12.6	1 (5)	3 (15)
26.0	12 (60)	20 (100)
51.6	20 (100)	20 (100)

- Median Immobilized Concentration (EiC50):

Table 3 Calculated EiC50 Values for Daphia magna Expoased to Diallyl phthalate Based on Measured Concentrations under Static Test Conditions

Time (h)	EC50 (mg/L)	95% Confidential Limit	S.M.
24	22.3	18.5 - 27.6	a
48	16.2	12.6 - 26.0	b

S.M., Statistic Method for analysis of the immobilized data
a, Moving Average; b, Binominal

- No Observed Effective Concentration of Immobility for 48 h-exposure (NOEC):

5.5 mg/L

- The lowest concentration producing 100 per cent immobility for 48-exposure:

26.0 mg/L

- Other effects:

No other effects on the validity of the test result.

RESULTS CONTROL:

Nothing to be described.

RESULTS: TEST WITH REFERENCE SUBSTANCE

This report described only that EC50(48 hours) of a standard substance, potassium dichromate was 0.60 mg/L.

Test condition: TEST ORGANISMS

- Source/supplier:

Daphnids were obtained from the National Institute of Environmental Studies, Japan and subcultured in the laboratory which conducts this test.

- Breeding method:

Macroscopically healthy and adult daphnids with juveniles were selected from a subculture and were each transferred into a beaker of freshly prepared holding water. The next day, offsprings produced from each of the adult daphnids were transferred into a beaker of the freshly prepared holding water. These offspring daphnids were used as parents for testing after acclimated on the breeding conditions described below for 20 days. Offsprings newly produced were removed twice or more per week after the parents became to produce juveniles.

The offsprings produced within 24 hours after removing the offsprings from the beakers were used for the exposure test.

Few mortal daphnids occurred; and neither dormant eggs nor males occurred.

- Breeding conditions

Breeding Animals per Beakers: 20 - 50 daphnids per 1 L of the breeding solution. For the adult daphnids, 25 or less daphnids per 1 L of the holding water.

Temperature of the holding water: 20 ± 1°C

Lighting: Room light, 16 hours light / 8 hours dark

Food: Chlorella vulugaris

- Age:

48 hours or less after produced.

- Feeding:

Feeding algae, chlorella vulugaris of 0.1 to 0.2 mg organic carbon per one daphnia per day.

- Feeding during test: None

- Control group:

The solution without test substance was used as a control group.

STOCK AND TEST SOLUTION AND THEIR PREPARATION

- Dispersion:

The test was conducted at the test substance concentration less than the solubility in water.

- Vehicle, solvent:

No vehicle to dissolve the test substance.

- Concentration of vehicle/ solvent:

No vehicle to dissolve the test substance.

- Other procedures:

To the diluting solution was added 100 mg/L test substance.

STABILITY OF THE TEST CHEMICAL SOLUTIONS:

The diallyl phthalate is liable to decompose by daphnids or chemically, or be taken by daphnids.

The chemical stability of the test substance in the test solution was not tested. However, the results of the Monitoring of Test Substance (See table 1 below) indicated that the concentrations at 48 hours after the exposure

decreased more than 20% of nominal concentrations.

REFERENCE SUBSTANCE:

This report outlined only that EC50 (48 Hours) of a standard substance, potassium dichromate (reagent grade) was 0.60 mg/L.

DILUTION WATER

The M4 media (OECD Test Guideline No. 211 adopted September 1998) was used as the dilution water.

- Hardness:

251 mg/L (as CaCO3)

- pH:

7.9

- Holding water:

The dilution water was also used as the holding water.

TEST SYSTEM

- Test type: static

- Concentrations:

0 mg/L (control), 3.18 mg/L, 5.72 mg/L, 10.3 mg/L, 18.5

mg/L, 33.3 mg/L, and 60.0 mg/L (nominal concentration)

Dose ratio: 1.8

- Renewal of test solution: no renewal

- Exposure vessel type: 100 mL beaker

- Number of replicates, individuals per replicate:

4 replicates per dose, 5 daphnids per replicates.

- Test temperature:

20 ± 1°C. Temperatures in the test solution during the test ranged from 19.3 to 20.8°C.

- Dissolved oxygen:

The dissolved oxygen in the test solution during the test ranged from 7.6 mg/L to 8.8 mg/L. The dissolved oxygen of all the test solutions were more than 60% of 8.84 mg/L,

saturated dissolved oxygen at 20.0°C.

- pH:

The pH in the test solution during the test ranged from 7.4 to 7.7.

- Adjustment of pH: No adjustment of pH

- Intensity of irradiation: room temperature

- Photoperiod: 16 hours light / 8 hours dark

DURATION OF THE TEST: 48 hours exposure

TEST PARAMETER:

No other environmental parameters affecting the validity of the test results.

SAMPLING:

Test solutions (1.5 mL) were sampled 0 hour and 48 hours after the exposure.

MONITORING OF TEST SUBSTANCE CONCENTRATION:

The concentrations at 0 hour and 48 hours after exposure were measured with the HPLC system.

Table 1. Measured Concentrations of Diallyl phthalate During a 48-Hour Exposure of Daphnia magna under Static Test Conditions

Nominal Conc. (mg/L)	Measured Conc. (mg/L)			Percent 0 Hour	Nominal 48 Hour
	0 Hour	48 Hour	Geometric	new	old

	new	old	Mean		
Control	<0.1	<0.1	-	-	-
3.2	3.1	0.2	0.8	96.9	6.3
5.7	4.6	1.5	2.6	80.7	26.3
10.3	8.9	3.4	5.5	86.4	33.0
18.5	17.0	9.3	12.6	91.9	50.3
33.3	31.0	21.9	26.1	93.1	65.8
60.0	57.1	46.5	51.5	95.2	77.5

Statistics:

EC50 and the 95% confidential limits were calculated by Moving Average method and Binomial method using the equations in the TOXDAT Multi-Method Program developed by EPA.

Test substance: Diallyl phthalate

Purity: 99% or more
Lot Number: D43493F
Supplier: Kishida Chemical K.K.
Volume: 25 ml x 2
Date Obtained: 17 September 1999
Appearance: Colorless, transparent liquid

The following descriptions are excerpted from the reference document.
Name: diallyl phthalate
Formula: C14H14O4
Molecular Weight: 246.26
Melting Point: -70°C
Boiling Point: 305°C
Solubility in Water: 182 mg/L (25°C)
LogPow: 3.23
Vapor Pressure: 2.4 mmHg/L (150°C)

The values described above were excerpted form the following database:

TOXNET: National Library of Medicine (Toxicology Data Network)

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
20-DEC-2004 (41)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC0: 11
EC50: 22
EC100: 41
Limit Test: no

Method: other
Year: 1982
GLP: no data

Method: METHOD FOLLOWED:

Bringmann, G. und Kühn, R.: Befunde der Schadwirkung wassergefährdender Stoffe gegen Daphnia magna. Z. Wasser Abwasser Forsch. 10, 162-166 (1977)

Result: RESULTS: EXPOSED

- Nominal/measured concentrations:

Not reported.
Dilution ratio, 1:2.

The report described the three dilutions for test fell into the range of LC0 to LC100.

- Concentration / response curve: No data

- ECx for immobility, confidential intervals:

EC50 = 22 mg/L P95% 20 - 24
EC0 = 11 mg/L
EC100 = 41 mg/L

- Effect concentration vs. test substance solubility: No data

- Statistical methods & Calculation method:

Scheicher & Schuell probability network No. 440 1/2 A4 was used for the graphic evaluation of EC50. In case of a normal deviation of the sensitiveness of the Daphnia the point between 16% and 84% approximately from a straight line. Then EC50 was determined by interpolation and the 95% confidence area of EC50 can be calculated. (Litchfield, J. T. and Wilcoxon, F.: A simplified method of evaluating dose-effect experiments. J. Pharm. exper. Ther. 96,99-113 (1949)).

For proving the middle-location of the regression line through the concentration-effect values pairs the Chi-square test is used as a measure for the quality of the fit. If the concentration-effect curve was so steep, that for concentration steps of 1:1.1 an insufficient number of values were obtained to determined EC50, the geometrical average between EC0 and EC100 was chosen for the EC50 values (Stepan, C. E.: Methods for calculating an LC50. In: Aquatic Toxicology and Hazard Evaluation, By F. L. Mayer and J. L. Hameling. ASTM-STP 634. p 65-84. American Society for Testing and Materials 1971.)

- Other effects: Not reported

RESULTS CONTROL: No data

RESULTS: TEST WITH REFERENCE SUBSTANCE

- Test Substance: Potassium dichromate

- Concentrations: Not reported.

- Results: EC50 1.3 mg/L

Test condition: TEST ORGANISMS

- Strain: Straus

- Source/supplier:

National Institute of Applied Chemical Research, France (IRCHA)

- Breeding method:

For the continuous breeding of the Daphnia magna a minimum of 20 - 30 individuals are transferred to 2 L beakers filled with minimum 1.6 L tap water.

Without suitability of the local available tap water as a culture medium, the standardized synthetic test culture medium described below for the continuous breeding of the Daphnia after the previous the experience of use. This study reported the effect of 183 substances including diallyl phthalate on the immobility of daphnia. This report dose not depict about which medium was used in each substance, of the tap water and the synthetic medium in each substance test.

A total number of 60 cultures were prepared. These yielded 24-h-old daphids every day. The parental daphnids from these culture were transferred every day from Monday to Friday, using wide-mouth pipette in fresh prepared culture beaker. The juvenile daphids placed from Tuesday to Friday every week
were concentrated every day on a 0.315 mm DIN sieve and were used as test organisms. The daphids placed from Friday to Monday every week are separated by size every Monday through a DIN 0.630 mm testing sieve and then concentrated on a DIN 0.315 mm test sieve. The larger class were cultivated separately for the further breeding. With kept animals separated in the stock and been able to be sieved by a 1.25 mm DIN testing sieve, as appropriate the blanks arisen in stocks of mother animals were filled, when the population per beaker fell down below 30 by natural death.

All culture beakers covered with concave glasses were placed on a white table surface.

For all Daphnia stem cultures, controlled chlorine-free and oxygen-saturated tap water (German Hardness 16°C , pH 7.6-7.7) was used 24 h after tapping every time. Before tapping, water was allowed to flow out for min. 1 h at maximum flow rate.

The temperature of the Daphnia room was controlled at a level of 20°C. The culture room was illuminated for 9 h per day by neon tubes Osram, color 25 (room illumination power E(D, sy) = 2.5 W/m2) and daylight was excluded, during the rest of the day the room was dark.

A synthetic culture medium according to DIN 38 412 was used as the test culture medium. The sum of Ca and Mg ions in the solution is 2.5 mmol/l. The molar ratio of Na:K is 10:1. The

water is saturated with oxygen and the pH measured 8.0 ±

0.2.

- Age:

24-h old

- Feeding:

The cultures were fed every day. Every Monday and every Friday the tap water of all cultures was exchanged, and every Friday the beakers also were exchanged. This was conducted during the routine daily selective withdrawals of the mother animals and young animals and the 24-h-old young animals.

The stem cultures of Daphnia were fed with standardized dry food "Mikroyzell" purchased from the company Dohse Aquaristik, Bonn. 30 g/L tap water were suspended and 10 ml of this suspension was added to each culture glass.

- Pretreatment: no data

- Feeding during test: none

- Control group:

Control groups were tested, but there are no detail description.

STOCK AND TEST SOLUTION AND THEIR PREPARATION

- Dispersion:

Diallyl phthalate was quantitatively dissolved in the test medium using closed vessels and a magnetic stirrer.

- Vehicle, solvent: No vehicle

- Concentration of vehicle/ solvent: No vehicle

- Other procedures: No other procedure

STABILITY OF THE TEST CHEMICAL SOLUTIONS:

No data about the stability of the chemical during test procedures, but the pH value and oxygen content the end of the test period was measured: the pH values in the test and the control vessels measured pH 8.0 ± 0.2, which is suitable range for Daphnia; and the oxygen content measured suitably above 2 mg/L.

REFERENCE SUBSTANCE:

EC50, Potassium dichromate, 1.3 mg/L

Potassium dichromate was used as a reference substance. The average of EC50 for this substance was 1.3 mg/L, which meets the specification in the DIN 38412 part 11 and chapter 8.4

of ISO 6341:1966. The test for this chemical was accompanied by other 182 water pollutants including the dichromate.

DILUTION WATER

- Source:

The synthetic test culture medium (DIN 38 412 part 1)was used as a dilution water.

- Aeration:

The dilution water was saturated with oxygen. At end of the test, the oxygen content measured suitably above 2 mg/L.

- Hardness:

250 mg/L as CaCO3, theoretically.

- Salinity:

$CaCl_2 \cdot 2H_2O$	7.35	mg/L
$MgSO_4 \cdot 7H_2O$	3.1	mg/L
$NaHCO_3$	1.62	mg/L
KCl	0.145	mg/L

- TOC:

no data

- Ca/Mg ratio:

4:1

- Na/K ratio:

10:1

- pH:

8.0 ± 0.2

- Oxygen content:

Oxygen content at the test end measured above 2 mg/L.

- Conductance:

no data

TEST SYSTEM

- Test type:

The Immobility of Daphnia magna, 24-h exposure time

- Concentrations:

No data about the test range, at least three dilutions fell between the EC0 and EC100.

- Renewal of test solution:

None

- Exposure vessel type:

20 mL test medium in 50 mL beakers, covered with a layer of filter paper.

- Number of replicates, individuals per replicate:

2 replicates; 10 individuals per culture vessel

- Test temperature:

20 - 22°C

- Dissolved oxygen:

The oxygen concentration measured above 2 mg/L at the end of the test.

- pH:

8.0 ± 0.2

- Adjustment of pH:

no adjustment of pH.

- Intensity of irradiation:

room illumination power E(D, sy) = 2.5 W/m2

- Photoperiod:

9 h per day in light and daylight was excluded; the rest of the day in dark.

DURATION OF THE TEST: 24 hours

TEST PARAMETER: immobilization of Daphnia

SAMPLING: no data

MONITORING OF TEST SUBSTANCE CONCENTRATION: no data

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)

Reliability: (2) valid with restrictions
Test procedures seem to be in compliance with the international standard ISO6341 and Germany National Standard DIN 38412 Part 11, which are referred in the OECD Test Guideline No 202.

This study dose not report the detail concentrations at which the test was conducted and the effect of doses; and the actual conentrations of the test substance dose not measured.

Hence, the reliability of this test is assigned to be 2

(reliable with restrictions).

But, this data is sufficient to evaluate the hazard effect of the chemical on the acute toxicity to aquatic invertebrates.

Flag: Critical study for SIDS endpoint

03-DEC-2004 (9)

Type: semistatic
Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC0: 6.3
EC50: 20
EC100: 50
Limit Test: no

Method: other
Year: 1977
GLP: no

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Conclusion: No detail methods and results. 24 hour duration of exposure.
Reliability: (4) not assignable
No analytical data. No recommended strain; wild strain. No report of the exposure concentrations; Short duration (24 hours).

03-DEC-2004 (4)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: 2.4 measured/nominal
EC10: measured/nominal
EC50: 14.9
Limit Test: no

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2000
GLP: yes
Test substance: other TS

Method: METHOD FOLLOWED:

OECD Guideline No. 201

DEVIATIONS FROM GUIDELINE:

NO

STATISTICAL METHODS:

The no observed adverse effect concentration (NOEC) is defined as the maximum concentration when a sample shows no significant difference at the 5 percent level in comparison with the control using the Bartlett's test for homogeneity

of variances, analysis of variance (ANOVA test), and Dunnett's multiple comparison test.

An EC50 were determined by Logit method, and a NOEC also estimated.

ANALITICAL METHOD:

The concentration of the test substance in the test solution was determined using a high performance liquid chromatography (HPLC).

Column: Capcellpak C19, 2.0 mm i.d. x 150 mm
Column Temperature: 40°C
Uv detector: 225 nm
Sample size: 2 µl
Mobile phase: 60% acetonitrile/40% Water
Flow rate: 0.2 mL/min

Result: RESULTS: EXPOSED
- Nominal/measured concentrations:

Table: Measured Concentrations of Diallyl phthalate During a 72-Hour Exposure to Selenastrum capricornutum

Nominal Conc. (mg/L)	Measured Concentration (mg/L)				
	0 Hour	Percent of nominal	72 Hour	Percent of nominal	Geometric mean of measured conc.
0*	<0.1	-	<0.1	-	
1.7	1.5	88.2	1.2	70.6	1.3
3.1	2.7	87.1	2.1	67.7	2.4
5.6	4.5	80.4	3.8	67.9	4.1
10.0	8.1	81.0	7.6	76.0	7.8
18.0	15.0	83.3	14.4	80.0	14.7
32.4	27.4	84.6	26.4	81.5	26.9

- Effect data/Element values:

(growth rete method)

ErC50(0-72) = 14.9 mg/L, 95% Confidential Interval, 13.8 - 16.2 mg/L, on the geometric mean basis of 0 and 72 hours-measured concentration basis.

NOECr(0-72) = 2.4 mg/L

- Cell density data:

Table Cell Density of Selenastrum capricornutum

Measured Conc. (mg/L)	No.	Cell Density (X10^4 cells/mL) 0 Hour	24 Hour	48 Hour	72 Hour
Control	1	1.00	6.3	35.5	207.3
	2	1.00	6.3	29.1	174.3
	3	1.00	6.6	31.6	177.1

	Mean	1.00	6.4	32.1	186.2
	S.D.	0.00	0.18	3.21	18.29
1.3	1	1.00	5.2	31.5	212.7
	2	1.00	5.7	35.2	188.0
	3	1.00	6.5	33.4	193.9
	Mean	1.00	5.8	33.3	198.2
	S.D.	0.00	0.64	1.86	12.87
2.4	1	1.00	5.7	26.3	189.2
	2	1.00	5.5	32.7	177.4
	3	1.00	5.3	29.4	182.5
	Mean	1.00	5.5	29.5	183.0
	S.D.	0.00	0.22	3.21	5.95
4.1	1	1.00	5.2	24.9	134.2
	2	1.00	4.8	28.7	140.1
	3	1.00	4.9	24.2	130.7
	Mean	1.00	4.9	25.9	135.0
	S.D.	0.00	0.21	2.41	4.74
7.8	1	1.00	3.7	13.9	59.8
	2	1.00	4.3	14.1	76.7
	3	1.00	3.8	14.7	68.2
	Mean	1.00	3.9	14.2	68.2
	S.D.	0.00	0.36	0.42	8.44
14.7	1	1.00	2.1	7.4	15.9
	2	1.00	2.4	7.6	14.8
	3	1.00	2.5	6.6	16.9
	Mean	1.00	2.3	7.2	15.9
	S.D.	0.00	0.21	0.53	1.04
26.9	1	1.00	1.7	2.3	3.6
	2	1.00	2.2	2.4	2.8
	3	1.00	1.7	2.2	2.1
	Mean	1.00	1.8	2.3	2.8
	S.D.	0.00	0.27	0.09	0.77

Each value represents the mean of three sample counts.

- Growth curves:

1. Average cell concentration after 72 hours in the control group was increased by 186 times, showing the normal growth under the test conditions.

2. Average cell concentration after 72 hours at the 1.7 mg/L dose group, the minimum dose group was increased by 198 times, showing the normal growth nearly similar to that of the control group.

3. Average cell concentration after 72 hours at the 32.4

mg/L dose group, the maximum dose group was increased a little, showing substantial growth inhibition.

4. Average cell concentrations after 72 hours at the concentrations other than those described above were increased by 16 to 183 times, showing growth inhibitions.

RESULTS CONTROL:

Average cell concentration after 72 hours in the control group was increased by 186, showing the normal growth under the test conditions.

RESULTS: TEST WITH REFERENCE SUBSTANCE

- Concentrations:

The report dose not describe detail experimental method and condition for reference substance.

- Results:

EbC50(72hours) of the organisms used in this test to a standard substance, potassium dichromate was reported to be 0.52 mg/L, showing that the test was conducted under the satisfactory test condition.

STATISTICAL RESULTS:

EbC50(0-72) = 8.5 mg/L, 95% Confidential Interval, 8.0 - 9.1 mg/L, on the nominal concentration basis. NOEC(0-72) = 3.1 mg/L on the biomass basis.

Test condition: TEST ORGANISMS

- Strain:

Selenastrum capricornutum ATCC-22662

- Source/supplier:

American Type Culture Collection

- Laboratory culture:

The Strain from the Supplier were subcultured.

- Method of cultivation:

The test was conducted under the following conditions:
Culture method, Shaking culture at 100 rpm
Temperature, 23±2°C
Exposure Duration, 72 hours
Test Volume, 100 mL (OECD medium)
Light, 4000 - 5000 lux (continuous irradiation)
pH, no adjustment of pH during the test cultivation.

All vessels were sterilized. Inoculations of the algae were conducted under the sterile condition.

- Pretreatment:

The algae was cultured 3 days before the exposure under the same condition to that of the test. After cultivation, no transformation and abnormal shape cell were observed by microscopic observation.

- Controls:

- Initial cell concentration:

10,000 cells/mL

STOCK AND TEST SOLUTION AND THEIR PREPARATION

- Dispersion:

Preparations of all stock solution and test solution were conducted at the diallyl phthalate concentration under the solubility in water.

- Vehicle, solvent:

No vehicle used.

- Concentration of vehicle/ solvent:

No vehicle used.

- Other procedures:

Test Stock Solution was prepared by solubilizing the test substace in culture medium prepared and sterilized according to the test guideline.

STABILITY OF THE TEST CHEMICAL SOLUTIONS:

The chemical monitoring showed the test substance was stable under the test condition however depression was observed as the measured concentrations at the start of test were lower than the nominal (ranging 80 - 88% of nominal), and during the test the test substance was decreased a little.

The concentrations at 72 hours after the start of the exposure ranged from 1.5 to 27.4 mg/L and from 1.2 to 26.4 mg/L, showing that the test chemical was stable during the test.

Therefore, it should be used a mean measured concentration or a initial measured concentration for estimating toxic values.

DILUTION WATER

Algal medium described in the OECD Test Guideline 201 as used as dilution water (See GROWTH/TEST MEDIUM CHEMISTRY).

GROWTH/TEST MEDIUM CHEMISTRY:

The Algal medium recommended in the OECD Test Guideline 201:

H3BO3	0.185	mg/L
MnCl2·4H2O	0.415	mg/L
ZnCl2	0.003	mg/L
FeCl2·2H2O	0.08	mg/L
Na2EDTA·2H2O	0.1	mg/L
CoCl2·2H2O	0.0015	mg/L
Na2MoO4·2H2O	0.007	mg/L
CuCl2·2H2O	0.0001	mg/L
CaCl2·2H2O	18	mg/L
NH4Cl	15	mg/L
KH2PO4	1.6	mg/L
NaHCO3	50	mg/L
MgCl2·6H2O	12	mg/L
MgSO4·7H2O	15	mg/L

TEST SYSTEM

- Test type:

static

- Concentrations:

0, 1.7, 3.1, 5.6, 10.0, 18.0, and 32.4 mg/L (nominal concentration)

- Renewal of test solution:

no renewal

- Exposure vessel type:

300 mL glass Erlenmeyer flask with a breathable silicone plug.

- Number of replicates:

3 replicates per doses

- Test temperature:

23 ± 2°C

- pH:

7.5 to 7.8

- Intensity of irradiation:

4000 to 5000 lux (continuous irradiation)

- Photoperiod:

Continuously

TEST PARAMETER:

No other parameter affects the validity of this study.

Test substance: Diallyl phthalate

Purity: 99% or more
Lot Number: D43493F
Supplier: Kishida Chemical K.K.
Volume: 25 ml x 2
Date Obtained: 17 September 1999
Appearance: Colorless, transparent liquid
The following descriptions are excerpt from the reference document.
Name: diallyl phthalate
Formula: C14H14O4
Molecular Weight: 246.26
Melting Point: -70°C
Boiling Point: 305°C
Solubility in Water: 182 mg/L (25°C)
LogPow: 3.23
Vapor Pressure: 2.4 mmHg (150°C)

The values described above were excerpted from the following database:

TOXNET: National Library of Medicine (Toxicology Data Network)

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
20-DEC-2004 (41)

Species: Scenedesmus subspicatus (Algae)
Endpoint: other: biomass/growth rate
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: 3.8 measured/nominal
EC50: 5.5 measured/nominal
Limit Test: no

Method: other: DIN 38412 L9 Part 9 (Draft)
Year: 1990
GLP: no data

Method: Apparatus to determine cell concentration:
The method to determine the biomass was measurement of the turbidity at 578 nm of the test and control experiments by using the Eppendorf digital photometer 6115 S and cell flasks with a light path of 2 cm.

Calculation:
The tested concentration was assigned to the respective inhibition values in the probability paper.

Result: RESULTS: EXPOSED

- Nominal/measured concentrations:

0 mg/L (control), 0.63 - 80 mg/L (nominal concentration)

- Effect data/Element values:

see STATISTICAL RESULTS.

- Cell density data:

measured but not reported.

- Growth curves:

not reported.

RESULTS CONTROL:

The average measurements of the control preparations in Erlenmeyer flasks were reported as the following results:

Time [hours]	Average Absorbency at 578 nm	Cells [Cells/mL]
0	0.002	1 E+4
24	0.012	9 E+4
48	0.056	30 E+4
72	0.215	90 E+4
96	0.370	180 E+4

RESULTS: TEST WITH REFERENCE SUBSTANCE

- Reference Substance:

Potassium dichromate.

This study reported the chemical as one of 68 test substances, not a reference substance.

- Concentrations:

0 mg/L (control), 0.08-10 mg/L (nominal concentration)

- Results

Statistical Results:

Test Period Range	EBC10	EµC10	EBC50	EµC50	Tested Concentration Range (nominal)
(h)	(mg/L)	(mg/L)	(mg/L)	(mg/L)	(mg/L)
Result of Test Substance					
0-48	1.9	1.9	5.3	11	0.63-80
0-72	1.6	3.0	3.8	5.5	
0-96	2.6	-	4.5	-	
Result of Reference Substance, Potassium dichromate					
0-48	0.15	2.1	0.55	13	0.08-10
0-72	0.09	1.8	0.38	10	
0-96	0.11	-	0.35	-	

Test condition: TEST ORGANISMS

- Strain:

Strain number 8681 SAG

- Source/supplier:

Collection of Algal Cultures
Inst. Plant Physiology
University of Göttingen
Nikolausberger Weg 18
D-3400 Göttingen
German, F.R.

- Laboratory culture:

The strain were maintained over a number of decades in submerged culture.

- Method of cultivation:

The required number of 100 ml Erlenmeyer flasks with metal caps containing 20 ml nutrient solution was sterilized in a steam sterilizer for 30 min or 2 consecutive days. After cooling, the contents of each flask were inoculated with 2 ml cell suspension taken from a 10-day old stock culture. The inoculated flasks were placed on a white surface, protected from daylight and exposed to constant lighting from two parallel fluorescent Osram 40 W/30 tubes (distance from each tube 60 cm: irradiance E0, Sy= 24.9 W/m2) at 24 ± 1°C and relative humidity of 50%. To maintain the test strain, fresh stock cultures were prepared at 10-day intervals.

- Pretreatment:

The cultivation of the preliminary cultures was undertaken 3 days prior to the preparation of the test solution. 50 mL nutrient solution was filled into 300 ml Erlenmeyer flasks with metal caps and inoculated with Scenedesmus from 7-day-old stock cultures. The cell concentration in the preliminary culture flasks amounted to 1E-4 cells/ml. Light and temperature conditions corresponded to those for the test preparation. The cell material of the preliminary cultures was used after 72 h to inoculate the dilution preparation after the cell concentration had been fixed at 1E-5 cells/ml.

- Controls:

culture medium without DAP.

- Initial cell concentration:

10,000 cells/ml (nominal)

STOCK AND TEST SOLUTION AND THEIR PREPARATION

- Dispersion:

The aqueous solution of DAP was resulted from quantitatively dissolving DAP to produce an optically clear stock solution

in 800 ml double-distilled water using magnetic stirrers (maximum 24 h). Before beginning the test the aqueous solution were adjusted to pH 8.0 ± 0.3 by adding acid or base.

- Vehicle, solvent:

no vehicle

STABILITY OF THE TEST CHEMICAL SOLUTIONS:

not described

REFERENCE SUBSTANCE:

Potassium dichromate, which is recommended to be used in the OECD test guideline 201, althogh this chemical was not reported as a reference substance, but as one of 68 test substances.

DILUTION WATER

- Source:

double-distilled water

- Aeration:

using magnetic stirrers (maximum 24 h).

GROWTH/TEST MEDIUM CHEMISTRY:

Growth medium was prepared according to the DIN 38412 Part 9 (Draft).

TEST SYSTEM

- Test type:

Static, shaken daily

- Concentrations:

0.63 - 80 mg/L

- Renewal of test solution:

no renewal

- Exposure vessel type:

50 ml medium in 300 ml Erlenmeyer flasks with metal caps.

- Number of replicates:

2 per concentration

- Test temperature:

23 ± 2°C

- pH:

8.O ± 0.3
- Intensity of irradiation:

E = 17.0 W/m2

- Photoperiod:

constant lighting

MONITORING OF TEST SUBSTANCE CONCENTRATION: None

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)

Reliability: (2) valid with restrictions
No detail cell denity, only caluculated ECx's were reported; None GLP Test

However, this test was conducted in consideration of DIN 38 412 Part 1, 1982, which is referred in the OECD Test Guideline No 201.

This test seems to be sufficient to evaluate the hazard on the aquatic plant of this test substance.

Flag: Critical study for SIDS endpoint

03-DEC-2004 (57)

Species: Microcystis aeruginosa (Algae, blue, cyanobacteria)
Endpoint: growth rate
Exposure period: 8 day(s)
Unit: mg/l **Analytical monitoring:** no data
TGK : .65
Limit Test: no

Method: other
Year: 1975
GLP: no data

Method: The culture media (each 10 ml) containing DAP as dilution series were prepared in tubes (18 x 180 mm). The test strains were inoculated into the media. The media were incubated for 8 days on the white surface irradiated in the center between two parallel neon tube lamps (lamb distance 60 cm) and not irradiated by day light at 27 °C and 50% relative humidity.

The cell amount was evaluated by the absorbency at 578 nm.

The evaluation of toxic threshold (TGK, Toxische Grenzkonzentration) was carried out in the pollutant-dilution series as follows:

For all test cultures which were free from both toxic influence and stimulation of growth and whose deviation of the extinction were less than 3%, the mean value (a) of the pollutant concentrations and the mean value (A) of the extinction's was plotted respectively as the abscissa and the ordinate.

For test cultures which had the lowest both toxic influence

and stimulation of growth, the mean value (b) of the pollutant concentrations and the mean value (B) of the extinction's was plotted respectively as the abscissa and the ordinate.

On the straight line between (a, A) and (b, B), the pollutant
initial concentration as TGK value was determined from the abscissa against the ordinate (A - 3%).

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
03-DEC-2004 (6) (11)

Species: Scenedesmus quadricauda (Algae)
Endpoint: growth rate
Exposure period: 8 day(s)
Unit: mg/l **Analytical monitoring:**
TGK : 2.9

Year: 1978
GLP: no data

Method: The culture media (each 10 ml) containing DAP as dilution series were prepared in tubes (18 x 180 mm). The test strains were inoculated into the media. The media were incubated for 8 days on the white surface irradiated in the center between two parallel neon tube lamps (lamb distance 60 cm) and not irradiated by day light at 27 °C and 50% relative humidity.

The cell amount was evaluated by the absorbency at 578 nm.

The evaluation of TGK was carried out in the pollutant-dilution series as follows:

For all test cultures which were free from both toxic influence and stimulation of growth and whose deviation of the extinction were less than 3%, the mean value (a) of the pollutant concentrations and the mean value (A) of the extinction's was plotted respectively as the abscissa and the ordinate.

For test cultures which had the lowest both toxic influence and stimulation of growth, the mean value (b) of the pollutant concentrations and the mean value (B) of the extinction's was plotted respectively as the abscissa and the ordinate.

On the straight line between (a;A) and (b;B), the pollutant initial concentration as TGK value was determined from the abscissa against the ordinate (A - 3%).

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (3) invalid
03-DEC-2004 (6) (7) (10)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)

Exposure period: 16 hour(s)
Unit: mg/l **Analytical monitoring:**
TGK : > 100 measured/nominal

Method: other
Year: 1977
GLP: no data

Method: The dilution series of the culture media (100 ml) containing diallyl phthalate and inoculated the test strain (Pseudomonas putida) for test or not inoculated for control in 300 ml flask were incubated for 16 hours at 25°C.

The cell amount was evaluated by the absorbency at 436 nm.

The evaluation of TGK was carried out in the pollutant-dilution series as follows:

For all test cultures which were free from both toxic influence and stimulation of growth and whose deviation of the extinction were less than 3%, the mean value (a) of the pollutant concentrations and the mean value (A) of the extinction's was plotted respectively as the abscissa and the ordinate.

For test cultures which had the lowest both toxic influence and stimulation of growth, the mean value (b) of the pollutant concentrations and the mean value (B) of the extinction's was plotted respectively as the abscissa and the ordinate.

On the straight line between (a;A) and (b;B), the pollutant initial concentration as TGK value was determined from the abscissa against the ordinate (A - 3%).

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
03-DEC-2004 (5)
Type: aquatic
Species: Entosiphon sulcatum (Protozoa)
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:**
TGK : 13

Year: 1978
GLP: no data

Method: Two dilution flask-series of the culture media (20 ml) containing diallyl phthalate as a pollutant and deactivated Escherichia coli as feed, adjusted to pH 6.9, and inoculated with the test protozoa strain were incubated for 72 hours at 25°C.

The number of the protozoa was counted with the cell counter.

The evaluation of TGK was carried out in the dilution series as follows:

For all test cultures which were free from both toxic

influence and stimulation of growth and whose deviation of the number of protozoa were less than 5%, the mean value (a) of the pollutant concentrations and the mean value (A) of the numbers of protozoa was plotted respectively as the abscissa and the ordinate.

For test cultures which had the lowest both toxic influence and stimulation of growth, the mean value (b) of the pollutant concentrations and the mean value (B) of the numbers of protozoa was plotted respectively as the abscissa and the ordinate.

On the straight line between (a,A) and (b,B), the pollutant initial concentration as TGK value was determined from the abscissa against the ordinate (A - 5%).

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
Not reported detail test conditions.

03-DEC-2004 (12)

Type: aquatic
Species: Entosiphon sp. (Protozoa)
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:**
TGK : 13

Method: other
Year: 1980
GLP: no data

Method: Two dilution flask-series of the culture media (20 ml) of diallyl phthalate as a pollutant and deactivated Escherichia coli as feed, adjusted to pH 6.9 and inoculated with the test protozoa strain (Entosiphon sulcatum) were incubated for 72 hours at 25°C.

The number of the protozoa was counted with an cell counter.

The evaluation of TGK was carried out in the dilution series as follows:

For all test cultures which were free from both toxic influence and stimulation of growth and whose deviation of the protozoa count were less than 5%, the mean value (a) of the pollutant concentrations and the mean value (A) of the number of protozoa was plotted respectively as the abscissa and the ordinate.

For test cultures which had the lowest both toxic influence and stimulation of growth, the mean value (b) of the pollutant concentrations and the mean value (B) of the number of protozoa was plotted respectively as the abscissa and the ordinate.

On the straight line between (a,A) and (b,B), the pollutant initial concentration as TGK value was determined from the abscissa against the ordinate (A - 5%).

Test condition: Species: Entosiphon sulcatum
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions

03-DEC-2004 (7)

Type: aquatic
Species: Uronema parduzci (Protozoa)
Exposure period: 20 hour(s)
Unit: mg/l **Analytical monitoring:**
TGK : 22

Method: other
Year: 1980
Test substance: other TS

Method: Two dilution flask-series of the culture media (20 ml) of diallyl phthalate as a pollutant and deactivated Escherichia coli as feed, adjusted to pH 6.9, and inoculated with the test protozoa strain (Entosiphon sulcatum) were incubated for 20 hours at 25°C.

The number of the protozoa was counted with the cell counter.

The evaluation of TGK was carried out in the dilution series as follows:

For all test cultures which were free from both toxic influence and stimulation of growth and whose deviation of the number of protozoa were less than 5%, the mean value (a) of the pollutant concentrations and the mean value (A) of the numbers of protozoa was plotted respectively as the abscissa and the ordinate.

For test cultures which had the lowest both toxic influence and stimulation of growth, the mean value (b) of the pollutant concentrations and the mean value (B) of the numbers of protozoa was plotted respectively as the abscissa and the ordinate.

On the straight line between (a,A) and (b,B), the pollutant initial concentration as TGK value was determined from the abscissa against the ordinate (A - 5%).
Test substance: diallyl phthalate. Source was not reported.
Reliability: (2) valid with restrictions
03-DEC-2004 (8)

Type: aquatic
Species: Chilomonas paramaecium (Protozoa)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
TGK : 29

Method: other
Year: 1980
GLP: no

Method: Two dilution flask-series of the culture media (20 ml) containing diallyl phthalate as a pollutant and deactivated Escherichia coli as feed, adjusted to pH 6.9, and inoculated with the test protozoa strain (Chilomonas paramacium Ehrenberg) were incubated for 48 hours at 20°C.

The number of the protozoa was counted with the cell counter.

The evaluation of TGK was carried out in the dilution series as follows:

For all test cultures which were free from both toxic influence and stimulation of growth and whose deviation of the number of protozoa were less than 5%, the mean value (a) of the pollutant concentrations and the mean value (A) of the numbers of protozoa was plotted respectively as the abscissa and the ordinate.

For test cultures which had the lowest both toxic influence and stimulation of growth, the mean value (b) of the pollutant concentrations and the mean value (B) of the numbers of protozoa was plotted respectively as the abscissa and the ordinate.

On the straight line between (a,A) and (b,B), the pollutant initial concentration as TGK value was determined from the abscissa against the ordinate (A - 5%).

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
03-DEC-2004 (13)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Endpoint: reproduction rate
Exposure period: 21 day(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: 1.16
LOEC: 4.95
EC50: 4.31
LC50 : 2.4

Method: OECD Guide-line 211
Year: 2000
GLP: yes
Test substance: other TS

Method: METHOD FOLLOWED:

OECD Guideline 211

DEVIATIONS FROM GUIDELINE:

NO

STATISTIC METHODS

-LC50:

Median lethal dose of parent daphnids (LC50) to 21-days

exposure of test substance and the 95% confidential interval were calculated by Probit Method using the mortality of parent daphnids and test daphnids number at the test concentrations.

-ErC50:

Fifty percent reduction in reproduction output (ErC50) of daphnids and the 95% confidential interval were calculated by Logit Method using the mean number of live offspring produced per parent animal surviving at the test concentrations.

Tested Offspring No.
= Cumulative mean number of offsprings produced in the control group (CMNco) in the Original Test,

Live Offspring No. at x dose group
= Cumulative mean number of offsprings produced at the x

dose group (CMNxo) in the Original Test, and

Live Offspring No. at x dose group in the Supplemental Test
= CMNxs x CMNcs / CMNco,

where CMNxs is cumulative mean number of offsprings produced at x dose group; and CMNcs is the cumulative mean number of offsprings produced in the control group in the Supplemental Test.

-NOECr and LOECr

Cumulative number of offsprings produced (Live Offsprings) per parent animal surviving 21 days after the start of the exposure were determined for each beaker. For each dose group and control group were conducted Bartlett's test for variance homogeneity, 1-way ANOVA test and Dunnett's multiple comparison test.

No Observed Effect Concentration on reproduction (NOECr), the maximum concentration at which no significant difference between the control group and sample group was shown; and Low Observed Effect Concentration on reproduction (LOECr), the minimum concentration at which significant difference between them were determined.

Result: RESULTS: EXPOSED

- Nominal/measured concentrations:

0(Control)/<0.003, 0.85/0.50, 1.52/1.16, 2.74/2.36, 4.94/4.27, 8.89/7.83, 16.0/14.5 mg/L in the Original Test

0*Control)/-, 6.18/4.95, 7.72/6.45 mg/L in the Supplemental Test

In the Original Test, ErC50 was not able to be decided because no reduction in reproduction in the concentration range 0.85 to 4.94 mg/L occurred and all the parent daphnids died at the concentration of 8.89 mg/L or

more. Hence, the supplemental test was conducted.

The measured concentrations were calculated as a time-weighted means of measured concentrations during a 21-day exposure.

Time-weight mean = Total Area / Total Days} x Days

Conc0 is the measured concentration at the start of each renewal period.

Conc1 is the measured concentration at the end of each renewal period.

Days is the number of days in the renewal period.

Ln(Conc0) is the living offsprings number at the start of each renewal period.

Ln(conc1) is the living offsprings number at the start of each renewal period.

Table Time-weighted Means of Measured Concentrations during a 21-day Exposure

Original Test

Nominal Conc. (mg/L)	Time-weighted Mean (mg/L)	Percent of Nominal (%)
Control	-	-
0.85	0.50	58.8
1.52	1.16	76.3
2.74	2.36	86.1
4.94	4.27	86.4
8.89	7.83	88.1
16.0	14.5	90.6

Supplemental Test

Nominal Conc. (mg/L)	Time-weighted Mean (mg/L)	Percent of Nominal (%)
Control	-	-
6.18	4.95	80.1
7.72	6.45	83.5

- Mortality and death rate:

In the control groups, the mortality of the parent daphnids was 0% in the Original Test and 10% in the Supplemental Test, showing that this test meets a requirement of the data validity (less than 20%).

At the dose groups, the death number and the mortality of parent daphnids after the exposure increased with the dose. At the minimum dose group (0.50 mg/L) the parent mortality was 10% and at the maximum dose group (14.5 mg/L) the parent

mortality was 100%.

Table Cumulative Numbers of Dead Parental Daphnia

	Measured Concentration (mg/L)								
Days	Control		0.50	1.16	2.36	4.27	4.95	6.45	7.83	14.5
	OR	SU	OR	OR	OR	OR	SU	SU	OR	OR
0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	1	0	0	1	0
9	0	0	0	0	1	2	0	0	2	0
10	0	0	0	0	1	2	0	0	2	7
11	0	0	0	0	1	3	0	1	3	9
12	0	0	0	0	1	4	0	1	4	10
13	0	0	0	0	2	5	1	2	8	10
14	0	0	0	0	4	6	3	3	10	10
15	0	0	0	0	4	6	3	5	10	10
16	0	0	1	1	4	6	3	10	10	10
17	0	0	1	1	4	6	6	10	10	10
18	0	0	1	1	4	6	6	10	10	10
19	0	1	1	2	4	6	8	10	10	10
20	0	1	1	2	4	6	8	10	10	10
21	0	1	1	2	4	6	8	10	10	10

OR, Original Test
SU, Supplemental Test
Supplemental Test

Table Mortality of Parental Daphnia

	Measured Concentration (mg/L)								
Days	Control		0.50	1.16	2.36	4.27	4.95	6.45	7.83	14.5
	OR	SU	OR	OR	OR	OR	SU	SU	OR	OR
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	40	60	30	30	100	100
21	0	10	10	20	40	60	80	100	100	100

- Day of first birth:

In the control group the days of the first birth were 8 to 14 days after the start of the exposure. At the minimum dose group (0.50 mg/L) the day of the first birth was 13 days after. At a dose group (4.95 mg/L) the days were 17 to 20

days after. At the maximum dose group (14.5 mg/L) all parent animals were died.

Table. Day of First Birth

	Measured Concentration (mg/L)									
Vessel No.	Control OR	Control SU	0.50 OR	1.16 OR	2.36 OR	4.27 OR	4.95 SU	6.45 SU	7.83 OR	14.5 OR
1	13	10	13	12	17	-	17	-	-	-
2	13	10	13	13	11	13	-	-	-	-
3	13	11	13	12	-	-	20	-	-	-
4	13	10	13	13	14	13	-	-	-	-
5	14	-	13	13	-	-	-	-	-	-
6	13	10	13	-	13	-	-	-	-	-
7	14	10	13	13	-	13	-	-	-	-
8	13	13	13	13	13	-	-	-	-	-
9	8	8	-	13	-	14	-	-	-	-
10	14	11	13	-	13	-	-	-	-	-
Mean	12.8	10.1	13.0	12.8	13.5	13.3	18.5	-	-	-

-
- Mean Numbers of juveniles produced per adults:

In the control groups, the mean numbers of juveniles produced per adults were 74.0 and 119.7 for the Original Test and the Supplemental Test, respectively, showing that the data meet the requirement for the test validity, more than 60.

The cumulative mean numbers of juveniles produced per adults at the minimum dose (0.50 mg/L), at a dose (4.95 mg/L) were 84 and 19.5, respectively. At the maximum dose (14.5 mg/L), all adults were dead.

Table Cumulative Numbers of Juveniles Produced per Adult

	Measured Concentration (mg/L)									
Days	Control OR	Control SU	0.50 OR	1.16 OR	2.36 OR	4.27 OR	4.95 SU	6.45 SU	7.83 OR	14.5 OR
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
8	0.9	0.9	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
9	0.9	0.9	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
10	0.9	9.8	0.0	0.0	0.0	0.0	0.0	--a	--a	--a
11	1.3	17.0	0.0	0.0	0.2	0.0	0.0	--a	--a	--a

12	1.3	17.0	0.0	0.8	0.2	0.0	0.0	--a	--a	--a
13	5.4	34.1	8.0	7.6	5.2	4.4	0.0	--a	--a	--a
14	10.0	42.2	9.4	7.6	8.0	6.0	0.0	--a	--a	--a
15	10.0	44.8	9.4	11.5	8.0	7.5	0.0	--a	--a	--a
16	23.2	65.4	33.3	29.4	18.8	19.5	0.0	--a	--a	--a
17	36.5	77.0	33.3	29.4	23.0	23.3	6.0	--a	--a	--a
18	36.5	79.1	33.3	38.9	23.0	23.3	6.5	--a	--a	--a
19	66.8	103.3	84.0	74.8	50.7	56.8	6.5	--a	--a	--a
20	74.0	115.1	84.0	74.8	56.7	60.8	19.0	--a	--a	--a
21	74.0	119.7	84.0	87.6	56.7	60.8	19.5	--a	--a	--a

--a: All parental Daphnia were dead during 21 days exposure period

- Dormant eggs:

No dormant eggs at all control and dose groups occurred.

- Median Lethal Concentration(LC50) of Parental Daphia

LC50 of parental daphnia for 21-days exposure was 2.40 mg/L and the 95% confidence interval was 1.56 to 3.44 mg/L.

- 50% Reproductive Inhibition Concentration (ErC50)

ErC50 for 21-days exposure was 4.31 mg/L and the 95% confidence interval was 3.91 to 4.86 mg/L.

- NOECr, LOECr

NOEC(21-d) on the number of offsprings produced by parental was 1.16 mg/L.

LOEC(21-d) on the number of offsprings produced by parental was 4.95 mg/L.

- Temperature, DO, PH, Hardness of Test Solution

The water temperature during 21-days exposure measured 19.6 to 20.8°C in the Original Test and 19.7 to 20.6°C in the Supplemental Test.

The concentration of dissolved oxygen (DO) measured 7.8 to 8.8 mg/L in the Original Test and 7.4 to 8.7 mg/L in the Supplemental Test. DO in all doses measured more than 60% of the saturated oxygen concentration at 20.0°C.

The pH measured 7.1 to 7.7 in the Original Test and 7.3 to 8.0 in the Supplemental Test. The PH deviation was less than 1.5 during the exposure.

The hardness of the water ranged 244 to 256 mg/L as CaCO3 in the Original Test and 245 to 258 mg/L as CaCO3 in the Supplemental Test.

These data indicates that temperature, DO, pH, and hardness fell into the appropriate range.

Test condition: TEST ORGANISMS

- Strain:

Daphnia magna

- Source/supplier:

The strain had been subcultured in Toray Research Inc. since obtained from National Institute of Environmental Studies, Japan (NIES) 15 November 1995.

- Breeding method:

Young female daphnids to test were bred as follows:
Select macroscopically healthy and large female daphnids and transfer them to a beaker of newly prepared medium. The juveniles produced next day were each transferred in a new beaker. These juveniles, born 9 May 2000 in the Original Test or 29 June 2000 in the Supplemental Test were used as parent animals of the testing daphnids. They were breeding in the Breeding Conditions described below.

After they became to produce juveniles, the juveniles were removed twice or more every week. At the week 3 after the start of the breeding, female adults with the juveniles in its brood chamber were selected from batches where the mortality was 0.0% in those fifteen days for the Original Test or in those twenty days for the Supplemental test before the selection. Juveniles produced from the female parents within 24 hours after the selection were used as testing daphnids.

- Breeding Conditions:

Holding water: dilution water was used as the holding water (See the Dilution Water).

Breeding density: 20 to 50 animals/L holding water.
For matured animals, 25 or less/L.

- Age:

24 hours or less

- Feeding:

0.1 to 0.2 mg of Chlorella vulugaris on the Organic Carbon basis per day per daphnia.

- Pretreatment:

- Feeding during test:

- Control group:

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion:
- Vehicle, solvent:
- Concentration of vehicle/ solvent:
- Other procedures:
STABILITY OF THE TEST CHEMICAL SOLUTIONS:

REFERENCE SUBSTANCE:

DILUTION WATER:

The medium described in the OECD Test Guideline 201 adopted September 1998 was used as the dilution water.

- Hardness:
 235 mg/L as CaCO3 in the Original Test
 252 mg/L as CaCO3 in the Supplemental Test

- pH:
 7.2 in the Original Test
 7.9 in the Supplemental Test

- Holding water:

The dilution water was used as the holding water.

TEST SYSTEM

- Test type:
 semi-static

- Concentrations:

control, 0.85, 1.52, 2.74, 4.94, 8.89, 16.0 mg/L (nominal concentration) in the Original Test
6.18 mg/L, 7.72 mg/L in the Supplemental Test

- Renewal of test solution:

The test solution was perfectly exchanged 3 times per week.

- Exposure vessel type:

100 mL glass vessel.

- Number of replicates, individuals per replicate:

10 per dose, 1 per vessel.

- Test temperature:

20 ± 1°C

- Dissolved oxygen:

not reported

- pH:

pHs at 0, 2, 7, 9 14, 16 days after the start of the exposure were measured.

- Adjustment of pH:

not adjusted.

- Intensity of irradiation:

room light

- Photoperiod:

16 hours light, 8 hours dark

DURATION OF THE TEST:

21 days

TEST PARAMETER:

No other test parameter affected the validity of the study results.

SAMPLING:

MONITORING OF TEST SUBSTANCE CONCENTRATION:

Yes

Test substance: Diallyl phthalate

Purity: 99% or more
Lot Number: D43493F
Supplier: Kishida Chemical K.K.
Volume: 25 ml x 2
Date Obtained: 17 September 1999
Appearance: Colorless, transparent liquid

The following descriptions are excerpt from the reference document.
Name: diallyl phthalate
Formula: C14H14O4
Molecular Weight: 246.26
Melting Point: -70°C
Boiling Point: 305°C
Solubility in Water: 182 mg/L (25°C)
LogPow: 3.23
Vapor Pressure: 2.4 mmHg/L (150°C)

The values described above were exerpted form the following database:

TOXNET: National Library of Medicine (Toxicology Data Network)

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
03-DEC-2004 (41)

Species: Daphnia magna (Crustacea)
Endpoint: reproduction rate
Exposure period: 21 day(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: 3.2 measured/nominal

Method: other
Year: 1989

GLP: no data
Test substance: no data

Method: METHOD FOLLOWED:
Federal Environmental Agency (Umweltbundesamt) (1984) Vorläufiger Verfahrensvorschlag: "Verlängerter Toxizitätstest bei Daphnia magna" (Bestimmung der NOEC für Reproduktionsrate, Mortalität und den Zeitpunkt des ersten Auftretens von Nachkommen) [Provisional Proposal: "Extended toxicity test using Daphnia magna" (determination of NOEC for reproduction rate, mortality and time of the appearance of the first offspring)].

GLP:
GLP not compulsory at time study was performed.

STATISTICAL METHODS:
The U-test and the Student's t-test (Sachs L.(1969)) (Methods of Statistical Evaluation, 2nd edition. Springer, New York)

METHOD OF CALCULATION:
no data

ANALYTICAL METHODS:
no data

Result: RESULTS: EXPOSED

- Nominal/measured concentrations:

nominal concentrations, 0.025-25 mg/L; dilution ratio, 1:2.

The concentration of diallyl phthalate was measured during the test, but the values were not reported.

- Concentration / response curve: not available

- Water quality:

PH in every control and test preparation was greater than 7.0
during the test. An average minimum oxygen saturation value for all tested substances including diallyl phthalate was 69%. No individual values of pH, oxygen saturation and other monitoring data were reported.

- Parent animal mortality at the end of the test: 7.1%

- Mean number of live offspring produced per parent animal surviving at the end of the test:

88.8 in all concomitantly conducted tests (SD = 13.1; coefficient of variation = 14.8%)

- Time of the first production of juveniles: 7th or 8th day

- Number of deaths among the parent animals and the day: no data

- Coefficient of variation for control fecundity: 14.8%

- Plot of total number of living offspring per parent animal (for each replicate) alive at the end of the test vs concentration of the test substance:

no data

- LOEC for reproduction: not reported

- NOEC for reproduction: 3.2 mg/L for nominal concentration

- LOEC/NOEC: not available

- ECx for reproduction, confidential intervals: not reported

- Effect concentration vs. test substance solubility:

The concentrations of test substance were measured during the test, but not reported.

- Statistical methods: Student’s t-test and the U-test

- Other effects:

The parameters of parent animal mortality and appearance of first offspring are as sensitive as the reproduction rate.

RESULTS CONTROL:

64 control solutions in beakers were prepared. The reproduction rate per parent animal after 21 days was 88.8 offspring (SD = 13.1; coefficient of variation = 14.8%). The "parent mortality" after 21 days was 7.1% The "first offspring" appeared on the 7th.

RESULTS: TEST WITH REFERENCE SUBSTANCE

- Test Substance:

Potassium dichromate was used as one of 73 test substances in this study.

However, the data was additionally described this dossier as reference, because the potassium dichromate was recommended as the reference substance to check of the Daphnia Magna and conformity with the procedure in ISO 6341:1996.

- Concentrations:

The test concentrations of potassium dichromate ranged from 0.8 to 50 mg/L. (Only range was reported.)

- Results:

21-d-NOEC of potassium dichromate is 0.018 mg/L in nominal value related to the active ion, Cr6+.

STATISTICAL RESULTS:

NOECs of 21 d Daphnia reproduction test

	Nominal value (mg/L)	Tested Concentration Range (mg/L)
diallyl phthalate	3.2	0.025 - 25
as reference Potassium dichromate	0.018	0.0046 - 0.142

*Chemical analysis showed that the loss of the test substances were below 20%.

Test condition: ORGANISMS

- Source/supplier:

IRCHA
The strain has been maintained in accordance with the procedure practiced since 1978.

- Breeding method:

Twenty-thirty specimens were placed in forty 2-l. beakers which had been filled with at least 1.6 l. Berlin tap water. They provided 24h-old animals when the offspring were removed daily from the cultures.

Temperature-controlled, dechlorinated and oxygen-saturated tap water (German hardness 16°, pH value 7.6-7.7) was used which had been left to stand for 24 h. Before collecting the water, the tap was turned on fully and left to run at least 1 h.

All beaker were covered with watch glasses and placed on a white supporting surface. Feeding with dry algae of the Scenedesmus genus took place daily. Nine g of feed were suspended in 1000 ml tap water and 2 ml of the suspension were added to each beaker.

The temperature of the culture area was regulated thermostatically at 20°C. Under exclusion of daylight, the area was lit by fluorescent lamps(Philips TL 65/33W) for 9 h between 7 a.m. and 4 p.m.

On Monday and Thursday of each week the tap water in all beakers was renewed as were the beakers themselves on Mondays. On Mondays, the offspring which had appeared between Thursday or Friday and Monday were concentrated using the 0.315 mm DIN sieve and separated according to size using the 0.630 mm DIN sieve. Daphnia in the different size categories were used separately for further cultivation.

In order to obtain 24h-old animals on the potential preparation days in a 21 d test series -- Wednesdays or Fridays -- it was necessary to remove the offspring from the

cultivation beakers on Tuesday and/or Thursday.
- Age:

24h-old animals

- Feeding:

Dry algae of the Scenedesmus genus was daily fed. Nine g of feed were suspended in 1000 ml tap water and 2 ml of the suspension were added to each beaker.

- Pretreatment:

The daphnids which were at most 24 h old were removed by pipette and concentrated on a 0.25 mm DIN sieve, placed in as small an amount of dilution water as possible and used as test organisms.

- Feeding during test:

daily

- Control group:

The controls comprising at least four vessels, were filled with 24 h-old Daphnia (1 animal/50 ml).

STOCK AND TEST SOLUTION AND THEIR PREPARATION

- Dispersion:

using magnetic stirrers with 24 h stirring.

- Vehicle, solvent:

no solvent used

- Concentration of vehicle/ solvent:

no solvent

- Other procedures:

no data

STABILITY OF THE TEST CHEMICAL SOLUTIONS:

It appears from the study report that the authors found the test substance to be stable during the test (i.e. less than 20% loss of initial concentration of test substance).

- Remark:

This result meets the requirements of OECD Test Guidline 211.
REFERENCE SUBSTANCE:

potassium dichromate

- Remark:

Seventy-three substances including diallyl phthalate and potassium dichromate were tested concomitantly. Potassium dichromate is a substance recommended in ISO 6341:1996 to use to check the sensitivity of Daphnia magna and to conform with the procedures.

DILUTION WATER

- Source:

11.76 g $CaCl_2 \cdot 2H_2O$ (A.R.) / 1 liter deionized water
4.93 g $MgSO_4 \cdot 7H_2O$ (A.R.) / 1 liter deionized water
2.59 g $NaHCO_3$ (A.R.) / 1 liter deionized water
0.23 g KCl (A.R.) / 1 liter deionized water.

Twenty-five milliliters of each solution was pipetted into a graduated flask and completed to 1
liter with deionized water. When using deionized water with a conductivity of < 1 µS / cm, the
dilution water was diluted with 10% Berlin tap water.

- Aeration:

The dilution water was aerated up to the water saturation level. determine the fate of the substance.

- Alkalinity:

no data

- Hardness:

The amount of calcium and magnesium ions was 2.5 mmol/L.

- Salinity:

$CaCl_2 \cdot 2H_2O$ 0.294 g/l
$MgSO_4 \cdot 7H_2O$ 0.124 g/l
$NaHCO_3$ 0.0648 g/l
KCl 0.0058 g/l

- TOC:

no data

- Ca/Mg ratio:

4:1

- Na/K ratio:

10:1

- pH:

8.0 ± 0.2

- Oxygen content:

no data

- Conductance:

no data

TEST SYSTEM

- Test type:

The 21-d reproduction test

- Concentrations:

0.025-25 mg/L

- Renewal of test solution:

semistatic system, 3 times a week (Mondays, Wednesdays and Fridays)

- Exposure vessel type:

400 mL beakers with 250 useful capacity, open test (beakers covered with watch glass)

- Number of replicates/individuals per replicate: 4/5

- Test temperature:

25 ± 1°C (The test area were set thermostatically at the temperature.)

- Dissolved oxygen:

An average minimum oxygen saturation value was measured 69% in all tests including ones concurrently conducted for the other substances at the end of the test period.

- pH:

The pH value was not lower than 7.0 (based on 8.0 ± 2).

- Adjustment of pH:

not conducted.

- Intensity of irradiation:

fluorescent lamps --Phlips TL 40/25W.

- Photoperiod:

lit from 7 a.m. to 4 p.m.

DURATION OF THE TEST: 21 days

SAMPLING:

one of the transfer days before 7th and one day between 16th

and 21st day.

MONITORING OF TEST SUBSTANCE CONCENTRATION:

Samples were taken twice from selected concentration levels of the test series during the test period and analyzed chemically: the first sampling took place on one of the transfer days before the 7th day, i.e. in the period during which no offspring appeared; the second sampling took place between the 16th and 21st day. For the corresponding dilution levels, the following parameters were determined:

The concentrations of the initially preparations in order to check the solution behavior and the dilution steps; the concentrations in the test and blank preparations (no test organisms or feed) after an interval of 48/72h in order to determine the fate of the substan

Test substance: diallyl phthalate (CAS NO. 131-17-9)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
03-DEC-2004 (58)

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo: In vivo
Type: Toxicokinetics
Species: other: Rats and Mice

Deg. product: yes

Method: other
Year: 1986
GLP: no data
Test substance: other TS

Method: Dose response toxicity studies:
Rats and mice were dosed orally with 300-900 mg/kg bw DAP or with 25 - 200 mg/kg of allyl alcohol with corn oil as a vehicle. After 24 h, SGPT activity of blood was analyzed. Histopathlogical evaluation of liver was performed.

Excretion and tissue distribution studies:
-Determination of dose effect on the elimination of DAP.
Rats and mice were dosed orally with 1, 10 or 100 mg/kg bw DAP. Dosing solutions were prepared in water:ethanol:Emulphor EL-620 (3:2:1). Rats and mice received 1 mL of dosing solution/kg bw (40 or 120 µCi/kg bw, respectively). Following dosing 14CO2, volatile metabolites, urine and feces were collected for 24 hours. At termination, selected tissues were removed and oxidized to 14CO2.

-Tissue distribution and pharmacokinetic studies
Rats and mice were dosed via the tail vein with 10mg/kg bw of [14C]DAP (40 or 120 µCi/kg bw, respectively) in water/ethanol/Emulphor (3:2:1). At 0.5, 1, 2, 4, 8, 12 and 24 hours after dosing animals were anesthetized and exsanguinated. Brain, lung, liver, kidney, spleen, testes, small intestine, renal fat, muscle (thigh), and skin (abdominal) were removed. Urine and intestinal contents were collected.

Metabolite Identification
Urine from a rat dosed orally with [14C]DAP (100 mg/kg bw) was acidified to pH 1-2 with 6M HCl and extracted with ethyl acetate. The sample was then saturated with NaCl and extracted with acetonitrile. After concentrating the ethyl acetate extract under a stream of nitrogen, the sample was chromatographed on a high-efficiency silica gel GF preparatory TLC plate. The silica was scraped from the plate in 0.5 cm bands and extracted with methanol. Extracts containing radioactivity were concentrated and reacted with diazomethane/ether prior to analysis by mass spectrometry using a Finnigan 3300 instrument. The acetonitrile extract was concentrated and then reacted with bis(trimethylsilyl)trifluoroacetamide and diazomethane/ether prior to mass spectral analysis using a Varian MAT311A mass spectrometer. For analysis of the aqueous phase (post acetonitrile extraction) the urine sample was treated with acetone to remove salt, and the acetone evaporated to dryness.

The residue was dissolved in methanol and treated with diazomethane/ether prior to analysis using a mass spectrometer.

Result:

The authors postulate that the differential hepatotoxicity of DAP is related to the extent of glutathione conjugation with allyl alcohol or acrolein (the active metabolite of AA).

(Histopathology)
Histopathological evaluation confirmed a marked species difference in DAP- and AA-induced hepatic injury.

In rats, 300 mg/kg of DAP resulted in periportal inflammation in four rats. At the higher doses (400-600 mg/kg), periportal hemorrhagic and coagulative necrosis was present in 80% of the rats treated with DAP (four - six rats/dose).

In mice, doses of DAP up to 700 mg/kg did not produce necrosis, although some of the mice had periportal inflammation. At 900 mg/kg, two of four mice developed periportal necrosis. Doses of AA (25, 50 and 75 mg/kg) were not hepatotoxic in mice.

In rats, periportal necrosis was evident in 9 of 12 animals treated with AA. The severity of the injury was greater at the 50- and 75-mg/kg doses than at the 25-mg/kg dose. Mice given 100-200 mg/kg bw of AA died within 24hr after administration. Therefore in mice it was not possible to identify a non-lethal dose of allyl alcohol that resulted in extensive liver damage.

AA is a product hydrolysed from DAP at the first stage in an animal body.

(Excretion, tissue distribution, and pharmacokinetic studies)
Fischer-344 rats and B6C3F1 mice were given [14C]DAP, 1, 10, or 100 mg/kg po or 10 mg/kg iv, and placed in metabolic cages for 24 hr. In rats, 25-30% of the DAP was excreted as CO_2, and 50-70% appeared in urine within 24 hr.

In mice, 6-12% of the DAP was excreted as CO_2, and 80-90 % was excreted in the urine within 24 hr. 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 DAP. The polar metabolite was present in the urine of rats after administration of DAP or AA, indicating that the compound is a metabolite of AA.

Following iv administration of DAP, the parent compound was rapidly cleared from the blood of rats and mice. The t½ for elimination from blood was approximately 2 min in both species. No DAP was found in blood, liver, kidney, muscle, skin, or small intestine 30 min after iv administration of DAP.

Monoallyl phthalate, formed from the metabolism of DAP, had a half-life in blood of 32 and 9 min in rats and mice, respectively. Within 4 and 2 hr after dosing rats and mice, respectively, with DAP, no MAP was detected in the blood, liver, kidney, skin muscle, or small intestine.

Table: Diallyl Phthalate Metabolites in Rat and Mouse Urine(a,b)

Species	Dose (mg/kg)	Allyl alcohol	Monoallyl phthalate	3-hydroxypropyl mercapturic acid	Polar metab(c)
Rat	1(po)	2.3±0.2	29.0±0.7	13.2±0.4	6.6±0.4
	10(po)	3.0±1.6	32.5±1.7	18.4±5.9	7.8±1.6
	100(po)	3.1±2.3	32.2±0.6	16.5±1.2	7.5±0.7
	10(iv)	2.9±2.0	38.0±1.0	20.6±1.1	8.3±1.1
Mouse	1(po)	3.6±1.1	39.2±1.9	27.0±1.0	19.1±1.7
	10(po)	4.8±2.3	37.7±4.2	29.7±0.2	19.0±1.4
	100(po)	2.3±0.6	44.7±1.9	21.1±1.9	19.4±1.4
	10(iv)	7.5±5.2	31.5±5.8	34.4±2.4	20.8±1.5

(a) Values are calculated as a percentage of the dose of 14-C administered
(b) Each value in the mean of three animals ±SE
(c) An unidentified metabolite which was not extracted by acetonitrile from urine.

Test condition: STRAIN: Ficher-344 rats (Male);6C3F1 mice (Male)
WEIGHT: Rats ca. 150 - 200 g; Mice ca. 20 - 25 g

Test substance: Test Substance: [14C]Diallyl phthalate (labeled on the 2,3 position of the allyl alcohol (AA) moiety, sp act 12.2 mCi/mmol from Midwest Research Institute (Kansas City, Mo.).

Purity: 99% (TLC)

Reliability: (2) valid with restrictions
20-DEC-2004 (39)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Fischer 344
Sex: male/female
No. of Animals: 45
Vehicle: other: Corn oil
Doses: 464, 681, 1,000, 1,470 mg/kg bw for male; 316, 464, 681, 1,000, 1,470 mg/kg bw for female

Method: other
Year: 1985
GLP: no
Test substance: other TS

Method: Route of administration: Gavage

STATISTICS METHOD:

The survival data from these studies were used to determined LD50 values by the Spearman-Karber method (Finney, 1964) and to select the dose for the 14-day repeated-administration.

Finney, 1964; Finney, D. (1964) Statistical Method in Biological Assay 2nd ed. London: Charles Griffin and Co., Ltd., p. 27.

Result: Value:

LD50

Sex	LD50 (mg/kg)	
	Mean Value	95% Confidential Intervals
Male	891	766 - 1,036
Female	656	545 - 789

Statistics Method: Spearman-Karber method (Finney, 1964)

*Finney, D(1964) Statistical Method in Biological Assay, 2nd ed. London: Charles Griffin and Co., Ltd., p.27.

MORTALITY
- Time of death: see TABLE Dose vs Death and Time of Death

- Number of deaths at each dose: TABLE Dose vs Death and Time of Death

- bodyweight: TABLE Bodyweight vs Dose

CLINICAL SIGNS

Diarrhea, inactivity, hunched posture, hypernea and watery secretions around the nose and mouth were observed in nearly all animals of both sexes at 1470 mg/kg before they died. These clinical signs occurred less frequently at 1000 mg/kg. Female rats receiving 681 mg/kg exhibited reduced activity on the day of dosing only.

NECROPSY FINDINGS

At necropsy, apparent hemorrhagic lesions were noted in the urinary bladder and the lungs appeared dark in animals receiving the 1470 mg/kg dose (chemical-induced deaths). The darkened appearance of the lungs was also noted frequently at 1000, 681 and 464 mg/kg. Fluid was found in the thoracic cavity and the intestines appeared to be reddened in two females in the 1000 mg/kg group that died early.

TABLE Dose vs Death and Time of Death

Dose (mg/kg)	Death	Time of Death (days after dosing)
MALE		

464	0/5	-
681	0/5	-
1,000	4/5	1, 2, 2, 4
1,470	5/5	2, 2, 2, 2, 2
FEMALE		
316	0/5	-
464	0/5	-
681	5/5	2, 2, 2, 2, 3
1,000	3/5	2, 2, 3
1,470	5/5	2, 2, 2, 2, 3

-, no death

TABLE Bodyweight vs Dose

Dose (mg/kg)	Mean Body Weight (g) Initial	Final	Change
MALE			
464	246	252	+6
681	250	275	+25
1,000	247	245	-2
1,470	247	-	-
FEMALE			
316	151	154	+3
464	150	161	+11
681	154	-	-
1,000	151	146	-5
1,470	149	-	-

-, no data due to 100% mortality of this group

Test condition: TEST ORGANISMS: F344/N rats

- Source: Frederick Cancer Research Center (Frederick, MD)

- Age: 10 weeks when placed on study.

- Weight at study initiation:Males 246 - 250 g mean weight/ group, females 149 - 154 g mean weight/group

- Controls:
  no controls

ADMINISTRATION: gavage, single administration

- Doses per time period: Single administration

- Volume administered or concentration: 50 mg/mll corn oil.

- Post dose observation period: 13 days after dosing.

EXAMINATIONS:

Observation every half hour on the day of dosing and then daily for the next 13 days.

Weighing on the day of dosing and then daily for the next 13

days.

Nacropsy after dead or killed.

No histopathological tissue examination.

Test substance: Chemical Name: diallyl phthalate (cas no. 131-17-9)

Supplier: Hardwicke Chemical Company (Elgin, SC)
Lot No.: 25-121
Purity: 99%(GC)

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
03-DEC-2004 (70)

Type: LD50
Species: mouse
Strain: B6C3F1
Sex: male/female
No. of Animals: 20
Vehicle: no data
Doses: 681, 1,000, 1,470, and 2,150 mg/kg bw/day for male; 1,000, 1,470, 2,150, and 3,160 mg/kg bw for female

Method: other
Year: 1983
GLP: no data
Test substance: other TS

Method: Male and female B6C3F1 mice were obtained 6 weeks before the test began. Animals were approximately 10 weeks old when placed on study.

Diallyl phthalate in corn oil was administered by gavage to groups of five male mice in single doses of 681, 1,000, 1,470, or 2,150 mg/kg and to groups of five female mice in single doses of 1,000, 1,470, 2,150, or 3,160 mg/kg. All animals were observed for mortality every 30 minutes on the day of dosing and then daily for the nest 13 days. Weights were measured on the day of dosing and on days 7 and 14, postdosing. Necropsies were performed on all animals.

Result: Value:

Table LD50

Sex	LD50 (mg/kg)
	Mean Value
Male	1070
Female	1690

MORTALITY

- Time of death: see TABLE Dose vs Death and Time of Death

- Number of deaths at each dose: TABLE Dose vs Death and Time of Death

CLINICAL SIGNS: not described

NECROPSY FINDINGS: No chemically-related lesions.

TABLE Dose vs Death and Time of Death

Dose (mg/kg)	Death	Time of Death (days after dosing)
MALE		
681	1/5	1
1,000	2/5	1, 1
1,470	4/5	1, 1, 1, 1
2,150	5/5	2, 2, 3, 3, 3
FEMALE		
1,000	0/5	-
1,470	1/5	1
2,150	5/5	1, 1, 1, 1, 2
3,160	5/5	2, 2, 2, 2, 2

* -, no de

Test condition: TEST ORGANISMS: B6C3F1 mice

- Source: Frederick Cancer Research Center (Frederick, MD)

- Age: 10 weeks when placed on study.

- Weight at study initiation:
  not reported

- Controls:
  no controls

ADMINISTRATION: gavage, single administration

- Doses per time period: Single administration

- Volume administered or concentration: 200 mg/ml corn oil.

- Post dose observation period: 13 days after dosing.

EXAMINATIONS:

Observation every half hour on the day of dosing and then daily for the next 13 days.

Weighing on the day of dosing and on days 7 and 14.

Necropsy after dead or killed.

Test substance: Chemical name: diallyl phthalate (CAS No. 131-17-9)
Supplier: Hardwicke Chemical Company (Elgin, SC)
Lot No.: 25-121
Purity: 99%(GC)

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
03-DEC-2004 (69)

Type: LD50
Species: rat

Strain: Wistar
Sex: male/female
No. of Animals: 30
Vehicle: no data
Doses: 250, 500, and 1,250 mg/kg bw
Value: 896 mg/kg bw

Method: other
Year: 1989
GLP: no
Test substance: other TS

Method: Thirty young adult albino rats (Wistar derived) weighing between 200-300 grams were distributed into three dosage groups with five males and five females in each group. The animals were housed in mesh bottom cages and fasted 24 hours prior to dosing, with food and water available ad libitum after dosage.

The test material was administrated by intragastric intubation.
Result: Value: Oral LD50, 896 ± 202 mg/kg
Test substance: Chemical Name: diallyl phthalate (cas no. 131-17-9)
Source: FMC Corporation (DAP, C8013-1)
Purity: 99 %
Reliability: (2) valid with restrictions
20-DEC-2004 (50)

Type: LD50
Species: dog
Sex: male/female
No. of Animals: 5
Doses: 800 mg/kg bw
Value: ca. 800 mg/kg bw

Method: other
Year: 1989
GLP: no
Test substance: other TS

Method: Three male and two female dogs were housed in individual wire mesh cages, and were fed food (700 g/dog/day) once daily, while water available ad libitum.

After an overnight fast, each dog received diallyl phthalate (800 mg/kg bw) by gavage. This was the LD50 dose calculated from studies in the rats.

The following parameters were studied - urinalysis, blood chemistry, hemoglobin, and hematocrit measured after 4 days post-treatment and food consumption, body weight and observations of behavior, emesis and feces daily for an eight day period following treatment.
Result: After dosing all five dogs vomited within ½ to 2 hr of treatment and emesis recurred throughout the day. One dog died 9 hr after dosing due to pulmonary edema and another dog died 26 hr after dosing. Autopsy of the second dog revealed widespread gastrointestinal bleeding with possible jaundice. The other 3 dogs returned to normal within a week.

Hematological and urinalysis in the three surviving dogs four days after treatment were within normal range. There was a significant elevation of the plasma concentrations of lever enzymes (SGOT, SGPT and SAP), indicating hepatotoxicity. There was also a marked elevation in serum alkaline phosphatase, suggesting possible obstructive jaundice and intrahepatic cholestasis Body weight and food consumption of the three surviving dogs were normal.

Test substance: FMC Corporation (DAP, C8013-3), purity: 99 %.
Reliability: (2) valid with restrictions
20-DEC-2004 (51)

Type: other
Species: rabbit

Method: other
GLP: no

Result: One rabbit died 3 hours after 1.5 ml/kg was given intragastrically. Death was preceded by diarrhoea and prostration. Two rabbits survived 1.0 ml/kg intragastrically.
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (4) not assignable
only result
03-DEC-2004 (64)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 70
Doses: 0.94; 3.09; 5.93; 6.66; 8.03; 9.17; 9.71 mg/l
Exposure time: 1 hour(s)
Value: 8.3 mg/l

Method: other: based on FIFRA Guidelines 43 FR 37336
Year: 1982
GLP: yes
Test substance: other TS

Result: VALUE

Table LC50 Data

		Mean	95% Confidential interval
Male	LC50	10.31	7.73 - 13.75
	LC1	3.49	1.34 - 9.06
	LC99	30.49	11.72 - 79.28
Female	LC50	5.20	3.23 - 8.36
	LC1	0.58	0.12 - 2.89
	LC99	46.36	9.36 - 229.67
Combined	LC50	8.30	5.80 - 11.88
	LC1	0.98	0.30 - 3.20

LC99 70.08 21.51 - 228.37

STATISTICS Method: Litchfield - Wilcoxon (1949)

Table Dose vs Death

Dose (mg/l)	Observed deaths	
	Male	Female
0.94	0/5	0/5
3.09*	0/5	2/5
5.93*	1/5	2/5
6.66*	0/5	3/5
8.03	3/5	4/5
9.17*	0/5	4/5
9.71*	3/5	3/5

* Data from ToxiGenics' study 420-0402. The data were cited but not described in detail. The report for study 420-0402 could not be obtained.

EXAMINATION

Table Examination

Physical/ Pharmacotoxic Parameter	day	rat s1	s2	s3	s4	s5		
High Dose Group, Male:								
Full observation	*a	N	N	Y	N	N		
							mean	sd
Body weight	0	261	264	208	235	242	242.0	22.6
(g)	7	279				249	264.0	21.2
	14	327				302	314.5	17.7
	FBW		164	198	215			
No Reaction.....	DE	-	-	-	-	-		
	SAE	-	-	-	-	-		
	DPE	1	-	-	-	-		
Damp Fur.....	DE	-	-	-	-	-		
	SAE	+	+	+	+	+		
	DPE	7	5	-	-	7		
Salivation.....	DE	-	-	-	-	-		
	SAE	+	+	+	-	+		
Crusty Nose....	DPE	5	-	-	-	-		
Crusty Eye.....	DPE	2	5	-	-	4		
Irregular Breathing.....	DPE	5	5	-	-	14		
Poor Coart Quality.....	DPE	7	-	-	-	8		
Crusty Muzzle..	DPE	-	5	-	-	5		
Yellow/Brown Stained Fur...	DPE	-	2	-	-	-		
Dead.....	PED	-	5	1	1	-		
	SAC	+	-	-	-	+		
Necropsy Findings.....		-	*1	*2	*3	-		
High Dose Group, Female:								

Full observation *a		N	N	N	N	N		
							mean	sd
Body weight	0	200	211	237	205	209	212.4	14.4
(g)	7	211					211.0	0.0
	14	216					216.0	0.0
	FBW		186	221	186	184		
No Reaction.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
	DPE	-	-	-	-	-		
Damp Fur.....DE		-	+	+	+	+		
	SAE	+	+	+	+	+		
	DPE	7	-	-	-	-		
Salivation.....DE		-	+	+	+	+		
	SAE	-	+	+	+	+		
Crusty Nose....DPE		-	-	-	-	-		
Crusty Eye.....DPE		1	-	-	-	-		
Irregular Breathing.....DPE		14	-	-	-	-		
Poor Coat Quality.....DPE		6	-	-	-	-		
Crusty Muzzle..DPE		2	-	-	-	-		
Yellow/Brown Stained Fur...DPE		12	-	-	-	-		
Dead.....PED		-	1	1	1	1		
	SAC	+	-	-	-	-		
Necropsy Findings.....		-	-	*2	-	*4		

Low Dose Group, Male:

Full observation *a		N	N	N	N	N		
							mean	sd
Body weight	0	225	230	220	221	228	224.8	4.3
(g)	7	286	281	276	278	292	282.6	6.5
	14	318	329	323	334	332	327.2	6.6
No Reaction.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
	DPE	14	14	12	14	4		
Damp Fur.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
	DPE	-	-	-	-	-		
Salivation.....DE		-	-	-	-	-		
	SAE	+	+	+	+	+		
Crusty Nose....DPE		-	-	-	-	-		
Crusty Eye.....DPE		-	-	-	-	-		
Irregular Breathing.....DPE		-	-	2	-	10		
Poor Coat Quority.....SAE		-	-	+	+	-		
	DPE	-	-	-	-	-		
Crusty Muzzle..DPE		-	-	-	-	-		
Yellow/Brown Stained Fur...DPE		-	-	-	-	-		
Dead.....PED		-	-	-	-	-		
	SAC	+	+	+	+	+		
Necropsy Findings.....		-	-	*5	-	*6		

Low Dose Group, Female:

Full observation *a		Y	Y	Y	Y	Y		
							mean	sd

Body weight	0	246	247	254	241	241	225.8	5.4
(g)	7	249	258	264	247	249	253.4	7.3
	14	255	270	268	250	250	258.6	9.7
No Reaction.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
	DPE	14	-	-	14	14		
Damp Fur.....DE		-	-	-	-	-		
	SAE	-	+	+	-	-		
	DPE	-	3	3	-	-		
Salivation.....DE		+	+	+	+	+		
	SAE	-	+	+	-	-		
Crusty Nose....DPE		-	-	-	-	-		
Crusty Eye.....DPE		-	1	2	-	-		
Irregular Breathing.....DPE		-	3	6	-	-		
Poor Coat Quality.....SAE		+	11	11	+	+		
	DPE	-	-	-	-	-		
Crusty Muzzle..DPE		-	-	-	-	-		
Yellow/Brown Stained Fur...DPE		-	6	8	-	-		
Dead.....PED		-	-	-	-	-		
	SAC	+	+	+	+	+		
Necropsy Findings.....		-	*7	-	-	-		

Parallel and Untreated Control for High Dose Group, Male:

Full observation *a		Y	Y	Y	Y	Y	mean	sd
Body weight	0	241	256	245	265	258	253.0	9.8
(g)	7	272	309	283	323	306	298.6	20.7
	14	291	341	318	360	346	331.2	27.1
No Reaction.....DE		+	+	+	+	+		
	SAE	+	+	+	+	+		
	DPE	14	13	14	14	14		
Damp Fur.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
	DPE	-	-	-	-	-		
Salivation.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
Crusty Nose....DPE		-	1	-	-	-		
Crusty Eye.....DPE		-	-	-	-	-		
Irregular Breathing.....DPE		-	-	-	-	-		
Poor Coat Quality.....SAE		-	-	-	-	-		
	DPE	-	-	-	-	-		
Crusty Muzzle..DPE		-	-	-	-	-		
Yellow/Brown Stained Fur...DPE		-	-	-	-	-		
Dead.....PED		-	-	-	-	-		
	SAC	+	+	+	+	+		
Necropsy Findings.....		-	-	-	-	-		

Parallel and Untreated Control for High Dose Group, Female:

Full observation *a		Y	Y	Y	Y	Y	mean	sd
Body weight	0	211	223	206	206	203	209.8	7.9
(g)	7	233	239	221	217	224	226.8	9.0

	14	260	243	232	231	224	238.0	14.1
No Reaction.....DE		+	+	+	+	+		
	SAE	+	+	+	+	+		
	DPE	14	14	14	14	14		
Damp Fur.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
	DPE	-	-	-	-	-		
Salivation.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
Crusty Nose....DPE		-	-	-	-	-		
Crusty Eye.....DPE		-	-	-	-	-		
Irregular Breathing.....DPE		-	-	-	-	-		
Poor Coat Quality.....SAE		-	-	-	-	-		
	DPE	-	-	-	-	-		
Crusty Muzzle..DPE		-	-	-	-	-		
Yellow/Brown Stained Fur...DPE		-	-	-	-	-		
Dead.....PED		-	-	-	-	-		
	SAC	+	+	+	+	+		
Necropsy Findings.....		-	-	-	-	-		

Parallel and Untreated Control for Low Dose Group, Male:

Full observation *a		Y	Y	Y	Y	Y		
							mean	sd
Body weight	0	231	222	242	222	216	226.6	10.1
(g)	7	295	287	319	280	272	290.6	18.0
	14	341	342	367	325	313	337.6	20.4
No Reaction.....DE		+	+	+	+	+		
	SAE	+	+	+	+	+		
	DPE	14	14	14	14	14		
Damp Fur.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
	DPE	-	-	-	-	-		
Salivation.....DE		-	-	-	-	-		
	SAE	-	-	-	-	-		
Crusty Nose....DPE		-	-	-	-	-		
Crusty Eye.....DPE		-	-	-	-	-		
Irregular Breathing.....DPE		-	-	-	-	-		
Poor Coat Quality.....SAE		-	-	-	-	-		
	DPE	-	-	-	-	-		
Crusty Muzzle..DPE		-	-	-	-	-		
Yellow/Brown Stained Fur...DPE		-	-	-	-	-		
Dead.....PED		-	-	-	-	-		
	SAC	+	+	+	+	+		
Necropsy Findings.....		-	-	-	-	-		

Parallel and Untreated Control for Low Dose Group, Female:

Full observation *a		Y	Y	Y	Y	Y		
							mean	sd
Body weight	0	284	259	268	230	235	255.2	22.6
(g)	7	273	264	280	232	248	259.4	19.4
	14	282	269	289	240	249	265.8	21.0
No Reaction.....DE		+	+	+	+	+		

	SAE	+	+	+	+	+
	DPE	14	14	14	14	14
Damp Fur.....DE		-	-	-	-	-
	SAE	-	-	-	-	-
	DPE	-	-	-	-	-
Salivation.....DE		-	-	-	-	-
	SAE	-	-	-	-	-
Crusty Nose....DPE		-	-	-	-	-
Crusty Eye.....DPE		-	-	-	-	-
Irregular Breathing.....DPE		-	-	-	-	-
Poor Coart Quality.....SAE		-	-	-	-	-
	DPE	-	-	-	-	-
Crusty Muzzle..DPE		-	-	-	-	-
Yellow/Brown Stained Fur...DPE		-	-	-	-	-
Dead.....PED		-	-	-	-	-
	SAC	+	+	+	+	+
Necropsy Findings.....		-	*8	*9	*10	-

*1, Opacity, diffuse, white, bilateral - Eyes
*2, Opacity, diffuse, white, right - Eye
*3, Discoloration, multiple, focal, black - Glandular Stomach
*4, Discoloration, diffuse, red, edematous - Large Intestine
*5, Discoloration, multiple, focal, white, raised - Spleen
*6, Glandular appearance, smooth, bilateral - Kidneys
*7, Depression, multiple, focal, right surface - Kidney
*8, Alopecia, diffuse, right - Rear Leg
*9, Dilated, diffuse, bilateral - Uterine Horns
Fluid, diffuse, pale green, bilateral - Uterine Horns
*10, Dilated, diffuse, right pelvis - Kidney
*a, Full observation: Y, performed observation throughout during the exposure period; N, not.
+, Present or positive
-, Not present, negative, or not observed.
FBW, Final body weight
DE, During exposure
SAE, Shortly after exposure
DPE, Days post exposure
PED, Post exposure day
SAC, Sacrificed
sd, Standard deviation
numeral, day of present or positive observation

Test substance: Chemical name: diallyl phthalate (CAS No. 131-17-9)
FMC Corporation
Lot No. E104-19
Purity: Unknown

Test condition: TEST ORGANISMS: young adult albino rats (Rattus norvegicus, CRL: CD®(SD) BR)

- Source: Charles River Breending Laboratories, Portage, MI

- Age: not described, but the animals were quarantined for at least 7 days after receipt from the source.

- Weight at study initiation:

Males 200 - 265g, females 216 - 284g

- Housing:

One rat / cage.

The cage size conformed to DHEW publication (NIH) 78.23 standard.

The quarantine and study chamber were cleaned daily according to the ToxiGenics' Standard Operating Procedures and were all ventilated and air-conditioned.

- Lighting: 12 hours light / 12 hours dark.

- Temperature: 13° to 24°C

- Relative humidity: 27 to 62%

- Feed: Purina Certified Rodent Chow 5002

- Water: filtered tap water libitum except during 1 hour exposure.

- Number of animals:
total 40 including controls.

- Controls:
20, no exposure to diallyl phthalate.

ADMINISTRATION:

- Type of exposure: Inhalation

- Concentrations:

Table Concentration

Chamber Condition Nominal Conc. (mg/l)	TWA* of Gravimetric Conc. (mg/l)	TWA of Analytical Conc. (mg/l)
184.2	7.70	8.03
4.6	0.83	0.94

TWA, Time-weighted average

Table Dose for the estimation of LDx.

DOSE (mg/l)	
0.94	
3.09	*
5.93	*
6.66	*

8.03
9.17 *
9.71 *
---

* Data from ToxiGenics' study 420-0402. The data were cited but not described in detail. The report for study 420-0402 could not be obtained.

- Particle size:

Table Particle Size Distribution

Chamber Condition Nominal Conc. (mg/l)	Mass Median Diameter (µm)	Standard Deviation (µm)
184.2	2.0611	1.8241
	2.1022	1.8177
4.6	2.0981	1.8443
	2.0775	1.8907

- Type or preparation of particles:

Each test atmosphere aerosol was generated by passing compressed outside air which was filtered, conditioned, and dried through a 1/4 J SS Air atomizing Nozzle Assembly (Spraying System, Inc., Wheaton, IL) equipped with a 1650 SS Fluid Cap and a 64 SS Air Cap. Diallyl phthalate was pumped in Teflon tubing (Alltech Associates, Arlington Heights, IL) to the nozzle using an FMI Lab Pump (Fluid Matering, Inc., Oyster Bay, NY). A rotameter (Dwyer Instruments, Inc., Michigan City, IN) and back pressure gauge (Ashcroft Dresser Industrial Valve and Istruments Div., Berea, KY) were attached upstream of diallyl phthalate contamination, and all airline attachments were made with Polyurethane tubing (Feed Control Co., Decatur, IL). The resulting air-aerosol mixture was then introduced at the top corner of a 500-liter stainless steel and glass inhalation chamber (containing the test rats) and exhausted at the bottom of the chamber.

- Post dose observation period: 14 days after dosing.

EXAMINATIONS

Observation: Mortality and reactions
Time : At least every 15 min
Duration : The one hour of exposure

Observation: Mortality and reactions
Time : Morning and late afternoon
Duration : Every day from 1 days to 14 days after exposure

Observation: Weighing
Time : Before exposure, on Days 7 and 14, or at death

Necropsy : External surface, body orifices,

cervical organs, Thoracic organs,
abdominal and pelvic organs, and the brain.
Specific Condition of the nasal passages,
trachea, bronchi, and lungs
Time : At the termination of
the 14-day observation period

Histopathologic studies:
Lungs, liver, kidney, and abnormal tissues

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
20-DEC-2004 (47)

Type: other
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 10
Doses: 4.47 mg/l (airborne test material concentration)
Exposure time: 4 hour(s)

Year: 1980
GLP: no
Test substance: other TS

Remark: Exposure to the test material produced immediate signs of irritation and 100% mortality by Day 1. Necropsy examination revealed discoloration of the nasal turbinates and lungs.
Result: Ten rats to an aerosol of DAP for four hours at a nominal concentration of 67.2 mg/L (airborne concentration, 4.47 mg/L) produced immediate signs of irritation and 100% mortality by Day 1. Necropsy examination revealed discoloration of the nasal turbinates and lungs.
Test substance: FMC Corporation (DAP, Compound "D", 179-313, E104-2)
Reliability: (2) valid with restrictions
no-GLP
20-DEC-2004 (46)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
No. of Animals: 30
Doses: 200; 2000; 5000 mg/kg
Value: 3300 mg/kg bw

Method: other
Year: 1989
GLP: no
Test substance: other TS

Result:

Dosage (mg/kg)	Mortality after 14 Days
200	3/10
2000	4/10
5000	6/10

Test substance: FMC Corporation (DAP, C8013-1), purity: 99 %.
Conclusion: The approximate acute Dermal LD50 obtained for the test material identified above is 3300 mg/kg of body weight estimated by interpolation from the probit response curve.
Reliability: (2) valid with restrictions
03-DEC-2004 (49)

Type: LD50
Species: rabbit
Value: 3360 mg/kg bw

Year: 1982

Remark: Original Reference:
McOmie (1949); Title and publication information unknown.
(Cited in Spector, 1956)

Sepector, W. S. (ed.): Handbook of toxicology. New York: Sunders (1956).
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (4) not assignable
03-DEC-2004 (81)

Type: LDLo
Species: rabbit
Value: 3140 mg/kg bw

Year: 1982

Remark: Original Reference:

Original Reference:
McOmie (1949); Title and publication information unknown.
(Cited in Spector, 1956)

Sepctor, W. S. (ed.): Handbook of toxicology. New York: Sunders (1956).
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (4) not assignable
03-DEC-2004 (81)

Type: LD50
Species: rabbit
Value: 3.4 ml/kg bw

Year: 1973
GLP: no data

Remark: Original Reference:
5c, Patty, F. A. Industrial Hygiene and Toxicology, Vol. II. Interscience Publishers, New York, 1967, pp. 1904-1096
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (4) not assignable
20-DEC-2004 (1) (71)

Type: other

Year: 1946
GLP: no

Result: One rabbit died after application of 2.8 ml/kg to approximately 14 per cent of the body surface.
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (4) not assignable
20-DEC-2004 (64)

5.1.4 Acute Toxicity, other Routes

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: .5 undiluted
Exposure: Occlusive
Exposure Time: 24 hour(s)
No. of Animals: 6
Vehicle: other: no vehicle
PDII: .5
Result: slightly irritating
EC classificat.: not irritating

Method: other:16 CFR 1500.41.
Year: 1998
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: Species/strain: Rabbit/New Zealand White
Result:

Rabbit No.	E=Erythema O=Oedema	24 hours Intact	24 hours Abraded	72 hours Intact	72 hours Abraded
1	E	0	1	0	0
	O	0	0	0	0
2	E	0	0	0	0
	O	0	0	0	0
3	E	0	1	0	0
	O	0	0	0	0
4	E	0	1	0	0
	O	0	0	0	0
5	E	1	1	0	0
	O	1	1	0	0
6	E	1	2	0	1
	O	0	1	0	0

AVERAGE SCORE
- Erythema: 9/12 = 0.75
- Oedema: 3/12 = 0.25
REVERSIBILITY: yes
OTHER EFFECTS: no signs of toxicity or ill health

Test condition: TEST ANIMALS:
- Strain: the New Zealand White strain
- Sex: Female
- Source: Froxfield (U.K.) Ltd., Petersfield, Hampshire, England.
- Age: approximately 10 to 13 weeks of age
- Weight at study initiation: 2.3 to 2.9 kg

- Number of animals: 6
- Controls: no
ADMINISTRATION/EXPOSURE
- Preparation of test substance: direct
- Area of exposure: dorso-lumbar region, one to the left and one to the right of the spine. The area on the right was abraded using the tip of a scalpel blade to make minor incisions through the stratum corneum.
- Occlusion: Yes. The treatment sites were covered with "Elastoplast" elastic adhesive dressing backed with "Spleek" waterproof strapping.
- Vehicle: on
- Concentration in vehicle: not applicable.
- Total volume applied: 0.5 ml
- Postexposure period: 24 hr
- Removal of test substance: At the end of the exposure period, the treatment sites were washed with warm water (30°C to 40°C) to remove any residual test substance. The treated areas were blotted dry with adsorbent paper.

EXAMINATIONS
- Scoring system:

The Primary Irritation Index

PII	Classification
0	non-irritant
>0-2.0	mildly irritating
2.1-5.0	moderate irritant
5.1-6.0	moderate to severe irritant
>6.0	severe irritant

Based on Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, (1959). The association of Feed and Drug Officials of the United States.

- Examination time points:
24 and 72 hr

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (1) valid without restriction
21-DEC-2004 (23)

Species: rabbit
Concentration: .5 other: ml
Exposure: Occlusive
Exposure Time: 4 hour(s)
No. of Animals: 6
Vehicle: other: no vehicle
PDII: 0
Result: not irritating
EC classificat.: not irritating

Method: other: DOT 49 CFR 173.1200
Year: 1976
GLP: no
Test substance: other TS

Result: AVERAGE SCORE
- Erythema: 0
- Edema: 0

REVERSIBILITY: No. Under the conditions of this experiment there was no skin corrosion evident with compound diallyl phthalate using albino rabbits.
OTHER EFFECTS: not reported.

Test condition: TEST ANIMALS:
- Strain: not reported (albino rabbits)
- Sex: Male
- Source: Small Stock Industries, Pea Ridge, Arkansa.
- Age: not reported
- Weight at study initiation: not reported
- Number of animals: 6
- Controls: no

ADMINISTRATION/EXPOSURE
- Preparation of test substance: 0.5 ml/rabbit in a surgical gauze measuring 1 in. by 1 in. and two single layers thick.
- Area of exposure: 1 in. x 1 in.
- Occlusion: yes. The rubber dam material aids in maintaining the trust patches.
- Vehicle: no
- Concentration in vehicle: not applicable
- Total volume applied: 0.5 ml/rabbit
- Postexposure period: 4-h exposure, after that, the rubber dam and patches were removed.
- Removal of test substance: Following the initial reading at 4 hours, the test site was washed with soap and water to prevent further exposure.

EXAMINATIONS
- Scoring system:

Evaluation of Skin Reaction
Erythema and eschar formation:
No erythema 0
Very slight erythema (barely perceptible)..... 1
Well-defined erythema..... 2
Moderate to severe erythema..... 3
Severe erythema (beet redness) to slight echar formation (injuries in depth)..... 4
Edema formation:
No edema..... 0
Very slight edema (barely perceptible)..... 1
Slight edema (edges of area well-defined by definite raisings)..... 2
Moderate edema (raised approximately 1 millimeter) 3
Severe edema (raised more than 1 mm and extending beyond area of exposure)..... 4

Total score (total average erythema : total average edema)
Primary Irritation Index (total score / 4)

- Examination time points: 4 hr and 48 hr after starting the exposure.

Test substance: Ethyl Corporation (DAP)
Reliability: (2) valid with restrictions
03-DEC-2004 (43)

Species: rabbit
Concentration: .5 mg
Exposure: Semiocclusive

Exposure Time: 24 hour(s)
No. of Animals: 6
Vehicle: other: no
PDII: 2.29
Result: moderately irritating
EC classificat.: irritating

Method: Draize Test
Year: 1989
GLP: no
Test substance: other TS

Method: The test were conducted by the Draize procedure as decribed in 16 CFR 1500.41.
Result: AVERAGE SCORE
- Erythema: 36 / 6 = 6
- Edema: 18 / 6 = 3

REVERSIBILITY: not described
OTHER EFFECTS: not described
Test condition: TEST ANIMALS:
- Strain: Not described. Albino Rabbits
- Sex: not described
- Source: not described
- Age: not described
- Weight at study initiation: not described
- Number of animals: 6
- Controls: no

ADMINISTRATION/EXPOSURE
- Preparation of test substance: The material introduced under a square path of surgical gauze measuring 1 inch x 1 inch.
- Area of exposure: 1 inch x 1 inch
- Occlusion: not described
- Vehicle: no vehicle
- Concentration in vehicle: not applicable
- Total volume applied: 0.5 ml or 0.5 g / rabbit
- Postexposure period: 24 hrs and 72 hrs after starting exposure
- Removal of test substance: 24 hrs after starting exposure

EXAMINATIONS
- Scoring system:
by the Draize procedure

- Examination time points: 24 hr and 72 hr

Test substance: FMC Corporation (DAP, C-8013-1)

Specifications

Specific gravity: 1.117-1.123 at 20°C/20°C
Solubility in methanol: 1 cm^3 in 5 cm^3, clear-only slightly turbid
Acidity as acetic acid, % by weight: 0.1 max
Moisture(Karl Fischer): 0.1 max
Color APHA Pt-Co: 90 max
Odor: mild

Conclusion: The rationales of non confidential.

This study was run prior to the publication of the TSCA Good Laboratory Practice Standards in 1983. The certified mail

indicates that the report was not audited by FMC's Quality Assurance Unit and this study was not conducted according to currently approved laboratory methods.
Reliability: (3) invalid
Flag: non confidential
03-DEC-2004 (49)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Comment: not rinsed
No. of Animals: 6
Vehicle: none
Result: not irritating
EC classificat.: not irritating

Method: other: FHSA 16 CFR Section 1500
Year: 1975
GLP: no
Test substance: other TS
Method: The right eye of each rabbit was treated with 0.1 ml of Compound diallyl phthalate. The left eyes served as untreated controls. The eyes were examined at 1 and 4 hr and 1, 2, 3, 4 and 7-day intervals, and scored according to the Federal hazardous Substance Act, 16 CFR 1500, 1975.
Remark: Species/strain: Rabbit/New Zealand White (female)
Result: Ophthalmoscopic examination did not reveal any positive grades of redness or chemosis in any rabbits. DAP was not a primary eye irritant.
Test substance: Ethyl Corporation compound diallyl phthalate
Conclusion: Results indicate that diallyl phthalate is not a primary eye irritant.
Reliability: (2) valid with restrictions
03-DEC-2004 (43)

Species: rabbit
Result: not irritating
EC classificat.: not irritating

Method: other
Year: 1946
GLP: no

Remark: The compound was instilled into the rabbit's eye and the extent of irritation graded by the scoring method of Draize et al. (J. Pharmacol. and Exper. Therap. 82:377, 1944). No significant difference was found between the one hour scores of diallyl phthalate (score = 1) dibutyl phthalate (score = 2) and ethylene glycol (score = 2). All were relatively non-irritating and caused only a mild and transient conjunctivitis.
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Conclusion: No detail methods and results.
Reliability: (4) not assignable
03-DEC-2004 (64)

Species: rabbit

Concentration: undiluted
Dose: .5 ml
Exposure Time: 24 hour(s)
Result: not irritating
EC classificat.: not irritating

Method: other
Year: 1946
GLP: no

Remark: Species/strain: Rabbit (albino)

Undiluted 0.5 ml of DAP was applied to the centre of the cornea while the lids were retracted. About one minute later, the lids were released. Eighteen to 24 hours later, eye was examined in strong diffuse daylight, and then stained with fluorescein, and the injury scored.

The injury grade is 1, which means that 0.5 ml undiluted DAP hardly affected the eyes.
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Conclusion: No detail methods and results.
Reliability: (4) not assignable
03-DEC-2004 (15)

5.3 Sensitization

Type: Mouse local lymphnode assay
Species: mouse
No. of Animals: 16
Vehicle: other: acetone/olive oil 4:1
Result: sensitizing
Classification: sensitizing

Method: other: OECD Guide-line 429
Year: 2002
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS OF TEST
Animals bodyweight at start and finish(at schedule killed):

Table Change of Bodyweights

Dose Group (w/v)	Bodyweight (g) Day 0 (at start)	Day 5 (at finish)
0 (vehicle control)	18, 19, 20, 19	19, 20, 21, 20
0.5	21, 18, 20, 19	21, 19, 21, 19
5	17, 21, 17, 19	18, 21, 18, 19
50	19, 19, 18, 18	19, 19, 17, 18

Table DPM, DPM/Node and Stimulation Index(SI) by pooled approach

Dose Group	DPM	DPM/Node (8 nodes per group)	SI	Classification(a)
0 (vehicle control)	9005.91	1125.74	N/A	N/A
0.5	8838.93	1104.87	0.98	Negative
5	29087.39	3635.92	3.23	Positive
50	96725.08	12090.64	10.74	Positive

a, SI of 3.0 or greater indicates a positive result
N/A, Not applicable

Clinical Observation:
No clinical observations throughout the definitive test duration recorded for all individuals.
In the Range-Finder test, one mouse treated with the undiluted test material was dead on Day 1.

HISTORICAL POSITIVE CONTROL

The following historical positive controls were reported which indicates the test result is reliable.

1. Test Material : 4-Ethoxymethylene-2-phenyl-2-oxazolin-5-one
Start Date : 22-Aug-2001
Finish Date : 28-Aug-2001
Conc. %(w/v) : 0.10, 0.25, 0.50
Vehicle : 4:1 acetone/olive oil
SI : 14.01, 57.28, 42.18
Classification : Positive

2. Test Material : Penicillin G Sodium Salt
Start Date : 12-Dec-2001
Finish Date : 18-Dec-2001
Conc. %(w/v) : 10, 25, 50
Vehicle : Dimethyl Formamide
SI : 1.7, 4.1, 4.0
Classification : Positive

3. Test Material : Polyoxyethylenesorbitan monooleate
Start Date : 22-Aug-2001
Finish Date : 28-Aug-2001
Conc. %(w/v) : 0.25, 2.5, 25
Vehicle : 4:1 acetone/olive oil
SI : 1.22, 2.90, 4.33
Classification : Positive

4. Test Material : Eugenol
Start Date : 06-Mar-2002
Finish Date : 12-Mar-2002
Conc. %(w/v) : 5, 25, 50
Vehicle : 4:1 acetone/olive oil
SI : 1.7, 9.9, 0.2
Classification : Positive

5. Test Material : Cobalt Chloride Hexahydrate
Start Date : 07-Mar-2002
Finish Date : 13-Mar-2002

Conc. %(w/v) : 0.005, 0.05, 0.50
Vehicle : Dimethyl Formamide
SI : 0.7, 1.4, 6.2
Classification : Positive

Test condition: TEST ANIMALS:

- Strain: mice of CBA/Ca (CBA/CaBkl)

- Sex: female

- Source: B & K Universal Ltd, Hull, UK

- Age: eight to twelve weeks old

- Weight at study initiation: 15 to 25 g

- Number of animals: 16

- Housing conditions
Animal/Cage: One animal per cage.

Cage: Suspended solid-floor polypropylene cages furnished with softwood woodflasks.

Water and Food: Free access to mains tap water and food was allowed throughout the study.

Temperature: target ranges of 19 to 25°C.

Although there were some occasional deviations from these targets, they were considered not to have affected the purpose or integrity of the study.

Humidity: target ranges of 30 to 70%.

Although there were some occasional deviations from these targets, they were considered not to have affected the purpose or integrity of the study.

The rate of air exchange: ca. 15 changes per hour

Lighting: 12 hours continuous light (06:00 to 18:00) and 12 hours darkness.

- Diet: Certified Rat and Mouse Diet (Code 5LF2) supplied by International Product Supplies Limited, Wellingborough, Northants, UK)

- Acclimatization: 5 days or more

- Individual Identification: a unique number on each tail using a black indelible marker pen.

ADMINISTRATION/EXPOSURE

- Study type: Local Lymph Node Assay

- Vehicle: acetone/olive 4:1. This vehicle was chosen as it produced the most suitable formulation at the required concentration.

- Preparation of test substance:

The test material was freshly prepared in acetone/olive 4:1.

- Application
Animals per Group: 4
Dose Groups: 0% (control), 0.5%, 5%, or 50% w/v in acetone/olive oil 4:1.
Dose Volume: 25 µl
Application loci: the surface of each ear
Duration of dosing: daily on three consecutive days (Days 0, 1, 2)
Dosing Method: The test material was administered using an automatic micropipette. The tip of the pipette was used to spread the test material.

- Justification for choosing doses
Range-Finder Test: yes
- Animals: two mice
- Test Material: 25 µl of the undiluted test material and 50% w/v in acetone/olive oil 4:1.
- Duration of dosing: daily in three consecutive days
- Application loci: dorsal surface of each ear daily
- Observation: daily in three consecutive days for administration and after that 2 consecutive days.
- Record: Any signs of toxicity or ill health. Bodyweight on Day 0 (prior to dosing) and on Day 5 (of surviving mouse).
- Result: The test material would not produce systemic toxicity or excessive local irritation at the maximum concentration of 50% w/v.
- Choice of doses: The highest concentration (50% w/v) and two lower concentrations (5%, 0.5% w/v) were chosen.

A further group of four mice received the vehicle alone in the same manner.

-3H-Methyl Tymidine Administration
Administration day: Day 5 post administering test materials
Administration locus: tail vein
Solution: 250 µl of PBS containing 3HTdR(80 µCi/ml, specific activity 2.0 Ci/mmol, Amersham Pharmacia Biotech UK LTD, a total of 20 µCi) to each mouse

-Observation
Clinical Observations: daily. Signs of Toxicity or ill health during the study were recorded.

Bodyweights: Day 0 (prior to dosing) and Day 5 (prior to termination).

-Terminal Procedures
Termination: 5 hours post administration of 3HTdR by carbon dioxide asphyxiation.

Excisation: Draining auricular lymph nodes from every mice and pooled for each dose group. Adding 1 mol of PBS per each dose group.

POSITIVE CONTROL
- Test Material:
alpha-Hexylcinnamaldehyde

- Application:
Three groups, each of four animals, were treated with 50 µl of the test material (25 µl per ear) as a solution in acetone/olive oil 4:1 at concentrations of 5%, 10% and 50% w/v. A further control grope of four animals were treated with acetone/olive oil 4:1 alone.

HISTORICAL POSITIVE CONTROL:

4-Ethoxymethylene-2-phenyl-2-oxazolin-5-one, Penicillin G Sodium Salt, Polyoxyethylenesorbitan monooleate, Eugenol, and Cobalt Chloride Hexahydrate were reported.

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
20-DEC-2004 (34)

5.4 Repeated Dose Toxicity

Type: Sub-acute
Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: gavage
Exposure period: Five days per week for 13 weeks
Frequency of treatment: One administration/day
Post exposure period: one day after the final administration
Doses: 0, 25, 50, 100, 200, and 400 mg/kg bw/day
Control Group: yes, concurrent vehicle

Method: other
Year: 1985
GLP: yes
Test substance: other TS

Result: NOAEL: 50 mg/kg bw (females), not determined (males)
LOAEL: 100 mg/kg bw (females), not determined (males)

- Primary target organ: Liver

- Lesion: periportal lesions of the hepatic lobules

- Histologic Sign : Cirrhosis--hepatic alterations: periportal hepatocellar necrosis and fibrosis, bile duct hyperplasia, and hepatocellular nodular hyperplasia.

- Other:
Only mild hepatocelluar alterations at 100 mg/kg.

ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX: See Table Dose vs Death

- Time of death: See TABLE Dose vs Death.

- Number of deaths at each dose: See TABLE Dose vs Death.

TABLE Dose vs Death

Dose (mg/kg)	Deaths(a)	Mean Body Weight (g)			Final Weight Relative to Vehicle Controls (%)
		Initial	Final	Change	
MALE					
0 (control)	0/10	186	311	+125	--(c)
25	0/10	185	321	+136	103
50	0/10	189	322	+133	104
100	0/10	188	312	+124	100
200	0/10	186	303	+117	97
400	8/10(b)	184	273	+ 89	88
FEMALE					
0 (control)	0/10	134	192	+ 58	--
25	0/10	133	202	+ 69	105
50	0/10	134	197	+ 63	103
100	0/10	135	199	+ 64	104
200	0/10	133	197	+ 64	103
400	0/10	134	191	+ 57	101

(a) Number deaths/number initial in group
(b), Weeks of death: 2,2,8,10,10(moribund kill),10,12,12(moribund kill)
(c) no data are presented due to the 100% mortality in this group.

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:

- Mortality and time to death: See TABLE Dose vs Death.

- Body weight gain: See TABLE Dose vs Death.

- Food/water consumption:

Groups		Mean consumption	Time
Dose	Sex	(g/animal/day)	
all	M	24	overall
all	F	24	overall
400 mg/kg	M/F	Lo	weeks 1-3
		Me,Hi	after that
other than 400 mg/kg	M/F	Me	weeks 1-3
vehicle control	M/F	Me	

Me, medium consumption; Lo, low consumption; Hi, High consumption

- Clinical Sign:

Groups dose (mg/kg)	Sex	Time	Clinical Signs
400	M/F	Throughout	Diarrhea Rough hair coat or alopecia around the head Hunched posture General emaciation(a)
200	M/F	Less frequently	No clinical signs

(a)The emaciation occurred most frequently in males.

- Examination at necropsy:

Groups dose (mg /kg bw)	Sex	Number	Organ	Signs
400	M	all	Liver	Enlarged, mottled(a),
400	F	most		and pale; Rough, granular,
200	M	5/10		or pitted surface
400	M(dead)	many	Lung	Darkened or bright
400	F		Kidneys	Greenish-brown coloration

-- Histologic examination:
Primary target organ: Liver

TABLE Incidences of Liver Lesions

Dose (mg/kg)	Lesion and Incidences (a)				
	HEP	NEC	FIB	CIR	HYP
Male:					
0(b)	0/10	0/10	0/10	0/10	0/10
50(c)	3/10(e)	0/10	0/10	0/10	0/10
100	2/10*	0/10	0/10	0/10	0/10
200	9/10	5/10	5/10	0/10	8/10
400(d)	--	--	--	10/10(f)	--
Female:					
0	0/10	0/10	0/10	0/10	0/10
50	0/10	0/10	0/10	0/10	0/10
100	8/10	0/10	0/10	0/10	0/10
200	10/10	7/10	4/10	0/10	0/10

400(d)	--	--	--	10/10	--

HEP, Periportal Hepatocellular Alterations
NEC, Periportal Necrosis
FIB, Periportal Fibrosis
CIR, Periportal Cirrhosis
HYP, Bile Duct Hyperplasia
(a) Incidences are presented as the number of animals with the specified lesion over the number of animals in the group.
(b) Vehicle controls
(c) Livers from the lowest dose group (25 mg/kg) were not examined because of the absence of (or the presence of only minimal) hepatic changes at 50 mg/kg.
(d) The presence of cirrhosis precluded the diagnosis of the other liver lesions listed in this table.
(e) HEP were observed with decreasing frequency and severity at dose as low as 50 mg/kg (males) or 100 mg/kg (females). HEP were characterized by hepatocellular basophilia, cellular and nuclear hypertrophy, and nuclear hyperchromatism. The severity of HEP were subjectively graded as moderate to severe in both sexes 200 mg/kg and mild at lower doses.
(f) Acute, necrotizing colitis, characterized by the loss of surface and glandular epithelium, varying degrees of mucosal and submucosal edema, and acute inflammatory cell infiltration, was diagnosed in seven of the eight early-death males at 400 mg/kg.
In addition, three of these male rats exhibited multifocal renal cortical tubular necrosis.

Test condition: TEST ORGANISMS: F344/N rats

- Source: Frederick Cancer Research Center (Frederick, MD)

- Age: 8 weeks when placed on study.

- Weight at study initiation:

TABLE DOSE AND INITIAL WEIGHT

Dose (mg/kg)	Size per Dose Group	Initial Mean Body Weight (g)
MALE		
0 (control)	10	186
25	10	185
50	10	189
100	10	188
200	10	186
400	10	184
FEMALE		
0 (control)	10	134
50	10	133
100	10	134
200	10	135
400	10	133
600	10	134

- Number of animals: See Weight at study initiation.

ADMINISTRATION / EXPOSURE

- Duration of test/exposure: 5 days per week for 13 weeks

- Type of exposure: Gavage

- Post exposure period:
1 day after the final administration.

- Vehicle: corn oil

- Concentration in vehicle: make up to 3.33 ml/kg of the total volume containing the nominal doses.

- Total volume applied: 3.33 ml/kg. Each animal received a total gavage volume of 3.33 ml/kg, based on weekly group mean body weights.

- Doses: See "Weight at study initiation".

CLINICAL OBSERVATIONS AND FREQUENCY:
Moribund animals and survivors at the end of the 13-week studies were killed for examination. The 13-week survivors were fasted overnight before being killed.

- Clinical signs: daily

- Mortality/Moribundity:
Checked twice daily Mon. through Fri., once per day on the weekends.

- Body weight: not described, but reported on the mean body weight of the initial, interim(7), and final day.

- Food consumption: not described

- Water consumption: not described

- Ophthalmoscopic examination:
not described

- Hematology: not described

- Biochemistry: not described

- Urinalysis: not described

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):

- Macroscopic: Necropsy performed on all animals.

- Microscopic:
0, 50, 100, 200, and 400 mg/kg groups:
kidneys
colon
liver
0, 400 mg/kg groups:

mandibular lymph node
salivary gland
sternebrae including marrow
tyroid gland
parathyroids
colon
small intestine
prostate/testes for male
ovaries/uterus for female
lungs and bronchi
heat
esophagus
stomach
brain
thymus
trachea
pancreas
spleen
pituitary gland
eyes (if glossly abnormal)
mammary gland
gross lesions
urinary bladder
adrenal glands

STATISTICAL METHODS:
Test substance: Supplier: Hardwicke Chemical Company (Elgin, SC)
Lot No.: 25-121
Purity: 99%(GC)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
21-DEC-2004 (70)

Type: Sub-acute
Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: gavage
Exposure period: Daily for 14 days
Frequency of treatment: one administration/day
Doses: 0, 50, 100, 200, 400, and 600 mg/kg bw/day
Control Group: yes, concurrent vehicle

Method: other
Year: 1985
GLP: yes
Test substance: other TS

Result: NOAEL 50 mg/kg bw/day(female)
LOAEL 50 mg/kg bw/day(male), 100 mg/kg bw(female)

ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX

- Time of death: See TABLE Dose vs Death.

- Number of deaths at each dose: See TABLE Dose vs Death.

TABLE Dose vs Death

Dose	Death(a)	Days of	Final Weight

(mg/kg)		death	Relative to Vehicle Controls (%)
MALE			
0 (control)	5/5	-	-
50	5/5	-	97
100	5/5	-	95
200	5/5	-	88
400	2/5	7, 13, 14	65
600	0/5	3, 4, 4, 5, 5	(b)
FEMALE			
0 (control)	5/5	-	-
50	5/5	-	98
100	5/5	-	101
200	5/5	-	99
400	4/5	8	83
600	0/5	4, 4, 5, 5, 5	(b)

(a) Number death/number initial in group
(b) No data are presented due to the 100% mortality in this group.

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:

- Mortality and time to death: See TABLE Dose vs Death.

- Clinical signs:

TABLE Examination at Necropsy

Dose (mg/kg)	Cecums	Spleens	Liver	Urinary bladder
Clinical Signs	Enlarged (a)	Enlarged	Enlarged, dark, mottled. (b)	Hemorrhagic lesions (c)
-Male:				
0		n	n	n
50	Y	n	2/5 (e)	n
100	Y	n	Y (e,d)	n
200	Y	Y	Y	n
400			Y	n
600			Y	n
Female:				
0		n	n	n
50		n	n	n
100		n	Y (e,d)	n
200	Y	Y	Y	n
400			Y	n
600			Y	n

Y, Observed; n, Not

(a), ca. twice normal size

(b), Not observed in one male at 200-600 mg; (d), Observed

in a few animals; 2/5, Observed in two animals. ;Small, yellowish spots on the surface of the liver in many rats. (e), Not grossly enlarged, less severe, infrequent yellowish spots.

(c), This clinical sign was observed in the Single Dose Administration Studies in the series of the tests described in the same report.

- Body weight gain: See TABLE Dose vs Death.

- Food/water consumption: Not reported.

- Ophthalmoscopic examination: Not reported.

- Clinical chemistry: Not reported.

- Haematology: Not reported.

- Urinalysis: Not reported.

- Organ weights: Not reported.

STATISTICAL RESULTS:

NOAEL(14-Days Repeated Dose) of the liver abnormality for male rats is less than 50 mg/kg; and that for female rats, from 50 to 100 mg/kg.

LOAEL(14-Days Repeated Dose) of it for male rats is 100 mg/kg; and that for female rat, 100 mg/kg.

Test condition: TEST ORGANISMS: F344/N rats

- Source: Frederick Cancer Research Center (Frederick, MD)

- Age: 10 weeks when placed on study.

- Weight at study initiation:
TABLE DOSE AND INITIAL WEIGHT

Dose (mg/kg)	conc. in vehicle (mg/ml)	volume of administer (ml)	Size per Dose Group	Initial Mean Body Weight (g)
MALE				
0 (control)	0	12	5	128
50	50	1	5	128
100	50	2	5	128
200	50	4	5	128
400	50	8	5	128
600	50	12	5	128
FEMALE				
0 (control)	0	12	5	103
50	50	1	5	103
100	50	2	5	103
200	50	4	5	103
400	50	8	5	103
600	50	12	5	103

- Number of animals: See Weight at study initiation.

ADMINISTRATION / EXPOSURE

- Duration of test/exposure: 14 concecutive days

- Type of exposure: Gavage

- Post exposure period: 14 days after administration

- Vehicle: corn oil

- Concentration in vehicle: 50 mg/l. See also "Weight at study initiation".

- Total volume applied: See "Weight at study initiation".

- Doses: See "Weight at study initiation".

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: daily observed
- Mortality: daily observed
- Body weight: days 0 (prestudy), 7 and 14 days
- Food consumption: not described
- Water consumption: not described
- Ophthalmoscopic examination: not described
- Haematology: not described
- Biochemistry: not described
- Urinalysis: not described

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: Necropsy performed on all animals.
- Microscopic: No tissue examined microscopically.

OTHER EXAMINATIONS: not examined histopathologically

Test substance: Supplier: Hardwicke Chemical Company (Elgin, SC)
Lot No.: 25-121
Purity: 99%(GC)

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

03-DEC-2004 (70)

Type: Sub-acute
Species: rat **Sex:** male/female
Strain: Crj: CD(SD)
Route of administration: gavage
Exposure period: 40 - 54 days
Post exposure period: 1 day
Doses: 0, 16.7, 50, 150 mg/kg
Control Group: yes, concurrent vehicle
NOAEL: 50 mg/kg bw

Method: other: OECD Test Guidline No. 421
Year: 2004
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result:

This study was conducted for screening for potential adverse effect on reproduction including embryo/foetal development in the rat, compling with OECD Guidelines for Testing of Chemicals No 421.

NOAEL (NOEL): 50 mg/kg bw/day (dystocia)

ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX:

TABLE

Sex	Dose Group	Dose (mg/kg bw/day)	Actual Total Dose (g) Mean	SD
Male	1	0	0	0
	2	16.7	295	21
	3	50	895	51
	4	150	2552	194
Female	1	0	0	0
	2	16.7	187	43
	3	50	607	39
	4	150	1745	264*

* total doses for groups dead or killed in extremis: 1490, 1710, 1420 g

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:

- Mortality and time to death:

Dose (mg/kg bw/day)	Number of deaths/Size of group			
	Maturation Phase		Littering Phase	
	Males	Females	Males	Females
0	0/10	0/10	0/10	0/10
16.7	0/10	0/10	0/10	0/10
50	0/10	0/10	0/10	0/10
150	0/10	0/10	0/10	3/10*

* On the day 37, a female was killed in extremis.
On the day 38, a female was found dead and another female was killed in extremis.

- Clinical signs:

- Body weight gain:

Table: Individual Bodyweight (g)

Dose mg/kg bw/day	Rat No.	Week 1	2	3	4	5	6	7

	MALE:							
0	1	325	369	386	405	427	449	467
	2	357	401	438	465	501	528	542
	3	351	391	431	456	492	521	539
	4	349	390	429	455	489	502	498
	5	324	366	392	415	437	450	460
	6	353	407	431	450	479	515	531
	7	334	382	400	420	457	467	489
	8	364	429	470	482	513	542	561
	9	330	373	416	437	469	482	501
	10	320	371	402	418	450	482	422
16.7	11	352	400	439	465	496	519	536
	12	345	367	442	474	512	552	585
	13	327	364	381	410	437	460	479
	14	320	361	392	415	442	468	486
	15	354	405	441	463	492	520	522
	16	355	413	449	486	524	536	563
	17	334	380	415	435	462	489	503
	18	321	361	386	409	437	468	473
	19	362	417	449	492	535	560	567
	20	332	358	371	379	402	418	496
50	21	366	411	422	469	506	518	536
	22	355	415	450	486	515	536	556
	23	327	378	415	458	494	517	536
	24	327	350	378	404	436	456	468
	25	320	362	387	406	434	456	472
	26	358	405	437	450	482	517	537
	27	327	369	399	421	460	490	506
	28	327	370	406	417	444	469	482
	29	339	381	415	430	462	494	501
	30	355	410	449	486	518	538	551
150	31	349	356	381	400	428	438	443
	32	331	366	396	416	435	452	458
	33	335	351	371	397	427	454	455
	34	363	393	424	465	493	523	537
	35	316	329	348	365	378	407	417
	36	308	348	379	407	426	463	475
	37	362	426	466	501	528	568	588
	38	328	373	403	420	439	473	489
	39	353	378	393	408	434	450	462
	40	329	375	393	401	432	453	468
	FEMALE:							
0	41	216	233	242				
	42	232	251	264				
	43	200	216	225				
	44	219	239	255				
	45	212	231	247				
	46	200	214	225				
	47	220	241	244				
	48	230	255	270				
	49	234	250	251				
	50	207	217	215				
16.7	51	229	236	265				
	52	223	231	261				
	53	230	242	275				
	54	202	223	237				
	55	196	221	232				
	56	217	230	240				
	57	230	249	263				

	58	223	253	270
	59	228	246	253
	60	213	227	240
50	61	224	228	251
	62	213	238	250
	63	224	236	260
	64	241	254	268
	65	225	224	253
	66	233	260	270
	67	218	236	244
	68	229	249	240
	69	221	233	267
	70	226	240	253
150	71	220	246	267
	72	222	238	265
	73	231	255	275
	74	206	217	234
	75	207	228	244
	76	217	244	264
	77	202	209	225
	78	225	244	247
	79	219	234	268
	80	227	244	251

- Gross pathology:

TABLE Macroscopic Findings

Sex	Dose (mg/kg bw/day)	Clinical Signs	Counts
Male	0	No abnormalities	
	16.7	No abnormalities	
	50	No abnormalities	
	150	Liver	
		- areas of patchy pallor	5/10
		- accentuated lobular pattern	2/10
Female	0	No abnormalities	
	16.7	No abnormalities	
	50	No abnormalities	
	150	Liver	
		- areas of patchy pallor	8/10
		- accentuated lobular pattern	3/10
		Stomach	
		- ulcerated with digested blood present	1/10

- Histopathology:

Mononuclear cell foci in liver was observed in almost animals at all dose grous including control group.

The following findings were obserbed sepcificaly in the

highest dose group of male and female rats:

Organ - pathology	Animal numbers (male, female)
Liver	
- Peripotal hepatocyte basophilia	(9/10 , 1/10) *
- Bile duct proliferation	(6/10 , 9/10) ***
- Periportal fibrosis	(6/10 , 9/10) ***
- Periportal hepatocyte necrosis	(5/10 , 7/10) ***
Stomach	
- Area mucosal ulceration	(0/10 , 1/10) *
- Autolysis	(0/10 , 1/10) *
Prostate	
- Chronic inflammatory cell foci	(2/10 , -/-)
Uterus/cervix	
- Areas myometrial haemorrhage/fibrosis	(-/- , 10/10) ***
- Dilatation horn	(-/- , 3/10) ***
- Endometrial proliferation	(-/- , 3/10) ***
- Haemorrhagic contents	(-/- , 2/10) **

* counts of animals dead or killed in extremis

Test condition: This study was conducted for screening for potential adverse effect on reproduction including embryo/foetal development in the rat, compling with OECD Guidelines for Testing of Chemicals No 421.

TEST ORGANISMS

- Age: not described

- Weight at study initiation:
  308 g to 366 g (males);
  196 g to 234 g (females)

- Number of animals:80.

10 Males and 10 Females per dose group, 4 dose groups.

ADMINISTRATION / EXPOSURE

- Duration of test/exposure:

  14 days in maturation
  Max. 14 days in mating
  approx. 22 days in gestation
  4 days post partum in lactation

- Type of exposure: gavage

- Post exposure period: 1 day.

On Day 5 post partum, all surviving animals were killed and

exmained macroscopically

- Vehicle: corn oil

- Concentration in vehicle: 0, 3.34, 10.0, and 30.0 g/L

- Total volume applied: 5 ml/kg bw per dose

- Doses: 0, 16.7, 50, and 150 mg/kg bw per dose

SATELLITE GROUPS AND REASONS THEY WERE ADDED: not reported.

CLINICAL OBSERVATIONS AND FREQUENCY:

- Clinical signs: reported.

All animals were observed daily, immediately before dosing, immediately after dosing and one hour after dosig, for clinical signs of toxicity.

- Mortality: reported.

All animals were checked twice daily during the normal working week and once daily on weekends and pyblic holidays.

- Body weight: reported.

During the maturation and mating period the parental generation animals were weighed weekly. Following mating the parental males were weekly until termination. Parental generation females showing evidence of mating were weighed on Days 0, 7, 14 and 20 post coitum. Parental generation females with a live litter weighed on Days 1 and 4 post partum.

- Food consumption: reported.

During the maturation period (which continued following mating for males) food consumption was recorded weekly for each cage of parental generation adults. For parental generation females showing evidnce of mating, food consumption was recorded for the periods covering Days 1 to 7, 7 to 14 and 14 to 20 post coitum. For parental generation females with live litters, food consumption was recorded for the period covering Days 1 to 4, pst partum.

- Water consumption: not reported.

- Ophthalmoscopic examination: not reported.

- Haematology:

- Biochemistry:

- Urinalysis:

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):

- Macroscopic:

The following list of organs were examined at histopathology for all adult males and female from the control and high dose levels and from adult males and females from the low and intermediate dose levels were applicable:

Cagulating glands, Pituitary, Epididymides, Ovaries, Prostate, Uterus/cervix, Seminal vesicles, Vagina, Testis, Stomach, Liver.
Stomach and Liver were examined from adult males and females from the low ad interediate dose groups.

- Microscopic: not described.

OTHER EXAMINATIONS:

Completion of parturition, the number of live and dead offspring.

All live offspring were observed for detachement of pinna and tested for their ability to surface righting reflex.

STATISTICAL METHODS:

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)
Reliability: (2) valid with restrictions
17-DEC-2004 (37)

Type: Sub-acute
Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: Five days per week for 13 weeks
Frequency of treatment: One administration per day
Post exposure period: None
Doses: 0; 25; 50; 100; 200; 400 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL: 400 mg/kg bw

Method: other
Year: 1983
GLP: no data
Test substance: other TS

Result: A single death occurred in male mice in the 400 mg/kg bw group and in female mice in every dose including the control. None of the deaths, however, were considered to be due to administration of chemical. Mean body weight gain in male mice administered was depressed 12 % relative to controls, but the variabilities in body weight gain amongst groups and the small absolute change over the 13-week period suggest that the perceived difference was of no toxicological
significance. Neither gross nor microscopic alteration related to chemical administration were observed in any of the high-dose mice. Doses of 150 and 300 mg/kg bw DAP were selected for the chronic test because of deaths in the 14-day study 400 and 600 mg/kg bw, although neither deaths

nor pathologic lesions related to chemical administration were produced by 400 mg/kg DAP in 13-week study.
Test substance: Hardwicke Chemical Company (Lot No. 25-121)
Purity: 99% (GC)

Reliability: (2) valid with restrictions
03-DEC-2004 (69)

Type: Sub-acute
Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: Daily for 14 days
Frequency of treatment: One administration/day
Doses: 0; 50; 100; 200; 400; 600 mg/kg bw/day
Control Group: yes, concurrent vehicle
NOAEL: 200 mg/kg bw
LOAEL: 400 mg/kg bw

Method: other
Year: 1983
GLP: no data
Test substance: other TS

Result: Deaths occurred in groups of mice receiving 400 or 600 mg/kg diallyl phthalate but not in groups receiving lower doses.

Mean body weight gains of dosed mice were not depressed relative to controls. No chemical-related lesions were observed at necropsy.
Test substance: Hardwicke Chemical Company (Lot No. 25-121)
Purity: 99% (GC)
Reliability: (2) valid with restrictions
17-DEC-2004 (69)

5.5 Genetic Toxicity 'in Vitro'

Type: Bacterial reverse mutation assay
System of testing: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537;Escherichia coli strains WP2uvrA/pKM101
Concentration: -S9:0, 1.22, 4.88, 19.5, 78.1, 313, 1250, 5000 ug/plate
Metabolic activation: with and without
Result: ambiguous

Method: other: OECD Guidelines No.471 and 472
Year: 2000
GLP: yes
Test substance: other TS

Method: Statistical Methods: No statistical analysis.
-Metabolic activation system:

S9 from rat liver, induced with Phenobarbital and 5,6-benzoflabone.

ADMINISTRATION:

-Number of replicates: 2

-Plates per test: 2

-Application: pre-incubation

-Positive control groups and treatment:

-S9mix, 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98, WP2), Sodium azide (TA1535) and 9-Aminoacridine (TA1537);

+S9mix, 2-Aminoanthracene (five strains)

-Solvent: DMSO

Result: Table 1. Mutagenicity of DAP with and without metabolic activation (first run)

- Conc. µg/	Number of Revertants/plate									
Plate	Base-substitution						Frame-shift			
	TA100		TA1535		WP2uvrA /pKM101		TA98		TA1537	
	S9-	S9+	S9-	S9+	S9-	S9+	S9-	S9+	S9-	S9+
DMSO	136	146	9	9	63	91	21	30	6	9
1.22	124	143	5	9	57	109	24	18	2	6
	106	156	7	13	59	94	21	28	5	5
	115	150	6	11	58	102	23	23	4	6
4.88	101	164	7	15	66	101	17	29	5	13
	142	141	7	10	64	104	14	26	6	7
	122	153	7	13	65	103	16	28	6	10
19.5	117	165	8	8	70	98	20	30	5	8
	114	151	6	10	60	85	14	26	3	2
	116	158	7	9	65	92	17	28	4	5
78.1	131	145	7	10	71	99	20	28	5	5
	127	144	7	6	64	98	20	24	5	8
	129	145	7	8	68	99	20	26	5	7
313	0*	104	0*	13	33*	94	13*	21	0*	6
	0*	106	0*	13	40*	99	14*	23	0*	7
	0*	105	0*	13	37*	97	14*	22	0*	7
1250	0*	43*	0*	3*	28*	91	13*	0*	0*	3*
	0*	51*	0*	5*	31*	94	9*	0*	0*	2*
	0*	47*	0*	4*	30*	93	11*	0*	0*	3*

5000	0*	0*	0*	0*	11*	155	8*	0*	0*	0*
	0*	0*	0*	0*	18*	123	10*	0*	0*	0*
	0*	0*	0*	0*	15*	139	9*	0*	0*	0*
Judgement	-	-	-	-	-	-	-	-	-	-
Specific mutagen										
Positive	AF2	2-AA	NaN3	2-AA	AF-2	2-AA	AF-2	2-AA	9-AA	2-AA
Control	735	1354	485	343	1467	1094	570	460	574	227

*Growth inhibition was observed.

Table 2. Mutagenicity of DAP with and without metabolic activation (second run)

- Conc. µg/	Number of Revertants/plate									
Plate	Base-substitution						Frame-shift			
	TA100		TA1535		WP2uvrA /pKM101		TA98		TA1537	
	S9-	S9+	S9-	S9+	S9-	S9+	S9-	S9+	S9-	S9+
DMSO	130	137	8	10	50	90	15	25	9	10
4.88	142		8		38		14		6	
	141		3		57		6		10	
	142		6		48		10		8	
9.77	133		8		41		18		13	
	156		7		66		15		6	
	122		9	13	54		17		10	
19.5	136	144	7	9	53		11	18	13	9
	120	139	8	8	52		20	28	3	8
	128	142	8	9	53		16	23	8	9
39.1	134	171	9	8	61		11	33	8	7
	145	166	8	10	38		16	20	3	14
	140	169	9	9	50		14	27	6	11
78.1	114	143	11	7	51	67	15	23	5	11
	139	174	13	8	56	81	20	28	7	10
	127	159	12	8	54	74	18	26	6	11
156	113*	145	7*	7	45	84	20	23	6*	3
	129*	123	7*	10	39	77	16	17	2*	8

	121*	134	7*	9	42	81	18	20	4*	6
313	81*	113	8*	8	37*	83	16*	22	7*	5
	90*	134	9*	9	30*	83	17*	21	1*	6
	86*	124	9*	9	34*	83	17*	22	4*	6
625		94		7		92		8*		6
		97		6		89		7*		8
		96		7		91		8*		7
1250		40*		2*		97		0*		3*
		69*		8*		119		0*		2*
		55*		5*		108		0*		3*
2500						131				
						144				
						138				
5000						146				
						122				
						134				
Judgement	-	-	-	-	-	-	-	-	-	-

Specific mutagenicity

Positive	AF2	2-AA	NaN3	2-AA	AF-2	2-AA	AF-2	2-AA	9-AA	2-AA
Control	740	1472	474	339	1617	1224	504	462	673	240

*Growth inhibition was observed.

Test substance: Source:Tokyo Kasei Kogyo (DAP) Purity: 98 % (Lot No. GD01)

Conclusion: Bacterial gene mutation is negative with and without metabolic activation excluding that it is weakly positvie in Escherichia coli strain WP2uvrA/pKM101 with metabolic activation.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

17-DEC-2004 (65)

Type: Ames test

System of testing: Salmonella typhimurium, TA1535, TA1537, TA98, and TA100

Concentration: 0, 33, 100, 333, 1000, 3333, 10000 µg/plate; 0, 1, 3.3, 10, 33, 100, 333, 1000, 3333 µg/plate

Metabolic activation: with and without

Result: negative

Method: other

Year: 1985

GLP: yes

Test substance: other TS

Method: Solvent: DMSO
Activator:
10% HLI, Aroclor 1254-induced Syrian hamster liver S-9

10% RLI, Aroclor 1254-induced rat liver S-9

Method:
Overnight cultures of Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 were used without activation (NA) or with the 9,000g supernatant of liver homogenates (S-9 fraction) from Aroclor 1254-induced male Sprague-Dawley rats (RLI) or male Syrian hamsters (HLI). Approximately 108 bacteria were mixed with 0.5 mL of either 0.1M sodium phosphate buffer (pH 7.4) or S-9 mix (containing 10% S-9 fraction), and 50 or 100 µL of the test chemical or solvent, in each of 3 tubes. This mixure was incubated at 37°C for 20 minutes, following which 2 mL of molten top agar containing a trace amount of biotin and a growth-limiting amount of histidine (0.05mM each) was added. The mixture was then poured onto minimal agar plates and incubated at 37°C for 48 hours, after which time histidine-revertant colonies were counted.

All chemicals in this study were tested at 5 does levels, separated by half-log intervals. The high dose was 10 mg/plate unless limited by solubility (determined visually) and/or toxicity. The final dose level selection was based on the results of a preliminary range-finding study conducted with TA100 in the presence and absence of S9.

Positive controls:
-S9 mix: sodium azide (TA1535, TA100),
4-nitro-o-phenylenediamine (TA98), 9-aminoacridine (TA1537)
+S9 mix: 2-aminoanthracene (all strains)

Testing was performed at two laboratories: Case Western Reserve University (CWR) and EG&G Mason Research Institute (EGG).

Result: As the first and second (repeat) experiments yielded similar results, the authors only presented the results from the second experiment.

In both laboratories, there was no reproducible dose-related increase in the number of histidine-independent colonies over the spontaneous incidence.

Table: Mutagenicity of diallyl phthalate in Ames test with and without metabolic activation (CWR laboratory)

	Dose (µg/plate)							
	0	33	100	333	1000	3333	10000	POS
TA100:								
NA	125 ±7.3	167 ±15.4	131 ±12.2	97 ±12.5	166 ±14.0	104 ±17.5		554 ±76.7
10% HLI	237 ±6.8	280 ±6.1	286 ±5.7	212 ±8.3	212 ±6.5	227 ±7.0		2030 ±222.9
10% RLI	244 ±12.5	287 ±18.2	305 ±15.6	121 ±9.2	72 ±9.5	27 ±3.6		1181 ±133.1
TA1535:								
NA	6 ±0.3	4 ±0.9	4 ±1.3	4 ±0.7	2 ±1.5	1 ±0.3		95 ±5.2

10% HLI	7	10	13	15	2	2		56
	±1.2	±2.6	±1.5	±2.6	±1.2	±1.2		±5.2
10% RLI	7	7	8	6	2	2		331
	±1.2	±0.7	±1.8	±1.5	±0.7	±0.6		±61.3
TA1537:								
NA	3	3	3	3	3	3		28
	±1.2	±0.6	±0.3	±0.6	±1.2	±0.9		±6.2
10% HLI	10	11	16	11	4	3		125
	±1.7	±3.0	±2.8	±2.6	±1.8	±1.5		±6.1
10% RLI	7	7	5	3	1	0		297
	±0.3	±1.5	±0.9	±0.9	±0.9	±0.3		±60.5
TA98:								
NA	14	12	12	7	11	13		156
	±2.5	±1.5	±2.0	±2.5	±2.6	±5.1		±8.8
10% HLI	18	12	7	5	3	1		1268
	±1.2	±0.9	±0.7	±1.2	±0.7	±0.0		±47.6
10% RLI	19	27	15	7	7	t		554
	±1.8	±1.2	±6.1	±0.7	±2.5			±19.1

-POS: Positive control. -S9 mix: TA1535, TA100 sodium azide 3.3 µg/plate; TA98 4-nitro-o-phenylenediamine 3.3 µg/plate; TA1537 9-aminoacridine 33 µg/plate. +S9 mix: TA100, TA1535, TA1537 and TA98 2-aminoanthracene 1.0, 2.0, 2.0 and 1.0 µg/plate, respectively
t: Complete clearing of background lawn, colonies not counted

Table: Mutagenicity of diallyl phthalate in Ames test with and without metabolic activation (CWR laboratory)

	Dose (µg/plate)								
	0	1.0	3.3	10	33	100	333	1000	POS
TA100:									
NA	113			121	130	127	112s	124s	1195
	±5.6			±14.2	±6.1	±4.5	±8.7	±5.8	±13.2
10% HLI	156	161	137	137	119	89			1151
	±11.1	±12.9	±0.7	±3.0	±11.9	±0.7			±49.7
10% RLI	161	167	158	152	136	100			1202
	±7.0	±6.2	±8.5	±4.0	±5.8	±2.4			±61.9
TA1535:									
NA	18			14	18	21	14s	24s	948
	±3.4			±2.3	±4.0	±3.2	±2.1	±2.8	±13.3
10% HLI	14	12	13	8	11	9			70
	±2.1	±1.0	±1.5	±0.7	±1.5	±1.0			±8.1
10% RLI	13	15	11	12	8	11			78
	±2.3	±2.1	±2.0	±0.9	±1.5	±0.9			±5.4
TA1537:									
NA	4			6	6	6	4s	6s	79
	±1.7			±1.2	±0.9	±0.7	±1.5	±1.2	±5.8
10% HLI	8	8	7	6	6	9			96
	±1.7	±1.7	±0.7	±1.2	±1.5	±3.4			±5.1
10% RLI	11	7	9	11	8	7			169
	±2.0	±1.5	±0.0	±2.7	±0.5	±0.0			±11.8

TA98:

NA	10			19	16	19	14	17	1168
	±1.9			±2.0	±2.6	±2.2	±2.2	±3.2	±33.3
10% HLI	28	32	30	29	25	23			1208
	±1.8	±2.3	±3.2	±2.4	±4.9	±3.2			±8.5
10% RLI	27	28	33	32	23	19			1066
	±2.2	±0.9	±0.3	±3.8	±3.0	±1.8			±61.6

-POS: Positive control. -S9 mix: TA1535, TA100 sodium azide 2.5 µg/plate; TA98 4-nitro-o-phenylenediamine 12.0 µg/plate; TA1537 9-aminoacridine 80 µg/plate. +S9 mix: TA100, TA1535, TA1537 and TA98 2-aminoanthracene 1.5 µg/plate, all strains: Slight clearing of background lawn

Test substance: Chemical name: Diallyl phthalate (CAS NO. 131-17-9)
Supplier: Hardwicke Chemical
Lot No. 25-121
purity: 98.9%

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
17-DEC-2004 (70) (84)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: 0, 0.01, 0.05, 0.10, 0.50, 1.0 µl/plate (-S9);0, 0.01, 0.05, 0.10, 0.50, 1.0 µl/plate (+S9)
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1979
GLP: no data
Test substance: other TS

Result: The experimental conditions meet the OECD Guideline 471.

No mutagenicities were observed.

Test condition: Positive mutagens:
-S9:
TA1535: MNNG, 5 µg/plate
TA100: MNNG, 5 µg/plate
TA1537: 9-AA, 100 µg/plate
TA1538: 2-NF, 5 µg/plate
TA98: 2-NF, 5 µg/plate
+S9:
TA1535: 2-AA, 5 µg/plate
TA100: Aflatoxin B1, 1 µg/plate
TA1537: 6-AU, 1 µg/plate
TA1538: 2-AF, 2 µg/plate
TA98: Aflatoxin B1, 1 µg/plate

Activator:
Aroclor-1254 induced Sparague-Dawley male rats liver

Test substance: Ethyl Corporation (DAP), purity: data not available.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
17-DEC-2004 (43)

Type: Ames test

System of testing: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538
Concentration: See Test conditions
Cytotoxic Concentration: See Result
Metabolic activation: with and without
Result: ambiguous

Method: other: similar to OECD Guide-line 471
Year: 1986
GLP: yes
Test substance: other TS

Method: This experiment was carried out by the Ames method.
The procedures and the experimental conditions are likely to meet OECD Guideline 471.
Remark: Experiment 1/4
Result: CYTOTOXIC CONCENTRATION:
>1000 µg/plate (TA100, preliminary test)

Table: Mutagenicity of diallyl phthalate in Ames test without metabolic activation - Experiment 1

-Dose (µg/plate)	Number of revertants (number of colonies/plate, mean ± S.D.)				
	TA98	TA100	TA1535	TA1537	TA1538
solvent control	16 25 27 (25 ± 1)	132 115 148 (132 ± 17)	18 19 28 (22 ± 6)	7 6 11 (8 ± 3)	8 15 16 (13 ± 4)
50	22 18 17 (19 ± 3)	134 120 130 (128 ± 7)	26 26 24 (25 ± 1)	6 6 9 (7 ± 2)	8 13 13 (12 ± 4)
100	25 12 18 (18 ± 7)	133 143 119 (132 ± 12)	25 25 36 (29 ± 6)	6 6 6 (6 ± 0)	14 10 12 (12 ± 2)
250	11 15 18 (15 ± 4)	141 103 137 (127 ± 21)	44 25 38 (36 ± 10)	8 4 3 (5 ± 3)	18 14 10 (14 ± 4)
500	16 24 22 (21 ± 4)	155 132 132 (140 ± 13)	39 41 46 (42 ± 4)	3 5 6 (5 ± 2)	15 20 15 (17 ± 3)
1000	16 25 15 (19 ± 6)	137 139 130 (135 ± 5)	52 40 38 (43 ± 8)	11 11 6 (9 ± 3)	19 23 25 (22 ± 3)
Positive Controls					
Chemical	2NF	SA	SA	9AA	2NF
Dose (µg/plate)	5	5	5	75	5

Number of colonies /plate	1070 1293 1293	1545 1531 1843	1902 1798 1694	461 700 526	1486 1278 1189
	(1219 ± 129)	(1640 ± 176)	(1798 ± 104)	(562 ± 124)	(1318 ± 152)

2NF: 2-nitrofluorene, SA: sodium azide, 9AA: 9-aminoacridine

Table: Mutagenicity of diallyl phthalate in Ames test with metabolic activation - Experiment 1

-Dose (µg/plate)	Number of revertants (number of colonies/plate, mean ± S.D.)				
	TA98	TA100	TA1535	TA1537	TA1538
solvent control	44 19 24 (29 ± 13)	134 140 132 (135 ± 4)	22 24 17 (21 ± 4)	9 9 10 (8 ± 3)	17 16 18 (17 ± 1)
50	28 37 25 (30 ± 6)	121 122 100 (114 ± 12)	10 18 6 (11 ± 6)	8 2 9 (6 ± 4)	29 20 20 (23 ± 5)
100	25 22 34 (27 ± 6)	93 115 92 (100 ± 13)	11 18 10 (13 ± 4)	6 4 4 (5 ± 1)	14 17 19 (17 ± 3)
250	15 20 26 (20 ± 6)	86 91 82 (86 ± 5)	12 15 18 (15 ± 3)	5 7 0 (4 ± 4)	11 17 7 (12 ± 5)
500	20 22 16 (19 ± 3)	74 73 75 (74 ± 1)	26 13 16 (18 ± 7)	4 6 6 (5 ± 1)	10 14 16 (13 ± 3)
1000	11 16 16 (14 ± 3)	52 53 38 (48 ± 8)	6 7 8 (7 ± 1)	2 4 1 (2 ± 2)	4 6 17 (9 ± 7)

	Positive Controls				
Chemical	2A	2A	2A	2A	2A
Dose (µg/plate)	4	4	4	4	4
Number of colonies /plate	5573 5023 4473	5558 4577 4265	257 254 285	520 386 520	3893 4101 390
	(5023 ± 550)	(4800 ± 675)	(265 ± 17)	(475 ± 77)	(3908 ± 116)

2A: 2-anthramine

Table: Mutagenicity of diallyl phthalate in Ames test

without metabolic activation - Experiment 2

Dose (µg/plate)	Number of revertants (number of colonies/plate, mean ± S.D.)				
	TA98	TA100	TA1535	TA1537	TA1538
solvent control	11 17 19 (16 ± 4)	121 153 141 (138 ± 16)	28 22 35 (28 ± 7)	6 7 7 (7 ± 1)	14 10 18 (14 ± 4)
250	23 20 10 (18 ± 7)	132 133 170 (145 ± 22)	41 37 46 (41 ± 5)	11 7 4 (7 ± 4)	11 18 15 (15 ± 4)
500	35 20 17 (24 ± 10)	148 160 143 (150 ± 9)	42 49 48 (46 ± 4)	6 9 5 (7 ± 2)	19 24 19 (21 ± 3)
1000	16 13 19 (16 ± 3)	156 110 152 (149 ± 8)	35 41 55 (44 ± 10)	6 5 7 (6 ± 1)	12 18 19 (16 ± 4)
1500	17 19 17 (18 ± 1)	164 152 153 (156 ± 7)	78 67 66 (70 ± 7)	5 6 4 (5 ± 1)	13 23 18 (18 ± 5)
3000	18 16 14 (16 ± 2)	151 142 132 (142 ± 10)	62 55 64 (60 ± 5)	3 2 2 (2 ± 1)	19 13 22 (18 ± 5)
Positive Controls					
Chemical	2NF	SA	SA	9AA	2NF
Dose (µg/plate)	5	5	5	75	5
Number of colonies /plate	1917 1694 2125	1308 996 1055	1694 1887 2036	643 627 452	1753 1367 1427
	(1912 ± 216)	(1120 ± 166)	(1872 ± 171)	(574 ± 106)	(1516 ± 208)

2NF: 2-nitrofluorene, SA: sodium azide, 9AA: 9-aminoacridine

Table: Mutagenicity of diallyl phthalate in Ames test without metabolic activation - Experiment 3

Dose (µg/plate)	Number of revertants (number of colonies /plate, mean ± S.D.)	
	TA98	TA1535
solvent	21 22 13	27 22 28

control	(19 ± 5)	(26 ± 3)
250	18 19 20	30 33 37
	(19 ± 1)	(33 ± 4)
500	14 21 24	41 36 21
	(20 ± 5)	(33 ± 10)
1000	18 21 24	40 54 48
	(21 ± 3)	(47 ± 7)
1500	22 16 17	63 65 50
	(18 ± 3)	(59 ± 8)
3000	19 17 18	36 36 63
	(18 ± 1)	(45 ± 18)

Positive Controls

Chemical	2NF	SA
Dose (µg/plate)	5	5
Number of colonies /plate	1976 2719 3076	2318 1872 1516
	(2590 ± 561)	(1902 ± 402)

2NF: 2-nitrofluorene, SA: sodium azide

Table: Mutagenicity of diallyl phthalate in Ames test without metabolic activation - Experiment 4

-Dose (µg/plate)	Number of revertants (number of colonies/plate, mean ± S.D.)				
	TA98	TA100	TA1535	TA1537	TA1538
-solvent	27 17 16	96 102 93	20 15 20	8 5 7	10 8 11
control	(23 ± 6)	(97 ± 5)	(18 ± 3)	(7 ± 2)	(10 ± 2)
150	30 27 22	100 86 78	15 16 24	7 5 10	14 11 10
	(26 ± 4)	(88 ± 11)	(18 ± 5)	(7 ± 3)	(12 ± 2)
300	18 16 23	120 104 91	24 18 27	8 9 12	11 9 7
	(19 ± 4)	(105 ± 15)	(23 ± 5)	(10 ± 2)	(9 ± 2)

600	30 20 20	101 102 130	35 27 18	4 7 7	13 13 6
	(23 ± 6)	(11 ± 16)	(27 ± 9)	(6 ± 2)	(11 ± 4)
1500	14 28 24	95 117 94	35 40 39	10 8 9	17 10 6
	(22 ± 7)	(102 ± 13)	(38 ± 3)	(9 ± 1)	(11 ± 6)
3000	13 17 13	58 49 86	35 37 33	5 5 5	10 7 8
	(14 ± 2)	(64 ± 19)	(35 ± 2)	(5 ± 0)	(8 ± 2)
6000	19 18 18	83 84 51	20 22 25	3 5 2	6 9 3
	(18 ± 1)	(73 ± 19)	(22 ± 3)	(3 ± 2)	(6 ± 3)
Positive Controls					
Chemical	2NF	SA	SA	9AA	2NF
Dose (µg/plate)	5	5	5	75	5
Number of colonies /plate	1144 906 1115	2244 2125 2229	2006 1293 1887	519 1172 1715	1144 1144 1115
	(1055 ± 130)	(2199 ± 65)	(1729 ± 382)	(1135 ± 599)	(1134 ± 17)

2NF: 2-nitrofluorene, SA: sodium azide, 9AA: 9-aminoacridine

Table: Mutagenicity of diallyl phthalate in Ames test with metabolic activation - Experiment 4

Dose (µg/plate)	Number of revertants (number of colonies/plate, mean ± S.D.)				
	TA98	TA100	TA1535	TA1537	TA1538
solvent control	33 24 36 (31 ± 6)	106 139 123 (123 ± 17)	19 15 16 (17 ± 2)	5 8 9 (7 ± 2)	23 27 17 (22 ± 5)
25	31 29 38 (33 ± 5)	95 115 82 (97 ± 17)	13 16 13 (14 ± 2)	4 3 4 (4 ± 1)	10 12 14 (12 ± 2)
50	38 34 36 (36 ± 2)	95 85 71 (84 ± 12)	16 14 10 (13 ± 3)	7 8 11 (9 ± 2)	16 14 15 (15 ± 1)
100	25 29 25 (26 ± 2)	82 79 74 (78 ± 4)	13 13 10 (12 ± 2)	5 5 9 (6 ± 2)	15 18 18 (17 ± 2)

250	24 28 22	75 71 75	14 12 12	7 7 5	18 12 14
	(25 ± 3)	(74 ± 2)	(13 ± 1)	(6 ± 1)	(15 ± 3)
500	20 30 15	67 68 55	17 11 13	3 0 5	13 10 9
	(22 ± 8)	(63 ± 7)	(14 ± 3)	(3 ± 3)	(11 ± 2)
1000	16 15 13	39 50 38	13 10 12	3 0 1	6 6 13
	(15 ± 2)	(42 ± 7)	(12 ± 2)	(1 ± 2)	(8 ± 4)
		Positive Controls			
Chemical	2A	2A	2A	2A	2A
Dose (µg/plate)	4	4	4	4	4
Number of colonies /plate	6390 6836 5498	6420 7712 7059	431 520 594	563 431 357	3388 3180 3730
	(6241 ± 681)	(7064 ± 646)	(515 ± 82)	(451 ± 105)	(3433 ± 278)

2A:
2-anthramine

Test condition: DOSES:
-S9 mix
50, 100, 250 500, 1000 µg/plate (Expt 1)
250, 500, 1000, 1500, 3000 µg/plate (Expt 2)
250, 500, 1000, 1500, 3000 µg/plate (Expt 3, TA98 & TA1535 only)
150, 300, 600, 1500, 3000, 6000 µg/plate (Expt 4)
+S9 mix
50, 100, 250, 500, 1000 µg/plate (Expt 1)
25, 50, 100, 250, 500, 1000 µg/plate (Expt 4)

METABOLIC ACTIVTATION: S9 - Rat liver, induced with Aroclor 1254

SOLVENT: dimethylsulfoxide

POSITIVE CONTROLS:
-S9 mix: sodium azide (TA100, TA1535), 9-aminoacridine (TA1537), 2-nitrofluorene (TA98, TA1538)
+S9 mix: 2-anthramine (TA98, TA100, TA1335, TA1537, TA1538)

PLATES/TEST: 3

REPLICATES: The study was repeated using a different batch of
diallyl phthalate.

The first and second experiment were performed with an old sample of the test substance. In the second experiment, a dilution error occurred with the titer determination for TA98. In experiment 1 and 2 a dose responsewas seen with TA1535. Because of this, a third experiment was performed

using TA98 and TA1535 without S9.

Finally, a fourth experiment was performed using a new lot of the test substance, with and without metabolic activation.

Test substance: FMC 495 (diallyl phthalate)
Viscous Colorless Liquid
Purity: Greater than 98%
Lot Number MLS-2;27 (Expt 1-3)
Lot Number MLS-B#86-15 T/T306 MLS-4;38 (Expt 4)

Conclusion: The strain TA1535 without metabolic activation showed a weakly positive. All other strains showed negative.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

08-DEC-2004 (48)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: 0, 0.01, 0.1, 1.0, 10, 100 µl/plate (with metabolic activation)
(1 % DAP in dioxane) 0, 0.01, 0.1, 1.0, 10, 100 µl/plate (without metabolic activation)
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1977
GLP: no
Test substance: other TS

Result: The experimental conditions meets the OECD Guideline 471.

The results show that no mutagenicity was observed in diallyl phthalate.

Test substance: DAP monomer (FMC Corporation, C-8013-3), purity: 99 %.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

17-DEC-2004 (45)

Type: Ames test
System of testing: Salmonella typhimurium TA98
Concentration: 0.5-500 µg/plate (with and without metabolic activation)
with 2 as the sequential dose ratio.
Result: negative

Method: other: According to Yahagi, T. et al. (1977), Mutat. Res., 48 121-130.
GLP: no
Test substance: other TS

Remark: Objective:

Test for the enhancement of mutagenicity of Trp-P-2 (3-amino-1-methyl-5H-pyrido-[4,3-b]indole) by DAP.

The other phthalates were tested whether to enhance the mutagenicity of Trp-P-2 and Trp-P-1 (3-amino-1,4-dimethyl-5H-pyrido-[4,3-b]indole).

Genotoxic effects: Negative (enhancement of mutagenicity of Trp-P-2 by DAP).
Test substance: Tokyo Kasei Co., purity: data not available (DAP). Trp-P-2 (Wako Junyaku Kogyo Co.), purity: data not available.
Reliability: (4) not assignable
The ojbective of this test is not to bacterial mutagenicity itself but to test the enhancement of mutagenicity of Trp-P-2 (3-amino-1-methyl-5H-pyrido-[4,3-b]indole) by DAP.
17-DEC-2004 (75)

Type: other: 8-Azaguanine resistance assay in Salmonella typhimurium
System of testing: Salmonella typhimurium TA100
Metabolic activation: with and without
Result: negative

Method: other
Year: 1982
GLP: no
Test substance: other TS

Result: The result of the mutagenicity of diallylphthalate (DAP) was negative in this test (the test concentration was not described.) This article reported that the other phthalate esters, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, and 2-ethylphexanol had mutagenicity and di-n-octyl phtalate, di(2-ethylhexyl) phthalate, di(2-ethylhexyl) adipate, diisodecyl phthalate, and diisobutyl phtalate had no mutagenicity as well as DAP.
Test substance: Hardwicke chemical
Reliability: (4) not assignable
17-DEC-2004 (76)

Type: Mouse lymphoma assay
System of testing: L5178Y mouse lymphoma cells, clone 3.7.2C
Concentration: 0, 30, 40, 50, 60, 80, 100, 120 nl/ml for -S9; 0, 12.5, 25, 50, 75, 100, 150, 200 nl/ml
Cytotoxic Concentration: 60, 80, 90, 100 nl/ml for -S9; 12.5, 50, 75, 100, 150 nl/ml for +S9
Metabolic activation: with and without
Result: positive

Method: other
Year: 1991
GLP: no data
Test substance: other TS

Remark: The Mouse lymphoma cell mutation assay was one of the in vitro test systems evaluated by the NTP for detecting chemical mutagenesis and its correlation with rodent carcinogenesis.

DAP was considered to be mutagenic in the absence and presence of S9 mix. Without S9, the mutagenic activity was associated only with treatments causing about 30% relative total growth (RTG) and less, which were not obtained in every experiment due to precipitous survival curves, whereas the primary effect of adding S9 mix was broaden the toxicity curve and allow doses as high as 150 nl/ml to be analyzed. DAP became mutagenic near 50-75 nl/ml (46-49% RTG) and

showed dose-related increases up to 150 nl/ml, which induced six- and nine fold increases in two experiments.

The mutagenic activity under non activation test conditions might be arguable or easily missed, the addition of S9 mix allowed clear detection of mutagenesis in two successive experiments.

Result: GENOTOXIC EFFECTS:
- With metabolic activation:

Trial 1
Postive, significant trend

conc. nL/mL	n	AVG MF
0 (ETOH)	4	52
12.5	3	120*
25	3	67
50	3	80*
75	3	109*
100	3	126*
150	3	323*
200	3	all lethal
MCA 2.5 µg/ml	3	557*

Trial 2
Positive, significant trend

conc. nL/mL	n	AVG MF
0 (ETOH)	4	90
12.5	3	64
25	3	100
50	3	124
75	3	173*
100	3	204*
150	3	789*
MCA 2.5 µg/ml	3	1156*

AVG MF, average mutant frequency
*, MF is greater than the control value at P<=0.5
ETOH, negative control containing 1% ethanol
MCA, positive control, 3-methyl-cholanthrene

- Without metabolic activation:

Trial 1
Negative

conc. nL/mL	n	AVG MF
0 (ETOH)	3	51
30	3	30
40	3	25

50	3	38
60	3	38
80	3	33
100	2	83*
MMS 5 µl/ml	3	366*

Trial 2
Negative

conc. nL/mL	n	AVG MF
0 (ETOH)	4	31
30	3	29
40	3	28
50	3	28
60	3	30
80	3	28
100	3	29
120	3	all lethal
MMS	3	324*

Trial 3
Positive; Significant trend

conc. nL/mL	n	AVG MF
0 (ETOH)	4	23
60	3	45*
80	3	110*
90	3	102*
100	3	125*
MMS 5 µl/ml	3	166*

AVG MF, average mutant frequency
*, MF is greater than the control value at P<=0.5
ETOH, negative control containing 1% ethanol
MMS, positive control, methyl methansulfonate

Test condition: SYSTEM OF TESTING

- Species/cell type: Thymidine Kinase (TK) locus in L5178Y mouse lymphoma cells, clone 3.7.2C

- Metabolic activation system: S9 was prepared from the livers of Aroclor 1254-induced male Fischer 344 rats.

- Dosing:
 0, 30, 40, 50, 60, 80, 100 nl/ml in trial 1 without S9;
 0, 30, 40, 50, 60, 80, 100, 120 nl/ml in trial 2 without S9;
 0, 60, 80, 90, 100 nl/ml in trial 3 without S9;
 0, 12.5, 25, 50, 75, 100, 150, 200 nl/ml in trial 1 with S9;
 0, 12,5, 25, 50, 75, 100, 150 nl/ml in trial 2 with S9.

- Number of replicates:
 3 replicates in almost all dose group.

- Positive and negative control groups and treatment:

Negative control : 1% Ethanol
Positive control : MMS or MCA

CRITERIA FOR EVALUATING RESULTS:

Minimum Criteria for Experiment Acceptability

Solvent control cultures

1. The cloning efficiency must be in the 50-120% range
2. At least two acceptable cultures must be available
3. The average mutant fequency for all acceptable culures must be between 15E-6 and 110E-6 for negative evaluations; for mutagenic test chemicals, the range is extended to 10E-6 to 150E-6
4. A chi-square test for consistency among the mutant frequencies of the acceptable cultures must be significant at P <= 0.05

Positive control cultures
1. The cloning efficiency must be in the 10-120% range
2. The relative total growth must not be less than 1%
3. At least one acceptable culture must be available
4. The average mutant frequency for all acceptable cultures must be within the historical range

Test chemical cultures
1. The cloning efficiency must be in the 10-120% range
2. The relative total growth must not be less than 1%
3. The relative suspension growth for the second day of expression must be 40% or greater
4. The test chemical must remain soluble during treatment
5. The maximum dose is 5 mg/ml for solids and 5 µl/ml for liquids
6. Each dose level must have two or more acceptable cultures
7. A qui-square test for consistency among the mutant frequencies of the acceptable cultures must be significant at P<= 0.05
8. At least three acceptable dose sets must be available, except when no response is obtained and sets are rejected due to precipitation

Test substance: Hardwicke Chemical
purity: 98.9%
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
17-DEC-2004 (67)

Type: Chromosomal aberration test
System of testing: Cultured Chinese hamster ovary (CHO)
Concentration: 0, 50, 100, 160, 200, 300 µg/ml for +S9; 0, 50, 100, 200, 300, 400, 500 µg/ml
Cytotoxic Concentration: 200, 300 µg/ml for +S9
Metabolic activation: with and without
Result: positive

Method: other

Year: 1989
GLP: no data
Test substance: other TS

Result: GENOTOXIC EFFECTS:
- With metabolic activation: Positive
- Without metabolic activation: Negative

STATISTICAL RESULTS:

Trial 1 of 2 (+9)
Positive

Dose µg/ml	Percent Cells with Abberrations Total
0	3
100	0
150	0
300	15*
CP	
7.5	41
10.0	480

Trial 2 of 2 (+9)
Positive

Dose µg/ml	Percent Cells with Abberrations Total
0	3
50	0
100	0
200	11*
CP	
5.0	63
7.5	72

Trial 1 of 3 (-9)
Negative

Dose µg/ml	Percent Cells with Abberrations Total
0	1
100	2
150	0
300	1
MMC	
0.125	32
0.25	42

Trial 2 of 3 (-9)
Negative

Dose µg/ml	Percent Cells with Abberrations Total
0	2
300	4
400	2
500	2
MMC	
0.063	34
0.125	58

Trial 3 of 3 (-9)
Negative

Dose µg/ml	Percent Cells with Abberrations Total
0	2
200	0
300	1
400	2
500	5
MMC	
0.063	32
0.125	44

Test condition: SYSTEM OF TESTING

- Species/cell type: hinese hamster ovary (CHO) cells

- Metabolic activation system: A liver fraction(S9) prepared from Aroclor 1254-induced male Sprague Dawley rats (Microbiological Associates, Bethesada, MD)

ADMINISTRATION:
- Dosing:
  0, 100, 150, 300 µg/ml in trial 1 of 3 with -9;
  0, 300, 400, 500 µg/ml in trial 2 of 3 with -9;
  0, 200, 300, 400, 500 µg/ml in trial 3 of 3 with -9;
  0, 100, 150, 300 µg/ml in trial 1 of 2 with +9;
  0, 50, 100, 200 µg/ml in trial 2 of 2 with +9.

Test substance: Hardwicke Chemical
Purity: 98.9 %

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
17-DEC-2004 (52)

Type: Micronucleus test in vitro
System of testing: Chinese hamster lung (CHL/IU) cells (National Institute of Health Sciences, Japan)
Concentration: -S9 (continous treatment): 0, 20, 40, 60, 80, 100, 120 µg/mL
+S9 (short-term treatment): 0, 1.3, 2.5, 5.0, 10, 20, 40 ug/mL
Cytotoxic Concentration: Toxicity was not observed up to 20 µg/mL in continuous treatment without S9 Mix and 78 µg/mL in short-term treatment with S9 Mix.
Metabolic activation: with and without

Result: positive

Method: OECD Guide-line 473
Year: 2002
GLP: yes
Test substance: other TS

Method: Matsushima, T. et al. (1999), Mutagenesis, Validation study of the in vitro micronucleus test in a Chinese hamster lung cell line (CHL/IU), vol. 14, 569-580. This study was conducted under auspices of the Japanese Ministry of Labour (MOL) and was adopted as a guideline for its use by MOL in Japan. In this study, methods for incubation of cells and treatment with chemical in the absence or presence of metabolic activation are essentially as same as those described in the OECD TG 473 (in vitro Mammalian chromosomal aberration test) with some modifications, if any. For the microscopic observation of micronucleus and statistical procedure, the study was conducted according to OECD 474 (Mammalian in vivo micronucleus test).

Result: DAP induced micronucleus in vitro at 11 ug/mL and higher on short-term treatment in the presence of S9 but not on continuous treatment in the absence of S9 over the all dose range tested. The results from in vitro micronucleus tests with S9 were considered to be positive because there was more than two-fold increase of micronucleus in the DAP treated cells in the presence of S9 in the concentration-dependent manner, when compared to the negative control (DMSO). Evaluation of micronucleus induction was conducted by counting only cells with the micronucleus, showing 1/10-1/3 of the diameter of a single main nucleus because cell with small or large micronucleus were omitted from the judgment. The frequency of micronucleus induction (0/00) and the concentration-dependency was evaluated at P=0.01 in the Fisher's exact test and at P=0.01 in the Cochran-Armitage test (Trend test), respectively. Cells with statistically significant micronucleus induction (Fisher's exact test) were judged to be positive only when observed with statistically significant concentration-dependency (Cochran-Armitage test), simultaneously.

Table In vitro Mammalian Micronucleus Test Result
(Short-term treatment: +S9)

Conc. (mg/mL)	Cells conted	Cells with MN (Frequency	Statistical method		Cell Proliferation (%)x1000)
			Fisher	Trend	
DMSO (1%)	1000	10	-	P<0.01	100
	1000	7			
	2000	17(8.5)			
0.0013	1000	9	n.s.	P<0.01	100
	1000	10			102
	2000	19(9.5)			(101)

0.0025	1000	15	P<0.05	P<0.01	95
	1000	15			102
	2000	30(15.0)			(99)
0.005	1000	10	n.s.	P<0.01	107
	1000	14			87
	2000	24(12.0)			(97)
0.01	1000	12	n.s.	P<0.01	97
	1000	17			100
	2000	29(14.5)			(99)
0.02	1000	30	P<0.01	P<0.01	89
	1000	33			98
	2000	63(31.5)			(94)
0.04		TOX			28
		TOX			34
B[a]P	1000	86			
0.008	1000	71			
	2000	157(78.5)			
DMSO	1000	6		n.s.	100
(1%)	1000	11			
	2000	17(8.5)			
0.02	1000	6	n.s.	n.s.	86
	1000	11			87
	2000	23(11.5)			(87)
0.04	1000	5	n.s.	n.s.	82
	1000	13			79
	2000	18(9.0)			(81)
0.06	1000	4	n.s.	n.s.	76
	1000	9			70
	2000	13(6.5)			(73)
0.08	1000	10	n.s.	n.s.	56
	1000	11			57
	2000	21(10.5)			(57)
0.10	1000	8	n.s.	n.s.	59
	1000	7			62
	2000	15(7.5)			(61)
0.12	1000	3	n.s.	n.s.	54
	1000	10			43
	2000	13(6.5)			(49)
MMC	1000	46			
0.00001	1000	64			
	2000	110(5.5)			

MMC, Mitomycin; C[a]P, Benzo[a]pyrene
TOX, No observation of proliferation
n.s., Not significant.

Test condition: SYSTEM OF TESTING
-Metabolic activation system: S9 from rat liver, induced

with phenobarbital and 5, 6-benzoflavone.

ADMINISTRATION:
-Plate per test: 2
-Application: For continuous treatment, cells were treated for 24 hrs without S9. For short-term treatment, cells were treated for 6 hrs with S9 and cultivated with fresh media for 12 hrs after rinsing cells with PBS.
Positive control groups and treatment: Mitomycin C for continuous treatment
Benzo-a-pyrene for short-term treatment.
-Solvent: DMSO

Test substance: Source: Wako Pure Chemical
Purity: 98.7 % (lot No. SEK5987)
Any other information: kept at 4°C.

Conclusion: in vitro Mammlian micronucleus tests in CHL/IU is positive with metabolic activation.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

17-DEC-2004 (66)

Type: Sister chromatid exchange assay
System of testing: Cultured Chinese hamster ovary (CHO)
Concentration: 0, 5, 16, 50, 100, 150, 160, 200, 250 µg/ml for +S9;0, 1.6, 5, 16, 50, 75, 100, 125 µg/ml for -S9
Cytotoxic Concentration: 160, 200, 250 µg/ml for +S9
Metabolic activation: with and without
Result: positive

Method: other
Year: 1989
GLP: no data
Test substance: other TS

Result: GENOTOXIC EFFECTS:

- With metabolic activation: Positve
- Without metabolic activation: Negative

STATISTICAL RESULTS:

Trial 1 of 2 (-S9)
Negative

Dose µg/ml	SCE per Cell
0	8.74
1.6	7.64
5.0	8.02
16.0	8.32
50.0	8.23
MMC	
0.0010	12.06
0.0050	23.90

Trial 2 of 2 (-S9)
Negative

Dose	SCE per Cell

µg/ml	
0	7.38
50	7.42
75	7.68
100	8.36
125	7.74
MMC	
0.0008	10.22
0.005	23.90

Trial 1 of 3 (+S9)
Positive

Dose µg/ml	SCE per Cell
0	8.10
5	7.78
16	7.50
50	8.22
160	14.70*
CP	
0.3	18.00
0.6	26.90

Trial 2 of 3 (+S9)
Positive

Dose µg/ml	SCE per Cell
0	8.46
5	8.54
16	8.84
50	9.24
160	10.92*
CP	
0.2	14.86
0.6	23.60

Trial 3 of 3 (+S9)
Positive

Dose µg/ml	SCE per Cell
0	8.92
100	9.96
150	10.00
200	12.52*
250	16.62*
CP	
0.2	14.76
0.6	27.00

Test condition: SYSTEM OF TESTING

- Species/cell type: Chinese hamster ovary (CHO) cells

- Metabolic activation system: A liver fraction (S9) prepared from Aroclor 1254-induced male Sprague Dawley rats (Microbiological Associates, Bethesda, MD)

ADMINISTRATION:
- Dosing:

- Number of replicates:

- Application:

- Positive and negative control groups and treatment:

- Pre-incubation time:

DESCRIPTION OF FOLLOW UP REPEAT STUDY:
CRITERIA FOR EVALUATING RESULTS:

Test substance: Hardwicke Chemical
purity: 98.9%

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

17-DEC-2004 (52)

5.6 Genetic Toxicity 'in Vivo'

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:** male
Strain: other: Canton-S
Route of admin.: other: feeding and injection
Exposure period: 72 hours for feeding; 24 hours for injection
Doses: 0, 100 (feeding), 140 (feeding), 500 (injection) ppm/kg
Result: negative

Method: OECD Guide-line 477 "Genetic Toxicology: Sex-linked Recessive Lethal Test in Drosophila melanogaster"
Year: 1985
GLP: no data
Test substance: other TS

Remark: The experimental plan was to test each chemical for sex-linked recessive lethals (SLALs) induction by feeding. If no significant mutagenicity was observed, the sample was then tested by injection. The initial solution was diluted with aqueous 5 % sucrose for feeding and with aqueous 0.7 % NaCl for injection.

Result: Table Results of the Sex-Linked Recessive Lethal Tests

Dose (ppm)	Route	Mortality (%)	Sterility (%)	vial#	Lethals (%)
100	Feeding	0	9	3	0.08
0					0.08
140	Feeding	31	10	3	0.11
0					0.12
500	Injection	0	12	3	0.05

0	0.11

Test substance: Hardwicke Chem. 25-121 Batch O1, purity: 98.9%.
Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint
17-DEC-2004 (83)

Type: Micronucleus assay
Species: mouse **Sex:** male
Strain: B6C3F1
Route of admin.: i.p.
Exposure period: 72 hours; The test chemical dissolved in corn oil was injected into mice three times at 24 hr intervals.
Doses: 0, 43.8, 87.5, 175 mg/kg bw
Result: negative

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 1993
GLP: no data
Test substance: other TS

Method: Species/Strain: Mice/B6C3F1

Mice were injected intraperitoneally three times at 24-hour intervals with DAP in corn oil. The total dosing volume was 0.4 ml. Twenty-four hours after the final injection, smears of the bone marrow cells from femurs were prepared. Air-dried smears were fixed and stained with acridine orange; 2,000 polychromatic erythrocytes (PCE) were scored per animal for frequency of micronucleated cells. In addition, the percentage of PCEs among the total erythrocyte population in the bone marrow was scored for each dose group as a measure of toxicity.

Result: Table Micronucleus Test Result

Dose (mg/kg)	MN-PCE/1,000	Survival (No. scored)
0	2.50 ± 0.41	5/5
43.8	3.20 ± 0.92	5/5
87.5	2.40 ± 0.19	5/5
175	2.40 ± 0.42	5/5

Test substance: Hardwicke Chemical
Conclusion: negative
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
21-DEC-2004 (78)

Type: other: Chromosome aberration test
Species: mouse **Sex:** male
Strain: B6C3F1
Route of admin.: i.p.
Exposure period: 17 hr
Doses: 0, 75, 150, 300 mg/kg
Result: positive

Method: OECD Guide-line 475 "Genetic Toxicology: In vivo Mammalian

Bone Marrow Cytogenetic Test - Chromosomal Analysis"
Year: 1995
GLP: no data
Test substance: other TS

Method: Male B6C3F1 mice (8 animals/dose group) received a single intraperitoneal injection with the chemical dissolved in corn oil or PBS (injection volume = 0.4 ml). Solvent control mice received equivalent injections of the solvent alone. Concurrent positive control groups were run for each test. Mice was subcutaneously implanted with a BrdUrd tablet 18 hr before the scheduled harvest. Two hours prior to sacrifice, the mice received an intraperitoneal injection of colchicine in saline. The animals were euthanized 17 hours after injection.
One or both femurs were removed and the marrow was flushed out with phosphate-buffered saline (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24 hr drying period, differential chromatid staining was accomplished. Fifty well-spread first-divison metaphase cells from each animal per treatment grope were scored for presence of chromosomal aberrations.

Result: Table Chromosome aberrations result

Harvest time (hr)	Trend P value	Dose (mg/kg)	% Cells with ABS	Survival
17	0.015*	0	3.25 ± 1.25	8/8
		75	6.50 ± 1.18	8/8
		150	2.75 ± 0.84	8/8
		300	7.50 ± 1.18*	8/8
17	0.011*	0	1.25 ± 0.37	8/8
		75	2.25 ± 0.80	8/8
		150	2.00 ± 0.76	8/8
		300	3.75 ± 0.96	8/8

*, significant positive effect
Test substance: Hardwicke Chemical
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
21-DEC-2004 (77)

5.7 Carcinogenicity

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 103 weeks
Frequency of treatment: five days per week for 103 weeks
Post exposure period: 3 weeks
Doses: 0; 150; 300 mg/kg administered in corn oil
Result: ambiguous
Control Group: yes, concurrent vehicle

Method: other
Year: 1983

GLP: no data
Test substance: other TS

Remark: A carcinogenicity study by the National Toxicology Program of DAP in male and female Fisher 344/N rats, employing daily gavage dose of 0 (vehicle control), 50, or 100 mg/kg body weight, was conducted.

Result: Survival rates and mean body weight of dosed animals were not different form those of controls, and pathological lesions unrelated to proliferative changes were not observed. Under the condition of this bioassay, the development of chronic inflammation and hyperplasia of the forestomach in both male and female mice was a considered to be related to the administration of DAP. The development of sqamous papilomas of the forestomach may also have been related to chemical administration, but the available data are insufficient to indicate a clear cause and effect relationship.

Table: Analyses of male mice with Primary Tumors (a)

	Vehicle control	Low dose	High dose
Hematopoietic System: Lymphoma			
Tumor rates			
Overall (b)	6/50 (12%)	5/50 (10%)	12/50 (24%)
Adjusted (c)	15.8%	13.2%	32.7%
Terminal (d)	6/38 (16%)	5/38 (13%)	8/32 (25%)
Statistical Tests (e)			
Life table	P=0.031	P=0.500N	P=0.051
Incidental tumor test	P=0.037	P=0.500N	P=0.058
Cochran-Armitage trend, Fisher exact tests	P=0.063	P=0.500N	P=0.096
Hematopoietic System: Lymphoma or Leukemia			
Tumor rates			
Overall (b)	6/50 (12%)	6/50 (12%)	12/50 (24%)
Adjusted (c)	15.8%	15.4%	32.7%
Terminal (d)	6/38 (16%)	5/38 (13%)	8/32 (25%)
Statistical Tests (e)			
Life table	P=0.034	P=0.620	P=0.051
Incidental tumor test	P=0.045	P=0.608	P=0.058
Cochran-Armitage trend, Fisher exact tests	P=0.067	P=0.620	P=0.096
Liver: Ademona			
Tumor rates			
Overall (b)	0/50 (0%)	0/49 (0%)	3/50 (6%)
Adjusted (c)	0.0%	0.0%	9.4%
Terminal (d)	0/38 (0%)	0/38 (0%)	3/32 (9%)
Statistical Tests (e)			
Life table	P=0.026	(f)	P=0.092
Incidental tumor test			

	P=0.026	(f)	P=0.092
Cochran-Armitage trend, Fisher exact tests			
	P=0.038	(f)	P=0.121
Liver:Carcinoma			
Tumor rates			
Overall (b)	7/50 (14%)	5/49 (10%)	4/50 (8%)
Adjusted (c)	15.5%	12.7%	12.5%
Terminal (d)	2/38 (5%)	4/38 (11%)	4/32 (13%)
Statistical Tests (e)			
Life table	P=0.286N	P=0.405N	P=0.347N
Incidental tumor test			
	P=0.233N	P=0.507N	P=0.312N
Cochran-Armitage trend, Fisher exact tests			
	P=0.210N	P=0.394N	P=0.262
Liver: Ademona or Carcinoma			
Tumor rates			
Overall (b)	7/50 (14%)	5/49 (10%)	7/50 (14%)
Adjusted (c)	15.5%	12.7%	21.9%
Terminal (d)	6/38 (16%)	5/38 (13%)	8/32 (22%)
Statistical Tests (e)			
Life table	P=0.445	P=0.405N	P=0.502
Incidental tumor test			
	P=0.510	P=0.507N	P=0.524
Cochran-Armitage trend, Fisher exact tests			
	P=0.560	P=0.394N	P=0.613

(a) dosed groups received 150 or 300 mg/kg of diallyl phthalate by gavage
(b) number of tumor bearing animals/number of animals examined at the site
(c) Kaplan-Meier estimated lifetime incidence after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence in indicated by (N).
(f) Not significant; no tumors in low dose or vehicle control group.

Table: Analyses of female mice with Primary Tumors (a)

	Vehicle control	Low dose	High dose
Hematopoietic System: Lymphoma or Leukemia			
Tumor rates			
Overall (b)	16/50 (32%)	14/50 (28%)	18/49 (37%)
Adjusted (c)	36.8%	34.7%	42.3%
Terminal (d)	11/38 (29%)	9/35 (26%)	15/39 (38%)

Statistical Tests (e)			
Life table	P=0.406	P=0.536N	P=0.440
Incidental tumor test			
	P=0.292	P=0.543	P=0.331
Cochran-Armitage trend, Fisher exact tests			
	P=0.348	P=0.414N	P=0.388
Liver: Ademona or Carcinoma			
Tumor rates			
Overall (b)	1/50 (2%)	2/49 (4%)	3/49 (6%)
Adjusted (c)	2.3%	5.1%	7.7%
Terminal (d)	0/38 (0%)	1/35 (3%)	3/39 (8%)
Statistical Tests (e)			
Life table	P=0.234	P=0.467N	P=0.316
Incidental tumor test			
	P=0.177	P=0.731N	P=0.254
Cochran-Armitage trend, Fisher exact tests			
	P=0.216	P=0.492N	P=0.30

(a) Dosed groups received 150 or 300 mg/kg of diallyl phthalate by gavage
(b) number of tumor bearing animals/number of animals examined at the site
(c) Kaplan-Meier estimated lifetime incidence after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence in indicated by (N).

Source: DAISO CO., LTD. Osaka
Test substance: Hardwicke Chemical Company (Lot No. 25-121)
Purity: 99% (GC)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
08-DEC-2004 (69)

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: gavage
Exposure period: 103 weeks
Frequency of treatment: five days per week for 103 weeks
Post exposure period: 1-2 weeks
Doses: 0; 50; 100 mg/kg
Result: ambiguous
Control Group: yes, concurrent vehicle

Method: other
Year: 1985
GLP: yes
Test substance: other TS

Result: No significant differences in survival were observed between any groups of either sex. Mononuclear cell leukaemia in female rats occurred with a significant positive trend, and the incidence in the high dose group (100 mg/kg) was significantly greater than that in the vehicle controls. This leukaemia was recognized as a diffuse infiltration of atypical mononuclear white blood cells into the liver sinusoids and the interfollicular pulp of the spleen.

Infiltrations into virtually all organs and tissues were observed in more advanced cases. No other types of leukaemia were diagnosed in this study. An increased incidence of mononuclear cell leukaemia was not observed in male rats.

DAP administration produced a dose-dependent chronic liver injury characterized by periportal necrosis and fibrosis, pigment accumulation in periportal histiocytes, and excessive bile duct hyperplasia. Bile duct hyperplasia is frequently observed in aged rats, but the severity of the lesion in the high dose (100 mg/kg) rats in this study was much greater than that in the vehicle controls.

Despite the occurrence of chemically induced non-neoplastic pathologic lesions in the livers of DAP-dosed rats, no increased occurrences of neoplastic lesions of the liver were observed in either male or female rats.

Because of the variability in the incidence of this neoplasm in aged Fisher 344 rats and the difficulty in definitively diagnosing this lesion in Fisher 344 rats, this increase was considered to be equivocal evidence of carcinogenicity of DAP in female rats. There was no evidence of carcinogenicity in male rats.

This study was peer reviewed by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts.

A principal reviewer stated that the data supported a finding of clear evidence of carcinogenicty for female rats, and noted that these findings were supported not only by the current data but also by the increased incidences of hemapoietic system tumors in rodents from other NTP studies of 'allyl' compounds.

A second principal reviewer stated that the incidence of mononuclear cell leukemia in high dose female rats should be considered equivocal evidence of carcinogenicity rather than some evidence of carcinogenicity as orginally stated in the draft report because an increased incidence was not observed in male rats and because this neoplasm occurs at a moderate rate in historical control rats.

A third principal reviewer believed that the data supported a designation of equivocal evidence of carcinogenicity in female rats since this leukemia is common in historical control rats (more so in males) and the historical control rate is variable. However, the high dose female rat group did have an incidence greater than that ever seen in female

vehicle historical control rats.

The committee accepted the conclusion of equivocal evidence of carcinogenicity in female rats.

Despite the occurrence of chemically induced non-neoplastic pathologic lesions in the livers of DAP-dosed rats, no increased occurrences of neoplastic lesions of the liver were observed in either male or female rats.

Because of the variability in the incidence of this neoplasm in aged Fisher 344 rats and the difficulty in definitively diagnosing this lesion in Fisher 344 rats, this increase was considered to be equivocal evidence of carcinogenicity of DAP in female rats. There was no evidence of carcinogenicity in male rats.

Table: Analysis of hematopoietic system tumors in female rats

	Vehicle control	50 mg/kg	100 mg/kg
Mononuclear Cell Leukemia (a)			
Overall rates	15/50 (30%)	15/43 (35%)	25/49 (51%)
Adjusted rates	32.2%	39.6%	56.0%
Terminal rates	10/41 (24%)	10/32 (31%)	16/35 (46%)
Life table tests	P=0.013	P=0.293	P=0.017
Incidental tumor tests	P=0.038	P=0.513	P=0.052
Week of Observation:			
	76	35	40
	88	54	72
	97	91	73
	97	93	79
	102	94	82
			90
	(b)T(10)	(b)T(10)	95
			96
			100

T, Terminal
(a) Mean historical incidence of all leukemias at the test laborator: 29.3% +/- 13.01% (no data on mononuclear cell leukemia only)
(b) Number of animals found to have mononuclear cell leukemia at the terminal kill

Table: Liver weights in rats in the 2-year gavage studies of diallyl phthalate

Dose (mg/kg)	Liver Wt(a) (g)	Liver/Body Wt(a) (%)
MALE		
0	12.8±0.4 (16)	3.06±0.10 (16)
50	(b)14.6±0.5 (15)	(b)3.61±0.14 (15)
100	13.5±0.7 (10)	3.25±0.14 (10)

FEMALE		
0	9.2±0.3 (16)	3.33±0.11 (16)
50	8.7±0.2 (14)	3.10±0.08 (14)
100	10.3±0.7 (12)	3.67±0.51 (12)

(a)Mean±standard error (no. of animals)
(b) Significantly greater than vehicle control (P<0.05) by Dunnet's test

Table: Incidences of liver lesions in rats in the 2-year gavage studies of diallyl phthalate

Dose	Lesions and incidences (%)			
	Pigmentation	Necrosis	Fibrosis	Bile Duct Hyperplasia
MALE				
0	0/50 (0%)	0/50 (0%)	0/50 (0%)	43/50 (86%)
50	7/49 (14%)	0/49 (0%)	3/49 (6%)	19/49 (39%)
100	45/49 (92%)	1/49 (2%)	43/49 (88%)	44/49 (90%)
FEMALE				
0	0/50 (0%)	0/50 (0%)	0/50 (0%)	17/50 (34%)
50	25/43 (58%)	0/43 (0%)	0/43 (0%)	24/43 (56%)
100	46/49 (94%)	1/49 (2%)	34/49 (69%)	47/49 (96%)

Table: Relative severity of liver lesions in female rats in the two year gavage studies of diallylphthalate

Severity of Lesion	Vehicle Control	50 mg/kg	100 mg/kg
Bile Dust Hyperplasia			
None	32/50 (64%)	19/43 (44%)	2/49 (4%)
Minimal	7/50 (14%)	11/43 (26%)	10/49 (20%)
Mild	10/50 (20%)	13/43 (30%)	19/49 (39%)
Moderate	1/50 (2%)	-	17/49 (35%)
Severe	-	-	1/49 (2%)
Periportal Fibrosis			
None	50/50 (100%)	43/43 (100%)	15/49 (31%)
Minimal	-	-	8/49 (16%)
Mild	-	-	25/49 (51%)
Moderate	-	-	1/49 (2%)
Severe	-	-	-
Pigmentation			
None	45/50 (90%)	18/43 (42%)	3/49 (6%)
Minimal	5/50 (10%)	24/43 (56%)	18/49 (37%)
Mild	-	1/43 (2%)	28/49 (57%)
Moderate	-	-	-
Severe	-	-	-

These diagnoses for severity were conducted independently of the principal histopathology diagnoses for this study and by different pathologists

Table: Relative severity of liver lesions in male rats in the two year gavage studies of diallylphthalate

Severity of Lesion	Vehicle Control	50 mg/kg	100 mg/kg
Bile Dust Hyperplasia			
None	7/50 (14%)	31/50 (62%)	6/49 (12%)
Minimal	2/50 (4%)	3/50 (6%)	5/49 (10%)
Mild	41/50 (82%)	15/50 (30%)	14/49 (29%)
Moderate	-	1/50 (2%)	24/49 (49%)
Severe	-	-	-
Periportal Fibrosis			
None	50/50 (100%)	47/50 (94%)	6/49 (12%)
Minimal	-	2/50 (4%)	11/49 (23%)
Mild	-	1/50 (2%)	28/49 (57%)
Moderate	-	-	4/49 (8%)
Severe	-	-	-
Pigmentation			
None	50/50 (100%)	42/50 (84%)	4/49 (8%)
Minimal	-	7/50 (14%)	18/49 (37%)
Mild	-	1/50 (2%)	22/49 (45%)
Moderate	-	-	5/49 (10%)
Severe	-	-	-

These diagnoses for severity were conducted independently of the principal histopathology diagnoses for this study and by different pathologists

Source: DAISO CO., LTD. Osaka

Test substance: Hardwicke Chemical Company (Lot No. 25-121)
Purity: 99% (GC)

Reliability: (2) valid with restrictions
Mononucleus cell leukaemia is a disease that commonly arised in the spleen of the F344/N rat but is rare in other rat strains, and the corn oil used in this study as vehicle is known to affect the incidence of mononucleus cell leukaemia in the F344/N rat.

Flag: Critical study for SIDS endpoint

21-DEC-2004 (70)

5.8.1 Toxicity to Fertility

Type: One generation study
Species: rat
Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure Period: Parental animals: pre-mating, 14 days;mating, up to 14 days; gestation, ca. 22 days; lactation, 4 days.
Offspring: no exposure
Frequency of treatment: daily

Premating Exposure Period
male: 14 days only for parental animals
female: 14 days only for parental animals
Duration of test: mating, up to 14 days; gestation, ca. 22 days; lactation, 4 days
No. of generation studies: 1
Doses: 0(Control), 16.7, 50, 150 mg/kg/day
Control Group: yes, concurrent vehicle
NOAEL Parental: 50 mg/kg bw
NOAEL F1 Offspring: 50 mg/kg bw
Result: See Freetext

Method: OECD Guide-line 421
Year: 2004
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: Method of calculation:
Food conversion ratio, mating performance and fertility (pre-coital interval, fertility indices), gestation and parturition data (gestation length, gestation and parturition index), lactation data (live birth and viability indices, sex ratio, offspring physical development).

Statistical methods:

Adult male and female bodyweight during the maturation, gestation and lactation periods, adult male food consumption, female food consumption during amturation, gestation and lactation, litter size, litter weight, individual offspring bodyweight, offspring landmarks of physical development, reproductive and viability indices and adult organ weights were all analysed to establish homogeneity of group variances using Bartlet's chi-square test followed by one-way analysis of variance. If the variances were unequal subsequent comparisons between control and treated groups were performed using t-test assuming unequal variances. If variances were equal subsequent comparisons between control and treated groups were performed using Dunnett's Multiple Comparison Method.

The Kruskal-Wallis non-parametric rank sum test was used to compare individual vales of adult pre-coital intervals, female gestation lengths, offspring reflexological responses, litter sex ratios and relative organ weights. Where significant differences were seen, pairwise comparison of control values against treated group values was performed using the Mann-Whitney 'U' test.

Chi-squared analysis performed for differences in incidence of lesion occuring with an overall frequency of 1 or greater.

Kruskal-Wallis one-way non-parametric analysis of variance was used for comparison of severity grades for the conditions observed more frequently during histopathology.

Remark: Dystocia is frequently observed as a secondary consequence of general toxicity. It is considered that the marked hepatotoxicity will have affected the females sufficiently to induce the effects upon parturition that were observed on

this study.

Result: Mortality:

At 150 mg/kg/day there were 3 adult mortalities. Two females were killed in extremis due to signs of distress around the expected time of parturition, including pilo-erection, pallor of the extremities and abdominal discomfort. One of the females was also bleeding from the vagina. These clinical signs are associated with possible dystocia. A third female was found dead at completion of parturition. There were no previous clinical signs of toxicity.

At 50 and 16.7 mg/kg/day there were no mortalities through the course of the study.

Clinical observations:

At 150 mg/kg/day all animals showed increased salivation immediately post dose for various durations. There were also isolated incidences of increased salivation pre dose.

At 50 mg/kg/day all males and most females showed increased salivation immediately post dose for various durations and to a lesser extent pre dose in both males and females.

At 16.7 mg/kg/day there were isolated incidents of increased salivation immediately post dose among males only.

Bodyweight:

At 150 mg/kg/day these was a slight reduction in bodyweight gain in males during the first two weeks of dosing which resulted in a slightly lower group mean bodyweight. This reduction in group mean bodyweight was not statistically significant when compared to controls.

At 50 and 16.7 mg/kg/day there were no treatment related effects on bodyweight.

Food consumption:

At 150 mg/kg/day there was a statistically significant increase ($p<0.05$) in the food eaten during the second week of maturation compared to control values.

At 50 mg/kg/day there were no statistically significant differences in the food eaten compared to controls.

At 16.7 mg/kg/day there was a statistically significant increase ($p<0.001$) in the food eaten during the same period.

This increase did not show a dose related trend and is thought not to be treatment related.

Mating performance:

There were no treatment related effects on fertility or mating performance.

At 150 mg/kg/day one female had a coital interval of 13

days. This was an isolated case and so was thought not to be treatment related. Every other female at all dose levels had a pre-coital interval of 4 days or less.

Gestation length and parturition:

At 150 mg/kg/day 3 females failed to complete parturition which may be attributable to test material. For other females at this dose level these was no treatmentrelated increase in gestation times. At 50 and 16.7 mg/kg/day all females with positive evidence of mating subsequently gave birth to live young and there was no effect on gestation.

Necropsy data:

At 150 mg/kg/day areas of patchy pallor and/or acentuated lobular pattern was seen on the livers of 5/10 males and 9/10 females at post mortem examination. In addition, one of the females killed in extremis showed ulceration of the glandular region of the stomach with digested blood present.

At 50 and 16.7 mg/kg/day there were no macroscopic abnormalities observed.

There were no significant differences in the number of corpora lutea or implantation sites between groups. Pre and post implantation losses and ofspring viability were comparable to controls at all dose levels.

Organ weights:

At 150 mg/kg/day the absolute epididymides weight was significantly ($p<0.05$) reduced compared to control weights but there was no significant difference in epididymides weights relative to bodyweight.

At 50 and 16.7 mg/kg/day there were no treatment-related effects on organ weights.

Offspring:

There were no treatment-related effects on offspring growth or development. There were no treatment related effects on offspring viability as shown by similar incidences of offspring clinical observations and mortalities across all dose groups. No macroscopic abnormalities were seen at terminal necropsy.

There were no adverse effects on litter size, pup weight, pinna unfolding, surfce righting refles or sex ratios. At 16.7 mg/kg/day the group mean total litter weight on Day 4 post partum was significantly ($p<0.05$) increased compared to control weights. This increase was not dose related and so is considered not to be treatment related.

Histopathology:

At 150 mg/kg/day histopathological changes in the livers of both males and females were observed including periportal hepatocyte necrosis, enlargement and basophilia, bile duct

proliferation and periportal fibrosis. The incidence of these findings were statistically significant, compared to control values (ranging from $p<0.05$ - 0.001).

Histopathological changes in the stomach were also observed in two females. Areas of mucosal ulceration were seen on the stomach of one of the females killed in extremis and moderate autolysis was seen on the stomach of another of the females killed in extremis.

Isolated incidences of focal hepatocyte necrosis were observed across all dose groups but were considered incidental as there were no significant differences in incidence or severity between dose groups.

At 50 and 16.7 mg/kg/day there were no treatment-related histopathological changes in the stomach.

Test condition: Test animals:

Number, age, sex per dose: 10 male/ 10 female per dose group. No information on age of parents at study initiation.

Weight at study initiation: males 308 - 366 g, females 196 - 234 g

Test Design:

Vehicle: Corn oil

Mating Procedures:

M/F ratios per cage: 1 male/1 female per cage

Length of cohabitation: up to 14 days (separated as soon as positive evidence of mating found).

Proof of pregnancy: Trays beneath each cage were checked daily for the presence of ejected copulation plugs. Additionally, each female was checked for the presence of a copulation plug in the vagina. A vaginal smear was prepared for each female and the stage of the oestrous cycle or the presence of sperm was recorded. The presence of sperm within the vaginal smear and/or vaginal plug in situ was taken as positive evidence of mating.

Parameters assessed during study:

Morbidity/mortality: Twice daily during the normal working week and once daily on weekends and public holidays.

Clinical observations: Daily, immediately before and after dosing and one hour after dosing.

Bodyweight: During maturation and mating, parents were weighed weekly. Following mating males were weighed weekly until termination. Females showing evidece of mating were weighed on Days 0, 7, 14 and 20 post coitum. Females with a live litter were weighed on Days 1 - 4 post partum.

Food consumption: Weekly/cage for adults during maturation

and for males following mating. For females showing evidence of mating, food consumption was recorded for Days 1-7, 7-14 and 14-20 post coitum. For females with live litters, food consumption was recorded for Days 1-4 post partum.

Pregnancy and parturition: Each pregnant female was observed 3 times daily at or around the period of expected parturition.

Litter data: At the observation of completion of parturition the number of live and dead offspring was recorded. For each litter the following was recorded: number of pups born; number and sex of pups alive recorded daily and reported on Day 1 and 4 post partum; clinical condition of pups from birth to Day 4 post partum; and individual litter weights on Day 1 and 4 post partum.

Physical development: All live offspring were observed for the following landmarks of development: detachment of pinna; surface righting reflex (on Day 1 post partum).

Post mortem studies:

Decedents: All adults kiled in extremis or found dead during the study were examined macroscopically for internal and external abnormalities. All offspring that died or were killed in extremis during the lactation period were examined macroscopically internally and externally.

Necropsy: On day 5 post partum all surviving adults were killed and examined macroscopically for both internal and external abnormalities. All offspring alive on Day 5 were killed and examined macroscopically for internal and external abnormalities.

Organ weights: Testis and epididymides for all adult males were weighed at necropsy and preserved in bouins solution.

Preserved organs: The following list of organs were preserved in buffered 10% formalin for all adult males and females at necropsy: ovaries; pituitary; prostate; liver; stomach; seminal vesicles/coagulating gland; uterus with cervix; and vagina.

Histology/histopathology: The following list of organs were examined at histopathology for all adult males and females from the control and high dose levels and from adult males and females from the low and intermediate dose levels where applicable (shown with *): coagulating glands; epidiymides; prostate; seminal vesicles; testis; liver*; pituitary; ovaries; uterus/cervix; vaginal; and stomach*.

Additional procedures: The corpora lutea of all ovaries from pregnant females were counted at necropsy. The uterine implantation sites were also counted. Additionally, the uteri of apparently non-pregnant females were examined.

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)

Conclusion: Administration of diallyl phthalate to male and female rats throughout maturation, mating, gestation and lactation phases of reproduction resulted in histopathological changes

in the liver at dose levels of 150 mg/kg/day. At the same dose level there was an increased incidence of dystocia which was attributable to treatment. There was no effect on offspring viability, growth and development.

The NOAEL for adults was 50 mg/kg bw/day.

There were no treatment-related effects seen on the fertility of male or female rats as shown by the high pregnancy rate for all treatment groups and the lack of significant differences in the distribution of precoital intervals for all dose groups.

The NOAEL for offspring was 50 mg/kg bw/day.

There was no effect on offspring viability, growth and development from conception to early lactation.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
17-DEC-2004 (37)

5.8.2 Developmental Toxicity/Teratogenicity

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

5.11 Additional Remarks

Type: other: Enhancement of the mutagenicity of amino acid pyrolysates

Method: The enhancement of the mutagenicity of a mutagen, Trp-P-2 (3-amino-1-methyl-5H-pyrido-[4,3-b]indole (CAS. No:62450-07-1) with Ames test.
Result: negative. Phthalic acid enhanced the mutagenicity of the Trp-P-2, i.e. the number of revertants was twice that induced by the mutagen alone.
Test condition: from 0.25 to 500 µmol/plate with 2 as the sequential dose ratio
Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)

24-JAN-2002

Type: other: Multivariate statistics of four in vitro short-term tests for the prediction of mutagenicity or carcinogenicity

Method: The multivariate statistics were carried out for the correlation among the rodent carcinogenicity, the existence of electrophilic sites in the molecules, four in vitro short-term mutagenicity tests: the Salmonella Typhimurium test (STY), the mouse lymphoma mutation (MLY), sister-chromatid exchange (SCE), and chromosomal aberration

test (CHA).

Test substance: Chemical Name: diallyl phthtalate (CAS No. 131-17-9)

Conclusion: The other in vitro short-term mutagenicity tests did not complement the Salmonella typhimurium test for prediction carcinogenicity, but were an important complement for describing the potential genotoxicity of chemicals.

All the endpoints ,refereed in this article, of diallyl phthalate are positive, this article says, according to the results from the four test and the report for rodent carcinogenicity classification by NCI/NTP and the report for the levels of carcinogenic effects derived from Ashby and Tennant (1988).

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