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DIACETONE ALCOHOL
CAS N°:123-42-2

COVER PAGE
SIDS Initial Assessment Report
for
10th SIAM
(Japan, March 15-17, 2000)

Chemical Name: Diacetone Alcohol
CAS No: 123-42-2
Sponsor Country: Japan

National SIDS Contact Point in Sponsor Country: Mr. Kazuhide Ishikawa
Ministry of Foreign Affairs, Japan

HISTORY:

SIDS Testing Plan were reviewed in SIDS Review Process, where the following SIDS Testing Plan was agreed:

no testing ()

testing (X) Water solubility, Vapour pressure, Octanol/water partition coefficient
Stability in water, Biodegradation
Chronic toxicity to daphnia
Acute and Combined repeat dose and reproductive toxicity
Gene mutation, Chromosomal aberration test in vitro

Deadline for circulation: November 30, 1999

Date of Circulation: December 16, 1999

(To all National SIDS Contact Points and the OECD Secretariat)

SIDS INITIAL ASSESSMENT PROFILE

CAS NO.	123-42-2
CHEMICAL NAME	Diacetone Alcohol
STRUCTURAL FORMULA	$ \begin{array}{c} \text{O} \qquad \text{CH}_3 \\ \parallel \qquad \\ \text{CH}_3-\text{C}-\text{CH}_2-\text{C}-\text{OH} \\ \qquad \qquad \qquad \\ \qquad \qquad \qquad \text{CH}_3 \end{array} $
<u>RECOMMENDATIONS OF THE SPONSOR COUNTRY</u>	
The chemical is currently of low priority for further work.	
<u>SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE RECOMMENDATIONS</u>	
Human Health	
<p>Oral LD₅₀ of diacetone alcohol is more than 4,000 mg/kg. This chemical is moderately irritating to skin and irritating to eyes but there is no available data for sensitisation. In oral rat study by an OECD combined repeated dose and reproductive/developmental toxicity screening test [TG 422] at doses of 0, 30, 100, 300 and 1,000 mg/kg/day for at least 44 days, decreased locomotor activity and less response to stimulation by knocking sounds or palpation were observed in males and females of the 300 and 1,000 mg/kg groups. Histopathological examination revealed increases of deposition of hyaline droplets in the proximal tubular epithelium at doses of 100 mg/kg or more, basophilic tubules at doses of 300 and 1,000 mg/kg and dilatation of the distal tubules at dose of 1,000 mg/kg in male kidneys. Slight but no significant increases of dilated distal tubules and fatty degeneration of the proximal tubular epithelium were observed in female kidneys at doses of 300 and 1,000 mg/kg. Furthermore, hepatocellular hypertrophy was evident in both sexes of the 1,000 mg/kg group, and vacuolization of the cells of the zona fasciculata in the adrenals of males receiving 1,000 mg/kg. Based on renal toxicity in male, NOAEL by oral administration was considered 30 mg/kg/day. An inhalation rat study conducted for 6 hr/day, 6 day/week, 6 weeks at doses of 0.232, 1.035 and 4.494 g/m³ demonstrated the histologic changes in the proximal tubules of the kidneys toxicity in males at the highest dose. As only liver weight was increased at mid dose, NOAEL was considered at 1.035 g/m³ for 6 hr/day, 6 day/week. The daily intake is roughly calculated as 156 mg/kg/day. In reproductive /developmental toxicity study [OECD TG 422], there were no statistically significant adverse effects noted at any dose. However, the composite of data at the 1,000 mg/kg suggest there may be chemically related adverse effects such as decreased tendency in the fertility index, number of implantations, implantation index and birth index with two mothers ability not to normally carry the litter. Therefore, a NOAEL for reproductive/developmental toxicity was considered to be 300 mg/kg/day. Evidence of malformations was not observed at any dose. This chemical was not genotoxic in bacterial test and chromosomal aberration test <i>in vitro</i> [OECD TG 471 & 473]. The lowest reported toxic concentration for human is 0.475 g/m³, although the reliability is not sure because of too old study and no detailed information.</p>	

Environment

Diacetone alcohol is readily biodegradable (OECD TG 301C: 100% after 14-day).

The lowest acute and chronic toxicity data were 96h LC₅₀ (420 mg/l) of fish (Bluegill; *Lepomis macrochirus*) and 21d NOEC (>100 mg/l) of *Daphnia magna*, respectively. Assessment factor of 100 was used to chronic toxicity data to determine PNEC, which is >1.0 mg/l. Toxicity of this chemical to aquatic organisms is low, because all toxicity data are higher than 100 mg/l.

Exposure

The production volume is 3,236 tonnes/year in 1995 in Japan. All of this chemical produced in Japan is used as solvent. A generic fugacity model (Mackey level III) shows this chemical would be distributed mainly to water. As this chemical is contained as a solvent for specific paint products and used in industrial sites, user exposure may take place at using sites in the industry.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

None recommended.

FULL SIDS SUMMARY

CAS NO: 123-42-2		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			< - 10 °C
2.2	Boiling Point			169 - 171 °C
2.3	Density			
2.4	Vapour Pressure		OECD	< 1.3 x 10 ² Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD	- 0.14
2.6 A.	Water Solubility		OECD	> 100 g/L at 25 °C
B.	pH			
	pKa			
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			
3.1.2	Stability in Water		OECD	Stable at pH 4 and 7 T _{1/2} = 127 days at pH 9
3.2	Monitoring Data			
3.3	Transport and Distribution		Calculated (Fugacity Level III type)	Release: 100% to Water In Air 0.2 % In Water 99.2 % In Sediment 0.2 % In Soil 0.4 %
			(local exposure)	6.1 x 10 ⁻⁶ mg/L (Japan)
3.5	Biodegradation		OECD TG 301C	Readily biodegradable 100% in 14 days
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	<i>Oryzias latipes</i>	OECD TG 203	LC ₅₀ (96 h): > 100 mg/l LC ₅₀ (14 d): > 100 mg/l
		<i>Lepomis macrochirus</i>	Other	LC ₅₀ (96 h): 420 mg/l
		<i>Menidia beryllina</i>	Other	LC ₅₀ (96 h): 420 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates <i>Daphnia</i>	<i>Daphnia magna</i>	OECD TG 202	EC ₅₀ (48hr): > 1000 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	<i>Selenastrum capricornutum</i>	OECD TG 201	EC ₅₀ (72hr): > 1000 mg/l NOEC: > 1000 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (<i>Daphnia</i>)	<i>Daphnia magna</i>	OECD TG 202	EC ₅₀ (21d,Repro): > 100 mg/l NOEC: > 100 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			None

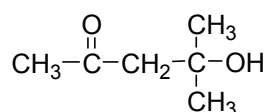
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			None
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Other (unknown)	LD ₅₀ = 4000 mg/kg b.w.
5.1.2	Acute Inhalation Toxicity	Rat	Other (unknown)	LC ₀ = 7.23 g/m ³ /8 h
5.1.3	Acute Dermal Toxicity	Rabbit	Other (unknown)	LD ₅₀ = 13630 mg/kg b.w.
5.2.1	Skin Irritation	Rabbit	Other (unknown)	Moderately irritating
5.2.2	Eye Irritation	Rabbit	Other (unknown)	Irritating
5.4	Repeated Dose Toxicity	Rat	OECD TG 422	NOAEL = 30 mg/kg/day
		Rat	Other (inhalation)	NOAEL = 1.035 g/m ³ /6 h, 6 day/wk
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	<i>S. typhimurium</i> <i>E. coli</i> WP2	Japanese TG and OECD TG 471	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	Chinese hamster CHL cells	Japanese TG and OECD TG 473	- (With metabolic activation) - (Without metabolic activation)
5.6	Genetic Toxicity In Vivo			No data
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOAEL = 300 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			No data
5.11	Experience with Human Exposure			Lowest Toxic Conc. = 475 mg/m ³

SIDS INITIAL ASSESSMENT REPORT

Diacetone Alcohol (CAS No. 123-42-2)

1. IDENTITY

- OECD Name: Diacetone alcohol
- Synonym: Diacetone alcohol; 4-Hydroxy-2-keto-4-methylpentane; 2-Methyl-2-Hydroxy-2-pentanone; Tyranton; Diacetone; 2-Hydroxy-2-methyl-4-pentanone; 4-Hydroxy-4-methylpentan-2-one
- CAS Number: 123-42-2
- Empirical Formula: C₆H₁₂O₂
- Structural Formula:



- Degree of Purity:
- Major Impurity:
- Essential Additives:
- Physical-chemical properties
 - Melting Point: < -10 °C
 - Vapour pressure: < 1.3 x 10² Pa at 20 °C
 - Water solubility: > 100 g/L
 - Log Pow: -0.14

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production and import

The production volume of diacetone alcohol in Japan is 3,236 tonnes/year in 1995.

2.2 Use pattern

All of diacetone alcohol produced in Japan is used as solvent.

2.3 Other information

None

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 General Discussion

Diacetone alcohol is readily biodegradable (OECD 301C: 100 % after 14 days) and stable in water. Direct photodegradation is not expected because diacetone alcohol has not absorption band in UV and VIS region.

Diacetone alcohol is low bioaccumulative based on Log Pow (-0.14 at 25 °C).

The potential environmental distribution of diacetone alcohol obtained from a generic Mackay level III fugacity model is shown in Table 1. Parameters used for this model are shown as Annex to this report. The results show that, if diacetone alcohol is released into water, it is unlikely to be distributed into other compartments. If diacetone alcohol is released into air and soil, it is likely to be distributed in other compartments.

Table 1 Environmental distribution of diacetone alcohol
Using a generic level III fugacity model.

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	23.4 %	0.2 %	0.7 %
Water	46.2 %	99.2 %	40.1 %
Soil	30.2 %	0.2 %	59.0 %
Sediment	0.2 %	0.4 %	0.2 %

As this chemical is used in closed system as an intermediate of chemical products and is used as solvent for some industrial paint not included in consumer products, its release to the environment may occur only from the production site and industrial sites.

3.1.2 Predicted Environmental Concentration

As diacetone alcohol is produced under the well-controlled closed system, amount of release to air phase is negligibly small. The waste of diacetone alcohol from the production system is released to water phase after treated its own wastewater treatment plant. Therefore, Predicted Environmental Concentration (PEC) will be calculated only for the water environment.

a. Regional exposure

According to report from a Japanese manufacturer, 147 kg/year (measured) of diacetone alcohol are treated in its own wastewater treatment plant with 85% of removal rate and are released with 3.6×10^{10} L/year of effluent into river. Local Predicted Environmental Concentration (PEC_{local}) is calculated to be 6.1×10^{-6} mg/L as a worst case scenario, employing the following calculation model and dilution factor of 100.

$$\frac{\text{Amount of release (1.47 x 10}^8 \text{ mg/y) x (1- Removal rate (85\%))}}{\text{Volume of effluent (3.6 x 10}^{10} \text{ L/y) x Dilution Factor (100)}}$$

3.2 Effects on the Environments

3.2.1 Effects on aquatic organisms

Acute and chronic toxicity data of diacetone alcohol to aquatic organisms are summarized in Table 2.

As the lowest acute and chronic toxicity data, 96h LC50 of Bluegill (420 mg/l) and 21d NOEC for reproduction of *Daphnia magna* (>100 mg/l) were selected, respectively (Table 2).

An assessment factor of 100 was chosen and applied to chronic toxicity data to determine PNEC, according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects (EXCH/MANUAL/96-4-5.DOC/May 1996), because chronic toxicity data for fish was not available. Thus, PNEC of diacetone alcohol is >1 mg/l.

Table 2. Acute and chronic toxicity data of diacetone alcohol to aquatic organisms at different trophic levels.

Species	Endpoint	Conc. (mg/l)	Remarks
<i>Selenastrum capricornutum</i> (algae)	Bms 72h EC50	> 1000	a, 1)
	Do. 72h NOEC	> 1000	c, 1)
<i>Daphnia magna</i> (Water flea)	Imm 24h EC50	> 1000	a, 1)
	Rep 21d EC50	> 100	c, 1)
	Rep 21d NOEC	> 100	c, 1), C
<i>Oryzias latipes</i> (fish, Medaka)	Mor 96h LC50	> 100	a, 1)
	Mor 14d LC50	> 100	a, 1)
<i>Lepomis macrochirus</i> (Bluegill)	Mor 96h LC50	420	a, 2), A

Notes: Bms; growth measured by biomass change, Mor; mortality, Rep; reproduction,

1),2); reference number, A), C); the lowest values of the acute (a) or chronic (c) toxicity data among algae, cladocera (water flea) and fishes.

References; 1) Environment Agency of Japan (1997), 2) Dawson, G.W., Jennings, A.L., Drozdowski, D. and Roder, E. (1977)

3.2.2 Terrestrial effects

No data available

3.2.3 Other effects

No data available

3.3 Initial Assessment for the Environment

Diacetone alcohol is readily biodegradable, and its potential for bioaccumulation is low based on low Log Pow. All toxicity data obtained were higher than 100 mg/l. Thus, this chemical is not hazardous to the aquatic environment.

PNEC of this chemical is > 1 mg/l based on 21d NOEC of *Daphnia* and the assessment factor 100. PEC from Japanese local exposure scenario is 6.1×10^{-6} mg/l. Thus,

$$PEC_{\text{local}} / PNEC = 6.1 \times 10^{-6} / >1 = <6.1 \times 10^{-6} < 1$$

4. HUMAN HEALTH

4.1 Human Exposure

4.1.1 Occupational exposure

Diacetone alcohol is produced in closed systems and used as a solvent. The occupational exposures in production sites are expected through inhalation and dermal route. The atmospheric concentration was measured at two production sites. The average concentrations, working schedules and EHEs for each operation are shown in the Table. Dermal exposure is also calculated, based on EASE model. The duration of dermal exposure is assumed to be 5 minutes. If a single worker (body weight; 70 kg, respiratory volume; 1.25 m³/hr) is assigned to implement all daily operation without protection, the highest daily intake (combined EHE) is calculated as 0.028 mg/kg/day as the worst case. Practically, workers always wear protective gloves and respiratory protective equipment (mask) during the operation.

	Frequency Times/day	Duration hr	Working hr/day	Average Concentration mg/m ³	Average EHE mg/kg/day	Combined EHE mg/kg/day
Case 1						
Sampling	3/7	0.05	0.022	<1.27	0.00048	
Sampling	1/30	0.05	0.002	0.95	0.00003	
Dermal			0.083	0.1 *	0.00625	0.0068
Case 2						
Drum Filling	0.1	2.50	0.250	1.23	0.00548	
Sampling	2	0.03	0.067	13.89	0.01654	
Dermal			0.083	0.1 *	0.00625	0.028

* dermal exposure; mg/cm²/day

EHE: Estimated Human Exposure

Diacetone alcohol is used as a solvent for some limited paints. The purpose of use is to adjust the solubility of paint resins and regulate the evaporation rate. The paints containing diacetone alcohol are used at the painting process of specific products in industrial sites but not in general such as construction materials, iron structural materials, etc. This chemical is contained in range from 1 to 5 % in low content cases and from 10 to 20 % in high content cases. Some Japanese company produces a few of products containing the high amount of diacetone alcohol and tens of products containing the low amount, among ten thousands of various kinds of paint products. The paint products containing diacetone alcohol are approx. 0.2 % of total paint products. Therefore, user exposure may take place at using sites in the industry but exposure level can not be estimated because of product confidential.

4.1.2 Consumer exposure

Diacetone alcohol is used as a solvent of paints in the industry. Therefore consumer exposure is not considered in Japan.

4.1.3 Indirect exposure via the environment

Although diacetone alcohol is readily biodegradable and low bioaccumulative, the exposure to the general population via the environment would be possible through drinking water processed from surface water and through fish which may accumulate this chemical.

The concentration in drinking water should be estimated to be equal to PEC calculated in Section 3.1, i.e. 6.1×10^{-6} mg/l. The daily intake through drinking water is calculated as 2.03×10^{-7} mg/kg/day (2 l/day, 60 kg b.w.).

Using the bioconcentration factor of 0.5 estimated from log Pow (0.14), the concentration of this chemical in fish can be calculated as follows:

$$\text{PEC}_{\text{fish}} = (6.1 \times 10^{-6} \text{ mg/l}) \times 0.5 = 3.05 \times 10^{-9} \text{ mg/g-wet}$$

As a daily intake of fish in Japan is estimated to be 90 g for 60 kg body weight person, a daily intake of this chemical will be 4.58×10^{-9} mg/kg/day.

4.2 Effects on Human Health

a) Acute toxicity

[SIDS data] Oral LD₅₀ value of rats was 4,000 mg/kg b.w. [Smyth & Carpenter: 1948]. Narcosis, decrease of blood pressure, respiratory failure, hemolytic effects (decreased in the hemoglobin and numbers of erythrocytes) and hepatic lesions after oral administration of a sublethal dose were observed.

Oral LD₅₀ values for mice and rabbits were 3,950 and 4,653 mg/kg b.w., respectively. No lethality of rats was reported by inhalation for 8 hrs at 7.23 g/m³. Dermal LD₅₀ for rabbits was 13,630 mg/kg b.w. Although LD₅₀ of 933 mg/kg b.w by i.p. was shown in mice, the lowest lethal doses of rats by i.v. route and rabbits by either i.v. or i.m. route were reported to be approx. 3,000 mg/kg b.w..

For human, effects on sense organs and special senses (eye), and headache, nausea or vomiting were reported at the lowest published toxic concentration of 475 mg/m³ (Silverman, *et al.*: 1946).

b) Irritation

Moderate skin irritation by 500 mg of application (Union Carbide Data Sheet: 1959) and moderate or highly irritating to eyes (*Am. J. Ophthalmol.*: 1946, Grant: 1974) in rabbits were reported. This chemical is irritant to eyes in IUCLID labelling and classification as in Directive 67/548/EEC.

Irritation of eyes, nose and throat was produced during an exposure of 15 min to concentrations of 100 ppm (475 mg/m³), and the majority of volunteer subjects complained of an unpleasant odour and taste at this level (Silverman, *et al.*: 1946).

c) Sensitisation

There are no available data.

d) Repeated toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test [OECD TG 422]. Administration was conducted at doses of 0 (vehicle; distilled water), 30, 100, 300 and 1,000mg/kg/day by gavage for 44 days in males and from 14 days before mating to day 3 of lactation in females. [MHW, Japan: 1997]

Changes in general condition, such as decreased locomotor activity and less response to stimulation by knocking sounds or palpation, were noted at the early stage of the administration period in males and females of the 300 and 1,000 mg/kg groups. A decrease in body weight gain was noted during the pre-mating period in females of the 1,000 mg/kg group. One female of this group had to be killed in extremes because of difficulty in delivery. Hematological and blood chemical examinations revealed increases of platelet count, GOT, total protein, total cholesterol, total bilirubin, blood urea nitrogen, creatinine and calcium, and a decrease of glucose at the dose of 1,000 mg/kg in males. Histopathological examination revealed increases of deposition of hyaline droplets in the proximal tubular epithelium at doses of 100 mg/kg or more, basophilic tubules at doses of 300 and 1,000 mg/kg and dilatation of the distal tubules at dose of 1,000 mg/kg in male kidneys. Slight but no significant increases of dilated distal tubules and fatty degeneration of the proximal tubular epithelium were observed in female kidneys at doses of 300 and 1,000 mg/kg. Hepatocellular hypertrophy was evident in both sexes of the 1,000 mg/kg group, and vacuolization of the cells of the zona fasciculata in the adrenals of males receiving 1,000 mg/kg. The NOAELs for repeat dose toxicity are considered to be 30 mg/kg/day for males and 100 mg/kg/day for females.

Oral toxicity study was performed in rats by drinking water at doses of 10 and 40 mg/kg for 30 days. There was some evidence of micropathological alteration at 40 mg/kg. [Smyth & Carpenter: 1948] However, this study is too old and there is no further detailed information.

Inhalation study in rat was conducted for 6 hr/day, 6 day/week, 6 weeks at doses of 0.232, 1.035 and 4.494 g/m³. There were no deaths during the experiment. At 4.494 g/m³, slight lethargy during and after exposure, reduced body weight gains and increased plasma LDH in females, increased liver and kidney weights were noted. Histologic changes in the proximal tubules of the kidneys were observed in males. At 1.035 g/m³, only liver weight was increased. Concentration of 1.035 g/m³ was considered as NOAEL. [SHELL Research Ltd: 1979]

e) Reproductive/developmental toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test at doses of 0 (vehicle; distilled water), 30, 100, 300 and 1,000 mg/kg. [MHW, Japan: 1997]

Only in the highest dose of 1,000 mg/kg, there was a tendency for decrease of reproductive parameters including fertility index, number of implantations and implantation index. In this group, one female with difficulty in delivery was killed and another with litter loss due to cannibalism or death was observed. There was also a tendency for decrease of developmental parameters such as total number of pups born, delivery index, live birth index, number of pups alive and viability index on day 4 of lactation, etc. at the highest dose. Although all of these changes were not statistically significant, it was considered that diacetone alcohol cause reproductive/developmental effects in the highest dose group of 1,000 mg/kg. Therefore, 300 mg/kg was considered as the NOAEL for reproductive/developmental toxicity.

f) Genetic toxicity

Bacterial test

[SIDS data] Diacetone alcohol was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *uvrA*, with or without an exogenous metabolic activation system. [MHW, Japan: 1997]

Another *Salmonella typhimurium* study indicated the negative results with or without metabolic activation. Mitotic recombination study in *Saccharomyces cerevisiae* showed the negative results with or without metabolic activation. [Brooks et al.: 1988]

Non-bacterial test in vitro

[SIDS data] Genotoxicity of diacetone alcohol was studied by chromosomal aberration test in cultured Chinese hamster lung (CHL/IU) cells. Structural chromosomal aberrations and polyploidy were not induced up to a maximum concentration of 1.2 mg/ml (10 mM) on continuous treatment, and with short-term treatment, with and without an exogenous metabolic activation system. [MHW, Japan: 1997]

4.3 Initial Assessment for Human Health

Oral LD₅₀ of diacetone alcohol is more than 4,000 mg/kg. This chemical is moderately irritating to skin and irritating to eyes but there is no available data for sensitisation. In an OECD combined repeated dose and reproductive/developmental toxicity screening test of rats by gavage, neurotoxicity was observed at and above 300 mg/kg groups. Histopathological examination revealed increases of deposition of hyaline droplets in the proximal tubular epithelium at doses of 100 mg/kg or more, basophilic tubules at doses of 300 and 1,000 mg/kg and dilatation of the distal tubules at dose of 1,000 mg/kg in male kidneys. Slight but no significant increases of dilated distal tubules and fatty degeneration of the proximal tubular epithelium were observed in female kidneys at doses of 300 and 1,000 mg/kg. Hepatocellular hypertrophy was evident in both sexes of the 1,000 mg/kg group, and vacuolization of the cells of the zona fasciculata in the adrenals of males receiving 1,000 mg/kg. Based on renal toxicity in male, NOAEL by oral administration was considered 30 mg/kg/day. In a rat inhalation study conducted for 6 hr/day, 6 day/week, 6 weeks at concentrations of 0.232, 1.035, 4.494 g/m³, the histological changes were induced in the proximal tubules of the kidneys in males at the highest dose. As only liver weight was increased at mid dose, NOAEL was considered at 1.035 g/m³. The daily intake is roughly calculated as 156 mg/kg/day. In reproductive/developmental toxicity study, there is some evidence that diacetone alcohol caused significant reproductive/developmental effects in rats at 1,000 mg/kg/day. The NOAEL for reproductive/developmental in animal is 300 mg/kg/day. This chemical was not genotoxic in bacterial test and chromosomal aberration test in vitro.

Occupational exposure

Diacetone alcohol is produced in a closed system at industries and workers wear protective gloves and respiratory protective equipment during the sampling operation. As the exposure route for human may be an inhalation and skin in limited workers, the atmosphere concentration was measured at two production sites. Based on the highest concentration and the possibility of exposure period, the daily intake including dermal exposure is calculated as 0.028 mg/kg/day as the worst case. Occupational risk is presumably low because the margin of safety is 1070, based on the oral NOAEL of 30 mg/kg/day.

This chemical is used as a solvent of paints for specific products in industrial sites. This chemical is contained in range from 1 to 5 % in low content cases and from 10 to 20 % in high content cases. The paint products containing diacetone alcohol are approx. 0.2 % of total paint products in certain Japanese company. User exposure may take place at using sites in the industries but exposure level can not be estimated because of product confidential.

Consumer exposure

This chemical is not used for consumer products. Therefore, no exposure is expected.

Indirect exposure via environment

As for indirect exposure via environment, PEC_{local} of 6.10×10^{-6} mg/l from local exposure scenario was used for the estimation. The daily intakes through drinking water and fish are calculated as 2.03×10^{-7} mg/kg/day and 4.58×10^{-9} mg/kg/day, respectively. Since the margin of safety is very large, such as 1.48×10^8 for drinking water and 6.56×10^9 for fish, health risk is presumably low.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Exposure

The production volume is 3,236 tonnes/year in 1995 in Japan. All of this chemical produced in Japan is used as solvent. A generic fugacity model (Mackey level III) shows this chemical would be distributed mainly to water. As this chemical is contained as a solvent for specific paint products and used in industrial sites, user exposure may take place at using sites in the industry.

Hazards to the Environment

Diacetone alcohol is readily biodegradable (OECD TG 301C: 100% after 14-days). The lowest acute and chronic toxicity data were 96h LC_{50} (420 mg/l) of fish (Bluegill; *Lepomis macrochirus*) and 21d NOEC (>100 mg/l) of *Daphnia magna*, respectively. Assessment factor of 100 was used to chronic toxicity data to determine PNEC, which is >1.0 mg/l. Toxicity of this chemical to aquatic organisms is low, because all toxicity data are higher than 100 mg/l.

Human Health Harzards

Oral LD_{50} of diacetone alcohol is more than 4,000 mg/kg. This chemical is moderately irritating to skin and irritating to eyes but there is no available data for sensitisation. In oral rat study by an OECD combined repeated dose and reproductive/developmental toxicity screening test [TG 422] at doses of 0, 30, 100, 300 and 1,000 mg/kg/day for at least 44 days, decreased locomotor activity and less response to stimulation by knocking sounds or palpation were observed in males and females of the 300 and 1,000 mg/kg groups. Histopathological examination revealed increases of deposition of hyaline droplets in the proximal tubular epithelium at doses of 100 mg/kg or more, basophilic tubules at doses of 300 and 1,000 mg/kg and dilatation of the distal tubules at dose of 1,000 mg/kg in male kidneys. Slight but no significant increases of dilated distal tubules and fatty degeneration of the proximal tubular epithelium were observed in female kidneys at doses of 300 and 1,000 mg/kg. Furthermore, hepatocellular hypertrophy was evident in both sexes of the 1,000 mg/kg group, and vacuolization of the cells of the zona fasciculata in the adrenals of males receiving 1,000 mg/kg. Based on renal toxicity in male, NOAEL by oral administration was considered 30 mg/kg/day. An inhalation rat study conducted for 6 hr/day, 6 day/week, 6 weeks at doses of 0.232, 1.035 and 4.494 g/m³ demonstrated the histologic changes in the proximal tubules of the kidneys toxicity in males at the highest dose. As only liver weight was increased at mid dose, NOAEL was considered at 1.035 g/m³ for 6 hr/day, 6 day/week. The daily intake is roughly calculated as 156 mg/kg/day. In reproductive /developmental toxicity study [OECD TG 422], there were no statistically significant adverse effects noted at any dose. However, the composite of data at the 1,000 mg/kg suggest there may be chemically related adverse effects such as decreased tendency in the fertility index, number of implantations, implantation index and birth index with two mothers ability not to normally carry the litter. Therefore, a NOAEL for reproductive/developmental toxicity was considered to be 300 mg/kg/day. Evidence of malformations was not observed at any dose.

This chemical was not genotoxic in bacterial test and chromosomal aberration test *in vitro* [OECD TG 471 & 473]. The lowest reported toxic concentration for human is 0.475 g/m³, although the reliability is not sure because of too old study and no detailed information.

5.2 Recommendations

None recommended.

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Appendix 1

Method for Prediction of Environmental Concentration of Pollutant in Surface Water

1. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into river

When decomposition, precipitation and vaporization of pollutant can be ignored, it is used that simplified equation by complete mixing model shown with equation (1) to calculate predicted environmental concentration in the local environment (PEC_{local}) as for release effluent into river.

$$PEC_{local} \text{ (mg/L)} = \frac{C_o Q + C_s Q_s}{Q + Q_s} \quad (1)$$

Where

C_o : Concentration of pollutant in upper stream of release point (mg/L)

C_s : Concentration of pollutant in effluent (mg/L)

Q : Flow rate of river (m^3/day)

Q_s : Flow rate of effluent released into river (m^3/day)

At the equation (1), when C_o can be considered as 0, dilution factor of pollutant in the river (R) can be shown with following equation.

$$R = C_s/C = (Q + Q_s) / Q_s \quad (2)$$

As the worst case, it is used to employ a flow rate at dry season as flow rate of river (Q). When flow rate at dry season is indistinct, it is estimated using the following equation in Japan.

$$\text{Flow rate at dry season} = \text{mean flow rate} / 2.5 \quad (3)$$

2. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into sea

For prediction of concentration of pollutant in the sea water with effluent, it is employed generally Joseph-Sendner's equation (4). This equation is one of analytic solution led under the following conditions from diffusion equation.

- 1 It is adopted large area of sea or lake.
- 2 The flow rate of effluent and concentration of pollutant in the effluent are constant, and distribution of concentration is able to regard as equilibrium state.
- 3 Effluent is distributed uniformly to vertical direction, and it spreads in a semicircle or segment to horizontal direction.
- 4 Diffusion coefficient of pollutant at the sea is in proportion to distance from release point of effluent.
- 5 There is not any effect of tidal current.
- 6 Decomposition of pollutant can be ignored.

$$C(x) = (C_s - C(r)) \left(1 - \exp \left(- \frac{Q_s}{\theta d p} \left(\frac{1}{x} - \frac{1}{r} \right) \right) \right) + C(r) \quad (4)$$

Where

- $C(x)$: Concentration of pollutant at distance x (m) from release point
 C_s : Concentration of pollutant in effluent
 $C(r)$: Concentration of pollutant at distance r (m) from release point
 Q_s : Flow rate of effluent (m^3/day)
 θ : Opening angle of seacoast (rad.)
 d : Thickness of diffusion layer (m)
 P : Diffusion velocity (m/day) (1.0 ± 0.5 cm/sec)

When $C(x)$ is 0 at $r = \infty$ and density stratification is ignored for simplification, Joseph-Sendner's equation (4) is simplified to equation (5)

$$C(x) = C_s \left(1 - \exp \left(- \frac{Q_s}{\theta d p x} \right) \right) \quad (5)$$

Because of $Q_s / \theta d p x \ll 1$ except vicinity of release point, dilution factor in distance x from release point $R(x)$ can be shown with equation (6).

$$R(x) = C_s / C(x) = \theta d p x / Q_s \quad (6)$$

When it is employed following parameters in equation (6) as default, dilution factor R can be shown with equation (7).

$$P = 1 \text{ cm/sec (860 m/day)}$$

$$\theta = 3.14$$

$$d = 10 \text{ m}$$

$$x = 1000 \text{ m}$$

$$R = 2.7 \times 10^7 / Q_s \quad (7)$$

Q_s : volume of effluent (m^3/day)

REVISED OECD HPV FORM 1

SIDS DOSSIER

ON THE HPV PHASE 5 CHEMICAL

Diacetone Alcohol

CAS No. 123-42-2

Sponsor Country: Japan

DATE: December 1, 1999

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6. REFERENCES

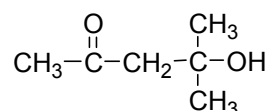
Appendix

Note: *; Data elements in the SIDS

†; Data elements specially required for inorganic chemicals

1. GENERAL INFORMATION**1.01 SUBSTANCE INFORMATION**

- *A. CAS number** 123-42-2
- B. Name (IUPAC name)** 4-Hydroxy-4-methylpentan-2-one
- *C. Name (OECD name)** Diacetone alcohol
- †D. CAS Descriptor**
- E. EINECS-Number** 204-626-7
- F. Molecular Formula** C₆H₁₂O₂
- *G. Structural Formula**

**H. Substance Group****I. Substance Remark****J. Molecular Weight** 116.16**1.02 OECD INFORMATION****A. Sponsor Country:** Japan**B. Lead Organisation:**

Name of Lead Organisation: Ministry of Health and Welfare (MHW)
 Ministry of International Trade and Industry (MITI)
 Environmental Agency (EA)
 Ministry of Labour (MOL)

Contact person: Mr. Kazuhide Ishikawa
 Director, Second International Organization Bureau
 Ministry of Foreign Affairs

Address:

Street: 2-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100 Japan
 Tel: 81-3-3581-0018
 Fax: 81-3-3503-3136

C. Name of responder

Name: Same as above contact person

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

element []; inorganic []; natural substance []; organic [**X**]; organometallic []; petroleum product []

B. Physical State (at 20°C and 1.013 hPa)

gaseous []; liquid [**X**]; solid []

C. Purity

99.6 %

1.2 SYNONYMS

Diacetone alcohol; 4-Hydroxy-2-keto-4-methylpentane; 2-Methyl-2-pentanol-4-one; Acetonyldimethylcarbinol; Diketone Alcohol; 4-Methyl-4-Hydroxy-2-pentanone; Tyranton; Diacetone; 2-Hydroxy-2-methyl-4-pentanone; 4-Hydroxy-4-methylpentan-2-one

1.3 IMPURITIES

None

1.4 ADDITIVES

None

***1.5 QUANTITY**

Remarks: 3,236 tonnes/year
Reference: MITI, Japan

1.6 LABELLING AND CLASSIFICATION

R11 Highly flammable.
R36 Irritating to eyes.

1.7 USE PATTERN*A. General****Type of Use:****Category:**

main	Solvent
industrial	Solvent
use	Solvent for paints

Remarks: None
Reference: MITI

1.8 OCCUPATIONAL EXPOSURE LIMIT

None

*1.9 SOURCES OF EXPOSURE

In Japan, this chemical is produced in 2 companies.

Source: Media of release: Bay
Quantities per media: 147 kg/year

Although consumer exposure is considered, details are not known.

Remarks:
Reference: MITI, Japan

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value: < -10 °C
Decomposition: Yes No Ambiguous
Sublimation: Yes No Ambiguous
Method:
GLP: Yes No ?
Remarks:
Reference: MITI, Japan

*2.2 BOILING POINT

Value: 169 - 171 °C
Pressure: 1,018 Pa
Decomposition: Yes No Ambiguous
Method:
GLP: Yes No ?
Remarks:
Reference: MITI, Japan

*2.4 VAPOUR PRESSURE

Value: < 1.3 x 10² Pa
Temperature: 20 °C
Method: calculated ; measured
OECD TG 104
GLP: Yes No ?
Test substance: purity: 99.1 %
Remarks:
Reference: MITI, JAPAN.

*2.5 PARTITION COEFFICIENT log₁₀P_{ow}

Log Pow: - 0.14

Temperature: 25 °C
 Method: calculated []; measured [X]
 OECD TG 107
 GLP: Yes [X] No [] ? []
 Test substance: purity: 99.1 %
 Remarks:
 Reference: MITI, JAPAN.

*2.6 WATER SOLUBILITY

A. Solubility

Value: > 100 g/l
 Temperature: 25 °C
 Description: Miscible []; Of very high solubility [];
 Soluble [X]; Slightly soluble []; Of low solubility [];
 Of very low solubility []; Not soluble []
 Method: OECD TG 105
 GLP: Yes [X] No [] ? []
 Remarks:
 Reference: MITI, JAPAN.

B. pH Value, pKa Value

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

*3.1.2 STABILITY IN WATER

Type: Abiotic (hydrolysis) [X]; biotic (sediment)[]
 Half life: Stable in pH 4 and 7 at 25 °C
 127 days in pH 9 at °C
 Method: OECD TG 111
 GLP: Yes [X] No [] ? []
 Test substance: purity: 99.1 %
 Remarks:
 Reference: MITI, JAPAN.

*3.2 MONITORING DATA (ENVIRONMENTAL)

Type of Measurement: Background []; At contaminated site []; Other []
 Media:
 Results:
 Remarks:
 Reference:

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION

***3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)**

Media: Air-biota []; Air-biota-sediment-soil-water [x]; Soil-biota [];
Water-air []; Water-biota []; Water-soil []; Other []

Method: Fugacity level I []; Fugacity level II []; Fugacity level III [x];
Fugacity level IV []; Other (calculation) []; Other (measurement)[]

Results:

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	23.4 %	0.2 %	0.7 %
Water	46.2 %	99.2 %	40.1 %
Soil	30.2 %	0.2 %	59.0 %
Sediment	0.2 %	0.4 %	0.2 %

Remarks: Appendix 1
Reference: MITI. Japan

***3.5 BIODEGRADATION**

Type: aerobic [X]; anaerobic []

Inoculum: adapted []; non-adapted [X];

Concentration of the chemical: related to COD []; DOC []; test substance [X]

Medium: water [X]; water-sediment []; soil []; sewage treatment []

Degradation: 90.3 % by BOD after 14 days
92 % by TOC after 14 days
100 % by GC after 14 days

Results: readily biodeg. [X]; inherently biodeg. []; under test condition no
biodegradation observed [], other []

Method: OECD TG 301C

GLP: Yes [X] No [] ? []

Test substance: Purity: 98.0 %

Reference: MITI, JAPAN.

4. ECOTOXICITY***4.1 ACUTE/PROLONGED TOXICITY TO FISH**

(a)

Type of test: static []; semi-static [X]; flow-through []; other (*e.g. field test*) []
open-system [X]; closed-system []

Species: Medaka (*Oryzias latipes*)

Exposure period: 96 h

Results: LC₅₀ (96h) > 100 mg/l

Analytical monitoring: Yes [X] No [] ? []

Method: OECD TG 203 (1992)

GLP: Yes [X] No [] ? []

Test substance: As prescribed by 1.1 - 1.4, purity: 99.6 %

Remarks: Groups of ten Medaka were placed to nominal concentration of 100 mg/l and dechlorinated tap water as control. Test water was renewed every 24h. Measured concentration after 24h was 99% of the nominal concentration.

Reference: Environment Agency of JAPAN (1996)

(b)

Type of test: static []; semi-static []; flow-through [**X**]; other (*e.g. field test*) []
open-system [**X**]; closed-system []

Species: Medaka (*Oryzias latipes*)

Exposure period: 14 d

Results: $LC_{50} (14d) > 100$ mg/l

Analytical monitoring: Yes [**X**] No [] ? []

Method: OECD TG 203 (1992)

GLP: Yes [**X**] No [] ? []

Test substance: As prescribed by 1.1 - 1.4, purity: 99.6 %

Remarks: Groups of ten Medaka were placed to nominal concentration of 100 mg/l and dechlorinated tap water as control. Measured concentrations were between 82 and 100% of the nominal concentration over the test period

Reference: Environment Agency of JAPAN (1996)

(c)

Type of test: static [**X**]; semi-static []; flow-through []; other (*e.g. field test*) []
open-system []; closed-system []

Species: Bluegill sunfish (*Lepomis macrochirus*)

Exposure period: 96 h

Results: $LC_{50} (96 h) = 420$ mg/l

Analytical monitoring: Yes [] No [] ? [**X**]

Method: Other

GLP: Yes [] No [] ? [**X**]

Test substance: Unknown

Remarks: Acclimated for 14 d before testing. 33-75 mm-size fish were used. If dissolved oxygen was being depleted rapidly, aeration was initiated. Potable well water (pH 7.6-7.9, hardness 55 mg/l as CaCO₃) was used as dilution water for testing. One liter of water was used for 1 g of fish. Three concentrations of the chemical were examined to calculate median lethal concentrations (LC50).

Reference: Dawson GW, Jennings AL, Drozdowski D & Rider E (1975/1977)

(d)

Type of test: static [**X**]; semi-static []; flow-through []; other (*e.g. field test*) []
open-system []; closed-system []

Species: Tidewater silversides (*Menidia beryllina*)

Exposure period: 96 h

Results: $LC_{50} (96 h) = 420$ mg/l

Analytical monitoring: Yes [] No [] ? [**X**]

Method: Other

GLP: Yes [] No [] ? [**X**]

Test substance: Unknown

Remarks: Acclimated for 14 d before testing. 40-100 mm-size fish were used. Continuously aerated during test period. Potable well water (pH 7.6-7.9, hardness 55 mg/l as CaCO₃) was used as the base for a synthetic seawater mix, added by the synthetic sea salt mix. One liter of water was used for 1 g of fish. Three concentrations of the chemical were examined to calculate median lethal concentrations (LC50).

Reference: Dawson GW, Jennings AL, Drozdowski D & Rider E (1975/1977)

*4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type of test: static []; semi-static [**X**]; flow-through []; other (*e.g. field test*) []; open-system [**X**]; closed-system []

Species: *Daphnia magna*.

Exposure period: 48 h

Results: EC₅₀ (48h) > 1000 mg/l

Analytical monitoring: Yes [**X**] No [] ? []

Method: OECD TG 202

GLP: Yes [**X**] No [] ? []

Test substance: As prescribed by 1.1 - 1.4 , purity: 99.6 %

Remarks: 20 daphnids (4 replicates; 5 organisms per replicate) were placed to nominal concentration of 1000 mg/l and dechlorinated tap water as control. Test water was renewed after 24h. Measured concentration after 24h was 97% of the nominal concentration.

Reference: Environment Agency of JAPAN (1996).

*4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

Species: *Selenastrum capricornutum* ATCC 22662

Endpoint: Biomass [**X**]; Growth rate []; Other []

Exposure period: 72 h

Results: Biomass EC₅₀ (72h) > 1000 mg/l
(Endpoint) NOEC > 1000 mg/l

Analytical monitoring: Yes [**X**] No [] ? []

Method: OECD TG 201 (1984)
open-system []; closed-system [**X**]

GLP: Yes [**X**] No [] ? []

Test substance: As prescribed by 1.1 - 1.4, purity: 99.6 %

Remarks: Static test. The EC₅₀ value for biomass was calculated based on measured concentration (1000 mg/l).

Reference: Environment Agency of JAPAN (1996)

4.4 TOXICITY TO BACTERIA (*Single species tests and tests on overall processes such as nitrification or soil respiration are included in this item.*)

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH (*effects on reproduction, embryo/larva, etc.*)

(*) 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test: static []; semi-static [**X**]; flow-through []; other (*e.g. field test*) []; open-system [**X**]; closed-system []

Species: *Daphnia magna*

Endpoint: Mortality []; Reproduction rate [**X**]; Other [**X**]

Exposure period: 21 d

Results: Reproduction rate: EC₅₀ (21 d) > 100 mg/l
(*Endpoint*) NOEC > 100 mg/l

Analytical monitoring: Yes [**X**] No [] ? []

Method: OECD TG 202(1984)

GLP: Yes [**X**] No [] ? []

Test substance: As prescribed by 1.1 - 1.4 , purity: 99.6 %

Remarks: 40 daphnids (4 replicates; 10 daphnids per replicate) were placed to nominal concentration of 100 mg/l and dechlorinated tap water as control. Test water was exchanged with freshly prepared one 2-3 times a week. Measured concentrations in the freshly prepared test solution and just before renewal were between 84-97% and 80-97%, respectively.

Reference: Environment Agency of JAPAN (1996)

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data

4.8 BIOTRANSFORMATION AND KINETICS

No data

4.9 ADDITIONAL REMARKS

5. TOXICITY

*5.1