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**High Production Volume (HPV)  
Chemical Challenge Program**

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**Data Review and Assessment**

**for**

**Allyl Alcohol**

**CAS RN 107-18-6**

June 02, 2005

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High Production Volume (HPV) Chemical Challenge  
Data Review and Assessment**

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## Plain English Summary

This document reviews and evaluates the data available for the EPA High Production Volume (HPV) chemical endpoints (physical-chemical properties, environmental fate and pathways, ecotoxicity and human/mammalian health effects) for allyl alcohol (CAS Registry Number 107-18-6).

There is adequate information available for allyl alcohol to meet all the HPV Chemical Challenge requirements for physical-chemical properties, environmental fate and pathways, ecotoxicity, and mammalian/human health effects

Allyl alcohol is an intermediate chemical used primarily in the manufacture of other chemicals. It is a clear, colorless liquid with a strong, mustard-like odor. Allyl alcohol is not persistent in the environment. It oxidizes at a moderate rate in the atmosphere and is expected to biodegrade in soil and water. It is expected to partition primarily to water and is not expected to bioaccumulate in food chains. Allyl alcohol is very toxic towards aquatic species. Allyl alcohol presents an acute toxic hazard to humans after exposure via inhalation, ingestion and skin contact. It is irritating or severely irritating to the eye, and may cause skin irritation especially if contact is repeated or prolonged. Results from repeat exposure studies in animals indicate it may pose a serious risk to health after prolonged exposure, with the lung, liver and kidneys identified as potential target organs. Results from *in vitro* genotoxicity tests of allyl alcohol are generally positive; whereas results from *in vivo* studies are consistently negative. There was no increase in tumors in rats exposed for 2 years via drinking water. Severe maternal toxicity (weight loss and liver toxicity) in pregnant animals resulted in pregnancy loss following oral exposures. No teratogenic or developmental effects were noted in the offspring from dams without pregnancy loss. No adverse changes were present in gonad structure or sperm parameters in rats after oral treatment.

**Data Assessment**

Allyl Alcohol CAS RN: 107-18-6		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY		Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
<b>PHYSICAL - CHEMICAL DATA</b>								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.4	Vapor Pressure	Y	N	N	Y	N	Y	N
2.5	Partition Coefficient	Y	N	N	Y	N	Y	N
2.6	Water Solubility	Y	N	N	Y	N	Y	N
<b>ENVIRONMENTAL FATE AND PATHWAYS DATA</b>								
3.1.1	Photodegradation	Y	N	N	Y	N	Y	N
3.1.2	Stability in Water	Y	N	N	N	N	Y	N
3.4	Transport and Distribution	Y	N	N	N	Y	Y	N
3.5	Biodegradation	Y	N	N	N	Y	Y	N
<b>ECOTOXICOLOGICAL DATA</b>								
4.1	Acute Toxicity to Fish	Y	N	N	Y	N	Y	N
4.2	Toxicity to Daphnia	Y	Y	Y	Y	N	Y	N
4.3	Acute Toxicity to Algae	Y	Y	Y	N	N	Y	N
<b>TOXICOLOGICAL DATA</b>								
5.1	Acute Toxicity	Y	N	N	Y	N	Y	N
5.4	Repeated Dose Toxicity	Y	N	N	Y	N	Y	N
5.5	Genotoxicity <i>In Vitro</i>	Y	Y	Y	Y	N	Y	N
5.6	Genotoxicity <i>In Vivo</i>	Y	N	Y	Y	N	Y	N
5.8	Reproductive Toxicity	Y	N	N	Y	N	Y	N
5.9	Developmental Toxicity / Teratogenicity	Y	Y	Y	Y	N	Y	N

## 1. Introduction

This Data Review and Assessment and accompanying Robust Summaries for allyl alcohol (CAS RN 107-18-6) were prepared by Lyondell Chemical Company (Lyondell) to meet its commitments under the United States Environmental Protection Agency HPV Chemical Challenge Program.

The purpose of this document is to identify, summarize, and evaluate key studies describing physical-chemical properties, environmental fate, ecotoxicity and mammalian/ human health effects in a manner consistent with the requirements of the HPV Chemical Challenge endpoints (equivalent to OECD SIDS Level 1 data package).

**Table 1. General Substance Information (Identify)**

Common Name	Allyl Alcohol
CAS No.	107-18-6
Molecular Formula:	C <sub>3</sub> H <sub>6</sub> O
Structural Formula:	CH <sub>2</sub> =CHCH <sub>2</sub> OH
Molecular Weight:	58.08
Physical state:	Liquid
Synonyms:	2-propen-1-ol; 1-propenol-3; vinyl carbinol

## 2. Production and Use

### 2.1 Production

Allyl alcohol (CAS 107-18-6) is an intermediate chemical manufactured by Lyondell at sites in the United States and The Netherlands. Projected global production is estimated at 175 million pounds. Approximately 140 million pounds are expected to be used captively by Lyondell for manufacture of downstream derivatives.

Allyl alcohol is also produced in Asia mainly by two Japanese producers, Showa Denka and Daicel. Estimated total Asian production is about 125 million pounds.

### 2.2 Use

Allyl alcohol is a bifunctional molecule used by chemical manufacturers for a multitude of purposes by reaction of the alkene functionality, the hydroxy functionality, or both.

A significant use for allyl alcohol is as an intermediate in the production of 1,4-Butanediol (CAS RN 110-63-4) and 2-Methyl-1,3-Propanediol (CAS RN 2163-42-0). Other commercial uses of allyl alcohol include manufacture of allyl diglycol carbonate (CAS RN 142-22-3), used in optical resins; allyl glycidyl ether (CAS RN

106-92-3), used as silane coupling agents for a multitude of applications, such as water treatment and glass adhesion; diallyl phthalate (CAS RN 131-17-9), which may be used as a plasticizer; and allyl methacrylate (CAS RN 96-05-9) and styrene allyl alcohol (CAS RN 25119-62-4) resins for coatings applications.

### 3. Evaluation of OECD SIDS Endpoints

#### 3.1. Physical-Chemical Data

Allyl alcohol is a clear, colorless liquid with a strong, mustard-like odor. The physical-chemical properties of allyl alcohol are summarized below:

**Table 2. Physical-Chemical Data**

Property	Value	Rel <sup>†</sup>	Source
Melting point	-129 °C	2	Howard (1989); JETOC (1992); Verschueren (1996)
Boiling point	96.9 °C	2	Verschueren (1996)
	97 °C		Weast and Astle (1985)
Relative density	0.825	2	Verschueren (1996)
	0.854		Windholz et al. (1983) Weast and Astle (1985)
Vapor pressure	20 mmHg, 20°C	2	Verschueren (1996)
	23.5 mm Hg, 25°C		Howard (1989)
	23.8mm Hg 25°C		Weast and Astle (1985)
	26.1mm Hg		EPI (2000)
Water solubility	1E+006 g/m <sup>3</sup>	2	EPI (2000)
	Forms constant boiling mixture, 72.3% allyl alcohol:27.7% water		Windholz et al. (1983)
Log K <sub>ow</sub>	0.17	2	Howard (1989); Sangster (1989); Verschueren (1996)
	-0.25		Lipnick et al. (1987)

<sup>†</sup> Reliability according to Klimisch criteria.

**Conclusion:** Adequate information is available to characterize all physical-chemical endpoints.

### 3.2. Environmental Fate and Pathways Data

A calculated half-life of 7.44 hours ( $1 \times 10^6$  OH/cm<sup>3</sup>) and rate constant of  $2.59 \times 10^{-11}$  cm<sup>3</sup>/molecule-sec has been obtained for reaction of allyl alcohol with hydroxyl radicals in air (Grosjean et al. (1993a), Rel 2). Reaction with ozone yields a removal half-life of 5.52 hours (100 ppb ozone) (Grosjean et al. (1993a), Rel 2) with formaldehyde, hydroxyacetaldehyde and a monofunctional carbonyl moiety formed as reaction products (Grosjean et al. (1993b), Rel 2). Approximately one-third of an initial concentration of allyl alcohol (100 ppm) was converted to CO<sub>2</sub> and CO following 2 hours irradiation at wavelengths of 230-300 nm, indicating some potential for photolytic degradation (Hustert and Parlar (1981), Rel 2).

Allyl alcohol contains no groups susceptible to hydrolysis.

Results of Mackay Fugacity Level I modeling indicate that environmental releases will partition mainly to water (95.96%) (Armstrong (2003a), Rel 2). Very little (0.17%) is expected to sorb to sediment. Results from the Fugacity Model Level III program indicate releases to air would remain in the air (71.5%), releases to water will remain in water (99.8%), and releases to soil are likely to remain in soil (79.6%) (Armstrong (2003a), Rel 2).

While no guideline biodegradation studies were located, handbook data report that aerobic removal exceeds 82-86% of theoretical BOD after 2-3 weeks (Howard (1989), Rel 2; JETOC (1992), Rel 2). A BOD of 1.6 to 1.8 g/g (Heukelekian and Rand (1955), Rel 2; Bridie et al. (1979a), Rel 2) and a ThOD of 2.21 g/g (Bridie et al. (1979a), Rel 2) indicate that allyl alcohol is readily biodegradable. Under anaerobic conditions, allyl alcohol was degraded by sediment microbes to propanol (Smith et al. (1995), Rel 2).

No measured BCF data were located, however log K<sub>ow</sub> values of -0.25 and 0.17 (see Section 2.1) and a predicted BCF of 3.16 (from BCFWin model; Armstrong (2003b), Rel 2) indicate that it is not likely to bioaccumulate in biological systems.

**Conclusion:** Adequate information is available to characterize all environmental endpoints. Allyl alcohol is not persistent in the environment. It oxidizes at a moderate rate in the atmosphere and there is also some potential for photolytic degradation. Allyl alcohol is expected to biodegrade under aerobic and anaerobic conditions. It is not susceptible to hydrolysis. Fugacity modeling indicates that over 95% of allyl alcohol in the environment partitions to water. Very little allyl alcohol will adhere to soil or sediment and it is not expected to bioaccumulate in food chains.

### 3.3 Ecotoxicological Data

Adequate information from guideline and other ecotoxicity studies is available to support a preliminary assessment of the effects of allyl alcohol on fish, aquatic invertebrates and aquatic plants.

**Table 3. Ecotoxicology Data**

Species	Result	Rel <sup>†</sup>	Source
Fish, 96 hours LC <sub>50</sub>	0.32 mg/L	2	Ewell et al. (1986)
Fish, 24 hours LC <sub>50</sub>	approx. 1 mg/L	2	Bridie et al. (1979b)
Daphnia, 96 hours EC <sub>50</sub>	0.25-0.4 mg/L	2	Ewell et al. (1986)
Daphnia, 48 hours EC <sub>50</sub>	1.65 mg/L	1	Hicks (2005a)
Alga 72 hours EC <sub>50</sub>	2.25 mg/L (biomass) 5.38 mg/L (growth)	1	Hicks (2005b)

<sup>†</sup> Reliability according to Klimisch criteria.

Ewell et al. (1986) reported results from a multi-species exposure system that allowed the simultaneous exposure of seven freshwater organisms (pillbug, water flea, flatworm, sideswimmer, snail, segmented worm, fathead minnow) to various concentrations of allyl alcohol. This returned a 96 hour LC<sub>50</sub> of 0.32 mg/L for *Pimephales promelas* (fathead minnow) and a 96 hour EC<sub>50</sub> of 0.25-0.4 mg/L for *Daphnia magna* (water flea). Other results are in broad agreement, with a 24 hour LC<sub>50</sub> of approx. 1 mg/L for *Carassius auratus* (goldfish) (Bridie et al. (1979), Rel 2).

An OECD Guideline 202 study was conducted in *Daphnia magna* (Hicks (2005a), Rel 1). Under static conditions, daphnids were exposed to nominal concentrations of 0 (control), 0.33, 0.65, 1.3, 2.5, 5.0, or 10 mg/L allyl alcohol. The measured mean test concentrations adjusted for analytical recovery were <0.040 (control, sample quantitation method), 0.373, 0.516, 1.06, 2.58, 4.85, and 10.5 mg/L. The daphnids were observed for immobilization and/or mortality 24 and 48 hours after test initiation. After 48 hours of exposure, immobility was 0, 0, 0, 0, 100, 100, and 100% in the 0 (control), 0.33, 0.65, 1.3, 2.5, 5.0, and 10 mg/L treatments, respectively. Quiescence was observed in the 2.5 and 5.0 mg allyl alcohol/L treatments at 24 hours. Based on the adjusted mean measured concentrations, the 24- and 48-hour EC<sub>50</sub> for allyl alcohol in the water flea (*Daphnia magna*) in this study were 3.66 mg/L and 1.65 mg/L, respectively, while the 48 hour NOEC was 1.06 mg/L.

Toxicity to aquatic plants was tested in an OECD Guideline 201 study (Hicks (2005b), Rel 1). Algal (*Pseudokirchneriella subcapitata*) cells were exposed under static conditions to 0 (control), 0.65, 1.3, 2.5, 5.0, or 10 mg allyl alcohol/L of test medium. The geometric measured mean test concentrations adjusted for analytical recovery were <0.040 (control, sample quantitation method), 0.343, 0.930, 2.41, 6.03, and 9.12 mg/L. Cell density was determined for the control and each test concentration at 24, 48, and 72 hours to evaluate algal growth (inhibition or enhancement). In addition to cell density determinations, microscopic

examinations were conducted to determine any morphological and physical effects on the algal cells. After 72 hours of exposure, the mean cell density in the control was  $118 \times 10^4$  cells/mL. This value represented an increase of 118 times the initial target inoculation density and demonstrated control growth was acceptable for the test. The mean cell density in the treatment groups at 72 hours ranged from  $1.0 \times 10^4$  in the 10 mg/L treatment to  $124 \times 10^4$  in the 0.65 mg/L treatment. Percent differences in cell density, as compared to the control, ranged from -99% in the 10 mg/L treatment to +5% in the 0.65 mg/L treatment. Based on the geometric mean of measured concentrations (adjusted for analytical recovery), the 72-hour  $E_bC_{50}$  (biomass) and  $E_rC_{50}$  (growth) for allyl alcohol in green algae were 2.25 mg/L and 5.38 mg/L, respectively, while the 78 hour NOECs were 0.930 mg/L.

**Conclusion:** Results from acute toxicity tests demonstrate that allyl alcohol is very toxic towards aquatic species.  $EC_{50}$  values for allyl alcohol in fish, aquatic invertebrates, and aquatic plants range from  $\leq 1$  mg/L to approximately 5 mg/L.

### 3.4 Toxicological Data

#### 3.4.1 Acute toxicity

Adequate data are available for an assessment of the acute toxicity of allyl alcohol in animals after inhalation, ingestion and skin contact. Data are also available on skin and eye irritation potential (non-SIDS endpoints).

**Table 4. Acute Toxicity Data**

Route	Species	Result	Comment	Rel <sup>†</sup>	Source
Inhalation LC <sub>50</sub>	Rat	125-140 ppm	4 hours exposure	2	Dunlap et al. (1958)
Oral LD <sub>50</sub>	Rat	70 mg/kg bwt		2	Jenner et al. (1964)
	Rat	99-105 mg/kg bwt			Dunlap et al. (1958)
	Mouse	96 mg/kg bwt			Smyth and Carpenter (1948)
Dermal LD <sub>50</sub>	Rabbit	89 mg/kg bwt		2	Dunlap et al. (1958)
Skin irritation	Rabbit	slightly irritating	24 hours, occlusion	2	Dunlap et al. (1958)
Eye irritation	Rabbit	Irritating	erythema, chemosis and corneal opacity at 24 hours, reversible	1,2	Jacobs and Martens, 1989; Dunlap et al. (1958)

<sup>†</sup> Reliability according to Klimisch criteria.

### 3.4.2. Repeated dose toxicity

Results from subchronic toxicity studies in rats provide adequate information on the consequences of repeated inhalation or oral (drinking water) exposure to allyl alcohol. Additional information on the repeated gavage exposure toxicity of allyl alcohol is also expected once results from completed NTP sub-chronic studies in rats and mice are finalized.

Dunlap et al. ((1958), Rel 2) exposed groups of male Long-Evans rats to atmospheres containing up to 150 ppm allyl alcohol for 7 hours/day, 5 days/weeks for 12 weeks. Clinical signs reported at the highest exposure level included severe irritation of the respiratory tract and eye, with 100% mortality after 10 exposures. Similar but less pronounced effects were present in animals exposed to 40-100 ppm. Body weight gain was significantly decreased in animals exposed to  $\geq 20$  ppm, with kidney weights increased after exposure to  $\geq 40$  ppm. Relative lung weights were also increased at  $\geq 40$  ppm (however incomplete data collection means that responses at lower concentrations were not characterized). Although pre-dating modern guidelines, these findings are consistent with a NOAEC for body weight effects of 5 ppm, and a systemic NOAEC (increased relative kidney weight) of 20 ppm.

This same author (Dunlap (1958), Rel 2) also reported results for male and female Long-Evans rats exposed to allyl alcohol via drinking water for 13 weeks, at exposure concentrations up to 1000 ppm. Water intake was decreased in all treated groups in a dose-related manner, presumably reflecting unpalatability of the dosing solutions, with a calculated received intake of 67 or 72 mg/kg bwt/day for high-dose females and males, respectively. Body weight gain was statistically significantly decreased in both sexes ingesting  $\geq 500$  ppm, with a dose-related increase in relative kidney wt (significant  $\geq 250$  ppm, both sexes) and relative liver weight (significant only in males  $\geq 250$  ppm). Although possible confounding effects due to decreased water intake cannot be excluded, these results are consistent with a NOAEL for organ weight changes of 11.6 mg/kg bwt/day in males and 13.2 mg/kg bwt/day in females given 100 ppm allyl alcohol in drinking water.

In a second ingestion study (Carpanini et al. (1978), Rel 2), Wistar rats of both sexes were allowed free access to drinking water containing 50-800 ppm allyl alcohol for up to 15 weeks (equivalent to 4.8-48.2 mg/kg bwt/day for males and 6.2-58.4 mg/kg bwt/day for females). Water intake and urine concentrating ability were decreased (generally statistically significant) in treated groups in a dose-related manner, with significant reductions in body weight and food intake in males at  $\geq 200$  ppm and females at 800 ppm. The majority of these findings appeared secondary to a reduction in water intake that was particularly pronounced in high dose animals. This was presumed to reflect poor palatability of the dosing solutions. Against this background, there was a more generalized increase in absolute kidney weight (females), relative kidney weight (both sexes) and relative

stomach weight (both sexes) in the intermediate and high dose groups. While local irritation (stomach) or dehydration (kidney) may have contributed in part to these findings, they may also be indicative of mild systemic renal toxicity with a sub-chronic NOAEL of 50 ppm in females (equivalent to 6.2 mg/kg bwt/day) and 100 ppm in males (8.3 mg/kg bwt/day).

No-effect levels and key findings from these studies are summarized in the table below:

**Table 5. Repeated Dose Toxicity Data**

Route	Species	NOAEC/NOAEL	Effects	Rel	Source
Inhalation	Rat	5 ppm 20 ppm	Decrease body weight gain Increase relative kidney weight	2	Dunlap et al. (1958)
Oral, drinking water	Rat	11.6-13.2 mg/kg bwt/day	Increase relative kidney weight Increase relative liver weight	2	Dunlap et al. (1958)
Oral, drinking water	Rat	6.2-8.3 mg/kg bwt/day	Increase relative kidney weight	2	Carpanini et al. (1978)

Information on the NTP website (<http://ntp-server.niehs.nih.gov/>) indicates that 13 week gavage studies have been performed in male and female F344 rats (0, 1.5, 3, 6, 12 or 25 mg/kg bwt/day) and B6C3F1 mice (0, 3, 6, 12, 25 or 50 mg/kg bwt/day), however no report of the findings is currently available.

Overall, the currently available data suggest that the kidney, liver, and lung are potential targets for allyl alcohol following repeated inhalation or ingestion exposure. Although pre-dating modern guidelines, these studies are considered adequate to characterize the sub-chronic toxicity of allyl alcohol. Additional information will be available when results from completed NTP studies are finalized.

### 3.4.3 Genetic toxicity

The majority of *in vitro* genotoxicity tests conducted for allyl alcohol in bacterial and mammalian cell systems have found positive genotoxicity findings. A positive mutation response was reported in *Salmonella typhimurium* TA1535 in a liquid preincubation assay in the presence of hamster S9 (negative with rat S9 and/or with plate incorporation) (Lijinsky and Andrews (1980), Rel 2), and in TA100 using liquid preincubation in the absence of S9 (weaker response in presence of S9, source not specified) (Lutz et al. (1983), Rel 2). While metabolism to acrolein by mammalian (or bacterial) alcohol dehydrogenases may explain these findings (see Section 3.4.6.), other bacterial mutation studies (Callander (2004), Rel 1; NTP

(unpublished results), Rel 2) found no evidence of mutagenic activity when bacterial stains were tested in the presence and absence of rat or hamster S9.

A recent guideline mutation study conducted in mammalian (mouse lymphoma L5178Y TK<sup>+</sup>) cells concluded allyl alcohol was mutagenic in the presence of S9-mix (Clay (2004) Rel 1). At the doses where mutagenicity was observed, there was significant toxicity to the cells as demonstrated by low relative survival. No toxicity or statistically or biologically significant increases in mutant frequency compared to the solvent control cultures were observed in the mouse lymphoma cells treated with allyl alcohol at any concentration tested in the absence of S9 mix. Other limited data suggests that allyl alcohol may induce mutations in mammalian V79 cells *in vitro*, as assessed from induction of resistance to 6-thioguanine (Smith et al. (1990), Rel 4). Chromosomal aberrations were assessed in a cytogenetic study conducted in human peripheral lymphocytes (Fox (2004), Rel 1). Statistically and biologically significant increases in the percentage of aberrant cells, compared to the solvent control values, were recorded in allyl alcohol treated cultures in the presence and absence of S9 mix.

In contrast to the above findings *in vitro*, results from *in vivo* studies performed by NTP ((unpublished data), Rel 2) show that allyl alcohol does not induce micronuclei in rat femoral bone marrow (no effect up to the limit of toxicity) or mouse blood (inactive following sub-chronic treatment). It also failed to induce dominant lethal effects in male SD rats given 25 mg/kg bwt/day by gavage (equivalent to approx. one quarter to one third of the LD50; see Section 3.4.1) for 11 weeks prior to mating with untreated females (Jenkinson and Anderson (1990), Rel 2).

**Table 6. Genetic Toxicity Data**

End point	Test system	Conditions	Result	Rel	Source
<i>in vitro</i>					
Gene mutation	Bacterial cells	S. typhimurium TA98, 100, 1535, 1537, 1538; liquid preincubation; hamster S9	Positive in TA1535 with S9	2	Lijinsky and Andrews (1980)
		S. typhimurium TA100; liquid preincubation; rat S9	Positive in TA100 without S9 (weak response +S9)	2	Lutz et al (1982)
		S. typhimurium TA100, 1535, 97, 98; liquid preincubation; rat and hamster S9	Negative	2	NTP (unpublished results)
		S. typhimurium TA98, 100, 1535, 1537 and E. coli WP2 uvrA (pKM101); preincubation; rat S9	Negative	1	Callander (2004)

	Mammalian cells	V79 cells (6-thioguanine resistance)	Positive	2	Smith et al. (1990)
		Mouse lymphoma cells (L5178Y TK <sup>+/+</sup> ); rat S9	Positive with S9	1	Clay (2004)
Chromosomal aberrations	Mammalian cells	Human lymphocytes; rat S9	Positive	1	Fox (2004)
<b><i>in vivo</i></b>					
Micronuclei	Bone marrow, F-344 rat	≤ 20 mg/kg bwt/day, i.p., 3 consecutive weeks	Negative (higher doses precluded by mortality)	2	NTP (unpublished results)
Micronuclei	Blood, B6C3F1 mouse	≤ 50 mg/kg bwt/day, gavage, 13 weeks	Negative	2	NTP (unpublished results)
Dominant lethal	SD rat	25 mg/kg bwt/day, 33 weeks	Negative	2	Jenkinson and Anderson, (1990)

#### 3.4.4 Carcinogenicity (non-SIDS endpoint)

There was no increase in tumors in male and female F344 rats administered allyl alcohol in drinking water (300 mg/L) for 106 weeks, followed by observation until natural death (weeks 123-132) (Lijinsky and Reuber (1987), Rel 2). Although small group sizes and use of a single dose level limit the overall reliability of these findings, the treatment level compares favorably with the 50-100 ppm NOAEC obtained from sub-chronic drinking water studies and the study is considered supportive of this assessment.

#### 3.4.5 Reproductive and Developmental toxicity

##### 3.4.5.1 Reproductive toxicity

While no guideline reproductive toxicity test results are available, no adverse histopathological changes were detected in testis, ovary or uterus from Wistar rats given up to 800 ppm allyl alcohol in drinking for 15 weeks (equivalent to a top dose of 48.2 or 58.4 mg/kg bwt/day in males and females, respectively) (Carpanini et al. (1978), Rel 2). Total sperm count, epididymal sperm concentrations and fertility were unaltered in SD rats given 25 mg/kg bwt/day for 11-15 weeks as part of a male dominant lethal assay (Jenkinson and Anderson (1990), Rel 2). Additional information on gonad weight weights and histopathology, together with data on sperm quality and vaginal cytology, are anticipated when results from an NTP 13 week study are finalized (NTP (unpublished results)).

### 3.4.5.2 Developmental toxicity / Teratogenicity

A guideline (OECD Guideline 414, EPA OPPTS 870.3700) prenatal developmental toxicity study was conducted for allyl alcohol in Sprague-Dawley rats (Stump (2005), Rel 1). Groups of rats (n = 25) received oral gavage dosages of 0, 10, 35, or 50 mg allyl alcohol/kg bwt daily on gestation weeks 9 through 19. Significant maternal toxicity occurred in dams that received  $\geq 10$  mg/kg bwt/day allyl alcohol and above dosages.

One and six females from the 35 and 50 mg/kg bwt/day groups, respectively, died between gestation weeks 9 and 20. Dams in these groups exhibited adverse clinical signs and reductions in body weight and/or body weight gain and feed consumption. Due to the mortality observed in this study and the number of animals not consuming an appreciable amount of feed, supplemental feed (an approximately 50/50 mixture of Hills Prescription Diet canine feed and water) was administered to animals in the 35 mg/kg bwt/day group consuming less than 10 g per day. Supplementation of the diet with the prescription diet for six animals in the 35 mg/kg/day group beginning on gestation day 14 allowed for mean feed consumption values to increase, albeit not to control values. Signs of liver toxicity were noted in dams in the  $\geq 10$  mg/kg bwt/day groups. Test article-related increases in mean liver weights (5.4% and 11.6%) were observed in the 35 and 50 mg/kg bwt/day groups, respectively, when compared to the control group. The increased liver weights correlated with the macroscopic liver findings observed in these two groups. No test article-related effects mean liver weight was noted in the 10 mg/kg bwt/day group. At the scheduled necropsy on gestation day 20, 11 of the surviving 24 and 12 of the surviving 19 females in 35 and 50 mg/kg bwt/day groups, respectively, had test article-related liver findings, including yellow and/or white areas on the liver, liver adhesions and/or misshapen or mottled livers. One female in the 10 mg/kg bwt/day group had yellow areas on the liver. The yellow areas on the liver were considered to be test article-related because this finding was observed at a higher incidence in the 35 and 50 mg/kg bwt/day groups but was not observed in any control group females.

The developmental toxicity observed was limited to an increased frequency of total litter loss in the 35 and 50 mg/kg bwt/day dose levels (2/group). In each instance of total litter loss, the dam experienced severe toxicity (loss of body weight, severe decreases in feed consumption, and evidence of significant liver toxicity). Despite the severe maternal toxicity observed, there were no test-article related increases in malformation rates or incidence of variations. Intrauterine growth and survival was not affected in the fetuses from dams that survived to necropsy

The dose level of 10 mg/kg bwt/day was considered to be the lowest-observed-adverse-effect level (LOAEL) for maternal toxicity in this study. Maternal toxicity in the 35 and 50 mg/kg bwt/day groups consisted of mortalities, clinical findings, reductions in body weight gain and feed consumption, macroscopic liver findings and increased liver weights. One female in the 10 mg/kg bwt/day group also had macroscopic liver findings. Developmental toxicity in the 35 and 50 mg/kg bwt/day

groups was expressed by an increase in postimplantation loss. Therefore, a dose level of 10 mg/kg bwt/day was considered to be the no-observed-adverse-effect level (NOAEL) for developmental toxicity when allyl alcohol was administered orally by gavage to pregnant rats.

#### 3.4.6. Metabolism (non-SIDS endpoint)

Extensive necrosis and covalent binding of radiolabel was observed in the periportal region of the liver in male SD rats given  $^{14}\text{C}$ -allyl alcohol by i.p. injection, whereas no necrosis and an 80% reduction in covalent binding was apparent in animals pre-treated with pyrazole (Reid (1972), Rel 2). These findings are compatible with decreased toxicity after inhibition of alcohol dehydrogenase activity *in vivo*. In other studies (Patel et al. (1983), Rel 2), greater hepatic necrosis, elevated levels of plasma GPT and greater covalent binding to liver protein was noted in SD rats given  $^{14}\text{C}$ -allyl alcohol compared with rats given an equivalent dose of deuterated allyl alcohol. This reduction in toxicity presumably corresponds with slower activation of the deuterated substrate by alcohol dehydrogenase (steric hindrance). *In vitro* studies showed significantly greater formation of acrolein and acrylic acid by liver fractions when  $^{14}\text{C}$ -allyl alcohol was substrate compared to that seen in incubations containing deuterated allyl alcohol (Patel et al. (1983), Rel 2). These NADH-dependent reactions were sensitive to inhibition by pyrazole and disulfuram, indicating a role for alcohol- and aldehyde dehydrogenases in the hepatic metabolism of allyl alcohol.

Overall these observations suggest that alcohol- and aldehyde dehydrogenases contribute to the toxicity of allyl alcohol *in vivo*.

**Conclusion:** Adequate data exist to demonstrate that allyl alcohol is acutely toxic after ingestion, inhalation or skin contact, while results from sub-chronic studies (inhalation, ingestion) provide evidence of potential effects on the kidney, liver, and lung, with a NOAEC of 20 ppm and a NOAEL of 6-8 mg/kg bwt/day. Additional information on repeat dose effects is also expected once results from completed NTP gavage studies in rats and mice are published. The SIDS requirements for acute and repeat dose toxicity are therefore met.

Results from *in vitro* genotoxicity tests of allyl alcohol are generally positive. The majority of studies indicate allyl alcohol causes gene mutations in bacterial and mammalian cells *in vitro*; although a few studies (using identical test conditions) gave negative results. While metabolism to acrolein and acrylic acid by alcohol- and aldehyde dehydrogenases may explain these positive findings, results from *in vivo* studies are consistently negative, with no increase in micronuclei in rat femoral bone marrow or mouse blood and no effect on male-mediated dominant lethality. These findings are consistent with efficient detoxication of allyl alcohol and its metabolites *in vivo*.

Results from a sub-chronic drinking water study demonstrate no adverse effect on gonadal histology in male and female rats given allyl alcohol at received doses of 48 or 58 mg/kg bwt/day, respectively, for 15 weeks. Additional information on gonad histopathology, sperm quality and vaginal cytology is expected once results from an NTP 13 week study are finalized. There was no functional impact on sperm quality or fertility in male rats given 25 mg/kg bwt/day allyl alcohol for 11-15 weeks as part of a dominant lethal investigation. Overall, the SIDS requirement for information on reproductive (fertility) effects is met.

A prenatal developmental toxicity study found an increased frequency of total litter loss in 35 and 50 mg/kg bwt/day dose level dams (2/group) that experienced severe toxicity (loss of body weight, severe decreases in feed consumption, and evidence of significant liver toxicity). Signs of liver toxicity were noted in dams in the 10 mg/kg bwt/day group. One and six females from the 35 and 50 mg/kg bwt/day groups, respectively, died between gestation weeks 9 and 20. Despite the severe maternal toxicity observed, there were no test-article related increases in malformation rates or incidence of variations. Intrauterine growth and survival was not affected in the fetuses from dams that survived to necropsy.

#### **4. Summary and Conclusion**

There is adequate information available for allyl alcohol to meet the HPV Chemical Challenge requirements for physical-chemical properties, environmental fate and pathway, ecotoxicity data, and mammalian/human health effects. A summary of the key hazard data for allyl alcohol for each of the HPV chemical endpoints is presented in Table 7.

Table 7. Summary of Key Allyl Alcohol Hazard Data

ENDPOINT	VALUE/RANGE	REFERENCE
<b>PHYSICAL - CHEMICAL DATA</b>		
Melting Point	-129 °C	Howard (1989); JETOC (1992); Verschueren (1996)
Boiling Point	96.9 °C	Verschueren (1996)
Vapor Pressure	20 mmHg, 20°C	Verschueren (1996)
Partition Coefficient	0.17	Howard (1989); Sangster (1989); Verschueren (1996)
Water Solubility	1E+006 g/m <sup>3</sup>	EPI (2000)
<b>ENVIRONMENTAL FATE AND PATHWAYS DATA</b>		
Photodegradation	7.44 hours (removal by OH half life) 5.52 hours (removal by ozone half life)	Grosjean et al. (1993a)
Stability in Water	No functional groups susceptible to hydrolysis	
Transport and Distribution	Fugacity Level I : 95.96% to water Fugacity Level III : 71.5% will remain in air ; 99.8% will remain in water ; 79.6% will remain in soil	Armstrong (2003a)
Biodegradation	82% - 86% of theoretical BOD (2-3 weeks)	Howard (1989) ; JETOC (1992)
Bioaccumulation	Predicted BCF = 3.16	From BCFWin model ; Armstrong (2003b)
<b>ECOTOXICOLOGICAL DATA</b>		
Acute Toxicity to Fish	96 hr LC <sub>50</sub> = 0.32 mg/L	Ewell et al. (1986)
Toxicity to Daphnia	48 hr EC <sub>50</sub> = 1.65 mg/L	Hicks (2005a)
Acute Toxicity to Algae	72 hr EC <sub>50</sub> (biomass) = 2.25 mg/L 72 hr EC <sub>50</sub> (growth) = 5.38 mg/L	Hicks (2005b)

**Table 7. Summary of Key Allyl Alcohol Hazard Data (Continued)**

ENDPOINT	VALUE/RANGE	REFERENCE
<b>TOXICOLOGICAL DATA</b>		
Acute Toxicity	4 hr LC <sub>50</sub> (inhalation) = 125-140 ppm LD <sub>50</sub> (oral) = 70 mg/kg bwt LD <sub>50</sub> (dermal) = 89 mg/kg bwt	Dunlap et al. (1958) ; Jenner et al. (1964)
Repeated Dose Toxicity	NOAEC (inhalation) = 5 ppm NOAEL (oral) = 6.2-8.3 mg/kg bwt/day	Dunlap et al. (1958) ; Carpanini et al. (1978)
Genotoxicity <i>In Vitro</i>	Positive	Lijinsky and Andrews (1980) ; Lutz et al (1982), Clay (2004) ; Fox (2004)
Genotoxicity <i>In Vivo</i>	Negative	NTP (unpublished results)
Reproductive Toxicity	NOAEL for reproductive organ structural changes = 48.2 mg/kg bwt/day (males) ; 58.4 mg/kg bwt/day (females)	Carpanini et al. (1978)
Development Toxicity / Teratogenicity	Maternal LOAEL = 10 mg/kg bwt/day Developmental NOAEL = 10 mg/kg bwt/day	Stump (2005)

## 5. References

Armstrong, T. (2003a) Allyl alcohol fate and transport modeling. Unpublished study (modeling) by BBL Inc. for Lyondell Chemical Co., 24 October 2003.

Armstrong, T. (2003b) Allyl alcohol bioaccumulation model. Unpublished study (modeling) by BBL Inc. for Lyondell Chemical Co., 17 November 2003.

Bridie, AL, Wolff, CJM and Winter, M (1979a) BOD and COD of some petrochemicals. *Water Research* 13, 627-630.

Bridie, AL, Wolff, CJM and Winter, M (1979b) The acute toxicity of some petrochemicals to goldfish. *Water Research* 13, 623-626.

Callander, RD (2004). Allyl alcohol: Bacterial mutagenicity assay in *S. typhimurium* and *E. coli*. CTL Study Number YV6638. Central Toxicology Laboratory, Cheshire, UK. Sponsored by Hercules Incorporated, Wilmington, DE.

Carpanini, FMB, Gaunt, IF, Hardy, J, Gangolli, SD, Butterworth, KR and Lloyd, AG (1978) Short-term toxicity of allyl alcohol in rats. *Toxicol.* 9, 29-45.

Clay, P (2004). Allyl alcohol: L5178Y TK <sup>+/-</sup> mouse lymphoma mutation assay. CTL Study Number VV0306. Central Toxicology Laboratory, Cheshire, UK. Sponsored by Hercules Incorporated, Wilmington, DE.

Dunlap, MK, Kodama, JK, Wellington, JS, Anderson, HH and Hine, CH (1958) The toxicity of allyl alcohol. *AMA Archives of Industrial Health* 18, 303-311.

EPI (2000) EPI Suite™ v3.10, EPA Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC).

Ewell, WS, Gorsuch, JW, Kringle, RO, Robillard, KA and Spiegel, RC (1986) Simultaneous evaluation of the acute effects of chemicals on seven aquatic species. *Envir Tox Chem* 5, 831-840.

Fox, V (2004). Allyl alcohol: In vitro cytogenetics assay in human lymphocytes. CTL Study Number SV1223. Central Toxicology Laboratory, Cheshire, UK. Sponsored by Hercules Incorporated, Wilmington, DE.

Grosjean, D, Grosjean, E and Williams, EL (1993a) Rate constants for the gas-phase reactions of ozone with unsaturated alcohols, esters, and carbonyls. *Int J Chem Kinetics* 25, 783-794.

Grosjean, D, Grosjean, E and Williams, EL (1993b) Atmospheric chemistry of unsaturated alcohols. *Environ Sci Technol* 27, 2478-2485.

Hicks, SL. (2005a). Acute toxicity of allyl alcohol 20906MB (Lyondell lot number CX30609214) to the water flea, *Daphnia magna*, determined under static-renewal test conditions. ABC Study No. 48909, ABC Laboratories, Inc., Columbia, Missouri. Sponsored by the Lyondell Chemical Company, Houston, TX.

Hicks, SL. (2005b). Toxicity of allyl alcohol 20906MB (Lyondell lot number CX30609214) to the unicellular green alga, *Pseudokirchneriella subcapitata*. ABC Study No. 48910, ABC Laboratories, Inc., Columbia, Missouri. Sponsored by the Lyondell Chemical Company, Houston, TX.

Howard, PH (1989) Allyl Alcohol. In Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Lewis Publishers, pp38-43.

Huekelekian, H and Rand, MC (1955) Biochemical oxygen demand of pure organic compounds. Sewage and Industrial Wastes 27, 1040-1053.

Hustert, K and Parlar, H (1981) Ein testverfahren zum photochemischen abbau von umweltchemikalien in der gasphase. Chemosphere 10, 1045-1050.

Jacobs, GA and Martens, MA (1989) An objective method for the evaluation of eye irritation in vivo. Fd Chem Toxic 27, 255-258.

Jenkinson, PC and Anderson, D (1990) Malformed fetuses and karyotype abnormalities in the offspring of cyclophosphamide and allyl alcohol-treated male rats. Mut Res 229, 173-184.

Jenner, PM, Hagan, EC, Taylor, JM, Cook, EL and Fitzhugh, OG (1964) Food flavourings and compounds of related structure. I. Acute oral toxicity. Fd Cosmet Toxicol 2, 327-343.

JETOC (1992) Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan. Japan Chemical Industry Ecology-Toxicology and Information Center (JETOC), compiled under the supervision of the Chemical Products and Safety Division, Basic Industries Bureau, Ministry of International Trade, Japan.

Lijinsky, W and Andrews, AW (1980) Mutagenicity of vinyl compounds in *Salmonella typhimurium* Terat Carc Mutagen 1, 259-267.

Lijinsky, W and Reuber, MD (1987) Chronic carcinogenesis studies of acrolein and related compounds. Toxicol Ind Hlth 3, 337-345.

Lipnick, RL, Watson, KR and Strausz, AK (1987) A QSAR study of the acute toxicity of some industrial organic chemicals to goldfish. Narcosis, electrophile and proelectrophile mechanisms. *Xenobiotica* 17, 1011-1025.

Lutz, D, Eder, E, Neudecker, T and Henschler, D. (1982) Structure-activity relationships in  $\alpha$ , $\beta$ -unsaturated carbonylic compounds and their corresponding allylic alcohols. *Mut res* 93, 305-315.

NTP unpublished results (<http://ntp-server.niehs.nih.gov/>).

Patel, JM, Gordon, WP, Nelson, SD and Leibman, KC (1983) Comparison of hepatic biotransformation and toxicity of allyl alcohol and [1,1-<sup>2</sup>H<sub>2</sub>]allyl alcohol in rats. *Drug Metab Disp* 11, 164-166.

Reid, W (1972) Mechanism of allyl alcohol-induced hepatic necrosis. *Experientia* 28, 1058-1061.

Sangster, J (1989) Octanol-water partition coefficients of simple organic compounds. *J Phys Chem Ref data* 18, 1111-1229.

Smith, AM, Mao, J, Doane, RA and Kovacs, MF (1995) Metabolic fate of [<sup>14</sup>C]acrolein under aerobic and anaerobic aquatic conditions. *J Agric Fd Chem* 43, 2497-2503.

Smith, RA, Cohen, SM and Lawson, TA (1990) Acrolein mutagenicity in the V79 assay - short communication. *Carcinogenesis* 11, 497-498.

Smyth, HF and Carpenter, CP (1948) Further experience with the range finding test in the industrial toxicology laboratory. *J Ind Hyg Toxicol* 30, 63-68.

Stump, DG (2005). A prenatal developmental toxicity study of allyl alcohol in rats. Study Number – WIL-14038, WIL Research Laboratories, LLC., Ashland, OH. Sponsored by the Lyondell Chemical Company, Houston, TX.

Verschueren, K (1996) Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold NY, p158.

Weast, RC and Astle, MJ (1985) CRC Handbook of Data on Organic Compounds, Vol.1, CRC Press, Inc Boca Raton, FL, p603.

Windholz, M, Budavari, S, Blumetti, RF and Otterbein, ES (1983) The Merck Index, 10th Edition, Merck and Co., Inc, Rahway NJ, p277.