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Environmental Protection
Agency

Provisional Peer-Reviewed Toxicity Values for

Allyl alcohol
(CASRN 107-18-6)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
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Commonly Used Abbreviations

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR
ALLYL ALCOHOL (CASRN 107-18-6)

Background

      On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
    ‣ Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
    ‣ California Environmental Protection Agency (CalEPA) values, and
    ‣ EPA Health Effects Assessment Summary Table (HEAST) values.

      A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

      Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

      Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

      It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths

and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Allyl alcohol (CASRN 107-18-6) is a high-production-volume (HPV) chemical listed in the toxic release inventory (TRI). It is widely considered a "classic" hepatotoxin, requiring metabolic activation to form the ultimate toxicant. It is also known as allyllic alcohol, propenol, vinyl carbinol, as well as the IUPAC standard nomenclature of 2-propen-1-ol. A chronic RfD of 5×10^{-3} mg/kg-day for allyl alcohol (1-propene-2-ol) is available on IRIS (U.S. EPA, 2008a). The RfD is based on a NOAEL of 50 mg/L (equivalent to a dose of 4.8 mg/kg-day) from a subchronic rat drinking water study (Carpanini et al., 1978). The LOAEL from the study is 100 ppm (equivalent to 6.9 mg/kg-day) based on increased liver and kidney weights and impaired renal function. The source document for this assessment, which was verified 2/26/86, is a Health and Environmental Effects Profile (HEEP) (U.S. EPA, 1985). The Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997) lists both the IRIS RfD and a corresponding subchronic RfD of 5×10^{-2} mg/kg-day. Allyl alcohol is not included in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). Neither IRIS (U.S. EPA, 2008a) nor HEAST (U.S. EPA, 1997) provide RfC values or cancer assessments for allyl alcohol. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) includes no relevant documents besides the previously mentioned HEEP (U.S. EPA, 1985). The Agency for Toxic Substances and Disease Registry (ATSDR, 2008) has not produced a Toxicological Profile for allyl alcohol, and no Environmental Health Criteria document is available from the World Health Organization (WHO, 2008). Neither the International Agency for Research on Cancer (IARC, 2008) nor the National Toxicology Program (NTP, 2005, 2008) has assessed allyl alcohol for carcinogenicity. NTP (2006) has however, recently published subchronic gavage studies in rats and mice. Data reviews for allyl alcohol are available under the High-Production-Volume (HPV) Challenge Program (U.S. EPA, 2007, 2008b) and the Organisation for Economic Co-operation and Development Screening Information Data Sets (OECD SIDS) program (2005).

The American Conference for Governmental Industrial Hygienists (ACGIH, 2001, 2007) recommends a time weighted average-threshold limit value (TWA-TLV) of 0.5 ppm (1.2 mg/m^3) for allyl alcohol to protect against eye and upper respiratory tract irritation. The National Institute for Occupational Safety and Health (NIOSH, 2005) has recommended exposure limits (RELs) of 2 ppm (5 mg/m^3) as TWA and 4 ppm (10 mg/m^3) for short-term exposure. The

Occupational Safety and Health Administration (OSHA, 2008) permissible exposure limit (PEL) is 2 ppm (5 mg/m³). Interim Acute Exposure Guideline Levels (AEGLs) ranging from 2.1−36 ppm have been derived for allyl alcohol (U.S. EPA, 2001). The California Environmental Protection Agency (CalEPA, 2002, 2005a, 2005b) has not derived risk values for allyl alcohol.

Literature searches were conducted in December 2007 using the following databases: MEDLINE, TOXLINE, BIOSIS (August 2000−December 2007), TSCATS1/2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents (last six months before the first draft), and updated in July 2009. Except where noted, the literature searches were not limited by date.

REVIEW OF PERTINENT DATA

Human Studies
Oral Exposure
A 55 year-old man consumed approximately 250 mL of a commercial weed killer that contained, by weight (w/v), 85% allyl alcohol and died within 100 minutes (Toennes et al., 2002). Autopsy revealed bloody fluid in the mouth, larynx, esophagus, and trachea, and a pungent green-black fluid in the stomach. All organs had a strong pungent odor, suggesting that the ingested substance was rapidly distributed throughout the body. The total amounts of allyl alcohol measured in urine, bile, and gastric contents were 0.5 mg, 15 mg, and 3.6 g, respectively. The concentration of allyl alcohol in the blood was 309 mg/L. A small amount of acrolein, a metabolic product of allyl alcohol, was detected in the bile and urine but not in the stomach contents. The concentration of acrolein in the blood was 7.2 mg/L. Death was attributed to cardiotoxicity induced by acrolein. These data were insufficient to assist in the derivation of reference values for allyl alcohol.

Inhalation Exposure
Of 10 human volunteers exposed to 2 ppm of allyl alcohol for 1−3 minutes, 5 reported a definite odor, but no irritation (Torkelson et al., 1959). Experimental exposure of seven volunteers (genders not reported) to 0.78, 6.25, 12.5, or 25 ppm of allyl alcohol (98.5% pure) for 5 minutes resulted in moderate nasal and eye irritation in volunteers exposed to 12.5 ppm of allyl alcohol but only slight nasal irritation at 0.78 ppm (Dunlap et al., 1958). No pulmonary discomfort was noted at any concentration tested. Dunlap et al. (1958) also reported that no signs of liver damage or kidney dysfunction were observed in workers exposed to allyl alcohol for 10 years, but gave no further details. These data were insufficiently detailed to assist in the derivation of reference values for allyl alcohol.

Animal Studies
Oral Exposure
Subchronic Studies—there are three subchronic studies evaluating exposure to allyl alcohol in rodents. In the first study, Wistar rats (15/sex/dose) were exposed to drinking water containing 0-, 50-, 100-, 200-, or 800-ppm (mg/L) allyl alcohol (99% purity min.) for 15 weeks (Carpanini et al., 1978). Additional groups of 5/sex/dose were exposed to 0, 200, or 800 ppm for interim evaluations after 2 and 6 weeks of exposure. U.S. EPA (2008a) reported that the

concentrations in drinking water based on water consumption data were equivalent to doses of 0, 4.8, 8.3, 14.0, and 48.2 mg/kg-day for males and 0, 6.2, 6.9, 17.1, and 58.4 mg/kg-day for females, respectively. Body weight and food and water consumption were monitored throughout the study. Hematology and serum chemistry were evaluated at study termination. Renal function was evaluated as on the second, fifth, and final weeks of the study by measuring the ability to concentrate and dilute urine—specifically the volume and specific gravity of urine produced following various periods of water deprivation or water loading. All animals received gross necropsy at their termination times (2, 6, or 15 weeks), and weights were recorded for brain, pituitary, thyroid, heart, liver, spleen, kidneys, adrenals, gonads, stomach, small intestines, and caecum. Major organs and tissues were preserved for histopathological examination, and the study authors imply—but do not specifically state—that all animals and tissues received evaluation.

Body weight was significantly ($p < 0.001$ at the high dose) reduced with respect to controls throughout the study in males at concentrations of 100, 200, and 800 ppm (-5, 11, and 43%, respectively at study termination) and in females at 800 ppm (-19% at study termination) (Carpanini et al., 1978). Mean water consumption was significantly reduced in all treatment groups (27.7, 24.2, 19.4, 15.5, and 10.0 mL/rat/day for 0-, 50-, 100-, 200-, and 800-ppm males, respectively, and 26.5, 22.0, 17.2, 14.4, and 9.8 mL/rat/day for 0-, 50-, 100-, 200-, and 800-ppm females, respectively). Mean food consumption was significantly reduced in males at 200 ppm and higher (18.5 and 14.1 g/rat/day in 200- and 800-ppm groups versus 20.9 g/rat/day in controls) and in females at 800 ppm (12.8 g/rat/day versus 15.7 g/rat/day for controls). Results of hematologic and clinical chemistry tests were unremarkable.

Both absolute and relative kidney weights were significantly ($p < 0.001$ at 100 mg/kg-day and above) increased with respect to controls in females exposed to 100 ppm and higher (Carpanini et al., 1978). As shown in Table 1, the mean absolute kidney weights at the end of the study were 1.48, 1.48, 1.65, 1.67, and 1.64 g for 0, 50 100, 200, and 800 ppm, respectively. Mean relative kidney weights in females at the end of the study were 0.59, 0.60, 0.67, 0.70, and 0.83 g kidney/g terminal body weight at 0, 50, 100, 200, and 800 ppm, respectively. Nothing remarkable was observed with regard to absolute or relative kidney weights in males. Weight changes in other organs were limited to decreases in absolute weight and/or increases in relative weight, primarily in the high-dose group, that occurred in parallel with decreased body weight, and, as such, are not indicative of any toxicological effects on specific organs.

Table 1. Organ Weights in Wistar Rats Following Oral Allyl Alcohol Treatment for 15 Weeks					
Dose	**0**	**50 ppm**	**100 ppm**	**200 ppm**	**800 ppm**
Mean Absolute Kidney Weight Females	1.48 g	1.48 g	1.65 g	1.67 g	1.64 g
Relative Kidney Weight Females	0.59 g	0.60 g	0.67 g	0.70 g	0.83 g

There were no histopathologic lesions attributable to treatment in any of the organs examined (Carpanini et al., 1978). The results of renal concentration/dilution tests (measured in terms of specific gravity of urine and urine volume following either water deprivation [concentration] or a water load [dilution]) were considered by the study authors to be attributable in part to allyl alcohol exposure, but, also, possibly due to reduced water intake. Effects were observed as follows in males exposed to allyl alcohol at concentrations greater than or equal to 100 ppm and in females exposed to 200 ppm and higher. In the concentration test administered after 15 weeks of exposure, significantly decreased urine volume (4.5, 2.7, 2.4, 1.8, and 0.8 mL in control, 50-, 100-, 200-, and 800-ppm groups) but no significant changes in specific gravity were observed in males at concentrations of 100 ppm and higher. In females, the same test resulted in decreased urine volume following allyl alcohol exposure to concentrations of 200 ppm and higher (1.4, 2.6, 1.7, 0.8, and 0.7 mL for control, 50-, 100-, 200-, and 800-ppm groups, respectively). Following administration of the dilution test after 15 weeks of allyl alcohol exposure, urine volume decreased with allyl alcohol concentration (significant for females at 200 [2.7 mL] and 800 ppm [0.4 mL compared with 5.1 mL for controls]; significant for males at 800 ppm [0.5 mL compared with 8.4 mL in controls]). Urine specific gravity values for females were significant at 200 and 800 ppm, with values of 1.004, 1.002, 1.005, 1.009, and 1.039 for control, 50-, 100-, 200- and 800-ppm groups, respectively. Urine specific gravity values were significant for males at 100 ppm and higher, with values of 1.005, 1.005, 1.007, 1.010, and 1.044 for control, 50-, 100-, 200-, and 800-ppm groups, respectively.

Based on these considerations, IRIS (U.S. EPA, posted 1987, revised 1989, sourced 2008a) identifies a NOAEL of 50 ppm (4.8 mg/kg-day) and LOAEL of 100 ppm (6.9 mg/kg-day) for the Carpanini et al. (1978) study, using impaired renal function and increased organ weights (liver and kidney) as the critical effects.

In the second subchronic study, also in rats, groups of six per gender Long-Evans strain rats were exposed to 0, 1.5, 50, 100, 250, 500, or 1,000 ppm of allyl alcohol (98.5% pure) in their drinking water for 90 days (Dunlap et al., 1958). The three highest doses were equivalent to 25.5, 41.0, and 72.0 mg/kg-day for males and 34.0, 43.7, and 67.4 mg/kg-day for females. This study is not clearly reported, and the methods and results for multiple concurrent studies are sometimes mingled together by these authors. The following methods appear to be relevant to the subchronic oral study with rats. Rats were weighed weekly and observed daily for general condition. All rats were given a gross necropsy and sections of liver, kidney, stomach, and jejunum were evaluated by light microscopy. Liver-to-body-weight and kidney-to-body-weight ratios were determined. The peritoneal fat was notably decreased in amount at 500 ppm and completely absent at 1,000 ppm. Gross (soft, spongy, yellow areas) and microscopic evidence (areas of necrosis and regeneration) of liver damage was observed in 2/6 females at 1,000 ppm. Increased kidney-to-body-weight ratios were observed at concentrations of 250 ppm and higher, but there was no gross or microscopic evidence of kidney damage. Based on these observations, the LOAEL for this study is 500 ppm (41.0 mg/kg-day) for decreased peritoneal fat in both sexes, with liver damage in females at higher concentrations (1,000 ppm or 67.4 mg/kg-day). The NOAEL for the study is 250 ppm (25.5 mg/kg-day).

In the final subchronic study, (the key study) NTP (2006) conducted a comparative toxicity study with allyl alcohol, allyl acetate, and acrolein. As part of that study, F344/N rats (10/sex/dose) and B6C3F1 mice (10/sex/dose) were administered allyl alcohol in 0.5% methylcellulose by gavage 5 days/week for 14 weeks. Rats received doses of 0, 1.5, 3, 6, 12, or

25 mg/kg-day. Mice received doses of 0, 3, 6, 12, 25, or 50 mg/kg-day. Body weight and clinical signs were assessed weekly. To evaluate metabolic conversion to acrolein, the concentration of 3-hydroxymercapturic acid (a primary conjugated metabolite of acrolein) was measured in urine that was collected after the first gavage dose and after the 45th dose. Hematology and clinical chemistry were evaluated on Days 4 and 23, and termination of the study for rats. Hematology was assessed at the end of the study for mice. All animals were necropsied. Histopathological examination of all major tissues was performed on the highest-dose group with at least 60% survivors and higher-dose groups. In addition, the liver and forestomach of rats and the glandular stomach of mice were examined in the lower-dose groups. Sperm motility and vaginal cytology were evaluated at study termination in both rats and mice.

There were no treatment-related effects on body weight, body weight gain, clinical signs, or mortality in rats (NTP, 2006). The concentration of 3-hydroxymercapturic acid increased linearly with dose, demonstrating that metabolic conversion of allyl alcohol to acrolein had occurred. Absolute liver weight was significantly increased at 25 mg/kg-day only in males and relative liver weights were significantly increased in males at doses ≥6 mg/kg-day. There were no effects on absolute or relative liver weights in female rats. There were no meaningful treatment-related changes in clinical chemistry or remarkable changes at gross necropsy. There were, however, several histological changes. There were significant increases in the incidence of bile duct hyperplasia (8/10) and periportal hepatocyte hypertrophy (8/10) in high-dose females. One of 10 high-dose males had bile duct hyperplasia, and one of 10 high-dose females had hepatocyte necrosis. The aforementioned lesions were not observed in any of the other dose groups (0/10 in all dose groups except 0/9 for 6 mg/kg-day females). An increased incidence of squamous epithelial hyperplasia of the forestomach was observed in male and female rats at doses ≥6 mg/kg-day. The incidences of forestomach hyperplasia were 0/10, 0/10, 0/10, 5/10, 7/10, and 6/10 for males, and 0/10, 0/10, 1/10, 4/9, 9/10, and 8/10 for females in the vehicle control, 1.5, 3, 6, 12, and 25 mg/kg-day groups, respectively. There was no clinical, gross, or microscopic evidence of kidney damage. There were no treatment-related effects on sperm motility. High-dose females spent more time in diestrus (38.3, 42.6, 55.8, and 60% of the cycle for control, 6, 12, and 25 mg/kg-day groups) and less time in metestrus (17.5, 12.0, 7.5, and 2.5% of the cycle for control, 6, 12, and 25 mg/kg-day groups) than controls. The NOAEL from this study was 1.5 mg/kg-day, while the LOAEL was 3 mg/kg-day, based on forestomach hyperplasia in female rats.

Allyl alcohol was administered via gavage in the NTP (2006) studies and is known to cause respiratory tract irritation (see "Acute Toxicity" below). However, no adverse effects on the esophagus were observed in either rats or mice administered allyl alcohol. Of the four toxicity studies described in this section using drinking water as the method of administration of allyl alcohol (Dunlap et al., 1958; Lijinsky and Reuber, 1987; Carpanini et al., 1978; Allyl Alcohol Consortium, 2004), forestomach hyperplasia was observed only in the reproductive/developmental toxicity study with rats (Allyl Alcohol Consortium, 2004). However, adequate descriptions of histopathological examinations are not reported in either the Carpanini (1978) or the Lijinsky and Reuber (1987) studies. While forestomach lesions are of questionable significance to humans, they do represent a toxicologic effect. Finally, it is U.S. EPA policy to use forestomach lesions as toxicologically adverse effects in the absence of chemical-specific information to the contrary, and that information is lacking.

There were no treatment-related effects on clinical signs or mortality in mice (NTP, 2006). Mean body weights measured at the end of the study were not affected by treatment. Body-weight gain was comparable to controls in all but high-dose males (significantly less than controls: 12.6 versus 15.1 g, respectively). As with rats, metabolic conversion of allyl alcohol to acrolein was supported by the observation of a dose-related linear increase in urinary 3-hydroxymercapturic acid. There were no treatment-related/ meaningful gross observations or changes in hematology. There were no treatment-related changes on organ weights. Increased incidence of squamous epithelial hyperplasia of the forestomach was observed with respect to controls in both sexes at doses ≥12 mg/kg-day (incidences of 0/10, 1/10, 3/10, 9/10, 10/10, and 10/10 for males and 0/10, 0/10, 0/10, 8/10, 10/10, and 9/10 for females in the control, 3-, 6-, 12-, 25-, and 50-mg/kg-day treatment groups respectively). Significant increases in the incidence of hepatic portal cytoplasmic vacuolization were observed in females at doses ≥25 mg/kg-day (incidences of 1/10, 1/10, 1/10, 5/10, 8/10, and 9/10 for the control, 3-, 6-, 12-, 25-, and 50-mg/kg-day treatment groups, respectively) and in males at 50 mg/kg-day (incidences of 0/10, 0/10, 0/10, 0/10, 2/10, and 10/10 for the control, 3-, 6-, 12-, 25-, and 50-mg/kg-day treatment groups, respectively). There were no treatment-related effects on the esophagus or other gastrointestinal structures. There were no effects on vaginal cytology or sperm motility and no gross or microscopic evidence of kidney damage. The LOAEL for this study is 3 mg/kg-day based on squamous hyperplasia of the forestomach epithelium in male mice and female rats.

Chronic Studies—F344 rats (20/sex/treatment) were administered drinking water containing 0 or 300 mg/L of allyl alcohol 5 days/week for 106 weeks (Lijinsky and Reuber, 1987). Male Syrian golden hamsters (20 per group) received gavage doses of 0 or 3 mg of allyl alcohol 5 days/week for 60 weeks (Lijinsky and Reuber, 1987). This study is poorly reported. Doses calculated from compound intake data in the report and reference body weights were 11.3 mg/kg-day for male rats, 18.8 mg/kg-day for female rats and 104.5 mg/kg-day for hamsters (based upon U.S. EPA, 1987 guidance). Animals that survived the treatment period were maintained without treatment for up to an additional 26 (rats) or 32 (hamsters) weeks prior to sacrifice. All animals were examined for gross lesions and for microscopic lesions in major organs. No other evaluations (e.g. body weight, clinical signs, hematology, or clinical chemistry) are reported.

In rats, treatment group mortality was similar to controls, but in treated hamsters mortality was increased such that only 13/20 survived to 48 weeks (versus 20/20 controls) (Lijinsky and Reuber, 1987). There were no significant differences between treated and control animals of either sex or species with regard to the incidence of any type of tumor. Leukemia, liver tumors, and pituitary tumors were the predominant tumors identified in rats, and tumors of the adrenal cortex were identified in hamsters. No forestomach tumors are reported. Although not statistically significant, treated rats had a higher combined incidence of liver tumors (6/20: described as hyperplastic nodules and some hepatocellular carcinomas; specific numbers were not presented) than untreated controls (2/20). No other endpoints are reported. These experiments are not adequate cancer bioassays because each included only a single dose-level that for rats may not have reached the maximum tolerated dose (MTD) and, for hamsters, appears to have greatly exceeded the MTD; only a small number of animals were tested; and only one sex (male) of hamster was tested.

Reproductive/Developmental Studies—In a combined reproduction/developmental toxicity test, Sprague-Dawley rats (12/sex/dose) were administered allyl alcohol in water by gavage at doses of 0 (water vehicle), 2, 8, or 40 mg/kg-day (Allyl Alcohol Consortium, 2004 as cited by OECD-SIDS, 2005). This study was comprehensively reported by OECD-SIDS (2005). Parental males were treated for a total of 42 days prior to mating. Parental females were treated 14 days prior to mating and throughout pregnancy and early lactation (Day 3). There were no treatment-related effects on body weight, food consumption, or mortality. Increased salivation decreased locomotor activity, irregular respiration, lacrimation and loose stools (males) were observed at the highest dose. High-dose parental males had rough liver surface, and thickening of the forestomach and limiting ridge[1] of the stomach. High-dose parental females had enlarged livers with yellowish patches and a rough surface. Histopathological changes were observed in both sexes at the high dose. Both sexes of parental animals had liver changes including necrosis, fibrosis, bile duct proliferation, diffuse clear cell changes, hypertrophy, and brown pigment deposition in perilobular hepatocytes. High-dose parental males had increased hyperplasia of squamous epithelium in the forestomach. High-dose parental females had thymic atrophy and ovarian luteal hyperplasia. There were no treatment-related effects on the testes or epididymides in males. Irregular estrous (4/12 versus 0/12 controls) and an increased mean length of estrus (4.3 days versus 4.0 days in controls) were observed in high-dose parental females. A decrease in the mean viability index on Day 4 for high-dose animals (99.39% ± 2.02, 12 litters, for controls versus 89.48 % ± 28.50, 11 litters, for high-dose animals) and total litter loss for one dam at the high dose were the only reproductive effects observed. There were no other effects on other indices of mating, fertility or fetal survival and growth. There were no treatment-related developmental delays or malformations in the F_1 animals. The NOAEL and LOAEL for parental, developmental and reproductive toxicity in the study are 8 and 40 mg/kg-day, respectively.

Pregnant Sprague-Dawley rats (25 per treatment) were administered allyl alcohol by gavage at doses of 0, 10, 35, or 50 mg/kg-day on Days 6−19 of gestation (Lyondell Chemical Company, 2005 as cited by OECD-SIDS, 2005). This study is comprehensively reported by OECD-SIDS (2005). Mortality (1/25 and 6/25 at 35 and 50 mg/kg-day, respectively), clinical signs (salivation, poor grooming, rocking, hunching, hypoactivity, red or yellow fluids on body, etc.), reductions in body weight gain (losses of 4 and 12 g at 35 and 50 mg/kg-day, versus gain of 11 g for controls), reduced feed consumption, significantly increased mean liver weights (5.4 and 11.6% of the control values at 35 and 50 mg/kg-day, respectively) and macroscopic evidence of liver toxicity (white/yellow patches, liver adhesions, mottled and misshapen livers) were observed at doses of 35 and 50 mg/kg-day. Macroscopic evidence of liver toxicity (yellow areas) was observed in one dam at 10 mg/kg-day, but increased mean liver weight in comparison with controls was not observed in the 10 g/kg-day treatment group. Mean postimplantational losses were increased relative to controls in the 35 and 50 mg/kg-day treatment groups, but they were not statistically significant (6.9% per litter for controls versus 16.2% and 14.3% for 35- and 50-mg/kg-day treatment groups). The values for mean postimplantational loss for the 35- and 50-mg/kg-day groups were attributed to two females in each group that had completely resorbed litters. Fetal weight was unaffected by treatment. Mean live litter size, fetal sex ratios, and numbers of corpora lutea and implantation sites were similar among the various treatment groups and controls. There were no

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[1]Junction between the stratified squamous epithelium of the forestomach and the columnar cells of the "true" stomach.

treatment-related skeletal or soft-tissue variations or malformations. The NOAEL for maternal and developmental toxicity is 10 mg/kg-day. The LOAEL for maternal toxicity is 35 mg/kg-day based on mortality, decreased body weight, and liver toxicity. The LOAEL for reproductive toxicity is 35 mg/kg-day based on increased postimplantational litter loss.

In a dominant-lethal test, six male Sprague-Dawley rats were administered allyl alcohol in saline by gavage at a dose of 25 mg/kg-day for 15 weeks (7 days/week for the first 12 weeks, then 5 days/week thereafter) (Jenkinson and Anderson, 1990). Males were paired with unexposed females during Weeks 1−11 of dosing. After 15 weeks of exposure, males were assessed for hematological variables, given a gross necropsy, and sperm counts were made. Mated females were assessed for number of corpora lutea, implants, early and late resorptions, and live and dead fetuses. Fetuses were weighed, examined for skeletal and grossly observable malformations, and karyotyped.

There were no statistically significant treatment-related effects on any endpoint (Jenkinson and Anderson, 1990). Body weight was reduced by about 10% relative to controls, and relative liver weights were slightly—but not significantly—elevated (data not shown). There were no treatment-related effects on testes/cauda weights, sperm count, or sperm morphology (data not shown). Red blood cell count, mean cell volume, percent cell volume, and hemoglobin values were reported to be similar among treatment groups (data not shown). The white blood cell count was not significantly different from controls. The differential white blood cell count was different from controls (significantly increased lymphocytes; significantly decreased neutrophils and eosinophils, but was within the historical control range for the author's laboratory—data not shown). There were no differences between controls and allyl alcohol-exposed rats with respect to preimplantational loss ($11.7 \pm 6.2\%$ versus $12.8 \pm 5.4\%$ for control) or postimplantational loss (mean control value of 6.2% with a range of 2.2 to 13.2% over the course of the 13 weeks versus a mean of 4.7% with a range of 1.7 to 8.7% for allyl alcohol-exposed rats). Similarly, there were no treatment-related effects on fetal mortality, fetal weight, skeletal malformations, grossly observable malformations, or chromosomal abnormalities.

Inhalation Exposure

Subchronic Studies—There are three subchronic inhalations studies in the literature. In the first, male Long-Evans rats (10/group) were exposed to 0, 1, 5, 20, 40, 60, 100, or 150 ppm (0, 2.4, 11.9, 47.4, 94.9, 237.2, or 355.8 mg/m^3) of allyl alcohol (98.5% pure) 7 hours/day, 5 days/week, for 12 weeks (Dunlap et al., 1958). This study is not clearly reported, as the methods and results for multiple concurrent studies are sometimes reported together by these authors. However, the following methods appear to be relevant to the subchronic inhalation study with rats. Rats were weighed weekly and observed daily for general condition. All rats were given a gross necropsy and sections of livers, kidneys, lungs, thyroid, heart, pancreas, spleen, adrenals, testes, bladder, and brain were evaluated by light microscopy. The upper respiratory tract was not examined. Liver-to-body-weight, lung-to-body-weight, and kidney-to-body-weight ratios were determined.

Mortality was observed in 1/10 animals exposed to 60 ppm (94.9 mg/m^3) (after the 4th exposure), 6/10 animals exposed to 100 ppm (237.3 mg/m^3) (all within 46 days) and all animals exposed to 150 ppm (355.8 mg/m^3) (4 after the first exposure; 4 between the first and second exposures; remaining 2 by the 10th exposure) (Dunlap et al., 1958). Rats that died

showed gasping, severe respiratory depression, nasal discharge and eye irritation. Signs of eye and nasal irritation were evident in rats exposed to 40 ppm (47.4 mg/m^3) and higher. Mean body weight gain was significantly reduced at 20 ppm (11.9 mg/m^3) and higher (133 ± 5.6, 126 ± 17, 110 ± 23, 90 ± 24, 75 ± 32, and 75 ± 4 % for the 1-, 5-, 20-, 40-, 60-, and 100-ppm groups, respectively; control-group values ranged from $128 \pm 43\%$ to $135 \pm 8\%$; there were no survivors at 150 ppm). Mean lung-to-body-weight ratios were significantly increased relative to controls in the 40- and 60-ppm treatment groups (data for 100 -ppm (237.3 mg/m^3) and 150-ppm (355.8 mg/m^3) groups were not reported, presumably due to high mortality). Mean kidney-to-body-weight ratios were significantly elevated in the 60-ppm (94.9 mg/m^3) treatment group relative to controls. No relative kidney weight data were reported for the 100- and 150-ppm (237.3 and 355.8 mg/m^3 respectively) groups.

The incidences of lesions observed following gross or microscopic evaluation were not reported by Dunlap et al. (1958). The narrative provided by the study authors indicates the following: At 150 ppm (all rats died prior to study termination), the enteric tract was usually bloated with air and mucus, and the enteric vessels were engorged. Livers were hemorrhagic and lungs were pale and spotted, but microscopic examination of the tissues showed only slight congestion of the lungs and liver. No effects were observed on kidney tissue. At 40, 60, and 100 ppm (47.4, 94.7, 237.2 mg/m^3), signs, lesions, and microscopic findings were reported to be similar to those observed at 150 ppm (355.8 mg/m^3), but less intense. No gross or microscopic lesions were found at exposure concentrations of 20 ppm (47.4 mg/m^3) or lower.

Based on the above results, the NOAEL for the study appears to be 20 ppm (47.4 mg/m^3). The LOAEL appears to be 40 ppm (94.7 mg/m^3) based on vaguely reported liver and lung pathology.

In the second subchronic study, Zissu (1995) reported the identification and comparison of the histopathological changes induced in the respiratory tract of Swiss mice (10 per gender per dose) exposed to repeated inhalation (4, 9, or 14 days) at typical concentrations of RD_{50}, $0.3 \times RD_{50}$, and $3 \times RD_{50}$ of airborne chemicals (the RD_{50} is the dose producing a 50% decrease in respiratory rate). These dose metrics are infrequently used, but they refer to sensory irritation and are sometimes called the "Allerie tests." There is a good correlation between the RD_{50} values and several standard reference values (Kuwabara, et al. 2007). These substances were selected from 10 chemical families: aldehydes, organic acids, alcohols, ketones, ethers, aromatic hydrocarbons, halogenated aromatic hydrocarbons, inorganic bases, amines, and isocyanates. These experiments showed that the lesion intensity observed in the nasal passages varied with exposure duration and type of airborne chemical, but they did not depend on the concentration of the substance. Results did not allow the establishment of a relationship between the histopathological changes and the type of chemical family. No injuries were observed in trachea and lungs. While a LOAEL of 2.4 ppm (5.7 mg/m^3) for allyl alcohol was derived from this study, the irregularities in the dose response, the limitation to histopathology endpoints, and the short duration of exposures preclude the use of this study in deriving a p-RfC.

The final subchronic inhalation study (the key study), was conducted in rats (five/sex), guinea pigs (four males) and a single female rabbit that were exposed to a mean analytical concentration of 7-ppm (16.6-mg/m^3) allyl alcohol (99.5% pure) for 7 hours/day, 5 days/week, for 5 weeks (Torkelson et al., 1959). Groups of air-exposed controls were shared with a parallel study on allyl chloride. Results for mortality, body weight, and organ weights (lung, liver,

kidneys, heart, spleen, and testes) are shown in the report. Microscopic evaluation of the liver and kidneys is discussed in the report, but incidence/severity data are not tabulated in the report. There were no treatment-related effects on mortality, body weight, or relative organ weights in comparison with controls. The authors also reported that there were no treatment-related effects on behavior or gross appearance. Microscopic examination showed degeneration in the liver and kidneys of almost all animals (incidences not reported). Liver damage was reported to be mild and reversible with cessation of treatment and included dilation of the sinusoids, cloudy swelling, and focal necrosis. Microscopic changes in the kidney were also reported to be mild and reversible upon cessation of treatment, and they included necrosis of the tubular epithelium and proliferation of the interstitial tissue. The upper respiratory tract was not examined. The LOAEL for this 5-week study is 7 ppm (16.6 mg/m^3) (only concentration tested) on the basis of liver and kidney damage.

Torkelson et al. (1959) also exposed groups of rats (24/sex), guinea pigs (9/sex), rabbits (3/sex) and dogs (1/sex) to a mean analytical concentration of 2-ppm (4.7 mg/m^3) allyl alcohol (99.5% pure) 7 hours/day, 5 days/week, for 6 months. Data on mortality, body weight, relative organ weights (lung, liver, kidneys, heart, spleen, and testes), blood-urea nitrogen (BUN), nonprotein nitrogen (NPN), and hematology (dogs only) were presented in the report. Absolute organ weights are neither reported nor discussed. Microscopic examinations were also conducted, but the report does not clearly state the protocol for these examinations and does not present data to back-up results reported in the narrative of the results.

Torkelson et al. (1959) reported that there were no treatment-related effects on evaluated gross behaviors. Final mean body weight and mean relative organ weights in rats, female guinea pigs, and rabbits were similar among treated and control animals. However, male guinea pigs had a 10% reduction in body weight and a parallel reduction in relative liver weight (-10%) compared with air-exposed controls. Among rats, guinea pigs, and dogs, the terminal values reported for blood urea nitrogen and nonprotein nitrogen were lower than those seen in controls but were within normal limits for historical controls. BUN and NPN values for rabbits did not differ from controls. The average hematological values (WBC count; cell hemoglobin, hematocrit, and white cell differential count) for dogs were within normal limits. The study authors reported a similar lack of treatment-related hematological effects for rats, but they do not mention whether blood from rabbits or guinea pigs was tested. The study authors reported that there were no treatment-related effects revealed upon gross or microscopic examination of unspecified tissues for any species. The authors do not report whether the upper respiratory tract was examined, and do not report signs of nasal irritation. In this study, systemic effects (histological changes in the liver and kidney) were observed with repeated exposure to concentrations that apparently did not produce overt signs of nasal irritation. This study identifies a NOAEL of 2 ppm (4.7 mg/m^3) in rats and female guinea pigs for subchronic exposure to allyl alcohol and a LOAEL for minor adverse effects of 2 ppm (4.7 mg/m^3) for reduced body weight and relative liver weight in male guinea pigs.

Chronic Studies—No studies were located regarding chronic inhalation exposure of animals to allyl alcohol.

Reproductive/Developmental Studies—No studies were located regarding reproductive/developmental toxicity following inhalation exposure of animals to allyl alcohol.

Other Studies
Toxicokinetics

Following intraperitoneal (i.p.) administration to rats at doses ranging from 5−50 mg/kg, allyl alcohol reached peak concentrations in the blood within 5 minutes and rapidly declined to nondetectable concentrations within 10−15 minutes. The concentration of allyl alcohol in the liver peaked within 10 minutes and declined thereafter in proportion to dose (Anand et al., 2003). Allyl alcohol is metabolized to acrolein by alcohol dehydrogenase (Patel et al., 1980, 1983). Acrolein is metabolized further to acrylic acid by aldehyde dehydrogenase and metabolites are eliminated in the urine in conjugated form, primarily as mercapturic acid derivatives (Parent et al., 1996). The toxic effects of allyl alcohol exposure are widely attributed to acrolein (NTP, 2006).

Acute/Short-term Toxicity

Acute oral exposure to allyl alcohol yields LD_{50} values ranging from 70−105 mg/kg-day in rats, mice, and rabbits (Dunlap et al., 1958; OECD-SIDS, 2005). Acute inhalation exposures of rats, rabbits, and monkeys to concentrations ≥1,000 ppm have generally been lethal (McCord, 1932; Smyth and Carpenter, 1948; Smyth, 1956). Dunlap et al. (1958) report LC_{50} values for the rat ranging from 76-(8-hour exposure)−1,060-ppm (1-hour exposure). The common gross findings in the animals that died following either oral or inhalation exposures were edema and congestion of the lungs, visceral congestion, and discolored livers—some with necrotic areas. Microscopic lesions observed in the liver varied from congestion of the periportal sinusoids to periportal necrosis and from central pallor to central necrosis (Dunlap et al., 1958). Experiments in Ssc:CF-1 mice have shown that exposure to 3.9 ppm of allyl alcohol for 30 minutes depresses the respiratory rate by 50% (RD_{50}), reflecting sensory irritation of the upper respiratory tract (no pulmonary irritation was found at this concentration, as indicated by the absence of effect on breathing rate in trachea cannulated mice) (Nielsen et al., 1984).

Zissu (1995, discussed previously in the subchronic section) found lesions of the respiratory and olfactory epithelium in mice exposed to ≥2.4 ppm of allyl alcohol for 6 hours/day, 5 days/week, for 4 days. Groups of 10 male Swiss OF1 mice (10 exposed mice per treatment group; five unexposed controls) were treated with repeated inhalation of allyl alcohol (0, 2.4, or 6.4 ppm) for 4, 9, or 14 days over a 1-, 2-, or 3-week period. Mice were sacrificed after 4, 9, and 14 exposures, and the respiratory tract was examined for histological abnormalities such as inflammatory exudate, rhinitis, or lesions. No abnormalities were noted in any part of the respiratory tract of control mice. Treated mice showed marked excitation, rougher hair, and a moderate decrease in body weight. Olfactory lesions seen in treated mice consisted of a slight loss of sensory cells while a rhinitis with metaplasia and necrosis was observed in the respiratory epithelium and in the underlying connective tissue and bone. Lesions were most severe at the 4-day exposure and were progressively less severe after 9 and 14 exposures. This decrease in severity with increased exposure suggests that regeneration of respiratory and olfactory epithelia may occur even with continued exposure. No differences were observed in the lungs of exposed and unexposed animals. This study indicates a LOAEL for damage to the respiratory tract of 2.4 ppm for acute inhalation exposure to allyl alcohol.

Developmental Toxicity via Uterine Injection

Allyl alcohol in saline was injected into one uterine horn of 13-day timed-pregnant Sprague-Dawley rats to yield total doses of 10, 100, or 1,000 µg/fetus (Slott and Hales, 1985). Saline was injected into the other uterine horn as a control. Fetuses were allowed to develop for

an additional 7 days, then rats were killed and the uterine contents were examined. There were five, eight, and seven litters assessed for the low-, mid- and high-dose groups. The number of control litters was not reported but would presumably be in the vicinity of 20 given that the collateral uterine horn of each dam served as a control. The only evidence of maternal toxicity was one death in the high-dose group. There was a dose-related increase in resorbed fetuses in allyl alcohol-exposed rats that was statistically significant at 100 and 1,000 μg/fetus-dose groups in comparison with saline-treated controls. High-dose fetuses also had significantly reduced body weight in comparison with collateral saline controls. There were no statistically significant treatment-related malformations (two high-dose fetuses had limb defects, one control had multiple defects, and one control had a minor limb defect).

Mechanistic

Allyl alcohol is known to produce periportal liver necrosis in rats and mice following acute exposures. The mechanisms responsible for this toxicity have been investigated in vitro and in vivo and are hypothesized to involve metabolism of allyl alcohol to acrolein, with subsequent depletion of glutathione, followed by lipid peroxidation and liver necrosis (Badr et al., 1986; Belinsky et al., 1986; Jaeschke et al., 1987; Penttila et al., 1987; Penttila, 1988; Miccadei et al., 1988; Burcham and Fontaine, 2001; Comporti et al., 1991). For example, mice given a single i.p. injection of allyl alcohol (1.5 mmol/kg) had maximal glutathione depletion within 30 minutes and had lipid peroxidation and liver necrosis within 2−4 hours of treatment (Pompella et al., 1988; Maellaro et al., 1990). The toxicity of allyl alcohol was studied in freshly isolated renal epithelial cells prepared from male and female rats. Cells from female rats demonstrated a greater susceptibility to allyl alcohol toxicity as assessed by glutathione depletion and loss of cell viability. The sensitivity of female rat renal cells appears to relate to the higher activity of alcohol dehydrogenase found in the female rat kidney, which metabolizes allyl alcohol to the highly reactive aldehyde, acrolein. Pyrazole, an inhibitor of alcohol dehydrogenase, abolished the cytotoxic effects of allyl alcohol whereas inhibition of aldehyde dehydrogenase by disulfiram treatment was found to increase the sensitivity of renal cells to the effects of allyl alcohol. These results indicate that acrolein is the toxic metabolite responsible for the renal cell injury following exposure to allyl alcohol, and, unless immediately inactivated, acrolein interacts with critical nucleophilic sites of the cell and initiates cell injury (Ohio et al., 1985).

NTP (2006) did not observe hepatotoxicity in rats or mice following subchronic gavage administration of acrolein, but observed hepatotoxicity in female mice and rats following subchronic allyl alcohol exposure. The observation of acrolein metabolites in the urine of both species following administration of allyl alcohol and acrolein validated the presence of active metabolic conversion, per the first steps in the proposed mechanism of liver toxicity.

Citing studies by Parent et al. (1996), NTP (2006) proposed that the relative lack of liver toxicity in its studies was consistent with the notion that food in the GI tract reacts with acrolein (rats were not fasted), effectively reducing the bioavailable concentration to levels that were still high enough to cause forestomach hyperplasia, but too low to be hepatotoxic (i.e., low enough to be detoxified effectively without causing damage). The observation of greater liver toxicity in females was explained by the studies of Rikens and Moore (1987) who observed that alcohol dehydrogenase activity is greater in female rats than in males. As male rats aged, their alcohol dehydrogenase activity increased parallel to their sensitivity to allyl alcohol-induced liver

damage. However, neither the liver damage nor the alcohol dehydrogenase activity reached levels equivalent to that of females of any age.

Another explanation for the relative lack of liver toxicity in the subchronic-duration oral studies is that repair mechanisms are stimulated following the initial toxic insult, such that liver damage is apparent following acute exposures but is reduced or absent, depending on dose and toxicity threshold, after longer-term exposures where repair mechanisms outpace the initial toxic response. Using allyl alcohol and other liver toxins, Anand et al. (2003, 2005) demonstrated that liver toxicity following initial exposures is reversible at low-to-threshold doses (5−35 mg/kg) and that liver regeneration via endogenous repair mechanisms must be taken into account to reliably assess the adverse outcome of the effects of chemical exposure on the liver.

Genotoxicity
Allyl alcohol has been assayed for genotoxicity in a number of tests with mixed results. Allyl alcohol was not mutagenic in *Streptomyces coelicolor* or *Aspergillus nidulans* or in the Ames test with *Salmonella typhimurium* strains TA100, TA1535, TA1537, TA1538, or TA98, with or without metabolic activation (Lijinsky and Andrews, 1980; Principe et al., 1981; Rosen et al., 1980; Yamaguchi, 1980; NTP, 2006). However, allyl alcohol was mutagenic in *S. typhimurium* strain TA1535 in a 45-minute liquid preincubation test (Lijinsky and Andrews, 1980) and in a modified liquid suspension test with *S. typhimurium* strain TA100 (Lutz et al., 1982). Allyl alcohol was also mutagenic in Chinese hamster V79 cells (Smith et al., 1990). In an in vivo assay, allyl alcohol failed to accelerate hepatocarcinogenesis of 2,7-bis(acetamido)fluorene in mice (Kozuka and Sassa, 1976). The dominant lethal test (reported earlier) was also negative (Jenkinson and Anderson, 1990).

As discussed in the subchronic oral toxicity section, groups of male and female mice were administered allyl alcohol by gavage at concentrations of 3−5 mg/kg-day for 14 weeks (NTP, 2006). There were no significant increases in the frequencies of micronucleated normochromatic erythrocytes in the peripheral blood of either sex and no evidence of bone marrow toxicity. A similar result was obtained in bone marrow samples taken from male rats given three i.p. injections of allyl alcohol (5−20 mg/kg) at 24-hour intervals (NTP, 2006).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR ALLYL ALCOHOL

Subchronic p-RfD
The subchronic toxicity of allyl alcohol has been tested in subchronic studies with rats and mice (Carpanini et al., 1978, Dunlap et al., 1958; NTP, 2006). The most sensitive endpoint observed in these studies is forestomach hyperplasia (NTP, 2006; Dunlap et al., 1958).

Allyl alcohol is known to cause periportal liver necrosis in rats and mice following acute exposures, and the mechanisms (metabolism to acrolein, followed by depletion of glutathione, lipid peroxidation and liver necrosis) responsible for this toxicity have been demonstrated. The study of Carpanini et al. (1978) failed to demonstrate adverse liver effects in rats exposed to allyl alcohol for 15 weeks in their drinking water. The decreased absolute and increased relative liver weights observed by Carpanini et al. (1978) are reflective of a general decrease in body weight

and occurred in the absence of supportive changes in serum chemistry and histopathology. Dunlap et al. (1958) observed areas of liver necrosis and regeneration in females given 1,000 ppm (64.7 mg/kg-day) in drinking water but did not report changes in liver weight. NTP (2006) observed no changes in absolute or relative liver weight in mice or female rats, but they reported an increased incidence of hepatic portal cytoplasmic vacuolization and bile duct hyperplasia in female mice (≥25 mg/kg-day), male mice (50 mg/kg-day), and female rats (25 mg/kg-day). Increased absolute (25 mg/kg-day) and relative liver weights (≥6 mg/kg-day) in the absence of effects on body weight were observed only in male rats in the NTP (2006) study. Liver toxicity was also observed among parental animals (35−40 mg/kg-day) in the available oral reproduction and developmental toxicity studies in rats (Allyl Alcohol Consortium, 2004; Lyondell Chemical Company, 2005).

Minimal effects on the kidney (increased relative kidney weight; changes in urine volume and specific gravity) were observed in rats in two studies (Carpanini et al., 1978; Dunlap et al., 1958). There were no gross or histopathological changes in either study to support the kidney as a significant target of allyl alcohol exposure.

Adverse effects on reproduction included increased litter loss at maternally toxic doses (35−40 mg/kg-day) (Allyl Alcohol Consortium, 2004; Lyondell Chemical Company, 2005), some marginal changes on time spent in estrus (25 mg/kg-day rats; NTP, 2006), and irregular estrus or increased mean length of estrus (both in rats at 40 mg/kg-day; Allyl Alcohol Consortium, 2004). No adverse effects on vaginal cytology, sperm count, sperm morphology, or other reproductive indices were observed in rats (Allyl Alcohol Consortium, 2004; Lyondell Chemical Company, 2005; Jenkinson and Anderson, 1990; NTP, 2006).

Table 2 summarizes the dose-response data for oral exposure to allyl alcohol.

Table 2. Summary of Oral Noncancer Dose-Response Information								
Species	Sex	Dose (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Adjusted LOAEL[a] (mg/kg-day)	Responses at the LOAEL	Reference
Subchronic Exposure								
Rat	M, F	0, 4.8, 8.3, 14.0, or 48.2 in males; 0, 6.2, 6.9, 17.,1 or 58.4 in females	Drinking water for 15 weeks	4.8	6.9	6.9	Increased relative and absolute kidney weights in F; impaired renal function in M at ≥8.3 and in F at ≥17.1 mg/kg-day	Carpanini et al. 1978
Rat	M, F	0, 0.13, 0.62, 5.9, 11.6, 25.5, 41, or 72 in males; 0, 0.17, 0.94, 7.84, 13.2, 34.0, 43.7, or 67.4 in females	Drinking water for 13 weeks	25.5	41	41	Decreased peritoneal fat in both sexes	Dunlap et al. 1958
Rat	M, F	0, 1.5, 3, 6, 12, or 25	Gavage in methylcellulose 5 days/week for 14 weeks	1.5	3	2	Squamous hyperplasia of forestomach epithelium in females	NTP, 2006
Mouse	M, F	0, 3, 6, 12, 25, or 50	Gavage in methylcellulose 5 days/week for 14 weeks	none	3	2	Squamous hyperplasia of the forestomach epithelium in males	NTP, 2006

Species	**Sex**	**Dose (mg/kg-day)**	**Exposure Regimen**	**NOAEL (mg/kg-day)**	**LOAEL (mg/kg-day)**	**Adjusted LOAEL[a] (mg/kg-day)**	**Responses at the LOAEL**	**Reference**
Reproductive/Developmental Toxicity								
Rat	M, F	0, 2, 8, or 40	Drinking water: males—42 days before mating; females—14 days before mating, through pregnancy to Day 3 of lactation	8	40	40	Parental (liver damage), reproductive (increased estrous length), and developmental toxicity (decreased viability on Day 4 and litter loss)	Allyl Alcohol Consortium, 2004
Rat	F	0, 10, 35, or 50	Gavage on Days 9−19 of gestation	Maternal: 10 Developmental: 10	35 35	35 35	Liver toxicity; mortality; decreased body weight total litter loss	Lyondell Chemical Company, 2005
Rat	M	0 or 25	Gavage for 15 weeks (7 days/week for first 12 weeks, then 5/7 days/week)	25	None	None	None	Jenkinson and Anderson, 1990

[a]Dose adjusted to 7 days exposure

The subchronic RfD listed in HEAST is 0.05 (5×10^{-2}) mg/kg-day based on the NOAEL of 4.8 mg/kg-day for Wistar rats from Carpanini et al. (1978). IRIS uses Carpanini et al. (1978) as the key study for the chronic RfD of 5×10^{-3} mg/kg-day. Higher doses were associated with increased absolute and relative kidney weights in females at 6.9 mg/kg-day and higher, and changes in urine volume and specific gravity, with respect to control values, in response to dehydration and water loads (8.3 mg/kg-day and higher for males; 17.1 mg/kg-day for females). Data from Carpanini et al. (1978) are not amenable to BMD modeling due to the lack of reported standard deviations for the continuous variables of interest (i.e., kidney weights, urine volume, and specific gravity).

The most sensitive relevant endpoint of toxicity observed in the available studies is squamous hyperplasia of the forestomach epithelium in mice and rats (NTP, 2006). In rats, these effects occurred at several doses tested and were not seen at all in the control animals. Forestomach hyperplasia was also observed in male and female mice at multiple doses. The incidences of this effect are similar but occur at a higher dose in mice.

The lowest NOAEL from the studies is 1.5 mg/kg-day, based on squamous hyperplasia of the forestomach in female rats. The lowest LOAEL from the NTP (2006) study is 3 mg/kg-day (the lowest dose) based upon squamous hyperplasia of the forestomach epithelium in male mice and female rats. The BMD (see Appendix B for BMD/BMDL calculations) was 2.6 mg/kg-day, and the BMDL was 1.3 mg/kg-day, based on the log-logistic model fitting to the female rat forestomach data. Therefore, the BMDL of 1.3 mg/kg-day is selected as the point of departure (POD) from which to derive a subchronic p-RfD.

$$
\begin{aligned}
\textbf{Subchronic p-RfD} \quad &= \quad \text{BMDL} \div \text{UF 300} \\
&= \quad 1.3 \text{ mg/kg-day} \div 300 \\
&= \quad \textbf{0.004 or } 4 \times 10^{-3} \textbf{ mg/kg-day}
\end{aligned}
$$

The composite uncertainty factor (UF) of 300 includes the following UFs:

- A UF_A of 10 is applied to account for potential pharmacokinetic and pharmacodynamic differences between rodents and humans.

- A UF_H of 10 is applied to account for the range of sensitivity within human populations due to the absence of information on the degree to which humans of varying gender, age, health status, or genetic makeup might vary in response to exposure.

- A UF_D of 3 is applied to account for database uncertainty; a combined reproductive/developmental toxicity screening study in rats, a developmental toxicity study in rats, and a reproduction/dominant lethal study in rats are available. The database lacks a multigeneration reproduction study and a developmental toxicity study in a second species.

Confidence in the key study is moderate to high. The study was well conducted and encompassed a wide variety of endpoints; but, due to its nature as a comparative toxicity screening study, only 10 animals/sex/dose were used. Confidence in the database is moderate. There are two older subchronic drinking water studies on two species and screening-level gavage

studies in two species. There are unpublished developmental and reproductive toxicity studies for rats, and a published dominant/lethal study for rats. However, the database lacks a multigeneration reproduction study and a developmental toxicity test in a second species. Confidence in the subchronic p-RfD is, therefore, moderate.

Chronic p-RfD

IRIS (U.S. EPA, 2008a) currently lists a chronic RfD of 0.005 (5×10^{-3}) mg/kg-day for allyl alcohol based on a NOAEL of 4.8 mg/kg-day from Carpanini et al. (1978) and a composite UF of 1,000 that includes 10 for interspecies extrapolation, 10 for human intraspecies variation, and 10 for subchronic to chronic extrapolation. Since the IRIS value exists (posted 1987, last updated in 1989), no p-RfD is derived.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR ALLYL ALCOHOL

Subchronic p-RfC

No human inhalation studies were located for derivation of a p-RfC for allyl alcohol. Human data are limited to measurements of sensory irritation after exposure to low concentrations of allyl alcohol ($\leq$12.5 ppm, (29.6 mg/m^3)) for five minutes (Dunlap et al., 1958; Torkelson et al., 1959). Only two subchronic ($\leq$1 year) animal inhalation studies (Dunlap et al., 1958; Torkelson et al., 1959) provide data from which a p-RfC might be derived.

The study by Torkelson et al. (1959) establishes a minimal LOAEL of 2 ppm (4.7 mg/m^3) for body and relative liver weight reductions in male guinea pigs, with accompanying histopathology. This is the longest duration study available, used multiple species of animals, and included a wide variety of endpoints—including histopathological examination of the liver and kidney but not including histological evaluation of the respiratory tract. Liver effects were reported at higher exposure levels in shorter inhalation studies in the same species (Torkelson et al., 1959) and in rats (Dunlap et al., 1958; Torkelson et al., 1959), rabbits (Torkelson et al., 1959) and dogs (Torkelson et al., 1959). Liver effects ranged from severe damage (periportal necrosis) in rats and rabbits exposed to lethal doses (not specified) of allyl alcohol for 1−8 hours (Dunlap et al., 1958) to mild microscopic alterations (dilation of the sinusoids, cloudy swelling and focal necrosis) in rats, guinea pigs and a rabbit exposed to 7 ppm (16.6 mg/m^3) of allyl alcohol for 5 weeks (Torkelson et al., 1959). A statement was located that liver effects were not reported in human workers exposed to allyl alcohol for 10 years (Dunlap et al., 1958), but no experimental data are provided.

A p-RfC derived from the study by Torkelson et al. (1959), which identifies a LOAEL for minimal biological effects of 2 ppm (4.7 mg/m^3) for body weight changes in male guinea pigs, is expected to be protective of irritant effects. Human volunteers reported no irritation with acute exposure at 2 ppm (4.7 mg/m^3) in one study (Torkelson et al., 1959) and only slight nasal irritation at 0.78 ppm (1.8 mg/m^3) in another (Dunlap et al., 1958), but it is not clear whether the effects would change with chronic exposure. A study by Zissu (1995) identifies an acute LOAEL of approximately 2.4 ppm (5.7 mg/m^3) (for necrosis of the respiratory epithelium in mice (Zissu, 1995) but noted that damage to the respiratory epithelium became less severe with repeated exposure. The subchronic studies of Dunlap et al. (1958) and Torkelson et al. (1959) do

not include histopathological examination of the respiratory tract, but they do examine the animals for clinical signs of irritation. Torkelson et al. (1959) reported no signs of irritation in guinea pigs, rats, rabbits, and a dog exposed to 7 ppm (16.6 mg/m^3) of allyl alcohol for 5 weeks or to 2 ppm (4.7 mg/m^3) of allyl alcohol for 6 months. Dunlap et al. (1958) reported that there were no signs of irritation in rats receiving 20 ppm (47.4 mg/m^3) of allyl alcohol for 12 weeks (a NOAEL) and only transitory signs of irritation in rats exposed to 40 ppm (94.9 mg/m^3) for 12 weeks (a LOAEL). These data suggest that irritant effects of allyl alcohol occur at concentrations similar to or greater than the systemic LOAEL and resolve within a period of days—even with continued exposure. The Torkelson (1959) study was chosen as the key study, because while the Dunlap et al. (1958) study used multiple doses, it is difficult to interpret and the exposures are limited to 12 weeks. The Zissu study was still shorter in duration. Finally, the Torkelson (1959) study yields a LOAEL that is an order of magnitude lower than the Dunlap et al. (1958) LOAEL.

Using the methodology presented in U.S. EPA (1994b), the guinea pig LOAEL of 2 ppm (4.7 mg/m^3) from Torkelson et al. (1959) is adjusted by the exposure period (4.75 mg/m^3 × 7/24 hr × 5/7 d = 1 mg/m^3) to obtain a duration-adjusted LOAEL (LOAEL$_{ADJ}$) of 1 mg/m^3. For purposes of deriving a p-RfC based on extrarespiratory effects, allyl alcohol is considered to be a Category 3 gas (U.S. EPA, 1994b. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry). Because of water solubility it might be considered Category 2, but the HEC calculations are the same. For a Category 3 gas, the human equivalent concentration (HEC) for extrarespiratory effects is calculated as follows:

$$\text{NOAEL}_{HEC} = \text{NOAEL}_{ADJ} \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

where $(H_{b/g})_A/(H_{b/g})_H$ is the ratio of blood:gas partition coefficients (animal:human). A default value of 1 is assumed for the ratio of blood:gas partition coefficients for allyl alcohol due to the lack of partition coefficients for humans and guinea pigs. As such,

$$\text{LOAEL}_{HEC \text{ allyl alcohol}} = \text{LOAEL}_{ADJ \text{ allyl alcohol}}$$

As derived from Torkelson et al. (1959),

$$\text{LOAEL}_{HEC \text{ allyl alcohol}} = 1 \text{ mg/m}^3$$

A subchronic p-RfC is calculated from the LOAEL$_{HEC}$ by dividing by an UF of 1,000 as follows:

$$
\begin{aligned}
\textbf{Subchronic p-RfC} \quad &= \quad \text{LOAEL}_{HEC} \div \text{UF} \\
&= \quad 1 \text{ mg/m}^3 \div 1,000 \\
&= \quad \textbf{0.001 or 1} \times \textbf{10}^{\textbf{-3}} \textbf{ mg/m}^3
\end{aligned}
$$

The composite UF of 1,000 includes the following UFs:

- A UF_A of 3 is applied to account for pharmacodynamic differences between rats and humans. No additional UF for pharmacokinetic differences is required because dosimetric equations were used to derive a $LOAEL_{HEC}$ from the rat exposure concentration and conditions.

- A UF_L of 3 is applied to account for the use of a LOAEL with minimal biologically significant effects (body weight reduction).

- A UF_H of 10 is applied to account for the range of sensitivity within human populations due to the absence of information on the degree to which humans of varying gender, age, health status, or genetic makeup might vary in response to exposure.

- A UF of 10 is applied to account for uncertainties in the inhalation database. Neither a multigenerational reproductive study nor developmental studies are available for the inhalation route of exposure.

Confidence in the principal study (Torkelson et al., 1959) is low. Positive aspects of the study include use of 12 animals/gender/dose and examination of several endpoints—including a histopathological examination of tissues. However, the study is limited in that the respiratory tract was not evaluated, a NOAEL for the critical effect is not defined, and the endpoints examined do not include histopathological examination of the respiratory tract. Confidence in the database is low. The database includes concentration-related systemic toxicity data in several species and the liver as the target organ for subchronic toxicity in guinea pigs is supported by the database. However, there are no data on reproductive or developmental effects, and there is uncertainty as to the significance for individuals undergoing subchronic exposure of the damage to the upper respiratory tract observed in acute exposures. Consequently, there is low confidence in the subchronic p-RfC.

FEASABILITY OF DERIVING A CHRONIC INHALATION p-RfC VALUE FOR ALLYL ALCOHOL

As the composite uncertainty for a chronic p-RfC based upon Torkelson et al. (1959) would be 10,000, the derivation of a chronic RfC is precluded. A screening value having limited confidence and limited applicability, however, is derived in Appendix A.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ALLYL ALCOHOL

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there are "*Inadequate Information to Assess* [the] *Carcinogenic Potential*" of allyl alcohol. The existing evidence is summarized below.

Oral administration of allyl alcohol to rats and hamsters for 106 and 60 weeks, respectively, produced no treatment-related increase in the incidence of neoplasms (Lijinsky and Reuber, 1987). However, these cancer bioassay experiments are of limited use in risk assessment due to previously discussed flaws in experimental design, including a single dose level and low numbers of animals.

Subchronic oral studies are of insufficient duration to be adequate cancer bioassays. Although no treatment-related neoplasms were identified in recent subchronic gavage studies in mice and rats (NTP, 2006), a treatment-related increased incidence of hyperplasia in the epithelium of the forestomach was noted in both species. It is unknown whether this lesion would have progressed to cancer if exposure had continued beyond 14 weeks. Several older subchronic oral studies that included gross and microscopic examination of tissues found no evidence of neoplastic lesions (Al'meev and Karmazin, 1969; Carpanini et al., 1978; Karmazin, 1969).

There are no studies of chronic human exposure to allyl alcohol and no chronic inhalation bioassays conducted with allyl alcohol in animals. There were two older subchronic inhalation studies in animals that were also identified (Dunlap et al., 1958; Torkelson et al., 1959), but these reports did not find any evidence of neoplastic lesions and they were of insufficient duration to be adequate cancer bioassays.

NTP (2006) proposed that because acrolein was not found to be carcinogenic in rats and mice (Parent et al., 1991, 1992), allyl alcohol, whose main metabolite is acrolein, is unlikely to be carcinogenic in properly conducted carcinogenicity studies.

Quantitative Estimates of Carcinogenic Risk
Quantitative estimates of carcinogenic risk cannot be derived due to a paucity of suitable human and animal data.

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APPENDIX A. DERIVATION OF A SCREENING VALUE
FOR ALLYL ALCOHOL

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for chronic exposure to allyl alcohol by the inhalation route of exposure. However, information is available for this chemical, which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

A screening chronic RfC is derived from Torkelson et al. (1959) data as was the subchronic p-RfC value. The value is calculated from the $LOAEL_{HEC}$ by dividing by a composite UF of 10,000 as follows:

$$
\begin{aligned}
\textbf{Screening Chronic p-RfC} \quad &= \quad LOAEL_{HEC} \div UF \\
&= \quad 1 \text{ mg/m}^3 \div 10,000 \\
&= \quad \textbf{0.0001 or 1} \times \textbf{10}^{\textbf{-4}} \textbf{ mg/m}^{\textbf{3}}
\end{aligned}
$$

The composite UF of 10,000 includes the same UFs as the subchronic p-RfC, as well as an additional factor of 10 for use of a subchronic study to approximate chronic exposure.

Therefore, the composite UF includes the following components:

- A UF_A of 3 is applied to account for pharmacodynamic differences between rats and humans. No additional UF for pharmacokinetic differences is required because dosimetric equations were used to derive a $LOAEL_{HEC}$ from the rat exposure concentration and conditions.

- A UF_L of 3 is applied to account for the use of a LOAEL with minimal biological significance (body weight reductions in one gender of guinea pigs).

- A UF_H of 10 is applied to account for the range of sensitivity within human populations due to the absence of information on the degree to which humans of varying gender, age, health status, or genetic makeup might vary in response to exposure.

- A UF_D of 10 is applied to account for uncertainties in the inhalation database. Neither a multigenerational reproductive nor developmental studies are available.

- A UF_S of 10 is applied to account for subchronic to chronic extrapolation.

APPENDIX B: DETAILS OF BENCHMARK DOSE MODELING
FOR A SUBCHRONIC p-RfD

Description of Model Fitting Procedure for Dichotomous Data

The model-fitting procedure for dichotomous data is as follows. All available dichotomous models in the EPA BMDS (version 2.0) are fit to the incidence data using the "extra risk" option. The multistage model is run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Goodness-of-fit is assessed by the χ^2 test. When several models provide adequate fit to the data (χ^2 $p \geq 0.1$), models are compared using the Akaike Information Criterion (AIC). The model with the lowest AIC is considered to provide the best fit to the data. When several models have the same AIC, the model resulting in the lowest BMDL is selected. Benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with an extra risk of 10% are calculated for all models.

Table B-1. Model Predictions for Incidence of Forestomach Hyperplasia in Male Mice						
Model	**Degrees of Freedom**	χ^2	χ^2 **Goodness of Fit** p**-Value**[a]	**AIC**	**BMD$_{10}$ (mg/kg-day)**	**BMDL$_{10}$ (mg/kg-day)**
Gamma (power ≥1)	4	6.13	0.1896	46.9757	2.25525	0.97
Log-logistic (slope ≥1)	**4**	**4.27**	**0.3713**	**44.6711**	**2.64749**	**1.32**
Logistic	4	15.10	0.0045	54.5855	3.60408	2.50
Multistage (betas ≥0)[b]	4	5.83	0.2119	48.193	1.2984	0.88
Log-probit (slope ≥1)	4	4.21	0.3784	44.8099	2.64642	1.38
Probit	4	13.36	0.0096	55.1683	3.65887	2.62
Weibull (power ≥1)	4	6.06	0.1948	47.5273	1.87757	0.93
Quantal	5	5.79	0.3271	46.196	1.27072	0.88

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria
[b]One degree polynomial shown. Higher degree polynomials default back to one degree

The female rat squamous hyperplasia of the forestomach epithelium is the most sensitive endpoint, in the most sensitive species, in the most sensitive gender—with an incidence of 1/10 at the low dose (3 mg/kg-day). It would be expected then, (since the incidence was 10% at that point) that the BMD would be close to this level in the model fitting. As shown in Table B-1, several models provided a fit where the chi-square value was greater than 0.1. Of the models with a chi-square over 0.1, the model with the lowest AIC score was the log-logistic model, with an AIC score of 44.67. A review of the various BMD and BMDL predictions of the models reveals that this dataset is not unduly model dependent. There is roughly a three-fold range of predictions of the various models, and only 1.5 fold differences between models with chi-square p-values indicating good fits. These values are all very close to the LOAEL. The log-logistic model provided a BMDL of 1.3 mg/kg-day and is chosen as the POD for the derivation of a subchronic p-RfD. Figure B-1 shows a graph of the log-logistic model for forestomach hyperplasia in female rats.
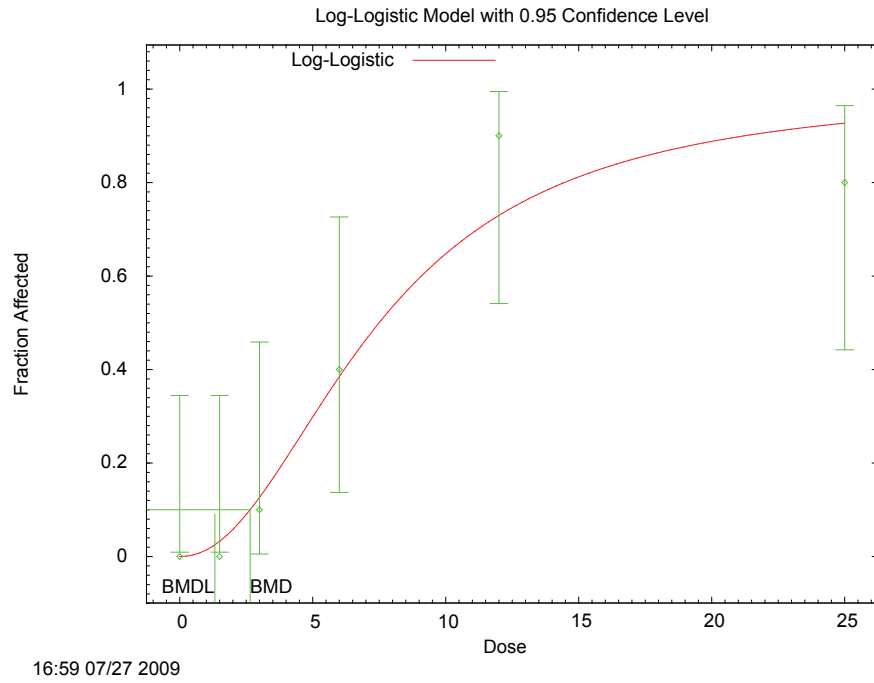
Figure B-1. Fit of Log-Logistic Model to Data on Forestomach Hyperplasia in Female Rats

BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day.