HAZARD ASSESSMENT
FORMAT EVALUATION REVIEW DRAFT
1,3-Dioxolane (CAS No. 646-06-0)

The sponsor, The Dioxolane Consortium, submitted a Test Plan and Robust Summaries to EPA for 1,3-Dioxolane (Dioxolane, CAS # 646-06-0) dated November 20, 2000. EPA posted the submission on the ChemRTK HPV Challenge Website on December 19, 2000. EPA comments were posted on April 18, 2001. The submitter responded by submitting revised documents dated June 12, 2001 which were subsequently posted to the ChemRTK HPV Challenge Website.

Hazard Group Assignment

Group 1
Triggered by: Human Health (Repeated-dose Toxicity, Group 2)
Modified to Group 1 by Reproductive/Developmental Toxicity and Biodegradation data

Tier 1: Dioxolane was placed into Group 2 based on a LOAEL of approximately 0.9 mg/L/day (face value)—Category 2 which is based on the GHS hazard classification criteria. Positive evidence in the reproductive and developmental toxicity studies (face values) and equivocal results for in vivo genetic toxicity (that were considered positive based on NPPTAC guidance) raised the chemical to **Group 1**. In addition, the chemical failed ready biodegradability test, confirming its Group1 designation, a priority chemical for further review.

Tier 2: Further review of the submitted data on Dioxolane confirmed the Tier 1 screen. The LOAEL placing the chemical into this hazard category was derived from a 90-day repeated-dose inhalation toxicity study—a GLP study with a reliability code of 1. EPA considered the study appropriate for use. Positive evidence from the reproductive and developmental toxicity studies, equivocal results from an *in vivo* chromosomal aberration study, and the fact that the chemical was not readily biodegradable confirmed its placement into **Group 1**.

Summary of Critical Studies

Human Health Effects

***Repeated-dose toxicity (Inhalation)*:** Male and female rats were exposed (whole body) to 1,3-Dioxolane vapor at 0, 298, 1000, or 3010 ppm (approximately 0.903, 3.030, or 9.121 mg/L/day), 6h/day, 5d/week for 13 weeks. There was a reduction in white blood cell counts at all levels, statistically significant at the high levels. In addition, there was a decrease in spleen (absolute) and liver (absolute and relative) weights for females at 1000 and 3010 ppm and males at 3010 ppm; decreased alertness at the end of each exposure; and decreased urine specific gravity in males exposed to highest level of 1,3-dioxolane. Microscopically, in male rats exposed to 3010 ppm Dioxolane, hepatocytes in centrilobular regions of lobules were slightly larger and had more cytoplasmic eosinophilia than controls.

LOAEL = 298 ppm (approx. 0.903 mg/L) based on decrease in WBC count in male rats.

Supporting/Modifying Studies

***Reproductive toxicity (Drinking water):* M**ale rats were administered Dioxolane in drinking water at doses of 0.5 or 1.0% prior to mating, during mating with untreated females, and then throughout gestation, lactation and weaning. Mating with males pretreated for 90days with dioxolane to produce the F1a litter resulted in treated groups copulating less frequently, fewer pregnant treated animals delivering than controls, a decrease in the number of pups delivered by the high dose group, an increase in the number of stillborn pups in both groups, reduced

survival in progeny in the high dose and a decrease in body weight of dams in both dose groups. Mating with proven breeders to produce the F1b litter showed the following effects in both dose groups: a decrease in the fecundity index and in the parturition index and a lower female fertility index for the exposed groups. A NOAEL was not achieved.

LOAEL = 0.5% for Parental and F1a generations

In another one-generation reproduction study, male rats were exposed to dioxolane in drinking water at concentrations of 0.01, 0.03, or 0.1% for 90 days prior to mating with previously untreated females. Treatment continued throughout mating, gestation, and lactation. No treatment-related effects were seen in this study.

NOAEL = 0.1% in drinking water

Developmental toxicity: Dose levels were 0, 125, 250, 500, or 1000 mg/kg bw/day (oral gavage in corn oil). Maternal toxicity was evident from statistically significant decreased body weight and food consumption at 500 and 1000 mg/kg/day. Effects of developmental toxicity were characterized by significant increases in litter and fetal incidences of externally evident vertebral malformations associated with tail malformations and septal defects in the heart at 1000 mg/kg/day. One high dose fetus had a cleft palate. Other alterations included reduced ossification of centra in the thoracic vertebrae, the lumbar vertebrae, absent sacral and caudal vertebrae and rib-vertebral malformations.

NOAEL (maternal toxicity) = 250 mg/kg/day (based on decrease in body weight gain)
LOAEL (maternal toxicity) = 500 mg/kg/day

NOAEL (developmental toxicity) = 500 mg/kg/day (based on reduced fetal body weights and gross external, soft tissue and skeletal malformations or variations at 1000 mg/kg/day)
LOAEL (developmental toxicity) = 1000 mg/kg/day

Genetic Toxicity

***Gene Mutations*:** Bacterial assays of Dioxolane showed negative evidence for gene mutations.

Chromosomal aberrations: The in vivo mouse micronucleus test for chromosomal aberrations in bone marrow was negative. However, a test for induction of single strand breaks of DNA in rat hepatocytes showed that Dioxolane induces single strand breaks in DNA as evident from significantly higher rates for alkaline elution.

Conclusion: Repeated exposure to Dioxolane via inhalation affected white blood cells (significant decrease in number), and pleen and liver (decreased weights) in rats. In male rats at high doses, microscopic examination showed significantly larger hepatocytes in centrilobular regions and more cytoplasmic eosinophilia than controls. Dioxolane affected mating performance of male rats, survival of pups (reduction in pups delivered, increase in the number of stillborn pups) and decrease in body weight of pups and dams. In the F1b litter, effects seen in both dose groups included decrease in the fecundity index and in the parturition index, and lower female fertility index for the exposed groups. Developmental effects included external malformations, septal defects in the heart, and reduced ossification of vertebrae. Although Dioxolane did not show a potential for gene mutation, it induced single strand breaks in DNA in rat hepatocytes.

Environmental Effects

Fish:	96h LC_{50} > 95.4 mg/L (*Lepomis macrochirus, bluegill sunfish*)
Invertebrates:	48h EC_{50} >772 mg/L (*Daphnia inagna*)
Algae:	72h $EbErC_{50}$ > 877 mg/L (*Pseudokirchneriella subcapitata*,)

Conclusion: The aquatic toxicity data indicate low acute toxicity to aquatic organisms based on NPPTAC criteria (Group 3—LC_{50} values greater than 10 mg/L).

Physicochemical Properties and Environmental Fate

Log Kow: -0.37 (experimental)

Biodegradation: **NOT READILY BIODEGRADABLE**

Conclusion: Dioxolane is a liquid at room temperature with high water solubility and relatively moderate volatility. Based on the low log Kow value, the potential for Dioxolane to bioaccumulate will be minimal. It will primarily distribute to water and secondarily to soil. Dioxolane is not readily biodegradable and is stable to hydrolysis; however, the estimated atmospheric half-life for 1,3-Dioxolane shows that it will rapidly undergo photodegradation.

OVERALL CONCLUSION

Hazard Identification

Repeated inhalation exposure to Dioxolane vapor caused a reduction in white blood cell counts; a decrease in spleen (absolute) and liver (absolute and relative) weights; decreased alertness at the end of each exposure; histopathological changes in the liver; and reproductive and developmental effects when orally administered to rats. The environmental effects indicated low acute toxicity to fish, aquatic invertebrates and algae. The potential of Dioxolane to bioaccumulate will be minimal based on its low log Kow value. It has moderate volatility and will primarily distribute to water and secondarily to soil. It is not readily biodegradable and is stable to hydrolysis; however, it will rapidly undergo photodegradation.

Use and Exposure

Dioxolane is used as a monomer in polymer production (polyacetal); as an intermediate and solvent for chemical reactions; and as a stabilizer. FDA has approved polyacetal for food contact and NSF has approved it for potable water.

Readily available exposure information (from the submission) suggests that exposure to dioxolane occurs in industrial settings although very low levels of free unpolymerized monomer may exist in final products. Worker exposure monitoring data showed air concentrations of 0.29 to 0.39 ppm (generally < 1 ppm). Environmental releases are from released vapors or from wastewater effluents (0.1 to 4 ppm).

Data Gaps

All SIDS endpoints have been adequately addressed and no additional testing is needed under the HPV Challenge Program.

Dioxolane shows a potential inhalation hazard and based on its exposure potential, additional testing may be necessary as a part of post-Tier II activity.

Regulatory History

1,3-Dioxolane is listed under the Clean Air Act and SARA 302A.

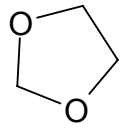
Post Tier 2 Considerations

The following additional considerations will support additional data needs:

- Determining the need for exposure information
- Collecting and reviewing toxicity data on appropriate analogs

U.S. HPV Chemicals Data Table

(As reported in submission under the HPV Challenge Program)

CHEMICAL IDENTITY		
Chemical Name		1,3-DIOXOLANE
CAS Registry Number (CAS RN)		646-06-0
Structure		
Molecular Weight		74.09
Molecular Formula		C3H6O2
Physical Form		Liquid
Submitter		Dioxolane Manufacturers' Consortium
PHYSICOCHEMICAL PROPERTIES		
Melting Point		-95 °C (CRC Handbook)
Boiling Point		78 °C @ 765 mm Hg (CRC Handbook)
Vapor Pressure		70 mm Hg at 20 °C (Hawley's Condensed Chemical Dictionary)
Log Kow		-0.37 (Measured)
Water Solubility		Soluble in all proportions (CRC Handbook)
Henry's Law Constant		2.45×10^{-5} atm m^3/mol at 25 °C
ENVIRONMENTAL FATE AND TRANSPORT		
Biodegradation		**NOT READILY BIODEGRADABLE** (3.7% of THOD after 35 days)
Stability in Water (Hydrolysis)		Stable at pH 4.0, 7.0, and 9.0 (less than 10% degradation at 50 °C in 4 days) T1/2 at 25 °C > one year at pH 4, 7 and 9
Photodegradation		Half-life for reaction with OH = 11.5 hours based on a rate constant of 1.1×10^{-11} cm^3/molecule sec (estimated)
Fugacity		Air: 4.1%, Water: 54%, Soil: 42%, Sediment: 0.1% (estimated)
ECOTOXICITY		
Vertebrates (LC_{50})		> 95.4 mg/L (*Lepomis macrochirus,* 96h LC_{50})
Invertebrates (EC_{50})		>772 mg/L (*Daphnia magna,* 48h EC_{50})
Algae (EC_{50})		> 877 mg/L (*Pseudokirchneriella subcapitata*, 72h $EbErC_{50}$)
Chronic Toxicity Data		N/A
Terrestrial Toxicity Data		N/A
HUMAN HEALTH EFFECTS		
Acute Toxicity (LD_{50} or LC_{50})		Oral LD_{50} = 5200 mg/kg (rat)
		Inhalation LC_{50} = 68.4 mg/L (rat)
Repeated-Dose Toxicity (LOAEL/NOAEL)		**LOAEL = 0.9 mg/L (males);** 3.03 mg/L (females) based on decrease in WBC (Inhalation)
Genetic Toxicity	**Gene Mutation (positive or negative)**	Negative evidence
	Chromosomal Aberration (positive or negative)	In vivo = Negative (bone marrow) Positive (rat hepatocytes) In vitro = Negative evidence (CHO cells)
	Overall	**Overall = Equivocal (Considered positive for this assessment)**

Reproductive Toxicity (positive or negative)	**Positive evidence**
Developmental Toxicity (positive or negative)	**Positive evidence**
Other (carcinogenicity, endocrine effects, neurotoxicity)	N/A
EPA Comments	Completed all SIDS endpoints but additional information needed on the assumptions and data inputs to the fugacity model
Submitter's Response to EPA Comments	The submitter has provided fugacity input information as requested by EPA, EPA has not yet posted comments on the submitter's revisions.
Public Comments	Received comments from the Physicians Committee for Responsible Medicine and Environmental Defense. EPA considered these comments in its response.