Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals

1, 3, 5-Trioxane (CASRN 110-88-3)

Contents:

BACKGROUND

Screening-level hazard, exposure and risk characterizations for high production volume chemicals (HPV) are important contributions to the chemicals cooperation work being done in North America[1] through the EPA Chemical Assessment and Management Program (ChAMP)[2]. These screening-level characterizations are developed by EPA for individual chemicals or chemical categories to support initial Risk-Based Prioritizations (RBPs) for HPV chemicals. These screening-level characterizations are technical documents intended primarily to inform the Agency's internal decision-making process. Accordingly, they are written for assessment professionals and assume a degree of technical understanding. Each of the support documents is described below.

The Risk-Based Prioritizations are found in an accompanying document and are written for a general audience. They present EPA's initial thinking regarding the potential risks presented by these chemicals and future possible actions that may be needed.

Hazard Characterizations for HPV Chemicals

EPA's screening-level hazard characterizations are based primarily on the review of the summaries of studies and other information submitted by the chemical sponsor(s) under the HPV Challenge Program[3]. These studies included in the scope of the HPV Challenge comprise the Screening Information Data Set (SIDS) of the Organization for Economic Cooperation and Development (OECD)[4], an internationally recognized battery of tests that provides the basic data necessary to make an initial evaluation of a chemical's hazards and fate. In preparing the initial hazard characterizations, EPA also consulted a variety of reliable sources[5] for additional relevant information and considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of an HPV submission, EPA also searched publicly available databases[6] for information entered from one year prior to the HPV submission through May 2008. The screening-level hazard characterization is performed according to established EPA guidance[7]. A more detailed description of the hazard characterization process is available on the EPA website[8].

With respect to chemicals for which internationally-accepted OECD SIDS Initial Assessment Profiles (SIAP) and Initial Assessment Reports (SIAR) were available, EPA did not generate its own screening-level hazard characterization, but did check for and incorporate updated information in the risk characterization.

Exposure Characterizations for HPV Chemicals

EPA recently received exposure-related data on chemicals submitted in accordance with the requirements of Inventory Update Reporting (IUR)[9]. The 2006 IUR submissions pertain to chemicals manufactured in

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[1] U.S. EPA – U.S. Commitments to North American Chemicals Cooperation: http://www.epa.gov/hpv/pubs/general/sppframework.htm.
[2] U.S. EPA – ChAMP information: http://www.epa.gov/champ/.
[3] U.S. EPA – HPV Challenge Program information: http://www.epa.gov/hpv.
[4] U.S. EPA – Technical Guidance Document, OECD SIDS Manual Sections 3.4 and 3.5: http://www.epa.gov/chemrtk/pubs/general/sidsappb.htm.
[5] U.S. EPA – Public Database Hazard Information: http://www.epa.gov/hpvis/hazardinfo.htm
[6] U.S. EPA – Public Database Update Information: http://www.epa.gov/chemrtk/hpvis/updateinfo.htm.
[7] U.S. EPA – Risk Assessment Guidelines: http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[8] U.S. EPA – About HPV Chemical Hazard Characterizations: http://www.epa.gov/hpvis/abouthc.htm.
[9] U.S. EPA – Basic IUR Information: http://www.epa.gov/opptintr/iur/pubs/guidance/basic-information.htm.

(including imported into) the U.S. during calendar year 2005 in quantities of 25,000 pounds or more at a single site. The reports include the identity, the quantity, and the physical form of the chemical manufactured or imported, and the number of workers reasonably likely to be exposed during manufacture of the chemical. For chemicals manufactured or imported in quantities of 300,000 pounds or more at a single site, additional reported information includes: the industrial processing and uses of the chemical; the number of industrial processing sites and workers reasonably likely to be exposed to the chemical at those sites; the consumer and commercial uses of the chemical; and an indication whether the chemical was used in products intended for use by children under 14 years of age.

EPA's screening-level exposure characterizations are based largely on the information submitted under the IUR reporting, although other exposure information submitted to the Agency (for example, in HPV submissions) or readily available through a limited set of publicly accessible databases[10] was also considered. The screening-level exposure characterizations identify a potential (high, medium, or low) that each of five populations – the environment, the general population, workers, consumers, and children – might be exposed to the chemical. In most cases, this potential doesn't address the quantity, frequency, or duration of exposure, but refers only to the likelihood that an exposure could occur.

In many instances EPA is not able to fully disclose to the public all the IUR exposure-related data reviewed or relied upon in the development of the screening-level documents because some of the material was claimed as confidential business information (CBI) when it was submitted to the Agency. These CBI claims do limit the Agency's ability to be completely transparent in presenting some underlying exposure and use data for chemicals in public documents. EPA does consider all data, including data considered to be CBI, in the screening-level exposure and risk characterization process, and endeavors whenever possible to broadly characterize supporting materials claimed as confidential in ways that do not disclose actual CBI.

Risk Characterizations for HPV Chemicals

EPA combines the information from the screening-level exposure characterization with the screening-level hazard characterization to develop a qualitative screening-level risk characterization, as described in the Agency's guidance on drafting risk characterizations[11]. These screening-level risk characterizations are technical documents intended to support subsequent priority-setting decisions and actions by OPPT. The purpose of the qualitative screening-level risk characterization is two-fold: to support initial risk-based decisions to prioritize chemicals, identify potential concerns, and inform risk management options; and to identify data needs for individual chemicals or chemical categories.

These initial characterization and prioritization documents do not constitute a final Agency determination as to risk, nor do they determine whether sufficient data are available to characterize risk. Recommended actions reflect EPA's relative judgment regarding this chemical or chemical category in comparison with others evaluated under this program, as well as the uncertainties presented by gaps that may exist in the available data.

[10] U.S. EPA – Summary of Public Databases Routinely Searched: http://www.epa.gov/chemrtk/hpvis/pubdtsum.htm.
[11] U.S. EPA – Risk Characterization Program: http://www.epa.gov/osa/spc/2riskchr.htm.

QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

1, 3, 5-Trioxane (CAS No. 110-88-3)
[9th CI Name: 1, 3, 5-Trioxane]

September 2008

Prepared by

Risk Assessment Division
Economics, Exposure and Technology Division
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR 1, 3, 5-Trioxane (CAS No. 110-88-3)

1. Physical-Chemical Properties and Environmental Fate

1,3,5-Trioxane is a white, crystalline solid at room temperature with a high vapor pressure and high water solubility. 1,3,5-Trioxane is expected to partition primarily to soil and water. It is highly mobile in soil and moderately volatile from water and moist soil surfaces. The rate of hydrolysis of 1,3,5-trioxane is considered negligible. In the atmosphere, 1,3,5-trioxane exists primarily in the vapor phase, where it is subject to slow photooxidation by the hydroxyl radical. It does not undergo direct photolysis. A bioconcentration factor (BCF) of 3.2 was estimated. 1,3,5-Trioxane is expected to have high persistence in the environment (P3) and low bioaccumulation potential (B1).

2. Hazard Characterization

Aquatic Organism Toxicity: The acute toxicity of 1,3,5-trioxane to fish, aquatic invertebrates and aquatic plants is low.

Human Health Toxicity: The acute oral and inhalation toxicity of 1,3,5-trioxane in rats and acute dermal toxicity in rabbits is low. Repeated-dose studies showed route-specific toxicity. An oral repeated-dose study in rats showed low toxicity and an inhalation study in rats showed high toxicity. Two dominant lethal studies (one oral and one inhalation), showed low reproductive toxicity. A separate oral repeated-dose toxicity study, conducted in female rats to evaluate estrous cycle, showed low toxicity. An oral prenatal developmental study in rats showed low developmental and maternal toxicity. 1,3,5-Trioxane did not induce gene mutations in bacteria. However, a dose-dependent increase in mutations was seen in mammalian cells with metabolic activation, but not in the absence of metabolic activation. 1,3,5-Trioxane did not induce chromosomal aberrations in an *in vivo* assay.

3. Exposure Characterization

1,3,5-Trioxane (CAS # 110-88-3) has an aggregated production and/or import volume in the United States of 100 million to 500 million pounds. Non-confidential Inventory Update Reporting (IUR) information for this chemical indicates that it is used as an intermediate in resin and synthetic manufacturing. Other minor uses associated with this chemical are as an adhesive and binding agent in electric lamp bulb and parts manufacturing, and other chemical products and preparations. There are no reported commercial or consumer uses. The High Production Volume (HPV) Challenge submission for this chemical stated that it is used primarily as a monomer for production of high-molecular weight polyacetals and secondarily as a chemical intermediate.

Potential Exposures to the General Population and the Environment: EPA identifies, for purposes of risk-based prioritization, a medium potential that the general population and the environment might be exposed to 1,3,5-trioxane. There is potential for environmental releases to

water and/or air during manufacturing, processing, and use. Persistence and bioaccumulation ratings for this chemical are P3 and B1. These ratings suggest that this chemical is very persistent in the environment, and is not bioaccumulative.

Potential Exposures to Workers: Based on the information considered, including the HPV Revised Test Plan and IUR data (both confidential business information (CBI) and non-CBI), and the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a high relative ranking for potential worker exposure. The high relative ranking is primarily based on the relatively high vapor pressure, which could result in significant worker exposure to vapor, as well as the potential for inhalation exposure to solid material. This chemical does not have OSHA Permissible Exposure Limits (PELs).

Potential Exposures to Consumers: EPA identifies, for the purposes of risk-based prioritization, a low potential that consumers might be exposed to 1,3,5-trioxane from products containing this chemical, based on the IUR data. IUR submissions indicate no uses in consumer products, nor were any found in other data sources.

Potential Exposures to Children: No uses in products specifically intended to be used by children were reported in the IUR, nor were any found in other data sources. Therefore, EPA identifies a low potential that children might be exposed to 1,3,5-trioxane.

4. Risk Characterization

The statements and rationale provided below are intended solely for the purpose of this screening-level and qualitative risk characterization and will be used for prioritizing substances for future work in the Chemical Assessment and Management Program (ChAMP).

Risk Statement and Rationale

Potential Risk to Aquatic Organisms from Environmental Releases: (LOW CONCERN). EPA identifies a medium potential that aquatic organisms might be exposed from environmental releases. 1,3,5-Trioxane has a high persistence and low bioaccumulation. These characteristics in combination with the low toxicity to fish, aquatic invertebrates and plants indicate a low concern for potential risk to fish, aquatic invertebrates and plants.

Potential Risk to the General Population from Environmental Releases: (HIGH CONCERN). EPA identifies a medium potential that the general population might be exposed from environmental releases to the air and water. The potential human health hazard is low for oral exposure. Therefore, there is a low concern for potential risk to the general population due to oral exposure from environmental releases. The potential human health hazard is high for inhalation exposure. Therefore, there is a high concern for potential risk to the general population from inhalation exposures from environmental releases.

Potential Risk to Workers: (HIGH CONCERN). EPA identifies a high relative ranking for potential worker exposure. The ranking is primarily based on the relatively high vapor pressure, which could result in significant worker exposure to vapor, as well as potential for inhalation exposure to solid material. There is not an OSHA Permissible Exposure Limit (PEL) for this chemical. The potential human health hazard is high for inhalation exposure. Therefore, there is a high concern for potential risk to workers.

Potential Risk to Consumers: (LOW CONCERN). EPA identifies a low potential that consumers might be exposed. The potential human health hazard is low for oral exposure and high for inhalation exposure. Therefore taken together, there is a low concern for potential risk to consumers.

Potential Risk to Children: (LOW CONCERN). EPA identifies a low potential that children might be exposed. There are no toxicology studies that specifically address potential toxicity at early life stages. However, 1,3,5-trioxane is not present in children's products or consumer products. Therefore, the available information suggests a low concern for potential risks to children.

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

1,3,5-Trioxane (CAS No. 110-88-3)
[9th CI Name: 1,3,5-Trioxane]

September 2008

Prepared by

Risk Assessment Division
Economics, Exposure, and Technology Division
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

SCREENING-LEVEL HAZARD CHARACTERIZATION
1,3,5-Trioxane (CAS No. 110-88-3)

Introduction

The sponsor, Trioxane Manufacturers Consortium and its member companies, BASF Performance Copolymers, LLC and Ticona, submitted a Test Plan and Robust Summaries to EPA for 1,3,5-trioxane (CAS No. 110-88-3; 9th CI name: 1,3,5-trioxane) on December 22, 2000. EPA posted the submission on the ChemRTK HPV Challenge website on January 12, 2001 (http://www.epa.gov/chemrtk/pubs/summaries/triox/trioxtc.htm). EPA comments on the original submission were posted to the website on May 14, 2001. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on July 16, 2001.

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from July 2000 to May 2008: the NLM databases (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical(s) is included in the appendix. The screening-level hazard characterization for environmental and human health toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Hazard Characterization

1,3,5-Trioxane is a white, crystalline solid at room temperature with a high vapor pressure and high water solubility. 1,3,5-Trioxane is expected to partition primarily to soil and water. It is highly mobile in soil and moderately volatile from water and moist soil surfaces. The rate of hydrolysis of 1,3,5-trioxane is considered negligible. In the atmosphere, 1,3,5-trioxane exists primarily in the vapor phase, where it is subject to slow photooxidation by the hydroxyl radical. It does not undergo direct photolysis. A bioconcentration factor (BCF) of 3.2 was estimated. 1,3,5-Trioxane is expected to have high persistence in the environment (P3) and low bioaccumulation potential (B1).

The acute toxicity of 1,3,5-trioxane to fish, aquatic invertebrates and aquatic plants is low.

The acute oral and inhalation toxicity of 1,3,5-trioxane in rats and acute dermal toxicity in rabbits is low. Repeated-dose studies showed route-specific toxicity. An oral repeated-dose study in rats showed low toxicity and an inhalation study in rats showed high toxicity. Two dominant lethal studies (one oral and one inhalation), showed low reproductive toxicity. A separate oral repeated-dose toxicity study, conducted in female rats to evaluate estrous cycle, showed low toxicity. An oral prenatal developmental study in rats showed low developmental and maternal toxicity. 1,3,5-Trioxane did not induce gene mutations in bacteria. However, a dose-dependent increase in mutations was seen in mammalian cells with metabolic activation, but not in the absence of metabolic activation. 1,3,5-Trioxane did not induce chromosomal aberrations in an *in vivo* assay.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of 1,3,5-trioxane are summarized in Table 1a, while its environmental fate properties are given in Table 1b. The structure of the compound is provided in the Appendix.

Physical-Chemical Properties Characterization

1,3,5-Trioxane is a white, crystalline solid at room temperature. It has both a high vapor pressure and high water solubility.

Table 1a. Physical-Chemical Properties of 1,3,5-Trioxane[1]

Property	Value
CAS No.	110-88-3
Molecular Weight	90.08
Physical State	White, crystalline solid[2,3]
Melting Point	64°C (measured)
Boiling Point	114.5°C at 759 mm Hg (measured)
Vapor Pressure	10 mm Hg at 20°C (measured)
Water Solubility	17.2 g/100 mL at 18°C (measured) 21.2 g/100 mL at 25°C (measured)
Dissociation Constant(s) (pKa)	Not applicable
Henry's Law Constant	1.97×10^{-7} atm-m^3/mol (estimated)[4]
Log K_{ow}	-0.47 (measured)

[1]Trioxane Manufacturers Consortium. 2001. Robust Summary for 1,3,5-Trioxane. http://www.epa.gov/chemrtk/pubs/summaries/triox/trioxtc.htm.
[2]HSDB. 2008. Hazardous Substances Data Bank., Accessed May 12, 2008. http://toxnet.nlm.nih.gov/
[3]Data not provided in robust summary.
[4]US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.

Environmental Fate Characterization

1,3,5-Trioxane is expected to partition primarily to soil and water, according to the results of a Level III fugacity model that assumes equal emissions to air, water, and soil. 1,3,5-Trioxane is expected to be highly mobile in soil based upon its K_{oc}. Its Henry's Law constant suggests that it is moderately volatile from water and moist soil surfaces. The rate of hydrolysis of 1,3,5-trioxane is considered negligible. In the atmosphere, 1,3,5-trioxane exists primarily in the vapor phase, where it is subject to slow photooxidation by the hydroxyl radical. It does not undergo direct photolysis. An estimated bioconcentration factor (BCF) of 3.2 suggests that 1,3,5-trioxane has a low bioaccumulation potential (B1). The rate of biodegradation of 1,3,5-trioxane is slow to negligible based on the results of a MITI ready biodegradation test; therefore, it is judged to have high persistence in the environment (P3).

Table 1b. Environmental Fate Characteristics of 1,3,5-Trioxane[1]	
Property	**Value**
Photodegradation Half-life	25 hours (estimated)[2]
Biodegradation	2% in 28 days (measured; not readily biodegradable)
Hydrolysis Half-life	780 days at pH 4, 840 days at pH 7, 2000 to 3200 days at pH 9 (measured)
Bioconcentration	BCF = 3.2 (estimated)[2]
Direct Photolysis	Not significant
K_{oc}	0.152 (estimated)[2]
Fugacity (Level III Model)[2]	Air = 4.9% Water = 53.4% Soil = 41.6% Sediment = 0.09%
Persistence[3]	P3 (high)
Bioaccumulation[3]	B1 (low)

[1]Trioxane Manufacturers Consortium. 2001. Robust Summary for 1,3,5-Trioxane. http://www.epa.gov/chemrtk/pubs/summaries/triox/trioxtc.htm.
[2]US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.
[3]FR. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) Page 60194–60204.

Conclusion: 1,3,5-Trioxane is a white, crystalline solid at room temperature with a high vapor pressure and high water solubility. 1,3,5-Trioxane is expected to partition primarily to soil and water. It is highly mobile in soil and moderately volatile from water and moist soil surfaces. The rate of hydrolysis of 1,3,5-trioxane is considered negligible. In the atmosphere, 1,3,5-trioxane exists primarily in the vapor phase, where it is subject to slow photooxidation by the hydroxyl radical. It does not undergo direct photolysis. A bioconcentration factor (BCF) of 3.2 was estimated. 1,3,5-Trioxane is expected to have high persistence in the environment (P3) and low bioaccumulation potential (B1

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

Golden orfe (*Leuciscus idus*) were exposed to 1,3,5-trioxane at nominal concentrations of 0, 1000, 2150, 4640 or 10,000 mg/L under static conditions for 96 hours. Mortality was 100% at the highest concentration at all observation periods starting at 1 hour.
96-h LC_{50} = 4030 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to 1,3,5-trioxane at nominal concentrations of 0, 0.1, 1, 10, 100 and 1000 mg/L under static conditions for 48 hours. No immobilization or deaths were seen in the study.
48-h EC_{50} > 1000 mg/L

Toxicity to Aquatic Plants

Green algae (*Scenedesmus subspicatus* strain SAG 86.81) were exposed to 1,3,5-trioxane at nominal concentrations of 0, 3.9, 7.8, 15.6, 31.3, 62.5, 125, 250 and 500 mg/L under static conditions for 72 hours.
96-h EC_{50} (growth) > 500 mg/L

Conclusion: The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of 1,3,5-trioxane to aquatic organisms is low.

3. Human Health Effects

Acute Oral Toxicity

Five male albino rats/group (unspecified strain) were administered 1,3,5-trioxane via gavage at doses of 2520, 5000 and 10,000 mg/kg-bw. Animals were observed for 14 days post-exposure. The numbers of deaths were 0/5, 0/5 and 4/5 for the 2520, 5000 and 10,000 mg/kg-bw dose groups, respectively. There was no observed effect on body weight at any dose. No information on clinical signs, time of death or target organs was provided.
LD_{50} = 8190 mg/kg-bw

Acute Dermal Toxicity

1,3,5-Trioxane was applied to skin of four male albino rabbits (two animals had abraded skin) at 3980 mg/kg-bw for 24 hours. No deaths were observed. 1,3,5-Trioxane resulted in slight to moderate erythema, which disappeared by study termination. Two rabbits had reduced body weights. Necropsy was normal.
LD_{50} > 3980 mg/kg-bw

Acute Inhalation Toxicity

Charles River CD rats (5/sex/dose) were exposed to 1,3,5-trioxane vapor at concentrations of 8370 or 10,643 ppm (approximately 30.8 or 39.2 mg/L, respectively) for 4 hours and were observed for 14 days after dosing. No deaths occurred. Lacrimation, shallow and irregular breathing, reduced activity and nasal discharge were observed at both doses. Body weights were reduced, but animals gained weight normally during the second week of the observation period. Although scattered effects were seen at both doses upon necropsy, findings were minor.
LC_{50} > ~ 39.2 mg/L

Repeated-Dose Toxicity

(1) Wistar rats (5/sex/dose) were administered 1,3,5-trioxane via gavage 28 times within 29 days at doses of 0, 40, 200 or 1000 mg/kg-bw/day. No clinical signs or changes in body weights or food consumption were seen. Leukocytes were significantly decreased at 1000 mg/kg-bw/day in males and females ($p < 0.05$). In the high-dose females, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) activities were increased and protein and glucose levels were decreased significantly ($p < 0.05$), but no corresponding histopathologic effects were observed. Absolute (but not relative) spleen weights of high-dose males were reduced compared with controls ($p < 0.05$).
LOAEL = 1000 mg/kg-bw/day (based on effects on hematology)
NOAEL = 200 mg/kg-bw/day

(2) Sprague-Dawley CD rats (5/sex/dose) were exposed to 1,3,5-trioxane for 12 days (5 days/week for 6 hours/day) via inhalation at vapor concentrations of 0, 103, 984 or 4940 ppm (approximately 0.38, 3.6 or 18 mg/L). Clinical signs were seen at higher incidences than the controls at different times throughout the study, but the sponsors suggested that the effects were sporadic at all doses other than at the highest dose; no statistical evaluation was done for these endpoints. At the high dose, decreased body weights, increased hemoglobin and hematocrit, increased red blood cells (RBC) (females), decreased RBC (males) and decreased white blood cells (males) were all significantly different from controls ($p < 0.01$). Also at the highest dose, clinical chemistry changes (e.g., increases in mean serum glutamic pyruvic transaminase, total protein and albumin values), but no corresponding histopathologic effects were observed. Mean absolute and relative spleen weights were decreased at all doses in males and at the highest two doses in females. Increased relative weights in other organs were considered to be related to decreased body weights at the high dose. In addition, squamous metaplasia of the anterior nasal cavity mucosa with necrosis and desquamation and acute rhinitis were observed.
LOAEL (male) = 0.38 mg/L (based on decreased absolute and relative spleen weights)
NOAEL (male) = Not established
LOAEL (female) = 3.6 mg/L (based on decreased absolute and relative spleen weights)
NOAEL (female) = 0.38 mg/L

Reproductive Toxicity

No data for reproductive toxicity were submitted. Evaluation of effects on fertility, male reproductive organs and reproduction from two dominant lethal assays and the availability of the developmental toxicity study addressed the reproductive toxicity endpoint for the purposes of the HPV Challenge Program.

(1) In a dominant lethal study, Wistar rats (10 males/dose) were administered 1,3,5-trioxane via gavage at doses of 0, 850, or 1700 mg/kg-bw/day 5 days/week for 8 weeks and were mated with untreated virgin females. Body weight gain was 50 and 42% of control at the mid- and high-doses, respectively. Absolute and relative liver, kidney and spermatic vesicle weights were increased. Histopathology of the testes showed focal necrosis of the seminiferous epithelium in 1/10 control, 3/10 low-dose and an unspecified number of high-dose males (testicular lesions were reported to be bilateral in 3/10 high-dose males); severity was reported to be dose-dependent. 1,3,5-Trioxane did not affect fertility rate, number of implants per female, live fetuses per female or pre-implantation loss per female. **1,3,5-Trioxane affected male reproductive organ histology, but not reproductive performance parameters in this assay.**

(2) In another dominant lethal study, Wistar rats (14 males/dose) were exposed to 1,3,5-trioxane at concentrations of 0 or 2.5 mg/L, 5 hours/day, 5 days/week for 12 months. At the end of the dosing period, treated males were mated with untreated virgin females. Although testicular histopathologic effects were similar in the treated and control groups, it was not stated whether seminiferous tubule pathology was evaluated. Fertility rate, number of pregnant females, average litter size and average number of implantations, pre-implantation losses and corpora lutea were similar between controls and treated groups.
1,3,5-Trioxane did not affect male reproductive organ histology or reproductive performance parameters in this assay.

(3) In a repeated-dose toxicity test conducted to determine the effect on the estrous cycle, female Wistar rats (10 or 12/group) were orally administered doses of 0, 190, 580 or 1160 mg/kg-bw/day 5 days/week for 7 weeks. A 6-week post-exposure period was also included. Body weights were measured each week and vaginal smears were taken three times during the study for the first 14 days of exposure, for 14 days during weeks 6 and 7 and for 14 days during the post-exposure period (weeks 11 and 12). Reduction in body weight gain was observed at all doses. Changes in behavior and appearance were seen at the highest dose, including ruffled haircoats, squealing when handled and nasal discharge. Estrous cycle length was increased at 1160 mg/kg-bw/day. All effects returned to normal after dosing ceased.
LOAEL = 1160 mg/kg-bw/day (based on estrous cycle effects)
NOAEL = 580 mg/kg-bw/day (based on estrous cycle effects)

Developmental Toxicity

Pregnant Wistar rats (20 – 21/dose) were administered 1,3,5-trioxane via gavage at doses of 0, 100, 315 or 1000 mg/kg-bw/day on days 7 – 20 of gestation. Body weight gain and food consumption were decreased in the high-dose females from day 10 to study termination (statistically significant); food consumption was slightly reduced at the intermediate group (also statistically significant). (Statistical significance was determined using several tests with p levels of 0.05 or 0.01; however, the p-level criterion was not always stated in the results tables.) At all doses, corrected body weight gain (minus gravid uterus weight at day 21) was significantly lower than controls. Gravid uterus weights were similar among all groups. The high-dose group had five dead fetuses (one per litter) (statistically significant) and one mid-dose litter had two dead fetuses. One high-dose dam and one low-dose dam aborted (showing only implantation sites). Litter size was comparable in all groups. At the highest dose, statistically significant differences included decreased fetal body weights and crown-rump lengths and increased placental weights. Pre-implantation loss was similar or slightly lower, although no statistical evaluation was conducted. Early and late intrauterine deaths as percent of implantations (measures of post-implantation loss) were statistically higher at the highest dose. The number of fetuses as a percent of implantations was statistically decreased at the intermediate- and high-doses. At the high dose, statistically significant increased 'retarded' fetuses (showing slow growth, external/visceral effects) were observed. Two high-dose fetuses had aplasia (absence) of the tail and vertebrae. A variety of other skeletal defects were seen in the high- and intermediate-dose pups. Exoccipital bone abnormalities were observed in one low-dose and one high-dose fetus; these effects were not dose-

dependent and were reported to be within historical controls for this rat strain (laboratory and years not stated). Additional skeletal retardations (non-ossified or weakly-ossified areas) were seen in all dose groups ($p < 0.01$ for some measures), with most effects occurring at the highest dose.
LOAEL (maternal toxicity) = 100 mg/kg-bw/day (based on reduced corrected body weight gain)
NOAEL (maternal toxicity) = Not established
LOAEL (developmental toxicity) = 315 mg/kg-bw/day (based on reduced pup weights and skeletal retardations)
NOAEL (developmental toxicity) = 100 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
(1) *Salmonella typhimurium* strains (TA98, TA100, TA1535 and TA1537) were exposed to 1,3,5-trioxane at concentrations of 20, 100, 500, 2500 and 5000 µg/plate with and without metabolic activation. Two trials (one with preincubation and one without preincubation) were conducted and both positive and negative controls were run. Positive control responses demonstrated the validity of the test. Cytotoxicity was not observed and no dose-dependent increases in revertants were seen.
1,3,5-Trioxane was not mutagenic in this assay.

(2) Mouse lymphoma L5178Y TK+/- cells were exposed to 1,3,5-trioxane at 0.313, 2.5, 6.25, 12.5 and 15 mg/mL with and without metabolic activation in the first trial. Concentrations tested in the second trial using metabolic activation only were 0, 0.156, 0.625, 2.5, 5.0 and 7.5 mg/mL. Triplicate plates were used for counting. Both positive and negative controls were run. Positive control responses demonstrated the validity of the test. No cytotoxicity occurred without activation; with activation, cytotoxicity was dose-dependent and was extensive at the highest concentrations. No dose-dependent increases in mutant numbers were observed in the absence of metabolic activation, but dose-dependent increases were observed with metabolic activation.
1,3,5-Trioxane was mutagenic in this assay with metabolic activation.

Genetic Toxicity – Chromosomal Aberrations

In vivo
(1) In a micronucleus assay, BALB/c mice (4 males/dose) were administered 1,3,5-trioxane via intraperitoneal injection at doses of 0, 2125 and 4250 mg/kg-bw. Mitomycin C was used as a positive control. Animals were sacrificed 5 hours after the second dose. The number of micronuclei per polychromatic erythrocytes was counted (a range of 2300 – 8000 cells counted depending on substance and dose). The positive control had more than 2 times the micronuclei of the negative control. There was no increase in the number of micronuclei at any dose.
1,3,5-Trioxane did not induce chromosomal aberrations in the assay.

Genetic Toxicity – Other

In vivo

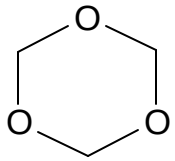
(1) In the oral dominant lethal study described previously, 1,3,5-trioxane did not affect number of implants per female, live fetuses per female or pre-implantation loss per female.
1,3,5-Trioxane did not induce dominant lethal effects in this assay.

(2) In the inhalation dominant lethal inhalation study described previously, 1,3,5-trioxane did not result in differences in number of pregnant females or females mating, average litter size, average number of implantations, pre-implantation losses or corpora lutea between controls and the treatment groups.
1,3,5-Trioxane did not induce dominant lethal effects in this assay.

(3) 1,3,5-Trioxane was administered to Wistar rats as single exposures at concentrations of 0, 250, 500, 1000, and 2000 mg/kg-bw via gavage. Hepatocytes were harvested 4 and 18 hours after dosing for assessment of cell viability and DNA repair activity. There were no treatment-related increases in the number of cells under repair.
1,3,5-Trioxane did not induce DNA repair in this assay.

Conclusion: The acute oral and inhalation toxicity of 1,3,5-trioxane in rats and acute dermal toxicity in rabbits is low. Repeated-dose studies showed route-specific toxicity. An oral repeated-dose study in rats showed low toxicity and an inhalation study in rats showed high toxicity. Two dominant lethal studies (one oral and one inhalation), showed low reproductive toxicity. A separate oral repeated-dose toxicity study, conducted in female rats to evaluate estrous cycle, showed low toxicity. An oral prenatal developmental study in rats showed low developmental and maternal toxicity. 1,3,5-Trioxane did not induce gene mutations in bacteria. However, a dose-dependent increase in mutations was seen in mammalian cells with metabolic activation, but not in the absence of metabolic activation. 1,3,5-Trioxane did not induce chromosomal aberrations in an *in vivo* assay.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL 1,3,5-Trioxane (CAS No. 110-88-3)**
Structure	
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC_{50} (mg/L)	4030
Aquatic Invertebrates 48-h EC_{50} (mg/L)	> 1000
Aquatic Plants 72-h EC_{50} (mg/L) (growth)	> 500
Summary of Human Health Data	
Acute Oral Toxicity LD_{50} (mg/kg-bw)	8190
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	> 3980
Acute Inhalation Toxicity LC_{50} (mg/L)	~ 39.2
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 200 (29-d) LOAEL = 1000 (12-d)
Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L/6-h/day) **(male)** **(female)**	 NOAEL = Not established LOAEL = 0.38 NOAEL = 0.38 LOAEL = 3.6
Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day)	No data submitted. No effects on mating, fertility or pre- and post-implantations in two dominant lethal assays.
Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) **Maternal Toxicity** **Developmental Toxicity**	 NOAEL = Not established LOAEL = 100 NOAEL = 100 LOAEL = 315
Genetic Toxicity – Gene Mutation ***In vitro***	Negative

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL 1,3,5-Trioxane (CAS No. 110-88-3)**
Genetic Toxicity – Chromosomal Aberrations *In vivo*	Negative
Genetic Toxicity – Other *In vivo* **DNA repair**	Negative

Screening Level Exposure Characterization for HPV Challenge Chemical

1,3,5-Trioxane

CAS # 110-88-3

September 2008

Prepared by

Exposure Assessment Branch
Chemical Engineering Branch
Economics, Exposure and Technology Division
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Screening Level Exposure Characterization
1,3,5-Trioxane (CAS# 110-88-3)

Non-CBI Executive Summary

1,3,5-Trioxane (CAS # 110-88-3) has an aggregated production and/or import volume in the United States of 100 million to 500 million pounds. Non-confidential Inventory Update Reporting (IUR) information for this chemical indicates that it is used as an intermediate in resin and synthetic manufacturing. Other minor uses associated with this chemical are as an adhesive and binding agent in electric lamp bulb and parts manufacturing, and other chemical products and preparations. There are no reported commercial or consumer uses. The High Production Volume (HPV) Challenge submission for this chemical stated that it is used primarily as a monomer for production of high-molecular weight polyacetals and secondarily as a chemical intermediate. The Hazardous Substances Data Bank (HSDB) indicates that 1,3,5-trioxane is used as an intermediate to make organic chemicals.

Potential Exposures to the General Population and the Environment: EPA identifies, for purposes of risk-based prioritization, a medium potential that the general population and the environment might be exposed to 1,3,5-trioxane. There is potential for environmental releases to water and/or air during manufacturing, processing, and use. Persistence and bioaccumulation ratings for this chemical are P3 and B1. These ratings suggest that this chemical is very persistent in the environment, and is not bioaccumulative.

Potential Exposures to Workers: Based on the information considered, including the HPV Revised Test Plan and IUR data (both confidential business information (CBI) and non-CBI), and the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a high relative ranking for potential worker exposure. The high relative ranking is primarily based on the relatively high vapor pressure, which could result in significant worker exposure to vapor, as well as potential for inhalation exposure to solid material. This chemical does not have an OSHA Permissible Exposure Limit (PEL).

Potential Exposures to Consumers: EPA identifies, for the purposes of risk-based prioritization, a low potential that consumers might be exposed to 1,3,5-trioxane from products containing this chemical, based on the IUR data. IUR submissions indicate no uses in consumer products, nor were any found in other data sources.

Potential Exposures to Children: No uses in products specifically intended to be used by children were reported in the IUR, nor were any found in other data sources. Therefore, EPA identifies a low potential that children might be exposed to 1,3,5-trioxane.

This exposure characterization was completed using both public, non-confidential sources, and one or more IUR submissions that were available as of this writing.

Volume and Use Information

1,3,5-Trioxane has an aggregated production and/or import volume in the United States of 100 million to 500 million pounds.[12] Non-confidential information in the IUR indicates that this chemical is manufactured and/or imported at the following company and site: Ticona/Bishop, TX. There may be other companies and sites that are claimed confidential. Persons submitting IUR information for 2005 asserted that some or all of the information was confidential. Data and information that are confidential have been excluded from this summary.

According to IUR submissions, there are some industrial processing and uses. Table 1 at the end of this summary provides additional details. There are no reported commercial/consumer uses.

The HPV submission for this chemical stated that it is used primarily as a monomer for production of high-molecular weight polyacetals and secondarily as a chemical intermediate.[13]

The HSDB indicates that 1,3,5-trioxane is used as an intermediate to make organic chemicals.[14]

Exposures to Workers

Based on the information considered, including the HPV Revised Test Plan and IUR data (both CBI and non-CBI), and the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a high relative ranking for potential worker exposure. The high relative ranking is primarily based on the relatively high vapor pressure, which could result in significant worker exposure to vapor, as well as potential for inhalation exposure to solid material. This chemical does not have an OSHA PEL.[15]

The following is a summary of relevant information affecting occupational exposure.

Summary of Parameters Affecting Worker Exposure

Parameter	
Volume*	100 million – 500 million pounds
Physical Form(s)*	liquid, pellets or large crystals, solid
Vapor Pressure	10 mm Hg
Concentration*	up to 100% by weight
Number of Industrial Workers	<1000 (including manufacturing, processing and use)
Uses*	chemical intermediate, organic synthesis, disinfectant, non-luminous, odorless fuel
Key MSDS Info	hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation (lung irritant)

* Only non-CBI IUR information is included.

[12] USEPA, 2006. Partial Updating of TSCA Chemical Inventory.
[13] Trioxane Manufacturers Consortium, 2001. Robust Summaries for 1,3,5-Trioxane, CAS Number 110-88-3. http://www.epa.gov/chemrtk/pubs/summaries/triox/c12863rt.pdf.
[14] HSDB, 2008. Hazardous Substances Data Bank. Accessed, 5/14/08. http://toxnet.nlm.nih.gov.
[15] NIOSH, 1988. OSHA PEL Project Documentation. Accessed, 5/14/08. http://www.cdc.gov/niosh/pel88/npelcas.html.

Based on IUR data, the maximum total number of workers reasonably likely to be exposed to this chemical during manufacturing and industrial processing and use may be between 100 and 999. This estimate does not include potentially exposed commercial workers. The National Occupational Exposure Survey (NOES) has no data for the total number of workers potentially exposed to this chemical under the CAS number 110-88-3.[16]

Based on IUR data, the chemical is manufactured in liquid form and worker exposure is possible for this chemical in this form. IUR reporting indicates the chemical is also manufactured as pellets, large crystals and solids. There may be other physical forms that are claimed confidential. Also, the non-confidential maximum concentration is up to 100% by weight. There may be other concentrations that are claimed confidential. This chemical has a vapor pressure of 10 mm Hg.[17] This chemical's vapor pressure could result in worker exposures to vapors if workers are proximal to the liquid.

This chemical does not have an OSHA PEL.[18]

Environmental Releases

Environmental releases may impact general population and environmental exposures. Factors affecting releases include volumes produced, processed and used; numbers of sites; and, processes of manufacture, processing, and use.

Based on IUR data, the maximum number of sites for manufacturing, processing, or using this chemical is confidential.

The following release statements are made based on inferences regarding the non-confidential use information reported in the IUR submissions.

Many chemicals processed as reactants have industrial releases that are a relatively low percentage of the volume. Lower percentage releases occur when a high percentage of the chemical reacts without excess loss during its use as an intermediate. The actual percentage and quantity of release of the reported chemical associated with this processing or use are not known.

Chemicals having industrial uses as "adhesives and binding agents" or "other" can have variable release percentages during industrial processing and use. The actual percentage and quantity of release of the reported chemical associated with these uses are not known.

The chemical is not on the Toxics Release Inventory.[19] No additional data on releases were found from other sources.

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[16] NIOSH, 1983. National Occupational Exposure Survey (NOES, 1981-1983). Accessed, 5/14/08. http://www.cdc.gov/noes/srch-noes.html.
[17] USEPA, 2008. Screening Level Hazard Characterization for 1,3,5-Trioxane (CAS #110-88-3).
[18] NIOSH, 1988. OSHA PEL Project Documentation. Accessed, 5/14/08. http://www.cdc.gov/niosh/pel88/npelcas.html .
[19] USEPA, 2006. Toxics Release Inventory. Accessed, 5/14/08. http://www.epa.gov/tri/.

This chemical's vapor pressure could result in significant air releases. Experience has shown that air releases due to volatilization may be significant for chemicals with vapor pressures above 0.01 mm Hg.

Exposures to the General Population and the Environment

Based on information indicating the potential for releases, it is likely that there would be some releases to water and/or air during manufacturing, processing, and use (reactants, chemical intermediates, "not readily obtainable," adhesives and binding agents, and "other"). A search of additional relevant databases did not provide any further information on releases of this chemical. EPA assumes, for the purposes of risk-based prioritization, that environmental release and subsequent exposure to the general population and the environment are likely. The IUR ranking for general population and the environment is medium, based on uncertainty that there will be exposure to this chemical based on the IUR data (reactants, chemical intermediates, "not readily obtainable," adhesives and binding agents, and "other").

Persistence and bioaccumulation ratings for this chemical are P3 and B1. These ratings suggest that this chemical is very persistent in the environment, and is not bioaccumulative. 1,3,5-Trioxane is expected to partition primarily to soil and water. It is highly mobile in soil and moderately volatile from water and moist soil surfaces.

Based on the information considered, including environmental fate, known uses, and the Agency's expert judgment, EPA identifies, for purposes of risk-based prioritization, a medium potential that the general population and the environment might be exposed to 1,3,5-trioxane.

Exposures to Consumers

There are no consumer uses reported in the IUR data, nor were any found in other data sources.

EPA identifies, for the purposes of risk-based prioritization, a low potential that consumers might be exposed to 1,3,5-trioxane from products containing this chemical, based on the IUR data.

Exposures to Children

There are no consumer uses reported in the IUR data, nor were any found in other data sources.

No uses in products specifically intended to be used by children were reported in the IUR, nor were any found in other data sources. Therefore, EPA identifies a low potential that children might be exposed to 1,3,5-trioxane.

Non Confidential IUR Data Summary: 1,3,5-Trioxane (CAS # 110-88-3)

Manufacturing/ Import Information

Production (including import volume):	100 million to 500 million pounds
List of non-CBI companies/sites:*	Ticona / Bishop, TX
Maximum number of exposed workers:**	between 100 and 999 (including those of manufacturing, industrial processing and use)
Highest non-CBI maximum concentration:*	up to 100% by weight
Non-CBI physical forms:*	pellets or large crystals, solid*** and liquid

* There may be other companies/ sites, concentrations and physical forms that are claimed confidential.
** There may be additional potentially exposed industrial workers that are not included in this estimate since not all submitters were required to report on industrial processing and use and/or there may be at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions.
*** It is not certain that it will be supplied in solid form.

Table 1
Industrial Processing and Use Information
Reported in 2006 IUR

Processing Activity ****	**Industrial Sector**	**Function in Industrial Sector**
Processing as a reactant	Resin and Synthetic Rubber Manufacturing	Intermediates
Not Readily Obtainable	Electric Lamp Bulb and Part Manufacturing	Adhesives and binding agents
Not Readily Obtainable	All Other Chemical Product and Preparation Manufacturing	Other
Additional line item(s) may be claimed as CBI		

**** It is not certain that other uses beyond chemical intermediate will occur.

There are no reported commercial/consumer uses.