SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

CHEMICAL CATEGORY NAME
Trimellitate Category

SPONSORED CHEMICALS

1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester CAS No. 3319-31-1
[9th CI Name: 1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester]

1,2,4-Benzenetricarboxylic acid, triisooctyl ester CAS No. 27251-75-8
[9th CI Name: 1,2,4-Benzenetricarboxylic acid, triisooctyl ester]

1,2,4-Benzenetricarboxylic acid, triisononyl ester CAS No. 53894-23-8
[9th CI Name: 1,2,4-Benzenetricarboxylic acid, triisononyl ester]

1,2,4-Benzenetricarboxylic acid, decyl octyl ester CAS No. 67989-23-5
[9th CI Name: 1,2,4-Benzenetricarboxylic acid, decyl octyl ester]

SUPPORTING CHEMICAL

1,2,4-Benzenetricarboxylic acid, mixed decyl, hexyl and octyl esters CAS No. 68130-50-7
[9th CI Name: 1,2,4-Benzenetricarboxylic acid, mixed decyl and hexyl and octyl esters]

June 2008
INTERIM

Prepared by

High Production Volume Chemicals Branch
Risk Assessment Division
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program[1] is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals. OPPT is using a hazard-based screening process to prioritize review of the submissions. The hazard-based screening process consists of two tiers described below briefly and in more detail on the Hazard Characterization website[3].

Tier 1 is a computerized sorting process whereby key elements of a submitted data set are compared to established criteria to "bin" chemicals/categories for OPPT review. This is an automated process performed on the data as submitted by the sponsor. It does not include evaluation of the quality or completeness of the data.

In Tier 2, a screening-level hazard characterization is developed by EPA that consists of an objective evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. The evaluation is performed according to established EPA guidance[2,4] and is based primarily on hazard data provided by sponsors. EPA may also include additional or updated hazard information of which EPA, sponsors or other parties have become aware. The hazard characterization may also identify data gaps that will become the basis for a subsequent data needs assessment where deemed necessary. Under the HPV Challenge Program, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. This approach often significantly reduces the need for conducting tests for all endpoints for all category members. As part of Tier 2, evaluation of chemical category rationale and composition and data extrapolation(s) among category members is performed in accord with established EPA[2] and OECD[5] guidance.

The screening-level hazard characterizations that emerge from Tier 2 are important contributors to OPPT's existing chemicals review process. These hazard characterizations are technical documents intended to support subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public. The public, including sponsors, may offer comments on the hazard characterization documents.

The screening-level hazard characterizations, as the name indicates, do not evaluate the potential risks of a chemical or a chemical category, but will serve as a starting point for such reviews. In 2007, EPA received data on uses of and exposures to high-volume TSCA existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule. For the chemicals in the HPV Challenge Program, EPA will review the IUR data to evaluate exposure potential. The resulting exposure information will then be combined with the screening-level hazard characterizations to develop screening-level risk characterizations[4,6]. The screening-level risk characterizations will inform EPA on the need for further work on individual chemicals or categories. Efforts are currently underway to consider how best to utilize these screening-level risk characterizations as part of a risk-based decision-making process on HPV chemicals which applies the results of the successful U.S. High Production Volume Challenge Program and the IUR to support judgments concerning the need, if any, for further action.

---

[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. HPV Chemicals Hazard Characterization website (http://www.epa.gov/hpvis/abouthc.html).
[4] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[5] OECD. Guidance on the Development and Use of Chemical Categories; http://www.oecd.org/dataoecd/60/47/1947509.pdf.
[6] U.S. EPA. Risk Characterization Program; http://www.epa.gov/osa/spc/2riskchr.htm.

SCREENING-LEVEL HAZARD CHARACTERIZATION
Trimellitate Category

Introduction

The sponsor, American Chemistry Council (ACC) Phthalate Esters (PE) Panel HPV Testing Group, submitted a Test Plan and Robust Summaries to EPA for the trimellitate category on December 14, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on February 20, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/trime/c13468tc.htm). EPA comments on the original submission were posted to the website on December 4, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on March 14, 2002 and July 31, 2007, which were posted to the ChemRTK website on December 4, 2002 and August 30, 2007, respectively. The sponsor submitted a response to EPA comments on October 2, 2007 which was posted to the website on January 7, 2008. The trimellitate category consists of the following substances:

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester, TOTM CAS No. 3319-31-1
[9th CI Name: 1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester]

1,2,4-Benzenetricarboxylic acid, triisooctyl ester, TIOTM CAS No. 27251-75-8
[9th CI Name: 1,2,4-Benzenetricarboxylic acid, triisooctyl ester]

1,2,4-Benzenetricarboxylic acid, triisononyl ester, TINTM CAS No. 53894-23-8
[9th CI Name: 1,2,4-Benzenetricarboxylic acid, triisononyl ester]

1,2,4-Benzenetricarboxylic acid, decyl octyl ester, DOTM CAS No. 67989-23-5
[9th CI Name: 1,2,4-Benzenetricarboxylic acid, decyl octyl ester]

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. The structures of the sponsored chemicals are included in the appendix. Summary tables of SIDS endpoint data are included in the document. 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.

Category Justification

The category consists of four chemicals containing individual trimellitate triesters or mixed trimellitate esters, which are defined as esters of 1,2,4-benzenetricarboxylic acids that have branched or branched and linear alkyl groups ranging in carbon number from C8 to C10. The sponsor grouped the members in this category on the basis of a common functionality (trimellitate esters) and the premise that a narrow range of ester carbon numbers (C8 – C10) will produce trends in the physicochemical, environmental and toxicological properties of the four category members. EPA considered the category reasonable.

For environmental and health effects endpoints, the category member, 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester (TOTM) is used as a representative compound to conservatively estimate the properties of the other members because it is the lowest molecular weight chemical and would likely be the most toxic of the category members. EPA concluded that it is reasonable to expect that 1,2,4-benzenetricarboxylic acid, triisooctyl ester (TIOTM), 1,2,4-benzenetricarboxylic acid, triisononyl ester (TINTM) and 1,2,4-benzenetricarboxylic acid, decyl octyl ester (DOTM) will behave similarly to TOTM or follow a trend based on the relative molecular weights, where TOTM will define the upper toxicity boundary for the toxicological properties of the four esters.

TOTM has been evaluated in the OECD HPV Program and the full data set can be found at the following link: http://cs3-hq.oecd.org/scripts/hpv/.

Justification for Supporting Chemical

The sponsor provided measured biodegradation data for the supporting chemical, 1,2,4-benzenetricarboxylic acid, mixed decyl, hexyl and octyl esters (DOHTM) (CAS No. 68130-50-7), to be read-across for the biodegradation endpoint of DOTM). The biodegradability of these two substances will depend on the degree of branching present in their respective ester chains. The degree of branching of the supporting chemical, DOHTM, is not specified in the test plan and its name implies that the esters are linear. In contrast, the sponsored substance, DOTM, is described by the sponsor to be branched and linear. The uncertainty surrounding the structure of the supporting chemical limits its applicability for evaluating this endpoint. However, the biodegradation data provided for DOHTM indicate that it is not readily biodegradable. This result is not likely to under-represent the persistence of the sponsored substance. Therefore, EPA accepts the use of DOHTM as a supporting chemical for the biodegradation endpoint of DOTM.

Summary-Conclusion

Estimated log K_{ow} values of the trimellitate category members are high. However, their low water solubilities ($3.9 \times 10^{-4} – 2.8 \times 10^{-9}$ mg/L) suggest that their potential to bioaccumulate in aquatic organisms is low. Members of the trimellitate category are not readily biodegradable, indicating that they are expected to persist in the environment.

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute and chronic hazards to aquatic organisms is low based on no effects observed at the water solubility limit (saturation).

Acute oral, inhalation and dermal toxicity for the members of the trimellitate category is low. 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester was not irritating to rabbit skin or eyes and was not a skin sensitizer. Repeated exposure of rats to 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester via the oral route resulted in reduced food consumption and effects on hematology parameters, clinical chemistry, liver biochemistry, organ weights (increased absolute and relative liver weights) and histopathology. In a combined oral reproductive/developmental toxicity study in rats with 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester, reproductive effects were limited to histopathological changes in the testes; no clear developmental effects were observed. 1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester did not induce gene mutation in bacteria, chromosomal aberrations in mammalian cells and unscheduled DNA synthesis *in vitro.*

The potential health hazard of the trimellitate category is low based on repeated-dose toxicity.

No data gaps have been identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

A summary of physical-chemical properties and environmental fate data submitted is provided in Table 1. For the purpose of the screening-level hazard characterization, the review and summary of these data was limited to the octanol-water partition coefficient and biodegradation endpoints as indictors of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
Log K_{ow}: 11.59 (estimated)

1,2,4-Benzenetricarboxylic acid, triisooctyl ester (TIOTM, CAS No. 27251-75-8)
Log K_{ow}: 11.59 (estimated)

1,2,4-Benzenetricarboxylic acid, triisononyl ester (TINTM, CAS No. 53894-23-8)
Log K_{ow}: 13.06 (estimated)

1,2,4-Benzenetricarboxylic acid, decyl octyl ester (DOTM, CAS No. 67989-23-5)
Log K_{ow}: 12.79 (estimated)

The model used to estimate the submitted log K_{ow} values (KOWWIN v.1.67) has been demonstrated to be accurate in predicting log K_{ow} values between -4 and 10. Given that the estimates for members of the trimellitate category are outside this range, the absolute values may not be accurate. Nonetheless, it is reasonable to conclude that these predictions indicate that the log K_{ow} values for these chemicals are high (> 8).

Biodegradation

1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
(1) In a Manometric Respirometry test using domestic, activated sludge as inoculum, 46.8% of 1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester had degraded after 28 days.
1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester is not readily biodegradable.

(2) In a modified MITI test, 4.2% of 1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester had degraded after 28 days.
1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester is not readily biodegradable.

1,2,4-Benzenetricarboxylic acid, triisooctyl ester (TIOTM, CAS No. 27251-75-8)
In a Manometric Respirometry test using domestic, activated sludge as inoculum, 5.36% of 1,2,4-benzenetricarboxylic acid, triisooctyl ester had degraded after 28 days.
1,2,4-Benzenetricarboxylic acid, triisooctyl ester is not readily biodegradable.

1,2,4-Benzenetricarboxylic acid, triisononyl ester (TINTM, CAS No. 53894-23-8)
In a Manometric Respirometry test using domestic, activated sludge as inoculum, 4.19% of 1,2,4-benzenetricarboxylic acid, triisononyl ester had degraded after 28 days.
1,2,4-Benzenetricarboxylic acid, triisononyl ester is not readily biodegradable.

1,2,4-benzenetricarboxylic acid, mixed decyl and hexyl and octyl esters (DOHTM, CAS No. 68130-50-7, supporting chemical)
In a Manometric Respirometry test using domestic, activated sludge as inoculum, 33.7% of 1,2,4-benzenetricarboxylic acid, mixed decyl and hexyl and octyl esters had degraded after 28 days.
1,2,4-benzenetricarboxylic acid, mixed decyl and hexyl and octyl esters is not readily biodegradable .

Conclusion: Estimated log K_{ow} values of the trimellitate category members are high. However, their low water solubilities ($3.9 \times 10^{-4} – 2.8 \times 10^{-9}$ mg/L) suggest that their potential to bioaccumulate in aquatic organisms is low.

Members of the trimellitate category are not readily biodegradable, indicating that they are expected to persist in the environment.

Table 1. Summary of Physical-Chemical Properties and Environmental Fate Data

Endpoints	**1,2,4-Benzene-tricarboxylic acid, tris(2-ethylhexyl) ester (3319-31-1)**	**1,2,4-Benzene-tricarboxylic acid, triisooctyl ester (27251-75-8)**	**1,2,4-Benzene-tricarboxylic acid, triisononyl ester (53894-23-8)**	**1,2,4-Benzene-tricarboxylic acid, decyl octyl ester (67989-23-5)**	**1,2,4-Benzene-tricarboxylic acid, mixed decyl, hexyl and octyl esters (68130-50-7, supporting chemical)**
Melting Point (°C)	**-46 (m)**	No Data -46 (RA)	No Data -46 (RA)	No Data -46 (RA)	–
Boiling Point (°C)	541 (e) 283 at 4 hPa (OECD HPV)	541 (e)	575 (e)	585 (e)	–
Vapor Pressure (hPa at 25°C)	**0.133 (m)** (200°C) **<2.8 x 10^{-4} (100°C; OECD HPV) (m)**	5.3×10^{-11} (e)	3.2×10^{-12} (e)	1.4×10^{-12} (e)	–
Log K_{ow}	11.59 (e) **5.94 (25°C; OECD HPV) (m)**	11.59 (e)	13.06 (e)	12.79 (e)	–
Water Solubility (mg/L at 25°C)	**3.9×10^{-4} (m)** **0.13 (OECD HPV) (m)**	5×10^{-8} (e)	1.3×10^{-9} (e)	2.8×10^{-9} (e)	–
Direct Photodegradation	No Data	No Data	No Data	No Data	–
Indirect (OH^-) Photodegradation ($t_{1/2}$)	3.9 h (e)	4.2 h (e)	3.7 h (e)	3.8 h (e)	–
Stability in Water (Hydrolysis) ($t_{1/2}$)	**17.5 d (m)**	0.4 yr (e)	0.9 yr (e)	1.0 yr (e)	–
Fugacity (Level III Model) **Air (%)** **Water (%)** **Soil (%)** **Sediment (%)**	 0 0 99.3 0.7	 0 0 99.3 0.7	 0 0 99.3 0.7	 0 0 99.3 0.7	–
Biodegradation at 28 days (%)	**46.8 (m)** **4.2 (m)** **Not readily biodegradable**	**5.36 (m)** **Not readily biodegradable**	**4.19 (m)** **Not readily biodegradable**	No Data 33.7 Not readily biodegradable (RA)	**33.7 (m)** **Not readily biodegradable**

(m) = measured data (i.e., derived from experiment); (e) = estimated data (i.e. derived from modeling); (RA) = Read Across; – indicates that endpoint was not addressed for this substance.

2. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 2. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Toxicity to Fish

1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
Medaka (*Oryzias latipes*, 10/concentration) were exposed to the test substance at nominal concentrations of 0 and 100 mg/L under semi-static conditions for 96 hours. Measured concentrations were <1 and 103, respectively at 0-hours and <1 and 102 mg/L at 24-hours. One fish from the each of the control (96 hours) and treated groups (48 hours) died. At 24 hours, one fish showed abnormal breathing behavior. No other effects were noted at 100 mg/L. EPA does not consider 100 mg/L as the no-effect concentration because this concentration exceeds the water solubility of the chemical. Assuming the exposure concentration is the water solubility limit (saturation) for 1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester, the no-effect concentration would be approximately 3.9×10^{-4} mg/L.
No effects at saturation

Acute Toxicity to Aquatic Invertebrates

1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
Water fleas (*Daphnia magna*, 20/replicate) were exposed to the test substance at nominal concentrations of 0, 17.1, 30.9, 55.6, 100 and 180 mg/L under static conditions for 48 hours. Measured concentrations were within 90 – 99% of the nominal concentrations. One daphnid was immobilized at 17.1 mg/L; no immobility was seen at the other concentrations. EPA does not consider 180 mg/L as the no effect concentration because this concentration exceeds the water solubility of the chemical. Assuming the exposure concentration is the water solubility limit (saturation) for 1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester, the no effect concentration would be approximately 3.9×10^{-4} mg/L.
No effects at saturation

Toxicity to Aquatic Plants

1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
Green algae (*Pseudokirchneriella subcapitata*) were exposed to the test substance at nominal concentrations of 0 and 100 mg/L under static conditions for 72 hours. Measured concentrations were <1, 80.6 and <1, and 68.7 mg/L, respectively at 0 and 72-hour intervals. There was no effect on growth and biomass. EPA does not consider 100 mg/L as the no effect concentration because this concentration exceeds the water solubility of the chemical. Assuming the exposure concentration is the water solubility limit (saturation) for 1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester, the no effect concentration would be approximately
3.9×10^{-4} mg/L.
No effects at saturation

Chronic Toxicity to Aquatic Invertebrates

1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
Water fleas (*Daphnia magna*) were exposed to the test substance at nominal concentrations of 0 and 100 µg/L under flow-through conditions for 21 days. The mean measured concentration was 82 µg/L. No significant effects were seen on survival, mean adult length or mean young/adult reproduction. Assuming the exposure concentration is the water solubility limit (saturation) for 1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester, the no effect concentration would be approximately 3.9×10^{-4} mg/L.
No effects at saturation

Conclusion: The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute and chronic hazards to aquatic organisms is low based on no effects observed at the water solubility limit (saturation).

Table 2. Summary of Environmental Effects – Aquatic Toxicity Data				
Endpoints	**1,2,4-Benzene-tricarboxylic acid, tris (2-ethylhexyl) ester (3319-31-1)**	**1,2,4-Benzene-tricarboxylic acid, triisooctyl ester (27251-75-8)**	**1,2,4-Benzene-tricarboxylic acid, triisononyl ester (53894-23-8)**	**1,2,4-Benzene-tricarboxylic acid, decyl octyl ester (67989-23-5)**
Fish 96-h LC_{50} (mg/L)	NES			
Aquatic Invertebrates 48-h EC_{50} (mg/L)	NES			
Aquatic Plants 72-h EC_{50} (mg/L)	NES			
Aquatic Invertebrates Chronic Toxicity 21-d NOEC (mg/L)	NES			

[a]NES = No effects at saturation (water solubility limit) due to low water solubility and high log K_{ow} values (> 8).

3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 3. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Oral Toxicity

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
Crj:CD(SD) rats (5/sex/dose) were administered 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester via gavage at 0 or 2000 mg/kg-bw in corn oil and observed for 14 days. No mortalities were observed. Clinical signs of toxicity included loose stool (attributed to corn oil). No abnormalities were seen during necropsy.
LD_{50} > 2000 mg/kg-bw

1,2,4-Benzenetricarboxylic acid, triisononyl ester (TINTM, CAS No. 53894-23-8)
Sprague-Dawley rats (5 males/dose) were administered 1,2,4-benzenetricarboxylic acid, triisononyl ester via gavage at 417, 1450, 5000 or 10,000 mg/kg-bw and observed for 14 days. No mortalities were observed. Clinical signs included decreased activity, excessive urination and/or diarrhea at the two highest dose levels.
LD_{50} > 10,000 mg/kg-bw

Acute Inhalation Toxicity

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
(1) Crj:CD(SD) rats (5/sex/dose) were exposed (whole-body) to 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester at 2600 mg/m^3 (2.6 mg/L) and observed for 14 days (duration of exposure not specified). No mortalities were observed. Clinical signs of toxicity included matted, drenched coats for the first 2 days. Necropsy findings included red patches on the lungs.
LC_{50} > 2.6 mg/L

(2) Rats (strain, sex not stated) were exposed to the test substance at 230, 2640 and 4170 mg/m^3 (equivalent to 0.230, 2.640, and 4.170 mg/L) for 6 hours Mortality was seen at 2 higher concentrations. Clinical signs included minimal irritation and normal weight gain among the survivors and severe irritation in decedents.
LC_{50} > 0.23 mg/L

Acute Dermal Toxicity

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
New Zealand White rabbits (5/sex/dose) were administered 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester dermally at 2.0 mL/kg-bw (2000 mg/kg-bw) on to the abraded skin for 24 hours and observed for 14 days. No mortalities or clinical signs of toxicity were observed.
LD_{50} > 2000 mg/kg-bw

Repeated-Dose Toxicity

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
(1) Fischer 344 rats (5/sex/dose) were administered 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester via the diet at 0, 184, 650 or 1826 mg/kg-bw/day for 28 days. Statistically significant ($p < 0.05$) decreases were seen in hemoglobin concentrations in mid- and high-dose males and females, increased leucocyte counts among mid- and high-dose males and females (statistically significant only for males) and decreased hematocrit and mean cell volume in low- and mid-dose females. Other effects included slightly decreased erythrocyte counts in males from all dose groups and decreased eosinophil and monocyte percentages among mid- and high-dose males. Statistically significant ($p < 0.05$) changes in clinical chemistry included an increased level of albumin in mid- and high-dose males and females, increased cholesterol levels in mid- and high-dose males, increased serum urea concentrations in high-dose males and decreased lipid concentration in low-dose females. In liver biochemistry studies, statistically significant ($p < 0.05$) changes included increased palmitoyl CoA activity among males from all dose groups and high-dose females, increased catalase activities among high-dose males and increased carnitine acetyltransferase activity among mid- and high-dose males and females. Males and females in the mid- and high-dose groups exhibited increased absolute and relative (to body weight) liver weights. Increased absolute brain and lung weights were also noted. Histopathology revealed focal interstitial pneumonitis and nephrocalcinosis in females and reductions in cytoplasmic basophilia in the liver among two female high-dose rats. Slightly increased numbers of peroxisomes were seen in the liver of high-dose animals. No treatment-related mortality or effects on body weight were noted.
LOAEL = 650 mg/kg-bw/day (based on hematology and liver biochemistry changes and changes in organ weights)
NOAEL = 184 mg/kg-bw/day

(2) Crj:CD(SD) rats (5/sex/dose) were administered 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester via the diet at 0 (corn oil vehicle), 100, 300 or 1000 mg/kg-bw/day for 28 days. Additional animals (group sizes not indicated) were exposed to 0 (vehicle) or 1000 mg/kg-bw/day for 28 days and were examined 2 weeks after termination of dosing. Decreases in spermatocytes and spermatids in males were observed in the two high doses. No effects on hematology, clinical chemistry, urinalysis, organ weights and histopathology were noted.. No effects were noted for clinical signs, mortality, and body weight or food consumption.
LOAEL (males) = 300 mg/kg-bw/day (based on decreases in spermatocytes and spermatids in males)
NOAEL (males) = 100 mg/kg-bw/day
NOAEL (females) = 1000 mg/kg-bw/day (based on no effects at the highest dose tested)

Reproductive/Developmental Toxicity

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
In a combined reproductive/developmental toxicity screening test, Crj: CD(SD) rats (12/sex/dose) were administered 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester via gavage at 0 (corn oil vehicle), 100, 300 or 1000 mg/kg-bw/day from 2 weeks prior to mating, during mating (males and females), gestation and or until day 3 of lactation (females). Histopathological examination of the testes revealed slight to moderate decreases in spermatocytes and spermatids in mid- and high-dose males. One high-dose male also exhibited multinucleate giant cells, slight vacuolization of sertoli cells, moderate amounts of cell debris in the epididymis and slight granuloma of spermatic plexus. Other effects included low values of round spermatids, elongate spermatids and ratio of sertoli cells among high-dose males. Effects on females included cyst of the corpus luteum of the ovary in two mid-dose animals. Pup body weights were slightly decreased among mid-dose males and females. No effects were detected on general appearance, body weight, food consumption, reproductive organ weights, necropsy findings, reproductive ability, delivery or maternal behavior. In the offspring, no developmental effects were detected on viability, general appearance and body weight or necropsy findings.
LOAEL (systemic/reproductive toxicity) = 300 mg/kg-bw/day (based on histopathological changes in the testes)
NOAEL (systemic/reproductive toxicity) = 100 mg/kg-bw/day
NOAEL (developmental toxicity) = 1000 mg/kg-bw/day (based on no effects at the highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
(1) *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 were exposed to 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester at concentrations of 0 (untreated control), 0 (DMSO vehicle control), 100, 333, 1000, 3333 or 10,000 µg/plate in the presence and absence of metabolic activation. Positive controls were tested, but their responses were not provided. The cytotoxic concentration was > 10,000 µg/plate.
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester was not mutagenic in this assay.

(2) In the NTP study, *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535 were exposed to 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester at concentrations of 0 (untreated control), 0 (DMSO vehicle control), 100, 333, 1000, 3333 or 10,000 µg/plate in the presence and absence of metabolic activation. Positive controls produced an appropriate response. The cytotoxic concentration was > 10,000 µg/plate.
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester was not mutagenic in this assay.

(3) *Salmonella typhimurium* strains TA100, TA1535, TA98 and TA1537 and *Escherichia coli* WP2 uvrA were exposed to 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester at concentrations of 0, 313, 625, 1250, 2500 or 5000 µg/plate in the presence and absence of metabolic activation. Positive controls were tested, but their responses were not provided. The cytotoxic concentration was > 5000 µg/plate.
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1)
Chinese hamster lung/IU cells were exposed to 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester at concentrations of 0, 1.3, 2.5 or 5.0 mg/mL in the absence of metabolic activation during continuous treatment for 24 or 48 hours and during short-term treatment of 6 hours in the presence and absence of metabolic activation. Positive controls were tested, but their responses were not provided. The cytotoxic concentration was > 5.0 mg/mL.
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester did not induce chromosomal aberrations in this assay.

Genetic Toxicity – Other

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (CAS No. 3319-31-1)

In an unscheduled DNA synthesis assay, rat primary hepatocytes were exposed to the test substance at concentrations ranging from 250 nL/mL to 5000 nL/mL for 18 hours. The test substance did not induce significant change in the nuclear labeling of primary rat hepatocytes. Little or no toxicity was observed; however, higher concentrations could not be assayed because of the insoluble nature of the test substance in medium. There was no indication of UDS by the treatments and no dose-response was observed. Positive control responded appropriately. (http://www.syrres.com/esc/tscats.htm)
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester did not induce UDS in this assay.

Additional Information

Skin Irritation

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (CAS No. 3319-31-1)
New Zealand White rabbits (6, sex not stated) were administered the test substance (0.5 mL) on to the clipped intact and abraded skin areas on the backs under occluded conditions for 24 hours. The treated areas were examined at 24 and 72 hours following exposure. Slight erythema was noted which cleared by 72-hour observation period. (http://www.syrres.com/esc/tscats.htm)
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester was not irritating to rabbit skin in this study.

Eye Irritation

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (CAS No. 3319-31-1)
New Zealand White rabbits (6, sex not stated) were instilled the test substance (0.1 mL) into right eyes; the other eyes remained untreated and served as controls. The exposure period was 4 hours. The treated eyes were not washed. The eyes were examined at 1, 2, 3, 4 and 7 days following instillation of the test substance according to Draize scale of scoring. Very slight conjunctival redness was seen in all rabbits on day one which was cleared completely by day 3. (http://www.syrres.com/esc/tscats.htm)
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester was not irritating to rabbit eyes in this study.

Skin Sensitization

1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester (CAS No. 3319-31-1)
Albino guinea pigs (10, sex not stated) were applied the test substance on to the intact skin sites under semi-occlusive conditions for 24 hours. After 1-day rest period, a second application of test substance was made at the same site. This sequence was repeated for a total of ten applications. After the tenth application followed by a two-week rest period, a challenge application was made on different sites. The challenge exposure was for 24 hours. The application sites were scored 24 hours following induction and 24 and 48 hours after the challenge applications according to Draize scale for irritation (http://www.syrres.com/esc/tscats.htm).
1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester was not sensitizing in this study.

Conclusion: Acute oral, inhalation and dermal toxicity for the members of the trimellitate category is low. 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester was not irritating to rabbit skin or eyes and was not a skin sensitizer. Repeated exposure of rats to 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester via the oral route resulted in reduced food consumption and effects on hematology parameters (decreased hemoglobin, hematocrit, erythrocyte counts, mean cell volume and percentages of eosinophils and monocytes and increased leucocyte counts), clinical chemistry (increased albumin, cholesterol and serum urea), liver biochemistry (increased activities of palmitoyl CoA, catalase and carnitine acetyltransferase), organ weights (increased absolute and relative liver weights) and histopathology (increased incidences of interstitial pneumonitis, nephrocalcinosis and liver peroxisomes). In a combined oral reproductive/developmental toxicity study in rats with 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester, reproductive effects were limited to histopathological changes in the testes (decreases in number of spermatocytes, number and ratio of round and elongated spermatids and ratio of sertoli cells); no clear developmental effects were seen. 1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester did not induce gene mutation in bacteria, chromosomal aberrations in mammalian cells and unscheduled DNA synthesis *in vitro.*

The potential health hazard of the trimellitate category is low based on repeated-dose toxicity.

Table 3. Summary of Human Health Data				
Endpoints	**1,2,4-Benzene-tricarboxylic acid, tris (2-ethylhexyl) ester (3319-31-1)**	**1,2,4-Benzene-tricarboxylic acid, triisooctyl ester (27251-75-8)**	**1,2,4 Benzene-tricarboxylic acid, triisononyl ester (53894-23-8)**	**1,2,4-Benzene-tricarboxylic acid, decyl octyl ester (67989-23-5)**
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	**> 2000**	No Data > 2000 (RA)	**> 10,000**	No Data > 10,000 (RA)
Acute Inhalation Toxicity **LC_{50} (mg/L)**	**> 2.6**	No Data > 2.6 (RA)	No Data > 2.6 (RA)	No Data > 2.6 (RA)
Acute Dermal Toxicity **LD_{50} (mg/kg-bw)**	**> 2000**	No Data > 2000 (RA)	No Data > 2000 (RA)	No Data > 2000 (RA)
Repeated-Dose Toxicity **Oral (mg/kg-bw/day)**	**NOAEL = 184** **LOAEL = 650**	No Data NOAEL = 184 LOAEL = 650 (RA)	No Data NOAEL = 184 LOAEL = 650 (RA)	No Data NOAEL = 184 LOAEL = 650 (RA)
Reproductive/Developmental Toxicity **Oral (mg/kg-bw/day)** **Systemic/Reproductive Toxicity** **Developmental Toxicity**	**NOAEL = 100** **LOAEL = 300** **NOAEL = 1000 (hdt)**	No Data NOAEL = 100 LOAEL = 300 NOAEL = 1000 (hdt) (RA)	No Data NOAEL = 100 LOAEL = 300 NOAEL = 1000 (hdt) (RA)	No Data NOAEL = 100 LOAEL = 300 NOAEL = 1000 (hdt) (RA)
Genetic Toxicity – Gene Mutation ***In vitro***	**Negative**	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	**Negative**	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)
Genetic Toxicity – Other ***UDS (In vitro)***	Negative	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)
Additional Information **Skin Irritation** **Eye Irritation** **Dermal Sensitization**	 Not irritating Not irritating Not a sensitizer	–	–	–

Measured data in bold text; (RA) = Read Across

4. Hazard Characterization

Estimated log K_{ow} values of the trimellitate category members are high. However, their low water solubilities ($3.9 \times 10^{-4} – 2.8 \times 10^{-9}$ mg/L) suggest that their potential to bioaccumulate in aquatic organisms is low. Members of the trimellitate category are not readily biodegradable, indicating that they are expected to persist in the environment.

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute and chronic hazards to aquatic organisms is low based on no effects observed at the water solubility limit (saturation)

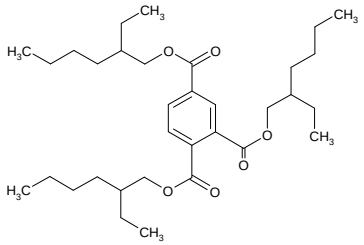
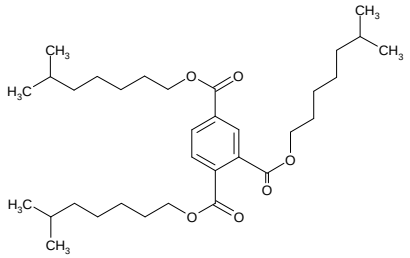
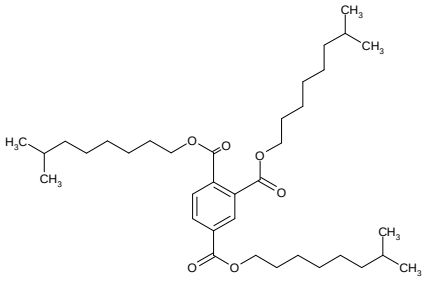
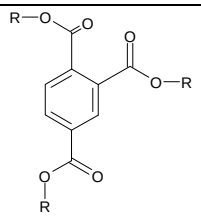
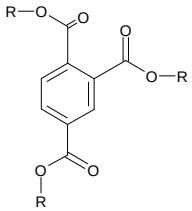
Acute oral, inhalation and dermal toxicity for the members of the trimellitate category is low. 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester was not irritating to rabbit skin or eyes and was not a skin sensitizer. Repeated exposure of rats to 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester via the oral route resulted in reduced food consumption and effects on hematology parameters (decreased hemoglobin, hematocrit, erythrocyte counts, mean cell volume and percentages of eosinophils and monocytes and increased leucocyte counts), clinical chemistry (increased albumin, cholesterol and serum urea), liver biochemistry (increased activities of PCoA, catalase and carnitine acetyltransferase), organ weights (increased absolute and relative liver weights) and histopathology (increased incidences of interstitial pneumonitis, nephrocalcinosis and liver peroxisomes). In a combined oral reproductive/developmental toxicity study in rats with 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester, reproductive effects were limited to histopathological changes in the testes (decreases in number of spermatocytes, number and ratio of round and elongated spermatids and ratio of sertoli cells); no clear developmental effects were seen. 1,2,4-Benzenetricarboxylic acid, tris (2-ethylhexyl) ester did not induce gene mutation in bacteria, chromosomal aberrations in mammalian cells and unscheduled DNA synthesis *in vitro.*

The potential health hazard of the trimellitate category is low based on repeated-dose toxicity.

5. Data Gaps

No data gaps were identified under the HPV Challenge Program.

APPENDIX

The Trimellitate Category		
CAS No.	**Chemical Name**	**Chemical Structure**
SPONSORED CHEMICALS		
3319-31-1	**1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester**	 $C_{33}H_{54}O_6$
27251-75-8	**1,2,4-Benzenetricarboxylic acid, triisooctyl ester**	 $C_{33}H_{54}O_6$
53894-23-8	**1,2,4-Benzenetricarboxylic acid, triisononyl ester**	 $C_{36}H_{60}O_6$
67989-23-5	**1,2,4-Benzenetricarboxylic acid, decyl octyl ester**	 R = linear or branched decyl (40%) or octyl (60%) $C_{35}H58O_6$
SUPPORTING CHEMICAL		
68130-50-7	**1,2,4-Benzenetricarboxylic acid, mixed decyl, hexyl and octyl esters**	 R = decyl, hexyl, or octyl $C_{33}H_{54}O_6$