

SCREENING-LEVEL HAZARD CHARACTERIZATION

4,5,6,7-Tetrachloro-1,3-isobenzofurandione (CASRN 117-08-8)

The High Production Volume (HPV) Challenge Program¹ was conceived as 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 sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did 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 by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, 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 one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

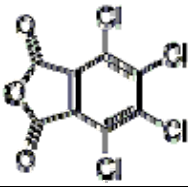
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

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. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

These hazard characterizations are technical documents intended to inform 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.

Chemical Abstract Service Registry Number (CASRN)	117-08-8
Chemical Abstract Index Name	1,3-Isobenzofurandione, 4,5,6,7-tetrachloro-
Structural Formula	
<p style="text-align: center;">Summary</p> <p>CASRN 117-08-8 is a flaked solid with low water solubility and low vapor pressure. It is expected to possess high mobility in soil. Volatilization is considered moderate based on the Henry's Law constant of this compound. The rate of hydrolysis is expected to be rapid; however, this rate appears to be attenuated by the low water solubility of this compound. The rate of atmospheric photooxidation is considered negligible. CASRN 117-08-8 is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute toxicity of CASRN 117-08-8 is low for the oral and dermal routes and moderate for the inhalation route. In an oral repeated-dose toxicity study, rats administered CASRN 117-08-8 for 13-weeks showed kidney lesions at 94 mg/kg-bw/day; the NOAEL for systemic toxicity was not established. In an oral repeated-dose toxicity study, mice administered CASRN 117-08-8 for 13 weeks showed a decrease in hemoglobin concentration observed in males at 375 mg/kg-bw/day and above; the NOAEL for systemic toxicity is 187 mg/kg-bw/day. In a repeated-dose toxicity study in rats via dust inhalation, administration of CASRN 117-08-8 showed histopathological changes of the lungs at 0.00073 mg/L/day; the NOAEC for systemic toxicity was not established. In a repeated-dose toxicity study in rats via fume inhalation, administration of CASRN 117-08-8 showed histopathological changes of the lungs at 0.0005 mg/L/day; the NOAEC for systemic toxicity was not established. No specific reproductive toxicity studies are available; however, in the 13-week repeated-dose toxicity studies in rats and mice, no effects on evaluated reproductive parameters were observed. An oral prenatal developmental toxicity study in rats showed lethargy in dams and skeletal malformations and reduced fetal weights at 2000 mg/kg-bw/day; the NOAEL for maternal toxicity is 2000 mg/kg-bw/day (highest dose tested) and for developmental toxicity is 1000 mg/kg-bw/day. CASRN 117-08-8 was negative for gene mutations in bacteria and chromosomal aberrations in mammalian cells <i>in vitro</i>. CASRN 117-08-8 was negative in a mouse micronucleus assay <i>in vivo</i> and was negative for sister chromatid exchange <i>in vitro</i> but positive <i>in vivo</i>. CASRN 117-08-8 is a respiratory sensitizer.</p> <p>The potential hazard of CASRN 117-08-8 to aquatic organisms cannot be evaluated because no adequate data were available on the aquatic toxicity of this chemical.</p> <p>The acute toxicity to fish and aquatic invertebrates, toxicity to aquatic plants and chronic toxicity to aquatic invertebrates for CASRN 117-08-8 were identified as data gaps under the HPV Challenge Program.</p>	

The sponsor, Solutia, Inc., submitted a Test Plan and Robust Summaries to EPA for 4,5,6,7-tetrachloro-1,3-isobenzofurandione (tetrachlorophthalic anhydride or TCPA, CASRN 117-08-8; CA Index name: 1,3-isobenzofurandione, 4,5,6,7-tetrachloro-) on November 8, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on November 20, 2002 (<http://www.epa.gov/hpv/pubs/summaries/tetrachlo/c14062tc.htm>). EPA comments on the original submission were posted to the website on March 25, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on May 22, 2003, which were posted to the ChemRTK website on June 19, 2003.

1. Chemical Identity

1.1 Identification and Purity

The following description is taken from the 2003 Test Plan and Robust Summary. CASRN 117-08-8 is described as a solid at room temperature. Test substance purity, when noted in the Robust Summaries, was given as 99%.

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 117-08-8 are summarized in Table 1. 1,3-Isobenzofurandione, 4,5,6,7-tetrachloro- is a flaked solid with low water solubility and low vapor pressure.

Property	Value
CASRN	117-08-8
Molecular Weight	285.9
Physical State	Flaked solid
Melting Point	254.5°C (measured)
Boiling Point	371°C (measured)
Vapor Pressure	0.16 mm Hg at 145°C (measured) 2.6×10 ⁻⁵ mm Hg at 25°C (extrapolated) ²
Water Solubility	<1 mg/L at 21°C (measured) ^{1,3} 0.05 mg/L (estimated) ⁴
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	1.9×10 ⁻⁶ atm-m ³ /mole (estimated) ⁴
Log K _{ow}	3.57 (measured) ^{3,5}

¹ Solutia, Inc. 2003. Revised Test Plan and Robust Summary for 4,5,6,7-Tetrachloro-1,3-isobenzofurandione. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/tetrachlo/c14062tc.htm> as of June 28, 2010.

² NOM05. 1987. PC-Nomograph- Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Chemicals. Version 2.0.

³ 1,3-Isobenzofurandione, 4,5,6,7-tetrachloro- hydrolyzes in water, and it is not clear which form of the substance (parent compound or hydrolysis product) the water solubility and log K_{ow} value has been reported for. However, it is anticipated that the water solubility of the corresponding diacid would be much greater than the reported value.

⁴ U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of June 28, 2010.

⁵ ECB Summary Fact Sheet. PBT Working Group PBT List 90 Tetrachlorophthalic Anhydride. Available online at http://ecb.jrc.ec.europa.eu/documents/PBT_EVALUATION/PBT_sum090_CAS_117-08-8.pdf as of June 28, 2010.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

CASRN 117-08-8 had an aggregated production and/or import volume in the United States between 1 and 10 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as flame retardants. Non-confidential commercial and consumer uses of this chemical include rubber and plastic products.

2.2 Environmental Exposure and Fate

Table 2 lists the environmental fate properties of CASRN 117-08-8.

1,3-Isobenzofurandione, 4,5,6,7-tetrachloro- is expected to possess high mobility in soil. 1,3-Isobenzofurandione, 4,5,6,7-tetrachloro- was found not readily biodegradable (0% degradation in 4 weeks) using a modified MITI test (OECD 301C). However, loss by HPLC (i.e. parent compound identity) was 100% in the same study, consistent with hydrolysis to yield more water soluble product(s). The rate of volatilization is considered low-to-moderate based on the Henry's Law constant of this compound. Conflicting data are reported for the rate of hydrolysis of this compound. The sponsor assumed that since phthalic anhydride possesses a hydrolysis half-life of about 90 seconds, 1,3-isobenzofurandione, 4,5,6,7-tetrachloro- will hydrolyze even more rapidly due to the presence of the electron-withdrawing chlorines that increase the susceptibility to base-catalyzed hydrolysis by reducing electron density at the carbonyl carbon and making the meta carboxyl group a better leaving group. However, no experimental data was presented, and the presence of the chlorines decreases the solubility of this substance. A study regarding the physical properties of 1,3-isobenzofurandione, 4,5,6,7-tetrachloro- and its corresponding acid salts indicated that hydrolysis occurred slowly at room temperature (24°C) due to the low water solubility of this substance. At elevated temperature (100°C), the solubility was higher, and complete hydrolysis occurred within a few hours. At 24°C, only about 10% hydrolysis occurred after 40 hours; however this rate is sufficient to account for complete loss by HPLC in the ready biodegradation test, since that test runs for 28 days (672 hr). Therefore, 1,3-Isobenzofurandione, 4,5,6,7-tetrachloro- is expected to have low persistence (P1). Bioaccumulation potential is also expected to be low (B1), based on the apparent hydrolysis rate ex-vivo and the statement in the National Institute of Technology and Evaluation database (see footnote 4, Table 2) that the substance is not highly bioaccumulative.

Table 2 Environmental Fate Characteristics of 1,3-Isobenzofurandione, 4,5,6,7-tetrachloro-¹	
Property	Value
Photodegradation Half-life	338.4 days (estimated) ²
Hydrolysis Half-life	Hydrolyzes slowly at room temperature and rapidly at 100°C ³
Biodegradation	0% after 4 weeks (not readily biodegradable) ⁴
Bioaccumulation Factor	BAF = 1,570 (estimated) ²
Log K _{oc}	1.4 (estimated) ²
Fugacity (Level III Model) ²	
Air (%)	2.1
Water (%)	36.0
Soil (%)	61.8
Sediment (%)	0.1
Persistence ⁵	P1 (low)
Bioaccumulation ⁵	B1 (low)

¹ Solutia, Inc. 2003. Revised Test Plan and Robust Summary for 4,5,6,7-Tetrachloro-1,3-isobenzofurandione. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/tetrachlo/c14062tc.htm> as of June 28, 2010.

² U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of June 28, 2010.

³ Lawlor FE. 1947. Tetrachlorophthalic anhydride and its salts. *Ind Eng Chem* 39(11):1242–1246.

⁴ National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online at http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of July 26, 2010.

⁵ Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: 1,3-Isobenzofurandione, 4,5,6,7-tetrachloro- is a flaked solid with low water solubility and low vapor pressure. It is expected to possess high mobility in soil. Volatilization is considered moderate based on the Henry’s Law constant of this compound. The rate of hydrolysis is expected to be rapid; however, this rate appears to be attenuated by the low water solubility of this compound. The rate of atmospheric photooxidation is considered negligible. 1,3-Isobenzofurandione, 4,5,6,7-tetrachloro- is expected to have low persistence (P1) and low bioaccumulation potential (B1).

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints are provided in Table 3.

Acute Oral Toxicity

Sprague-Dawley rats were administered CASRN 117-08-8 as a 33% corn oil suspension via single dose gavage to groups of fasted rats at dosages of 500 (1 F), 1000 (1 M), 1580 (1F), 2510 (1M), 3980 (1F), 5010 (1M, 1F), 10000 (1M:1F) and 15800 (2M:1F) to define a Minimum Lethal Dose. Animals were observed daily and weighed on day 0 and day 5. No deaths were observed.

LD₅₀ > 15,800 mg/kg bw

Acute Inhalation Toxicity

Sprague-Dawley rats (5/sex/dose) were exposed whole-body to CASRN 117-08-8 as dust at 3.16 or 3.60 mg/L for 4 hours and observed for 14 days following dosing. No mortalities were observed.

LC₅₀ > 3.60 mg/L

Acute Dermal Toxicity

Groups of single New Zealand white rabbits were treated dermally with either 501 (1F), 794 (1M), 1260 (1F), 2000 (1M), 3160 (1F) or 5010 (1M) mg/kg test article (ground powder in a 10% corn oil suspension) to define a Minimum Lethal Dose. All animals had their dorsal region closely shaved and test material applied to intact skin under an occlusive patch and held in place for 24 hours. Thereafter, the test article was wiped off. All animals were observed daily for signs of toxicity and weighed prior to and at study term (5 days). No deaths occurred in the study at any dose level.

LD₅₀ > 5010 mg/kg bw

Repeated-Dose Toxicity

(1) In a repeated-dose toxicity study conducted by the National Toxicology Program (NTP), Fischer 344 rats (10/sex/dose) were administered CASRN 117-08-8 in corn oil via gavage at 0, 94, 187, 375, 750 or 1500 mg/kg-bw/day for 5 days/week for 13 weeks. Animals were observed twice daily for morbidity and mortality. Clinical observations, food consumption and body weight were recorded weekly. Clinical chemistries were analyzed on days 6 and 20 and at study completion. At the end of the study, a hematology evaluation and complete necropsy were conducted. Other observations included organ weights, organ/tissue lesions and histopathology. Mortality occurred at 750 and 1500 mg/kg-bw/day. Mean final body weights and weight gains were statistically significantly reduced in males exposed to ≥ 375 mg/kg-bw/day and in females exposed to ≥ 94 mg/kg-bw/day. Decreased food consumption was seen in both males and females at ≥ 94 mg/kg-bw/day. Absolute and relative kidney weights increased in a dose-dependent manner in females. Relative kidney weight was increased in males exposed to ≥ 187 mg/kg-bw/day. Both males and females exhibited microscopic kidney lesions at ≥ 94 mg/kg-bw/day, consisting of renal tubular degenerative changes.

LOAEL = 94 mg/kg-bw/day (based on microscopic kidney lesions in males and females)

NOAEL = Not established

(2) In a repeated-dose toxicity study conducted by the NTP, B6C3F1 mice (10/sex/dose) were administered CASRN 117-08-8 in corn oil via gavage at 0, 94, 187, 375, 750 or 1500 mg/kg-bw/day for 5 days/week for 13 weeks. Animals were observed twice daily for morbidity and mortality. Clinical observations, food consumption and body weight were recorded weekly. At the end of the study, a hematology evaluation and complete necropsy were conducted. Other observations included organ weights, organ/tissue lesions and histopathology. A decrease in hemoglobin concentration was observed in males exposed to ≥ 375 mg/kg-bw/day and in females exposed to ≥ 750 mg/kg-bw/day. Decreases in hematocrit and red blood cell concentration were observed in males receiving 1500 mg/kg-bw/day.

LOAEL = 375 mg/kg-bw/day (based on reduced hemoglobin concentration in males)

NOAEL = 187 mg/kg-bw/day

(3) Sprague-Dawley rats (15/sex/concentration) were exposed whole-body to CASRN 117-08-8 as dust at nominal concentrations of 0, 0.0005, 0.005 or 0.05 mg/L for 6 hours/day for 5 days/week for 13 weeks. Mean measured concentrations were 0, 0.00073, 0.00415 and 0.0363 mg/L, although extreme variations in chamber concentrations were observed from day to day, as well as during any given day. Animals were observed twice daily for morbidity and mortality. Clinical observations and body weight were recorded weekly. Hematology, blood chemistry and urinalysis parameters were measured at 7 and 13 weeks. At 13 weeks, complete necropsies were conducted. Other observations included organ weights and weight ratios, lung examination and microscopic tissue examination. Increased red nasal discharge, dry and moist rales, ano-genital staining and excessive lacrimation were observed at 0.0363 mg/L. Absolute and relative lung weights increased at ≥ 0.00415 mg/L in males and at 0.0363 mg/L in females. Petechial hemorrhages were observed in the lungs at 0.0363 mg/L. Histopathological changes in the lungs were observed at ≥ 0.00073 mg/L and included irregular thickening of the alveolar septa, scattered pigmented macrophages and multinucleate giant cells, multifocal accumulation of alveolar macrophages and multifocal alveolar hemorrhages. Mild centrilobular hepatocellular hypertrophy was observed at 0.0363 mg/L.

LOAEC = 0.00073 mg/L/day (based on histopathological changes in the lungs)

NOAEC = Not established

(4) Sprague-Dawley rats (15/sex/dose) were exposed whole-body to CASRN 117-08-8 as fumes at nominal concentrations of 0, 0.0005, 0.005 or 0.05 mg/L for 6 hours/day, 5 days/week for 13 weeks. Mean measured concentrations were 0, 0.0005, 0.0056 and 0.0266 mg/L, although extreme variations in chamber concentrations were observed from day to day, as well as during any given day. Animals were observed twice daily for morbidity and mortality. Clinical observations and body weight were recorded weekly. Hematology, blood chemistry and urinalysis parameters were measured at 7 and 13 weeks. At 13 weeks, complete necropsies were conducted. Other observations included organ weights and weight ratios, lung examination and microscopic tissue examination. At all concentrations, increased red nasal discharge was observed. Effects seen at 0.0266 mg/L included dry rales, increased blood glucose levels, increased absolute and relative lung weight and mild centrilobular hepatocellular hypertrophy. Petechial hemorrhages were observed in the lungs of several treated rats at 0.0266 mg/L. Histopathological changes in the lungs were observed at ≥ 0.0005 mg/L and included irregular thickening of the alveolar septa, scattered pigmented macrophages and multinucleate giant cells, multifocal accumulation of alveolar macrophages and focal to multifocal alveolar hemorrhages.

LOAEC = 0.0005 mg/L/day (based on histopathological changes in the lungs and red nasal discharge)

NOAEC = Not established

Reproductive Toxicity

No data were submitted to address the reproductive toxicity endpoint for CASRN 117-08-8. Evaluations of reproductive parameters reported in the repeated-dose toxicity studies for 13

weeks and an available developmental toxicity study were used to address the reproductive toxicity endpoint for the purposes of the HPV Challenge Program.

(1) In the repeated-dose toxicity study described previously, male Fischer 344 rats were administered CASRN 117-08-8 at 0, 94, 375 or 750 mg/kg-bw/day and female Fischer 344 rats were administered 0, 94, 375 or 1500 mg/kg-bw/day. No effects on the reproductive parameters evaluated (sperm morphology, sperm density, proportion of motile sperm and vaginal cytology) were observed.

(2) In the repeated-dose toxicity study described previously, B6C3F1 mice were administered CASRN 117-08-8 at 0, 94, 375 or 1500 mg/kg-bw/day. No effects on the reproductive parameters evaluated (sperm morphology, sperm density, proportion of motile sperm and vaginal cytology) were observed.

Developmental Toxicity

Pregnant Sprague-Dawley rats (24 mated females/dose) were administered CASRN 117-08-8 in corn oil via gavage at 0, 250, 1000 or 2000 mg/kg-bw/day during gestation days 6 – 19. Animals were observed twice daily for mortality and abnormal behavior. Clinical observations and body weight were recorded at several intervals throughout the study. On gestation day 20, animals were sacrificed and uterine horns were examined for implantation sites, resorptions and the number of viable or non-viable fetuses. The number of corpora lutea was also recorded. The sex and weights of all live fetuses were recorded and all fetuses were examined for external abnormalities. One half of the fetuses were examined for skeletal malformations and the other half were examined for internal anomalies. No treatment-related parental mortality was observed. Lethargy was observed in several adult females soon after dosing at 2000 mg/kg-bw/day, as early as gestation day 6. Pale eye color was observed in four adults at 2000 mg/kg-bw/day on gestation day 20. Developmental effects were observed at 2000 mg/kg-bw/day and included reduced fetal body weight, a slight increase in the incidence of asymmetric/unossified sternebra and incompletely ossified thoracic vertebral centra and an increase in the incidence of rib and vertebral malformations.

NOAEL (maternal toxicity) = 2000 mg/kg-bw/day (highest dose tested)

LOAEL (developmental toxicity) = 2000 mg/kg-bw/day (based on skeletal malformations and reduced fetal weight)

NOAEL (developmental toxicity) = 1000 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro

In two studies conducted by the NTP, *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 were exposed to CASRN 117-08-8 in either water at concentrations ≤ 6666.7 $\mu\text{g}/\text{plate}$ or in dimethylsulfoxide (DMSO) at concentrations ≤ 1000 $\mu\text{g}/\text{plate}$ with and without metabolic activation. Positive and negative controls were used and yielded the expected results. No mutagenicity was observed with or without activation, regardless of solvent used.

Cytotoxicity was observed at 3333.3 µg/plate (in water) and > 1000 µg/plate (in DMSO).
CASRN 117-08-8 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

In a NTP chromosomal aberration assay, Chinese Hamster Ovary (CHO) cells were exposed to CASRN 117-08-8 at concentrations ≤ 750 µg/mL without metabolic activation and ≤ 250 µg/mL with metabolic activation. Positive and negative controls were used and yielded the expected results. No cytotoxicity was observed. No treatment-related increase in chromosomal aberrations was observed with or without activation. Additional details are from NTP study 996344.

CASRN 117-08-8 did not induce chromosomal aberrations in this assay.

In vivo

In a NTP chromosomal aberrations study, B6C3F1 mice (8 males/dose) were administered CASRN 117-08-8 in DMSO by intraperitoneal injection at 100, 200 or 400 mg/kg-bw and sacrificed after 17 hours. Positive and negative controls were used and yielded the expected results. CASRN 117-08-8 did not induce chromosomal aberrations in mouse bone marrow. Additional details are from NTP study 927311, which was not included in the robust summaries submitted by the sponsor.

CASRN 117-08-8 did not induce chromosomal aberrations in this assay.

Genetic Toxicity – Other

(1) In a sister chromatid exchange (SCE) study conducted by the NTP, B6C3F1 mice (4 males/dose) were administered CASRN 117-08-8 in DMSO by intraperitoneal injection at 100, 200 or 400 mg/kg-bw and sacrificed after 23 hours. Positive and negative controls were used and yielded the expected results. An increase in SCE was observed in bone marrow at ≥ 200 mg/kg-bw. Additional details are from NTP study 927311, which was not included in the robust summaries submitted by the sponsor.

CASRN 117-08-8 induced SCE in this assay.

(2) In a SCE assay conducted by the NTP, CHO cells were exposed to CASRN 117-08-8 at concentrations ≤ 750 µg/mL with or without metabolic activation. Positive and negative controls were used and yielded the expected results. The overall conclusion from the study was that CASRN 117-08-8 did not cause SCE, although one trial yielded a weak positive result in the presence of activation. The weak positive result was not confirmed in a subsequent trial. Additional details are from NTP study 996344.

CASRN 117-08-8 did not induce SCE in this assay.

Additional Information

Respiratory Sensitization

Five workers in the production of epoxy resins developed recurrent respiratory symptoms and physiological abnormalities following exposure to CASRN 117-08-8. Inhalation challenge with CASRN 117-08-8 reproduced their symptoms and demonstrated both an immediate and late (4-6 hours) physiological response. [Schlueter, D. P. et al. Occupational Asthma to Tetrachlorophthalic Anhydride: JOM 20 (3) 183 (1978)]

CASRN 117-08-8 is a respiratory sensitizer.

Conclusion: The acute toxicity of CASRN 117-08-8 is low for the oral and dermal routes and moderate for the inhalation route. In an oral repeated-dose toxicity study, rats administered CASRN 117-08-8 for 13-weeks showed kidney lesions at 94 mg/kg-bw/day; the NOAEL for systemic toxicity was not established. In an oral repeated-dose toxicity study, mice administered CASRN 117-08-8 for 13 weeks showed a decrease in hemoglobin concentration observed in males at 375 mg/kg-bw/day and above; the NOAEL for systemic toxicity is 187 mg/kg-bw/day. In a repeated-dose toxicity study in rats via dust inhalation, administration of CASRN 117-08-8 showed histopathological changes of the lungs at 0.00073 mg/L/day; the NOAEC for systemic toxicity was not established. In a repeated-dose toxicity study in rats via fume inhalation, administration of CASRN 117-08-8 showed histopathological changes of the lungs at 0.0005 mg/L/day; the NOAEC for systemic toxicity was not established. No specific reproductive toxicity studies are available; however, in the 13-week repeated-dose toxicity studies in rats and mice, no effects on evaluated reproductive parameters were observed. An oral prenatal developmental toxicity study in rats showed lethargy in dams and skeletal malformations and reduced fetal weights at 2000 mg/kg-bw/day; the NOAEL for maternal toxicity is 2000 mg/kg-bw/day (highest dose tested) and for developmental toxicity is 1000 mg/kg-bw/day. CASRN 117-08-8 was negative for gene mutations in bacteria and chromosomal aberrations in mammalian cells *in vitro*. CASRN 117-08-8 was negative in a mouse micronucleus assay *in vivo* and was negative for sister chromatid exchange *in vitro* but positive *in vivo*. CASRN 117-08-8 is a respiratory sensitizer.

Table 3. Summary of the Screening Information Data Set under the U.S. HPV Challenge Program – Human Health Data	
Endpoints	SPONSORED CHEMICAL 4,5,6,7-Tetrachloro-1,3-isobenzofurandione (117-08-8)
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	> 15,800
Acute Inhalation Toxicity LC₅₀ (mg/L)	> 3.6
Acute Dermal Toxicity LD₅₀ (mg/kg bw)	> 5010
Repeated-Dose Toxicity (rats) (NOAEL/LOAEL) Oral (mg/kg-bw/day)	NOAEL=Not established LOAEL = 94

Table 3. Summary of the Screening Information Data Set under the U.S. HPV Challenge Program – Human Health Data	
Endpoints	SPONSORED CHEMICAL 4,5,6,7-Tetrachloro-1,3-isobenzofurandione (117-08-8)
Repeated-Dose Toxicity (mice) (NOAEL/LOAEL) Oral (mg/kg-bw/day)	NOAEL = 187 LOAEL = 375
Repeated-Dose Toxicity (rats) (NOAEC/LOAEC) Inhalation (mg/L/day)	NOAEC=Not established LOAEC = 0.00073
Repeated-Dose Toxicity(rats) (NOAEC/LOAEC) Inhalation (mg/L/day)	NOAEC=Not established LOAEC = 0.0005
Reproductive Toxicity (NOAEL/LOAEL) Oral (mg/kg-bw/day)	There were no treatment-related changes in sperm morphology or vaginal cytology in either a rat or mouse 90 day oral repeated-dose study.
Developmental Toxicity (NOAEL/LOAEL) Oral (mg/kg-bw/day) Maternal toxicity Developmental toxicity	NOAEL = 2000 (highest dose tested) NOAEL = 1000 LOAEL =2000
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Negative
Genetic Toxicity – Other Sister Chromatid Exchange <i>In vitro</i> <i>In vivo</i>	Negative Positive
Additional Information Respiratory Sensitization	Positive

Measured data in bold text

4. Hazard to the Environment

The environmental hazard data are summarized in Table 4. No adequate data were available. Existing data for CASRN 117-08-8 for all aquatic species for SIDS endpoints were tested above the water solubility limit of ~ 1.0 mg/L.

Acute Toxicity to Fish

No adequate data

Acute Toxicity to Aquatic Invertebrates

No adequate data

Toxicity to Aquatic Plants

No adequate data

Conclusion: The potential hazard of CASRN 117-08-8 to aquatic organisms cannot be evaluated because no adequate data were available on the aquatic toxicity of this chemical.

Table 4. Summary of the Screening Information Data Set under the U.S. HPV Challenge Program – Aquatic Toxicity Data	
Endpoints	SPONSORED CHEMICAL 4,5,6,7-Tetrachloro-1,3-isobenzofurandione (117-08-8)
Fish 96-h LC₅₀ (mg/L)	No adequate data
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	No adequate data
Aquatic Plants 72-h EC₅₀ (mg/L)	No adequate data
Chronic Toxicity to Invertebrates 21-day EC₅₀ (mg/L)	No data