SCREENING-LEVEL HAZARD CHAR ACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

"Weston 618"
O,O'-dioctadecylpentaerythritol bis(phosphite) (CAS No. 3806-34-6)
[9th CI Name: [2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5,5]undecane, 3,9-bis(octadecyloxy)-]

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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.

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[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
2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5,5]undecane, 3,9-bis(octadecyloxy)-
(CAS No. 3806-34-6)

Introduction

The sponsor, Chemtura (formerly, Crompton Corporation), submitted a Test Plan and Robust Summaries to EPA for O,O'-dioctadecylpentaerythritol bis(phosphite) (Weston 618, CAS No. 3806-34-6; 9th CI name 2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5,5]undecane 3,9-bis(octadecyloxy)-) on December 22, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 17, 2004 (http://www.epa.gov/chemrtk/pubs/summaries/24810tet/c14967tc.htm). EPA comments on the original submission were posted on to the website on July 15, 2004. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on October 21, 2004, which were posted to the ChemRTK website on November 17, 2004.

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. 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.

Summary-Conclusion

The estimated log K_{ow} of Weston 618 is high. However, based on its estimated low value for water solubility (2.95×10^{-12} mg/L) and log BCF (3.2), the potential of this chemical to bioaccumulate is expected to be low. Weston 618 not readily biodegradable (estimated), indicating it has the potential to persist in the environment.

Due to the high log K_{ow} and very low water solubility, aquatic toxicity testing was not performed with Weston 618. The estimated aquatic toxicity to fish, aquatic invertebrates and aquatic plants all exceeded the expected water solubility of Weston 618. The acute hazard of Weston 618 to aquatic organisms is low.

Acute oral and dermal toxicity of Weston 618 in rats and rabbits, respectively, is low. Weston 618 was slightly irritating to eyes. Following repeated oral exposures of rats for approximately 46-54 days in a combined reproductive/developmental toxicity screening test, there were no effects on body weight, clinical signs, individual organ weights or histopathology observed. In a combined reproductive/developmental toxicity screening study in rats, there were no effects on parents, reproductive outcome or pups born at the limit dose. Weston 618 did not show a potential to induce gene mutation in bacteria and did not induce chromosomal aberrations in mice in an *in vivo* test.

The potential health hazard of Weston 618 is low.

No data gaps were 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 the Appendix. 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

Log K_{ow}: 15 (estimated)

The model used to estimate the K_{ow} submitted (KOWWIN v.1.66) has been demonstrated to be accurate in predicting log K_{ow} between -4 and 10. Given the estimate for Weston 618 is outside this range indicates the absolute value may not be accurate. It is reasonable to conclude that this prediction is indicative that the log K_{ow} for this chemical is high (> 4).

Biodegradation

Measured biodegradation data were not provided. Ready biodegradability for Westin 618, estimated using BIOWIN 4.0, indicates Weston 618 is not readily biodegradable.
Weston 618 is not readily biodegradable.

Conclusion: The estimated log K_{ow} of Weston 618 is high. However, based on its estimated low value for water solubility (2.95×10^{-12} mg/L) and log BCF (3.2), the potential of this chemical to bioaccumulate is expected to be low. Weston 618 not readily biodegradable (estimated), indicating it has the potential to persist in the environment.

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

Due to the high log K_{ow} and very low water solubility, aquatic toxicity testing was not performed. An estimated fish 96-hour LC_{50} of 2.94×10^{-10} mg/L was calculated using ECOSAR (version 0.99g). This value exceeds the estimated water solubility (2.95×10^{-12} mg/L) for Weston 618.
96-h LC_{50} = 2.94×10^{-10} mg/L (estimated)

Acute Toxicity to Aquatic Invertebrates

Due to the high log K_{ow} and very low water solubility, aquatic toxicity testing was not performed. An estimated invertebrate 48-hour LC_{50} value of 7.76×10^{-10} mg/L was calculated using ECOSAR (version 0.99g). This value exceeds the estimated water solubility (2.95×10^{-12} mg/L) for Weston 618.
48-h EC_{50} = 7.76×10^{-10} mg/L (estimated)

Toxicity to Aquatic Plants

Due to the high log K_{ow} and very low water solubility, aquatic toxicity testing was not performed. An estimated aquatic plant 96-hour LC_{50} value of 1.03×10^{-9} mg/L was calculated using ECOSAR (version 0.99g). This value exceeds the estimated water solubility (2.95×10^{-12} mg/L) of Weston 618.
96-h EC_{50} (growth) = 1.03×10^{-9} mg/L (estimated)

Conclusion: Due to the high log K_{ow} and very low water solubility, aquatic toxicity testing was not performed with Weston 618. The estimated aquatic toxicity to fish, aquatic invertebrates and aquatic plants all exceeded the expected water solubility of Weston 618. The acute hazard of Weston 618 to aquatic organisms is low.

3. Human Health Effects

Acute Oral Toxicity

Sherman rats (5/sex/dose) were administered Weston 618 via oral gavage at a single dose of 10,000 mg/kg-bw. No deaths were observed over the 14-day observation period. No clinical signs of toxicity were observed.
LD_{50} > 10,000 mg/kg-bw

Acute Dermal Toxicity

New Zealand White rabbits (5/sex/dose) were administered Weston 618, neat, to the skin at a dose of 2000 mg/kg-bw and were observed for 14 days. No deaths were observed. All animals exhibited very slight to moderate erythema and 8 rabbits exhibited very slight edema. Desquamation was present in eight animals by day 7 and in one animal by day 14; desquamation and/or very slight edema was present in three animals at study termination. There were no changes in body weights and minimal clinical signs (soft stools in two females on day 1).
LD_{50} > 2000 mg/kg-bw

Repeated-Dose Toxicity

(1) Assessment of the repeated-dose toxicity was taken from the combined reproductive/developmental toxicity screening study in which male rats (10/dose) were administered Weston 618 via gavage at doses of 0, 100, 400, and 1000 mg/kg-bw/day (in 0.5% aqueous carboxymethyl cellulose suspensions) for two weeks prior to mating, during mating, and two weeks post-mating and female rats (10/dose) were given the same doses for two weeks prior to mating, during gestation, and up to postnatal day 4. There were no treatment-related effects in the parental males or females on body weights, clinical signs, organ weight changes and histopathology.
NOAEL = 1000 mg/kg-bw/day (based on no effects at the highest dose tested)

(2) The sponsor submitted a repeated-dose toxicity study in which Charles River albino rats (15/sex/dose) were fed diets containing 0, 300, 1,000, or 3,000 ppm (approximately 15, 50 or 150 mg/kg-bw/day) of Weston 618 daily for 90 days. No significant differences were noted between treated and control rats with respect to body weight, food and water consumption, clinical signs, ophthalmologic findings, hematologic and blood chemistry values, urinalysis, mortality, gross pathology, individual organ weight changes or histology. Changes in liver/body weight ratios seen in males only at the highest dose tested were not considered treatment related. The study was conducted at the Industrial Bio-Test Laboratories (IBT) in 1972. The U.S. EPA did not consider this study as the primary study for addressing the repeated-dose toxicity endpoint in the HPV Challenge Program. However, the study is considered supporting evidence for the recently completed (2006) combined reproductive/developmental toxicity screening study, described above.

Reproductive Toxicity

In a combined reproductive/developmental toxicity screening study, male rats (10/dose) were administered Weston 618 via gavage at doses of 0, 100, 400, and 1000 mg/kg-bw/day (in 0.5% aqueous carboxymethyl cellulose suspensions) for two weeks prior to mating, during mating, and two weeks post-mating. Female rats (10/dose) were given the same doses for two weeks prior to mating, during gestation, and up to postnatal day 4. There were no treatment-related effects in the parental males or females (body weights, clinical signs, organ weight changes/histopathology) and Weston 618 did not affect mating and fertility, or alter sperm motility or morphology.
NOAEL (systemic toxicity) = 1000 mg/kg-bw/day (based on no effects at highest dose tested)
NOAEL (reproductive toxicity) = 1000 mg/kg-bw/day (based on no effects at highest dose tested)

Developmental Toxicity

In the combined reproductive/developmental toxicity screening study described previously, there was no effect of Weston 618 on the mean number or weight of male/female pups born. In addition, there were no treatment-related effects on live litters, sex ratio at birth, number of pups born dead, or the number of pups alive on days 0, 1, and 4.
NOAEL (maternal toxicity) = 1000 mg/kg-bw/day (based on no effects at highest dose tested)
NOAEL (developmental toxicity) = 1000 mg/kg-bw/day (based on no effects at highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro
Salmonella strains TA97, TA98, TA100, TA102 and Escherichia *coli* strain WP2/pKM101 were exposed to Weston 618 at concentrations of 0, 0.05, 0.1, 0.2 and 9.5 mg/plate with and without metabolic activation. The use of

positive and/or negative controls was not mentioned in the robust summary. Results indicated no cytotoxicity and no increase in the number of revertant cells.
Weston 618 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo
In a micronucleus assay, ICR mice (5/sex/dose) were administered single doses of Weston 618 via intraperitoneal injection at 0, 500, 1000 or 2000 mg/kg-bw and were euthanized 24 hours later. Another group of mice (5/sex/dose) were administered the test substance (also via intraperitoneal injection) at doses of 0 or 2000 mg/kg-bw and euthanized 48 hours later. Cyclophosphamide (50 mg/kg-bw) was used as a positive control. The number of micronuclei/1000 polychromatic erythrocytes was counted (2000 cells counted). The positive control produced a statistically significant increase in micronuclei, but there was no significant increase in micronuclei in either of the 2 Weston 618 treated groups.
Weston 618 did not induce micronuclei in the assay.

Additional Information

Eye Irritation

Six rabbits were administered a solution of 10% Weston 618 in cottonseed oil. Two out of 6 animals experienced a mild conjunctival effect that cleared up by the second day.
Weston 618 was slightly irritating to rabbit eyes.

Conclusion: Acute oral and dermal toxicity of Weston 618 in rats and rabbits, respectively, is low. Weston 618 was slightly irritating to eyes. Following repeated oral exposures of rats for approximately 46-54 days in a combined reproductive/developmental toxicity screening test, there were no effects on body weight, clinical signs, individual organ weights or histopathology observed. In a combined reproductive/developmental toxicity screening study in rats, there were no effects on parents, reproductive outcome or pups born at the limit dose. Weston 618 did not show a potential to induce gene mutation in bacteria and did not induce chromosomal aberrations in mice in an *in vivo* test.

The potential health hazard of Weston 618 is low.

4. Hazard Characterization

The estimated log K_{ow} of Weston 618 is high. However, based on its estimated low value for water solubility (2.95×10^{-12} mg/L) and log BCF (3.2), the potential of this chemical to bioaccumulate is expected to be low. Weston 618 not readily biodegradable (estimated), indicating it has the potential to persist in the environment.

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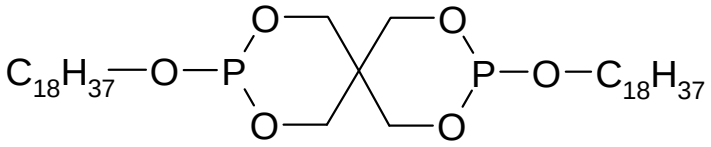
The potential health hazard of Weston 618 is low.

5. Data Gaps

No data gaps were identified under the HPV Challenge Program.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL** **2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5,5]undecane 3,9-bis(octadecyloxy)-** **(Weston 618)** **(3806-34-06)**
Structure	
Summary of Physical-Chemical Properties and Environmental Fate Data	
Melting Point (°C)	37-46
Boiling Point (°C)	705
Vapor Pressure (hPa at 25°C)	1.06×10^{-18}
Log K_{ow}	15
Water Solubility (mg/L at 25°C)	2.95×10^{-12} (estimated)
Direct Photodegradation	–
Indirect (OH^-)Photodegradation Half-Life ($t_{1/2}$)	0.689 h
Stability in Water (Hydrolysis) Half-Life ($t_{1/2}$)	Unable to perform test due to extremely low estimated water solubility.
Biodegradation	Not readily biodegradable (estimated)
Fugacity (Level III Model)	
Air (%)	0.02
Water (%)	2.4
Soil (%)	28.6
Sediment (%)	68.9
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-hr LC_{50} (mg/L)	2.94×10^{-10} (estimated value, greater than water solubility)
Aquatic Invertebrates 48-hr EC_{50} (mg/L)	7.76×10^{-10} (estimated value, greater than water solubility)
Aquatic Plants 96-hr EC_{50} (mg/L) (growth) (biomass)	1.03×10^{-9} (estimated value, greater than water solubility)

Summary Table of the Screening Information Data Set as submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL 2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5,5]undecane 3,9-bis(octadecyloxy)- (Weston 618) (3806-34-06)**
Summary of Human Health Data	
Acute Oral Toxicity LD_{50} (mg/kg-bw)	>10000
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	> 2000
Repeated-Dose Toxicity in Rats NOAEL/LOAEL (mg/kg-bw/day)	NOAEL = 1000
Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day) Systemic/Reproductive toxicity	NOAEL = 1000
Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) Maternal/Developmental toxicity	NOAEL = 1000
Genetic toxicity - Gene Mutations *In vitro*	Negative
Genetic Toxicity - Chromosomal Aberrations *In vivo*	Negative
Additional Information Eye irritation	Slightly irritating

– indicates endpoint was not addressed for this chemical.