SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

1,6-Hexamethylene bis (3,5-di-(*tert*)-butyl-4-hydroxyhydrocinnamate)
(IRGANOX 259; CAS No. 35074-77-2)
[9th CI Name: Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 1,6-hexanediyl ester]

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INTERIM

Prepared by

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SCREENING-LEVEL HAZARD CHARACTERIZATION
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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
IRGANOX 259
(1,6-Hexamethylene bis (3,5-di-(*tert*)-butyl-4-hydroxyhydrocinnamate))
(CAS No. 35074-77-2)

Introduction

The sponsor, Ciba Specialty Chemicals Corporation, submitted a Test Plan and Robust Summaries to EPA for 1,6-hexamethylene bis (3,5-di-(*tert*)-butyl-4-hydroxyhydrocinnamate) (IRGANOX 259; CAS No. 35074-77-2; 9th CI name: benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 1,6-hexanediyl ester) dated July 29, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on August 22, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/16hexhyd/c13896tc.htm). EPA comments on the original submission were posted to the website on December 20, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 26, 2003, which were posted to the ChemRTK website on October 23, 2003.

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 effects 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 Kow for IRGANOX 259 is high. However, the low water solubility (3.3×10^{-7} mg/L, estimated) and estimated BCF (3.2) suggest the potential for this chemical to bioaccumulate is low. IRGANOX 259 is not readily biodegradable, indicating that it has the potential to persist in the environment.

The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants and physical-chemical properties indicates the potential acute hazard of IRGANOX 259 to aquatic organisms is low. The aquatic toxicity data submitted were difficult to interpret because the concentration of chemical in the test water was not measured and effects concentrations reported were above the chemical's water solubility limit. The data were judged unreliable, but EPA could conclude qualitatively that there were no effects observed at saturation. In addition, the water solubility (3.3×10^{-7} mg/L, estimated) and log K_{ow} (> 8) of the chemical indicate it is unlikely that water column concentrations that would result in toxicity of moderate or high concern could be achieved.

Acute oral toxicity of IRGANOX 259 to mice is low and acute dermal toxicity to rabbits is low. Acute inhalation toxicity to rats appears to be low based on no deaths occurring when tested up to ~ 1.69 mg/L. Following repeated oral exposures of rats and mice for 90 days, target organs for toxicity included the liver and thyroid. In the 90-day repeated-dose toxicity tests, no macroscopic or microscopic effects on reproductive organs were observed at any dose. In a developmental toxicity study in rats, reduced fetal weights and increased number of incompletely ossified phalangeal nuclei were seen, but only at the high dose. In a 2-year chronic dietary toxicity study, IRGANOX 259 did not cause toxicity or pathological changes or tumors in rats.

The potential health hazard of IRGANOX 259 is moderate based on repeated-dose toxicity. IRGANOX 259 did not increase the incidence of tumors in a 2-year dietary toxicity study.

Gene mutation and chromosomal aberrations were identified as data gaps under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

A summary of physical-chemical 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 were limited to the octanol-water partition coefficient and biodegradation endpoints as indicators of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

Log K_{ow}: > 11.74 (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 IRGANOX 259 is outside this range, the absolute value may not be accurate. 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 IRGANOX 259 is outside this range, the absolute value may not be accurate. Nonetheless, it is reasonable to conclude that this prediction is indicative that the log K_{ow} for this chemical is high (> 4).

Ready Biodegradation

In a Modified Sturm test using fresh sewage sludge from the sewage treatment plant 1% of IRGANOX 259 had degraded after 28 days.
IRGANOX 259 is not readily biodegradable.

Conclusion: The estimated log Kow for IRGANOX 259 is high. However, the low water solubility (3.3×10^{-7} mg/L, estimated) and estimated BCF (3.2) suggest the potential for this chemical to bioaccumulate is low. IRGANOX 259 is not readily biodegradable, indicating that it has the potential to persist in the environment.

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

Zebrafish (*Brachydanio rerio*) were exposed to IRGANOX 259 at a nominal concentration of 100 mg/L under static conditions for 96 hours. There were no mortalities. The substance was tested above its water solubility limit. EPA considers the no effect concentration as the water solubility limit (saturation) which for IRGANOX 259 would be approximately 3.30×10^{-7} mg/L.
No effects at saturation

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to IRGANOX 259 at nominal concentrations of 0, 10, 18, 32, 58 or 100 mg/L under static conditions for 24 hours. There were no mortalities and no immobilization was seen at any concentration. The substance was tested above its water solubility limit. EPA considers the no effect concentration as the water solubility limit (saturation) which for IRGANOX 259 would be approximately 3.30×10^{-7} mg/L.
No effects at saturation

Toxicity to Aquatic Plants

Green algae (*Scenedesmus subspicatus*) were exposed to IRGANOX 259 at nominal concentrations of 0, 1.23, 3.7, 11, 33 or 100 mg/L under static conditions for 72 hours. Results of cell densities at each test concentration were not provided. Based on the limited information provided in the study summary, cell density appears to have been the only endpoint measured. The substance was tested above its water solubility limit. EPA considers the no effect concentration as the water solubility limit (saturation) which for IRGANOX 259 would be approximately 3.30×10^{-7} mg/L.
No effects at saturation

Conclusion: The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants and physical-chemical properties indicates the potential acute hazard of IRGANOX 259 to aquatic organisms is low. The aquatic toxicity data submitted were difficult to interpret because the concentration of chemical in the test water was not measured and effects concentrations reported were above the chemical's water solubility limit. The data were judged unreliable, but EPA could conclude qualitatively that there were no effects observed at saturation. In addition, the water solubility (3.3×10^{-7} mg/L, estimated) and log K_{ow} (> 8) of the chemical indicate it is unlikely that water column concentrations that would result in toxicity of moderate or high concern could be achieved.

3. Human Health Effects

Acute Oral Toxicity

Tif:MAG (SPF) mice (5/sex/dose) were administered IRGANOX 259 via gavage at 0, 4640, 6000 or 7750 mg/kg-bw and observed for 14 days. There were no mortalities. Clinical signs included sedation, dyspnea and ruffled fur (all treatment levels). There were no abnormalities at necropsy.
LD_{50} > 7750 mg/kg-bw

Acute Inhalation Toxicity

Nine female Tif:RAI rats were administered IRGANOX 259 via inhalation as a mist of 20% suspension in ethanol at 1688 mg/m^3 (approximately 1.69 mg/L) for 4 hours and observed for 14 days. There were no mortalities. Clinical signs included lateral position and apathy. There were no abnormalities at necropsy.
LC_{50} > 1.69 mg/L

Acute Dermal Toxicity

New Zealand White rabbits (4/sex/dose) were administered IRGANOX 259 via the dermal route at 0, 2500 or 10,000 mg/kg-bw in a 50% suspension (in NaCl solution) to intact and abraded skin under occluded conditions for 24 hours and were observed for 14 days. At the end of the observation period, rabbits were sacrificed and tissues were preserved and examined microscopically. Specific results were not reported.
LD_{50} > 10,000 mg/kg-bw

Repeated-Dose Toxicity

(1) Charles River rats (15/sex/dose) were administered IRGANOX 259 via the diet at 0, 1000, 3000 or 10,000 ppm (approximately 0, 50, 150 or 500 mg/kg-bw/day) for 13 weeks. There were no mortalities. Comprehensive sets of tissues and organs were examined microscopically. Hyperplasia and hypertrophy of the thyroid follicular epithelium were the only exposure-related lesions observed. Rats showed diffuse or focal hyperplasia and hypertrophy at all doses, with average severity scores higher at the high dose than at the low and middle dose. Incidences of rats with follicular epithelial hypertrophy or hyperplasia were 2/10, 7/12, 10/11 and 7/7 for males and 0/10, 8/13, 11/11 and 8/8 for females. Liver-to-body weight ratios, heart weights and heart-to-body weight ratios were increased in females at all doses.
LOAEL ~ 50 mg/kg-bw/day (based on increased heart weights and heart-to-body weight ratios, increased liver-to-body weight ratio and hyperplasia and hypertrophy of the thyroid follicular epithelium)
NOAEL = Not established

(2) Sprague-Dawley rats (sex and group size not specified) were administered IRGANOX 259 via the diet at 0, 2000, 10,000 or 30,000 ppm (approximately 0, 100, 500 or 1500 mg/kg-bw/day) for 13 weeks. Comprehensive sets of tissues and organs were examined microscopically. Hematologic, serum chemistry and urinalytic variables were also measured. There were no mortalities. Body weights and food consumption were decreased at the two highest doses. Histopathologic examination revealed hypertrophy of the thyroid and the liver in all treated groups. Rats in the high- and mid-dose groups showed moderate to marked hypertrophy of the follicular epithelium and the liver hypertrophy in the high-dose group was accompanied with fatty infiltration. In the low-dose group, the thyroid lesions were graded as mild and only a few livers showed mild hypertrophy.
LOAEL ~ 100 mg/kg-bw/day (based on liver and thyroid hypertrophy)
NOAEL = Not established

(3) SPF Wistar rats (10/sex/dose) were administered IRGANOX 259 via the diet at 0, 400, 2000, 10,000 or 30,000 ppm (approximately 0, 20, 100, 500 or 1500 mg/kg-bw/day) for 13 weeks. Comprehensive sets of tissues and organs were examined microscopically. Hematologic and urinalytic variables were affected by exposure. There were no mortalities. Increased liver weights were seen in high-dose males and increased thyroid weight was seen in animals at the two highest doses. Histological examination revealed epithelial hyperplasia of the thyroid at ≥ 2000 ppm. The robust summary provided no other details of the results.
LOAEL ~ 100 mg/kg-bw/day (based on increased liver and thyroid weight and thyroid epithelial hyperplasia)
NOAEL ~ 20 mg/kg-bw/day

(4) Beagle dogs (4/sex/dose) were administered IRGANOX 259 via the diet at 0, 500, 1500 or 5000 ppm (approximately 0, 25, 75 and 250 mg/kg-bw/day) for 13 weeks. Comprehensive sets of tissues and organs were examined microscopically. There were no mortalities. Congestion of the intestinal mucosa was seen in some dogs at all dose levels. Other changes observed were considered insignificant and/or not related to test article administration. High-dose animals showed increased liver weights, which were considered treatment-related.
LOAEL ~ 250 mg/kg-bw/day (based on increased liver weights)
NOAEL ~ 75 mg/kg-bw/day

(5) Charles River rats (60/sex/dose) were administered IRGANOX 259 via the diet at 0, 50, 150 or 450 ppm (approximately 0, 2.5, 7.5 or 22.5 mg/kg-bw/day) for 104 weeks. Comprehensive sets of tissues and organs were examined microscopically. The only treatment-related effect reported was reduced food consumption in females at the highest test concentration.
LOAEL ~ 22.5 mg/kg-bw/day (based on reduced food consumption)
NOAEL ~ 7.5 mg/kg-bw/day

Reproductive Toxicity

A reproductive toxicity test was not submitted. Evaluation of reproductive organs from the 90-day repeated-dose toxicity studies and availability of a developmental toxicity study address the reproductive toxicity endpoint for the purposes of the HPV Challenge Program.

In the 90-day repeated-dose toxicity tests described previously, no macroscopic or microscopic effects on reproductive organs were observed at any dose level in the studies.

Developmental Toxicity

Pregnant Sprague-Dawley female rats (25/group) were administered IRGANOX 259 via gavage at 0, 150, 750 or 2000 mg/kg-bw/day on days 6 – 15 of gestation. Dams were sacrificed and fetuses removed on gestation day 21. Fetuses were examined for visceral and skeletal malformations and abnormalities. Reduced food consumption was seen at all doses and body weight gains were reduced at 750 and 2000 mg/kg-bw/day. The average weight of fetuses was reduced at 2000 mg/kg-bw/day (about 4% decrease compared with control). The only other fetal effect was an increased percentage of fetuses with incompletely ossified phalangeal nuclei seen at 2000 mg/kg-bw/day. For the control through high-dose groups, percentages of examined fetuses with this skeletal delay were: 0.5, 0, 1.5 and 5.7% for forelimbs and 9.9, 4.8, 13.4 and 17.5% for hind limbs.
LOAEL (maternal toxicity) = 750 mg/kg-bw/day (based on reduced body weight gains in dams)
NOAEL (maternal toxicity) = 150 mg/kg-bw/day
LOAEL (developmental toxicity) = 2000 mg/kg-bw/day (reduced fetal body weight and increased incidence of fetuses with incompletely ossified phalangeal nuclei)
NOAEL (developmental toxicity) = 750 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

No adequate data were submitted for this endpoint.

Genetic Toxicity – Chromosomal Aberrations

No adequate data were submitted for this endpoint.

Additional Information

Chronic Toxicity/Carcinogenicity

In a 2-year chronic dietary toxicity study, Charles River rats (60/sex/group) were administered IRGANOX 259 at 0, 50, 150 or 450 ppm (approximately 0, 2.5, 7.5 or 22.5 mg/kg-bw/day) in the diet for 104 weeks. These treatment levels did not cause signs of toxicity or pathological changes in organ tissue. The study authors concluded that the test substance at a dietary level of 450 ppm (equivalent to an average daily intake of 15.4 mg/kg-bw for males and 20.0 mg/kg-bw for females) was not tumorigenic to rats.
IRGANOX 259 did not increase the incidence of tumors in a 2-year dietary toxicity study.

Conclusion: Acute oral toxicity of IRGANOX 259 to mice is low and acute dermal toxicity to rabbits is low. Acute inhalation toxicity to rats appears to be low based on no deaths occurring when tested up to ~ 1.69 mg/L. Following repeated oral exposures of rats and mice for 90 days, target organs for toxicity included the liver and thyroid. In the 90-day repeated-dose toxicity tests, no macroscopic or microscopic effects on reproductive organs were observed at any dose. In a developmental toxicity study in rats, reduced fetal weights and increased number of incompletely ossified phalangeal nuclei were seen, but only at the high dose. In a 2-year chronic dietary toxicity study, IRGANOX 259 did not cause toxicity or pathological changes or tumors in rats.

The potential health hazard of IRGANOX 259 is moderate based on repeated-dose toxicity. IRGANOX 259 did not increase the incidence of tumors in a 2-year dietary toxicity study.

4. Hazard Characterization

The estimated log Kow for IRGANOX 259 is high. However, the low water solubility (3.3×10^{-7} mg/L, estimated) and estimated BCF (3.2) suggest the potential for this chemical to bioaccumulate is low. IRGANOX 259 is not readily biodegradable, indicating that it has the potential to persist in the environment.

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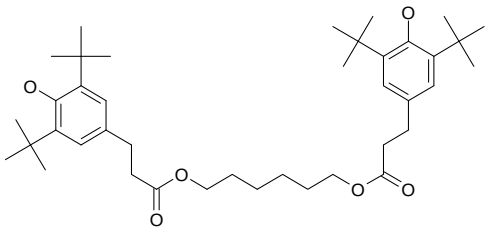
The potential health hazard of IRGANOX 259 is moderate based on repeated-dose toxicity. IRGANOX 259 did not increase the incidence of tumors in a 2-year dietary toxicity study.

5. Data Gaps

Gene mutation and chromosomal aberrations were identified as data gaps 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** **IRGANOX 259** **(1,6-hexamethylene bis (3,5-di-(*tert*)-butyl-4-hydroxyhydrocinnamate))** **(35074-77-2)**
Structure	
Summary of Physical-Chemical Properties and Environmental Fate Data	
Melting Point (ºC)	104 – 108
Boiling Point (ºC)	654.41 (estimated)
Vapor Pressure (hPa at 25ºC)	2.33×10^{-17} (estimated)
Log K_{ow}	> 11.74 (estimated)
Water Solubility (mg/L at 25ºC)	3.30×10^{-7} (estimated)
Indirect (OH^-) Photodegradation Half-life ($t_{1/2}$)	2.73 h (estimated)
Stability in Water (Hydrolysis) ($t_{1/2}$)	1.6 yr (pH 7); 59 d (pH 8) (estimated)
Fugacity (Level III Model) **Air (%)** **Water (%)** **Soil (%)** **Sediment (%)**	 0.0118 1.1 41 57.9
Biodegradation at 28 days (%)	1 Not readily biodegradable
Summary of Environmental Effects – Aquatic Toxicity Data	
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) **(growth)** **(biomass)** **(cell number)**	 **–** **–** NES

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL IRGANOX 259 (1,6-hexamethylene bis (3,5-di-(*tert*)-butyl-4-hydroxyhydrocinnamate)) (35074-77-2)**
Summary of Human Health Data	
Acute Oral Toxicity LD_{50} (mg/kg-bw)	> 7750
Acute Inhalation Toxicity LC_{50} (mg/L)	> ~ 1.69
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	> 10,000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL ~ 7.5 LOAEL ~ 22.5
Reproductive Toxicity	No effects were seen in evaluation of reproductive organs from 13-week repeated-dose toxicity studies in rats and dogs.
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day) **Maternal Toxicity** **Developmental Toxicity**	 NOAEL = 150 LOAEL = 750 NOAEL = 750 LOAEL = 2000
Genetic Toxicity – Gene Mutation	— Data Gap
Genetic Toxicity – Chromosomal Aberrations	— Data Gap
Additional Information – Carcinogenicity	IRGANOX 259 did not increase the incidence of tumors in a 2-year dietary toxicity study.

NES = No effects at saturation; **–** indicates that endpoint was not addressed for this chemical.