

**SCREENING-LEVEL HAZARD CHARACTERIZATION
OF HIGH PRODUCTION VOLUME CHEMICALS**

SPONSORED CHEMICAL

**Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate) methane
(IRGANOX 1010, CAS No. 6683-19-8)**

**[9th CI Name: Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 2,2-bis[[3-
[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxopropoxy]methyl]-1,3-propanediyl ester]**

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INTERIM**

Prepared by

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SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program¹ 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 website³.

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 EPA² and OECD⁵ 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 IRGANOX 1010 (CAS No.6683-19-8)

Introduction

The sponsor, Ciba Specialty Chemicals, submitted a Test Plan and Robust Summaries to EPA for IRGANOX 1010 (CAS No. 6683-19-8; 9th CI name: Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 2,2-bis[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxopropoxy]methyl]-1,3-propanediyl ester]) on June 12, 2000. EPA posted the submission on the ChemRTK HPV Challenge website on July 20, 2000 (<http://www.epa.gov/chemrtk/pubs/summaries/cibaspec/12667b1t.htm>). EPA comments on the original submission were posted to the website on November 20, 2000. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on February 20, 2001 which were posted to the ChemRTK website on March 5, 2001.

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. 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 submitted log K_{ow} of IRGANOX 1010 is outside of the domain of the model used to estimate it. The high molecular weight of IRGANOX 1010 indicates that its uptake across biological membranes may be limited. It is therefore concluded that the potential for IRGANOX 1010 to bioaccumulate is expected to be low. IRGANOX 1010 is not readily biodegradable, indicating that it has the potential to persist in the environment.

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of IRGANOX 1010 to aquatic organisms is low based on no effects observed at the water solubility limit (saturation).

Acute oral and inhalation toxicity of IRGANOX 1010 in rats and acute dermal toxicity in rabbits is low. Following repeated oral exposures of dogs for 13 weeks, no adverse effects were reported up to 250 mg/kg-bw/day (highest dose tested). In a two-generational reproductive toxicity study in rats, no effects on the reproductive capacity as assessed by mating performance, pregnancy rate or duration of gestation was evident. In a developmental toxicity study in mice, fetuses had increased incidence of incompletely ossified sternebrae when compared to controls. IRGANOX 1010 did not show a potential to induce gene mutation in bacterial cells and did not induce chromosome mutation in hamsters in nuclear anomaly tests. IRGANOX 1010 did not induce dominant lethal effects in mice.

The potential health hazard of IRGANOX 1010 is moderate based on the results of the developmental toxicity.

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 indicators of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

Log K_{ow} : 23.0 (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. The estimate for IRGANOX 1010 is outside this range indicates that the absolute value may not be accurate. The high molecular weight of IRGANOX 1010 indicates that its uptake across biological membranes may be limited. It is therefore concluded that the potential for IRGANOX 1010 to bioaccumulate is expected to be low.

Biodegradation

In a ready biodegradation test using the Modified Sturm method and activated sludge as inoculum, 4–5% IRGANOX 1010 degraded after 28 days.

IRGANOX 1010 is not readily biodegradable.

Conclusion: The submitted log K_{ow} of IRGANOX 1010 is outside of the domain of the model used to estimate it. The high molecular weight of IRGANOX 1010 indicates that its uptake across biological membranes may be limited. It is therefore concluded that the potential for IRGANOX 1010 to bioaccumulate is expected to be low. IRGANOX 1010 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 1010 at a nominal concentration of 100 mg/L under flow-through conditions for 96 hours. A vehicle (950 mg/L DMF and 4 mg/L Marlopon AT50) was used to facilitate chemical solubility. Mean measured concentrations (average of day 0 and day 4) were 88.5 and 77.5 mg/L. Mortality was not observed in either replicate. The 96-hour LC_{50} was reported as > 88.5 mg/L, however, this value is above the water solubility limit (2.3×10^{-16} mg/L, estimated) for IRGANOX 1010. Therefore, it is concluded that there are no effects at saturation.

No effects at saturation

Acute Toxicity to Aquatic Invertebrates

Daphnia magna were exposed to IRGANOX 1010 at nominal concentrations of 10, 18, 32, 58 and 100 mg/L under static conditions for 24 hours. A vehicle (950 mg/L DMF and 4 mg/L Marlopon AT50) was used to facilitate chemical solubility and the maximal concentration deviated from OECD Guideline recommendations. Mean measured concentrations (average of hour 0 and hour 24) were 4.5, 9.5, 26.5, 30.5 and 85.5 mg/L. Mortality and/or immobilization were observed at concentrations \leq 85.5 mg/L ($EC_0 = 30.5$ mg/L). However, given the effects were observed well above the water solubility limit (2.3×10^{-16} mg/L, estimated) of IRGANOX 1010, it is concluded they are likely due to physical toxicity rather than systemic toxicity.

No systemic effects at saturation

Toxicity to Aquatic Plants

Green algae (*Scenedesmus subspicatus*) were exposed to IRGANOX 1010 at nominal concentrations of 0, 1.23, 3.7, 11.0, 33.0 and 100 mg/L under static conditions for 72 hours. A vehicle (alkylphenol-polyglycoether) was used to facilitate chemical solubility. Mean measured concentrations (hour 0 and hour 72) were 1.1, 2.55, 12.5, 41.7 and 141.0 mg/L. No decrease in cell density, area under the growth curve or growth rate was seen after 72 hours of exposure. The 72-hour EC_{50} was reported as > 100 mg/L, however, this value is above the water solubility limit (2.3×10^{-16} mg/L, estimated) of IRGANOX 1010. Therefore, it is concluded that there are no effects at saturation.

No effects at saturation

Conclusion: The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates the potential ACUTE hazard of IRGANOX 1010 to aquatic organisms is low based on no effects observed at the water solubility limit (saturation).

3. Human Health Effects

Acute Oral Toxicity

Sprague Dawley rats (2/sex/group) were administered IRGANOX 1010 in corn oil via oral gavage at doses of 4556, 6834 or 10250 mg/kg-bw. No mortality occurred; clinical signs of toxicity included hypoactivity, ruffled fur in animals at all treatment and at the high-dose group labored breathing and diuresis were observed. Animals returned to normal on day 2 of the 14-day observation period.

LD₅₀ > 10,250 mg/kg-bw

Acute Dermal Toxicity

IRGANOX 1010 was dermally administered to abraded skin of two rabbits/dose or intact skin of two rabbits/dose at 100, 316, 1000 or 3160 mg/kg-bw under occluded conditions for 24 hours and were observed for 14 days. No mortality was observed. All animals exhibited slight erythema at the end of the exposure period; however, this response had subsided between days 2 and 5.

LD₅₀ > 3160 mg/kg-bw

Acute Inhalation Toxicity

Rats (10/sex/dose, no strain reported) were exposed to IRGANOX 1010 vapor at concentrations of 0.76 or 1.95 mg/L for 4 hours and were observed for 14 days after the exposure period. No mortality was observed; clinical signs of toxicity included slight dyspnea and ruffled fur in both treatment groups. Animals appeared to have recovered by the end of the 14-day observation period, no pathological changes were observed at necropsy.

4-h LC₅₀ > 1.95 mg/L

Repeated-Dose Toxicity

Beagle dogs (6/sex/dose) were administered IRGANOX 1010 in the diet at concentrations of 1000, 3000 or 10,000 ppm (approximately 25, 75 or 250 mg/kg-bw/day) for 13 weeks. Following the exposure period, one animal/sex/dose was fed control diet for an additional 4 weeks. There were no adverse effects that could be related to treatment, no clinical symptoms and no signs of systemic toxicity. No mortality occurred; food consumption and body weight gain were unaffected by treatment. An increase in bilirubin was observed at weeks 4 and 9, but not at week 13. All absolute and relative organ weights of treated dogs were similar to control animals. Macroscopic and microscopic examinations did not reveal any treatment-related effects.

LOAEL > ~ 250 mg/kg-bw/day

NOAEL ~ 250 mg/kg-bw/day (based on no effects at the highest dose tested)

Reproductive Toxicity

In a two-generation reproductive study Crl:COBS CD (SD) BR rats (F₀ generation) were administered IRGANOX 1010 in the diet for 13 weeks (males) and 10 weeks (females) prior to mating at concentrations of 1000, 3000 and 10,000 ppm (approximately 50, 150 and 500 mg/kg-bw/day). One male and one female were paired for mating for a period of 20 days and vaginal smears were taken daily throughout the mating period. Dams were allowed to rear their young to day 21 postpartum; 24 male and 24 female pups were retained as the F1 generation. Following selection of the F1 generation, a male and a female from each litter were selected for organ weight analysis and preservation of tissues. The remaining animals were euthanized and examined macroscopically. No mortality occurred among animals of either the F0 or F1 generation nor were there any consistent effects that could be attributed to treatment, including clinical signs of toxicity, food consumption, body weight gain and efficacy of food utilization, reproductive capacity as assessed by mating performance, pregnancy rate and duration of gestation, findings at necropsy.

LOAEL (systemic/reproductive toxicity) > 500 mg/kg-bw/day

NOAEL (systemic/reproductive toxicity) ~ 500 mg/kg-bw/day (based on no effects at the highest dose tested)

Developmental Toxicity

(1) Pregnant Sprague-Dawley rats were administered IRGANOX 1010 via oral gavage at doses of 150, 500 or 1000 mg/kg-bw/day during days 6 through 15 of gestation. Rats were sacrificed on gestation day 21, females necropsied and fetuses were removed by caesarean section. At the low- and intermediate-dose levels, an increase in food consumption was noted in dams during treatment period (no effect on body weight gain). Increased rate of delayed ossification was seen at low and intermediate doses, but at the high dose, the delayed ossification rate was comparable to the control group. Because there was no dose-response, this finding was not considered treatment related. There were no other effects reported.

LOAEL (maternal/developmental toxicity) > 1000 mg/kg-bw/day

NOAEL (maternal/developmental toxicity) = 1000 mg/kg-bw/day (based on no effects at the highest dose tested)

(2) Pregnant female mice were administered IRGANOX 1010 via oral gavage at doses of 150, 500 or 1000 mg/kg-bw/day during days 6 through 15 of gestation. Mice were sacrificed on gestation day 18; females were necropsied and fetuses were removed by caesarean section. No maternal toxicity was apparent in any of the treated animals when compared to control. The rates of implantation and resorptions, as well as the average weights of the fetuses were comparable for all groups. Low- and high-dose group fetuses had minor skeletal deviations from controls. Fetuses from the 150 mg/kg-bw/day group had higher incidences of ossification of the phalangeal nuclei of the hind limb and the calcanei were also markedly different from controls. In a dose-response trend, there were increasing fetuses with incompletely ossified sternebrae, leading to a marked increase at the high-dose when compared to controls. No other findings were reported.

LOAEL (maternal toxicity) > 1000 mg/kg-bw/day (based on no effects at the highest dose tested)

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

LOAEL (developmental toxicity) = 150 mg/kg-bw/day (based on incompletely ossified sternebrae)

NOAEL (developmental toxicity) = Not established

Genetic Toxicity – Gene Mutation

In vitro

IRGANOX 1010 was tested in several *Salmonella typhimurium* strains (TA98, TA100, TA1535 and TA1537) at concentrations of 10, 25, 50, 100 and 250 µg/0.1 mL (with) and 5, 10, 25, 50 and 100 µg/0.1 mL (without) metabolic activation. Positive controls were also included; however, their responses were not reported.

Precipitation of the test material was evident at the 100 µg/0.1 mL. No increase was observed in reverse mutations with or without metabolic activation.

IRGANOX 1010 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo

(1) In a nuclear anomaly test, male and female Chinese hamsters received 500, 1000 or 2000 mg/kg-bw IRGANOX 1010 in 0.5% carboxymethyl cellulose for 2 consecutive days. Animals were sacrificed 24 hours following the second treatment and bone marrow scored for chromosomal anomalies. Positive and negative controls were also used. The percentage of cells displaying anomalies of nuclei did not differ from the negative control.

IRGANOX 1010 did not induce chromosomal aberrations in this assay.

(2) In a chromosomal aberration assay, Chinese hamsters (4/sex/dose) were administered 0, 500, 1000 or 2000 mg/kg-bw IRGANOX 1010 in 2.0% sodium carboxymethyl cellulose for 2 consecutive days. Animals were sacrificed and bone marrow was harvested after the colcemide injection 2 hours after the second dose. Positive and negative controls were used in the assay.

IRGANOX 1010 did not induce chromosomal aberrations in this assay.

(3) In a dominant lethal assay, albino male mice (20/dose) were administered IRGANOX 1010 via oral gavage at single doses of 0, 1000 or 3000 mg/kg-bw/day. Males were mated with a pair of untreated females each week for up to 6 weeks. Females were examined daily for evidence of pregnancy (vaginal plug). Pregnant females were necropsied on day 14 and the number of live embryos and embryonic deaths were recorded. Mating ratio, number of implantations and embryonic deaths did not differ between control and treated animals. No evidence of dominant lethal effects was noted.

IRGANOX 1010 was negative in this dominant lethal effect assay.

Conclusion: Acute oral and inhalation toxicity of IRGANOX 1010 in rats and acute dermal toxicity in rabbits is low. Following repeated oral exposures of dogs for 13 weeks, no adverse effects were reported up to 250 mg/kg-bw/day (highest dose tested). In a two-generational reproductive toxicity study in rats, no effects of the reproductive capacity as assessed by mating performance, pregnancy rate or duration of gestation was evident. In a developmental toxicity study in mice, fetuses had increased incidence of incompletely ossified sternebrae when compared to controls. IRGANOX 1010 did not show a potential to induce gene mutation in bacterial cells and did not induce chromosome mutation in hamsters in a nuclear anomaly test. IRGANOX 1010 did not induce dominant lethal effect in mice.

The potential health hazard of IRGANOX 1010 is moderate based on the developmental toxicity.

4. Hazard Characterization

The submitted log K_{ow} of IRGANOX 1010 is outside of the domain of the model used to estimate it. The high molecular weight of IRGANOX 1010 indicates that its uptake across biological membranes may be limited. It is therefore concluded that the potential for IRGANOX 1010 to bioaccumulate is expected to be low. IRGANOX 1010 is not readily biodegradable, indicating that it has the potential to persist in the environment.

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of IRGANOX 1010 to aquatic organisms is low based on no effects observed at the water solubility limit (saturation).

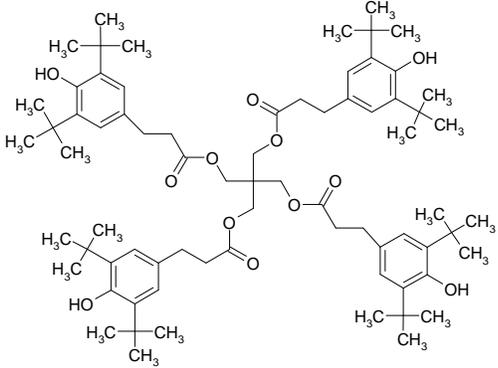
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The potential health hazard of IRGANOX 1010 is moderate based on the results of the developmental toxicity.

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 IRGANOX 1010 [Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate) methane) (CAS No. 6683-19-8)
Structure	
Summary of Physical-Chemical Properties and Environmental Fate Data	
Melting Point (°C)	115 – 118
Boiling Point (°C)	1130 (estimated)
Vapor Pressure (hPa at 25°C)	7.1×10^{-31} (estimated)
Log K_{ow}	23.0 (estimated) ¹
Water Solubility (mg/L at 25°C)	2.3×10^{-16} (estimated)
Direct Photodegradation	—
Indirect (OH⁻) Photodegradation Half-life (t_{1/2})	1.2 hours
Stability in Water (Hydrolysis) (t_{1/2})	2.1 years
Fugacity (Level III Model)	
Air (%)	0
Water (%)	0
Soil (%)	99.4
Sediment (%)	0.6
Biodegradation at 28 days (%)	4 – 5 Not readily biodegradable
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC₅₀ (mg/L)	No effects at saturation
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	No effects at saturation
Aquatic Plants 72-h EC₅₀ (mg/L)	No effects at saturation

¹ 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. The estimate for IRGANOX 1010 is outside this range indicates that the absolute value may not be accurate.

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL IRGANOX 1010 [Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate) methane) (CAS No. 6683-19-8)
Summary of Human Health Data	
Acute Oral Toxicity LD ₅₀ (mg/kg-bw)	> 10,250
Acute Inhalation Toxicity LC ₅₀ (mg/L)	> 1.95
Acute Dermal Toxicity LD ₅₀ (mg/kg-bw)	> 3160
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 250 LOAEL > 250
Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day)	NOAEL ~ 500 LOAEL > ~ 500
Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day)	
Maternal and Developmental	(Rat) NOAEL = 1000 LOAEL >1000
Maternal	(Mice) NOAEL = 1000 LOAEL >1000
Developmental	NOAEL = Not established LOAEL = 150
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Negative

— indicates that endpoint was not addressed for this chemical.