

SCREENING-LEVEL HAZARD CHARACTERIZATION

2-Propenamide, N-(1,1,3,3-tetramethylbutyl)- (CASRN 4223-03-4)

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.

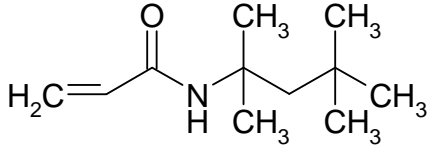
¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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 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.

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.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p>4223-03-4</p>
<p>Chemical Abstract Index Name</p>	<p>2-Propenamamide, N-(1,1,3,3-tetramethylbutyl)-</p>
<p>Structural Formula</p>	
<p style="text-align: center;">Summary</p> <p>CASRN 4223-03-4 is an off-white, waxy solid with moderate water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of CASRN 4223-03-4 is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate. CASRN 4223-03-4 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).</p> <p>The acute oral toxicity of CASRN 4223-03-4 is moderate in rats and mice. In an oral gavage repeated-dose/reproductive/developmental toxicity screening test, CASRN 4223-03-4 showed a decreasing trend in forelimb grip strength and increased relative liver weights at all doses in male rats and decreased body weight gain and increased relative liver weights at and above 155 mg/kg-day in females. The NOAEL for systemic toxicity in male rats was not established; the NOAEL for systemic toxicity in female rats is 70 mg/kg-day. No effects on reproductive parameters were seen; the NOAEL for reproductive toxicity is 350 mg/kg-day (highest dose tested). The NOAEL for maternal toxicity was 70 mg/kg-day based on decreased body weight gain and increased relative liver weights seen at and above 155 mg/kg-day. The NOAEL for developmental toxicity is 155 mg/kg-day based on decreased implantations, litter size, body weight and pup viability seen at 350 mg/kg-day. CASRN 4223-03-4 did not induce gene mutations in bacteria or mammalian cells <i>in vitro</i> and did not induce micronuclei in mice bone marrow <i>in vivo</i>.</p> <p>For CASRN 4223-03-4, the 96-hour LC₅₀ for fish is > 100 mg/L, the 48-hr EC₅₀ for aquatic invertebrates is 26.2 mg/L and the 72-hour EC₅₀ values for aquatic plants are 10.1 and > 100 mg/L for biomass and growth rate, respectively.</p> <p>No data gaps were identified under the HPV Challenge Program.</p>	

As part of the ICI group and on behalf of ICI Americas Inc, National Starch and Chemical Company, submitted a Test Plan and Robust Summaries to EPA for 2-Propenamide, N-(1,1,3,3-tetramethylbutyl)- (CASRN 4223-03-4) on December 19, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on December 20, 2002 (<http://www.epa.gov/oppt/chemrtk/pubs/summaries/2propena/c14153tc.htm>). EPA comments on the original submission were posted on the website on May 13, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on December 10, 2003 and June 16, 2005 which were posted to the ChemRTK website on December 11, 2003 and August 24, 2010, respectively.

1. Chemical Identity

1.1 Identification and Purity

CASRN 4223-03-4 is also known as *tert*-octylacrylamide and is produced by the addition of acrylonitrile and diisobutylene in an acidic environment. As indicated in the robust summaries, purity of CASRN 4223-03-4 was 99.7%.

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 4223-03-4 are summarized in Table 1. 2-Propenamide, N-(1,1,3,3-tetramethylbutyl)- is a solid with moderate water solubility and moderate vapor pressure.

Property	Value
CASRN	4223-03-4
Molecular Weight	183.3
Physical State	Off-white, waxy solid
Melting Point	55–60°C (measured) 83°C (crystallized from benzene) ² 51°C (measured) ³
Boiling Point	140–142°C at 20 mm Hg (measured) ² 250–252°C (estimated) ⁴
Vapor Pressure	0.019 mm Hg at 25°C (estimated) ⁴
Water Solubility	<100 mg/L (method unknown); 222 mg/L at 25°C (estimated) ⁵
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	9.4×10 ⁻⁸ atm·m ³ /mole (estimated) ⁵
Log K _{ow}	2.9 (estimated) ⁵

¹ National Starch and Chemical Company. 2003. Revised Robust Summary for 2-Propenamamide, N-(1,1,3,3-tetramethylbutyl)-. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/2propena/c14153tc.htm> as of June 12, 2010.

² Beilstein Search. February 5, 2003.

³ Lide DR; Milne GWA. 1994. Handbook of Data on Organic Compounds, 3rd Edition. Boca Raton, LA: CRC Press, p. 4508.

⁴ NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.

⁵ 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 July 12, 2010.

2. General Information on Exposure

2.1 Production Volume and Exposure

CASRN 4223-03-4 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 “other.” No commercial and consumer uses were reported.

2.2 Environmental Exposure and Fate

The environmental fate characteristics of CASRN 4223-03-4 are summarized in Table 2.

2-Propenamide, N-(1,1,3,3-tetramethylbutyl)- is expected to have moderate mobility in soil. Biodegradation data for the test substance were not available; however, measured data for a structurally similar compound, N,N-dimethylacrylamide (CAS RN 2680-03-7), indicate that biodegradability may be limited for 2-propenamide, N-(1,1,3,3-tetramethylbutyl)-. The rate of volatilization of 2-propenamide, N-(1,1,3,3-tetramethylbutyl)- is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. 2-Propenamide, N-(1,1,3,3-tetramethylbutyl)- is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of 2-Propenamide, N-(1,1,3,3-tetramethylbutyl)-	
Property	Value
Photodegradation Half-life	7.6 hours (estimated) ²
Hydrolysis Half-life	Stable
Biodegradation	3% in 28 days (not readily biodegradable, data measured for N,N-Dimethylacrylamide, CASRN 2680-03-7) ³
Bioaccumulation Factor	BAF = 36 (estimated) ²
Log K _{oc}	2.3 (estimated) ²
Fugacity (Level III Model) ²	
Air (%)	0.3
Water (%)	18.4
Soil (%)	81.1
Sediment (%)	0.2
Persistence ⁴	P2 (moderate)
Bioaccumulation ⁴	B1 (low)

¹National Starch and Chemical Company. 2003. Revised Robust Summary for 2-Propenamide, N-(1,1,3,3-tetramethylbutyl)-. Available online at

<http://www.epa.gov/chemrtk/pubs/summaries/2propena/c14153tc.htm> as of July 12, 2010.

²U.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 July 12, 2010.

³National 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 12, 2010.

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

Conclusion: 2-Propenamide, N-(1,1,3,3-tetramethylbutyl)- is an off-white, waxy solid with moderate water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of 2-propenamide, N-(1,1,3,3-tetramethylbutyl)-

is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate. 2-Propenamide, N-(1,1,3,3-tetramethylbutyl)- is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

3. Human Health Hazard

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

Acute Oral Toxicity

(1) In the range-finding study for a repeated-dose/reproductive/developmental toxicity screening test, male and female Crl:WI(Glx/BRL/Han)BR rats (number not specified) were administered CASRN 4223-03-4 (in corn oil containing 5% ethanol) either once (to determine the maximum tolerated single dose) or daily for 14 days (to determine the maximum tolerated dose over two week) at 0, 200, 300, 400, 500, 600, 750 or 1000 mg/kg. At 500 mg/kg one male and one female rat were sacrificed because of severe clinical signs. Data for 600 mg/kg and above doses are not included in the robust summary. Based on these findings, the LD₅₀ value can be estimated to be >500 and <1000 mg/kg.

500 < LD₅₀ < 1000 mg/kg

(2) In two range-finding studies for the *in vivo* mouse micronucleus assay, male and female Crl:CD-1(ICR) BR mice (number not specified) were administered CASRN 4223-03-4(in corn oil) via gavage at 200, 500, 600, 700, 800, 1500 or 2000 mg/kg and observed for 24 hours. Mortality was high at 800 mg/kg and above. Based on these findings, the LD₅₀ value can be estimated to be > 700 and < 800 mg/kg.

700 < LD₅₀ < 800 mg/kg

Repeated-Dose Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test, Crl:WI(Glx/BRL/Han)BR rats (10/sex/dose) were administered CASRN 4223-03-4 (in 5% v/v ethanol in corn oil) via gavage at 0, 70, 155, 350 mg/kg-day. [The dose levels were selected from the range-finding study where post-dosing clinical signs were seen at 300 mg/kg-day and above.] Males were dosed 2 weeks before mating, throughout mating and until the day before necropsy (at least 4 weeks of treatment) and females were dosed 2 weeks before mating, throughout mating, gestation and until Day 4 *post-partum*. There was no mortality. At 350 mg/kg-day, the majority of males showed a body weight loss compared to control; females at this dose and at 155 mg/kg-day had lower body weight gain (statistical significance not stated). Males and females had reduced food intake compared to controls during the pre-mating period at 350 mg/kg-day. Mean food intake for females at this dose was slightly lower than controls during gestation. Functional observation battery tests showed a dose-related decreasing trend in forelimb grip strength in males during Week 7 (P<0.05). No effects were seen in locomotor activity. In males,

relative mean kidney weights were increased ($P < 0.001$) at 350 mg/kg-day and in all treated males, relative mean liver weight was increased ($P < 0.05$, $P < 0.001$, $P < 0.001$ at 70, 155 and 350 mg/kg-day respectively). In females, relative adrenal weight was increased at 350 mg/kg-day ($P < 0.05$) and relative mean liver weight was increased 155 and 350 mg/kg-day ($P < 0.001$ and $P < 0.01$ respectively). Histopathologically, at 350 mg/kg-day, centrilobular hypertrophy was reported in the majority of males and females; an increased level of hyaline droplets was seen in the kidneys of all males and a minor increase in the level of foamy histiocytes in lungs was observed in males and females.

LOAEL_{males} = 70 mg/kg-day (based on increased relative liver weight and decreasing trend in forelimb strength)

NOAEL_{males} = not established

LOAEL_{females} = 155 mg/kg-day (based on decreased body weight gain and increased relative liver weight)

NOAEL_{females} = 70 mg/kg-day

Reproductive/Developmental Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test, CrI:WI(Glx/BRL/Han)BR rats (10/sex/dose) were administered CASRN 4223-03-4 according to the protocol described above. No treatment-related effects on numbers of males and females mating or on male or female fertility indices. Qualitative assessment of testes staging did not indicate any abnormalities in the integrity of the various cell types present within the different stages of the spermatogenic cycle. At 350 mg/kg-day, numbers of implantations, litter sizes and Day 4 body weights were decreased compared to controls. There was also a reduction in pup viability at this dose. Total litter loss occurred for two females at 350 mg/kg-day and one from each of the 70 and 155 mg/kg-day groups. Total embryo/fetal loss occurred for one high dose female. [The difference between the total litter loss and total embryo/fetal loss is not explained in the robust summary.] Malformed/shortened limbs occurred in one pup at 155 mg/kg-day and one pup at 350 mg/kg-day groups; however, as this effect occurred in only one pup in one litter in these groups, the robust summary states that its toxicological significance is unclear (further specifics, including incidence by dose group, was not provided in the robust summary).

NOAEL (reproductive toxicity) = 350 mg/kg-day (highest dose tested)

LOAEL (maternal toxicity) = 155 mg/kg-day (based on decrease body weight gain and increased relative liver weight gain)

NOAEL (maternal toxicity) = 70 mg/kg-day

LOAEL (developmental toxicity) = 350 mg/kg-day (based on decreased implantations, litter size, body weights and pup viability)

NOAEL (developmental toxicity) = 155 mg/kg-day

Genetic Toxicity – Gene Mutations

In Vitro

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2uvrA were exposed to CASRN 4223-03-4 at 0, 33.3, 100, 333, 1000, 3330, or 5000 µg/plate, in the presence and absence of metabolic activation in a bacteria reverse mutation assay. Positive and vehicle (DMSO) controls were used. The cytotoxic concentration was 5000 µg/plate. Responses of the positive controls are not included in the robust summary. CASRN 4223-03-4 did not cause an increase in the number of revertants per plate in any of the tester strains either in the presence or absence of metabolic activation.

CASRN 42233-03-4 was not mutagenic in this assay.

(2) Mouse lymphoma cells (L5178Y) were exposed to CASRN 4223-03-4 with metabolic activation at 0, 50, 100, 200, 300, 400, 450, 500, or 550 µg/mL and without metabolic activation at 0, 50, 100, 200, 300, 400, 450, or 500 µg/mL. Positive and vehicle (DMSO) controls were used in the assay. The cytotoxic concentration was 500 µg/mL. Responses of the positive controls are not included in the robust summary. CASRN 4223-03-4 did not induce gene mutations with and without metabolic activation.

CASRN 42233-03-4 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo

Male CD-1 mice (6/dose/harvest time) were exposed to CASRN 4223-03-4 for 24 hours via gavage doses of 175, 350, or 700 mg/kg. The doses were selected based on the range-finding study in which high mortality was seen at 800 mg/kg. Bone marrow was harvested at 24 hours (all doses) and 48 hours (control and 700 mg/kg). The polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE) ratio and the number of micronucleated PCEs were determined. The test article induced signs of clinical toxicity in the treated animals and was cytotoxic to the bone marrow as indicated by a significant decrease in the PCE:NCE ratio in the 700 mg/kg group at the 48 hour harvest time point. No change in micronucleated PCEs was observed at any dose level or harvest time point. The positive control produced the expected increase in micronucleated PCEs. CASRN 4223-03-4 did not induce a statistically significant increase in micronuclei in bone marrow polychromatic erythrocytes

CASRN 42233-03-4 did not induce increase in micronuclei in bone marrow in this study.

Conclusion: The acute oral toxicity of CASRN 4223-03-4 is moderate in rats and mice. In an oral gavage repeated-dose/reproductive/developmental toxicity screening test, CASRN 4223-03-4 showed a decreasing trend in forelimb grip strength and increased relative liver weights at all doses in male rats and decreased body weight gain and increased relative liver weights at and above 155 mg/kg-day in females. The NOAEL for systemic toxicity in male rats was not established; the NOAEL for systemic toxicity in female rats is 70 mg/kg-day. No effects on reproductive parameters were seen; the

NOAEL for reproductive toxicity is 350 mg/kg-day (highest dose tested). The NOAEL for maternal toxicity was 70 mg/kg-day based on decreased body weight gain and increased relative liver weights seen at and above 155 mg/kg-day. The NOAEL for developmental toxicity is 155 mg/kg-day based on decreased implantations, litter size, body weight and pup viability seen at 350 mg/kg-day. CASRN 4223-03-4 did not induce gene mutations in bacteria or mammalian cells *in vitro* and did not induce micronuclei in mice bone marrow *in vivo*.

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data	
Endpoints	SPONSORED CHEMICAL 2-Propenamide, N-(1,1,3,3-tetramethylbutyl)- (CASRN 4223-03-4)
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	(rat) > 500 < 1000 (mice) > 700 < 800
Repeated-Dose Toxicity (rats) (NOAEL/LOAEL) Oral (mg/kg-bw/day)	(males) NOAEL = Not established LOAEL = 70 (females) NOAEL = 70 LOAEL = 155
Reproductive Toxicity (NOAEL/LOAEL) Oral (mg/kg-bw/day) Reproductive Toxicity	NOAEL = 350 (highest dose tested)
Developmental Toxicity (NOAEL/LOAEL) Oral (mg/kg-bw/day)	
Maternal Toxicity	NOAEL = 70 LOAEL = 155
Developmental Toxicity	NOAEL = 155 LOAEL = 350
Genetic Toxicity – Gene Mutations <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Negative

Measured data in bold text

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4.

Acute Toxicity to Fish

Rainbow trout (*Oncorhynchus mykiss*) were exposed to CASRN 4223-03-4 for 96 hours under static conditions. Nominal concentrations were 0, 6.25, 12.5, 25, 50 and 100 mg/L. Measured concentrations were 90 – 98 % of nominal but values were not reported. There was no mortality at any of the exposure concentrations, including the control treatment, during the definitive test.

96-hr LC₅₀ > 100 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to CASRN 4223-03-4 for 48 hours under static conditions. Nominal concentrations were 0, 6.25, 12.5, 25, 50 and 100 mg/L. Measured concentrations were 93 – 107 % of nominal but values were not given. Mortalities were observed in the 25, 50 and 100 mg/L test concentrations.

48-hr EC₅₀ = 26.2 mg/L

Toxicity to Aquatic Plants

Green algae (*Selenastrum capricornutum*) were exposed to CASRN 4223-03-4 for 72 hours under static conditions. Nominal concentrations were 0, 0.0827, 0.182, 0.401, 0.882, 1.94, 4.27, 9.39, 20.7, 45.5 and 100 mg/L. Measured concentrations were within 93 – 100 % of nominal but values were not given.

72-hr EC₅₀ (biomass) = 10.1 mg/L

72-hr EC₅₀ (growth rate) > 100 mg/L

Conclusion: For CASRN 4223-03-4, the 96-hour LC₅₀ for fish is > 100 mg/L, the 48-hr EC₅₀ for aquatic invertebrates is 26.2 mg/L and the 72-hour EC₅₀ values for aquatic plants are 10.1 and > 100 mg/L for biomass and growth rate, respectively.

Table 4. Summary of the Screening Information Data Set as Submitted Under the U.S. HPV Challenge Program – Aquatic Toxicity Data	
Endpoints	SPONSORED CHEMICAL 2-Propenamide, N-(1,1,3,3-tetramethylbutyl)- (4223-03-4)
Fish 96-h LC₅₀ (mg/L)	> 100
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	26.2
Aquatic Plants 72-h EC₅₀ (mg/L) (biomass) (growth rate)	10.1 > 100

bold = measured data (i.e., derived from testing)