

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### 4-Methylphenol, reaction products with dicyclopentadiene and isobutylene (CASRN 68610-51-5)

The High Production Volume (HPV) Challenge Program<sup>1</sup> 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<sup>1,2</sup>) 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<sup>2,3</sup> and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

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

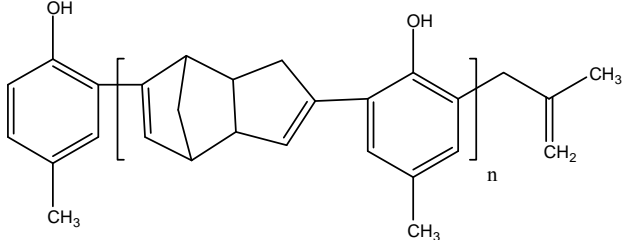
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<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

<sup>2</sup> U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

<sup>3</sup> U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

<p><b>Chemical Abstract Service Registry Number (CASRN)</b></p>	<p><b>68610-51-5</b></p>
<p><b>Chemical Abstract Index Name</b></p>	<p><b>Phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene</b></p>
<p><b>Structural Formula</b></p>	
<p style="text-align: center;"><b>Summary</b></p> <p>CASRN 68610-51-5 is a solid with negligible water solubility and negligible vapor pressure. It is expected to have low mobility in soil. Volatilization of CASRN 68610-51-5 is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered rapid; however, this is not expected to be an important environmental fate process because this substance is not expected to exist in the vapor phase in the atmosphere. CASRN 68610-51-5 is expected to have moderate persistence (P2) and high bioaccumulation potential (B3).</p> <p>The acute oral toxicity and acute dermal toxicity of CASRN 68610-51-5 in rats and rabbits, respectively, are low. Dietary exposure of rats to CASRN 68610-51-5 for 90 days resulted in increases in prothrombin times and activated partial thromboplastin times at 270 mg/kg-bw/day in males, and higher serum cholesterol levels at 225 mg/kg-bw/day in females; the NOAEL for systemic toxicity is 90 mg/kg-bw/day in males and 75 mg/kg-bw/day in females. No reproductive toxicity studies with CASRN 68610-51-5 are available; however, a 90-day repeated-dose toxicity study showed no effects on reproductive organs with doses up to 225 mg/kg-bw/day in females and 270 mg/kg-bw/day in males. In an oral gavage prenatal developmental toxicity study in rats with CASRN 68610-51-5, depressed weight gain occurred in the dams at 3000 mg/kg-day; the NOAEL for maternal toxicity is 2000 mg/kg-day. Fetuses exhibited increased incidences of common fetal skeletal variations at 1000 mg/kg-day, the lowest dose tested; the NOAEL for developmental toxicity is 740 mg/kg-day (benchmark dose). CASRN 68610-51-5 did not induce gene mutation in bacterial and mammalian cells <i>in vitro</i>, chromosomal aberrations in Chinese hamster ovary cells <i>in vitro</i> or DNA damage in <i>Escherichia coli</i>. CASRN 68610-51-5 was slightly irritating to rabbit skin and eyes and was a dermal sensitizer in guinea pigs.</p> <p>The 96-hr LC<sub>50</sub> of CASRN 68610-51-5 for fish, is &gt;0.2 mg/L. The 48-hr EC<sub>50</sub> of CASRN 68610-51-5 for aquatic invertebrates is &gt;0.2 mg/L, and the 72-hr EC<sub>50</sub> for aquatic plants is &gt;0.2 mg/L (growth rate).</p> <p>The chronic invertebrate toxicity endpoint has been identified as a data gap under the HPV Challenge Program.</p>	

The sponsor, Rubber and Plastic Additives Panel of the American Chemistry Council, submitted a Test Plan and Robust Summaries to EPA for hindered phenols (CASRN 68457-74-9, CASRN 61788-44-1, CASRN 96-69-5, CASRN 85-60-9, CASRN 79-96-9, CASRN 7786-17-6, CASRN 68610-51-5 and CASRN 27676-62-6) on December 18, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 15, 2002 (<http://www.epa.gov/HPV/pubs/summaries/hndrdphn/c13382tc.htm>). EPA comments on the original submission were posted to the website on December 10, 2002. Public comments were also received and posted to the website. In response to EPA comments on the original submission, the sponsor subsequently divided the hindered phenols category into two separate categories (styrenated phenols and bridged alkyl phenols) and two separate stand-alone chemicals, 4-methylphenol, reaction products with dicyclopentadiene and isobutylene (CASRN 68610-51-5) and 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (CASRN 27676-62-6). The sponsor submitted a test plan and robust summaries for CASRN 68610-51-5 on July 11, 2003, which EPA posted to the ChemRTK website on September 1, 2004. EPA comments on the submission for 4 CASRN 68610-51-5 were posted to the website on March 22, 2007.

## **1. Chemical Identity**

### **1.1 Identification and Purity**

The number of the isobutylene-derived C4 groups on the phenolic rings is unspecified. The sponsor does not provide information on the proportion of the three feedstocks used to manufacture the test substance; however, they do state that dicyclopentadiene and 4-methylphenol are first reacted with each other, followed by alkylation with isobutylene. The test plan shows a structure in which double bonds are present in the dicyclopentadiene and isobutylene-derived C4 groups, but these bonds are unlikely to be present in the final test substance.

The submitter states in the Robust Summary states that the typical molecular weight of the substance is 650 amu, while the Test Plan provides a range of 750–850 amu. The robust summary further mentions that the sponsored chemical has a purity of >98% .

### **1.2 Physical-Chemical Properties**

The physical-chemical properties of CASRN 68610-51-5 are summarized in Table 1. CASRN 68610-51-5 is a solid with negligible water solubility and negligible vapor pressure.

<b>Property</b>	<b>Value</b>
CASRN	68610-51-5
Molecular Weight	650 (typical for n=2)
Physical State	Solid
Melting Point	118.3°C (measured)
Boiling Point	>300°C (estimated) <sup>2,3</sup>
Vapor Pressure	<2.4×10 <sup>-7</sup> mm Hg at 25°C (measured); <1.0×10 <sup>-10</sup> mm Hg at 25°C (estimated) <sup>2,3</sup>
Water Solubility	<0.2 mg/L at 20°C (measured)
Dissociation Constant (pK <sub>a</sub> )	9.48 (estimated) <sup>3,4</sup> ; 9.42 (estimated) <sup>3,4</sup> ; 8.94 (estimated) <sup>3,4</sup>
Henry's Law Constant	<1.0×10 <sup>-10</sup> atm·m <sup>3</sup> /mole (estimated) <sup>2,3</sup>
Log K <sub>ow</sub>	7.17–8.17 at 30°C (measured)

<sup>1</sup> Rubber and Plastic Additives Panel of The American Chemistry Council. July 2003. Revised Test Plan and Robust Summary for Phenol, 4-Methyl-, Reaction Products with Dicyclopentadiene and Isobutylene. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/hndrdphn/c13382tc.htm> as of May 7, 2010.

<sup>2</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of May 7, 2010.

<sup>3</sup> All estimations performed on a representative structure having approximate molecular weight of 650.

<sup>4</sup> SPARC. 2010. Online pK<sub>a</sub> and Property Calculator, v.4.2.1405-s4.2.1408. Available online from: <http://ibmlc2.chem.uga.edu/sparc/> as of May 7, 2010.

## **2. General Information on Exposure**

### **2.1 Production Volume and Use Pattern**

According to the 2006 IUR submissions, CASRN 68610-51-5 had an aggregated production and/or import volume in the United States between 1 and 10 million pounds.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include resin and synthetic rubber manufacturing as stabilizers. No commercial and consumer uses were reported.

### **2.2 Environmental Exposure and Fate**

The environmental fate properties of CASRN 6810-51-5 are provided in Table 2.

CASRN 68610-51-5 is expected to have low mobility in soil. CASRN 68610-51-5 was reported to be not inherently biodegradable when tested using a modified Zahn-Wellens test (OECD 302B); however, no quantitative details of the study were supplied. Its use as an antioxidant suggests it has the potential to oxidize to the quinone like other sterically-hindered phenols which may lower its persistence in the environment. The rate of volatilization of CASRN 68610-51-5 from water and moist soil is considered low based on its estimated Henry's Law

constant. The rate of hydrolysis is considered negligible under environmental conditions. CASRN 68610-51-5 is expected to have moderate persistence (P2) and high bioaccumulation potential (B3).

<b>Table 2. Environmental Fate Characteristics of CASRN 68610-51-5<sup>1</sup></b>	
<b>Property</b>	<b>Value</b>
Photodegradation Half-life	0.3 hours (estimated) <sup>2,3</sup>
Hydrolysis Half-life	Stable
Biodegradation	Not inherently biodegradable
Bioaccumulation Factor	BAF = $5.7 \times 10^4$ (estimated) <sup>2,3</sup>
Log K <sub>oc</sub>	12.6 (estimated) <sup>2,3</sup>
Fugacity (Level III Model) <sup>2,3</sup>	
Air (%)	<0.1
Water (%)	0.7
Soil (%)	38.7
Sediment (%)	60.6
Persistence <sup>4</sup>	P2 (moderate)
Bioaccumulation <sup>4</sup>	B3 (high)

<sup>1</sup> Rubber and Plastic Additives Panel of The American Chemistry Council. July 2003. Revised Test Plan and Robust Summary for Phenol, 4-Methyl-, Reaction Products with Dicyclopentadiene and Isobutylene Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/hndrdphn/c13382tc.htm> as of May 7, 2010.

<sup>2</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of May 7, 2010.

<sup>3</sup> All estimations performed on a representative structure having approximate molecular weight of 650.

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

**Conclusion:** CASRN 68610-51-5 is a solid with negligible water solubility and negligible vapor pressure. It is expected to have low mobility in soil. Volatilization of CASRN 68610-51-5 is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered rapid; however, this is not expected to be an important environmental fate process because this substance is not expected to exist in the vapor phase in the atmosphere. CASRN 68610-51-5 is expected to have moderate persistence (P2) and high bioaccumulation potential (B3).

### 3. Human Health Effects

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

#### *Acute Oral Toxicity*

(1) Rats of an unspecified strain (5/sex) were administered the test substance in corn oil via a single oral dose of 5010 mg/kg and observed for 14 days after dosing. No mortalities occurred.  
**LD<sub>50</sub> > 5010 mg/kg**

(2) Sprague-Dawley rats (5/sex) were administered a single dose of 5000 mg/kg of the test substance in corn oil via gavage and observed for 15 days after dosing. No mortalities occurred.  
**LD<sub>50</sub> > 5000 mg/kg**

#### *Acute Dermal Toxicity*

New Zealand albino rabbits (2/sex) were administered the test substance in deionized water via the dermal route at a dose of 5010 mg/kg-bw under unspecified conditions for 24 hours and observed for 14 days after dosing. No mortalities occurred.  
**LD<sub>50</sub> > 5010 mg/kg-bw**

#### *Acute Inhalation Toxicity*

Male albino rats (strain not specified) were exposed to the test substance for one hour to an aerosol of ~ 200 mg/L test substance in a flow-through inhalation chamber. Nominal concentration was 165 mg/L. No mortalities occurred.  
**LC<sub>50</sub> > 165 mg/L**

#### *Repeated-Dose Toxicity*

(1) In a 28-day range-finding study, Sprague-Dawley rats (5/sex/group) were administered CASRN 68610-51-5 in the diet at 0, 1000, 5000, 10,000, 25,000 or 50,000 ppm (~ 0 (control), 60, 300, 600, 1500 and 3000 mg/kg-bw/day and ~ 0 (control), 50, 250, 500, 1250 and 2500 mg/kg-bw/day for males and females, respectively). During the first week of treatment, 3 rats (2 males and 1 female) died at 50,000 ppm and 1 male died at 25,000 ppm. Decreased body weight and food consumption were also observed at 25,000 and 50,000 ppm and hemorrhaging was noted at necropsy (sex not specified). The 25,000 and 50,000 ppm treatment groups were discontinued at 10 days due to systemic toxicity and mortality. At the 10,000 ppm dose, 1 male and 1 female died and internal hemorrhage was observed at necropsy. At 5000 and 10,000 ppm, dose-related increases in prothrombin time and activated partial thromboplastin time, measures of blood coagulation, were observed in males. Mean absolute and relative liver weight was increased (significance not stated) in female rats at 5000 and 10,000 ppm. Histopathology was not performed on any organs. The robust summary for this study did not include any information on clinical chemistry parameters. Therefore, biological significance of these organ weight changes is unknown. No mortalities were observed at 1000 and 5000 ppm.

**LOAEL (males) ~ 300 mg/kg-bw/day** (based on increased prothrombin time and activated partial thromboplastin time)

**NOAEL (males) ~ 60 mg/kg-bw/day**

**NOAEL (females) ~ 500 mg/kg-bw/day** (based on no treatment-related adverse effects observed at the adjusted highest dose tested)

(2) Sprague-Dawley rats (15/sex/group) were administered CASRN 68610-51-5 in the diet at 0, 500, 1500 or 4500 ppm (~ 0 (control), 30, 90 and 270 mg/kg-bw/day for males and ~ 0 (control), 25, 75 and 225 mg/kg-bw/day for females) for 90-days. No effects on body weight, food consumption, or clinical observations were seen. Prothrombin time and activated partial thromboplastin time were statistically significantly increased in males at 270 mg/kg-bw/day. Higher serum cholesterol occurred in females at 225 mg/kg-bw/day (statistical significance not specified). Liver weight (relative/absolute not specified) was statistically significantly increased in males at 270 mg/kg-bw/day and in females at 225 mg/kg-bw/day. At 225 mg/kg-bw/day, the weight of the adrenal gland (relative/absolute not specified) was statistically significantly increased in females. Histological evaluation of tissues showed no treatment-related changes. No other effects were reported. The biological significance of the organ weight changes is unknown since no corresponding evidence of histological and/or statistically significant clinical chemistry changes were reported.

**LOAEL (males) = ~ 270 mg/kg-bw/day** (based on higher prothrombin time and activated partial thromboplastin time)

**NOAEL (males) = ~ 90 mg/kg-bw/day**

**LOAEL (female) ~ 225 mg/kg-bw/day** (based on increased serum cholesterol)

**NOAEL (female) ~ 75 mg/kg-bw/day**

### ***Reproductive Toxicity***

There are no reproductive toxicity studies available with CASRN 68610-51-5. However, reproductive organs were evaluated in the 90-day repeated-dose toxicity study described previously. No treatment-related changes were noted for reproductive organs at doses up to 270 mg/kg-bw/day in males and 225 mg/kg-bw/day in females.

### ***Developmental Toxicity***

Timed-pregnant Sprague-Dawley rats (25/dose) were administered CASRN 68610-51-5 in corn oil via gavage at doses of 0, 1000, 2000 or 3000 mg/kg-day on gestation days 6 through 19. Pregnancy rates were not affected by treatment. No dams died, aborted or delivered early and there were no clinical signs of toxicity. Maternal body weight was not affected by treatment. Maternal body weight gain was significantly decreased at 3000 mg/kg-day on gestation days 6-9. At the 3000 mg/kg-day dose group, food consumption was significantly decreased on gestation days 6-9 and increased on gestation days 18 – 20. Mean maternal absolute and relative liver weights were significantly increased at all doses. No information on liver histopathology or clinical chemistry parameters was provided in the robust summaries, therefore, the biological significance of these weight changes is not known. The percentage of fetuses with variations on a per litter basis was increased at all doses when sexes were combined, as indicated by treatment-related increases in the incidence of rudimentary rib on lumbar 1 and reduced ossification in the

thoracic centra. Fetuses with skeletal variations numbered 3, 65, 72 and 94 in controls, 1000, 2000 or 3000 mg/kg/day doses, respectively. No other effects were reported. The robust summary noted that the consequences of these fetal skeletal variations are unknown in the absence of effects on fetal body weight. Benchmark dose analysis on the incidence of the fetal skeletal variations was performed by the study authors to estimate a dose ED<sub>05</sub> associated with a 5% increase relative to controls. The resulting ED<sub>05</sub> was 740 mg/kg-day.

**LOAEL (maternal toxicity) = 3000 mg/kg-day** (based on decreases in body weight gain)

**NOAEL (maternal toxicity) = 2000 mg/kg-day**

**LOAEL (developmental toxicity) = 1000 mg/kg/day** (based on skeletal variations)

**NOAEL (developmental toxicity) = 740 mg/kg-day** (benchmark dose calculation)

### ***Genetic Toxicity – Gene Mutation***

#### ***In vitro***

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2uvrA were exposed to the test substance dissolved in DMSO at concentrations of 5, 10, 50, 100, 500, 1000 or 5000 µg/plate (range-finding assay) or 100, 250, 500, 750 or 1000 µg/plate (definitive assay) with and without metabolic activation (rat liver S9). Negative and positive controls were included. No positive control response data were provided. Cytotoxicity was observed at 1000 µg/plate without metabolic activation and at all doses with metabolic activation. Precipitation was observed at concentrations ≥ 1000 µg/plate.

**CASRN 68610-51-5 was not mutagenic in this assay.**

(2) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to the test substance dissolved in ethanol at concentrations of 50, 167, 500, 1670 or 5000 µg/plate with and without metabolic activation (rat liver S9). Solvent and positive controls were included. No positive control response data were provided. A preliminary range-finding test of concentrations ranging from 50 to 5000 µg/plate noted cytotoxicity and precipitation at 5000 µg/plate.

**CASRN 68610-51-5 was not mutagenic in this assay.**

(3) CHO-K1-BH4 Chinese hamster ovary (CHO) cells were exposed to the test substance dissolved in DMSO at concentrations of 100, 200, 400, 600, 800 or 1000 µg/mL with and without metabolic activation. Solvent, negative and positive controls were included. Results of positive control testing were not specified. Mutation assays indicated that the test substance was moderately toxic without activation at high-dose levels and weakly toxic with activation at all dose levels.

**CASRN 68610-51-5 was not mutagenic in this assay.**

### ***Genetic Toxicity – Chromosomal Aberrations***

#### ***In vitro***

CHO cells were exposed to the test substance at concentrations ranging from 0.0333 to 1010 µg/mL for ~ 23 hours in the presence and absence of metabolic activation in a range-finding assay. In a second test, CHO cells were exposed at concentrations of 100, 250, 500, 750 or 1000 µg/mL for 10 or 20 hours (in the presence of metabolic activation) or 50.0, 100, 225 or 300

µg/mL for 20 hours (in the absence of metabolic activation). Solvent (DMSO), negative and positive controls were included. Positive control responses were not specified. Without metabolic activation, total cellular toxicity was observed at 1010 µg/mL, severe cell cycle delay was observed at 101 and 337 µg/mL and a marked reduction in the mitotic index was seen in cultures exposed to 99.7, 332 or 997 µg/mL. No cell cycle delays or significant reductions in mitotic index were observed in cultures with metabolic activation. Slight toxicity was observed at 1010 µg/mL with metabolic activation.

**CASRN 68610-51-5 did not induce chromosomal aberrations in this assay.**

### *Genetic Toxicity – Other*

#### *In vitro*

*Escherichia coli* strains W3110 (pol A+) and p3478 (pol A1-) were exposed to the test substance at concentrations of 10, 100, 320 or 1000 µg/plate without metabolic activation or 10, 100 or 1000 µg/plate with metabolic activation.

**CASRN 68610-51-5 did not induce DNA damage in this assay.**

### *Additional Information*

#### *Skin Irritation*

(1) Six New Zealand White rabbits (sex not specified) were administered 0.5 grams of the test substance via dermal application to intact and abraded skin for 24 hours under semi-occluded conditions. Observations were made at 24 and 72 hours after exposure stopped. No skin irritation was observed.

**CASRN 68610-51-5 was not a skin irritant in this study.**

(2) Rabbits (strain and sex not specified) were administered 0.5 g of test substance via dermal application to the intact skin of two groups (one for 4 hours and the other for either 6 or 24 hours – the robust summary is unclear. No other study details were provided. No skin irritation occurred.

**CASRN 68610-51-5 was not a skin irritant in this study.**

(3) New Zealand White rabbits (3/sex) were administered 500 mg of the test substance via dermal application to intact skin on three separate sites (2 sites on the upper dorsal area and 1 site on the mid-dorsal area) under occluded conditions. The total exposure for the three sites was 1500 mg. Exposure durations were 3 minutes and 60 minutes for the upper dorsal sites and 4 hours for the mid-dorsal site. Skin irritation was evaluated at 24, 48, and 72 hours. Very slight erythema was observed after exposures of 1 and 4 hours.

**CASRN 68610-51-5 was slightly irritating to rabbit skin in this study.**

### ***Eye Irritation***

Six New Zealand White rabbits (sex not specified) were administered 0.1 g (or 40 mg – both amounts are listed in the robust summary) the test substance for 24 hours. No other study details were provided.

**CASRN 68610-51-5 was slightly irritating to the rabbit eye in this study.**

### ***Sensitization***

In a guinea pig maximization test, Hartley guinea pigs (10/sex) were administered the test substance during the intradermal induction phase as a 5% solution (vehicle not specified) via intradermal injection at three sites (0.1 ml each) between the shoulders. After 1 week, the skin was occluded with 25% (w/v) of the test substance in petrolatum for 48 hours during the topical induction phase. Two weeks later, test animals were challenged with dermal application of 5% (w/v) test substance under occluded conditions for 24 hours and assessed for skin reactions at 24 and 48 hours. Animals were challenged again 6 days later with 5% test substance. Controls included petrolatum vehicle (10/sex) and positive (3/sex; 0.1% 1-chloro-2,4-dinitrobenzene) controls, but results were not specified. Mild dermal sensitization (Grade II) was observed following dermal challenge and rechallenge with 5% of the test substance.

**CASRN 68610-51-5 was sensitizing in the guinea pig maximization test.**

### ***Absorption, Distribution and Excretion***

BRL-HAN Wister rats (4/sex) were administered the test substance as a single oral dose via gavage at average doses of 29.3 mg/kg in males and 29.9 mg/kg in females and observed for 7 days following dosing. The specific radioactivity and the concentration of the administration were 3.87  $\mu\text{Ci}/\text{mg}$  and 3.01 mg/mL, respectively. Approximately 90% of the dose was excreted in feces 48 hours after dosing. An additional 1.9 – 2.9% was excreted in feces over the next 5 days. Urinary excretion during 7 days postdosing amounted to 0.1 – 0.2% of the dose. Only 1.5 – 2.4% of the radioactivity remained in the tissue after 7 days, the highest concentration being in the fat.

**CASRN 68610-51-5 was rapidly excreted in this study.**

**Conclusion:** The acute oral toxicity and acute dermal toxicity of CASRN 68610-51-5 in rats and rabbits, respectively, are low. Dietary exposure of rats to CASRN 68610-51-5 for 90 days resulted in increases in prothrombin times and activated partial thromboplastin times at 270 mg/kg-bw/day in males, and higher serum cholesterol levels at 225 mg/kg-bw/day in females; the NOAEL for systemic toxicity is 90 mg/kg-bw/day in males and 75 mg/kg-bw/day in females. No reproductive toxicity studies with CASRN 68610-51-5 are available; however, a 90-day repeated-dose toxicity study showed no effects on reproductive organs with doses up to 225 mg/kg-bw/day in females and 270 mg/kg-bw/day in males. In an oral gavage prenatal developmental toxicity study in rats with CASRN 68610-51-5, depressed weight gain occurred in the dams at 3000 mg/kg-day; the NOAEL for maternal toxicity is 2000 mg/kg-day. Fetuses exhibited increased incidences of common fetal skeletal variations at 1000 mg/kg-day, the lowest dose tested; the NOAEL for developmental toxicity is 740 mg/kg-day (benchmark dose). CASRN 68610-51-5 did not induce gene mutation in bacterial and mammalian cells *in vitro*,

chromosomal aberrations in Chinese hamster ovary cells *in vitro* or DNA damage in *Escherichia coli*. CASRN 68610-51-5 was slightly irritating to rabbit skin and eyes and was a dermal sensitizer in guinea pigs.

<b>Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data</b>	
<b>Endpoints</b>	<b>SPONSORED CHEMICAL 4-Methylphenol, reaction products with dicyclopentadiene and isobutylene (68610-51-5)</b>
<b>Acute Oral Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>&gt; 5000</b>
<b>Acute Dermal Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>&gt; 5010</b>
<b>Acute Inhalation Toxicity LC<sub>50</sub> (mg/L)</b>	<b>&gt; 165</b>
<b>Repeated-Dose Toxicity NOAEL/LOAEL Oral diet (mg/kg-bw/day)</b>	<b>NOAEL ~ 90 (males) LOAEL ~ 270(males) NOAEL ~ 75 (female) LOAEL ~ 225 (female)</b>
<b>Reproductive Toxicity NOAEL/LOAEL Oral diet (mg/kg-bw/day)  Reproductive Toxicity</b>	Reproductive organs were evaluated in a 90-day, repeated-dose toxicity study. No effects were observed at doses up to 270 mg/kg-bw/day in males and 225 mg/kg-bw/day in females.
<b>Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-day) maternal toxicity  developmental toxicity</b>	<b>NOAEL = 2000 LOAEL = 3000 NOAEL = 740 LOAEL = 1000</b>
<b>Genetic Toxicity – Gene Mutation <i>In vitro</i></b>	<b>Negative</b>
<b>Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i></b>	<b>Negative</b>

<b>Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data</b>	
<b>Endpoints</b>	<b>SPONSORED CHEMICAL 4-Methylphenol, reaction products with dicyclopentadiene and isobutylene (68610-51-5)</b>
<b>Additional Information</b> <b>Skin irritation</b> <b>Eye irritation</b> <b>Dermal Sensitization</b>	<b>Slightly irritating</b> <b>Mildly irritating</b> <b>Positive (guinea pig)</b>

#### **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 68610-51-5 at a nominal concentration of 0.2 mg/L for 96-hrs under semi-static conditions. Measured concentrations were only made for stock solutions of the test chemical in methanol (20 and 2 mg/L) and represented mean measured concentrations of 93 and 101% of the respective nominal stock solutions. The final test concentration (0.2 mg/L) was achieved by adding dilution water to the 2 mg/L stock solution. No precipitation of the test substance was observed. Two controls were included (0.01% methanol and dilution water). No mortalities were observed in fish exposed to the solubility limit of the test substance (0.2 mg/L).

**96-h LC<sub>50</sub> > 0.2 mg/L**

##### ***Acute Toxicity to Aquatic Invertebrates***

Water fleas (*Daphnia magna*) were exposed to CASRN 68610-51-5 at a nominal concentration of 0.2 mg/L for 48-hrs under semi-static conditions (renewal every 24 hours). Measured concentrations were not provided. Stock solutions of the test chemical at 20 and 2 mg/L were prepared by dilution of test chemical in methanol. The final test concentration was made by diluting the 2 mg/L stock solution with water. No precipitation of the substance was observed. *Daphnia* experienced no immobility after exposure to the water solubility limit of the test substance (0.2 mg/L).

**48-h EC<sub>50</sub> > 0.2 mg/L**

##### ***Toxicity to Aquatic Plants***

Green algae (*Pseudokirchneriella subcapitata*) were exposed to CASRN 68610-51-5 at a nominal concentration of 0.2 mg/L for 72-hrs under static condition. Measured concentrations were only made for stock solutions of the test chemical in methanol (20 and 2 mg/L) and represented mean measured concentrations of 93 and 101% of the respective nominal stock solutions. The final test concentration (0.2 mg/L) was achieved by adding dilution water to the 2

mg/L stock solution. The growth rate of algae exposed to the test substance was found to be comparable to that of the negative controls.

**72-h ErC<sub>50</sub> > 0.2 mg/L**

**Conclusion:** The 96-hr LC<sub>50</sub> of CASRN 68610-51-5 for fish, is >0.2 mg/L. The 48-hr EC<sub>50</sub> of CASRN 68610-51-5 for aquatic invertebrates is >0.2 mg/L, and the 72-hr EC<sub>50</sub> for aquatic plants is >0.2 mg/L (growth rate).

<b>Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Aquatic Toxicity Data</b>	
<b>Endpoints</b>	<b>4-Methylphenol, reaction products with dicyclopentadiene and isobutylene (CASRN 68610-51-5)</b>
<b>Fish</b> <b>96-h LC<sub>50</sub> (mg/L)</b>	<b>&gt; 0.2</b>
<b>Aquatic Invertebrates</b> <b>48-h EC<sub>50</sub> (mg/L)</b>	<b>&gt; 0.2</b>
<b>Aquatic Plants</b> <b>72-h EC<sub>50</sub> (mg/L)</b> <b>(growth rate)</b>	<b>&gt; 0.2</b>
<b>Chronic Toxicity to Invertebrates</b> <b>21-day EC<sub>50</sub> (mg/L)</b>	No data

**Bold= measured data**