SCREENING-LEVEL HAZARD CHARACTERIZATION
C_5-Non-Cyclics Category

Sponsored Chemicals
10 Different Process Streams Which Include 16 Different CAS Registry Numbers
(See Section 1.0 for Details)

The High Production Volume (HPV) Challenge Program[1] 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. These documents are presented in an international forum that involves review and endorsement by governmental

[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.

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.

CASRN	**10 Different Process Streams, Each Containing One or More of 16 Different CASRNs (See Section 1.0)**
Chemical Name	**C_5 Non-Cyclics Category**
Structural Formula	**See Section 1.0**

Summary

The C_5 non-cyclics category is comprised of 10 "streams"- eight of which are mixtures and two of which are relatively pure substances. The hazard data set for this category is based on testing in two of the eight mixtures and also with the two pure substances.

The complex mixtures in the C_5 non-cyclic category are volatile liquids which contain components possessing moderate water solubility and high vapor pressure. The various individual components of the C_5 non-cyclic category are expected to have high mobility in soil. Volatilization is expected to be high for most of the components of these complex mixtures given the Henry's Law constants of these substances. The rate of atmospheric photooxidation is considered moderate. The weight of evidence suggests that the members of this category have low (P1) to moderate (P2) persistence and low bioaccumulation potential (B1).

The acute toxicity of C_5 non-cyclics category members is low via oral, dermal and inhalation routes. All the repeated-dose studies with the four substances tested (two stream mixtures and two pure substances) used inhalation as the route of exposure. Combined repeated-dose/reproductive/ developmental toxicity studies in rats were performed with the two streams. One stream (pyrolysis $C_{5's}$ - a mixture with five CASRNs) showed no effects at the highest concentration tested after 28 days of exposure (1012 ppm). Exposure to the other stream (hydrotreated $C_{5's}$ – a mixture with three CASRNs) caused general (unspecified) systemic and kidney effects in males (at the lowest concentration tested – 992 ppm) and kidney and nasal turbinate effects in females at the mid-concentration (3033 ppm).

In a similar combined repeated-dose/reproductive/developmental toxicity study in rats, inhalation exposure to CASRN 513-35-9 induced lesions in the heart and kidneys of males in the mid-concentration group (5.72 mg/L, or 2000 ppm). The other pure substance (CASRN 78-79-5) was extensively studied by the NTP and others in both rats and mice. In multiple repeated-dose studies, mice appeared more susceptible to toxicity than rats. Effects were seen at concentrations as low as 0.613 mg/L (220 ppm) in rats (spleen and kidney effect s in males following 104 weeks of exposure) and 0.195 mg/L (70 ppm) in mice (spinal cord degeneration, respiratory and olfactory epithelial changes, and effects on the forestomach and Harderian gland from 26 weeks

to 80 weeks of exposure).

The combined studies performed with the two streams and CASRN 513-35-9 showed no effects on measured reproductive parameters up to the highest tested inhalation concentrations (20 mg/L [7000 ppm] for 513-35-9, 8502 ppm for hydrotreated $C_{5's}$, and 1012 ppm for pyrolysis $C_{5's}$). Although there were no conventional reproductive toxicity studies conducted with CASRN 78-79-5, reproductive organs were evaluated in NTP 13 week studies and the following effects were observed: increased incidence of interstitial cell hyperplasia of the testes in rats (at the highest tested dose of 19.5 mg/L, or 7000 ppm), and increases in estrous cycle length, testicular atrophy, and sperm effects (spermatid head count, sperm concentration, motility), and decreased epididymal weight – all in mice and all at concentrations of 1.95 mg/L (700 ppm) and higher.

The combined studies performed with the two streams and CASRN 513-35-9 showed no effects on measured developmental toxicity parameters up to the highest tested inhalation concentrations (20 mg/L, or 7000 ppm for CASRN 513-35-9, 8502 ppm for hydrotreated $C_{5's}$, and 1012 ppm for pyrolysis $C_{5's}$). However, maternal toxicity was observed in two of the three studies (hematological/spleen effects at the highest tested concentration of 20 mg/L in the CASRN 513-35-9 study and effects on nasal turbinates and the kidney at the mid-concentration of 3033 ppm in the hydrotreated $C_{5's}$ study). Conventional prenatal developmental toxicity studies in rats and mice with CASRN 78-79-5 via the inhalation route showed some maternal toxicity in both species (increased kidney weights in rats reduced maternal body weight gain and increased relative kidney, uterine and liver weights in mice; all at the highest tested concentration of 19.5 mg/L, or 7000 ppm). Developmental toxicity was only observed in the mouse study (reduced fetal body weights at the lowest tested concentration of 0.78 mg/L, or 280 ppm).

The four members of the C_5 non-cyclics category which were tested in i*n vitro* gene mutation assays in bacteria did not cause gene mutations and so read-across for this negative effect across all members is appropriate. However, for chromosomal effects, the two tested streams were negative whereas the CASRNs 78-79-5 and 513-35-9 were positive for inducing chromosomal effects in both *in vitro* and *in vivo* assays (see Table 5 for read-across conclusions). Limited data with CASRNs 78-79-5 and 513-35-9 show these chemicals to be mildly irritating to rabbit skin. CASRN 78-79-5 was shown to be irritating to eyes (no specific information provided on species). CASRN 513-35-9 did not cause eye irritation or skin sensitization in rabbits and guinea pigs, respectively. CASRN 78-79-5 has been shown to be carcinogenic in rats and mice in NTP studies.

The acute toxicity to fish is 5.0- 8.4 mg/L, to aquatic invertebrates is 3.0 -5.8 mg/L, and to aquatic plants is 10.1- 15.5 mg/L (biomass) and 13.2-18.4 mg/L (growth rate) for the chemicals in the C_5 Non-cyclics Category.

No data gaps are identified under the HPV Challenge Program.

Hazard Characterization of

C_5 Noncyclics Category

The sponsor, the American Chemistry Council (ACC) Olefins Panel, submitted a Test Plan and Robust Summaries to EPA for the "C_5 Non-cyclics Category" on November 6, 2000. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 1, 2000 (http://www.epa.gov/chemrtk/pubs/summaries/c5ncyl/c12801tc.htm). EPA comments on the original submission were posted to the website on March 29, 2001. Public comments were also received and posted to the website. The sponsor submitted revised and final documents which were posted to the ChemRTK HPV Challenge Website on January 11, 2002, May 4, 2004, and February 1, 2005 for the revised, and February 2, 2005 for the final documents. The C_5 Non-cyclics Category contains information for substances described by 16 CAS numbers that are associated with 10 process streams (See Section 1 below).

Category Justification

The category consisting of 10 C_5 non-cyclics production streams was based on the structural similarity between chemical constituents in the streams and substantial overlap of stream compositions (see Section 1 below for details on the streams and their constituents). Two of the streams, Pyrolysis C_5s and Hydrotreated C_5s, contain a range of chemical constituents largely found in most of the other complex streams and from which most of the other streams are derived. Two of the streams are considered single, pure substances: isoprene (CASRN 78-79-5) and 2-methyl-2-butene (2M2B) (CASRN 513-35-9); each of which are found in most of the other streams in the category. The available human health, environmental effects and environmental fate data for all endpoints other than biodegradation, were sufficiently similar to consider the substances described above a category. For the human health effects endpoints, the 10 category members are divided into two subgroups for read-across purposes. The divisions are based on constituent content of each stream (see Appendix) and are described in further detail in the human health section.

Isoprene and 2-methyl-2-butene have been assessed in the OECD HPV program and the data can be reviewed at the following website: http://cs3-hq.oecd.org/scripts/hpv/ , clicking on search in the left-hand column and typing in the appropriate CASRNs (79-78-5 and 513-35-9, respectively).

1 Chemical Identity

1.1 Identification and Purity

The 10 streams in the C_5 non-cyclics category include eight process streams that are complex mixtures and two streams that contain relatively high purity hydrocarbons; all streams are composed predominantly of C_5 hydrocarbons. These streams contain significant levels of olefins. Table 1 below is taken directly from a document submitted by the sponsor. The Appendix contains both a table listing the predominant constituents for each stream and a figure showing how the streams are made and used.

Table 1[1]: Production Streams, CAS Numbers[2] and CASRN Names		
Streams	**CAS Nos.**	**CAS RN Names**
Pyrolysis C_5s (23)[4]	68476-55-1[3]	Hydrocarbons, C_5-rich
	68476-43-7	Hydrocarbons, C_4-C_6, C_5-rich
	68527-19-5	Hydrocarbons, C_{1-4}, debutanizer fraction
	68603-00-9	Distillates, petroleum, thermal cracked naphtha and gas oil
	68956-55-8	Hydrocarbons, C_5-unsaturated
Hydrotreated C_5s (15)	68602-79-9[5]	Distillates, petroleum, benzene unit hydrotreater dipentanizer overheads
	68410-97-9	Distillates, petroleum, light distillate hydrotreating process, low-boiling
	68603-00-9	Distillates, petroleum, thermal cracked naphtha and gas oil
Pentenes (9)	68476-55-1	Hydrocarbons, C_5-rich
	68527-11-7	Alkenes, C_5
	68603-03-2	Distillates, petroleum, thermal cracked naphtha and gas oil, extractive
Piperylene Concentrates (17)	68477-35-0	Distillates, petroleum, C_{3-6}, piperylene-rich
	64742-83-2	Naphtha, petroleum, light steam-cracked,
Isoprene Concentrates (19)	68514-39-6	Naphtha, petroleum, light steam-cracked, isoprene-rich
	68476-43-7	Hydrocarbons, C_4-C_6, C_5-rich
	78-79-5	1,3-Butadiene, 2-methyl-
Isoprene-Piperylene Concentrates (13)	68514-39-6	Naphtha, petroleum, light steam-cracked, isoprene-rich
	68476-55-1	Hydrocarbons, C_5-rich
Isoprene, High Purity (1)	78-79-5	1,3-Butadiene, 2-methyl-
Isoprene Purification Byproducts (9)	68606-36-0	Hydrocarbons, C_5-unsaturated rich, isoprene purification by-product
	68476-55-1	Hydrocarbons, C_5-rich
2-Methyl-2-Butene (2)	513-35-9	2-Butene, 2-methyl-
Metathesis Byproduct (7)	68606-29-1	Hydrocarbons, C_4 and C_8, butane concentrator by-product

[1]This table is reproduced from Table 1, which is on p. 1 in *US High Production Volume Chemical Program Category Summary for C5-Noncyclics Category* (dated December 13, 2004) and available at http://www.epa.gov/chemrtk/pubs/summaries/c5ncyl/c12801tc.htm - click on revised test plan next to February 2, 2005 date. Footnotes 2 and 5 below are taken verbatim from footnotes 1 and 3 in the cited table.

[2] "The CAS numbers associated with corresponding production streams are shown in the table above. The definitions found in the TSCA Chemical Substance Inventory of the CAS RNs in this category can be vague with respect to composition. Therefore, it is not uncommon to find that one CAS RN is correctly used to describe different streams (different compositions) or that two or more CAS RNs are used to describe one stream (similar composition). The Olefins Industry or others may use these same CAS RNs to represent substances that may, in various degrees, be dissimilar to the category streams. CAS RNs, other than those shown in this table, may be used to describe these streams in future reporting."

[3] Substances with the same highlighted color are found in more than one stream.

[4] This number represents the total number of possible components in each stream. The number was generated by tallying the information in Table 2 (pp.3-5 in *Category Summary* document cited above).

[5] "This CAS RN was not included in the original list of CAS RNs sponsored in this category. It has been added to this category summary report because it is an additional CAS RN that is sometimes used to represent the indicated process stream."

This is one of 10 categories that the same sponsor (ACC Olefins Panel) has submitted to the US HPV Challenge Program that, in addition to having structurally similar members, are formed from a series of process reactions resulting in complex mixtures that are not easily characterized. The figure in the Appendix provides a flow-chart showing how the 10 C_5 non-cyclics process streams are created.

As shown in Table 1 above, 8/10 streams are complex mixtures with many components and so purity of these mixtures is not a relevant attribute. For the two other streams, purity is 99.7% (isoprene) and 93% (2-methyl-2-butene). For the latter substance, there is one major impurity (6.7%, 2-methyl-1-butene). For many streams, substances (antioxidants) are added (and so may be considered impurities) with a target concentration of 10-50 ppm.

1.2 Physical-Chemical Properties

A summary of the physical-chemical properties for the CASRNs in the C_5 non-cyclics category is provided in Table 2.

The process streams of the C_5 non-cyclic category members are - with two exceptions - complex mixtures of varying composition. It is unclear what some of the physical chemical properties in Table 2 mean for such mixtures. As an example, in the case of water solubility, the mixture in the water phase will be clearly different from that in the unsolubilized phase and the chemicals in the water phase might affect the amount of chemicals solubilized. An analogous situation occurs with the octanol-water partition coefficient and other physical chemical properties. Therefore, one must interpret the measured values carefully. Where measured values are unavailable, ranges of values for the common components of the category members are listed.

Table 2. Physical-Chemical Properties of the Process Streams that Characterize the C_5 Non-Cyclic Category[1]

Property	Pyrolysis C_5s (or C_5 Fraction)[2]	Hydrotreated C_5s[3]	Pentenes	Piperylene Concentrates	Isoprene Concentrate	Isoprene-Piperylene Concentrate	Metathesis Byproduct	Isoprene Purification Byproduct	2-Methyl-2-Butene	Isoprene High Purity
CASRN	68476-55-1, 68476-43-7, 68527-19-5, 68603-00-9, 68956-55-8	68602-79-9, 68410-97-9, 68603-00-9	68476-55-1, 68527-11-7, 68603-03-2	68477-35-0, 64742-83-2	68514-39-6, 68476-43-7, 78-79-5	68514-39-6, 68476-55-1	68606-29-1	68606-36-0, 68476-55-1	513-35-9	78-79-5
Molecular Weight	Complex mixture								70.1	68.1
Physical State	Volatile liquid									
Melting Point	**-168.5 to -105.5°C (measured)[1,4]**								**-133.7°C (measured)**	**-145.9°C (measured)**
Boiling Point	**25.0–56.5°C (measured)**	**23.5–52.0°C (measured)**	**23.5–56.5°C (measured)[2,3]; 0.8–44.2°C(measured)[1,4]**						**38.5°C (measured)**	**34°C (measured)**
Vapor Pressure	**439 mm Hg at 25°C (measured)**	**617 mm Hg at 25°C (measured)**	**439–617 mm Hg at 25°C (measured)[2,3]; 380–1,752 mm Hg at 25°C(measured)[1,4]**						**468 mm Hg at 25°C (measured)**	**550 mm Hg at 25°C (measured)**
Dissociation Constant (pK_a)	Not applicable									
Henry's Law Constant	**0.064–1.4 atm-m^3/mole (measured)[4,5]**								**0.22 atm-m^3/mole (measured)[5]**	**0.077 atm-m^3/mole (measured)[5]**
Water Solubility	**720 mg/L at 20°C (measured)**	**910 mg/L at 20°C (measured)**	**720–910 mg/L at 20°C(measured)[2,3]; 49.8–910 mg/L at 25°C (measured)[1,4]**						**206.1 mg/L at 25°C (measured)**	**338.6 mg/L at 25°C (measured)**
Log K_{ow}	**3.19–3.25 at 21.0°C (measured)**	**2.64–4.21 at 21.5°C (measured)**	**2.64–4.21 (measured)[2,3]; 2.31–3.39 (measured)[1,4]**						**2.67 (measured)**	**2.42 (measured)**

[1]American Chemical Council Olefins Panel of the. December 7 and December 16, 2004. Revised Robust Summary and Test Plan for C_5 Non-Cyclic Category. http://www.epa.gov/chemrtk/pubs/summaries/c5ncyl/c12801tc.htm

[2]The complex mixture identified as the pyrolysis C_5 stream consisted of isoprene (18%), *cis*- and *trans*-pentadiene-1,3 (16%), cyclopentadiene + dicyclopentadiene (14%), *n*-pentane (10%), cyclopentene (7%), 2-methyl-2-butene (3%), and cyclopentane (1%). The balance consists of other hydrocarbons with similar boiling points (C_5s).

[3]The complex mixture identified as the hydrotreated C_5 stream consisted of 1,3-butadiene (7%), isopentane (8%), *n*-pentane (15%), *cis*- and *trans*-pentene-2 (12%), 2-methyl-2-butene (8%), cyclopentene (22%), cyclopentane (8%), and balance (20%).

[4]Data range represents measured values when available for representative constituent compounds: *trans*-butene-2, *cis*-pentene-2, 3-methyl-1-butene, 1,4-pentadiene, isopentane, isoprene, *n*-pentane, 2-methyl-2-butene, and cyclopentene.

[5]SRC. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available from http://www.syrres.com/esc/physprop.htm as of November 25, 2008.

2 General Information on Exposure

2.1 Production Volume and Use Pattern

Chemicals in the C_5 non-cyclics category had an aggregated production and/or import volume in the United States of greater than 6.8 billion pounds during calendar year 2005 (Table 3). There are a total of sixteen CASRNs representing the 10 process streams in this category. Four CASRNs had no IUR submissions: CASRNs 68603-00-9; 68602-79-9; 68603-03-2; and 68606-29-1.

Table 3: Production Volumes Reported for C_5 Noncyclic Streams

Streams	CAS Nos.	Production Volume for 2005
Pyrolysis C_5s	68476-55-1[1]	Greater than 1 billion pounds
	68476-43-7	Greater than 1 billion pounds
	68527-19-5	Greater than 1 billion pounds
	68603-00-9	No reported submissions in IUR
	68956-55-8	100 million to 500 million pounds
Hydrotreated C_5s	68602-79-9	No reported submissions in IUR
	68410-97-9	Greater than 1 billion pounds
	68603-00-9	No reported submissions in IUR
Pentenes	68476-55-1	Greater than 1 billion pounds
	68527-11-7	100 million to 500 million pounds
	68603-03-2	No reported submissions in IUR
Pyperylene Concentrates	68477-35-0	100 million to 500 million pounds
	64742-83-2	Greater than 1 billion pounds
Isoprene Concentrates	68514-39-6	500 million to 1 billion pounds
	68476-43-7	Greater than 1 billion pounds
	78-79-5	500 million to 1 billion pounds
Isoprene-Pyperylene Concentrates	68514-39-6	500 million to 1 billion pounds
	68476-55-1	Greater than 1 billion pounds
Isoprene, High Purity	78-79-5	500 million to 1 billion pounds
Isoprene Purification Byproducts	68606-36-0	500 million to 1 billion pounds
	68476-55-1	Greater than 1 billion pounds
2-Methyl-2-Butene	513-35-9	10 million to 50 million pounds
Metathesis Byproduct	68606-29-1	No reported submissions in IUR

[1] Substances with the same highlighted color are found in more than one stream.

Two of the twelve chemicals with IUR submissions reported processing and use information. Non-confidential information in the IUR[4] for CASRN 78-79-5 indicated that the industrial processing and uses of the chemical include processing as an intermediate in petrochemical and resin and synthetic rubber manufacturing, and that the commercial and consumer products containing the chemical include rubber and plastic products.

[4] USEPA, 2006. Inventory Update Reporting Database. v. 1.02.

The HPV submission for this category states that the category chemicals are used as: intermediates to produce other streams in the category; intermediates to produce hydrocarbon resins or elastomers; and feedstocks for motor gasoline production.[5]

The Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS) dossier for 1,3-butadiene, 2-methyl- (CASRN 78-79-5) states that the chemical is used as a chemical intermediate to manufacture primarily polymers. Other uses include manufacture of specialty chemicals, intermediates and derivatives, which are then used in the production of vitamins, pharmaceuticals, flavorings and perfumes, and epoxy hardeners.[6] The SIDS dossier for 2-butene, 2-methyl- (CASRN 513-35-9) states that this chemical is used as a chemical intermediate, primarily in the production of isoprene and hydrocarbon resins. It is also used as an intermediate in the production of tertiary pentyl alcohol and as a constituent of gasoline (typically at levels below 1%).[7]

The Hazardous Substances Data Bank (HSDB) for 1,3-butadiene, 2-methyl- (CASRN 78-79-5) states that the chemical is used in the manufacture of polyisoprene and butyl rubber.[8] The HSDB for 2-butene, 2-methyl- (CASRN 513-35-9) states that the chemical is used as a chemical intermediate for isoprene and as an additive for high octane fuel.[9]

2.2 Environmental Exposure and Fate

Although there is no quantitative information available on releases of these chemicals to the environment, there is potential for environmental releases to various media including water, land and air.

As noted earlier, 8/10 process streams of the C_5 non-cyclic category members are complex mixtures of varying composition. It is unclear what some of the environmental fate characteristics in Table 4 might mean. For example, the residue mixture in a biodegradation study will be different than the original mixture, being enriched in the less biodegradable components. Therefore, one must interpret the measured values carefully. Where measured values are unavailable, ranges of values for the common components of the category members are listed.

[5] Olefins Panel of the American Chemistry Council, December 13, 2004. Category Summary for C5 Non-cyclics Category. Accessed, 12/10/08. http://www.epa.gov/chemrtk/pubs/summaries/c5ncyl/c12801rt3.pdf.
[6] OECD, 2007. Organization for Economic Cooperation and Development. Isoprene (CAS No: 78-79-5). Accessed, 01/02/09. http://www.chem.unep.ch/irptc/sids/OECDSIDS/78795.pdf.
[7] OECD, 2007. Organization for Economic Cooperation and Development. 2-Methyl-2-butene (CAS No: 513-35-9). Accessed, 01/02/09. http://www.chem.unep.ch/irptc/sids/OECDSIDS/513359.pdf.
[8] HSDB, 2008. Hazardous Substances Data Bank. 1,3-Butadiene, 2-methyl- (CASRN 78-79-5). Accessed, 12/31/08. http://toxnet.nlm.nih.gov/.
[9] HSDB, 2008. Hazardous Substances Data Bank. 2-Butene, 2-methyl- (CASRN 513-35-9). Accessed, 12/31/08. http://toxnet.nlm.nih.gov/.

Table 4. Environmental Fate Properties of the Process Streams that Characterize the C_5 Non-Cyclic Category[1]

Property	Pyrolysis C_5s (or C_5 Fraction)[2]	Hydrotreated C_5s[3]	Pentenes	Piperylene Concentrates	Isoprene Concentrate	Isoprene-Piperylene Concentrate	Metathesis Byproduct	Isoprene Purification Byproduct	2-Methyl-2-Butene	Isoprene High Purity
CASRN	68476-55-1, 68476-43-7, 68527-19-5, 68603-00-9, 68956-55-8	68602-79-9, 68410-97-9, 68603-00-9	68476-55-1, 68527-11-7, 68603-03-2	68477-35-0, 64742-83-2	68514-39-6, 68476-43-7, 78-79-5	68514-39-6, 68476-55-1	68606-29-1	68606-36-0, 68476-55-1	513-35-9	78-79-5
Photodegradation Half-life	1.2–31.8 hours (estimated)[1,4]								1.5 hours (estimated)	1.2 hours (estimated)
Biodegradation	8% after 28 days (not readily biodegradable) 0% after 28 days (not readily biodegradable)	51% after 28 days (not readily biodegradable); 0–19% after 28 days (not readily biodegradable)	0–51% after 28 days (not readily biodegradable)[2,3]						4–10% after 28 days (not readily biodegradable); 0% after 28 days (not readily biodegradable)	60% after 28 days (readily biodegradable); 53–75% after 28 days (readily biodegradable)
Hydrolysis	Stable									
Log K_{oc}	1.6–1.9 (estimated)[4,5]								1.8 (estimated)[5]	1.8 (estimated)[5]
Bioconcentration	BCF = 12–25 (estimated)[4,5]								BCF = 16 (estimated)[5]	BCF = 5-20 (measured in carp)[6] ; BCF = 15 (estimated)[5]
Fugacity (Level III Model)[4,5]										
Air	1–42%								1%	4%
Water	54–94%								94%	90%
Soil	1–7%								4%	5%
Sediment	<1–1%								1%	<1%
Persistence[7]	P1 (low) to P2 (moderate)	P1 (low) to P2 (moderate)	P1 (low) to P2 (moderate)	P1 (low) to P2 (moderate)	P1 (low) to P2 (moderate)	P1 (low) to P2 (moderate)	P1 (low) to P2 (moderate)	P1 (low) to P2 (moderate)	P1 (low) to P2 (moderate)	P1 (low) to P2 (moderate)
Bioaccumulation[7]	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)

[1]ACC Olefins Panel of the. December 16, 2004. Revised Robust Summary and Test Plan for C_5 Non-Cyclic Category. http://www.epa.gov/chemrtk/pubs/summaries/c5ncyl/c12801tc.htm

[2] The pyrolysis C_5 stream consists of isoprene (18%), *cis*- and *trans*-pentadiene-1,3 (16%), cyclopentadiene + dicyclopentadiene (14%), *n*-pentane (10%), cyclopentene (7%), 2-methyl-2-butene (3%), and cyclopentane (1%). The balance consists of other hydrocarbons with similar boiling points (C_5s).

[3]The hydrotreated C_5 stream consists of 1,3-butadiene (7%), isopentane (8%), *n*-pentane (15%), *cis*- and *trans*-pentene-2 (12%), 2-methyl-2-butene (8%), cyclopentene (22%), cyclopentane (8%), and balance (20%).

[4]Data range represents estimated values for representative constituent compounds: *trans*-butene-2, *cis*-pentene-2, 3-methyl-1-butene, 1,4-pentadiene, isopentane, isoprene, *n*-pentane, 2-methyl-2-butene, and cyclopentene.

[5]U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. US EPA, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.

[6] National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.

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

3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 5. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

For human health effects, the decisions for read-across were based on the constituent content of the different streams (see Appendix). The table in the Appendix is color-coded to show the assignment of the different streams to one of two groups: "primarily dienes" and "C5s with little or no diene content".

Acute Oral Toxicity

Isoprene (CASRN 78-79-5)
Wistar rats (15/sex/dose) were administered CASRN 78-79-5 in corn oil. No other details were provided.
LD_{50} = 2043 - 2210 mg/kg-bw

2-Methyl-2-butene (CASRN 513-35-9)
Wistar rats (6/sex/dose) were administered 2-methyl-2-butene at 1.0, 1.6, 2.5, 4.0, 6.3 and 10 ml/kg-bw and observed for 14 days. Mortality occurred within the first 3 days following dosing.
LD_{50} = 700 - 2600 mg/kg-bw

Acute Dermal Toxicity

2-Methyl-2-butene (CASRN 513-35-9)
Wistar rats (6/sex/dose) were administered 2-methyl-2-butene dermally onto intact (shaved) skin at 3.03 mL/kg-bw (~2000 mg/kg-bw) under occluded conditions for 24 hours and observed for up to 14 days. No mortalities were reported and there were no signs of systemic toxicity.
LD_{50} > 2000 mg/kg-bw

Acute Inhalation Toxicity

Isoprene (CASRN 78-79-5)
In studies that provided minimal details the reported LC50 values were as follows (four hour exposures for rats and two hours for mice):
LC_{50} (rat) = 180 mg/L (63,000 ppm)
LC_{50} (mice) = 157 mg/L (56,000 ppm)

2-Methyl-2-butene (CASRN 513-35-9)
Wistar rats (5/sex) were exposed to 2-methyl-2-butene at 6.1% (61,000 ppm or ~170 mg/L) for 4 hours and observed for 14 days. During the four-hour exposure period, animals were narcotic; which ended 30 minutes following cessation of exposure. There were no mortalities.
LC_{50} > 170 mg/L (61,000 ppm)

Repeated-Dose Toxicity Study

Isoprene (CASRN 78-79-5)
The NTP performed three different studies of varying exposure durations (13 weeks, 26 weeks and 104 weeks) in rats and two studies (13 weeks and 26 weeks) in mice. The rat and mouse studies are reported separately below.

(1) F344 rats (10/sex/group) were exposed to CASRN 78-79-5 via inhalation at 0, 70, 220, 700, 2200 and 7000 ppm (corresponding to 0, ~ 0.195, 0.613, 1.95, 6.13, and 19.5 mg/L/day, respectively), 6 hours/day, 5 days/week for 13 weeks. After 13 weeks of exposure, all rats were sacrificed and evaluated histopathologically. Organ weights were recorded. There were no exposure-related effects observed for survival, body weight gain, clinical signs of toxicity, hematology or clinical chemistry parameters, urinalysis, organ weights, or the incidence of gross or microscopic lesions.
NOAEC (systemic) = 7000 ppm (based on no effects at the highest dose tested)

(2) Fischer 344 rats (40/sex/concentration) were exposed to CASRN 78-79-5 vapor by inhalation at 0, 70, 220, 700, 2200, or 7000 ppm (corresponding to 0, ~ 0.195, 0.613, 1.95, 6.13, and 19.5 mg/L/day, respectively) for 6 hours/day, 5 days/week for 26 weeks in an NTP study designed to be a cancer study (26 weeks of exposure followed by 26 weeks on study without exposure). At the end of the 26-week exposure period, 10 rats per concentration were sacrificed and evaluated and all the other animals remained on study with no additional CASRN 78-79-5 exposure. There were no treatment-related mortalities, and no changes in body weight or clinical pathology parameters. The only treatment-related effect was an increased incidence and severity of interstitial cell hyperplasia of the testis at 7000 ppm (10/10, mild severity) compared with controls (1/10; minimal severity); this lesion was seen in all recovery groups (28/30-30/30 animals per group at 70 - 7000 ppm), but also occurred at a high incidence in controls (25/30), and there was no concentration-related trend.
NOAEC (systemic) = 7000 ppm (based on no effects at the highest dose tested)

(3) F344/N rats (50/sex/concentration) were exposed to CASRN 78-79-5 vapor via inhalation at 0, 220, 700, or 7,000 ppm (corresponding to 0, ~0.613, 1.95 and 19.5 mg/L/day, respectively), 6 hours per day, 5 days per week, for 104 weeks. The survival and body weights of exposed animals were similar to controls. Non-neoplastic effects were observed in male rats only. They included renal tubule hyperplasia and splenic fibrosis. The incidence of renal tubule hyperplasia was as follows: 0/50, 2/50, 6/50, and 8/50, for controls, low, mid- and high dose groups, respectively. When standard and extended evaluations were combined, the incidences were: 7/50, 6/50, 13/50, and 18/50, respectively. The incidence of splenic fibrosis was as follows: 11/50, 14/50, 24/50, and 22/50, respectively. No other clear treatment-related non-neoplastic changes were observed. Additional details about tumors that occurred in this study are given in the carcinogenicity section.
LOAEC (systemic) = 220 ppm (based on effects in the spleen and kidneys in males)
NOAEC (systemic) = Not established

(4) B6C3F1 mice (10/sex/concentration/species) were exposed to CASRN 78-79-5 via inhalation at 0, 70, 220, 700, 2200 and 7000 ppm (corresponding to 0, ~ 0.195, 0.613, 1.95, 6.13, and 19.5 mg/L/day, respectively), 6 hours/day, 5 days/week for 13 weeks. After 13 weeks of exposure, all

mice were sacrificed and evaluated histopathologically. Organ weights were recorded. There were no effects on survival, body weight gain, or clinical signs of toxicity. However, males and females exposed to 1.95 mg/L/day and higher showed hematologic effects indicative of a nonresponsive, macrocytic anemia at day 24 and after 13 weeks. Focal epithelial hyperplasia of the forestomach was also observed in both males and females at the top three dose levels. Degeneration of the olfactory epithelium and cytoplasmic degeneration of the liver and reduced testes weights were also observed in male mice at 19.5 mg/L/day.
LOAEC (systemic) = 700 ppm (based on effects on hematology parameters and effects on forestomach)
NOAEC (systemic) = 220 ppm

(5) B6C3F1 mice (40/sex/concentration/species) were exposed to CASRN 78-79-5 vapor by inhalation at 0, 70, 220, 700, 2200, or 7000 ppm (corresponding to 0, ~ 0.195, 0.613, 1.95, 6.13, and 19.5 mg/L/day, respectively) for 6 hours/day, 5 days/week for 26 weeks in an NTP study designed to be a cancer study (26 weeks of exposure followed by 26 weeks on study without exposure). At the end of the 26-week exposure period, 10 mice per concentration were sacrificed and evaluated and all the other animals remained on study with no additional CASRN 78-79-5 exposure. Twenty mice per concentration were evaluated for forelimb and hindlimb grip strength after 26 weeks exposure; 10 mice/group were also evaluated at 2 days, 1-, 3- and 6-months post-exposure. Results showed reduced survival at 19.5 mg/L/day from approximately 18 weeks onwards. Early mortality was attributed to neoplastic lesions as well as sacrifice of animals showing hindlimb paralysis towards the end of the exposure period, primarily at 19.5 mg/L/day. Hematologic effects indicative of a nonresponsive, macrocytic anemia were seen at this concentration. Hindlimb grip strength was statistically significantly reduced at 0.613 mg/L/day and above, up to approximately 4 weeks post-exposure. Statistically significantly increased incidences of testicular atrophy (5/10), degeneration of olfactory epithelium (10/10) and minimal degeneration of the spinal cord white matter (10/10) were seen at 7000 ppm after 26 weeks exposure. In recovery groups, these lesions were seen with statistically significantly increased incidences in the lower exposure concentration groups also. Degeneration of olfactory epithelium in recovery groups occurred at 0.613 mg/L/day and above (5/29 at 0.613 mg/L/day, 28/28 at 19.5 mg/L/day) compared with control (1/30). The incidence of spinal cord degeneration was increased at 0.195 mg/L/day and above (20/30 at 0.195 mg/L/day, 13/28 at 19.5 mg/L/day, 4/30 in controls); the incidence of testicular atrophy in recovery exposure groups was not statistically significantly different from controls. The NTP reported there was no NOAEC for the spinal cord lesions. The sponsor cites an unpublished re-analysis (Garman 2001 as cited on pdf page 63 of the 2002 revised robust summaries) of the spinal cord slides that refutes this result. Without a full copy of the re-analysis to review, EPA will abide by the NTP conclusions.
LOAEC (systemic) = 70 ppm (based on spinal cord degeneration)
NOAEC (systemic) = not established

(6) Given that mice are more sensitive to CASRN 78-79-5 toxicity than rats, and that NTP reported positive cancer studies with B6C3F1 mice at less-than-lifetime exposures (see carcinogenicity section in this document), a group of investigators conducted an unusual concentration x time chronic exposure study with CASRN 78-79-5 in mice that was reported in the HPV submission (Placke et al,. 1996). Twelve different groups of B6C3F1 mice were exposed to CASRN 78-79-5 vapor via inhalation:

- 0, 10 and 70 ppm (eight hours/day, five days/week, 50/sex/dose, for 80 weeks)
- 70, 140 and 2200 ppm (eight hours/day, five days/week, 50/males/dose, for 40 weeks)
- 280 ppm (eight hours/day, five days/week, 50 males, for 20 weeks)
- 280, 700 and 2200 ppm (eight hours/day, five days/week, 50/males/dose, for 80 weeks)
- 2200 ppm (four hours/day, five days/week, 50 males, for 20 weeks)
- 2200 ppm (four hours/day, five days/week, 50/sex/dose, for 80 weeks)

The concentrations of 0, 10, 70, 140, 280, 700 or 2200 ppm correspond to 0, ~0.028, 0.195, 0.390, 0.780, 1.95, and 6.13 mg/L/day, respectively. All animals were held until 104 weeks. Survival rate was reduced to less than 50% of control, from week 80 onwards at 0.780 mg/L/day and above; animals in these groups were necropsied at week 96. No clinical signs of toxicity were seen other than those associated with tumor development. Bodyweight and hematological parameters were unaffected by treatment. At necropsy, treatment-related gross lesions observed were opacity of the eyes, often with protrusion due to Harderian gland enlargement. Nodules and masses in the forestomach mucosa, liver and lung; enlargement of the spleen and mesenteric lymph node; and reduction in size and weight of testis were also observed. Effects were apparent at 0.780 mg/L/day and above, but the dose levels at which particular effects were seen was not clearly stated. In females, there was a reduction in ovarian weight at 0.028 and 0.195 mg/L/day, which did not reach statistical significance, and which may have been treatment-related. A slightly increased incidence of hyperplasia of the alveolar lining and of the forestomach mucosa were seen at higher doses in males; there was an increased incidence of mild metaplasia of focal areas of the olfactory epithelium down to the respiratory epithelium in males at 6.13 mg/L/day and in females at 0.195 mg/L/day. No other clear treatment-related non-neoplastic changes were observed. Additional details about tumors that occurred in this study are given in the carcinogenicity section.
LOAEC (systemic) = 70 ppm (based on effects on respiratory and olfactory epithelium, forestomach and Harderian gland)
NOAEC (systemic) = 10 ppm

2-Methyl-2-butene (CASRN 513-35-9)
In a combined repeated-dose/reproduction/developmental toxicity screening test, Sprague-Dawley rats (12/sex/concentration) were exposed to CASRN 513-35-9 via inhalation to 0, 580, 2000, or 7,000 ppm (approximately 1.66, 5.72 or 20 mg/L) for approximately 6 hours/day. In the repeated-dose portion of the study, male and female rats were exposed for 28 days. Although some general systemic effects were observed in this study, these effects were slight and most apparent in animals exposed to the highest dose and to a lesser extent to those exposed to the mid-dose. These included half-closed eyes (Day 1 only, high and mid dose); slight decrease in body weight gain (high dose, gender, incidence and significance not noted); and slightly longer clotting times (mid dose – females only, high dose – both males and females; incidence and significance not noted). A neurological functional observational battery was performed and showed no effects. Changes were noted among the high dose females in the liver (increased organ weight and minimal centrilobular hepatocyte hypertrophy). There was a decreased incidence of extramedullary hematopoiesis in the spleen in the high dose animals, and an increase in goblet cell hyperplasia in the nasal passages of the high dose males. A slight increase

in severity of myocardial inflammatory heart lesions and in cortical/medullary tubular basophilia in the kidneys was observed in the high and mid dose males.
LOAEC (systemic) = 2000 ppm (based on effects in the kidney and heart in males)
NOAEC (systemic) = 580 ppm

Hydrotreated C5s
In a combined repeated-dose/reproductive/developmental study, Sprague-Dawley rats (12/sex/group) were exposed to the test substance[10] via inhalation at nominal concentrations of 0, 1000, 3000 or 8500 ppm (measured at 992, 3033 or 8502 ppm – conversion to mg/L is was not done because the test substance is a mixture) for 6 hours daily, 7days/week, for 28 days. Salivation was noted in high dosed animals (8502 ppm) during the exposure period. No treatment-related changes were observed in motor activity[11] or in the functional observational battery. Slight (but unspecified) effects on general systemic toxicity were reported in the robust summary for males in all dose groups. Relative kidney weights were increased in males (all treated groups, but statistically significant in the mid- and high-dose groups only) and females (all treated groups, statistical significance not stated). Histopathological examination in all male rats revealed dose-related increases in hyaline droplets in the kidneys. Basophilic cortical tubules were also increased in incidence and severity in all male exposure groups, and in the female mid- and high-groups, compared to controls. In the high dose male group, relative liver weight and minimal centrilobular hepatocyte hypertrophy were reported; the latter being statistically significant (significance of the organ weight effect was not stated). In the nasal turbinates, atrophy/disorganization of the olfactory epithelium was seen in several males in the high dose group, and in the females in the mid- and high dose groups. Although the incidences had not achieved statistical significance it is considered that they are above background levels, and the finding is considered to be treatment-related in these groups.
LOAEC (systemic, males) = 992 ppm (based on general systemic effects, and kidney effects)
NOAEC (systemic, males) = Not established
LOAEC (systemic, females) = 3033 ppm (based on effects on nasal turbinates and the kidney)
NOAEC (systemic, females) = 992 ppm

Pyrolysis C5s
In a combined repeated-dose/reproduction/developmental toxicity screening test, Sprague-Dawley rats (12/sex/concentration) were exposed to the Pyrolysis C5s[12] stream via inhalation at 0, 98, 302 or 1012 ppm (conversion to mg/L is was not done because the test substance is a

[10] After the initial HPV submission in 2001, the sponsor conducted a number of tests for a variety of endpoints with a representative mixture for the hydrotreated C5 stream. Following is the makeup of the test mixture: 1,3-butadiene (7%); isopentane (8%); n-pentane (15%); cis- and trans-pentene-2 (12%); 2-methyl-2-butene (8%); cyclopentene (22%); cyclopentane (8%); the remaining balance (20%) is unspecified.
[11] This reflects what is in the HPV Submission *Category Summary Report* (2004); but the robust summary for this study states that motor activity was reduced in males in the high dose group.
[12] After the initial HPV submission in 2001, the sponsor conducted a number of tests for a variety of endpoints with a representative mixture for the pyrolysis C5 stream. Following is the makeup of the test mixture: isoprene (18%); cis- and trans-pentadiene1,3- (16%); cyclopentadiene + dicyclopentadiene (14%); n-pentane (10%); cyclopentene (7%); 2-methyl-2-butene (3%); and cyclopentane (1%). The remainder (~31%) consists of other unspecified hydrocarbons with similar boiling points.

mixture) for 6 hours daily, 7days/week for 28 days. The robust summary reports no signs of general systemic effects observed during clinical exams, but some hematology and biochemical parameters showed "intergroup differences". These differences were not considered relevant, but information allowing for an independent assessment was lacking. High dose rats had slightly elevated liver weights and some histopathological changes (minimal centrilobular hepatocyte hypertrophy. These effects were considered to be adaptive, not adverse. Male rats also exhibited increased kidney weights and associated increases in hyaline droplets in cortical tubules in all treatment groups, with other (not specified) associated kidney lesions. No changes were observed in the kidneys of treated females. The reported effects on kidneys are considered a male rat-specific phenomenon. However, if one considers only those effects considered potentially relevant to humans, a NOAEC of 1,000 ppm was established for male rats. In females, a NOEL of 1000 ppm was established.
NOAEC (systemic) = 1012 ppm (highest dose tested)

Reproductive Toxicity

Isoprene (CASRN 78-79-5)
In the 13 week NTP studies described above, a satellite group of F344 rats and B6C3F1 mice (10/sex/concentration/species) were exposed to the test substance via inhalation at 0, 70, 220, 700, 2200 or 7000 ppm (corresponding to 0, ~ 0.195, 0.613, 1.95, 6.13, and 19.5 mg/L/day, respectively) were evaluated for effects on reproductive organs. No effects on reproductive organs were seen in rats except increased incidences of interstitial cell hyperplasia of the testis at the highest dose level (19.5 mg/L/day). Observed effects in mice at 1.95 mg/L/day or higher included increased estrous cycle length, testicular atrophy, decreased epididymal weight, and sperm effects (decreases in spermatid head count, sperm concentration, and motility).

2-methyl-2-butene (CASRN 513-35-9)
In a repeated-dose/reproductive/developmental toxicity screening test, female Sprague-Dawley rats (12/dose/concnetration) were exposed to the test substance via inhalation at 0, 580, 2000 or 7000 ppm (corresponding to 0, ~1.66, 5.72 or 20 mg/L/day, respectively) for 6 hours daily, 7 days/week, two weeks prior to breeding, during breeding, and continuing through day 19 of gestation. Males from the repeated dose toxicity study were used to breed these females. The dams were allowed to deliver their litters, which were retained until lactation day 4. The clinical condition, bodyweight, food consumption, oestrus cycles, mating performance, litter data, organ weights and microscopic pathology were noted in the study. There were no observed effects on reproductive endpoints to female rats for two weeks prior to paring, and up to day 19 of gestation. The oestrus cycle, mating performance, fertility indices and gestation length were not affected by the exposure of test substance.
NOAEC (reproductive toxicity) = 7000 ppm (based on no effects at the highest dose tested)

Hydrotreated C5s
In a repeated-dose/reproductive/developmental toxicity screening test, female Sprague-Dawley rats (12/dose/concnetration) were exposed to the test mixture (see footnote 10 for mixture content) via inhalation at doses of 0, 992, 3033 or 8502 ppm (conversion to mg/L is was not done because the test substance is a mixture) for 6 hours daily, 7 days/week, two weeks prior to breeding, during breeding, and continuing through day 19 of gestation. Males from the repeated dose toxicity study were used to breed these females. The dams were allowed to deliver their

litters, which were retained until lactation day 4. The clinical condition, bodyweight, food consumption, oestrus cycles, mating performance, litter data, organ weights and microscopic pathology were noted in the study. There were no observed effects on reproductive endpoints to female rats for 2 weeks prior to pairing, and up to day 19 of gestation. The oestrus cycle, mating performance, fertility indices and gestation length were not affected by the exposure of test substance.
NOAEC (reproductive toxicity) = 8502 ppm (based on no effects at the highest dose tested)

Pyrolysis C5s
In a repeated-dose/reproductive/developmental toxicity screening test identified above, female Sprague-Dawley rats (12/dose/concentration) were exposed to the test mixture (see footnote 12 for mixture content) via inhalation at 0, 98, 302 or 1012 ppm (conversion to mg/L is was not done because the test substance is a mixture) for 6 hours daily, 7 days/week, two weeks prior to breeding, during breeding, and continuing through day 19 of gestation. Males from the repeated dose toxicity study were used to breed these females. The dams were allowed to deliver their litters, which were retained until lactation day 4. The clinical condition, bodyweight, food consumption, oestrus cycles, mating performance, litter data, organ weights and microscopic pathology were noted in the study. There were no observed effects on reproductive endpoints to female rats for 2 weeks prior to pairing, and up to day 19 of gestation. The oestrus cycle, mating performance, fertility indices and gestation length were not affected by the exposure of test substance.
NOAEC (reproductive toxicity) = 1012 ppm (based on no effects at the highest dose tested)

Developmental Toxicity

Isoprene (CASRN 78-79-5)
(1) Pregnant Sprague-Dawley rats (29/dose/concentration) were exposed to the test substance via inhalation at 0, 280, 1400 or 7000 ppm (0, ~0.78, 3.9, or 19.5 mg/L/day) from gestation days 6-19. The only observed maternal toxicity effect in the dams was an increased relative kidney weights at 19.5 mg/L/day. A small (non-statistically significant) increase in the incidence of reduced vertebral ossifications in fetuses was noted at19.5 mg/L/day.
LOAEC (maternal toxicity) = 7000 ppm (based on increased relative kidney weights)
NOAEC (maternal toxicity) = 1400 ppm
NOAEC (developmental toxicity) = 7000 ppm (based on no significant effects at the highest tested dose)

(2) Pregnant CD-1/Swiss mice (30/dose/concentration) were exposed to the test substance via inhalation at 0, 280, 1400 or 7000 ppm (0, ~0.78, 3.9, or 19.5 mg/L/day) from gestation days 6-17. Significant reductions in maternal body weight, body weight gain and uterine weight were observed at 19.5 mg/L. Increased relative liver weights at the mid- and high dose levels and increased relative kidney weights at the highest dose level were seen. Developmental toxicity was evidenced by reduced fetal body weights at all dose levels for female fetuses and the mid and high dose levels for male fetuses. Two fetuses with cleft palate were found, one each of the two highest dosed groups.
LOAEC (maternal toxicity) = 7000 ppm (based on reduced maternal body weight, and increased relative kidney, uterine and liver weights)
NOAEC (maternal toxicity) = 1400 ppm

LOAEC (developmental toxicity) = 280 ppm (based on reduced mean fetal body weights)
NOAEC (developmental toxicity) = Not established

2-methyl-2-butene (CASRN 513-35-9)
In the combined repeated-dose/reproductive/developmental toxicity test described above, female Sprague-Dawley rats (12/dose/concentration) were exposed to the test substance via inhalation at 0, 580, 2000 or 7000 ppm (corresponding to 0, ~1.66, 5.72 or 20 mg/L/day, respectively) for 6 hours/day, 7 days/week, two weeks prior to breeding, during breeding, and continuing through day 19 of gestation. The dams were allowed to deliver their litters, which were retained until lactation day 4. As noted in the repeated-dose section above, maternal toxicity was observed and included slightly longer clotting times (mid and high doses; incidence and significance not noted). Changes were noted among the high dose females in the liver (increased organ weight and minimal centrilobular hepatocyte hypertrophy). There was a decreased incidence of extramedullary hematopoiesis in the spleen in the high dose animals. There were no adverse effects upon survival or growth of the offspring in utero or up to day 4 of lactation.
LOAEC (maternal toxicity) = 7000 ppm (based on effects in some hematological parameters and the spleen)
NOAEC (maternal toxicity) = 2000 ppm
NOAEC (developmental toxicity) = 7000 ppm (based on no effects at the highest dose tested)

Hydrotreated C5s
In the combined repeated-dose/reproductive/developmental toxicity study summarized above, female Sprague-Dawley rats (12/dose/concentration) were exposed to the test mixture (see footnote 10 for mixture content) via inhalation at concentrations of 0, 992, 3033 or 8502 ppm (conversion to mg/L is was not done because the test substance is a mixture) for 6 hours daily, 7 days/week, two weeks prior to breeding, during breeding, and continuing through day 19 of gestation. The dams were allowed to deliver their litters, which were retained until lactation day 4. Maternal effects were described above in the repeated-dose section. There were no adverse effects upon survival or growth of the offspring in utero or up to day 4 of lactation.
LOAEC (maternal toxicity) = 3033 ppm (based on effects on nasal turbinates and the kidney)
NOAEC (maternal toxicity) = 992 ppm
NOAEC (developmental toxicity) = 8502 ppm (based on no effects at the highest dose tested)

Pyrolysis C5s
In a combined repeated-dose/reproductive/developmental toxicity study summarized above, female Sprague-Dawley rats (12/dose/concentration) were exposed to the test substance (see footnote 12 for mixture content) via inhalation at concentrations of 0, 98, 302 or 1012 ppm (conversion to mg/L is was not done because the test substance is a mixture) for 6 hours/day, 7 days/week, two weeks prior to breeding, during breeding, and continuing through day 19 of gestation. The dams were allowed to deliver their litters, which were retained until lactation day 4. The robust summary reports no signs of general systemic effects observed during clinical exams, but noted some hematology and biochemical parameters showed "intergroup differences". These differences were not considered relevant, but information allowing for an independent assessment was lacking. High dose rats (including females) had slightly elevated liver weights and some histopathological changes (minimal centrilobular hepatocyte

hypertrophy. These effects were considered to be adaptive, not adverse. There were no adverse effects upon survival or growth of the offspring in utero or up to day 4 of lactation.
NOAEC (maternal toxicity) = 1012 ppm (no effects at highest dose tested)
NOAEC (developmental toxicity) = 1012 ppm (no effects at highest dose tested)

Genetic Toxicity- Gene mutation

In vitro
Isoprene (CASRN 78-79-5)
Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 were exposed to CASRN 78-79-5 at doses of 0, 3, 100, 333, 1000, 3333 and 10000 ug/plate; all in the presence and absence of metabolic activation. Cytotoxicity was observed at the highest dose level. The test included concurrent solvent and positive controls with and without metabolic activation. The test substance did not cause mutations.
CASRN 78-79-5 was not mutagenic in this assay.

2-methyl-2-butene (CASRN 513-35-9)
Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to CASRN 513-35-9 at concentrations of 0, 0.2, 2, 20, 500 and 2000 ug/plate in the presence and absence of metabolic activation. The test included concurrent solvent and positive controls with and without metabolic activation. The test substance did not cause mutations to *Salmonella typhimurium* in this *in vitro* genetic toxicity test.
2-Methyl-2-butene was not mutagenic in this assay.

Hydrotreated C5s
Salmonella typhimurium strains (TA98, TA100, TA1535 and TA1537) and *E. Coli* strain WP2 uvrA/pKM101 (CM891) were exposed to Hydrotreated C5s (see footnote 10 for mixture content) in the vapor phase at concentrations of up to 8500 ppm with and without S-9 activation. The test included positive controls with and without metabolic activation. The test substance did not cause mutations to *Salmonella typhimurium* and *E. Coli* in this *in vitro* genetic toxicity test.
Hydrotreated C5s was not mutagenic in this assay.

Pyrolysis C5s
Salmonella typhimurium strains (TA98, TA100, TA1535 and TA1537) and *E. Coli* strain WP2 uvrA/pKM101 (CM891) were exposed to Pyrolysis C5s (see footnote 12 for mixture content) in the vapor phase at concentrations up to 5250 ppm (50% of the lower explosive limit) with and without S-9 activation. The test included positive controls with and without metabolic activation. The test substance did not cause mutations to *Salmonella typhimurium* and *E. Coli* in this *in vitro* genetic toxicity test.
Pyrolysis C5s was not mutagenic in this assay.

Genetic Toxicity- Chromosomal Effects

In vitro
Isoprene (CASRN 78-79-5)
(1) Chinese hamster ovary (CHO) cells were exposed to CASRN 78-79-5 up to 5000 ug/ml (in the presence of metabolic activation) or up to 1600 ug/ml (in the absence of metabolic

activation). The test included concurrent solvent and positive controls and four doses of CASRN 78-79-5. No increases in SCEs were noted in cultured CHO cells treated with CASRN 78-79-5, with or without S9.
CASRN 78-79-5 did not induce SCEs in this assay.

(2) Chinese hamster ovary (CHO) cells were exposed to CASRN 78-79-5 at up to 5000 ug/ml in the presence and absence of metabolic activation. The test included concurrent solvent and positive controls and four doses of CASRN 78-79-5. No increases in chromosomal aberrations were noted in cultured CHO cells treated with CASRN 78-79-5, with or without S9.
CASRN 78-79-5 did not induce chromosomal aberrations in this assay.

In vivo
Isoprene (CASRN 78-79-5)
(1) In three different studies (all reported in the same publication), male B6C3F1 mice (15/dose) were exposed to 0, 438, 1750 and 7000 ppm CASRN 78-79-5 via inhalation for six hours/day for 12 days. Sister Chromatid Exchanges (SCEs), micronucleated polychromatic erythrocytes (MN-PCEs), and chromosomal aberrations were each assessed in separate experiments by examining bone marrow cells. Results showed that CASRN 78-79-5 statistically significantly induced SCEs and MN-PCEs in all dose groups, but chromosomal aberrations were only slightly elevated (and not statistically significantly different from controls) in the treated mice.
CASRN 78-79-5 induced SCEs and micronucleated erythrocytes, but not chromosomal aberrations in separate studies.

(2) A micronucleus assay was also conducted in male/female Fischer 344 rats (10/sex/group) at 0, 220, 700 or 7000 ppm via inhalation for 4 weeks (six hours/day, five days/week). The observed frequency of micronucleated lung fibroblasts was not increased in male and female rats treated with CASRN 78-79-5 for 4 weeks.
CASRN 78-79-5 did not induce micronuclei in rat lung fibroblasts in this assay.

2-methyl-2-butene (CASRN 513-35-9)
In two separate experiments reported in one citation, male B6C3F1 mice and male *Crl*CDBR rats (10/dose/group) were exposed to CASRN 513-35-9 at mean measured concentrations of 0, 1005, 3207 or 9956 ppm via inhalation for six hours/day for two days. The test included positive and negative controls. Bone marrow cells were harvested and evaluated for micronucleated erythrocytes. The test substance induced a dose-related increase in micronucleated PCEs at 3207 and 9956 ppm in both species. Also, in mice a dose-related decrease in the mean percent PCEs was observed at 9956 ppm.
CASRN 513-35-9 induced micronucleated erythrocytes in rats and mice in this assay.

Hydrotreated C5s
Hydrotreated C5s (see footnote 10 for mixture content) was evaluated in a micronucleus assay conducted in CD-1 male mice (7/dose/group) via inhalation at concentrations of 0, 2000, 4000, and 8000 ppm (six hours/day for two successive days). The test included positive and negative controls. There were no increases in the frequency of micronucleated PCEs, but there was a decrease in the proportion of immature erythrocytes at all doses. This decrease was significant according to one statistical analysis (trend analysis) but not for another (pairwise anaylsis). Not enough details were provided in the summary to critically evaluate the results.

Hydrotreated C5s did not increase the frequency of micronucleated PCEs in this assay.

Pyrolysis C5s

Pyrolysis C5s (see footnote 12 for mixture content) was evaluated in a micronucleus assay conducted in CD-1 male mice (7/dose/group) via inhalation at concentrations of 0, 40, 125, and 500 ppm (six hours/day for two successive days). The test included positive and negative controls. The incidence of micronucleated PCE were not increased in the Pyrolysis C5s treated animals compared to the controls.

Pyrolysis C5s did not increase the frequency of micronucleated PCEs in this assay.

Additional Information

Skin Irritation

Isoprene (CASRN78-79-5)

New Zealand White rabbits (2, sex not reported) were painted with 100% CASRN 78-79-5 (volume not provided) on the skin of the ear twice per day for 5 consecutive days. Reversible erythema was observed. No other information was provided. The data suggest that CASRN 78-79-5 has a low potential for skin irritation.

CASRN 78-79-5 was mildly irritating to rabbit skin.

2-methyl-2-butene (CASRN 513-35-9)

New Zealand White rabbits (3/sex) were administered neat CASRN 513-35-9 dermally onto intact and abraded test sites for 24 hours and scored for erythema and edema at 24, 48 and 72 hours and 7 days post-dosing following the Draize method. Based on the mild erythema and edema, CASRN 513-35-9 was regarded as mildly irritating to rabbit skin.

CASRN 513-35-9 was mildly irritating to rabbit skin.

Eye Irritation

Isoprene (CASRN.78-79-5)

CASRN 78-79-5 was reported to cause eye irritation (species not listed) and no other study details are provided (taken from the OECD document on CASRN 78-79-5).

2-Methyl-2-butene (CASRN. 513-35-9)

New Zealand White rabbits (6, sex not reported) were instilled with 0.2 ml of CASRN 513-35-9 in the eye and assessed at 1 hour, 1 day, 2 days, 3 days, and 7 days after instillation. The instillation of CASRN 513-35-9 into the eye resulted in a moderate initial pain response (grade 4 – based on a scale of 1-6 with six being severe) in all animals. The mean total irritation scores for the responses of the conjunctiva, cornea and iris at 1 hour, 1, 2, 3, and 7 days were 0.5, 0, 0, 0, and 0, respectively. Based on these results, CASRN 513-35-9 is considered to be non-irritating to rabbit eyes (from OECD document on CASRN 513-35-9).

CASRN 513-35-9 was non-irritating to rabbit eyes.

Skin Sensitization

2-methyl-2-butene (CASRN. 513-35-9)
In the Magnusson and Kligman guinea-pig maximization test, 0.1% CASRN 513-35-9 was administered at 1% w/v in corn oil (intradermal induction), 50% w/v in corn oil (topical induction), and 25% w/v in corn oil (topical challenge) to a total of 20 guinea pigs (number per dose not clear). None of the twenty test animals showed any positive reactions 24 or 48 hours after the removal of the challenge patch.
CASRN 513-35-9 is not a skin sensitizer in this study.

Carcinogenicity

There have been several NTP studies evaluating the carcinogenicity of isoprene (CASRN 78-79-5): rat and mouse (26 weeks of exposure followed by 26 weeks on study without exposure) and a two-year rat study. In addition, there was a mouse cancer study reported in the literature. Non-cancer results for these studies were presented in the repeated-dose section above. The protocols and cancer results are presented here:

NTP - 26 Week Rat Study: Fischer 344 rats (40/sex/concentration) were exposed to CASRN 78-79-5 vapor by inhalation at 0, 70, 220, 700, 2200, or 7000 ppm (corresponding to 0, ~ 0.195, 0.613, 1.95, 6.13, and 19.5 mg/L/day, respectively) for 6 hours/day, 5 days/week for 26 weeks in an NTP cancer study (26 weeks of exposure followed by 26 weeks on study without exposure). At the end of the 26-week exposure period, 10 rats per concentration were sacrificed and evaluated and all the other animals remained on study with no additional CASRN 78-79-5 exposure. There was a marginal increase in the incidence of benign testicular adenomas in the male high dose group only. The NTP concluded that it was premature to make a determination on the carcinogenicity of CASRN 78-79-5 from this less-than-lifetime study, although they did acknowledge the testes as a possible target given the interstitial cell hyperplasia results observed in addition to the benign adenomas seen at the end of the study.

NTP 2-Year Rat Study: F344/N rats (50/sex/concentration) were exposed to CASRN 78-79-5 vapor via inhalation at 0, 220, 700, or 7,000 ppm (corresponding to 0, ~0.613, 1.95 and 19.5 mg/L/day, respectively), 6 hours per day, 5 days per week, for 104 weeks. As stated in the HPV submission, the NTP concluded that there was clear evidence of carcinogenic activity in males based on increased incidences of mammary gland fibroadenoma and carcinoma, renal tubule adenoma, and testicular interstitial cell adenoma and there was some evidence of carcinogenic activity females based on increased incidences and multiplicity of mammary gland fibroadenoma. The NTP further concluded that the low incidence of brain tumors in female mice may have been treatment related. (EPA notes that the submitter has a slightly different conclusion).

26 Weeks: B6C3F1 mice (40/sex/concentration/species) were exposed to CASRN 78-79-5 vapor by inhalation at 0, 70, 220, 700, 2200, or 7000 ppm (corresponding to 0, ~ 0.195, 0.613, 1.95, 6.13, and 19.5 mg/L/day, respectively) for 6 hours/day, 5 days/week for 26 weeks in an NTP cancer study (26 weeks of exposure followed by 26 weeks on study without exposure). At the end of the 26-week exposure period, 10 mice per concentration were sacrificed and evaluated and all the other animals remained on study with no additional CASRN 78-79-5 exposure.

Results showed reduced survival at 19.5 mg/L/day from approximately 18 weeks onwards. Early mortality was attributed to neoplastic lesions as well as sacrifice of animals showing hindlimb paralysis towards the end of the exposure period, primarily at 19.5 mg/L/day. CASRN 78-79-5 was carcinogenic to the liver, lung, forestomach and harderian gland of male mice (after both the 26 week exposure and the 26 week recovery periods).

Published Mouse Study: Given that mice are more sensitive to CASRN 78-79-5 toxicity than rats, and that NTP reported positive cancer studies with B6C3F1 mice at less-than-lifetime exposures, a group of investigators conducted an unusual concentration x time chronic exposure study with CASRN 78-79-5 in mice that was reported in the HPV submission (Placke et al,. 1996). Twelve different groups of B6C3F1 mice were exposed to CASRN 78-79-5 vapor via inhalation (see repeated dose section for the different groups/scenarios). The concentrations of 0, 10, 70, 140, 280, 700 or 2200 ppm correspond to 0, ~0.028, 0.195, 0.390, 0.780, 1.95, and 6.13 mg/L/day, respectively. All animals were held until 104 weeks. Survival rate was reduced to less than 50% of control, from week 80 onwards at 0.780 mg/L/day and above; animals in these groups were necropsied at week 96. General toxicity and non-neoplastic effects were reported earlier in this document. Results showed that CASRN 78-79-5 was carcinogenic to male (lung, liver, harderian gland, forestomach, and lymphoreticular system) and female (harderian and pituitary glands) mice.

Conclusion: The acute toxicity of C_5 non-cyclics category members is low via oral, dermal and inhalation routes. All the repeated-dose studies with the four substances tested (two stream mixtures and two pure substances) used inhalation as the route of exposure. Combined repeated-dose/reproductive/ developmental toxicity studies in rats were performed with the two streams. One stream (pyrolysis $C_{5's}$ - a mixture with five CASRNs) showed no effects at the highest concentration tested after 28 days of exposure (1012 ppm). Exposure to the other stream (hydrotreated $C_{5's}$ – a mixture with three CASRNs) caused general (unspecified) systemic and kidney effects in males (at the lowest concentration tested – 992 ppm) and kidney and nasal turbinate effects in females at the mid-concentration (3033 ppm).

In a similar combined repeated-dose/reproductive/developmental toxicity study in rats, inhalation exposure to CASRN 513-35-9 induced lesions in the heart and kidneys of males in the mid-concentration group (5.72 mg/L, or 2000 ppm). The other pure substance (CASRN 78-79-5) was extensively studied by the NTP and others in both rats and mice. In multiple repeated-dose studies, mice appeared more susceptible to toxicity than rats. Effects were seen at concentrations as low as 0.613 mg/L (220 ppm) in rats (spleen and kidney effect s in males following 104 weeks of exposure) and 0.195 mg/L (70 ppm) in mice (spinal cord degeneration, respiratory and olfactory epithelial changes, and effects on the forestomach and Harderian gland from 26 weeks to 80 weeks of exposure).

The combined studies performed with the two streams and CASRN 513-35-9 showed no effects on measured reproductive parameters up to the highest tested inhalation concentrations (20 mg/L [7000 ppm] for 513-35-9, 8502 ppm for hydrotreated $C_{5's}$, and 1012 ppm for pyrolysis $C_{5's}$). Although there were no conventional reproductive toxicity studies conducted with CASRN 78-79-5, reproductive organs were evaluated in NTP 13 week studies and the following effects were observed: increased incidence of interstitial cell hyperplasia of the testes in rats (at the highest tested dose of 19.5 mg/L, or 7000 ppm), and increases in estrous cycle length, testicular atrophy,

and sperm effects (spermatid head count, sperm concentration, motility), and decreased epididymal weight – all in mice and all at concentrations of 1.95 mg/L (700 ppm) and higher.

The combined studies performed with the two streams and CASRN 513-35-9 showed no effects on measured developmental toxicity parameters up to the highest tested inhalation concentrations (20 mg/L, or 7000 ppm for CASRN 513-35-9, 8502 ppm for hydrotreated $C_{5's}$, and 1012 ppm for pyrolysis $C_{5's}$). However, maternal toxicity was observed in two of the three studies (hematological/spleen effects at the highest tested concentration of 20 mg/L in the CASRN 513-35-9 study and effects on nasal turbinates and the kidney at the mid-concentration of 3033 ppm in the hydrotreated $C_{5's}$ study). Conventional prenatal developmental toxicity studies in rats and mice with CASRN 78-79-5 via the inhalation route showed some maternal toxicity in both species (increased kidney weights in rats reduced maternal body weight gain and increased relative kidney, uterine and liver weights in mice; all at the highest tested concentration of 19.5 mg/L, or 7000 ppm). Developmental toxicity was only observed in the mouse study (reduced fetal body weights at the lowest tested concentration of 0.78 mg/L, or 280 ppm).

The four members of the C_5 non-cyclics category which were tested in i*n vitro* gene mutation assays in bacteria did not cause gene mutations and so read-across for this negative effect across all members is appropriate. However, for chromosomal effects, the two tested streams were negative whereas the CASRNs 78-79-5 and 513-35-9 were positive for inducing chromosomal effects in both *in vitro* and *in vivo* assays (see Table 5 for read-across conclusions). Limited data with CASRNs 78-79-5 and 513-35-9 show these chemicals to be mildly irritating to rabbit skin. CASRN 78-79-5 was shown to be irritating to eyes (no specific information provided on species). CASRN 513-35-9 did not cause eye irritation or skin sensitization in rabbits and guinea pigs, respectively. CASRN 78-79-5 has been shown to be carcinogenic in rats and mice in NTP studies.

(See Table 5 for how the available information on tested category members was used for read-across to the other, untested members).

Table 5. Summary of Human Health Data

Endpoints	Primarily Dienes					C5s With Little or no Diene Cont.				
	Isoprene	**Isoprene Conc.**	**Isoprene-Piperylene Conc.**	**Pyrolysis C5s**	**Piperylene Conc.**	**2-Methyl-2-Butene**	**Metath. Byproduct**	**Pentenes**	**Hydro-treated C5s**	**Isoprene Pur. Byproduct**
Acute Toxicity (Oral) LD_{50} (mg/kg bw)	**(Rat) 2043-2210**	No Data 2043-2210 (RA)				**Rat 700-2600**	No Data 700-2600 (RA)			
Acute Toxicity (Dermal) LD_{50} (mg/kg bw)	No Data (RA/NA)					**(Rat) >2000**	No Data >2000 (RA)			
Acute Toxicity (Inhalation) LC_{50} (ppm)	**(Rat) 63,000 (Mice) 56,000**	No Data ~56,000 – 63,000 (RA)		No Data (RA/NA)		**Rat > 61,000**	No Data >~61,000 (RA)			
Repeated Dose Toxicity (Inhalation) (ppm)	**(Mice, 26 Wks) NOAEC = NE LOAEC = 70** **(Mice, 80 Wks) NOAEC = 10 LOAEC = 70** **(Rat, 104 Wks) NOAEC = NE LOAEC = 220**	No Data NOAEC = 10 LOAEC = 70 (RA)		**(Rat, 28 Days) NOAEC =1012 (hdt)**	No Data NOAEC =1012 (RA)	**(Rat, 28 Days) NOAEC = 580 LOAEC = 2000**	No Data NOAEC = NE LOAEC = 992 (RA)		**(Rat, 28 Days) Males NOAEC = NE LOAEC = 992** **Females NOAEC = 992 LOAEC = 3033**	No Data NOAEC = NE LOAEC = 992 (RA)
Reproductive Toxicity (Inhalation) (ppm)	13-wk studies indicate effects on testes (Rat & Mice). Mice also showed effects on estrus cycle and sperm.	No Data Possible effect on estrus cycle and sperm (RA)		**(Rat) NOAEC =1012 (hdt)**	No Data NOAEC =1012 (RA)	**NOAEC = 7000 (hdt)**	No Data NOAEC= 8502 (RA)		**NOAEC= 8502 (hdt)**	No Data NOAEC= 8502 (RA)
Developmental Toxicity (Inhalation) (ppm) **Maternal Toxicity**	**(Rat,Mice) NOAEC = 1400 LOAEC = 7000**	No Data NOAEC = 1400 LOAEC = 7000 (RA)		**(Rat) NOAEC =1012 (hdt)**	No Data NOAEC =1012 (RA)	**(Rat) NOAEC = 2000 LOAEC = 7000**	NO Data NOAEC = 992 LOAEC = 3033		**(Rat) NOAEC = 992 LOAEC = 3033**	No Data NOAEC = 992 LOAEC = 3033

Table 5. Summary of Human Health Data

Endpoints	Primarily Dienes					C5s With Little or no Diene Cont.				
	Isoprene	**Isoprene Conc.**	**Isoprene-Piperylene Conc.**	**Pyrolysis C5s**	**Piperylene Conc.**	**2-Methyl-2-Butene**	**Metath. Byproduct**	**Pentenes**	**Hydro-treated C5s**	**Isoprene Pur. Byproduct**
Developmental Toxicity	**(Rat) NOAEC = 7000 (hdt)** **(Mice) NOAEC = NE LOAEC =280**	No Data NOAEC = NE LOAEC = 280 (RA)		**NOAEC =1012 (hdt)**	No Data NOAEC =1012 (RA)	**(Rat) NOAEC = 7000 (hdt)**	NOAEC = 8502 (RA)		**NOAEC = 8502 (hdt)**	NOAEC = 8502 (RA)
Genetic Toxicity-Gene Mutation (In vitro)	**Negative**	No Data Negative (RA)		**Negative**	No Data Negative (RA)	**Negative**	No Data Negative (RA)		**Negative**	No Data Negative (RA)
Genetic Toxicity-Chrom. Aberrations (In vitro)	**Negative (SCE and Chrom. Ab)**	No Data Negative (RA)		No Data (RA/NA)		No Data (RA/NA)	No Data (RA/NA)		No Data (RA/NA)	No Data (RA/NA)
Genetic Toxicity-Chrom. Aberrations (In vivo)	**Positive (SCE & Micronucl.-RBCs)** **Negative (Chrom. Ab & Micronucl.-lung fibroblasts)**	No Data Positive (RA)		**Negative**	No Data Negative (RA)	**Positive (micronucleated RBCs)**	No Data Negative (RA)		**Negative**	No Data Negative (RA)
Additional Information										
Skin Irritation	**Mild**	—	—	—	—	**Mild**	—	—	—	—
Eye Irritation	**Irritating**	—	—	—	—	**Non-irritating.**	—	—	—	—
Skin Sensitization	—	—	—	—	—	**Non-sensitizing.**	—	—	—	—
Carcinogenicity	**Positive**	—	—	—	—	—	—	—	—	—

NOTES: Based on constituent data in the Appendix, the isoprene data are used to for isoprene concentrate and isoprene-piperylene concentrate; pyrolysis C5s are used for piperylene concentrate; and hydrotreated C5s are used for metathesis byproduct, pentenes, and isoprene purification by-product.
KEY: NE=not established; hdt = highest dose tested; **Bold = measured/experimental data;** RA = read across; RA/NA = no appropriate data for RA; — = data not necessary for HPV challenge program

2. Environmental Effects- Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 6. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Toxicity to Fish

Pyrolysis C_{5s}
Rainbow trout (*Oncorhynchus mykiss*) were exposed to pyrolysis C_{5s} under closed system for 96 hours. The overall mean measured concentrations were 1.42, 2.49, 6.40, 12.8 and 27.0 mg/L.
96-h LC_{50} = 8.4 mg/L

Hydrotreated C_{5s}
Rainbow trout (*Oncorhynchus mykiss*) were exposed to hydrotreated C_{5s} under closed system for 96 hours. The overall mean measured concentrations were 1.12, 2.79, 5.33, 10.3 and 19.6 mg/L.
96-h LC_{50} = 5.3 mg/L

Isoprene (CASRN 78-79-5)
Rainbow trout (*Oncorhynchus mykiss*) were exposed to CASRN 78-79-5 under closed system for 96 hours. The overall mean measured concentrations were 1.68, 3.57, 6.71, 15.0 and 28.7 mg/L.
96-h LC_{50} = 7.4 mg/L

2-methyl-2-butene (CASRN 513-35-9)
Rainbow trout (*Oncorhynchus mykiss*) were exposed to 2-methyl-2-butene under closed system for 96 hours. The overall mean measured concentrations were 1.67, 2.93, 5.33, 8.51 and 25.9 mg/L.
96-h LC_{50} = 5.0 mg/L

Acute Toxicity to Aquatic Invertebrates

Pyrolysis C_{5s}
Daphnia magna were exposed to pyrolysis C_{5s} under closed system for 48 hours. The overall mean measured concentrations were 1.41, 3.23, 6.83, 15.6 and 27.2 mg/L.
48-h EC_{50} = 4.7 mg/L

Hydrotreated C_{5s}
Daphnia magna were exposed to hydrotreated C_{5s} under closed system for 48 hours. The overall mean measured concentrations were 0.338, 0.783, 3.60, 6.77 and 15.3 mg/L.
48-h EC_{50} = 3.0 mg/L

Isoprene (CASRN 78-79-5)
Daphnia magna were exposed to CASRN 78-79-5 under closed system for 48 hours. The overall mean measured concentrations were 0.648, 1.55, 3.52, 9.47 and 25.4 mg/L.
48-h EC_{50} = 5.8 mg/L

2-methyl-2-butene (CASRN 513-35-9)
Daphnia magna were exposed to CASRN 513-35-9 under closed system for 48 hours. The overall mean measured concentrations were 0.691, 1.74, 2.95, 6.63 and 23.6 mg/L.
48-h EC_{50} =3.8 mg/L

Toxicity to Aquatic Plants

Pyrolysis C_{5s}
Green algae (*Pseudokirchneriella subcapitata.*) were exposed to pyrolysis C_{5s} under closed system for 96 hours. Results for the measured concentrations ranged between 15 and 38 % of their nominal values. The overall mean measured concentrations were 1.22, 3.26, 6.47, 7.84 and 30.6 mg/L.
96-h EC_{50} (growth rate) = 18.4 mg/L
96-h EC_{50} (biomass) = 11.7 mg/L

Hydrotreated C_{5s}
Green algae (*Pseudokirchneriella subcapitata.*) were exposed to hydrotreated C_{5s} under closed system for 96 hours. Results for the measured concentrations varied and ranged between 21and 147 % of their nominal values. The overall mean measured concentrations were 16.9, 12.1, 13.1, 24.7 and 25.1 mg/L.
96-h EC_{50} (growth rate) > 25.1 mg/L
96-h EC_{50} (biomass) > 25.1 mg/L

Isoprene (CASRN 78-79-5)
Green algae (*Pseudokirchneriella subcapitata.*) were exposed to CASRN 78-79-5 under closed system for 96 hours. The overall mean measured concentrations were 0.846, 1.68, 6.00, 10.3 and 35.2 mg/L. .
96-h EC_{50} (growth rate) > 35.2 mg/L
96-h EC_{50} (biomass) = 15.5 mg/L

2-methyl-2-butene (CASRN 513-35-9)
Green algae (*Pseudokirchneriella subcapitata.*) were exposed to CASRN 513-35-9 under closed system for 96 hours. The overall mean measured concentrations were 0.689, 1.53, 3.61, 7.22 and 21.1 mg/L.
96-h EC_{50} (growth rate) = 13.2 mg/L
96-h EC_{50} (biomass) = 10.1 mg/L

Conclusion: The acute toxicity to fish is 5.0- 8.4 mg/L, to aquatic invertebrates is 3.0 -5.8 mg/L, and to aquatic plants is 10.1- 15.5 mg/L (biomass) and 13.2-18.4 mg/L (growth rate) for the chemicals in the C_5 non-cyclics category.

Table 6. Summary of Environmental Effects – Aquatic Toxicity Data			
Endpoints	**Fish 96-h LC_{50} (mg/L)**	**Aquatic Invertebrates 48-h EC_{50} (mg/L)**	**Aquatic Plants 72-h EC_{50} (mg/L)**
Pyrolysis C5s (CASRN 68476-55-1) (CASRN 68476-43-7) (CASRN 68527-19-5) (CASRN 68603-00-9) (CASRN 68956-55-8)	**8.4 (m)**	**4.7 (m)**	**11.7 (biomass, m)** **18.4 (growth rate, m)**
Hydrotreated C5s (CASRN 68602-79-9) (CASRN 68410-97-9) (CASRN 68603-00-9)	**5.3 (m)**	**3.0 (m)**	**>25.1 (biomass, m)** **>25.1(growth rate, m)**
Pentenes (CASRN 68476-55-1) (CASRN 68527-11-7) (CASRN 68603-03-2)	No data 5.0-8.4 (RA)	No data 3.0-5.8 (RA)	No data 10.1-15.5 (biomass) 13.2 -18.4 (growth rate) (RA)
Piperylene Concentrate (CASRN 68477-35-0) (CASRN 68742-83-2)	No data 5.0-8.4 (RA)	No data 3.0-5.8 (RA)	No data 10.1-15.5 (biomass) 13.2 -18.4 (growth rate) (RA)
Isoprene Concentrate (CASRN 68514-39-6) (CASRN 68476-43-7) (CASRN 78-79-5)	No data 5.0-8.4 (RA)	No data 3.0-5.8 (RA)	No data 10.1-15.5 (biomass) 13.2 -18.4 (growth rate) (RA)
Isoprene-Piperylene Concentrate (CASRN 68514-39-6) (CASRN 68476-55-1)	No data 5.0-8.4 (RA)	No data 3.0-5.8 (RA)	No data 10.1-15.5 (biomass) 13.2 -18.4 (growth rate) (RA)
Isoprene (CASRN 78-79-5)	**7.4 (m)**	**5.8 (m)**	**15.5 (biomass, m)** **>35.2 (growth rate, m)**
Isoprene Purification Byproduct (CASRN 68606-36-0) (CASRN 68476-55-1)	No data 5.0-8.4 (RA)	No data 3.0-5.8 (RA)	No data 10.1-15.5 (biomass) 13.2 -18.4 (growth rate) (RA)
2-Methyl-2-Butene (CASRN 513-35-9)	**5.0 (m)**	**3.8 (m)**	**10.1 (biomass, m)** **13.2 (growth rate, m)**
Metathesis Byproduct (CASRN 68606-29-1)	No data 5.0-8.4 (RA)	No data 3.0-5.8 (RA)	No data 10.1-15.5 (biomass) 13.2 -18.4 (growth rate) (RA)

(m) = measured data (i.e. derived from testing)**;** (RA) = Read across

APPENDIX

The next two pages show:

- A table with a list of the major constituents in the category streams
- A figure showing how the C5 noncyclics category group of streams are made and used (taken from p. 28 in the revised Test Plan submission dated September 21, 2001 and posted January 11, 2002 on the HPV Challenge website [http://www.epa.gov/chemrtk/pubs/summaries/c5ncyl/c12801tc.htm])

Major Constituents in C5 Noncyclic Streams[1] (Expressed as Percentage of Stream)											
	"Primarily Dienes Streams"					"C5s With Little or No Diene Content"					No. of Streams Present @ >3%
Constituent	**Isoprene**[2]	Isoprene Conc.	Isoprene-Piperylene Conc	**Pyrolysis C5s**[2]	Piperylene Conc	**2-Methyl-2-Butene**[2]	Metathesis By-Product	Pentenes	**Hydrotreated C5s**[2]	Isoprene Purification By-product	
2-Butene (isomer mix)		1-20					3				2
1,3-Butadiene				0-3							1
Isoprene	99.7	14-80	20	9-25	0-6					1-12	6
1,4-Pentadiene		0-4	3	1-6						1-10	4
1,3-Pentadiene		1-15	14	6-23	31-60						4
3-Methyl-1,2-butadiene		3.5									1
1,3-Cyclopentadiene		0-15		2-23	4				5		4
Dicylclopentadiene				1-19							1
Cyclopentene		0-10	4	1-11	8-20				15-20		5
Cyclopentane		8-15									1
Isopentene									15-20		1
1-Pentene		0-10	6	3-12			3	13.7		3-11	6
2-Pentene		1-16	5	2-10	1-10		41	18		3-9	7
2-Methyl-2-butene		0-9	3	1-5	5-15	93		4	11		7
2-Methyl-1-butene		1-16	6	1-8		6.7		17.5			5
3-Methyl-1-butene				0-12							1
Pentane		0-26	16	4-30	0-5			31.7	15-20	0-10	7
Methyl butenes										3-21	1
2-Methyl-butane		21	16	3-29				12.3	15-25	50-70	6
n-Pentene									10-15		1
Methyl-pentenes					5						1
C6 Hydrocarbons		0-3		2-4	1-5						3
Hexenes				0-3			27				2
Methyl-2-Pentenes							24				1
2-Methyl-Pentane									5		1
Methylpentanes					16						1
Hexane					3.3						1

[1] Adapted from Table 2 in *Category Summary for C5 Noncyclics Category* (dated Dec 13, 2004 and found at: http://www.epa.gov/chemrtk/pubs/summaries/c5ncyl/c12801tc.htm). Only constituents listed as >3% are presented. If a range was reported, and 3% fell within the range, it was reported. The original Table 2 listed 37 total constituents, by restricting this listing to those >3% (and combining four different hexenes into one), 27 constituents are presented. Dienes are highlighted in yellow.
[2] Animal studies are available for these four category members.

Figure 1. Chemical process operations associated with process streams in the C5 Noncyclics category.