

Robust Summary - Group 3: C5 Non-Cyclics

Acute Toxicity

<p><u>Test Substance</u></p>	Isoprene, CAS# 78-79-5
<p><u>Method</u> Method/guideline followed Type (test type) GLP Year Species/Strain Sex No. of animals per sex per dose Vehicle Route of administration</p>	<p>Other. Acute inhalation -LC₅₀ Pre-GLP 1969 Rat and mouse (strains not specified) Not specified Not specified Not applicable Inhalation (vapor)</p>
<p>Test Conditions</p>	<p>Age, number, and sex of test animals not specified. Number of groups and exposure concentrations not specified. Dynamic flow exposure system; no description of exposure chambers or conditions. Rats exposed four hours; mice exposed two hours. No post-exposure observation period - mortality study only. Exposure concentrations "controlled" by gas chromatography. LC50 calculation by probit-analysis according to Litchfield and Wilcoxon.</p>
<p><u>Results</u> LC₅₀ with confidence limits.</p>	<p>Rat LC₅₀ (4 hr) = 180 mg/L (64,620 ppm); confidence limits 130-181 mg/L (p≤0.05). Mouse LC₅₀ (2 hr) = 157 mg/L (56,363 ppm); confidence limits 129-252 mg/L (p≤0.05).</p> <p>No clinical observations or necropsy findings reported. Objective of study was to determine hydrocarbon concentrations in various tissues at lethal exposure concentrations.</p>
<p><u>Conclusions</u> (study author)</p>	<p>LC50 value reported to be 180 mg/L (64,620 ppm) in rats, 157 mg/L (56,363 ppm) in mice.</p>
<p><u>Data Quality</u> Reliability</p>	<p>4 - Not assignable. Lethality study only; insufficient experimental detail to assess quality.</p>
<p><u>References</u></p>	<p>Shugaev, B.B. (1969) Concentrations of Hydrocarbons in Tissues as a Measure of Toxicity. Arch. Environ. Health 18:878-882.</p>
<p><u>Other</u> Last changed</p>	<p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>

Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vitro

<p><u>Test Substance</u> <i>Test substance</i></p> <p><u>Method</u> Method/guideline followed Type System of testing GLP Year Species/Strain Metabolic activation Species and cell type Quantity Induced or not induced Concentrations tested Statistical Methods</p> <p>Test Conditions</p> <p><u>Results</u> Genotoxic effects</p> <p><u>Conclusions</u> (contractor)</p> <p><u>Data Quality</u> <i>Reliabilities</i></p> <p><u>Reference</u></p> <p><u>Other</u> <i>Last changed</i></p>	<p>Isoprene, CAS# 78-79-5 Purity >99%.</p> <p>OECD 471 Ames <i>Salmonella</i>/bacterial reverse mutation test (pre-incubation assay). Bacterial. Yes. 1986 <i>Salmonella</i> / TA98, TA100, TA1535, TA1537. With and without. Rat and hamster liver S9 fraction. 0.5 ml/plate. Arochlor 1254-induced (500 mg/kg for 5 days). 0, 100, 333, 1000, 3333, 10000 ug/plate. A positive response was defined as a reproducible, dose-related increase in revertant colonies in any one strain/activation combination. There was no minimum percentage or fold increase required for the chemical to be judged positive or weakly positive.</p> <p>The preincubation modification of the <i>Salmonella</i>/mammalian microsome assay was used to test isoprene in five different <i>Salmonella</i> strains in the presence and absence of rat and hamster liver S-9. Five dose levels were tested , with three plates per dose level. The high dose was limited by toxicity to 10,000 ug/plate. Concurrent positive controls were also tested with and without metabolic activation. The assay was repeated less than one week after completion of the initial test.</p> <p>Negative. Isoprene was not mutagenic in any of the five strains of <i>Salmonella</i> tested in the presence or absence of Arochlor-induced rat or hamster liver S9.</p> <p>Isoprene was not mutagenic in the Ames Salmonella mutagenicity test.</p> <p>1 - Reliable without restrictions. Evaluated as part of a NTP-sponsored interlaboratory study of 270 chemicals.</p> <p>Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., and Zeiger, E. (1986) <i>Salmonella</i> mutagenicity tests: II. Results from the testing of 270 chemicals. <i>Environ. Mutagen.</i> 8 (Suppl. 7): 1-119.</p> <p>20-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vitro

<p><u>Test Substance</u> Test substance</p> <p><u>Method</u> Method/guideline followed Type System of testing GLP Year Metabolic activation Concentrations tested Control groups and treatment</p> <p>Statistical Methods</p> <p>Test Conditions</p> <p><u>Results</u> Genotoxic effects</p> <p><u>Conclusions</u> (contractor)</p> <p><u>Data Quality</u> Reliabilities</p> <p><u>Reference</u></p> <p><u>Other</u> Last changed</p>	<p>Isoprene, CAS# 78-79-5 Purity >99%.</p> <p>OECD 479 <i>In vitro</i> Sister Chromatid Exchange (SCE) Assay in Mammalian Cells Chinese hamster ovary (CHO) cells. Yes. 1987. Aroclor 1254-induced Sprague-Dawley rat liver S9. 50, 160, 500, 1600 ug/ml (without S9), or 160, 500, 1600, 5000 ug/ml (with S9). Solvent controls: dimethylsulfoxide; positive controls: Mitomycin-C (without S9), cyclophosphamide (with S9). Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points. A frequency 20% above the solvent control group was considered positive. Positive trend tests ($p \leq 0.05$) in the absence of a significant difference at any one dose were considered equivocal.</p> <p>Isoprene was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) both in the presence and absence of Aroclor 1254-induced Sprague-Dawley rat liver S9. The test included concurrent solvent and positive controls and four doses of isoprene. A single flask per dose was used. All slides were scored blind and those from a single test were read by the same person. Fifty 2nd-division metaphase cells were scored for frequency of SCEs/cell from each dose level.</p> <p>Negative. No increases in SCEs were noted in cultured CHO cells treated with isoprene, with or without S9.</p> <p>Isoprene did not induce sister chromatid exchanges <i>in vitro</i> in cultures of Chinese hamster ovary cells.</p> <p>1 - Reliable without restrictions. Evaluated as part of an NTP-sponsored study of 108 chemicals.</p> <p>Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. <i>Environ Mol. Mutagen</i> 10:1-175.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vitro

<p><u>Test Substance</u> Test substance</p> <p><u>Method</u> Method/guideline followed Type System of testing GLP Year Metabolic activation Concentrations tested Control groups and treatment</p> <p>Statistical Methods</p> <p>Test Conditions</p> <p><u>Results</u> Genotoxic effects</p> <p><u>Conclusions</u> (contractor)</p> <p><u>Data Quality</u> Reliabilities</p> <p><u>Reference</u></p> <p><u>Other</u> Last changed</p>	<p>Isoprene, CAS# 78-79-5 Purity >99%.</p> <p>OECD 473 <i>In vitro</i> Mammalian Chromosomal Aberration Test. Chinese hamster ovary (CHO) cells. Yes. 1987. Aroclor 1254-induced Sprague-Dawley rat liver S9. 1600, 3000, 5000 ug/ml. Solvent control: dimethylsulfoxide; positive controls: Mitomycin-C (without S9), cyclophosphamide (with S9). Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points. A statistically significant ($p \leq 0.05$) difference for one point and a significant trend ($p \leq 0.015$) was considered positive. Positive trend tests ($p \leq 0.05$) in the absence of a significant difference at any one dose were considered equivocal.</p> <p>Isoprene was tested in cultured Chinese hamster ovary (CHO) cells for induction of chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced Sprague-Dawley rat liver S9. The test included concurrent solvent and positive controls and three doses of isoprene. A single flask per dose was used. All slides were scored blind and those from a single test were read by the same person. Two hundred 1st-division metaphase cells were scored for chromosomal aberrations at each dose level.</p> <p>Negative. No increases in chromosomal aberrations were noted in cultured CHO cells treated with isoprene, with or without S9.</p> <p>Isoprene did not induce chromosomal aberrations <i>in vitro</i> in cultures of Chinese hamster ovary cells.</p> <p>1 - Reliable without restrictions. Evaluated as part of a NTP-sponsored study of 108 chemicals.</p> <p>Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. <i>Environ Mol. Mutagen</i> 10:1-175.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity – In Vivo

<p><u>Test Substance</u></p> <p>Remarks</p> <p><u>Method</u></p> <p>Method/guideline followed</p> <p>Type</p> <p>GLP</p> <p>Year</p> <p>Species</p> <p>Strain</p> <p>Sex</p> <p>Route of administration</p> <p>Doses/concentration levels</p> <p>Exposure period</p> <p>Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u></p> <p>Genotoxic effects</p> <p>NOAEL (NOEL)</p> <p>LOAEL (LOEL)</p> <p><u>Conclusions</u></p> <p>(study authors)</p> <p><u>Data Quality</u></p> <p>Reliabilities</p> <p><u>References</u></p> <p>Other</p> <p>Last changed</p>	<p>Isoprene, CAS# 78-79-5</p> <p>Purity >98%.</p> <p>Other.</p> <p><i>In vivo</i> Sister Chromatid Exchange (mouse bone marrow cytogenetics study) .</p> <p>Yes.</p> <p>1988.</p> <p>Mouse</p> <p>B6C3F1.</p> <p>15 male/group.</p> <p>Inhalation (vapor).</p> <p>0, 438, 1750, 7000 ppm.</p> <p>6 hours/day for 12 days.</p> <p>The frequencies of sister chromatid exchanges (SCEs) were analyzed for increasing trend by the one-tailed Cochran-Armitage trend test ($p < 0.05$). For data exhibiting a significant trend, pairwise comparisons between each exposure group and the concurrent control were performed using either the one-tailed or two-tailed t-test.</p> <p>Fifteen male B6C3F1 mice (approximately 6-7 weeks old) per group were exposed for 12 days, 6 h/day to 0, 438, 1750, or 7000 ppm of isoprene by inhalation. The exposure regimen was 3 exposure days, 2 days off, 5 exposure days, 2 days off, then 4 exposure days. Exposure concentrations were monitored by gas chromatography. The animals were implanted with a BrdU tablet 1 hour before the 12th exposure. Two hours before sacrifice on the following day, the animals received an intraperitoneal injection of colchicine. For analysis of SCE, 5 mice per exposure group were killed 24 hours after BrdU implantation. Bone marrow was removed, fixed onto slides, and stained using differential chromatid staining. Twenty-five second-division metaphase cells were scored for SCEs from 4 mice/group. Additionally, 100 randomly selected metaphase cells per slide were scored for replication history to provide data on cell generation time, a measure of cell proliferation kinetics. The percentage of cell in metaphase among 1000 cells/sample was used to calculate the mitotic index.</p> <p>Positive.</p> <p><438 ppm.</p> <p>438 ppm.</p> <p>Exposure to isoprene for 6 h/day at 0, 438, 1750, or 7000 ppm for 12 days induced a significant increase in the frequency of SCEs in bone marrow cells. The increased SCE responses in the exposed groups were not significantly different from each other. Analysis of average generation time and mitotic index data indicated no change in the percentage of bone marrow cells engaged in division but a significant lengthening of the cell cycle duration of proliferating cells in the 7000 ppm group. There were no significant clinical signs or mortality throughout the study.</p> <p>Isoprene was found to be genotoxic and cytotoxic to mouse bone marrow <i>in vivo</i> - inducing SCE, inhibiting cellular proliferation, and suppressing the rate of erythropoiesis. The lack of significant difference in SCEs among the three exposed groups suggests a saturation of the metabolic capacity of male mice to form reactive species.</p> <p>1 - Reliable without restrictions. NTP-sponsored study.</p> <p>Tice, R.R., Boucher, R., Luke, C.A., Paquette, D.E., Melnick, R.L., and Shelby, M.D. (1988). Chloroprene and isoprene: cytogenetic studies in mice. <i>Mutagenesis</i> 3(2):141-146.</p> <p>26-Apr-00</p> <p>Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Type GLP Year Species Strain Sex Route of administration Doses/concentration levels Exposure period Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u> Genotoxic effects NOAEL (NOEL) LOAEL (LOEL)</p> <p><u>Conclusions</u> (study authors)</p> <p><u>Data Quality</u> Reliabilities</p> <p><u>References</u></p> <p>Other Last changed</p>	<p>Isoprene, CAS# 78-79-5 Purity >98%.</p> <p>OECD 475 Mammalian Bone Marrow Chromosomal Aberration Test. Yes. 1988. Mouse B6C3F1 15 male/group. Inhalation (vapor). 0, 438, 1750, 7000 ppm. 6 hours/day for 12 days. The frequencies of chromosomal aberrations (Abs) were analyzed for increasing trend by the one-tailed Cochran-Armitage trend test (p<0.05). For data exhibiting a significant trend, pairwise comparisons between each exposure group and the concurrent control were performed using either the one-tailed or two-tailed t-test.</p> <p>Fifteen male B6C3F1 mice (approximately 6-7 weeks old) per group were exposed for 12 days, 6 h/day to 0, 438, 1750, or 7000 ppm of isoprene by inhalation. The exposure regimen was 3 exposure days, 2 days off, 5 exposure days, 2 days off, then 4 exposure days. Exposure concentrations were monitored by gas chromatography. The animals were implanted with a BrdU tablet 1 hour before the 12th exposure. Two hours before sacrifice on the following day, the animals received an intraperitoneal injection of colchicine. For analysis of Abs, 10 mice per exposure group were killed 17-20 hours after BrdU implantation. Bone marrow was removed, fixed onto slides, and stained using differential chromatid staining. Fifty first-division metaphase cells were scored for Abs from 8 mice/group.</p> <p>Negative. 7000 ppm >7000 ppm</p> <p>Exposure to isoprene for 6 h/day at 0, 438, 1750, or 7000 ppm for 12 days did not induce a statistically significant increase in the frequency of chromosomal aberrations (Abs) in bone marrow cells. The incidence of bone marrow cells with chromosomal aberrations (Abs) was slightly elevated in the exposed groups compared to the control, but these increases were not statistically significant.</p> <p>The incidence of bone marrow cells with chromosomal aberrations in male mice treated with isoprene for 12 days was not significantly increased.</p> <p>1 - Reliable without restrictions. NTP-sponsored study.</p> <p>Tice, R.R., Boucher, R., Luke, C.A., Paquette, D.E., Melnick, R.L., and Shelby, M.D. (1988). Chloroprene and isoprene: cytogenetic studies in mice. <i>Mutagenesis</i> 3(2):141-146.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Type GLP Year Species Strain Sex Route of administration Doses/concentration levels Exposure period Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u> Genotoxic effects NOAEL (NOEL) LOAEL (LOEL)</p> <p><u>Conclusions</u> (study authors)</p> <p><u>Data Quality</u> Reliabilities</p> <p><u>References</u></p> <p>Other Last changed</p>	<p>Isoprene, CAS# 78-79-5 Purity >98%.</p> <p>OECD 474 Mammalian Erythrocyte Micronucleus Test Yes. 1988. Mouse B6C3F1 15 male/group. Inhalation (vapor). 0, 438, 1750, 7000 ppm. 6 hours/day for 12 days. The number of micronucleated erythrocytes (MN) were summed across animals within each group and analyzed for increasing trend by a one-tailed trend test (p<0.05). For data exhibiting a significant trend, pairwise comparisons between each exposure group and the concurrent control were performed using a one-tailed Pearson Chi square test to determine the minimal effective dose.</p> <p>Approximately 24 hours following the last exposure peripheral blood samples were obtained from each animal by tail snip, immediately air-dried and fixed with methanol. One thousand polychromatic erythrocytes (PCEs) and 1000 normochromatic erythrocytes (NCEs) were scored per animal for frequency of micronucleated erythrocytes (MN). The percentage of PCEs in 1000 erythrocytes was also determined as a measure of isoprene-induced toxicity.</p> <p>Positive. <438 ppm. 438 ppm.</p> <p>Exposure to isoprene for 6 h/day at 0, 438, 1750, or 7000 ppm for 12 days induced a statistically significant increase in the frequency of micronucleated PCEs and NCEs in male mice at all exposure levels tested. The responses at the 1750 and 7000 ppm levels were greater than the 438 ppm level, but not different from each other. There were no significant clinical signs or mortality throughout the study.</p> <p>Isoprene was found to be genotoxic to mouse bone marrow <i>in vivo</i> by inducing increased MN in the peripheral blood of male mice.</p> <p>1 - Reliable without restrictions. NTP-sponsored study.</p> <p>Tice, R.R., Boucher, R., Luke, C.A., Paquette, D.E., Melnick, R.L., and Shelby, M.D. (1988). Chloroprene and isoprene: cytogenetic studies in mice. <i>Mutagenesis</i> 3(2):141-146.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Type GLP Year Species Strain Sex Route of administration Doses/concentration levels Exposure period Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u> Genotoxic effects</p> <p><u>Conclusions</u> (study authors)</p> <p><u>Data Quality</u> Reliabilities</p> <p><u>References</u></p> <p>Other Last changed</p>	<p>Isoprene, CAS# 78-79-5 Purity >99.7%.</p> <p>Other. Rat Lung Fibroblast Micronucleus Test Yes. 1997. Rat Fischer 344 10 male and 10 female/group. Inhalation (vapor). 0, 220, 700, or 7000 ppm. 6 hours/day, 5 days/week, for 4 weeks. Means, standard deviations, and standard error of the mean for the number of mononucleated cells/1000 binucleated cells and micronuclei/1000 binucleated cells were calculated. A two-way analysis of variance was used to analyze the measurements. Intergroup differences were delineated by Tukey's studentized range test.</p> <p>This study was performed in conjunction with a two-year carcinogenicity study. Groups of 10 male and 10 female rats (approximately 6-7 weeks old) per group were exposed for 4 weeks (17-19 total exposures) to 0, 220, 700, or 7000 ppm of isoprene by inhalation. The rats received at least two consecutive days of exposure prior to sacrifice and lung cell isolation. Lung fibroblasts were isolated and cultured in single-chamber slides for 72 hours. The slides were fixed and stained (acridine orange), and 1000 binucleated cells on each of two slides per animal were scored. The number of mononucleated cells and micronuclei were recorded following a standard scoring criteria.</p> <p>Negative.</p> <p>There were no statistically significant differences between the male or female exposed and control groups for micronucleated rat lung fibroblasts. There were no significant clinical signs or mortality during the exposure period.</p> <p>No significant increase in the frequency of micronucleated lung fibroblasts was observed in male and female rats exposed to isoprene for 4 weeks.</p> <p>2 - Reliable with restrictions. Non-standard method, but comparable to guideline study. Conducted as part of NTP two-year carcinogenicity study.</p> <p>National Toxicology Program (1997). Toxicology and Carcinogenesis Studies of Isoprene (CAS No. 78-79-5) in F344/N Rats (Inhalation Studies). Report No. TR-486.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Repeated Dose Toxicity

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Test type GLP Year Species Strain Route of administration Duration of test Doses/concentration levels Sex Exposure period Frequency of treatment Control group and treatment Post exposure observation period Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u> NOAEL (NOEL) LOAEL (LOEL)</p> <p><u>Conclusions</u> (contractor)</p> <p><u>Data Quality</u> Reliabilities</p> <p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>Isoprene, CAS# 78-79-5 Purity >99%.</p> <p>Other. 2-week inhalation study. Yes. 1990. Rat and mouse. F344 rats and B6C3F1 mice. Inhalation (vapor). 2 weeks. 0, 438, 875, 1750, 3500, or 7000 ppm. 20 male, 20 female per group. 6 hours/day. 5 days/week. 20 male, 20 female, air-only exposed. Not applicable. Group mean body weights, organ weights, organ weight ratios, and clinical pathology results compared to controls by Dunnett's t-test.</p> <p>Groups of 20 animals /sex /group/species (6-8 weeks age at study initiation) were exposed to various levels of isoprene for 6 hrs/day, 5 days/week for two weeks (10 exposures). Ten animals/sex/group/species were used for clinical pathology evaluations after 4 (rats) or 5 (mice) exposures. The remaining ten animals per group were used for histopathology at the end of the study. Body weights and clinical observations were recorded weekly. Necropsies were performed and major tissues/organs preserved. Histopathologic examinations were performed on the control and high exposure animals (7000 ppm), and lower dose groups until an apparent no-observed -effect level was found.</p> <p>7000 ppm rats, not determined for mice. >7000 ppm rats, 438 ppm mice.</p> <p>In rats, there were no exposure-related effects observed for survival, body weight gain, clinical signs, hematologic or clinical chemistry parameters, organ weights, or the incidence of gross or microscopic lesions. In mice, there were no effects on survival; the mean body weight gain of males in the 7,000 ppm group was less than that of the controls. In mice, exposure to isoprene caused decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts in all exposed groups. Organ weight changes were observed in both male and female mice; increased liver weights and decreased thymus, spleen, and testis weights were observed in all exposed groups. Microscopic lesions observed in the exposed mice included atrophy of the testis and thymus, cytoplasmic vacuolization of the liver, olfactory epithelial degeneration in the nasal cavity, and epithelial hyperplasia in the forestomach.</p> <p>Isoprene exposures over 2 weeks induced changes in hematological parameters, body and organ weights, and microscopic appearances in certain tissues at levels as low as 438 ppm in the mouse whereas no changes were noted in measured parameters in the rat at exposures up to 7000 ppm. The lack of any observable toxicological effects in F344 rats exposed to isoprene for two weeks provides evidence for a species difference between rats and mice in susceptibility to isoprene.</p> <p>1 - Reliable without restrictions. Comparable to guideline study (OECD 412).</p> <p>Melnick, R.L., Roycroft, J.H., Chou, B.J., Ragan, H.A., and Miller, R.A. (1990). Inhalation toxicology of isoprene in F344 and B6C3F1 mice following two-week exposures. Environ. Health Perspect. 86:93-98.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Repeated Dose Toxicity

<p><u>Test Substance</u></p> <p>Remarks</p> <p><u>Method</u></p> <p>Method/guideline followed</p> <p>Test type</p> <p>GLP</p> <p>Year</p> <p>Species</p> <p>Strain</p> <p>Route of administration</p> <p>Duration of test</p> <p>Doses/concentration levels</p> <p>Sex</p> <p>Exposure period</p> <p>Frequency of treatment</p> <p>Control group and treatment</p> <p>Post exposure observation period</p> <p>Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u></p> <p>NOAEL (NOEL)</p> <p>LOAEL (LOEL)</p> <p><u>Conclusions</u></p> <p>(contractor)</p> <p><u>Data Quality</u></p> <p>Reliabilities</p> <p><u>References</u></p> <p><u>Other</u></p> <p>Last changed</p>	<p>Isoprene, CAS# 78-79-5</p> <p>Purity >99%.</p> <p>Other.</p> <p>13-week inhalation study.</p> <p>Yes.</p> <p>1994.</p> <p>Rat and mouse.</p> <p>F344 rats and B6C3F1 mice.</p> <p>Inhalation (vapor).</p> <p>13 weeks.</p> <p>0, 70, 220, 700, 2200, or 7000 ppm.</p> <p>10 male, 10 female per group.</p> <p>6 hours/day.</p> <p>5 days/week.</p> <p>10 male, 10 female, air-only exposed.</p> <p>Not applicable.</p> <p>Analysis of survival and incidence of neoplastic and nonneoplastic lesions was performed. Clinical chemistry, hematology, and urine data were analyzed by nonparametric methods.</p> <p>Groups of 10 animals /sex /group/species (6-8 weeks age at study initiation) were exposed to various levels of isoprene for 6 hrs/day, 5 days/week for thirteen weeks. Body weights and clinical observations were recorded weekly. Blood samples were collected for clinical pathology evaluations on days 4, 24, and at the end of the study. Urine samples were collected from rats during week 12. After thirteen weeks of exposures, all rats and mice were sacrificed and evaluated histopathologically. Organ weights were recorded.</p> <p>7000 ppm rats, 220 ppm mice.</p> <p>>7000 ppm rats, 700 ppm mice.</p> <p>In rats, 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. In mice, there were no effects on survival, body weight gain, or clinical signs of toxicity. The male and female mice exposed to 700 ppm and higher showed hematologic effects indicative of a nonresponsive, macrocytic anemia at day 24 and after thirteen weeks. The incidences of focal epithelial hyperplasia of the forestomach were 0, 0, 0, 9, 8, 9 in the males, and 0, 0, 0, 10, 9, 10 in the females at 0, 70, 220, 700, 2200, and 7000 ppm (n=10). Degeneration of the olfactory epithelium and cytoplasmic degeneration of the liver were observed in 10/10 male mice at 7000 ppm. The male mice exposed to 7000 ppm exhibited testicular weights reduced 35% compared to the controls.</p> <p>No toxicological effects were evident in rats exposed up to 7000 ppm isoprene for 13 weeks. In mice, hematological and histopathological changes were observed at exposures of 700 ppm and higher. This 13-week subchronic inhalation study, conducted as part of a 26-week carcinogenicity study, confirmed the species difference between rats and mice in susceptibility to isoprene.</p> <p>1 - Reliable without restrictions. Comparable to guideline study (OECD 413).</p> <p>Melnick RL; Sills RC; Roycroft JH; Chou BJ; Ragan HA; Miller RA (1994). Isoprene, an endogenous hydrocarbon and industrial chemical, induces multiple organ neoplasia in rodents after 26 weeks of inhalation exposure. Cancer Res. 54:5333-5339.</p> <p>21-Aug-00</p> <p>Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Repeated Dose Toxicity

<p><u>Test Substance</u></p> <p>Remarks</p> <p><u>Method</u></p> <p>Method/guideline followed</p> <p>Test type</p> <p>GLP</p> <p>Year</p> <p>Species</p> <p>Strain</p> <p>Route of administration</p> <p>Duration of test</p> <p>Doses/concentration levels</p> <p>Sex</p> <p>Exposure period</p> <p>Frequency of treatment</p> <p>Control group and treatment</p> <p>Post exposure observation period</p> <p>Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u></p> <p>NOAEL (NOEL)</p> <p>LOAEL (LOEL)</p> <p><u>Conclusions</u></p> <p>(study authors)</p> <p><u>Quality</u></p> <p>Reliabilities</p>	<p>Isoprene, CAS# 78-79-5 Purity >99%.</p> <p>Other.</p> <p>26-week inhalation study.</p> <p>Yes.</p> <p>1994.</p> <p>Rat and mouse.</p> <p>F344 rats and B6C3F1 mice.</p> <p>Inhalation (vapor).</p> <p>26 weeks.</p> <p>0, 70, 220, 700, 2200, or 7000 ppm.</p> <p>40 male rats and 40 male mice per group.</p> <p>6 hours/day.</p> <p>5 days/week.</p> <p>40 male rats and 40 male mice, air-only exposed.</p> <p>26-week post-exposure recovery period.</p> <p>Analysis of survival and incidence of neoplastic and nonneoplastic lesions was performed. Clinical chemistry, hematology, and urine data were analyzed by nonparametric methods.</p> <p>Groups of 40 animals /sex /group/species (6-8 weeks age at study initiation) were exposed to various levels of isoprene for 6 hrs/day, 5 days/week for 26 weeks. At the end of the 26-week exposure period, 10 rats and 10 mice/group were sacrificed and evaluated. The remaining animals were allowed to recovery for an additional 26 weeks without exposure at which time they were also sacrificed and evaluated. Body weights and clinical observations were recorded weekly throughout the study. Blood samples were collected for clinical pathology evaluations after 26 weeks exposure. Tissues preserved at the 26 and 52 week sacrifices were examined microscopically. Organ weights were recorded at both intervals. Twenty mice/group 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.</p> <p>>7000 ppm rats, 70 ppm mice. 7000 ppm rats, 700 ppm mice.</p> <p>The only effect observed in the male rats after 26 weeks of exposure was interstitial cell hyperplasia of the testis (10/10) in the 7000 ppm group; following the 26-week recovery period the only effect in rats was a marginal increase in benign testicular interstitial cell tumors (9/30 at 7000 ppm). Survival of mice was reduced in the 7000 ppm group; early deaths were attributed to various neoplastic lesions and moribund sacrifices due to hindlimb paralysis. In male mice, incidences of malignant neoplastic lesions in the liver, lung, forestomach, and harderian gland were significantly increased following the 26-week exposure and 26-week recovery periods at 700 ppm and higher exposures. Non-neoplastic lesions were observed in male mice exposed to isoprene and included spinal cord degeneration (≥ 70 ppm) and degeneration of the olfactory epithelium (≥ 220 ppm). Slight increases in testicular atrophy, epithelial hyperplasia of the forestomach, partial hindlimb paralysis and a nonresponsive macrocytic anemia were also seen in male mice.</p> <p>Isoprene was carcinogenic to the liver, lung, forestomach, and harderian gland of male mice after 26 weeks exposure and 26 weeks recovery. In contrast, the only effect observed in male rats was a marginally increased incidence of benign testicular adenomas at the highest exposure level (7000 ppm).</p> <p>2 - Reliable with restrictions. Comparable to guideline studies. This study involved exposures of male rats and male mice to isoprene for 6 months, therefore provided</p>
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<p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>additional data on repeated dose toxicity and carcinogenicity.</p> <p>Melnick RL; Sills RC; Roycroft JH; Chou BJ; Ragan HA; Miller RA (1994). Isoprene, an endogenous hydrocarbon and industrial chemical, induces multiple organ neoplasia in rodents after 26 weeks of inhalation exposure. Cancer Res. 54:5333-5339.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Repeated Dose Toxicity

<p><u>Test Substance</u></p> <p>Remarks</p> <p><u>Method</u></p> <p>Method/guideline followed</p> <p>Test type</p> <p>GLP</p> <p>Year</p> <p>Species</p> <p>Strain</p> <p>Route of administration</p> <p>Duration of test</p> <p>Doses/concentration levels</p> <p>Sex</p> <p>Exposure period</p> <p>Frequency of treatment</p> <p>Control group and treatment</p> <p>Post exposure observation period</p> <p>Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u></p> <p>NOAEL (NOEL)</p> <p>LOAEL (LOEL)</p> <p><u>Conclusions</u> (contractor)</p>	<p>Isoprene, CAS# 78-79-5 Purity >99.7%.</p> <p>Other 2-year carcinogenicity study. Yes. 1997. Rat. Fisher 344. Inhalation (vapor). 104 weeks. 0, 220, 700, or 7000 ppm. 50 male, 50 female per group. 6 hours/day. 5 days/week for 104 weeks. 50 male, 50 female, exposed to air only. None. Analysis of survival and incidence of neoplastic and nonneoplastic lesions was performed. Urine data was analyzed by nonparametric methods.</p> <p>Groups of 50 rats/sex /group (approx. 6 weeks age at study initiation) were exposed to various levels of isoprene for 6 hrs/day, 5 days/week for 104 weeks. Individual clinical observations were recorded initially, monthly through week 89, and then every 2 weeks until the end of the study. Individual body weights were recorded initially, monthly through week 91, and then every 2 weeks until the end of the study. Urine samples were collected 3, 6, 12, and 18 months from 10 rats/sex/group and analyzed for urine weight, creatinine, and vinyl lactic acid (a metabolite of isoprene). After 104 weeks of exposure, necropsies were performed on all rats and all major tissues preserved. Histopathologic examinations were performed on all tissues from all study animals. No blood analyses or organ weights were performed.</p> <p>Not determined Not determined</p> <p>Survival of all exposed groups was similar to the chamber controls. There were no exposure-related changes in clinical observations or body weights. The incidences of mammary gland fibroadenoma in 7,000 ppm males and in all groups of exposed females were significantly greater than those in the chamber control groups. The incidences of renal tubule adenoma in 700 and 7,000 ppm males and of renal tubule hyperplasia in 7,000 ppm males were significantly greater than those in the chamber controls. The severity of kidney nephropathy was slightly increased in 7,000 ppm males when compared to chamber controls. An exposure-related increase in the incidences of interstitial cell adenoma of the testis was observed in male rats. The incidences of bilateral interstitial cell adenoma and of unilateral and bilateral interstitial cell adenoma (combined) of the testis in 700 and 7,000 ppm males were significantly greater than those in the chamber controls. Single incidences of several rare neoplasms including benign astrocytoma, malignant glioma, malignant medulloblastoma, benign meningeal granular cell tumor, and meningeal sarcoma were observed in the brains of female rats in all three exposure groups. The incidences of splenic fibrosis in the 700 and 7,000 ppm males were significantly greater than that in the chamber control group.</p> <p>Isoprene exposures were associated with increases in rates of benign tumors in the testes and kidney (male), and mammary gland (male and female). No significant increases were seen for malignant tumors in this study. For this reason, and the fact that brain tumors in females were of several distinct cell types, the overall level of evidence presented for the</p>
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<p><u>Data Quality</u> Reliabilities</p> <p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>carcinogenicity of isoprene in rats is, at most, limited.</p> <p>1 - Reliable without restrictions.</p> <p>National Toxicology Program (1997). Toxicology and Carcinogenesis Studies of Isoprene (CAS No. 78-79-5) in F344/N Rats (Inhalation Studies). Report No. TR-486.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Repeated Dose Toxicity

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Test type GLP Year Species Strain Route of administration Duration of test Doses/concentration levels Sex Exposure period Frequency of treatment Control group and treatment Post exposure observation period Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u> NOAEL (NOEL) LOAEL (LOEL)</p> <p><u>Conclusions</u> (study authors)</p>	<p>Isoprene, CAS# 78-79-5 Purity >99.0%.</p> <p>Other 2-year carcinogenicity study. Yes. 1996. Mouse. B6C3F₁. Inhalation (vapor). 105 weeks. 0, 10, 70, 140, 280, 700, 2200 ppm. 50 male, 50 female per group. 4 or 8 hours/day. Variable - 5 days/week for 20, 40, or 80 weeks. 50 male, 50 female, exposed to air only. Variable - animals held following exposures until week 96 or 105. Body weights, organ weights and hematology data were evaluated by analysis of variance (ANOVA) followed by Duncan's new multiple range test. Incidences of tumor types were analyzed using Fischer's exact test applied to each combination of exposure group and tumor type.</p> <p>Twelve groups of 50 male mice were exposed to 0, 10, 70, 140, 280, 700, or 2200 ppm for 4 or 8 hours/day, 5 days/week for 20, 40, or 80 weeks followed by a holding period until week 105. Three groups of 50 female mice were exposed to 0, 10, and 70 ppm for 8 hours/day for 80 weeks and also held for observation until week 105. Clinical observations and body weights were recorded weekly for 13 weeks and then monthly. Hematology and micronucleus evaluations were performed on 10 mice/group at 40 and 80 weeks. Complete histopathology evaluations were performed on organs and tissues from all mice.</p> <p>10 ppm 70 ppm</p> <p>The carcinogenic potential of isoprene was evaluated as a function of concentration, length of daily exposure, and weeks of exposure as independent variables. Exposure of mice to the varied concentrations and schedules did not produce any significant signs of general toxicity. There was a concentration-related effect on survival due to increases in selected tumor development and associated mortality. Survival was near or below 50% after 95 weeks for mice exposed >280 ppm for 80 weeks; surviving mice in these groups were necropsied during week 96. Isoprene exposure caused an increase in neoplasms of the lung, liver, Harderian gland, forestomach, lymphoreticular system of male mice and in the Harderian gland and pituitary gland of female mice at concentrations of 70 ppm and higher. The product of concentration and length/duration of exposure was not a sufficient basis for prediction of tumor risk. In the micronucleus evaluation, the mean incidence of micronuclei in peripheral blood was significantly increased at 700 ppm and higher after 80 weeks, and at 2200 ppm after 40 weeks (the 280 and 700 ppm groups were not sampled by protocol design).</p> <p>The results of this study indicated that concentration, length of daily exposure, and weeks of exposure did not affect tumor incidence equivalently and total cumulative exposure was not sufficient for predicting oncogenic risk from isoprene exposure in mice. There appeared to be threshold for oncogenic effects in mice, which varied by organ and tumor type. For male mice, the LOEL was 700ppm for lung tumor and hemangiosarcoma, 280</p>
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<p><u>Data Quality</u> Reliabilities</p> <p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>ppm for malignant forestomach tumors and histiocytic sarcomas, 140 ppm for liver tuors, and 70 pmm for Harderian gland tumors. For female mice, the LOEL was 70 ppm for total non-liver, non-lung adenomas and possibly for hemagiosarcomas.</p> <p>1 - Reliable without restrictions.</p> <p>Placke ME, Griffis L, Bird M, Bus J, Persing RL, and Cox LA Jr (1996). Chronic inhalation oncogenicity study of isoprene in B6C3F1 mice. Toxicology 113:253-62.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Developmental Toxicity/Teratogenicity

<p><u>Test Substance</u> Remarks</p>	<p>Isoprene, CAS# 78-79-5 Purity >99.7%.</p>
<p><u>Method</u> Method/guideline followed Test type GLP Year Species Strain Route of administration Concentration levels Sex Exposure period Frequency of treatment Control group and treatment Duration of test Statistical methods</p>	<p>OECD 414 Developmental toxicity (teratogenicity) study. Yes. 1989. Rat and mouse. Sprague-Dawley (rat) and CD-1/Swiss (mouse). Inhalation (vapor). 0, 280, 1400, or 7000 ppm. ~30 pregnant females per group; plus 10 virgin females per group for comparison. Gestation days 6-19 (rats) or 6-17 (mice). 6 hours/day. Air-exposed only. Females sacrificed on gestation day 20 (rats) or 18 (mice). Not specified.</p>
<p>Test Conditions</p>	<p>Positively mated mice were exposed on days 6-17 of gestation and rats on days 6-19. The day of plug or sperm detection was designated as day 0. Body weights were recorded throughout the study period, and uterine and fetal body weights were obtained at sacrifice. Implants were enumerated and their status recorded. Live fetuses were sexed and examined for gross, visceral, skeletal, and soft-tissue craniofacial defects.</p>
<p><u>Results</u> NOAEL maternal toxicity NOAEL developmental toxicity</p>	<p>7000 ppm (rats), 1400 ppm (mice). 7000 ppm (rats), <280 ppm (mice).</p>
<p>Maternal effects</p>	<p>Exposure of pregnant rats to these concentrations of isoprene did not result in apparent maternal toxicity. The only effect observed in the rat dams was an increased kidney to body weight ratio at the highest level (7000 ppm). Exposure of Swiss (CD-1) mice to isoprene resulted in (from day 12 onward) significant reductions in maternal body weight, body weight gain during treatment, and uterine weight for the 7000 ppm group. Liver to body weight ratios for pregnant mouse dams were significantly increased in the 1400 and 7000 ppm groups compared to the control group, and kidney to body weight ratios were significantly increased in the 7000 ppm group.</p>
<p>Embryo/fetal effects</p>	<p>In rats, there was no adverse effect on any reproductive index at any level and there was no increase in fetal malformations or variations. A slight, but not statistically significant, increase in the incidence of reduced vertebral ossifications (centra) was noted at 7000 ppm. In mice, there was an exposure-related and statistically significant reduction in fetal body weights at the 280 ppm level for female fetuses and at the 1400 ppm level for male fetuses. No embryotoxicity in the form of increased intrauterine death was present at any exposure level. There was no significant increase in the incidence of fetal malformations or variations, although two fetuses with cleft palate were found, one in each of the two highest exposure groups (1400 and 7000 ppm). Cleft palates were not detected in the control group. An increased incidence of supernumerary ribs was observed at 7000 ppm, although this skeletal variation is generally considered a secondary effect of maternal toxicity or stress and its significance is unclear.</p>
<p><u>Conclusions</u> (study authors)</p>	<p>Pregnant Sprague-Dawley rats and their offspring exhibited no significant toxic effects of isoprene at any exposure level in this study. Swiss (CD-1) mouse dams exhibited significant toxic effects only at the 7000 ppm level; however the offspring exhibited significant signs of toxicity, including reductions in fetal body weight at all exposure concentrations.</p>

<p><u>Data Quality</u> <i>Reliabilities</i></p> <p><u>References</u></p> <p><u>Other</u> <i>Last changed</i></p>	<p>1 - Reliable without restrictions. NTP-sponsored study.</p> <p>National Toxicology Program (1989). Inhalation Developmental Toxicology Studies: Teratology Study of Isoprene in Mice and Rats. TER88045; NTIS#DE89008095.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Toxicity to Reproduction

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Test type GLP Year Species Strain Route of administration Duration of test Concentration levels Sex Exposure period Frequency of treatment Control group and treatment Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u> NOAEL</p> <p><u>Conclusions</u> (contractor)</p> <p><u>Data Quality</u> Reliabilities</p> <p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>Isoprene, CAS# 78-79-5 Purity >99%.</p> <p>Other. 13-week inhalation study. Yes. 1994. Rat and mouse. F344 rats and B6C3F1 mice. Inhalation (vapor). 13 weeks. 0, 70, 700, or 7000 ppm. 10 male, 10 female per group. 6 hours/day. 5 days/week. 10 male, 10 female, air-only exposed. Analysis of incidence of neoplastic and nonneoplastic lesions was performed.</p> <p>Groups of 10 animals /sex /group/species (6-8 weeks age at study initiation) were exposed to various levels of isoprene for 6 hrs/day, 5 days/week for thirteen weeks. Sperm motility, vaginal cytology, and histopathologic evaluations of the reproductive organs were performed on all rats and mice as part of the terminal sacrifice for the core 13-week subchronic inhalation study.</p> <p>2200 ppm (rats). 220 ppm (mice).</p> <p>There were no exposure -related effects in rats except a slight increase in the incidence and relative severity of interstitial cell hyperplasia of the testis in the 7000 ppm group. In mice, testicular weight was reduced 35% in the 7000 ppm group, and morphological changes (seminiferous tubular atrophy) were detected in 2/10 mice. Males in the 700 and 7000 ppm groups had 12% and 30% lower epididymal weights, 12% and 46% lower spermatid head counts, 12% and 46% lower sperm concentrations, and 6% and 23% reductions in sperm motility, respectively. The female mice exposed to 7000 ppm exhibited estrous cycle lengths significantly longer than the control group (4.8 vs. 4.2 days).</p> <p>No significant effects on reproductive endpoints were observed in rats except slight changes in the testis at the highest exposure level (7000 ppm). Mice exhibited significant effects at 700 ppm or higher, including increased estrous cycle length and testicular atrophy, and decreased epididymal weight, sperm head count, sperm concentration, and sperm motility.</p> <p>2 - Reliable with restrictions. Limited reproductive toxicity data obtained as part of a NTP-sponsored subchronic inhalation toxicity study.</p> <p>Melnick RL; Sills RC; Roycroft JH; Chou BJ; Ragan HA; Miller RA (1994). Isoprene, an endogenous hydrocarbon and industrial chemical, induces multiple organ neoplasia in rodents after 26 weeks of inhalation exposure. Cancer Res. 54:5333-5339.</p> <p>21-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Biodegradation

Test Substance	
CAS #	78-79-5
Chemical Name	Isoprene
Remarks	Purity Unknown
Method	
Method/Guideline Followed	OECD 301C, Ready Biodegradability: Modified MITI Test
Test Type (aerobic/anaerobic)	Aerobic
GLP (Y/N)	Unknown
Year (study performed)	Unknown
Contact time (units)	28 days
Inoculum (source)	Mixture from several sources in Japan that included 4 sewage plants, 3 rivers, 2 bays, and 1 lake.
Remarks For Test Conditions	<p>Inoculum: A mixed inoculum was developed and maintained that used several sources and included: return sludge from 1 industrial and 3 city sewage plants; and water from 3 rivers, 2 bays, and 1 lake, with soil from land adjacent to these bodies of water. A filtrate from the combination of these samples was prepared and added to an existing culture that had been developed from the same sources as above and maintained under aeration and with a synthetic feed composed of glucose, peptone, and monopotassium phosphate. The inoculum used for this biodegradation test was removed from the mixed culture and added to the test systems at a concentration of 2 mg of inoculum per liter of test medium.</p> <p>Controls: Blank and positive controls were used per guideline. Positive control was aniline added to the control vessel at a loading of 100 mg/L.</p> <p>Test material: Test systems contained 2 and 10 mg test substance per liter of medium.</p> <p>Temperature of incubation: 24 - 26°C</p> <p>Analytical method: Oxygen consumption was monitored using an O2 probe from Ohkura Electric Co., Ltd.</p> <p>Method of calculating biodegradation values: Percent biodegradation was calculated as a percent ratio of the biological oxygen demand (BOD) in the test system less the BOD of the blank control, to the calculated theoretical oxygen demand of the added test material.</p> <p>Test validity: The positive control percent biodegradation had to have achieved 40% and 60% by days 7 and 14, respectively, for the test to be considered valid.</p>
Results	
Degradation % After Time	Test substance: 2% in 28 days
Kinetics (for sample, positive and negative controls)	Not available

Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vitro

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Type System of testing GLP Year Species/Strain Metabolic activation Species and cell type Quantity Induced or not induced Concentrations tested Statistical Methods</p> <p>Test Conditions</p> <p><u>Results</u> Genotoxic effects</p> <p><u>Conclusions</u> (contractor)</p> <p><u>Data Quality</u> Reliabilities</p> <p><u>Reference</u></p> <p><u>Other</u> Last changed</p>	<p>2-Butene, 2-methyl. CAS# 513-35-9 (2-methyl-2-butene, 85% purity)</p> <p>OECD 471 Ames <i>Salmonella</i>/bacterial reverse mutation test (pre-incubation assay). Bacterial. Yes. 1980. <i>Salmonella typhimurium</i>/ TA98, TA100, TA1535, TA1537, TA1538 With and without. Rat liver S9 fraction. 0.5 ml/plate. Arochlor 1254-induced. 0, 0.2, 2, 20, 500, and 2000 ug/plate. A positive response was defined as a minimum consistent doubling of the spontaneous reversion frequency, or if the number of induced revertants is less than twice the spontaneous rate then a reproducible, dose-related increase in any one strain/activation combination was interpreted as positive.</p> <p>The preincubation modification of the <i>Salmonella</i>/mammalian microsome assay was tested in five different <i>Salmonella</i> strains in the presence and absence of rat liver S-9. Five dose levels were tested, with three plates per dose level. Bacteria (0.5 ml) and S9 mix or pH 7.4 phosphate buffer (2.5 ml) were incubated at 37°C with the test substance in ethanol (0.1 ml) 30 minutes before incorporation of 0.5 ml of this mixture into 2 ml of top agar. Concurrent positive and solvent controls were also tested with and without metabolic activation. Two replicate assays were performed on different days to confirm the reproducibility of the results.</p> <p>Negative. The test substance was not mutagenic in any of the five strains of <i>Salmonella</i> tested in the presence or absence of metabolic activation (rat liver S9).</p> <p>The test substance was not mutagenic in the Ames Salmonella mutagenicity test.</p> <p>1 - Reliable without restrictions.</p> <p>Dean, B.J., Brooks, T.M., Hodson-Walker, G., and Hutson, D.H. (1985). Genetic toxicology testing of 41 industrial chemicals. <i>Mutation Research</i> 153:57-77.</p> <p>16-Oct-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Type GLP Year Species Strain Sex Route of administration Doses/concentration levels Exposure period No. of animals per dose Control groups and treatment</p> <p>Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u></p> <p><u>Conclusions</u> (study author)</p> <p><u>Data Quality</u> Reliability</p> <p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>Isoamylene, CAS# 26760-64-5 (90% 2-Butene, 2-methyl; 10% 1-Butene, 2-methyl).</p> <p>OECD 474. Mammalian erythrocyte micronucleus test. Yes. 1990. Mouse. B₆C₃F₁ Males. Inhalation (vapor). 0, 1034, 3258 or 10,350 ppm (analytical mean concentrations). 6 hours/day for 2 consecutive days. 10 males/exposure level. 10 males exposed to air (negative control), 10 males exposed to 1000 ppm 1,3 butadiene (positive control). Means and standard deviations of micronuclei data. ANOVA to test for equality of group means followed by Duncan's Multiple Range Test if appropriate. Standard regression analysis to test for dose-related response. Wilk's Criterion for normality.</p> <p>Ten male B₆C₃F₁ mice (weighing 22-26 g, approximately 8-9 weeks old) per group were exposed for 2 consecutive days, 6 h/day to 0, 1034, 3258, or 10,350 ppm (analytical means) of the test substance by inhalation. Exposure concentrations were determined by on-line gas chromatography. Bone marrow smears were prepared and stained 24 hours after the last exposure. 1000 polychromatic erythrocytes (PCEs) per animal were scored for the incidence of micronucleated PCEs. The proportion of PCEs to normochromatic erythrocytes (NCEs) was determined by counting a total of 1000 erythrocytes per animal.</p> <p>The test substance induced a statistically significant (p<0.01) and dose-related increase in micronucleated PCEs at 3258 and 10,350 ppm. The mean micronucleated PCE values were 15.7 and 31.5 at 3258 and 10,350 ppm, respectively, compared to 2.6 micronucleated PCEs for the negative control and 4.6 at 1034 ppm. Statistically significant (p<0.01) and dose-related decreases in the mean percent PCEs, which is a measure of hematotoxicity, were also observed at 3258 and 10,350 ppm. The positive control produced a statistically significant increase in micronucleated PCEs (29.1).</p> <p>Under the conditions of this study, inhalation exposure to 3258 and 10,350 ppm of the test substance induced statistically significant increases in micronucleated polychromatic erythrocytes in male B₆C₃F₁ mice.</p> <p>1 - Reliable without restrictions.</p> <p>ExxonMobil Biomedical Sciences, Inc. (1990). In Vivo Mammalian Bone Marrow Micronucleus Assay. Unpublished study.</p> <p>30-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Type GLP Year Species Strain Sex Route of administration Doses/concentration levels Exposure period No. of animals per dose Control groups and treatment</p> <p>Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u></p> <p><u>Conclusions</u> (study author)</p> <p><u>Data Quality</u> Reliabilities</p> <p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>2-Butene, 2-methyl. CAS# 513-35-9 (2-methyl-2-butene, >99.2% purity)</p> <p>OECD 474. Mammalian erythrocyte micronucleus test. Yes 1991. Mouse. B₆C₃F₁ Males. Inhalation (vapor). 0, 1005, 3207, or 9956 ppm (analytical mean concentrations). 6 hours/day for 2 consecutive days. 10 males/exposure level. 10 males exposed to air (negative control), 10 males exposed to 1000 ppm 1,3 butadiene (positive control). Means and standard deviations of micronuclei data. ANOVA to test for equality of group means followed by Duncan's Multiple Range Test if appropriate. Standard regression analysis to test for dose-related response. Wilk's Criterion for normality.</p> <p>Ten male B₆C₃F₁ mice (weighing 24-28 g, approximately 6-7 weeks old) per group were exposed for 2 consecutive days, 6 h/day to 0, 1005, 3207 or 9956 ppm (analytical mean) of the test substance by inhalation. Exposure concentrations were determined by on-line gas chromatography. Bone marrow smears were prepared and stained 24 hours after the last exposure. 1000 polychromatic erythrocytes (PCEs) per animal were scored for the incidence of micronucleated PCEs. The proportion of PCEs to normochromatic erythrocytes (NCEs) was determined by counting a total of 1000 erythrocytes per animal.</p> <p>The test substance induced statistically significant (p<0.01) and dose-related increases in micronucleated PCEs at 3207 and 9956 ppm. The mean micronucleated PCE values were 4.2, 16.6 and 36.1 at 1005, 3207 and 9956 ppm, compared to 3.4 micronucleated PCEs for the negative control. A statistically significant (p<0.01) decrease in the mean percent PCEs, which is a measure of hematotoxicity, was also observed at 9956 ppm. The positive control produced a statistically significant increase in micronucleated PCEs (29.7).</p> <p>Under the conditions of this study, inhalation exposure to 3207 and 9956 ppm of the test substance induced statistically significant increases in micronucleated polychromatic erythrocytes in male B₆C₃F₁ mice.</p> <p>1 - Reliable without restrictions</p> <p>ExxonMobil Biomedical Sciences, Inc. (1991). In Vivo Mammalian Bone Marrow Micronucleus Assay - Inhalation Dosing Method. Unpublished study.</p> <p>30-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u> Remarks</p>	<p>2-Butene, 2-methyl. CAS# 513-35-9 (2-methyl-2-butene, >99.2% purity)</p>
<p><u>Method</u> Method/guideline followed Type GLP Year Species Strain Sex Route of administration Doses/concentration levels Exposure period No. of animals per dose Control groups and treatment Statistical methods</p>	<p>OECD 474. Mammalian erythrocyte micronucleus test. Yes. 1991. Rat. CrICDBR Males. Inhalation (vapor). 0, 1005, 3207, or 9956 ppm (analytical mean concentrations). 6 hours/day for 2 consecutive days. 10 males/exposure level. 10 males exposed to air (negative control). Means and standard deviations of micronuclei data. ANOVA to test for equality of group means followed by Duncan's Multiple Range Test if appropriate. Standard regression analysis to test for dose-related response. Wilk's Criterion for normality.</p>
<p>Test Conditions</p>	<p>Ten male CrICDBR rats (weighing 295-345 g, approximately 9 weeks old) per group were exposed for 2 consecutive days, 6 h/day to 0, 1005, 3207 or 9956 ppm (analytical means) of the test substance by inhalation. Exposure concentrations were determined by on-line gas chromatography. Bone marrow smears were prepared and stained 24 hours after the last exposure. 1000 polychromatic erythrocytes (PCEs) per animal were scored for the incidence of micronucleated PCEs. The proportion of PCEs to normochromatic erythrocytes (NCEs) was determined by counting a total of 1000 erythrocytes per animal.</p>
<p><u>Results</u></p>	<p>The test substance induced statistically significant ($p < 0.01$) and dose-related increases in micronucleated PCEs at 3207 and 9956 ppm. The mean micronucleated PCE values were 4.2 and 4.9 at 3207 and 9956 ppm, respectively, compared to 2.7 for the negative control (air) and 2.2 at 1005 ppm. Statistically significant decreases in the mean percent PCEs, which is indicative of hematotoxicity, were also observed at all three exposure levels. Although the mean PCE frequencies at 1005, 3207 and 9956 ppm (48.62, 50.96, 49.76%, respectively) were slightly decreased from the negative control (54.86%), they were not different from each other and did not show evidence of a dose-response. Therefore, the biological significance of this observation is unclear.</p>
<p><u>Conclusions</u> (study author)</p>	<p>Under the conditions of this study, inhalation exposure to 3207 and 9956 ppm of the test substance induced small but statistically significant increases in micronucleated polychromatic erythrocytes in male rats.</p>
<p><u>Data Quality</u> Reliability</p>	<p>2 - Reliable with restrictions. No concurrent positive control was used.</p>
<p><u>References</u></p>	<p>ExxonMobil Biomedical Sciences, Inc. (1991). In Vivo Mammalian Bone Marrow Micronucleus Assay - Inhalation Dosing Method. Unpublished study.</p>
<p><u>Other</u> Last changed</p>	<p>30-Aug-00 Robust summary prepared by a contractor to the Panel.</p>

Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u> Remarks</p>	<p>1-Butene, 2-methyl CAS# 26760-64-5 (2-methyl-1-butene, >99.2% purity)</p>
<p><u>Method</u> Method/guideline followed Type GLP Year Species Strain Sex Route of administration Doses/concentration levels Exposure period No. of animals per dose Control groups and treatment</p>	<p>OECD 474. Mammalian erythrocyte micronucleus test. Yes. 1991. Mouse. B₆C₃F₁. Males. Inhalation (vapor). 0, 1038, 3312, or 10,116 ppm (analytical mean concentrations). 6 hours/day for 2 consecutive days. 10 males/ exposure level. 10 males exposed to air (negative control), 10 males exposed to 1000 ppm 1,3 butadiene (positive control).</p>
<p>Statistical methods</p>	<p>Means and standard deviations of micronuclei data. ANOVA to test for equality of group means followed by Duncan's Multiple Range Test if appropriate. Standard regression analysis to test for dose-related response. Wilk's Criterion for normality.</p>
<p>Test Conditions</p>	<p>Ten male B₆C₃F₁ mice (weighing 24-30 g, approximately 7-8 weeks old) per group were exposed for 2 consecutive days, 6 h/day to 0, 1038, 3312 or 10,116 ppm (analytical means) of the test substance by inhalation. Exposure concentrations were determined by on-line gas chromatography. Bone marrow smears were prepared and stained 24 hours after the last exposure. 1000 polychromatic erythrocytes (PCEs) per animal were scored for the incidence of micronucleated PCEs. The proportion of PCEs to normochromatic erythrocytes (NCEs) was determined by counting a total of 1000 erythrocytes per animal.</p>
<p><u>Results</u></p>	<p>A dose-related increase in mean micronucleated PCEs was observed (2.4, 3.7, 3.6, and 4.6 at 0, 1038, 3312 and 10,116 ppm). However, since none of the exposed groups were statistically different from the negative control this finding was not considered to be biologically significant. The mean micronucleated PCE value of 4.6 at 10,116 ppm was slightly outside the normal range of the negative control (0-4), although it was not statistically significant (p<0.09). The mean percent of PCEs were within the normal range for all exposure groups. The positive control produced a statistically significant increase in micronucleated PCEs (43.1).</p>
<p><u>Conclusions</u> (study author)</p>	<p>Under the conditions of this study, inhalation exposure to the test substance did not induce a statistically significant increase in micronucleated polychromatic erythrocytes in male B₆C₃F₁ mice.</p>
<p><u>Data Quality</u> Reliability</p>	<p>1 - Reliable without restrictions.</p>
<p><u>References</u></p>	<p>ExxonMobil Biomedical Sciences, Inc. (1991). In Vivo Mammalian Bone Marrow Micronucleus Assay - Inhalation Dosing Method. Unpublished study.</p>
<p><u>Other</u> Last changed</p>	<p>30-Aug-00 Robust summary prepared by a contractor to the Panel.</p>

Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Type GLP Year Species Strain Sex Route of administration Doses/concentration levels Exposure period No. of animals per dose Control groups and treatment Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u></p> <p><u>Conclusions</u> (study author)</p> <p><u>Data Quality</u> Reliability</p> <p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>1-Butene, 2-methyl CAS# 26760-64-5 (2-methyl-1-butene, >99.2% purity)</p> <p>OECD 474. Mammalian erythrocyte micronucleus test. Yes. 1991. Rat. CrICDBR Males. Inhalation (vapor). 0, 1038, 3312, or 10,116 ppm (analytical mean concentrations). 6 hours/day for 2 consecutive days. 10 males/exposure level. 10 males exposed to air (negative control). Means and standard deviations of micronuclei data. ANOVA to test for equality of group means followed by Duncan's Multiple Range Test if appropriate. Standard regression analysis to test for dose-related response. Wilk's Criterion for normality.</p> <p>Ten male CrICDBR rats (weighing 337-414 g, approximately 10-11 weeks old) per group were exposed for 2 consecutive days, 6 h/day to 0, 1038, 3312 or 10,116 ppm (analytical means) of the test substance by inhalation. Exposure concentrations were determined by on-line gas chromatography. Bone marrow smears were prepared and stained 24 hours after the last exposure. 1000 polychromatic erythrocytes (PCEs) per animal were scored for the incidence of micronucleated PCEs. The proportion of PCEs to normochromatic erythrocytes (NCEs) was determined by counting a total of 1000 erythrocytes per animal.</p> <p>The test substance did not induce a statistically significant increase in micronucleated PCEs at 24 hours in any of the exposure groups. The mean percent PCEs were within the normal range of the negative controls.</p> <p>Under the conditions of this study, inhalation exposure to the test substance did not induce a statistically significant increase in micronucleated polychromatic erythrocytes in male CrICDBR rats.</p> <p>2 - Reliable with restrictions. No concurrent positive control was used.</p> <p>ExxonMobil Biomedical Sciences, Inc. (1991). In Vivo Mammalian Bone Marrow Micronucleus Assay. Unpublished study.</p> <p>30-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u> Remarks</p> <p><u>Method</u> Method/guideline followed Type GLP Year Species Strain Sex Route of administration Doses/concentration levels Exposure period No. of animals per dose Control groups and treatment</p> <p>Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u></p> <p><u>Conclusions</u> (study author)</p> <p><u>Data Quality</u> Reliability</p> <p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>Isoamylene, CAS# 26760-64-5 (~92% 2-Butene, 2-methyl; ~7% 1-Butene, 2-methyl).</p> <p>OECD 474. Mammalian erythrocyte micronucleus test. Yes. 1991. Mouse. B₆C₃F₁ Males. Inhalation (vapor). 0, 1034, 3266 or 10,097 ppm (analytical mean concentrations). 6 hours/day for 2 consecutive days. 10 males/exposure level. 10 males exposed to air (negative control), 10 males exposed to 1000 ppm 1,3 butadiene (positive control). Means and standard deviations of micronuclei data. ANOVA to test for equality of group means followed by Duncan's Multiple Range Test if appropriate. Standard regression analysis to test for dose-related response. Wilk's Criterion for normality.</p> <p>Ten male B₆C₃F₁ mice (weighing 24-30 g, approximately 8-9 weeks old) per group were exposed for 2 consecutive days, 6 h/day to 0, 1034, 3266, or 10, 097 ppm (analytical means) of the test substance by inhalation. Exposure concentrations were determined by on-line gas chromatography. Bone marrow smears were prepared and stained 24 hours after the last exposure. 1000 polychromatic erythrocytes (PCEs) per animal were scored for the incidence of micronucleated PCEs. The proportion of PCEs to normochromatic erythrocytes (NCEs) was determined by counting a total of 1000 erythrocytes per animal.</p> <p>The test substance induced statistically significant (p<0.01) and dose-related increases in micronucleated PCEs at 3266 and 10,097 ppm. The mean micronucleated PCE values were 3.7, 22.6 and 42.1 at 1034, 3266 and 10,097 ppm, compared to 2.5 micronucleated PCEs for the negative control. Statistically significant (p<0.01) decreases in the mean percent PCEs, which is a measure of hematotoxicity, were also observed at 3266 and 10,097 ppm. The positive control produced a statistically significant increase in micronucleated PCEs (39.5).</p> <p>Under the conditions of this study, inhalation exposure to 3266 and 10,097 ppm of the test substance induced statistically significant increases in micronucleated polychromatic erythrocytes in male B₆C₃F₁ mice.</p> <p>1 - Reliable without restrictions</p> <p>ExxonMobil Biomedical Sciences, Inc. (1991). In Vivo Mammalian Bone Marrow Micronucleus Assay. Unpublished study.</p> <p>30-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vivo

<p><u>Test Substance</u></p> <p>Remarks</p> <p><u>Method</u></p> <p>Method/guideline followed</p> <p>Type</p> <p>GLP</p> <p>Year</p> <p>Species</p> <p>Strain</p> <p>Sex</p> <p>Route of administration</p> <p>Doses/concentration levels</p> <p>Exposure period</p> <p>No. of animals per dose</p> <p>Control groups and treatment</p> <p>Statistical methods</p> <p>Test Conditions</p> <p><u>Results</u></p> <p><u>Conclusions</u> (study author)</p> <p><u>Data Quality</u> Reliability</p> <p><u>References</u></p> <p><u>Other</u> Last changed</p>	<p>Isoamylene, CAS# 26760-64-5 (~92% 2-Butene, 2-methyl; ~7% 1-Butene, 2-methyl).</p> <p>OECD 474. Mammalian erythrocyte micronucleus test. Yes. 1991. Rat. CrICDBR Males. Inhalation (vapor). 0, 1034, 3266 or 10,097 ppm (analytical mean concentrations). 6 hours/day for 2 consecutive days. 10 males/exposure level. 10 males exposed to air (negative control). Means and standard deviations of micronuclei data. ANOVA to test for equality of group means followed by Duncan's Multiple Range Test if appropriate. Standard regression analysis to test for dose-related response. Wilk's Criterion for normality.</p> <p>Ten male CrICDBR rats (weighing 348-447 g, approximately 11-12 weeks old) per group were exposed for 2 consecutive days, 6 h/day to 0, 1034, 3266, or 10, 097 ppm (actual mean exposures) of the test substance by inhalation. Exposure concentrations were determined by on-line gas chromatography. Bone marrow smears were prepared and stained 24 hours after the last exposure. 1000 polychromatic erythrocytes (PCEs) per animal were scored for the incidence of micronucleated PCEs. The proportion of PCEs to normochromatic erythrocytes (NCEs) was determined by counting a total of 1000 erythrocytes per animal.</p> <p>The test substance induced a statistically significant ($p < 0.01$) increase in micronucleated PCEs at 10,097 ppm. The mean micronucleated PCE values were 3.4, 4.2, and 7.0 at 1034, 3266 and 10,097 ppm compared to 3.3 micronucleated PCEs for the negative control. The slight increase in mean micronucleated PCEs (4.2) noted at 3266 ppm was slightly above the normal range for the negative control (0-4) although it was not statistically significant. The mean percent PCEs were within the normal range of the negative control for all exposed groups.</p> <p>Under the conditions of this study, inhalation exposure to 10,097 ppm of the test substance induced a statistically significant increase in micronucleated polychromatic erythrocytes in male rats.</p> <p>2 - Reliable with restrictions. No concurrent positive control was used.</p> <p>ExxonMobil Biomedical Sciences, Inc. (1991). In Vivo Mammalian Bone Marrow Micronucleus Assay - Inhalation Dosing Method. Unpublished study.</p> <p>30-Aug-00 Robust summary prepared by a contractor to the Panel.</p>
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Robust Summary - Group 3: C5 Non-Cyclics

Acute Toxicity

<u>Test Substance</u>	Neohexene (3,3-dimethylbutene-1) CAS# 558-37-2 98.5% purity.
<u>Method</u>	OECD 401. Acute oral toxicity study. Not specified. 1982. Rat/Sprague-Dawley. Male and female. 5/sex/group. None. Oral gavage.
Method/guideline followed	
Type (test type)	
GLP	
Year	
Species/Strain	
Sex	
No. of animals per sex per dose	
Vehicle	
Route of administration	
Test Conditions	One group of five rats/sex was dosed orally at a level of 5000 mg/kg of body weight. The animals were observed at 1, 2, and 4 hours after dosing, and daily for a period of 14 days for mortality and signs of systemic toxicity. Body weights were recorded prior to treatment and at 7 and 14 days. The animals were necropsied at the end of the 14-day period and observed for gross abnormalities.
<u>Results</u>	LD ₅₀ = >5 g/kg No animals died after dosing at 5000 mg/kg. Clinical signs of toxicity noted 1 hour after dosing included depression, soft feces, a hunched appearance, and rough fur coat. All animals appeared normal from Day 2 through termination of the study. All animals gained weight during the study. There were no significant findings at necropsy.
LD ₅₀ .	
<u>Conclusions</u>	The acute oral LD ₅₀ for the test substance was >5 g/kg.
(contractor)	
<u>Data Quality</u>	1 - Reliable without restrictions.
Reliability	
<u>References</u>	Hazleton Laboratories America, Inc. (1982). Acute Oral Toxicity Study in Rats. Conducted for Phillips Petroleum Company, unpublished report.
<u>Other</u>	22-Aug-00 Robust summary prepared by a contractor to the Panel.
Last changed	

Robust Summary - Group 3: C5 Non-Cyclics

Acute Toxicity

<p><u>Test Substance</u></p>	<p>Neohexene (3,3-dimethylbutene-1) CAS# 558-37-2 98.5% purity.</p>
<p><u>Method</u> Method/guideline followed Type (test type) GLP Year Species/Strain Sex No. of animals per sex per dose Vehicle Route of administration</p>	<p>OECD 403. Acute inhalation toxicity study. Not specified. 1982. Rat/Sprague-Dawley. Male and female. 5/sex/group. None. Inhalation.</p>
<p>Test Conditions</p>	<p>One group of five rats/sex was placed in a 38 liter exposure chamber and exposed for four hours to the maximum practical vapor concentration. Analytical chamber concentrations were measured using a total hydrocarbon monitor (method or frequency not specified). The animals were observed hourly during the exposure and twice daily for a period of 14 days for mortality and signs of systemic toxicity. Body weights were recorded prior to treatment and at 2, 3, 4, 7, and 14 days. The animals were necropsied at the end of the 14-day period and observed for gross abnormalities.</p>
<p><u>Results</u> LC₅₀</p>	<p>LC₅₀ = >51,000 ppm. The mean analytical exposure concentration was 51,000 ppm. No animals died during the study. All the rats were observed prostrate in their cages during the exposure. All animals appeared normal throughout the post-exposure observation period. All animals gained weight during the study except the females at the Day 3 interval (slight group mean weight loss). There were no significant findings at necropsy.</p>
<p><u>Conclusions</u> (contractor)</p>	<p>The acute inhalation LC₅₀ for vapors of the test substance was >51,000 ppm.</p>
<p><u>Data Quality</u> Reliability</p>	<p>1 - Reliable without restrictions.</p>
<p><u>References</u></p>	<p>Hazleton Laboratories America, Inc. (1982). Acute Inhalation Toxicity Test in Rats. Conducted for Phillips Petroleum Company, unpublished report.</p>
<p><u>Other</u> Last changed</p>	<p>22-Aug-00 Robust summary prepared by a contractor to the Panel.</p>

Robust Summary - Group 3: C5 Non-Cyclics

Acute Toxicity

<p><u>Test Substance</u></p>	<p>Neohexene (3,3-dimethylbutene-1) CAS# 558-37-2 98.5% purity.</p>
<p><u>Method</u> Method/guideline followed Type (test type) GLP Year Species/Strain Sex No. of animals per sex per dose Vehicle Route of administration</p>	<p>Other. Respiratory tract irritancy study in mice. Not specified. 1982. Mouse/CD-1. Male 4/group. None. Inhalation.</p>
<p>Test Conditions</p>	<p>One group of four mice was placed in individual head-only plethysmographs attached to an exposure chamber. Baseline respiratory rates were first established with exposure to room air, then the mice were sequentially exposed to vapors of the test substance for 1 minute, next to room air for 10 minutes, then a second 1 minute vapor exposure, and finally a 5 minute room air recovery period. Individual respiratory rates and breathing patterns were recorded (methods not described). Group mean respiratory rates changes (% decrease) during exposure were presented; individual rates were categorized (0-25%, 25-50%, etc.). Analytical chamber concentrations were measured by a total hydrocarbon monitor.</p>
<p><u>Results</u> RD₅₀</p>	<p>The RD₅₀ (50% respiratory rate decrease) was greater than 55,000 ppm. The mean analytical exposure concentration was 55,000 ppm. Extremely slight decreases in respiration rates were noted 1 of 4 mice during the first one minute exposure and in 3 of 4 mice during the second exposure. The breathing patterns indicated slight upper airway irritancy only in 2 of the 4 mice during the second exposure. One mouse could not be evaluated during the first exposure due to excessive movement within the plethysmograph.</p>
<p><u>Conclusions</u> (study author)</p>	<p>Based on these results, exposure to the vapors of the test substance at an analytical concentration of 51,000 ppm produced very slight upper airway irritancy in mice.</p>
<p><u>Data Quality</u> Reliability</p>	<p>1 - Reliable without restrictions.</p>
<p><u>References</u></p>	<p>Hazleton Laboratories America, Inc. (1982). Respiratory Tract Irritancy Study in Mice. Conducted for Phillips Petroleum Company, unpublished report.</p>
<p><u>Other</u> Last changed</p>	<p>22-Aug-00 Robust summary prepared by a contractor to the Panel.</p>

Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vitro

<p><u>Test Substance</u></p>	Neohexene (3,3-dimethylbutene-1) CAS# 558-37-2 98.5% purity.
<p><u>Method</u> Method/guideline followed Type System of testing GLP Year Species/Strain Metabolic activation Species and cell type Quantity Induced or not induced Concentrations tested Control groups and treatment</p>	OECD 471 <i>Salmonella typhimurium</i> mammalian microsome plate incorporation assay (Ames Assay). Bacterial. Not specified. 1982. <i>Salmonella</i> / TA98, TA100, TA1535, TA1537, and TA1538. With and without. Rat liver S9 fraction. 0.5 ml/plate. Arochlor 1254-induced (500 mg/kg for 5 days). 0, 32.3, 96.5, 289.5, 868.4, and 2605 ug/plate. Solvent control: dimethylsulfoxide (DMSO). Positive controls: N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG), 9-aminoacridine (9-AA), 2-nitrofluorene (2-NF), 2-aminoanthracene (2-AA).
<p>Statistical Methods</p>	A positive response was defined as a reproducible, dose-related increase in revertant colonies over three concentrations with the baseline increase twice the solvent control level.
<p>Test Conditions</p>	Five different <i>Salmonella</i> strains were tested in the presence and absence of rat liver S-9. The test substance was soluble in the solvent (dimethylsulfoxide, DMSO) at 100 mg/ml. Five dose levels were tested , with three plates per dose level. The maximum dose selected was 2605 ug/plate based on observed growth inhibition during an initial toxicity test. Concurrent positive controls were also tested with and without metabolic activation.
<p><u>Results</u> Genotoxic effects</p>	Negative. The test substance was not mutagenic in any of the five strains of <i>Salmonella</i> tested in the presence or absence of Arochlor-induced rat liver S9.
<p><u>Conclusions</u> (study author)</p>	The test substance was not mutagenic in the Ames Salmonella mutagenicity test.
<p><u>Data Quality</u> Reliabilities</p>	1 - Reliable without restrictions.
<p><u>Reference</u></p>	Hazleton Laboratories America, Inc. (1982). <i>Salmonella typhimurium</i> mammalian microsome plate incorporation assay. Conducted for Phillips Petroleum Company, unpublished report.
<p><u>Other</u> Last changed</p>	22-Aug-00 Robust summary prepared by a contractor to the Panel.

Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vitro

<p><u>Test Substance</u></p>	<p>Neohexene (3,3-dimethylbutene-1) CAS# 558-37-2 98.5% purity.</p>
<p><u>Method</u></p>	<p>OECD 479.</p>
<p>Method/guideline followed</p>	<p><i>In vitro</i> sister chromatid exchange (SCE) assay in Chinese hamster ovary cells.</p>
<p>Type</p>	<p>Chinese hamster ovary (CHO) cells.</p>
<p>System of testing</p>	<p>Not specified.</p>
<p>GLP</p>	<p>1982.</p>
<p>Year</p>	<p>Aroclor 1254-induced Sprague-Dawley rat liver S9.</p>
<p>Metabolic activation</p>	<p>0, 1.3, 4.4, 13.2, 44, and 132 ug/ml.</p>
<p>Concentrations tested</p>	<p>Solvent controls: dimethylsulfoxide (DMSO). Positive controls: ethylmethanesulfonate (without S9), cyclophosphamide (with S9).</p>
<p>Control groups and treatment</p>	<p>Not specified.</p>
<p>Statistical Methods</p>	<p>The test substance was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) both in the presence and absence of Aroclor 1254-induced Sprague-Dawley rat liver S9. The test included concurrent solvent and positive controls and five doses of the test substance. The test substance was soluble in the solvent (DMSO) at 100 mg/ml. The maximum dose selected was 132 ug/plate based on observed growth inhibition in an initial toxicity study. Duplicate cultures were prepared for all dose levels and controls. Cells were exposed to the test substance for 2 hours, washed twice, and BrdU added to each culture. Cells were sampled 24 hours after BrdU addition; colcemid was added 2 hours prior to fixation. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.</p>
<p>Test Conditions</p>	<p>Negative.</p>
<p><u>Results</u></p>	<p>No increases in SCEs were noted in cultured CHO cells treated with the test substance, with or without S9.</p>
<p>Genotoxic effects</p>	<p>Under the conditions of this study, the test substance did not exhibit a positive response and is therefore considered not to be mutagenic in this test system.</p>
<p><u>Conclusions</u></p>	<p>1 - Reliable without restrictions.</p>
<p>(study author)</p>	<p>Hazleton Laboratories America, Inc. (1982). <i>In vitro</i> sister chromatid exchange assay in Chinese hamster ovary cells. Conducted for Phillips Petroleum Company, unpublished report.</p>
<p><u>Data Quality</u></p>	<p><u>Reference</u></p>
<p>Reliabilities</p>	<p><u>Other</u></p>
<p><u>Reference</u></p>	<p>22-Aug-00</p>
<p><u>Other</u></p>	<p>Robust summary prepared by a contractor to the Panel.</p>
<p>Last changed</p>	<p></p>

Robust Summary - Group 3: C5 Non-Cyclics

Genetic Toxicity - in Vitro

<u>Test Substance</u>	Neohexene (3,3-dimethylbutene-1) CAS# 558-37-2 98.5% purity.
Test substance	
<u>Method</u>	OECD 476.
Method/guideline followed	
Type	Mouse lymphoma forward mutation assay.
System of testing	Mammalian cell (mouse lymphoma cells/L5178Y).
GLP	Not specified.
Year	1982.
Metabolic activation	With and without Arochlor-induced rat liver S9 mixture.
Concentrations tested	0, 82, 117, 168, 240, 343, 490, 700, and 1000 µl/ml.
Control groups and treatment	Ethylmethanesulfonate (EMS) was used as a positive control in the assays without S9 activation. 3-methylcholanthrene (MCA), which requires metabolic activation, was used as a positive control for assays with S9. The concurrent negative control was the vehicle (dimethylsulfoxide, DMSO).
Statistical Methods	A mutagenic response was defined as a dose-related response in two or more dose levels (in the absence of severe toxicity) with a greater than two-fold increase in the number of revertant colonies over the concurrent vehicle control value.
Test Conditions	Suspension cultures of mouse lymphoma cells, heterozygous for thymidine kinase activity, were grown in Fisher medium supplemented with 0.1% pluronic and 10% heat-inactivated horse serum (F10P) and exposed to the test substance in the same medium. Treated cells were grown for 48 hours to allow mutation expression. Approximately 500,000 cells from each culture were then plated in three selective media plates containing 2 µg/ml trifluorothymidine (TFT) to select mutant clones. 100 cells from each culture were also seeded in non-selective plates without TFT to assess viability. The plates were incubated for approximately 12 days. The mutant colonies were counted on the selective (TFT) plates and the survivors on the non-selective (no TFT) plates.
<u>Results</u>	
Genotoxic effects	Positive.
	There was a slight increase in the induction of mutations without metabolic activation (maximum 2.7-fold increase). There were no significant increases with metabolic activation. The positive and negative controls responded in an appropriate manner.
<u>Conclusions</u>	
(contractor)	Under conditions of this study, the test substance was weakly mutagenic in the mouse lymphoma assay without metabolic activation.
<u>Data Quality</u>	
Reliabilities	1 - Reliable without restrictions.
<u>Reference</u>	
	Hazleton Laboratories America, Inc. (1982). Mouse lymphoma forward mutation assay. Conducted for Phillips Petroleum Company, unpublished report.
<u>Other</u>	
Last changed	22-Aug-00 Robust summary prepared by a contractor to the Panel.