United States Environmental Protection Agency

EPA/690/R-09/032F
Final
9-30-2009

Provisional Peer-Reviewed Toxicity Values for Midrange Aliphatic Hydrocarbon Streams

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Commonly Used Abbreviations

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR MIDRANGE ALIPHATIC HYDROCARBON STREAMS

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore,

users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

The midrange (i.e., medium carbon number range) hydrocarbon streams that are the subject of this PPRTV document include isoparaffinic hydrocarbon-containing streams (IPH, composed of isoparaffins or of isoparaffins with *n*-alkanes and naphthenes), dearomatized white spirit (DAWS, composed of paraffins and naphthenes), and Stoddard Solvent IIC. The hydrocarbons in these streams fall within the carbon number range of C9–C18, and the content of aromatic compounds is <1.0%. Isoparaffinic hydrocarbons are branched chain alkanes and naphthenes are cyclic alkanes.

No chronic or subchronic RfDs or RfCs or cancer assessment for IPH, DAWS, or Stoddard Solvent IIC are available on IRIS (U.S. EPA, 2009), the Drinking Water Standards and Health Advisory list (U.S. EPA, 2006), or in the HEAST (U.S. EPA, 1997). No documents for these mixtures are listed in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA 1991a, 1994a). The Occupational Safety and Health Administration (OSHA), the National Institute of Occupational Safety and Health (NIOSH), and the American Conference of Governmental Industrial Hygienists (ACGIH) have not derived occupational exposure limits for midrange aliphatic hydrocarbon streams of low aromatic content (OSHA, 2008; NIOSH, 2008; ACGIH, 2007). An ATSDR (1995) toxicological profile for Stoddard solvent, a World Health Organization (WHO, 1996) Environmental Health Criteria document on white spirit or Stoddard solvent, and an International Agency for Research on Cancer (IARC, 1989) monograph on petroleum solvents were reviewed for relevant information. However, with few exceptions, the studies reviewed for these documents pertained to mixtures containing substantial aromatic content (>10%) and were not relevant to this PPRTV document[1]. Pertinent information on these mixtures was not located through the Petroleum High Production Volume (HPV) Testing Group (2007) publications or the Organisation for Economic Co-operation and Development (OECD)

[1]ATSDR, WHO, and IARC prepared general overviews on the toxicity of Stoddard solvent, white spirit, or petroleum solvents and, thus, included information on formulations of these mixtures that included a significant proportion of aromatic compounds. Because this document is intended to review mixtures that are representative of the midrange aliphatic fraction of hydrocarbon compounds, those mixtures that contained a nontrivial proportion (>1.0%) of aromatic compounds are not considered further.

HPV Programme Screening Information Dataset (SIDS) documents (OECD/SIDS, 2007). Reviews of these mixtures (IPH, DAWS, and Stoddard Solvent IIC) by the Massachusetts Department of Environmental Protection (MADEP, 2003) and the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG, 1997) were consulted for relevant information. In addition, a review of the toxicology of IPH published by Mullin et al. (1990) was consulted. The National Toxicology Program (NTP, 2004) has assessed the toxicity and carcinogenicity of Stoddard Solvent IIC. Finally, the Voluntary Children's Chemical Evaluation Program (VCCEP) Peer Consultation Meeting report on *n*-alkanes (decane, *n*-dodecane, and undecane) was reviewed for studies of relevant mixtures.

One unpublished developmental toxicity study performed by Exxon Biomedical Sciences could not be located, thus, the study information presented in this PPRTV document is based on secondary sources (i.e., Mullin et al., 1990; VCCEP submission). In addition, partial copies of the three oral studies (Anonymous, 1990, 1991a,b) were obtained from MADEP; important sections including data tables and pathology appendices were missing. Efforts to obtain full copies of these reports from MADEP, API, ExxonMobil Biomedical Sciences, and the USAF were not successful.

To identify toxicological information pertinent to the derivation of provisional toxicity values for IPH or DAWS and to identify studies published since the MADEP (2003) review, updated literature searches (January 2002–July 2009) of the following databases were conducted: MEDLINE, TOXLINE, BIOSIS, TSCATS, CCRIS, GENETOX, DART/ETIC, HSDB, and Current Contents (last 6 months). Stoddard Solvent IIC was identified as a potentially relevant mixture through screening of the initial searches. For this mixture, a comprehensive review of previous data by NTP (2004) was used as a starting point for the literature search, and second updated literature searches were conducted in March 2008 to identify studies published since the review. A final updated literature was conducted in July 2009.

REVIEW OF PERTINENT DATA

Human Studies

Pederson and Cohr (1984a,b) conducted two studies of acute inhalation exposure to white spirits with low aromatic content. In the first study (Pedersen and Cohr, 1984a), 12 volunteers (average age 25 years) were exposed for 6 hours to 610 mg/m^3 Shellsol TS (99% paraffins), 605 mg/m^3 Exsol D 40 (52% paraffins and 48% naphthenes) or 610 mg/m^3 Varnolene (57% paraffins, 25% naphthenes, and 18% aromatics). The same volunteers were exposed to each of the three mixtures with a 1-week interval between exposures and served as their own controls. After exposure, blood and urine were collected for serum chemistry (glucose, triglycerides, cholesterol, urate, α-amylase, creatine kinase, orosomucoid [a measure of inflammatory response], sodium, and potassium), and urine parameters (albumin and ß2-microglobulin). In addition, lung function, echocardiogram (ECG), blood pressure, pulse, and mucociliary function were assessed. Examination for neurological effects (Romberg's test and nystagmus) was performed. No symptoms were reported by the volunteers. The only statistically significant ($p < 0.05$) differences from preexposure values were decreases in serum α-amylase (9%) and potassium (9%) 48 hours after exposure to Exsol D 40. A subsequent study

published in the same paper (Pedersen and Cohr, 1984a) further evaluated exposure to Exsol D 40 at concentrations of 304, 611, or 1228 mg/m^3 for 6 hours and observed the decreases in serum α-amylase (7%; 6 hours after exposure began) and urate (4%; 48 hours after exposure began).

In the second study, seven of the same volunteers were exposed to 616 mg/m^3 Shellsol (99% paraffins), 6 hours/day, for 5 days (Pedersen and Cohr, 1984b). The remaining five volunteers served as untreated controls. Blood samples were collected 24, 96, and 168 hours after exposure began for measurement of serum levels of immunoglobulins, orosomucoid, creatine kinase, and follicle stimulating hormone. Average creatine kinase was statistically significantly ($p < 0.05$) increased above preexposure levels after 96 (59% higher) and 168 hours (76% higher). Follicle stimulating hormone was statistically significantly decreased ($p < 0.05$) below baseline after 24 (11% decrease) and 96 hours (9%). However, the authors noted marked inter- and intraindividual variation in these parameters. For both of these studies, the toxicological significance of the observed changes is uncertain.

Ernstgard et al. (2009a,b) conducted two studies of acute inhalation exposure to standard white spirits (15–20% aromatics; stdWS) and DAWS (0.002% aromatics). In the first study (i.e., Ernstgard et al, 2009a), the aim of the study was to identify thresholds (dose-finding) of irritation and central nervous system (CNS) effects. Eight volunteers (four female and four male healthy volunteers) were exposed to increasing levels of stdWS or DAWS in eight 10-min steps from 0.5 to 600 mg/m^3. The study authors reported that the stdWS caused more severe effects of irritation and CNS than that of DAWS. In the second study (i.e., Ernstgard et al, 2009b), 12 volunteers (6 female and 6 male healthy volunteers) were exposed on five occasions to 100 or 300 mg/m^3 DAWS or stdWS (19% aromatics), or to clean air (as a control group), for 4 hours at rest. The study authors did not observe any exposure-related effects for DAWS but did note eye irritation at the high stdWS exposure only—but not for the DAWS at any level. However, the study authors (Ernstgard et al., 2009b) claimed that the slightly more irritating effects by stdWS than DAWS could "not be confirmed by objective measurements." For both of these studies, the toxicological significance of the observed effects in either irritation or CNS for DAWS is uncertain. No effect levels are identified for DAWS.

No other human studies of exposure to midrange aliphatic compounds with low aromatic content were identified. NTP (2004) reviewed case studies and human exposure studies of white spirits with significant aromatic content (>10%); however, it is not possible to determine whether the observed effects were attributable to the aliphatic or aromatic constituents. In addition, NTP (2004) discussed a number of studies reporting neurological or neuropsychological effects of occupational exposure to alkyd paints, but the nature of the exposures (e.g., composition of the inhaled mixture) is not reported, so exposure to compounds or mixtures other than midrange aliphatics cannot be discounted.

Animal Studies

Oral Exposure

There were three studies of oral exposure to midrange aliphatic hydrocarbon streams (C11–C17, C9–C12, and C10–C13, respectively) that were identified in the searches (Anonymous, 1990, 1991a,b). The copies of these three studies obtained for this review were missing many tables and appendices and repeated efforts to obtain these studies from a variety of sources were unsuccessful. As a result, the summaries of the studies contained herein rely on the

information available in the text of the reports, as well as information provided by MADEP (2003) and TPHCWG (1997) from their reviews of the complete reports. Limitations in the data available for analysis of these studies increase the uncertainty associated with using these data for toxicity assessment. No other oral studies of midrange aliphatic hydrocarbon streams were located.

Subchronic Studies

A subchronic study of the oral toxicity of an isoparaffinic mixture (C11–C17, typical aromatic content <0.05%) was conducted in Crl: CDBR (Sprague-Dawley) rats (Anonymous, 1990). Groups of 10 rats/sex/dose were given gavage doses of 0, 100, 500, or 1000 mg/kg-day of the test material in corn oil 7 days/week for 13 weeks. Due to gavage deaths in the control and 500 mg/kg-day group, 10 additional males were added to each of these groups. Most of the deaths occurred prior to Day 12 of the study; however, the studies authors did not indicate when the additional males were added. Control and high-dose-recovery groups of 10 animals/sex were treated as above and then maintained for 28 days after treatment was terminated to evaluate reversibility of effects. Daily mortality checks and clinical observations were made and both body weights and food intake were recorded weekly. Ophthalmoscopic examinations were performed on all rats prior to study initiation and at terminal sacrifice. Blood was collected on Day 32, at terminal sacrifice and on Day 120 (for the recovery groups) for evaluation of hematology (erythrocyte count, hematocrit [Hct], hemoglobin [Hgb], total and differential leukocyte count, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelet count, and reticulocyte count), and serum chemistry (albumin, blood urea nitrogen [BUN], calcium, cholesterol, creatinine, electrolytes, gamma glutamyl transferase [GGT], glucose, phosphorus, alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, total protein, and triglycerides). All animals were necropsied and selected organs (adrenals, kidneys, brain, liver, and ovaries/testes) were weighed. Microscopic examination was performed on a comprehensive list of tissues (>35) from control and high-dose animals, as well as any gross lesions, tissue masses, liver, lungs and kidneys from low- and mid-dose groups. In the recovery group, comprehensive histopathology examination was performed after the conclusion of the observation period.

There were no treatment-related differences in mortality, in the incidence of clinical observations or in ophthalmoscopic findings (Anonymous, 1990). As noted earlier, a number of deaths due to gavage errors occurred early in the study, prompting the investigators to add two groups of 10 males (control and 500 mg/kg-day). Treated females had occasional dose-related increases in body weight and food consumption, but the only statistically significant ($p < 0.05$) difference was an increase in food consumption in high-dose females. Dose-related decreases in hematology parameters were observed in male rats at both interim (Day 32) and terminal evaluation. Statistically significant ($p < 0.05$) decreases in erythrocyte count, Hct, and Hgb were noted in high-dose males at both time points, and mid-dose males had significantly lower erythrocyte count and Hgb at study termination. At Day 32—but not at study termination—low-dose males had lower erythrocyte counts and lower Hgb and MCHC levels than controls. Data tables reflecting these endpoints were missing from the report, so statistical significance and magnitude of change cannot be reported. Hematology was not affected by treatment at any dose in female rats. The authors also noted a dose-related increase in platelet count. Statistically significant differences in hematology parameters (increases in Hgb, MCHC, and MCH; $p < 0.05$) in the recovery groups were considered to be within normal limits. In male rats, statistically

significant ($p < 0.05$) serum chemistry changes at both interim and terminal evaluation were reported to be within the range of normal variation, with the exception of decreased triglycerides in high-dose males. The authors considered this effect to be treatment-related. The text of the report indicated that triglycerides were statistically significantly increased at the mid-dose at study termination ($p < 0.05$). In female rats, decreases in AST at both the mid- and high doses were considered by the researchers to be potentially related to exposure. As with the hematology, data tables are missing from the report.

Both absolute and relative liver weights were significantly increased ($p < 0.05$) over control values in mid- and high-dose animals of both sexes (Anonymous, 1990). Absolute kidney weight was increased in females of the mid- and high doses, but relative kidney weights were not different from controls. No other treatment-related changes in organ weights were noted. High-dose rats in the recovery group had lower relative liver weights than high-dose animals terminated after 13 weeks. Data tables showing the organ weights were missing from the report. There were no treatment-related findings on gross necropsy or histopathology evaluation of any exposure group, nor were there any findings in the recovery group.

In the absence of data tables to support the observations in the text of the report, it is difficult to identify effect levels with any degree of confidence. MADEP (2003) identified the low-dose (100 mg/kg-day) as a NOAEL and the mid-dose (500 mg/kg-day) as a LOAEL based on changes in serum chemistry and liver weight. In the absence of histopathology findings, the biological significance of these effects is not clear as the liver weights were increased at the mid-dose while serum chemistry indicated decreases in AST in females and decreased triglycerides in males. However, the hematology findings provide a more consistent basis for identifying the LOAEL. Decreases in erythrocyte count, Hct and Hgb at both the mid- and high-doses in male rats were observed at both the interim (Day 32) and terminal evaluations. The authors characterized the changes as trending toward anemia at the high-dose. Thus, a LOAEL of 500 mg/kg-day is identified based on hematology findings in male rats, with a NOAEL of 100 mg/kg-day.

A subchronic study of a related mixture was also conducted in rats (Anonymous, 1991a). The mixture was characterized by MADEP (2003) as C10–C13 isoparaffins/naphthenes/ *n*-alkanes, with a typical aromatic content of 0.1%. In this study, groups of 10/sex/dose Sprague-Dawley rats were given gavage doses of 0, 100, 500, or 1000 mg/kg-day of the mixture in corn oil, 7 days/week for 13 weeks. A recovery group of 10 additional high-dose animals was maintained for 28 untreated days after exposure was terminated. Toxicological evaluations were the same as described above for the C11–C17 mixture.

Treatment did not result in statistically significant differences ($p \leq 0.05$) in survival, body weight, food consumption, or ophthalmoscopic findings, nor were there treatment-related clinical signs of toxicity (Anonymous, 1991a). The authors noted a trend toward reduced body weight in males exposed at the mid- and high doses, but this trend apparently did not reach statistical significance. Hematology analysis indicated a statistically significant ($p \leq 0.01$) increase in platelet count in high-dose males evaluated at termination; no other treatment-related effects on hematology parameters were noted. Serum chemistry changes noted at termination were dose-related increases in BUN ($p \leq 0.05$ in mid- and high-dose males), creatinine ($p \leq 0.05$ in low- and high-dose males), phosphorous ($p \leq 0.01$ in high-dose males), and ALT ($p \leq 0.01$ in

high-dose males) in males and cholesterol ($p \leq 0.05$ in high-dose females) in females. The data tables showing the magnitude of change were missing from the report; however, the authors indicated that these changes were within normal physiological limits. At the interim blood collection, a statistically significant decrease in AST levels was observed in the high-dose females; at termination, this decrease persisted in the high-dose and AST was also decreased in the mid-dose ($p \leq 0.05$). Glucose levels were decreased in mid- and high-dose animals of both sexes ($p \leq 0.05$). Absolute and relative kidney weights were increased in mid- and high-dose males ($p \leq 0.05$), as were relative liver weights, while relative testicular weights were increased only at the high dose. In females, absolute and relative liver weights were increased at the high dose ($p \leq 0.01$) and relative—but not absolute—liver weight was increased at the mid-dose ($p \leq 0.05$). In the high-dose-recovery group, there was some evidence of return to normal in the relative liver and kidney weights.

Histopathology evaluation indicated treatment-related effects on the kidneys (males only) and livers (both sexes) (Anonymous, 1991a). Kidney changes were indicative of hyaline droplet nephropathy. The changes included hyaline droplet accumulation, an increased incidence of multifocal cortical tubular basophilia, degeneration and regeneration of tubular epithelium, and dilated medullary tubules with granular casts. The incidence and severity were reported to increase with dose, but additional details were not provided in the text, and the tables and appendices were not available. The severity of this effect was reduced in the recovery group rats, in which no hyaline droplets were observed, but granular casts and multifocal cortical tubular basophilia persisted. No kidney histopathology was observed in female rats. In high-dose male rats and mid- and high-dose females, centrilobular hepatocellular hypertrophy (minimal to slight) was observed. Rats in the high-dose-recovery group did not show evidence of this change.

The authors identified the low dose (100 mg/kg-day) as a NOAEL, but they did not discuss the basis for choosing the NOAEL. MADEP (2003) likewise identified this dose as a NOAEL, citing serum chemistry changes and liver weight increases as the critical effects. Kidney histopathology in male rats was consistent with male-rat specific hyaline droplet nephropathy—a condition that is not relevant to humans (U.S. EPA, 1991b) but a detailed analysis of the mode of action has not been conducted. Therefore, this effect is considered relevant to humans. Regarding liver effects, the authors suggested that the hepatocellular hypertrophy was likely adaptive, but that it might account for mild serum chemistry changes (increased ALT in males, increased cholesterol in females, and decreased glucose in both sexes[2]). The authors also indicated that many of the statistically significant changes ($p \leq 0.05$) in serum chemistry parameters were within normal physiological limits. Data showing the magnitude of change in liver weights and serum chemistry parameters were not available; therefore, the biological significance is difficult to discern. A LOAEL of 500 mg/kg-day is identified based on liver effects (serum chemistry, liver weight and histopathology), with a NOAEL of 100 mg/kg-day. These effect levels are subject to change upon examination of the actual data tables and/or appendices that were not available at the time of this review.

[2]In the discussion of liver effects, the authors also cited increased bilirubin in males and increased triglycerides in females, effects that had not been reported in the results section. Without the data tables and appendices, it is not possible to determine whether these endpoints were also affected or not.

In a third study, apparently conducted by the same organization as the other two, groups of 10/sex Sprague-Dawley rats were given gavage doses of 0, 500, 2500, or 5000 mg/kg-day of a hydrocarbon mixture (Anonymous, 1991b). MADEP (2003) characterized the mixture as containing isoparaffins, *n*-alkanes, and naphthenes in the C9–C12 range and a typical aromatic content of 0.1%. Doses were administered 7 days/week for 13 weeks. A high-dose recovery group was observed for 28 days after exposure was terminated; this group consisted of 10 male and 6 female rats. The numbers of females in the high-dose and high-dose-recovery groups were 14 and 6, respectively, although the section that was referenced as an explanation of why the numbers of females differed in these groups was missing from the report. Evaluations were as reported for the C11–C17 mixture with two exceptions: (1) there was no interim blood sampling for hematology and serum chemistry, which were evaluated only at sacrifice and (2) in addition to gross lesions, tissue masses, liver, lungs and kidney, the stomach was also examined microscopically in all dose groups, as it was identified as a target organ in the high-dose group.

A number of gavage-related deaths occurred (1/10, 1/10, 4/14, and 3/6 in the control, mid-dose, high-dose and high-dose-recovery females and 2/10 each in the control and high-dose-recovery males). A second female death in the 2500 mg/kg-group was not explained. The incidences of certain clinical signs (especially swollen anus, anogenital staining, emaciation, and alopecia) were reported to be increased in the rats treated at 5000 mg/kg-day, while clinical signs in the remaining groups were unremarkable. Occasional statistically significant ($p \leq 0.05$) reductions (from control values) in body weight were noted in mid-dose males and persistent reductions occurred in high-dose males between Day 49 and study termination ($p \leq 0.01$). Female body weights were likewise reduced in both the mid- and high-dose groups at study termination ($p \leq 0.01$). Data tables from which to estimate the magnitude of difference were missing from the report and the authors did not note the magnitude in the text. Food consumption was increased in mid- and high-dose animals of both sexes when compared with control values. No treatment-related ophthalmoscopic findings were reported.

Hematology analysis indicated a dose-related increase in platelet count in both male and female rats, with statistical significance reached at all doses in males and at the high dose in females ($p \leq 0.05$). Leukocyte count was also reportedly increased with dose in males, and segmented neutrophils were increased in high-dose and high-dose-recovery animals of both sexes. However, additional information and statistical significance were not reported. No other hematology changes were noted. Serum chemistry changes in males included dose-related increases in BUN (statistically significantly different from control at mid- and high-doses, $p \leq 0.01$), GGT (significant at high-dose only, $p \leq 0.01$) and ALT (mid- and high doses, $p \leq 0.01$), while cholesterol was increased in both sexes at doses of ≥2500 mg/kg-day ($p \leq 0.01$) and bilirubin was increased in both sexes at the high dose ($p \leq 0.05$). Glucose levels were decreased in all male treatment groups and in females at the mid- and high doses ($p \leq 0.05$). The authors noted that hematology and serum chemistry analyses in recovery groups indicated reversibility of some changes (data tables and appendices not available).

Organ weight changes were described in the text, but data tables supporting the discussion were missing from the report (Anonymous, 1991b). Relative liver weights were significantly ($p \leq 0.05$) increased over controls in mid- and high doses in animals of both sexes, and absolute liver weights were increased in all treated female groups. Relative kidney weights were increased in treated males and females at all doses ($p \leq 0.01$); absolute kidney weights were

increased in all treated male groups. Absolute and relative adrenal weights were increased in mid- and high-dose females and in high-dose males; relative adrenal weight was also increased in mid-dose males. Finally, relative—but not absolute—testicular weights were increased in high-dose males. Histopathologic findings in the livers and kidneys corroborated the organ weight changes. Hepatocellular hypertrophy was noted at increased incidence in all treated animals except the high-dose-recovery group. Kidney changes indicative of hyaline droplet nephropathy (hyaline droplet accumulation, granular casts in medullary tubules, increased basophilia of cortical tubules) occurred at increased incidence and severity in the treated males; fewer of these changes were noted in the recovery-group males. In addition to the liver and kidney changes, gross or microscopic evidence for gastrointestinal irritation was observed: hyperplasia and hyperkeratosis of the nonglandular stomach, as well as irritation of the skin and mucosa of the anus (necrosis, neutrophilic inflammatory cell infiltrations and pustule formation of the anus). Although the text of the report did not clearly identify doses at which these irritant effects were observed, TPHCWG (1997) and MADEP (2003) both reported that these effects occurred in males and females of the mid- and high-dose groups. Effects in the stomach persisted in 3/8 high-dose males in the recovery group but not in the females or the other five males; no gross lesions of the anus were observed in recovery animals.

The authors indicated that a NOAEL could not be identified from these data, citing liver and kidney effects in the low-dose groups. Effects at the low dose included increased absolute liver weight in females, increased absolute and relative kidney weight in males and increased relative kidney weight in females, hepatocellular hypertrophy in both sexes, and increased incidence or severity of hyaline droplet nephropathy. The low dose (500 mg/kg-day) is identified as a LOAEL based on these changes and no NOAEL is identified. These effect levels are subject to change upon examination of the actual data tables and/or appendices that were not available at the time of this review. Table 5 summarizes the available oral noncancer dose-response information.

Table 5. Summary of Oral Noncancer Dose-Response Information

Species	Sex	Dose (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Rat	M/F	0, 500, 2500, 5000	Gavage 7 d/wk for 13 wks	NA	500	Increased liver and kidney weights and hepatocellular hypertrophy.	C9–C12 Isoparaffins/*n*-Alkanes/ Naphthenes (0.1% aromatic)	Anonymous, 1991b
Rat	M/F	0, 100, 500, 1000	Gavage 7 d/wk for 13 wks	100	500	Increased liver weight, serum chemistry changes, hepatocellular hypertrophy.	C10–C13 Isoparaffins/ Naphthenes/*n*-Alkanes (0.1% aromatic)	Anonymous, 1991a
Rat	M/F	0, 100, 500, 1000	Gavage 7 d/wk for 13 wks	100	500	Hematology changes trending toward anemia. Increased liver weight and serum chemistry changes also occurred at LOAEL.	C11–C17 Isoparaffinic Solvent (<0.05% aromatic)	Anonymous, 1990

Inhalation Exposure
Subchronic Studies

Mullin et al. (1990) reviewed an unpublished study performed by the Phillips Petroleum Company in 1986. According to the review, four rhesus monkeys received exposure to Soltrol 130 for 6 hours/day, 3 days/week, for 13 exposures at a mean concentration of 4200 mg/m^3. Mullin et al. (1990) did not provide any information on the exposure chamber or nature of the exposure composition (e.g., vapor or aerosol, particle size, etc.). Soltrol 130 was reported to be a mixture of C10–C13 hydrocarbons with an average molecular weight of 158 g/mol. Though the review is unclear, it appears that there was no control group. The monkeys were examined for behavioral changes and both body weight and food consumption were measured. Clinical chemistry, urinalysis, gross necropsy, and histopathology were apparently evaluated, although Mullin et al. (1990) provided no details of these examinations. The only effects noted were lymphocytopenia and neutrophilia (characterized as slight by Mullin et al. [1990]) when measured both at the midpoint and at the end of the study. In the absence of a control group, it is not possible to assign effect levels from these data.

Shell Research Limited (1980) conducted a subchronic toxicity study of Shell Sol TD, a mixture described as primarily isoparaffins in the C10–C12 range (~16% C10, 38.7% C11, and 44.4% C12). Groups of 18 male and female Wistar rats were exposed for 6 hours/day, 5 days/week, for 13 weeks to measured concentrations of 0, 2529, 5200, or 10,186 mg/m^3 (200, 5200, or 1800 ppm). The exposure atmospheres were generated by completely evaporating the test material via electrically heated quartz tubes. Solvent vapor was mixed with ventilating air, and concentrations were quantified by flame ionization detection. Animals were observed daily, and body weight, food consumption, and water intake were measured weekly. Prior to sacrifice, blood was collected for hematology (Hgb, Hct, erythrocyte count, total and differential leukocyte counts, MCV, MCH, MCHC, prothrombin time, and coagulation time) and serum chemistry (protein, BUN, alkaline phosphatase [ALP], ALT, AST, electrolytes, chloride, albumin, glucose). All animals received gross necropsies, and selected organs were weighed (brain, heart, kidney, liver, spleen, testes). Animals of all but the low concentration group were evaluated for histopathology (29 tissues including nasal cavity) and kidneys of low concentration males were also examined microscopically.

Exposure to the high concentration induced lethargy in rats of both sexes for up to 1 hour after the exposure time (Shell Research Limited, 1980). There was a statistically significant ($p \leq 0.05$) reduction in the body weight of females at all concentrations and in males at the high concentration during the first part of the study. In both sexes, body weight decrements never exceeded 6% of control values. Food consumption was also reduced in males during the first part of the study and occasionally in females throughout the study. High concentration males consumed more water than controls—at times as much as 46% more. The authors reported that all male rats exhibited low-grade anemia based on reductions in Hgb, Hct, and erythrocyte counts (see Table 1); however, all of these measures were within reference ranges for rats (Wolford et al., 1986). Leukocyte counts were also decreased (20% below controls; $p \leq 0.01$) at the high concentration in males. Hematology changes in females were limited to small changes in the differential leukocyte count. Serum chemistry changes included decreases in AST and ALT in all exposed females and increases in protein and albumin at the highest concentration. The toxicological significance of these changes is uncertain. In males, serum chemistry changes were observed at the high concentration only and included increases in ALP, potassium,

chloride, and albumin. Increased water consumption and changes in potassium, chloride, and albumin may be related to kidney effects in male rats, as confirmed by histopathology (see below). Statistically significant ($p \leq 0.05$) organ-weight changes were observed in both sexes, as shown in Table 1. Liver weights were increased at all concentrations in males (8–36%) and at all but the lowest concentration in females (13–42%). Spleen and heart weights were also increased in high-concentration males; however, the magnitude of change is small (<10%) and the toxicological significance of these changes is uncertain. Kidney weights were increased in all treated males and in high-concentration females. Histopathology evaluation indicated kidney changes in all treated male rats but no effects in female rats. Kidney changes were described as hyaline intracytoplasmic inclusions, increased incidence of tubular degeneration and dilatation of cortical tubules. The histopathology changes in male rats are consistent with the α2u-globulin nephrotoxicity commonly observed in male rats; however, a mode of action analysis ws not conducted. Therefore, this effect can be considered relevant to humans (U.S. EPA, 1991b).

Table 1. Selected Changes in Rats Exposed to ShellSol TD via Inhalation for 13 Weeks[a]

	Control	**2529 mg/m^3**	**5200 mg/m^3**	**10,186 mg/m^3**
Males				
Hematology				
Hemoglobin (g/dL)	15[b]	14.6[c]	14.3[d]	14.4[d]
Hematocrit (%)	41	40[d]	39[d]	39[d]
Erythrocyte count (10^6/mm^3)	7.79	7.57[c]	7.46[d]	7.46[d]
Leukocyte count (10^3/mm^3)	4.5	4.6	4.0	3.6[d]
Clinical Chemistry				
Alkaline phosphatase (IU)	86	87	92	100[c]
Organ Weights[e]				
Liver weight (g)	15.4	16.59[d]	17.40[d]	21.00[d]
Kidney weight (g)	2.77	3.33[d]	3.45[d]	3.83[d]
Heart weight (g)	1.17	1.22	1.22	1.27[d]
Spleen weight (g)	0.79	0.82	0.82	0.86[c]
Females				
	Control	**2529 mg/m^3**	**5200 mg/m^3**	**10,186 mg/m^3**
Clinical Chemistry				
ALT (IU)	27	(21)[c, f]	(21)[c, f]	19[d]
AST (IU)	54	43[d]	43[d]	37[d]
Organ Weights[e]				
Liver weight (g)	8.92	9.29	10.09[d]	12.67[d]
Kidney weight (g)	1.78	1.87	1.88	2.06[d]

[a]Shell Research Limited, 1980
[b]Mean reported; group-wise variability not given
[c]Significantly different from control at $p \leq 0.05$
[d]$p \leq 0.01$
[e]Organ weights as given in the report after adjustment for terminal body weight
[f]Authors did not provide simple means for these values, but rather statistically modified estimates (Williams means, shown in parentheses).

The study authors stated that changes in hematology parameters in all treated males were within reference ranges and, thus, not considered toxicologically significant. Signs of liver toxicity included increased liver weight in all exposed males and in mid- and high-concentration

females, as well as increased ALP (males at 10,186 mg/m^3) and decreased ALT and AST (all exposed females). Changes in ALP, ALT, and AST included a 16% increase in ALP and ~30% decrease in ALT and AST, and there were no histopathology findings in the livers of treated animals. The serum chemistry changes and increased liver weights were observed in the females at higher concentration levels (5200 and 10,186 mg/m^3). A LOAEL of 5200 mg/m^3 is identified based on these effects. In addition, at the highest concentration (10,186 mg/m^3), rats of both sexes exhibited lethargy for up to 1 hour after exposure. The NOAEL is 2529 mg/m^3.

Phillips and Egan (1984a) evaluated the subchronic toxicity of two midrange aliphatic hydrocarbon streams: dearomatized white spirit (DAWS) and isoparaffinic hydrocarbons (IPH). DAWS was characterized as containing 58% paraffins (straight chain alkanes), 42% naphthenes, and <0.5% aromatics, with hydrocarbons in the C11–C12 range. IPH was characterized as consisting entirely of isoparaffins of the C10–C11 range. Sprague-Dawley rats (35/sex/concentration) were exposed for 6 hours/day, 5 days/week, for up to 12 weeks at concentrations of 1970 or 5610 mg/m^3 DAWS or 1910 or 5620 mg/m^3 IPH, with a common chamber control group. The test materials were flash evaporated from heated flasks and then mixed with intake air to obtain the exposure concentrations. During exposure days, the chamber concentrations were measured using infrared spectroscopy, and the hydrocarbon compositions were verified by gas chromatography analysis after 8 and 11 weeks on study. Daily checks for clinical signs of toxicity were made and body weights were measured weekly. Interim sacrifices of 10 rats/sex/group were made after 4 and 8 weeks of exposure; the remaining rats were sacrificed after 12 weeks. After 12 weeks of exposure, blood was collected for hematology (Hgb, Hct, erythrocyte count, clotting time, MCV, and total and differential leukocyte count) and serum chemistry (BUN, glucose, ALT, and ALP). Upon sacrifice, the kidneys, liver, lungs, brain, adrenals, and gonads were weighed. All animals were examined for histopathology of 23 tissues; no tissues of the respiratory tract were examined.

Because of a malfunctioning thermostat, the low-concentration DAWS group was inadvertently exposed to combustion products of DAWS and was replaced with another group with a concurrent chamber control group (Phillips and Egan, 1984a). The authors indicated that this event occurred early in the study, but they did not provide further details. Exposure to DAWS did not affect survival, but it did result in significant reductions in the body weight of male rats at the high concentration beginning in Week 5. Based on graphical presentation of the data, the terminal body weights in this group appeared to be reduced by about 7% from control values. Hematology parameters did not appear to be affected by treatment with DAWS, as statistically significant ($p < 0.05$) differences from control values (Hgb and erythrocyte count) were only observed at the low concentration and not at the high concentration. At Weeks 4 and 8, serum glucose levels were significantly ($p < 0.05$) decreased (10–16% below controls) in both males and females exposed to the high concentration of DAWS; however, no difference from control values was apparent at 12 weeks. No other treatment-related effects on serum chemistry were observed. Relative liver and kidney weights were significantly ($p < 0.05$) increased (14–20% higher than control for liver and 12–18% for kidney) at all time points in male rats exposed to 5610 mg/m^3 DAWS; absolute kidney weight was also increased (12%) at Week 4 only. In male rats exposed to 1970 mg/m^3 DAWS, the only organ weight change was an increase (12%) in relative kidney weight at Week 8. As with males, relative liver weights were significantly ($p < 0.01$) increased (10–18% higher than controls) at all time points in female rats exposed to 5610 mg/m^3 DAWS. At Week 12, absolute liver weights were increased in female

rats at both concentrations (10 and 25% for low and high concentration, respectively; $p < 0.05$). Kidney weights in female rats were unaffected by treatment with DAWS.

The only histopathology findings observed after DAWS treatment were in the kidneys of male rats and consisted of increased incidence of regenerative epithelium in the cortex and dilated tubules containing proteinaceous casts in the corticomedullary areas (Phillips and Egan, 1984a). These changes were observed at both 1970 and 5610 mg/m^3 exposures of DAWS as early as the 4-week sacrifice and the severity of the lesions increased with time. The authors did not report the incidences or severity ratings of these lesions. The lesions were described as similar to those observed early in the development of chronic progressive nephropathy (CPN), an age-related phenomenon commonly observed in rats. Data from oral studies of similar mixtures (Anonymous, 1991a,b), as well as a mechanistic study of kidney effects after inhalation exposure to isoparaffinic hydrocarbons (Viau et al., 1986, described below under Other Studies), coupled with the lack of effects in female rats, suggest that the kidney lesions could be related to male rat-specific hyaline droplet nephropathy (U.S. EPA, 1991b). However, a mode of action analysis was not conducted, thus this effect can be considered relevant to humans. The high concentration (5610 mg/m^3 DAWS) is considered a NOAEL. The only changes observed at this concentration were (1) mild (<10%) body weight reduction in males and (2) increased relative—but not absolute—liver weight in both sexes and transient decreases in glucose levels. The body weight reductions were not biologically significant. No changes in ALT or ALP were observed.

There were no effects of IPH treatment on survival, but significant (*p*-value not reported) reductions in the body weight of male rats were observed at both concentrations; reductions were significant beginning during Week 5 (Phillips and Egan, 1984a). Based on graphical presentation of the data, the terminal body weights were reduced by about 5–7% from control values. Erythrocyte count was significantly ($p < 0.05$) decreased (~5 % relative to controls) in males exposed to both concentrations of IPH; no other hematology parameters were affected. The only serum chemistry parameter that differed from controls was serum glucose, which was reduced (8–14%) in males of both exposure groups at 8 weeks and in females of both groups at 4 weeks. Relative kidney weight was significantly ($p < 0.05$) increased at all time points in male rats exposed to both concentrations of IPH; absolute kidney weight was increased only at Week 8 in the high concentration group. Relative kidney weight increases (over control values) at the low concentration of IPH ranged from 11–12% while increases at the high concentration were from 13–19%. In females, absolute and relative kidney weights were increased at Week 8 but not at Weeks 4 or 12. Significant ($p < 0.05$) increases in absolute and relative liver weight were observed after exposure at the high concentration in both sexes. In males, absolute and relative liver weights were increased (15 and 14% higher than controls, respectively) at Week 4, and relative weight was increased (8%) at Week 12. In females, relative liver weight was increased at Week 4 and Week 8 (13 and 8%, respectively), and absolute liver weight was increased (9%) at Week 8. Liver weights in females did not differ from controls at study termination. The study authors indicated that other organ weight changes were sporadic and not considered treatment-related.

As with DAWS, histopathology findings after IPH treatment were limited to the kidneys of male rats (regenerative epithelium in the cortex and dilated tubules containing proteinaceous casts) and were described as similar to age-related CPN (Phillips and Egan, 1984a). The authors reported these findings at both 1910 and 5620 mg/m^3 exposures of IPH beginning at the 4-week

sacrifice, with increasing severity over time. Incidence data were not reported. As discussed for the study of DAWS, the kidney changes observed after IPH exposure may be related to male rat-specific hyaline droplet nephropathy (U.S. EPA, 1991b); however, a mode of action analysis was not conducted, thus this effect is considered relevant to humans. The high concentration of IPH (5620 mg/m^3) is considered a NOAEL. The only changes observed at this concentration were small (<10%) reductions in body weight in males, slight decreases in erythrocyte count and serum glucose, as well as increases in liver and kidney weights in both sexes. At study termination, the only statistically significant ($p < 0.05$) organ weight changes were increased relative kidney weight in males at both exposure levels, and a small (8%) increase in relative liver weight in high-concentration males.

In preparation for chronic studies, NTP (2004) conducted subchronic inhalation studies of Stoddard Solvent IIC in F344/N rats and B6C3F1 mice. The test material was characterized as a mixture of *n*-paraffins, isoparaffins, and cycloparaffins with 10–13 carbons; the aromatic content was measured as <1.0%. Stoddard Solvent IIC vapor was generated by pumping the material through a preheater and into a heated glass column; heated nitrogen resulted in vaporization of the mixture as it left the generator, and the line transporting the vapor to the exposure chamber was heated to prevent condensation. A particle detector used during the 2-week and 3-month studies confirmed that the test material was present as a vapor and not an aerosol in the exposure chamber. Exposure concentrations were verified by gas chromatography during the studies. Exposure concentrations were selected based on the results of 2-week studies in both species, in which exposure concentrations ranging from 138–2200 mg/m^3 were used. Neither survival nor body weights of either species were affected at concentrations up to 2200 mg/m^3 in the 2-week studies. In male rats, relative liver weights were increased at exposures to 550 mg/m^3 and greater; in female rats, absolute liver and kidney weight increases occurred at concentrations of 275 mg/m^3 and above. Minimal diffuse cytoplasmic vacuolization of hepatocytes occurred in all female rats exposed to 2200 mg/m^3 and only one control. In mice, absolute and relative liver weights were increased in both sexes at 275 mg/m^3 and above and kidney weights were increased in females exposed to 1100 mg/m^3 and greater. Liver cytomegaly occurred in all male and female mice exposed to 2200 mg/m^3 in the 2-week studies (NTP, 2004).

The same exposure concentrations were used in the subchronic studies (NTP, 2004). Groups of 10/sex/species were exposed to vapor concentrations of 0, 138, 275, 550, 1100, or 2200 mg/m^3 for 6 hours/day, 5 days/week, for 14 weeks. Chamber concentrations were verified by GC analysis throughout the study. Animals were observed twice daily and body weights and clinical signs were recorded weekly. Prior to sacrifice, blood was collected from mice for hematology (Hct, packed cell volume, Hgb, erythrocyte count, platelet count, total and differential leukocyte count, reticulocyte count, nucleated erythrocyte/leukocyte ratios, MCV, MCH, and MCHC); clinical chemistry was not performed on blood samples from mice. Hematology (detailed previously) and clinical chemistry evaluations (BUN, creatinine, total protein, albumin, globulin, albumin/globulin ration, ALT, ALP, creatine kinase, sorbitol dehydrogenase, bile acids, and hemolysis) were performed on blood samples collected intermittently from groups of 10 rats/sex/dose used for clinical pathology and from all rats at termination. Sperm count and motility were evaluated in male rats and mice from the 550-, 1100-, and 2200-mg/m^3 groups and vaginal cytology and estrous cyclicity were evaluated in females of the same groups. All animals were necropsied at sacrifice and the heart, right kidney, liver, lung, right testis, and thymus were weighed. A large number of tissues (>31) from

control and high concentration animals were examined microscopically. In addition, the larynx, lung, nose, and trachea of all groups in both species were examined, as were the kidneys of rats and the spleens of female mice of all groups.

There were no deaths among rats of either sex (NTP, 2004). The incidence of clinical signs was not affected by treatment. Mean terminal body weights of female rats were higher than controls in all exposure groups, but the difference was statistically significant ($p \leq 0.01$) only in the group exposed to 275 mg/m^3. Male body weights were comparable to controls in all exposure groups. Exposure to Stoddard Solvent IIC resulted in concentration-related decreases in ALT levels in both sexes (see Table 2) and an increase (albeit not persistent) in serum bile acid in exposed females at all concentrations. The authors attributed increases in creatinine (males and females), total protein (males), and albumin (males) in rats exposed to levels of 550 mg/m^3 or more to a decrease in plasma volume. Decreases in Hct, Hgb, and erythrocyte counts were recorded among high-concentration males, but the study authors did not consider the changes to be toxicologically relevant. Relative kidney, liver, and testes weights were significantly ($p \leq 0.05$) increased in all exposed male groups (see Table 2). Absolute kidney weights were also increased in males exposed to concentrations of 550 mg/m^3 and higher, but absolute liver and testes weights were not different from controls. Female organ weights were not affected by treatment at any concentration. Sperm motility was reduced at all the exposure levels evaluated for this endpoint (≥550 mg/m^3). Estrous cyclicity and vaginal cytology were not affected by treatment.

Histopathology changes considered by the authors to be indicative of α_{2u}-globulin nephropathy were observed in male rats exposed to concentrations of 550 mg/m^3 and greater (NTP, 2004). The changes consisted of increased incidence of renal tubule granular casts and increased severity of hyaline droplet accumulation and renal tubular regeneration. No microscopic changes were observed in the kidneys of female rats at any exposure level. Both male and female rats exhibited increased incidences of goblet cell hypertrophy of the nasal respiratory epithelium when exposed to higher concentrations of Stoddard Solvent IIC (≥1100 mg/m^3 in females and at 2200 mg/m^3 in males). The incidences and severity scores are shown in Table 2.

NTP (2004) did not identify effect levels. The kidney changes reported in male rats, including kidney weight increases and histopathology, are considered indicative of α_{2u}-globulin nephropathy; however a mode of action analysis was not conducted, thus this effect is considered relevant to humans. (U.S. EPA, 1991b). Statistically significant ($p < 0.05$) decreases in sperm motility were observed at concentrations of 550 mg/m^3 and higher, but the maximum decrease was only 12%. It is unclear whether a decrease in sperm motility of this magnitude will affect fertility. NTP (2004) reported that studies in mice indicate little or no effect on fertility until sperm motility is reduced by 40% or more; there are no corresponding studies in rats to inform this question. Relative testes weights were increased in all exposed males, but the toxicological significance of this finding is uncertain. Relative—but not absolute—liver weights were increased (up to 13%) in males at all exposure levels, and decreases in ALT were observed in both sexes at 550 mg/m^3 and higher concentrations. Exposure-related increases in the incidence of nasal goblet cell hypertrophy were observed in both sexes (at 2200 mg/m^3 in males and ≥1100 mg/m^3 in females). This endpoint may reflect an irritant property of the test material. For the

Table 2. Selected Changes in Rats Exposed to Stoddard Solvent IIC via Inhalation for 13 Weeks[a]						
	Control	**138 mg/m^3**	**275 mg/m^3**	**550 mg/m^3**	**1100 mg/m^3**	**2200 mg/m^3**
Males						
Clinical Chemistry						
ALT (IU/L)	80 ± 5[b]	73 ± 6	71 ± 4	62 ± 6[d]	46 ± 1[d]	42 ± 2[d]
Organ Weights						
Right kidney weight (g)	0.917 ± 0.021	0.958 ± 0.016	0.967 ± 0.025	0.984 ± 0.026[c]	1.022 ± 0.022[d]	1.020 ± 0.024[d]
Right kidney / body weight (mg/g)	2.747 ± 0.045	2.901 ± 0.042[c]	2.911 ± 0.040[d]	2.972 ± 0.041[d]	3.073 ± 0.029[d]	3.235 ± 0.050[d]
Liver / body weight (mg/g)	28.6 ± 0.4	30.1 ± 0.5[c]	30.2 ± 0.4[c]	30.4 ± 0.4[d]	30.8 ± 0.5[d]	32.4 ± 0.4[d]
Right testis / body weight (g)	4.076 ± 0.081	4.258 ± 0.059[c]	4.294 ± 0.053[c]	4.332 ± 0.047[d]	4.285 ± 0.068[d]	4.459 ± 0.040[d]
Reproductive Evaluations						
Epididymal sperm motility (%)	90.28 ± 1.40	Not evaluated	Not evaluated	77.27 ± 3.99[c]	80.38 ± 2.62[c]	79.44 ± 1.59[c]
Histopathology						
Nasal Goblet Cell, Respiratory Epithelial Hypertrophy	2/10[e] (1.0)[f]	2/10 (1.0)	2/10 (1.0)	2/10 (1.0)	4/10 (1.5)	7/10[c] (1.9)
Females						
	Control	**138 mg/m^3**	**275 mg/m^3**	**550 mg/m^3**	**1100 mg/m^3**	**2200 mg/m^3**
Clinical Chemistry						
ALT (IU/L)	52 ± 3	55 ± 3	56 ± 4	42 ± 2[c]	46 ± 3	39 ± 2[d]
Histopathology						
Nasal Goblet Cell, Respiratory Epithelial Hypertrophy	0/10	1/10 (2.0)	1/10 (1.0)	0/10	4/10[c] (1.0)	9/10[d] (1.7)

[a]NTP, 2004
[b]Mean ± standard deviation
[c]Significantly different from control at $p < 0.05$
[d]$p < 0.01$
[e]Number affected/number examined
[f]Severity score in parentheses (1 = minimal, 2 = mild, 3 = moderate, 4 = marked)

purpose of this review, a LOAEL is established at 1100 mg/m^3 based on nasal goblet cell hypertrophy in females. The NOAEL is 550 mg/m^3.

In mice, one male in the lowest exposure group was sacrificed prematurely due to moribund condition, but no other effects on survival were observed (NTP, 2004). There were no statistically significant ($p \leq 0.01$) effects on body weight; however, exposed males were reported to appear thin. Exposure to Stoddard Solvent IIC did not affect other clinical signs or hematology findings. Absolute liver weight was increased (11% higher than control, $p \leq 0.01$) in males at the highest concentration and relative liver weight was increased in males at 1100 and 2200 mg/m^3 (8% and 14%, respectively). No other organ weight changes were observed. Sperm motility was reduced (10% below controls; $p \leq 0.05$) at the highest concentration only. Female reproductive evaluations were not affected by treatment. The only histopathology finding was an increase ($p < 0.01$ by Fisher's exact test performed for this review) in the incidence of hematopoietic cell proliferation in the spleens of all exposed females (1/10, 8/10, 7/10, 7/10, 9/9, 9/10 in control through high-concentration groups). The authors did not consider this effect to be toxicologically significant. Although sperm motility was reduced at the high concentration (10% decrease), NTP (2004) reported that studies in mice indicate little or no effect on fertility until sperm motility is reduced by 40% or more; thus, this effect is not considered as the basis for a LOAEL determination. Clinical chemistry was not evaluated in mice. The high concentration (2200 mg/m^3) is considered a LOAEL in the mice study, based on statistically significantly increased absolute and relative liver weight.

Chronic Studies

Lund et al. (1996) evaluated the neurotoxicity of DAWS (carbon range and aromatic content not reported) in groups of 36 male Mol:Wist rats exposed to concentrations of 0, 2339, or 4679 mg/m^3 for 6 hours/day, 5 days/week, for 6 months. The authors did not describe the inhalation exposure conditions or equipment. After the exposure period, animals were followed for 70–80 untreated days before neurophysiological and neurobehavioral testing was conducted. Body weights were recorded weekly and water consumption was measured for the last 5 weeks of exposure and first 6 weeks postexposure. After exposure was terminated, groups of 10 rats/exposure were placed in metabolism cages for 24-hour urine collection, after which blood was collected for serum chemistry (ALT, ALP, glucose, creatinine, urea, protein, phosphate, and uric acid). After two unexposed months, neurobehavioral testing was initiated, including motor activity (control and high-exposure groups only), functional observational battery, passive avoidance test, eight-arm radial maze test, and Morris water maze (with and without scopolamine [an anticholinergic agent] challenge). Another 10 rats/group were used for electrophysiological measurements, including visual flash evoked potentials (FEP), somatosensory evoked potentials (SEP), and auditory brainstem response (ABR) 3 months after exposure concluded. After 6 untreated months, 10 animals/group were sacrificed for necropsy, organ weight measurements (liver, kidneys, adrenals, heart, spleen, and testes), and histopathology of these organs together with the sciatic nerve.

The authors reported that exposed rats showed "signs of discomfort" at both exposure levels (Lund et al., 1996). Lacrimation and bloody nasal discharge were noted, as was a narcotic effect during the first 2 weeks of exposure, but incidences and difference from controls were not described. Body weights were not affected by exposure, but water consumption was increased relative to controls when measured during the last 5 weeks of exposure. Urine output was

increased in rats exposed to the high concentration of DAWS and serum levels of uric acid were increased; no other changes in urine or serum chemistry parameters were noted. Dose-dependent increases in the amplitude of early latency peaks were observed during measurements of FEP, SEP, and ABR, as shown in Table 3. Early latency peak-to-peak amplitudes (both FEP and SEP) were significantly ($p < 0.05$) larger than controls at both concentrations of DAWS and later-latency amplitude (FEP only) was increased at the high concentration. No treatment-related differences in FOB parameters were noted. Motor activity was significantly lower than controls in the high-concentration group at various time points, but was not consistently affected at each evaluation. No effects of treatment were noted on other neurobehavioral tests (passive avoidance, Morris water maze, radial arm maze) or on histopathology findings. A LOAEL of 2339 mg/m^3 for clinical signs of toxicity (lacrimation and bloody nasal discharge) and neurophysiological changes is identified. No NOAEL can be identified.

Table 3. Significant Changes in Rat Neurophysiological Measures (Evoked Potentials) 3 Months after Exposure to DAWS for 6 Months[a]

Endpoint and Measurement	Control	2339 mg/m^3 (400 ppm)	4679 mg/m^3 (800 ppm)
Flash Evoked Potential			
N1P2 peak to peak amplitude (µV)	124.5 ± 33.2	163.5 ± 25.1[b]	179.2 ± 54.7[b]
N2P3 peak to peak amplitude (µV)	47.2 ± 22.1	53.9 ± 18.0	83.4 ± 32.2[b]
Somatosensory Evoked Potential			
P1 amplitude (µV)	18.8 ± 8.8	37.3 ± 14.1[b]	43.9 ± 21.2[b]
Root Mean Square (RMS) voltage (µV)	19.0 ± 8.1	23.0 ± 8.5	30.4 ± 8.9[c]
Auditory Brainstem Response			
4 kHz Ia amplitude (µV)	4.4 ± 1.1	5.8 ± 2.1	6.4 ± 1.3[b]
4 kHz Root Mean Square (RMS) voltage (µV)	6.6 ± 1.1	9.2 ± 2.1[c]	8.2 ± 1.3[c]
8 kHz Ia amplitude (µV)	6.5 ± 1.4	8.3 ± 2.9	8.8 ± 2.1[c]
8 kHz IV amplitude (µV)	15.2 ± 3.1	19.6 ± 5.2	18.5 ± 2.5[c]
8 kHz Root Mean Square (RMS) voltage (µV)	7.9 ± 1.4	10.8 ± 2.9[c]	9.7 ± 1.3[c]
16 kHz Ia amplitude (µV)	6.1 ± 1.1	7.3 ± 2.6	7.7 ± 1.6[c]

[a]Lund et al., 1996
[b]Significantly different from control by one-way ANOVA, $p < 0.01$
[c]$p < 0.05$

Chronic inhalation studies of Stoddard Solvent IIC (mixture of *n*-paraffins, isoparaffins and cycloparaffins with 10–13 carbons; aromatic content <1.0%) were performed by NTP (2004) in F344/N rats and B6C3F1 mice. Groups of 50 animals/sex/species were exposed to vapor concentrations of 0, 138 (male rats only), 550, 1100, or 2200 (male and female mice and female rats only) mg/m^3 for 6 hours/day, 5 days/week, for 2 years. Chamber concentrations were verified by GC analysis throughout the study. Animals were observed twice daily and body weights and clinical signs were recorded weekly through the first month, monthly until Week 89

and biweekly thereafter. All animals were necropsied at sacrifice; organ weights were not recorded. Comprehensive histopathology evaluations (>31) were performed on all treated animals. A separate study evaluating the role of α_{2u}-globulin nephropathy in rats was conducted; this study is discussed under Mechanistic Studies (page 28) below.

In rats, survival was significantly ($p \leq 0.01$) reduced at 138 and 1100 mg/m^3 (but not at 550 mg/m^3) in males and at 2200 mg/m^3 in females. The mean body weights and incidences of clinical signs in exposed rats were comparable to controls. Male rats exhibited increases in the incidence of renal tubule hyperplasia, transitional epithelial hyperplasia of the renal pelvis and renal papillary mineralization. With the exception of increased renal papillary mineralization, which occurred at all concentrations, these effects were restricted to the mid- and high-concentration groups. Based on the constellation of renal findings in male rats, coupled with the results of the satellite kidney toxicity study (discussed below under Mechanistic Studies), the kidney effects were attributed to α_{2u}-globulin nephropathy (NTP, 2004); however, a mode of action analysis was not conducted. Thus, this endpoint is considered relevant to human health (U.S. EPA, 1991b). In female rats exposed to 2200 mg/m^3 and in male rats exposed to 138 mg/m^3 Stoddard Solvent IIC, the incidences of olfactory epithelial hyaline degeneration were increased (females: 28/50 exposed vs. 12/49 controls; males: 8/50 exposed vs. 2/50 controls). However, NTP (2004) considered this effect to be of questionable biological significance because this lesion is commonly observed in the nasal passages of rats, especially during inhalation studies. Nonneoplastic lesions attributed to Stoddard Solvent IIC exposure included an increased incidence of adrenal medullary hyperplasia in males at the mid concentration but not at the high concentration (see Table 4). The LOAEL is established at 550 mg/m^3 based on the increase in adrenal medullary hyperplasia in male rats, and the NOAEL is 138 mg/m^3. The apparent lack of dose-response trend at the highest concentration treatment group (decreased incidence at the highest dose; 15/50 at 1100 mg/m^3 vs. 23/50 at 550 mg/m^3) may be related to other unknown (and perhaps more serious effects) at the same level of exposure. It is unclear whether the incidence of hyperplasia is part of cancer progression (increased tumor incidences at higher levels) or an independent event itself. Since there is no incidence of hyperplasia in the subchronic study (NTP, 2004) under the same experimental conditions, and because there is high background level in the chamber control group (12/50) in the chronic study, it is not possible to determine if this effect is a precursor event (preneoplastic change) based on the limited information.

The incidences of renal tubular adenoma and/or carcinoma were not statistically significantly increased over controls in rats of either sex at any exposure level (NTP, 2004). A nonsignificant increase in renal adenoma incidence was observed at the highest concentration (7/50 vs. 3/50 in controls in extended histopathology evaluations). The incidence of clitoral gland adenoma was significantly ($p \leq 0.05$) increased at 1100 and 2200 mg/m^3 and the incidence of clitoral gland adenoma or carcinoma was significantly increased at the high concentration. However, the incidences at all exposure levels were reported to be within historical control ranges for chamber controls. Based on this observation, along with the absence of exposure-related increases in clitoral gland hyperplasia or carcinoma (clitoral adenoma is part of a morphologic continuum from hyperplasia to carcinoma), NTP (2004) concluded that the clitoral gland adenomas were not treatment-related. The incidences of benign and benign or malignant (combined) pheochromocytoma of the adrenal glands were increased over both chamber controls and over historical control incidences in males exposed to 550 and 1100 mg/m^3 (see Table 4).

Table 4. Incidence of Neoplastic and Nonneoplastic Changes in the Adrenal Medulla of Male Rats Exposed to Stoddard Solvent IIC for 2 Years[a]

Lesion	Chamber Control	Historical Control	138 mg/m^3	550 mg/m^3	1100 mg/m^3
Hyperplasia	12/50 (2.5)[b]	Not reported	14/50 (2.6)	23/50[d] (2.6)	15/50 (2.2)
Benign pheochromocytoma	5/50	42/298 (14%)	9/50	13/50[c]	17/50[d]
Benign or malignant (combined) pheochromocytoma	6/50	48/298 (16%)	9/50	13/50[c]	19/50[d]

[a]NTP, 2004
[b]Number affected/number examined; severity score in parentheses (1=minimal, 2=mild, 3=moderate, 4=marked)
[c]Significantly different from chamber control at $p \leq 0.05$
[d]$p \leq 0.01$

Significant ($p < 0.001$) concentration-related trends were also evident in both the benign and combined incidence rates. NTP (2004) noted that, although some studies have demonstrated a correlation between the severity of nephropathy and adrenal pheochromocytoma, correlation analysis performed on the Stoddard Solvent IIC data failed to indicate a similar correlation, suggesting that the increase in adrenal tumors was not explained by kidney toxicity. The observation of increased incidences of adrenal neoplasms served as the basis for a finding of *some evidence of carcinogenic activity* for Stoddard Solvent IIC in male rats (NTP, 2004).

Survival of mice in the 2-year study was not affected by treatment (NTP, 2004). Clinical signs were comparable among all groups including control and the body weights of male mice were unaffected. Mean body weights of all exposed female mice were increased over controls (6–12% higher); statistical comparisons of the differences were not reported, nor were data with which to perform such comparisons. Nonneoplastic histology findings were restricted to the liver. The incidences of basophilic and eosinophilic foci were increased in males exposed to 1100 mg/m^3 but not in those exposed to 2200 mg/m^3; thus, the relationship to exposure is uncertain. The incidence of eosinophilic foci in female mice was significantly ($p \leq 0.05$) increased at the high concentration (4/50, 9/50, 6/50, 11/50 in control through high concentration). This lesion was considered mild in all groups including controls. For the purpose of this PPRTV document, the high concentration (2200 mg/m^3) is considered a LOAEL for the increased incidence of eosinophilic foci of the liver in female mice and 1100 mg/m^3 is a NOAEL.

Statistically significant ($p \leq 0.05$) increases in the incidences of multiple hepatocellular adenoma (males and females) and hepatocellular adenoma (females only) were observed in the high concentration group, but there was no difference in the rate of hepatocellular carcinoma formation (NTP, 2004). The increase in multiple adenomas in males was not considered to be exposure-related, as the incidence of all adenomas was not increased in males at any exposure level. Thus, NTP (2004) concluded that there was *no evidence of carcinogenic activity* in male mice. Since liver tumors in this strain of mouse are affected by body weight, NTP (2004) conducted a statistical analysis to evaluate the relationship between liver neoplasm incidence and body weight in the female mice and concluded that the increase in liver tumors was primarily due to the increased body weights in the exposed females. NTP (2004) concluded that there was

equivocal evidence of carcinogenic activity of Stoddard Solvent IIC in female mice. It should be noted that the maximum exposure concentration in this study was not a Maximum Tolerated Dose, but rather was limited by the maximum vapor concentration that could be attained.

Reproductive/Developmental Studies—Both Mullin et al. (1990) and TPHCWG (1997) reviewed an unpublished study performed by Exxon Corporation (1988) on the developmental toxicity of IPH. The test material was Isopar G, which was characterized by Mullin et al. (1990) as a mixture of predominantly C10–C11 hydrocarbons with an average molecular weight of 149 g/mol. No information on the exposure conditions or equipment was provided. According to the review, mated CD rats were exposed to 0, 300, or 900 ppm Isopar G for 6 hours/day on gestation days (GD) 6–15, followed by sacrifice on GD 21. Based on the reported average molecular weight, these exposures (300 and 900 ppm) are estimated to be equivalent to 1828 and 5485 mg/m^3, respectively. Parameters evaluated included live and dead fetuses, early and late resorptions, implantation sites, number of corpora lutea, fetal weight, length, and sex, in addition to external, visceral, and skeletal malformations. Mullin et al. (1990) reported that there were no effects on any of these parameters; thus, the high concentration of 900 ppm (5485 mg/m^3) was a developmental NOAEL. While Mullin et al. (1990) did not address maternal toxicity parameters, TPHCWG (1997) reported that no maternal toxicity was observed; thus, the high concentration is apparently a maternal NOAEL as well. Given the reliance on secondary sources, these effect levels should be considered with caution.

Hass et al. (2001) evaluated the neurobehavioral effects of gestational exposure to DAWS (<0.4 wt. % aromatic, carbon range not specified) in Mol:WIST rats. The authors did not describe the inhalation exposure conditions or equipment. Groups of time-mated rats were exposed to 0 or 4679 mg/m^3 of DAWS for 6 hours/day on GD 7–20. While group sizes were not explicitly noted, there were 14 litters in the controls and 13 in the exposed group. Maternal body weights were recorded on GD 11, 15, 17, and 21. Dams were allowed to give birth, at which time pups were counted, sexed and examined grossly and maternal and pup weights were recorded. Pup body weights were also measured on PND 1, 2, 3, 6, 10, 14, 19, and 21. Upon weaning on postnatal (PND) 21, one rat/sex/litter was tested for neuromotor ability (Rotarod testing on 2 consecutive days at 16 weeks of age), motor activity in an open field (on 2 consecutive days at age 17 weeks), learning and memory (Morris Water Maze, in which a hidden platform must be located, beginning at age 3 weeks and testing periodically up to age 19 weeks). The remaining pups were sacrificed and necropsied at this time. Reflex ontogeny and sexual maturation of the offspring selected for testing were recorded. All dams were sacrificed and necropsied at PND 21 and uterine implantation sites were counted.

Exposure to DAWS resulted in reduced maternal body-weight gain during the exposure period (26% below controls, $p = 0.007$) (Hass et al., 2001). While litter sizes were smaller and postimplantation loss higher in the exposed rats than in controls, neither change was statistically significant. Birth weight of exposed pups was higher than controls, but there were no body-weight differences during lactation or postweaning. Reflex development and sexual maturation occurred normally in exposed rats, and neither neuromotor ability nor motor activity was significantly affected ($p < 0.05$) by treatment. In the tests of learning and memory, however, significant differences between exposed and control offspring were observed. When rats were tested at age 2 months for recall of maze information learned at age 1 month, exposed male rats took longer to locate a hidden platform ($p = 0.022$). When reversal learning was tested (platform

relocated), latency (time to find the hidden platform) and path length (distance traveled to hidden platform) were significantly higher in exposed female rats ($p < 0.05$). Finally, when rats were tested for memory of the water maze at age 19 weeks, both sexes (when combined) showed significantly increased latency ($p = 0.019$); when analyzed separately by sex, the difference was borderline significant in females and not significant in males. The exposure concentration in this study (4679 mg/m^3) is both a maternal and a developmental LOAEL based on decreased body-weight gain in dams and effects on memory and learning in offspring. No NOAEL can be identified from this study.

Other Studies

Genotoxicity—Stoddard Solvent IIC was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535, with and without rat or hamster S9 mix (NTP, 2004). This mixture did not induce an increase in the frequency of micronucleated peripheral blood erythrocytes in B6C3F1 mice exposed for 3 months to concentrations from 138 to 2200 mg/m^3. In its review of other genotoxicity assays, NTP (2004) did not provide any other data on white spirit/Stoddard Solvent of low aromatic content.

In their review of industry studies of isoparaffinic hydrocarbons, Mullin et al. (1990) reported that Isopar L, Isopar G, and Soltrol 130[3] were not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 with or without S9. In addition, Isopar G gave negative results in tests for DNA damage in Pol A-*Escherichia coli* and for mutagenicity in *E. coli* strain WP2. Isopar G did not induce micronuclei in erythrocytes of mice treated intraperitoneally and was not mutagenic in rats in a dominant lethal test. Soltrol 130 tested negative in the mouse lymphoma assay for forward mutations and in an assay for sister chromatid exchanges in Chinese hamster ovary (CHO) cells (reviewed by Mullin et al., 1990).

Mechanistic Studies—Lam et al. (1992) observed dose-related increases in levels of reduced glutathione in brain tissue removed from male Wistar rats after 3 weeks of inhalation exposure (6 hours/day, 7 days/week) to DAWS (≤0.4% aromatic) at concentrations of 2339 or 4679 mg/m^3. Increased generation of reactive oxygen species was observed in hippocampal fractions from rats exposed to the higher concentration. These findings suggest a possible mechanism for neurotoxicity of DAWS.

To further evaluate the kidney effects they observed after exposing rats to isoparaffinic hydrocarbons, Phillips and Egan (1984b) and Phillips and Cockrell (1984) exposed groups of 50 male and female F344 rats to concentrations of 0, 1830, or 5480 mg/m^3 via inhalation for 6 hours/day, 5 days/week, for up to 8 weeks. Kidney function was assessed through urinalysis, hematology, serum chemistry, creatinine clearance, urine-concentrating ability and kidney weights, and both light and electron microscopy of the kidneys. Ability to concentrate urine was reduced in male rats at both exposure levels after 4 and 8 weeks of exposure and in high-exposure males after the 4-week recovery period; females were not affected. At both exposure concentrations, increases in urinary levels of glucose and protein were observed in males after 4 and 8 weeks of exposure, but not after the recovery period. Excretion of epithelial cells in the urine was markedly increased in male rats exposed to both concentrations after 4 and 8 weeks of exposure, but not after the 4-week recovery. Creatinine clearance rates were reduced

[3]Mullin et al. (1990) indicated a carbon range of C10–C11 for Isopar G, C11–C13 for Isopar L, and C10–C13 for Soltrol 130. Aromatic content was not reported.

only in the high-concentration group in male rats exposed for 8 weeks. Statistically significant ($p < 0.05$) concentration- and time-related changes in serum chemistry parameters (reduced glucose, increased BUN and creatinine) were observed in male—but not female—rats after both 4 and 8 weeks of exposure. Clinical chemistry parameters were comparable to controls in treated rats after 4 weeks of recovery.

Relative kidney weights were increased over controls in both groups of treated males throughout the study, while absolute kidney weights were increased in high-concentration males only (Phillips and Egan, 1984b; Phillips and Cockrell, 1984). The increase in relative kidney weight persisted through the recovery period in high-concentration males. In females, relative kidney weights were increased at the high concentration after 8 weeks. Microscopic examination of kidneys revealed increased incidence and severity of regenerative epithelium, tubular dilatation with intratubular protein, and protein droplets in male rats; the severity increased with time among treated males. Exposure-related changes in these findings were not observed in females. Treated male rats also exhibited tubular nephrosis, lymphoid infiltration of the renal interstitium, and thickening of the tubular basement membranes. Electron microscopy of the protein droplets showed electron dense, angular, crystalline structures surrounded by remnants of membrane-bound phagolysosomes. Focal loss of brush border and degeneration and sloughing of necrotic cells were also shown.

In a series of experiments aimed at exploring the nature of the renal effects of isoparaffinic hydrocarbons, Viau et al. (1986) exposed Sprague-Dawley rats to Shell Sol TD (consisting of C10–C12 isoparaffins) for 8 hours/day, 5 days/week, for up to 16 months. Exposure concentrations were 0, 580 or 6500 mg/m^3. In one experiment, groups of 24 male rats were exposed to 0 or 6500 mg/m^3 for 46 or 68 weeks. In a second experiment, 12 rats/sex were exposed to these concentrations for 13 weeks followed by a 6-week recovery period. A third experiment involved exposure of groups of 12 male rats to 0 or 580 mg/m^3 for 16 weeks. Finally, groups of 6 male and 5–6 castrated male rats were exposed to 0 or 6500 mg/m^3 for 5.5 weeks. Urine was collected at study intermittently for evaluation of enzymes (ß-N acetyl-D-glucosaminidase and lactate dehydrogenase [LDH]) and proteins (α_{2u}-globulin and albumin). Tests of renal function (urinary concentration, acidification, sodium retention, and glomerular filtration rate) were performed. Histopathology evaluation was performed on animals exposed for 5.5, 46 weeks or 68 weeks of exposure, including Mallory-Heidenhain (M-H) staining for hyaline droplets. Subgroups of rats treated for 68 weeks were treated with ^{3}H-thymidine for evaluation of kidney cortex labeling index.

All male rats—except the castrated ones—exposed at the high concentration showed a marked increase in the urinary excretion of lactate dehydrogenase (LDH) (Viau et al., 1986). Albuminuria was also observed in male rats, but the difference from control declined over time due to the effect of age-related chronic progressive nephrosis in the controls. Functional tests showed that exposure at the high concentration decreased the ability to concentrate urine and reduced capacity to reduce sodium loss during reduced sodium intake. Glomerular filtration rate was slightly reduced (6% less than controls, $p < 0.05$) in intact males exposed to the high concentration. While urinary clearance and reabsorption of α_{2u}-globulin were unaffected by exposure in all male rats, serum and kidney concentrations of this protein were much higher noncastrated exposed male rats than in unexposed controls. After exposure for 5.5, 46, or 68 weeks, numerous hyaline droplets were observed in intact male rats using M-H staining.

Kidney histopathology (zones of tubular dilatation filled with granular material at the cortico-medullary junction) was observed in the male rats treated at the high concentration for 5.5 weeks but not in the rats exposed for longer durations. The kidney cortex labeling index was not different in the animals treated for 46 or 68 weeks.

In the NTP (2004) chronic study, a separate study of renal toxicity in rats was performed, in which 10 rats/sex were exposed to 0, 138, 550, or 1100 mg/m^3 Stoddard Solvent IIC (NTP, 2004). At sacrifice after 13 weeks, the kidneys were weighed and examined microscopically, and the α_{2u}-globulin and protein content of the right kidneys was measured. Cell proliferation in the left kidney was measured as BrdU uptake. Significant, exposure-related increases in both number of labeled cells and labeling index were observed in male rats exposed to 550 or 1100 mg/m^3 but not in females at any concentration. Overall soluble protein content was not changed in an exposure-related fashion, but the α_{2u}-globulin content was significantly increased over controls in the mid- and high-exposure males and in high-exposure females. Histopathology examination of treated males indicated concentration-related increases in the severity of hyaline droplets and increased incidences of granular casts (550 and 1100 mg/m^3), cortical tubule degeneration (1100 mg/m^3) and cortical tubule regeneration (550 and 1100 mg/m^3). These changes were not observed in females. The study authors considered the renal changes to be characteristic of male-rat specific α_{2u}-globulin nephropathy; however, a mode of action analysis was not conducted.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR MIDRANGE ALIPHATIC HYDROCARBON STREAMS

Because the toxicity data based on the three unpublished studies (Anonymous, 1990, 1991a,b) are not peer-reviewed, no provisional chronic or subchronic RfDs are developed. However, the Appendix of this document contains screening chronic and subchronic p-RfD values that may be useful in certain instances. Please see the attached Appendix A for details.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR MIDRANGE ALIPHATIC HYDROCARBON STREAMS

Inhalation studies available for use in developing subchronic and/or chronic provisional RfCs (p-RfC) for midrange aliphatic hydrocarbon streams include chronic bioassays of Stoddard Solvent IIC in rats and mice (NTP, 2004); a chronic study of neurophysiological and neurobehavioral effects in rats exposed to DAWS (Lund et al., 1996); subchronic toxicity studies of Stoddard Solvent IIC in rats and mice (NTP, 2004); a subchronic toxicity study of DAWS and IPH in rats (Phillips and Egan, 1984a); an unpublished subchronic study of ShellSol TD in rats (Shell Research Limited, 1980); and a developmental neurobehavioral toxicity study of DAWS in rats (Hass et al., 2001). An unpublished developmental toxicity study by Exxon Corp. identified a freestanding NOAEL for maternal and developmental effects (5485 mg/m^3); however, the original study was not located and the available information is derived from

secondary sources, precluding it for use in p-RfC derivation. All of the remaining studies were generally well conducted, with adequate numbers of animals and appropriate reporting. Table 6 summarizes the available inhalation noncancer dose-response information.

To provide a basis for comparing the studies, LOAEL and NOAEL values were adjusted for continuous exposure and then converted to human equivalent concentrations (HEC). The mixtures were treated as Category 3 gases if the observed toxicological effect was extrarespiratory and as Category 1 gases if the observed effect was in the respiratory tract (U.S. EPA, 1994b). Only one study (NTP, 2004 subchronic study in rats) documented respiratory tract effects (nasal goblet cell hypertrophy) at the lowest concentration and is selected as the critical effect for the derivation of the subchronic p-RfD. For this LOAEL and NOAEL, the HEC was derived by multiplying the adjusted animal effect level by an interspecies dosimetric adjustment for effects in the extrathoracic area of the respiratory tract, according to the following calculation (U.S. EPA, 1994b):

$$RGDR(ET) = (MV_a \div S_a)/(MV_h \div S_h)$$

where

RGDR(ET) = regional gas dose ratio for the extrathoracic area of the respiratory tract
MV_a = animal minute volume (rat = 0.167 L/min)
MV_h = human minute volume (13.8 L/min)
S_a = surface area of the extrathoracic region in the animal (rat = 15 cm^2)
S_h = surface area of the extrathoracic region in the human (200 cm^2).

Using default values for surface area and human minute volume, along with the rat minute volume estimated using the female rat body weight and recommended algorithm (all provided in U.S. EPA, 1994b), the RGDR(ET) = 0.16 for nasal effects in rats, calculated as follows:

$$RGDR(ET) = (MV_a \div S_a)/(MV_h \div S_h)$$
$$= (0.167 \text{ L/min} \div 15 \text{ cm}^2) / (13.8 \text{ L/min} \div 200 \text{ cm}^2)$$
$$= 0.011 \text{ L/min-cm}^2 \div 0.069 \text{ L/min-cm}^2$$
$$= 0.16$$

All of the other studies identified extrarespiratory effects and the dosimetric adjustments were made using the ratio of blood:gas partition coefficients. Blood:gas partition coefficients for the pertinent mixtures were not located. In a pharmacokinetic model of white spirit, Hissink et al. (2007) identified *n*-decane as the predominant nonaromatic compound in white spirit and reported blood:gas partition coefficients of 21 and 37 for rats and humans, respectively. Other coefficients for *n*-decane were also located. Imbriani et al. (1985) reported a human blood:gas partition coefficient of 84 for humans. Meulenberg and Vijverberg (2000) reported a value of 17 for decane in rats, citing a 1994 study. The values reported by Hissink et al. (2007) were chosen over the other options because the estimations for humans and rats were made using the same protocols; the resulting ratio of partition coefficients was 0.57 (21/37). This ratio was selected to represent the partitioning of Stoddard Solvent IIC and DAWS, as both mixtures are white spirits with low aromatic content. The composition of ShellSol TD contained a greater proportion of higher carbon-range constituents (~16% C10,

Table 6. Summary of Inhalation Noncancer Dose-Response Information

Species	Sex	Exposure Concentration (mg/m^3)	Exposure Regimen	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses	Comments	Reference
Subchronic								
Rat	M/F	0, 138, 275, 550, 1100 or 2200	6 hr/d, 5 d/wk for 14 weeks	550	1100	Nasal goblet cell hypertrophy in females	Stoddard Solvent IIC (*n*-paraffins, isoparaffins and cycloparaffins; C10–C13; <1.0% aromatic). Minimal LOAEL.	NTP, 2004
Rat	M/F	0, 2529, 5200, 10,186	6 hr/d, 5 d/wk for 13 weeks	2529	5200	Lethargy at highest concentration in both sexes; serum chemistry changes and increased liver weights in females	Shell Sol TD (primarily isoparaffins; ~16% C10, 38.7% C11 and 44.4% C12).	Shell Research Limited, 1980
Rat	M/F	0, 1970, 5610	6 hr/d, 5 d/wk for 12 weeks	5610	NA	None	Dearomatized white spirit (58% paraffins, 42% naphthenes; C11–C12; <0.5% aromatics).	Phillips and Egan, 1984a
Rat	M/F	0, 1910, 5620	6 hr/d, 5 d/wk for 12 weeks	5620	NA	None	Isoparaffinic hydrocarbons (isoparaffins; C10–C11).	Phillips and Egan, 1984a
Mouse	M/F	0, 138, 275, 550, 1100 or 2200	6 hr/d, 5 d/wk for 14 weeks	NA	2200	Increased absolute and relative liver weight (>10 %)	Stoddard Solvent IIC (*n*-paraffins, isoparaffins and cycloparaffins; C10–C13; <1.0% aromatic).	NTP, 2004
Chronic								
Rat	M/F	0, 138 550, 1100 (M); 0, 550, 1100 or 2200 (F)	6 hr/d, 5 d/wk for 2 years	138	550	Adrenal medullary hyperplasia in males	Stoddard Solvent IIC (*n*-paraffins, isoparaffins and cycloparaffins; C10–C13; <1.0% aromatic).	NTP, 2004
Rat	M	0, 2339, 4679	6 hr/d, 5 d/wk for 6 months	NA	2339	Neurophysiological changes (increased amplitude of evoked potentials and auditory brainstem response)	Dearomatized white spirit. Carbon range and aromatic content not specified. Effects evaluated 3 months after exposure concluded.	Lund et al., 1996

Table 6. Summary of Inhalation Noncancer Dose-Response Information								
Species	**Sex**	**Exposure Concentration (mg/m^3)**	**Exposure Regimen**	**NOAEL (mg/m^3)**	**LOAEL (mg/m^3)**	**Responses**	**Comments**	**Reference**
Mouse	M/F	0, 550, 1100 or 2200	6 hr/d, 5 d/wk for 2 years	1100	2200	Increased incidence of eosinophilic foci in females	Stoddard Solvent IIC (*n*-paraffins, isoparaffins and cycloparaffins; C10–C13; <1.0% aromatic).	NTP, 2004
Reproductive/Developmental								
Rat	F	0, 1828, 5485	6 hr/d on GD 6–15	5485	NA	No maternal or developmental effects	Isopar G (C10–C11). Unpublished data. Summary based on reviews by Mullin et al. (1990) and TPHCWG (1997). Inadequate data for use in p-RfC derivation.	Unpublished study by Exxon Corp., 1988; reviewed by Mullin et al., 1990
Rat	F	0, 4679	6 hr/d on GD 7–20	NA	4679	Decreased body-weight gain in dams and neurobehavioral effects in offspring	Dearomatized white spirit (<0.4% aromatic). Carbon range not specified.	Hass et al., 2001

38.7% C11, and 44.4% C12) than white spirits and no data were found on the partitioning of C11 or C12 compounds; the default ratio of 1.0 was used for this mixture. In the absence of a blood:gas partition coefficient for mice, the default ratio of 1.0 was used to perform the dosimetric adjustment for the NTP (2004) study in mice. Table 7 shows the NOAEL and LOAEL values from the pertinent studies along with the $NOAEL_{HEC}$ and $LOAEL_{HEC}$ calculations.

Subchronic p-RfC

Among the subchronic and developmental toxicity studies, the lowest $LOAEL_{HEC}$ (31 mg/m^3; see Table 7 for calculation) was identified for nasal lesions (goblet cell hypertrophy) in rats exposed subchronically (NTP, 2004). Goblet cell hypertrophy was significantly increased in both male and female rats in a dose-related fashion in the subchronic NTP study. Nasal goblet cells in mammals, including humans, produce mucous in the upper airways, and effects on the nasal mucociliary system, including goblet cell hypertrophy and/or hyperplasia, are believed to be sensitive indicators of toxicity or injury (Harkema et al., 2006; Schwart et al., 1994). Hypertrophy of these cells may represent an early response to an inhaled irritant. Although an increased incidence of nasal goblet cell hypertrophy was not observed in the chronic NTP study of Stoddard Solvent IIC, this does not mean the observations in the subchronic study are not relevant. The absence of this effect after chronic exposure may reflect the development of tolerance to the chemical insult, or this effect could be concentration-dependant rather as time-dependent. Alternatively, in a chronic study that spans the lifetime of the animal tested, age-related changes may mask treatment-related effects that may be evident in a subchronic study. Consequently, the nasal effects in rats observed in the subchronic study (NTP, 2004) were considered relevant for use in deriving the subchronic p-RfC.

To select a POD for subchronic p-RfC derivation, the incidence of goblet cell hypertrophy in female rats (see Table 2) was modeled using U.S. EPA's Benchmark Dose Software (v. 1.4.1c). Appendix B provides details of the modeling effort and the selection of the best fitting model. The best-fitting model, as assessed by AIC (model with lowest AIC after excluding an outlier [$BMCL_{10}$ of 131 mg/m^3]) was the logistic model. The BMC_{10} and $BMCL_{10}$ predicted by this model for the nasal lesion data are 597 and 410 mg/m^3, respectively. The $BMCL_{10}$ was adjusted to an equivalent continuous exposure concentration as follows:

$$\begin{aligned} BMCL_{10ADJ} &= BMCL_{10} \times 6/24 \text{ hours} \times 5/7 \text{ days} \\ &= 410\ mg/m^3 \times 6/24 \times 5/7 \\ &= 73\ mg/m^3 \end{aligned}$$

The $BMCL_{10HEC}$ was then calculated using the RGDR value of 0.16 calculated earlier for the nasal effects in rats. The $BMCL_{10HEC}$ was thus calculated as $BMCL_{10ADJ}$ (73 mg/m^3) × 0.16 = 12 mg/m^3. The $BMCL_{10HEC}$ (12 mg/m^3) was used as the POD for the subchronic p-RfC.

The **subchronic p-RfC** for midrange aliphatic hydrocarbon streams is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= BMCL_{10HEC} \div UF \\ &= 12\ mg/m^3 \div 100 \\ &= \textbf{0.1 or } \mathbf{1 \times 10^{-1}\ mg/m^3} \end{aligned}$$

Table 7. Calculation of Human Equivalent Concentrations						
Study	**Species**	**Effect**	**Effect Level (mg/m^3)**	**Duration-Adjusted Effect Level[a] (mg/m^3)**	**Dosimetric Adjustment**	**Human Equivalent Concentration[b] (mg/m^3)**
Subchronic Exposure						
NTP, 2004	Rat	Nasal goblet cell hypertrophy in females	LOAEL = 1100 NOAEL = 550	$LOAEL_{ADJ}$ = 196 $NOAEL_{ADJ}$ = 98	0.16[c]	$LOAEL_{HEC}$ = 31 $NOAEL_{HEC}$ = 16
Shell Research Limited, 1980	Rat	Lethargy at highest concentration in both sexes; serum chemistry changes and increased liver weights in females	LOAEL = 5200 NOAEL = 2529	$LOAEL_{ADJ}$ = 929 $NOAEL_{ADJ}$ = 452	1.0[d]	$LOAEL_{HEC}$ = 929 $NOAEL_{HEC}$ = 452
Chronic Exposure						
NTP, 2004	Rat	Adrenal medullary hyperplasia in males	LOAEL = 550 NOAEL = 138	$LOAEL_{ADJ}$ = 98 $NOAEL_{ADJ}$ = 25	0.57[d]	$LOAEL_{HEC}$ = 56 $NOAEL_{HEC}$ = 14
Lund et al., 1996	Rat	Neurophysiological changes (increased amplitude of evoked potentials and auditory brainstem response)	LOAEL = 2339 No NOAEL	$LOAEL_{ADJ}$ = 418	0.57[d]	$LOAEL_{HEC}$ = 238
NTP, 2004	Mouse	Increased incidence of eosinophilic foci in females	LOAEL = 2200 NOAEL = 1100	$LOAEL_{ADJ}$ = 393 $NOAEL_{ADJ}$ = 196	1.0[d]	$LOAEL_{HEC}$ = 393 $NOAEL_{HEC}$ = 196
Reproductive/Developmental Toxicity						
Hass et al., 2001	Rat	Decreased body-weight gain in dams and neurobehavioral effects in offspring	LOAEL = 4679 No NOAEL	$LOAEL_{ADJ}$ = 1170	0.57[d]	$LOAEL_{HEC}$ = 667

[a]Adjusted for continuous exposure using exposure regimen shown in Table 6 (example: $LOAEL_{ADJ}$ = 196 mg/m^3 = 1100 mg/m^3 x 6 hrs/24 hrs x 5 days/7 days)
[b]Product of duration-adjusted effect level and dosimetric adjustment factor (example: $LOAEL_{HEC}$ = 31 mg/m^3 = 196 mg/m^3 x 0.16)
[c]RGDR for extrathoracic respiratory tract effects; see text for details
[d]Ratio of blood:gas partition coefficients for extrarespiratory effects; see text for details

The composite UF of 100 is composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating variability in human populations are lacking.
- UF_A: An UF of 3 ($10^{0.5}$) is applied to account for interspecies extrapolation (toxicodynamic portion only) because a dosimetric adjustment was made.
- UF_D: An UF of 3 ($10^{0.5}$) is applied for database deficiencies. The database for these mixtures includes subchronic and chronic toxicity studies in two species, a chronic neurotoxicity study in rats, a developmental neurotoxicity study in rats, and limited information on a developmental toxicity study in rats. The database lacks a multigeneration reproductive toxicity study. Evidence that subchronic exposure to Stoddard Solvent IIC affects sperm motility in rats and mice and testes weight in rats (NTP, 2004) highlights the need for additional study of potential reproductive effects.

Confidence in the principal study (NTP, 2004) is high. The study used adequate numbers of animals, employed a wide range of exposure concentrations, and measured a variety of endpoints. Confidence in the database is medium because there are no multigenerational reproductive toxicity studies and there are limited developmental toxicity data. Confidence in the subchronic p-RfC is medium.

Chronic p-RfC

Among all of the available toxicity studies, the lowest $LOAEL_{HEC}$ (31 mg/m^3) is identified for nasal goblet cell hypertrophy in rats exposed subchronically (NTP, 2004). The $LOAEL_{HEC}$ for adrenal hyperplasia in male rats exposed chronically was only slightly higher (56 mg/m^3). To determine whether the adrenal effects in chronically exposed male rats would result in a lower POD for the chronic p-RfC derivation, the incidence of adrenal hyperplasia in male rats (see Table 4) was modeled using U.S. EPA's Benchmark Dose Software (v. 1.4.1c). As noted earlier in the description of the chronic rat study (NTP, 2004), the incidence of adrenal hyperplasia in male rats of the highest exposure group (1100 mg/m^3) was not increased over controls, and the incidence at this concentration was lower than that observed at 550 mg/m^3. Because the highest dose is not part of the dose-response relationship (the effect levels were determined at the lower dose levels) or is not based on the treatment-related effect, this exposure group (1100 mg/m^3) is not included in the dose-response modeling. Appendix B provides details of the modeling effort and the selection of best-fitting model. The logistic model provided the best fit according to model selection guidance given by U.S. EPA (2000). The BMC_{10} and $BMCL_{10}$ predicted by this model for the adrenal hyperplasia data are 210 and 144 mg/m^3, respectively. The $BMCL_{10}$ was first adjusted to an equivalent continuous exposure concentration as follows:

$$\begin{aligned} BMCL_{10ADJ} &= BMCL_{10} \times 6/24 \text{ hours} \times 5/7 \text{ days} \\ &= 144 \text{ mg/m}^3 \times 6/24 \times 5/7 \\ &= 26 \text{ mg/m}^3 \end{aligned}$$

The $BMCL_{10HEC}$ was then calculated using the ratio of blood:gas partition coefficients (0.57) calculated earlier for rats. The $BMCL_{10HEC}$ was, thus, calculated as $BMCL_{10ADJ}$

(26 mg/m^3) × 0.57 = 15 mg/m^3. This value is similar to the $BMCL_{10HEC}$ calculated for nasal goblet cell hypertrophy in rats exposed subchronically (12 mg/m^3). These two values of $BMCL_{10HEC}$ from the subchronic (12 mg/m^3) and chronic (15 mg/m^3) studies are potential PODs. Because the lower value (12 mg/m^3) is considered to be a more sensitive indicator of midrange aliphatic hydrocarbon streams exposure, and is not likely to be time-independent, the POD is chosen as 12 mg/m^3 based on the nasal effect for the derivation of chronic p-RfC. Use of the lower value ensures that the resulting p-RfC is protective for both nasal and adrenal lesions. The **chronic p-RfC** for midrange aliphatic hydrocarbon streams is derived as follows:

Chronic p-RfC = $BMCL_{10HEC}$ ÷ UF
= 12 mg/m^3 ÷ 100
= **0.1 or 1 × 10^{-1} mg/m^3**

The composite UF of 100 was composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for variability in human populations are lacking.
- UF_A: An UF of 3 ($10^{0.5}$) is applied to account for interspecies extrapolation (toxicodynamic portion only) because a dosimetric adjustment was made.
- UF_D: An UF of 3 ($10^{0.5}$) for database deficiencies is applied. The database for these mixtures includes subchronic and chronic toxicity studies in two species, a chronic neurotoxicity study in rats, a developmental neurotoxicity study in rats, and limited information on a developmental toxicity study in rats. The database lacks a multigenerational reproductive toxicity study. Evidence that subchronic exposure to Stoddard Solvent IIC affects sperm motility in rats and mice and testes weights in rats (NTP, 2004) highlights the need for additional study of potential reproductive effects.
- UF_S: An UF of 1 for subchronic-to-chronic extrapolation is applied. Although the POD was derived from a subchronic study, no UF is included for extrapolation from subchronic-to-chronic exposure because nasal goblet cell hypertrophy was not observed in rats exposed under equivalent conditions in a chronic study (NTP, 2004). No duration extrapolation is necessary for this critical effect.

As stated in the derivation of subchronic p-RfC, confidence in the principal study (NTP, 2004) is high. Confidence in the database is medium because there are no multigenerational reproductive toxicity studies and there are limited developmental toxicity data. Confidence in the chronic p-RfC is medium as for the subchronic p-RfC.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR MIDRANGE ALIPHATIC HYDROCARBON STREAMS

Weight-of-Evidence Classification

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Suggestive Evidence for the Carcinogenic Potential*" of Stoddard Solvent IIC and "*Inadequate Information to Assess the Carcinogenic Potential*" of other mixtures described in this review.

NTP (2004) tested Stoddard Solvent IIC in chronic inhalation carcinogenicity assays using F344 rats and B6C3F1 mice. NTP (2004) concluded that there was "*some evidence"* of carcinogenic activity for Stoddard Solvent IIC in male rats based on the dose-related increase in adrenal pheochromocytomas and "*equivocal evidence"* of carcinogenic activity in female mice based on a slightly increased incidence of hepatocellular adenomas. Testing of Stoddard Solvent IIC for genotoxicity has given uniformly negative results (NTP, 2004).

Mode-of-Action Discussion

The U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment* defines mode of action (MOA) as "a sequence of key events and processes, starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes and resulting in cancer formation." Toxicokinetic processes leading to the formation or distribution of the active agent (i.e., parent material or metabolite) to the target tissue are not part of the MOA. Examples of possible modes of carcinogenic action include mutagenic, mitogenic, antiapoptotic (inhibition of programmed cell death), cytotoxic with reparative cell proliferation and immunologic suppression.

Very little information is available on the potential mode by which Stoddard Solvent IIC increases the incidence of adrenal tumors in male rats. No effects on the adrenal glands were reported in the one available subchronic toxicity study in rats (NTP, 2004). While there are studies that suggest an association between nephropathy and the formation of adrenal pheochromocytomas (NTP, 2004), statistical analysis for a correlation between these effects in the study of Stoddard Solvent IIC failed to indicate such a relationship in this case. The slightly increased incidence of hepatocellular adenomas in female mice was associated with body-weight increases in the exposed females. No other information on potential mode of liver carcinogenesis was identified. These limited data do not provide any basis for potential key events in the MOA for either adrenal or hepatocellular tumors induced by Stoddard Solvent IIC.

Derivation of Provisional Cancer Values

Provisional Oral Slope Factor Derivation

There are no oral studies of Stoddard Solvent IIC; thus, a quantitative estimate of cancer risk from oral exposure cannot be derived.

Provisional Inhalation Unit Risk Derivation

The data are considered adequate to develop a quantitative estimate of cancer risk from inhalation exposure. However, because the WOE indicates *"Suggestive Evidence for the Carcinogenic Potential,"* there is some uncertainty associated with the quantification. For these reasons, Appendix A of this document contains a screening p-IUR that may be useful in certain instances. Please see the attached Appendix for details.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2007. TLVs® and BEIs®: Threshold Limit Values for Chemical Substances and Physical Agents, Biological Exposure Indices. ACGIH, Cincinnati, OH.

Anonymous. 1990. Aliphatic petroleum hydrocarbon fluid aromatic content <0.05%, carbon range C11–C17. Completion Date: December 20, 1990. Study provided by American Petroleum Institute, Washington, DC.

Anonymous. 1991a. 90-day oral toxicity study in the rat. Aliphatic petroleum hydrocarbon fluid. Carbon range C_{10}–C_{13}, aromatic content 0.1%. Completion date: October 15, 1991. Study provided by American Petroleum Institute, Washington, DC.

Anonymous. 1991b. 90-day subchronic oral toxicity study in rats. Aliphatic petroleum hydrocarbon fluid (less than 0.5% aromatics), boiling point range 180–210^{o}C, Carbon range C_9–C_{12}. Completion Date: October 24, 1991 under Guideline 82-1. Study provided by American Petroleum Institute, Washington, DC.

ATSDR (Agency for Toxic Substances and Disease Registry). 1995. Toxicological profile for stoddard solvent. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available at www.atsdr.cdc.gov/toxprofiles/tp79.pdf.

Ernstgård, L., Lind, B., Johanson, G. 2009a. Acute effects of exposure to vapours of standard and dearomatized white spirits in humans. 1. Dose-finding study. J Appl Toxicol. 29(3):255–262.

Ernstgård, L., Iregren, A., Juran, S., Sjögren, B., van Thriel, C., Johanson, G. 2009b. Acute effects of exposure to vapours of standard and dearomatized white spirits in humans. 2. Irritation and inflammation. J Appl Toxicol. 29(3):263–274.

Exxon Corporation. 1988. Material Safety Data Sheets 133464-00644, 133466-0640, 133467-00636, 133465-00637 and 133468-00635. Houston, TX. (as cited in Mullin et al., 1990)

Harkema, J.R., S.A. Carey, J.G. Wagner. 2006. The nose revisited: A brief review of the comparative structure, function, and toxicologic pathology of the nasal epithelium. Toxicol. Pathol. 34:252–269.

Hass, U., O. Ladefoged, H.R. Lam et al. 2001. Behavioural effects in rats after prenatal exposure to dearomatized white spirit. Pharmacol. Toxicol. 89:201–207.

Hissink, A.M., J. Kruse, B.M. Kulig et al. 2007. Model studies for evaluating the neurobehavioral effects of complex hydrocarbon solvents. III. PBPK modeling of white spirit test data. Neurotoxicology. 28(4):751–760.

IARC (International Agency for Research on Cancer). 1989. Some petroleum solvents. Available at http://www.inchem.org/documents/iarc/vol47/47-01.html.

Imbriani, M., S. Ghittori, G. Pezzagno et al. 1985. Urine/air partition coefficients for some industrially important substances. G. Ital. Med. Lav. 7:133–140.

Lam, H.R., A. Lof and O. Ladefoged. 1992. Brain concentrations of white spirit components and neurotransmitters following a three week inhalation exposure of rats. Pharmacol. Toxicol. 70 (5 Pt 1):394–396.

Lund, S.P., L. Simonsen, U. Hass et al. 1996. Dearomatized white spirit inhalation exposure causes long-lasting neurophysiological changes in rats. Neurotoxicol. Teratol. 18(1):67–76.

MADEP (Massachusetts Department of Environmental Protection). 2003. Updated petroleum hydrocarbon fraction toxicity values for the VPH/EPH/APH methodology. Office of Research and Standards, Massachusetts Department of Environmental Protection, Boston, MA.

Meulenberg, C.J.W. and H.P.M. Vijverberg. 2000. Empirical relations predicting human and rat tissue: Air partition coefficients of volatile organic compounds. Toxicol. Appl. Pharmacol. 165(3):206–216.

Mullin, L.S., A.W. Ader, W.C. Daughtrey et al. 1990. Toxicology update: Isoparaffinic hydrocarbons: A summary of physical properties, toxicity studies, and human exposure data. J. Appl. Toxicol. 10(2):135–142.

NIOSH (National Institute for Occupational Safety and Health). 2008. NIOSH Pocket Guide to Chemical Hazards. Index by CASRN. Available at http://www2.cdc.gov/nioshtic-2/nioshtic2.htm.

NTP (National Toxicology Program). 2004. Toxicology and carcinogenesis studies of Stoddard Solvent IIC (CAS NO. 64742-88-7) in F344/N rats and B6C3F1 mice (inhalation studies). NTP TR 519. National Toxicology Program, Research Triangle Park, NC. September. Available at http://ntp.niehs.nih.gov/files/tr519-full.pdf.

OECD/SIDS (Organisation for Economic Co-operation and Development/Screening Information DataSet). 2007. Chemical Screening Information Dataset (SIDS) for High Volume Chemicals. Available at http://www.inchem.org/pages/sids.html.

OSHA (Occupational Safety and Health Administration). 2008. OSHA Standard 1915.1000 for Air Contaminants. Part Z, Toxic and Hazardous Substances. Available at www.osha-slc.gov/OshStd_data/1915_1000.html.

Pedersen, L.M. and K.H. Cohr. 1984a. Biochemical pattern in experimental exposure of humans to white spirit. I. The effects of a 6 hours single dose. Acta Pharmacol. Toxicol. 55:317–324.

Pedersen, L.M. and K.H. Cohr. 1984b. Biochemical pattern in experimental exposure of humans to white spirit. II. The effects of repetitive exposure. Acta Pharmacol. Toxicol. 55:325–330.

Petroleum High Production Volume (HPV) Testing Group. 2007. The Petroleum High Production Volume Testing Group [Home page]. Available at http://www.petroleumhpv.org/.

Phillips, R.D. and V.Y.Y. Cockrell. 1984. Kidney structural changes in rats following inhalation exposure to C_{10} - C_{11} isoparaffinic solvent. Toxicology. 33:261–273.

Phillips, R.D. and G.F. Egan. 1984a. Subchronic inhalation exposure of dearomatized white spirit and C_{10} - C_{11} isoparaffinic hydrocarbon in Sprague-Dawley rats. Fund. Appl. Toxicol. 4:808–818.

Phillips, R.D. and G.F. Egan. 1984b. Effect of C10–C11 isoparaffinic solvent on kidney function in Fischer 344 rats during eight weeks of inhalation. Toxicol. Appl. Pharmacol. 73:500–510.

Schwartz L.W., F.F. Hahn, K.P. Keenan, et al. 1994. Proliferative lesions of the rat respiratory tract. In: Guides for Toxicologic Pathology. STP/ARP/APIP, Washington, D.C. 26 p.

Shell Research Limited. 1980. The inhalation toxicity of Shellsol TD to rats following 13 weeks' exposure. Group Research Report TLGR 80.041. Shell Research Limited, London. With cover letter dated October 23, 1980. Submitted by Shell Oil Co. Document No. 8EHQ-1079-0312. Fiche No. OTS0200630.

TPHCWG (Total Petroleum Hydrocarbons Criteria Working Group). 1997. Development of fraction specific reference doses (RfDs) and reference concentrations (RfCs) of Total Petroleum Hydrocarbons (TPHs). Prepared for Chevron, British Petroleum and the Total Petroleum Hydrocarbons Criteria Working Group by Exxon Biomedical Sciences, Inc., EA Engineering, Science, and Technology, Inc. and Remediation Technologies, Inc.

U.S. EPA. 1991a. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1991b. Alpha2u-Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Male Rat. Risk Assessment Forum, Washington, DC. EPA/625/3-91/019F.

U.S. EPA. 1994a. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1994b. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F, October 1994. Available at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. 1997. Health Effects Assessment Summary Tables (HEAST). FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB 97-921199.

U.S. EPA. 2000. Benchmark Dose Technical Guidance Document [external review draft]. EPA/630/R-00/001. http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. 2005. Guidelines for Cancer Risk Assessment. Risk Assessment Forum, Washington, DC. EPA/630/P-03/001F. Available at http://www.epa.gov/raf.

U.S. EPA. 2006. 2006 Edition Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. Summer 2006. Available at http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf.

U.S. EPA. 2009. Integrated Risk Information System (IRIS). Online. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. http://www.epa.gov/iris/. Accessed July, 2009.

Viau, C., A. Bernard, F. Gueret, P. Maldague, P. Gengoux and R. Lauwerys. 1986. Isoparaffinic solvent-induced nephrotoxicity in the rat. Toxicology. 38:227–240.

Wolford, S.T., R.A. Schroer, F.X. Gohs et al. 1986. Reference range data base for serum chemistry and hematology values in laboratory animals. J. Toxicol. Environ. Health. 18:161–188.

WHO (World Health Organization). 1996. White spirit (Stoddard solvent). Available at http://www.inchem.org/documents/ehc/ehc/ehc187.htm.

APPENDIX A. DERIVATION OF A SCREENING VALUE FOR MIDRANGE ALIPHATIC HYDROCARBON STREAMS

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for mid range aliphatic hydrocarbon streams. However, information is available for this chemical, which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

Three screening values are presented in this Appendix: subchronic and chronic p-RfDs, and an IUR. The NOAEL of 100 mg/kg-day identified in the two unpublished 90-day studies (Anonymous 1990, 1991a) serve as the basis for development of screening subchronic and chronic p-RfD. The $BMCL_{10HEC}$ of 22 mg/m^3 after duration and dosimetry adjustments from the POD indentified in the NTP (2004) study serve as the basis for development of screening IUR.

Oral Toxicity Values

Subchronic Screening p-RfD

Available oral toxicity information on midrange aliphatic hydrocarbon streams is limited to three unpublished studies on three different mixtures (Anonymous, 1990, 1991a,b). The reports of these studies obtained for this review were missing data tables and appendices reporting details of the findings described in the reports. Repeated efforts to obtain the complete reports through a variety of sources were unsuccessful. In the absence of other studies with which to assess the oral toxicity of midrange aliphatic hydrocarbon streams, the limited unpublished studies were used for this Appendix; however, uncertainty in the resulting screening values must be acknowledged.

Effect levels for these studies were identified based on tentative interpretations of the effects described in the text, which, in turn, are supported by interpretations prepared by MADEP (2003) and TPHCWG (1997) based on their reviews of the original reports. In addition, because quantitative results were not available, BMD modeling of critical effects was not possible for any of the studies.

As shown in Table 5, the LOAELs identified for all three studies were the same (500 mg/kg-day), and the effects are similar for the three mixtures (liver and/or kidney weight increases, serum chemistry changes, hematology changes and/or hepatocellular hypertrophy). Since Anonymous (1991b) failed to identify a NOAEL, Anonymous (1990, 1991a) are considered as cocritical studies and the NOAEL (100 mg/kg-day) identified by Anonymous (1990, 1991a) was selected as the POD. The **screening subchronic p-RfD** for midrange aliphatic hydrocarbon streams is derived as follows:

Screening Subchronic p-RfD = NOAEL ÷ UF
= 100 mg/kg-day ÷ 1000
= **0.1 or 1×10^{-1} mg/kg-day**

The composite UF of 1000 is composed of the following UFs:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating variability in human populations are limited.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are limited.
- UF_D: A factor of 10 is applied for database inadequacies because data for evaluating developmental and reproductive toxicity for oral exposure are not available.

Confidence in the critical studies is low, stemming in large part from the lack of data tables and appendices necessary for an independent review of the study quality and findings. Information in the studies indicates that adequate numbers of animals were used and thorough toxicological evaluations were conducted; however, gavage errors occurred in two of the studies (Anonymous, 1990, 1991b). Confidence in the database is low, reflecting the limited subchronic toxicity data and developmental and reproductive toxicity studies. Confidence in the subchronic p-RfD is low.

Chronic Screening p-RfD

The **screening chronic p-RfD** for midrange aliphatic hydrocarbon streams is derived below:

Screening Chronic p-RfD = NOAEL ÷ UF
= 100 mg/kg-day ÷ 10,000
= **0.01 or 1×10^{-2} mg/kg-day**

The composite UF of 10,000 is composed of the following UFs:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation as data for evaluating variability in human populations are limited.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are limited.
- UF_D: A factor of 10 is applied for database inadequacies, as data for evaluating developmental and reproductive toxicity for oral exposure are not available.
- UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure because data for evaluating response after chronic exposure are not available.

Confidence in the critical studies is low as stated in the derivation of a subchronic p-RfD. Confidence in the database is low, reflecting the limited subchronic toxicity data, and lack of chronic toxicity data and developmental and reproductive toxicity studies. Confidence in the chronic p-RfD is low.

Inhalation Cancer Risk

Screening Inhalation Unit Risk

The WOE for midrange aliphatic hydrocarbon streams is characterized as "*Suggestive Evidence of Carcinogenic Potential*,". The inhalation data are sufficient to derive a quantitative estimate of cancer risk using BMD. Male F344 rats exhibited increased incidences of benign or benign and malignant (combined) pheochromocytomas of the adrenal glands in a chronic bioassay (NTP, 2004). The incidences of benign or benign and malignant tumors were significantly increased at the mid- and high-exposure levels (550 and 1100 mg/m^3). While the incidence of hepatocellular adenomas was increased in female mice exposed in the companion study (NTP, 2004), the increase was statistically significant only at the highest concentration (2200 mg/m^3). Because adrenal tumors in male rats were induced at a much lower concentration (550 mg/m^3), the IUR is derived using the adrenal tumor data.

The MOA for adrenal tumors produced by Stoddard Solvent IIC has not been fully elucidated. Although the available genotoxicity data do not suggest a direct genotoxic action, the contribution of a linear MOA to induction of adrenal tumors cannot be ruled out based on available data; thus, a linear approach was applied. The dose-response data used in the quantitative cancer assessment are shown in Table A-1.

Table A-1. Dose-Response Data for Adrenal Tumors in Male F344 Rats[a]

Exposure Concentration (mg/m^3)	Incidence of Benign or Malignant Pheochromocytomas
0	6/50
138	9/50
550	13/50
1100	19/50

[a]NTP, 2004

Dose-response modeling of the data in Table A-1 was performed to obtain a point of POD for a quantitative assessment of cancer risk. The POD is an estimated dose (expressed in human-equivalent terms) near the lower end of the observed range that marks the starting point for extrapolation to lower doses. Appendix C provides details of the modeling effort and the selection of the best fitting model. The multistage-cancer model with 1-degree polynomial was selected based on U.S. EPA (2000) guidance. The BMC_{10} and $BMCL_{10}$ predicted by this model for the adrenal tumor data are 340 and 216 mg/m^3, respectively. The $BMCL_{10}$ (216 mg/m^3) was used as the POD for the screening IUR. The $BMCL_{10}$ of 216 mg/m^3 was first adjusted to an equivalent continuous exposure concentration (216 mg/m^3 × 6/24 hours × 5/7 days = 39 mg/m^3). The adjusted concentration was then converted to a human equivalent concentration. Because adrenal tumors represent extrarespiratory effects, the mixture was treated as a Category 3 gas and the ratio of blood:gas partition coefficients was used to make the dosimetric adjustment. As noted earlier, blood:gas partition coefficients for *n*-decane (21 and 37 for rats and humans, respectively) published by Hissink et al. (2007) were used to represent the partitioning of Stoddard Solvent IIC; the ratio of coefficients was 0.57. The resulting $BMCL_{10HEC}$ is 22 mg/m^3 (39 mg/m^3 × 0.57). The **Screening p-IUR** for midrange aliphatic hydrocarbon streams is derived below:

Screening p-IUR = $0.1 \div BMCL_{10HEC}$
= $0.1 \div 22\ mg/m^3$
= $\mathbf{4.5 \times 10^{-3}\ (mg/m^3)^{-1}}$

The IUR for Stoddard Solvent IIC should not be used with exposures exceeding the POD ($BMCL_{10HEC}$ = 22 mg/m^3) because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of Stoddard Solvent IIC.

APPENDIX B: DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC AND CHRONIC p-RfCs

Subchronic p-RfC

Modeling Procedure for Dichotomous Data

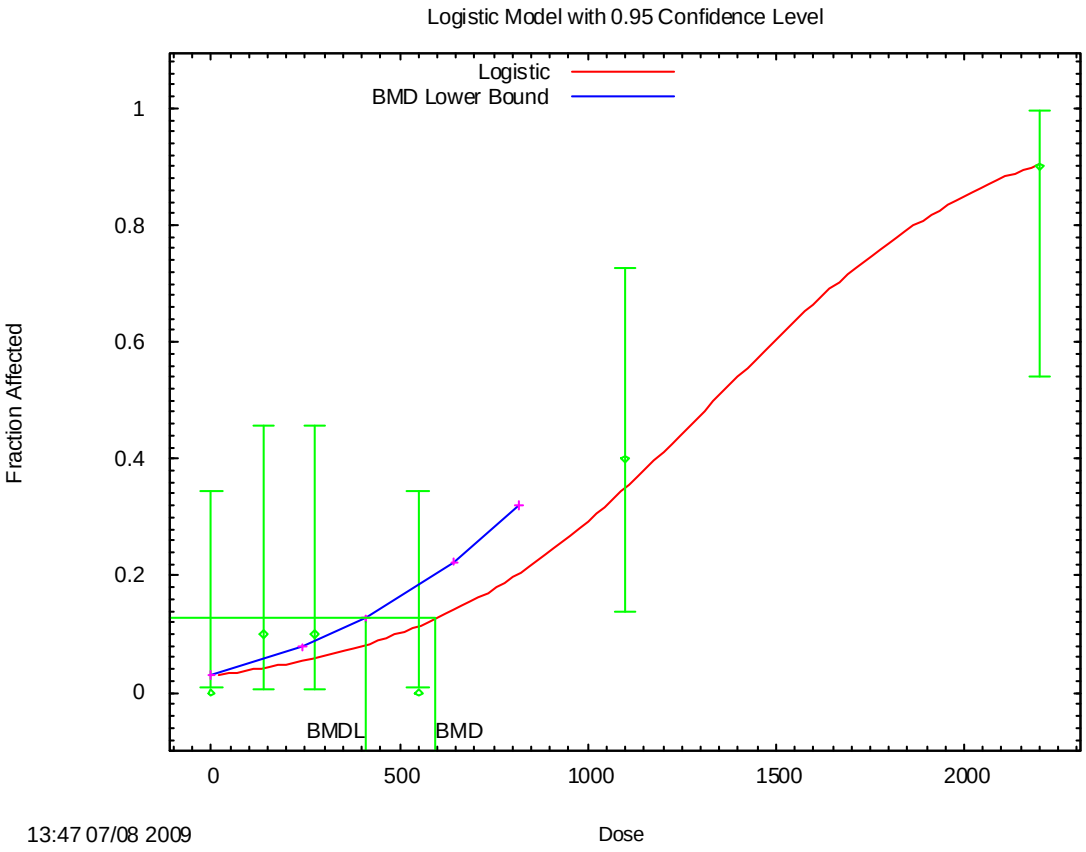
The benchmark dose (BMD) modeling for dichotomous data was conducted with the EPA's BMD software (BMDS version 2.1). For all the dichotomous data, the original data were modeled with all the dichotomous models (i.e., Gamma, Multistage, Logistic, Log-logistic, Probit, Log-Probit, Weibull, and Quantal linear models) available within the software with a default benchmark response (BMR) of 10% extra risk. An adequate fit was judged based on the goodness of fit *p* value ($p > 0.1$), scaled residual at the range of benchmark response (BMR), and visual inspection of the model fit. Among all the models providing adequate data fit, the lowest BMDL will be selected if the BMDLs estimated from different models if the range is not sufficiently close; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) would be considered appropriate for the data set.

Model-Fitting Results for Nasal Goblet Cell Hypertrophy in Female Rats Exposed for 13 Weeks (NTP, 2004)

The data on nasal goblet cell hypertrophy in female rats are shown in Table 2 on page 19. Exposure concentrations as reported in the study were used in the dose-response modeling. Applying the modeling protocol outlined above, all models in the software provided adequate fits to the data for the incidence of goblet cell hypertrophy in female rats (χ^2 $p \geq 0.1$) (see Table B-1). Even though the BMCL values are not sufficiently close, the BMCL of 131 mg/m^3 from either the quantal linear or multistage (degree of polynomial = 1) model is considered as an outlier. Excluding the BMCL of 131 mg/m^3, the best-fitting model, as assessed by AIC (model with lowest AIC) was the logistic model. The fit of the logistic model to the data is shown in Figure B-1. The BMC_{10} and $BMCL_{10}$ associated with this model are 597 and 410 mg/m^3, respectively.

Table B-1. Model Predictions for Nasal Goblet Cell Hypertrophy in Female Rats[a]						
Model	**Degrees of Freedom**	**χ^2**	**χ^2 Goodness of Fit *p*-Value**	**AIC**	**BMC_{10} (mg/m^3)**	**$BMCL_{10}$ (mg/m^3)**
Logistic	4	2.84	0.58	40.96	596.65	409.76
Probit	4	3.01	0.56	41.11	546.12	378.87
Log-probit (slope ≥ 1)	3	2.29	0.51	42.19	801.84	502.66
Log-logistic (slope ≥ 1)	3	2.40	0.49	42.37	795.39	459.27
Gamma (power ≥ 1)	3	2.47	0.48	42.47	788.64	398.64
Weibull (power ≥ 1)	3	2.73	0.43	42.95	720.44	285.42
Quantal Linear	5	5.78	0.33	43.65	198.21	130.87
Multistage (degree of polynomial = 1)[b]	5	5.78	0.3281	43.65	198.21	130.87
Multistage (degree of polynomial = 2)[b]	4	3.24	0.52	41.74	516.08	200.19
Multistage (degree of polynomial = 3)[b]	3	2.74	0.44	42.93	649.00	201.85
Multistage (degree of polynomial = 4)[b]	3	2.74	0.44	42.93	649.00	191.83
Multistage (degree of polynomial = 5)[b]	3	2.74	0.44	42.93	649.00	188.14
Quantal Linear	Invalid model choice per BMDS software					

[a]NTP, 2004
[b]Degree of polynomial initially set to (n-1) where n = number of dose groups including control. Betas restricted to ≥0.



BMCs and BMCLs indicated are associated with an extra risk of 10% and are in units of mg/m^3.

Figure B-1. Fit of Logistic Model to Data on Goblet Cell Hypertrophy in Female Rats

```
================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21Beta\Temp\2tmp157D.(d)
        Gnuplot Plotting File: C:\USEPA\BMDS21Beta\Temp\2tmp157D.plt
                                          Wed Jul 08 13:47:53 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*dose)]


   Dependent variable = Incidence
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     background =            0   Specified
                      intercept =     -2.86336
                          slope =   0.00208246


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

              intercept        slope

 intercept            1        -0.82

     slope        -0.82            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
      intercept         -3.48793         0.760362            -4.97821            -
1.99765
          slope       0.00261023      0.000654725            0.001327
0.00389347


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
```

Full model	-16.4826	6			
Fitted model	-18.4789	2	3.99258	4	0.407
Reduced model	-33.7401	1	34.515	5	<.0001

AIC: 40.9578

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0297	0.297	0.000	10	-0.553
138.0000	0.0420	0.420	1.000	10	0.915
275.0000	0.0590	0.590	1.000	10	0.551
550.0000	0.1138	1.138	0.000	10	-1.133
1100.0000	0.3505	3.505	4.000	10	0.328
2200.0000	0.9050	9.050	9.000	10	-0.054

Chi^2 = 2.84 d.f. = 4 P-value = 0.5848

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 596.652

BMDL = 409.761

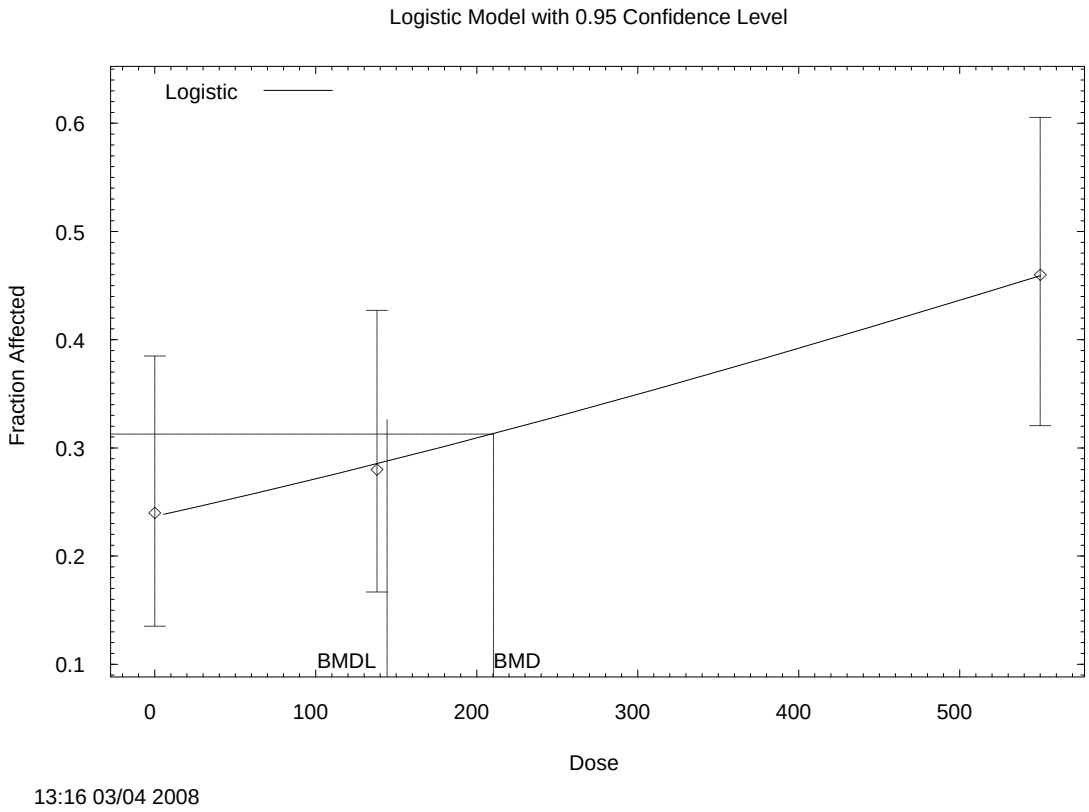
Chronic p-RfC

Model-Fitting Results for Adrenal Medullary Hyperplasia in Male Rats Exposed for 2 Years (NTP, 2004)

The data on adrenal hyperplasia in male rats exposed chronically to Stoddard Solvent IIC are shown in Table 4. According to the study, exposure concentrations were used in the dose-response modeling. As noted earlier in the description of the chronic rat study (i.e., NTP, 2004), the incidence of adrenal hyperplasia in male rats of the highest-exposure group (i.e., 1100 mg/m^3) was not increased over controls, and the incidence at this concentration was lower than that observed at 550 mg/m^3. Because the highest dose is not part of the dose-response relationship (the effect levels were determined at the lower dose levels), or because it is not based on the treatment-related effect, this exposure group (1100 mg/m^3) is not included in the dose-response modeling. Applying the modeling protocol outlined earlier, all of these models provided adequate fit to the data for the incidence of adrenal hyperplasia in male rats (χ^2 $p \geq 0.1$) (see Table B-2). The best-fitting model, as assessed by AIC, was the logistic model. The fit of the logistic model to the data is shown in Figure B-2. The BMC_{10} and $BMCL_{10}$ associated with this model are 210 and 144 mg/m^3, respectively.

Table B-2. Model Predictions for Adrenal Hyperplasia in Male Rats						
Model	**Degrees of Freedom**	**χ^2**	**χ^2 Goodness of Fit *p*-Value**	**AIC**	**BMC_{10} (mg/m^3)**	**$BMCL_{10}$ (mg/m^3)**
Logistic	**1**	**0.01**	**0.9202**	**187.408**	**210.35**	**144.25**
Probit	1	0.01	0.9062	187.412	205.74	139.53
Log-probit (slope ≥ 1)	1	0.06	0.8082	187.457	270.25	170.72
Multistage (degree = 1)[a]	1	0.08	0.7783	187.477	169.15	96.07
Log-logistic (slope ≥ 1)	0[b]	0.00	NA	189.398	223.25	77.71
Gamma (power ≥ 1)	0[b]	0.00	NA	189.398	225.39	96.73
Weibull (power ≥ 1)	0[b]	0.00	NA	189.398	227.56	96.73
Quantal Linear	Invalid model choice per BMDS software					

[a]Degree of polynomial initially set to (*n*-1) where *n* = number of dose groups including control; model selected is lowest degree model providing adequate fit. Betas restricted to ≥0.
[b]Too few dose groups to apply these models.



BMCs and BMCLs indicated are associated with an extra risk of 10% and are in units of mg/m^3.

Figure B-2. Fit of Logistic Model to Data on Adrenal Hyperplasia in Male Rats

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21Beta\Temp\2tmp167B.(d)
        Gnuplot Plotting File: C:\USEPA\BMDS21Beta\Temp\2tmp167B.plt
                                            Wed Aug 12 16:05:55 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*dose)]


   Dependent variable = Incidence
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
```

Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
background = 0 Specified
intercept = -1.14386
slope = 0.00178243

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.74
slope	-0.74	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-1.17301	0.262986	-1.68845	-0.657565
slope	0.00183216	0.000744182	0.000373592	0.00329073

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-91.6989	3			
Fitted model	-91.7039	2	0.0100324	1	0.9202
Reduced model	-94.7689	1	6.14015	2	0.04642

AIC: 187.408

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2363	11.816	12.000	50	0.061
138.0000	0.2849	14.246	14.000	50	-0.077
550.0000	0.4588	22.938	23.000	50	0.018

Chi^2 = 0.01 d.f. = 1 P-value = 0.9202

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

```
Confidence level =           0.95

             BMD =        210.347

            BMDL =        144.253
```

APPENDIX C: DETAILS OF BENCHMARK DOSE MODELING FOR INHALATION UNIT RISK

Model-Fitting Procedure for Cancer Incidence Data

The model-fitting procedure for dichotomous cancer incidence data is as follows. The multistage-cancer model in the EPA Benchmark Dose (BMD) Software (version 2.1) is fit to the incidence data using the extra risk option. The multistage model is run for all polynomial degrees up to *n*-1 (where n is the number of dose groups including control); the lowest degree polynomial providing adequate fit is selected, per U.S. EPA (2000) guidance. Goodness-of-fit is assessed by the χ^2 test; adequate fit is indicated by a *p*-value greater than 0.1. In accordance with U.S. EPA (2000) guidance, BMDs and lower one-sided confidence limits on the BMD (BMDLs) associated with an extra risk of 10% are calculated.

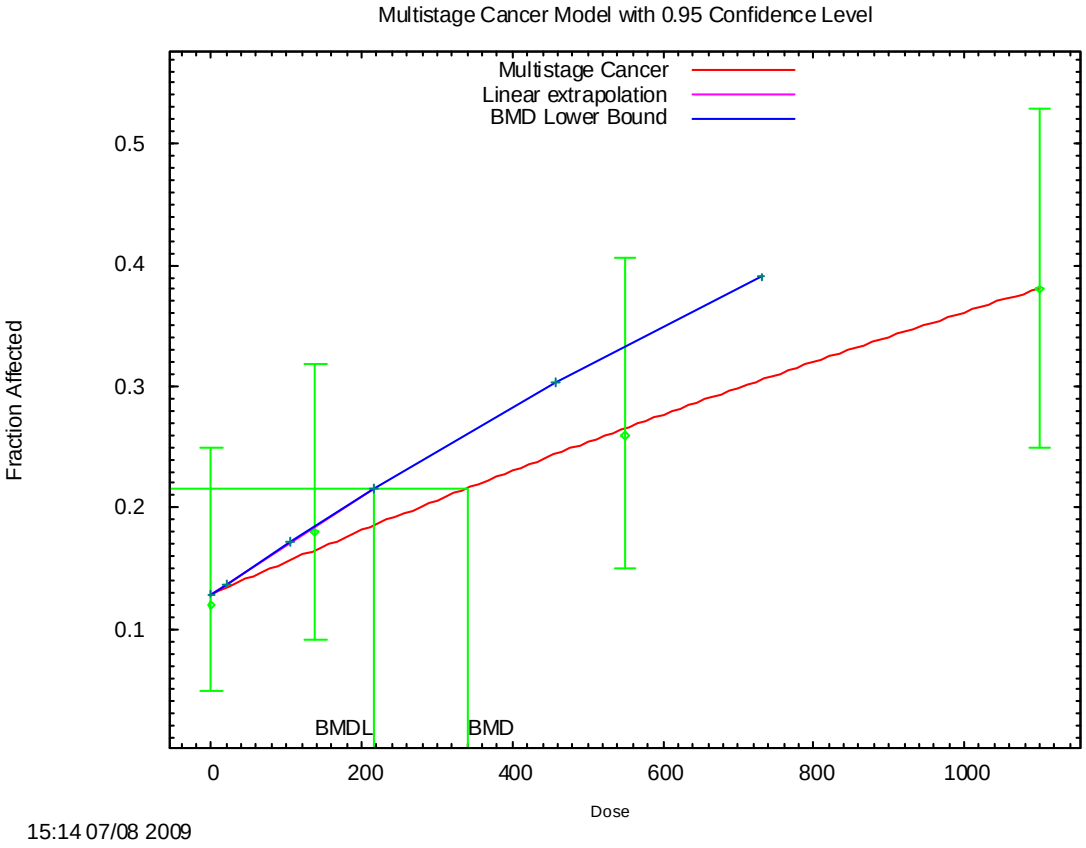
Model-Fitting Results for Adrenal Tumors in Rats (NTP, 2004)

The incidence of benign and malignant adrenal pheochromocytomas in male rats exposed for 2 years was modeled. The data on adrenal tumors in male rats are shown in Table 4 and Table A-1. Exposure concentrations as reported in the study were used in the dose-response modeling. Applying the modeling protocol outlined above, the multistage model with 1-degree polynomial was the lowest degree polynomial providing adequate fit to the tumor data (χ^2 $p \geq 0.1$) (see Table C-1). The fit of this model to the data is shown in Figure C-1. The BMC_{10} and $BMCL_{10}$ associated with this model are 340 and 216 mg/m^3, respectively.

Table C-1. Model Predictions for Adrenal Tumors in Male Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Multistage (degree = 1)[b]	2	0.12	0.94	211.66	339.95	215.68
Multistage (degree = 2)[b]	2	0.12	0.94	211.66	339.95	215.68
Multistage (degree = 3)[b]	2	0.12	0.94	211.66	339.95	215.68

[a]NTP, 2004
[b]Degree of polynomial initially set to (*n*-1) where *n* = number of dose groups including control. Betas restricted to ≥0.



BMCs and BMCLs indicated are associated with an extra risk of 10% and are in units of mg/m^3.

Figure C-1. Fit of Multistage-Cancer Model (1-Degree Polynomial) to Data on Adrenal Tumors in Male Rats

```
================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21Beta\Data\3MulMidMul.(d)
        Gnuplot Plotting File: C:\USEPA\BMDS21Beta\Data\3MulMidMul.plt
                                          Wed Jul 08 15:14:06 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****


                  Default Initial Parameter Values
                     Background =     0.129941
                        Beta(1) =   0.00030685


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.69

   Beta(1)        -0.69            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background         0.128767            *               *                 *
        Beta(1)       0.00030993            *               *                 *

* - Indicates that this value is not calculated.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-103.772	4			
Fitted model	-103.832	2	0.119374	2	0.9421
Reduced model	-109.05	1	10.5551	3	0.01439

AIC: 211.663

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1288	6.438	6.000	50	-0.185
138.0000	0.1652	8.262	9.000	50	0.281
550.0000	0.2653	13.266	13.000	50	-0.085
1100.0000	0.3805	19.023	19.000	50	-0.007

Chi^2 = 0.12 d.f. = 2 P-value = 0.9415

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 339.949

BMDL = 215.677

BMDU = 714.34

Taken together, (215.677, 714.34) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000463657