2,2,4-Trimethylpentane; CASRN 540-84-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 2,2,4-TRIMETHYLPENTANE

File First On-Line 11/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	qualitative discussion	07/31/2007
Inhalation RfC (I.B.)	qualitative discussion	07/31/2007
Carcinogenicity Assessment (II.)	yes	07/31/2007

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name — 2,2,4-Trimethylpentane
CASRN — 540-84-1
Section I.A. Last Revised — 07/31/2007

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of

these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

A number of acute and short-term studies were identified in the literature. Overall, these studies provide focused or limited information as they were designed to investigate only endpoints specific to alpha$_{2u}$-globulin-associated nephropathy in male rats or found no other significant 2,2,4-trimethylpentane-induced effects. The majority of noncancer effects induced by 2,2,4-trimethylpentane exposure were found to occur primarily in the kidney of male rats as the majority of the studies examined only the kidney. The effects reported included altered renal function, an increase in alpha$_{2u}$-globulin protein and hyaline droplet accumulation in the proximal tubules, necrosis of the tubule epithelium, increased cell turnover, and foci of regenerative epithelium (Blumbach et al., 2000; Saito et al., 1996, 1992; Borghoff et al., 1992; Burnett et al., 1989; Lock et al., 1987a,b; Short et al., 1986; Stonard et al., 1986; API, 1985, 1983). No increases in alpha$_{2u}$-globulin protein and hyaline droplet accumulation in the proximal tubules, or necrosis of the tubule epithelium were noted to occur in female rats (Blumbach et al., 2000; Lock et al., 1987a,b).

Detailed studies that identify sufficient dose-response and duration information for other endpoints are currently lacking for 2,2,4-trimethylpentane. Liver effects were noted in a few acute or short-term oral studies. For example, Fowlie et al. (1987) observed centrilobular necrosis and hydrophobic degeneration of hepatocytes induced by 2,2,4-trimethylpentane and Lock et al. (1987a) observed increases in liver weight and liver-to-body weight ratios in both treated males and females. The effects noted by Lock et al. (1987a) were thought to result from an induction in cytochrome P-450 and peroxisome proliferation. Short et al. (1986) found no significant histological changes in the liver.

The available studies provide evidence that the kidney toxicity induced by 2,2,4-trimethylpentane in male rats is related to alpha$_{2u}$-globulin accumulation in the proximal tubules. Since this response is specific to male rats, as a matter of science policy, U.S. EPA (1991) has concluded that "if a chemical induces alpha$_{2u}$-globulin accumulation in male rats, the associated nephropathy is not used as an endpoint for determining noncarcinogenic hazard." No other studies were considered suitable for the derivation of an RfD. Therefore, an oral RfD was not derived. The previous IRIS assessment (11/01/1991) did not contain a derivation of an oral RfD.

I.A.1. CHRONIC ORAL RfD SUMMARY

Not applicable.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES

Not applicable.

I.A.3. UNCERTAINTY FACTORS

Not applicable.

I.A.4. ADDITIONAL STUDIES/COMMENTS

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document — U.S. EPA (2007).

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the *Toxicological Review of 2,2,4-Trimethylpentane* (U.S. EPA, 2007). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)***.

Agency Completion Date — 07/31/2007

I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name — 2,2,4-Trimethylpentane
CASRN — 540-84-1
Section I.B. Last Revised — 07/31/2007

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

Only one subchronic inhalation study was identified for 2,2,4-trimethylpentane (Short et al., 1989a). In this study, male and female F344 rats were exposed for 3 to 50 weeks to 50 ppm 2,2,4-trimethylpentane to characterize the pathogenesis of alpha$_{2u}$-globulin-associated nephropathy. Body weight was the only other endpoint evaluated. As observed in the oral studies, the notable effects in this study were limited to the male rat kidney and consisted of an increase in alpha$_{2u}$-globulin protein and hyaline droplet accumulation in the P_2 segment of the proximal tubules, necrosis of the tubule epithelium, sustained regenerative tubule cell proliferation, and enhancement of CPN in male rats. Control and exposed female rats exhibited no evidence of alpha$_{2u}$-globulin nephropathy, increases in cell turnover, or chronic nephrosis.

The available data provide evidence that the kidney toxicity induced by 2,2,4-trimethylpentane in male rats is related to alpha$_{2u}$-globulin accumulation in the proximal tubules. Since this response is specific to male rats, as a matter of science policy, U.S. EPA (1991) has concluded that "if a chemical induces alpha$_{2u}$-globulin accumulation in male rats, the associated nephropathy is not used as an endpoint for determining noncarcinogenic hazard." No other studies were considered suitable for the derivation of the RfC. Therefore, an inhalation RfC was not derived. The previous IRIS assessment (11/01/1991) contained a determination that data were inadequate for the derivation of an inhalation RfC.

I.B.1. CHRONIC INHALATION RfC SUMMARY

Not applicable.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES

Not applicable.

I.B.3. UNCERTAINTY FACTORS

Not applicable.

I.B.4. ADDITIONAL STUDIES/COMMENTS

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document — U.S. EPA (2007).

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the *Toxicological Review of 2,2,4-Trimethylpentane* (U.S. EPA, 2007). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)***.

Agency Completion Date — 07/31/2007

I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name — 2,2,4-Trimethylpentane
CASRN — 540-84-1
Section II. Last Revised — 07/31/2007

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is an upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water or per $\mu g/m^3$ air breathed. Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

In accordance with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), there is "inadequate information to assess carcinogenic potential" for 2,2,4-trimethylpentane. No chronic bioassay studies are available that assess the carcinogenic effects of 2,2,4-trimethylpentane. The majority of the reported studies contribute information specifically related to the histopathological sequence of alpha$_{2u}$-globulin-associated nephropathy. Thus, these studies did not examine any other tissue/organ except for the kidney. In comparing the tumor promoting capability between 2,2,4-trimethylpentane and unleaded gasoline (UG) (a mixture), Short et al. (1989b) showed that both agents had promoting potential in male, but not female, rats. However, the results were not sufficiently descriptive to ascribe the portion of the promoting potential of UG that could be attributable to 2,2,4-trimethylpentane. The few studies available on its genotoxic potential were negative, as 2,2,4-trimethylpentane does not increase mutations at the TK locus (Richardson et al., 1986), induce DNA double-strand breaks (McLaren et al., 1994), or stimulate unscheduled DNA synthesis (Loury et al., 1986). This overall lack of information represents a data gap and does not allow for a quantitative assessment of the carcinogenicity of 2,2,4-trimethylpentane. The previous IRIS assessment (11/01/1991) did not contain a determination of the potential for 2,2,4-trimethylpentane to exhibit carcinogenic activity in humans.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not applicable.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not applicable.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document — U.S. EPA (2007).

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the *Toxicological Review of 2,2,4-Trimethylpentane* (U.S. EPA, 2007). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)***.

II.D.2. EPA REVIEW

Agency Completion Date — 07/31/2007

II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. BIBLIOGRAPHY

Substance Name — 2,2,4-Trimethylpentane
CASRN — 540-84-1

VI.A. ORAL RfD REFERENCES

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VI.B. INHALATION RfC REFERENCES

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VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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VII. REVISION HISTORY

Substance Name — 2,2,4-Trimethylpentane
CASRN — 540-84-1
File First On-Line — 11/01/1991

Date	Section	Description
11/01/1991	I.B.	Inhalation RfC discussion on-line

Date	Section	Description
12/03/2002	I.B.	Screening-Level Literature Review Findings message has been added.
07/31/2007	I., II.	New RfD, RfC, and cancer assessment.

VIII. SYNONYMS

Substance Name — 2,2,4-Trimethylpentane
CASRN — 540-84-1
Section VIII. Last Revised — 07/31/2007

- Pentane, 2,2,4-trimethyl-
- Iso-octane
- 2,2,4-Trimethylpentane
- AI3-23976
- HSDB 5682
- Isobutyltrimethylmethane
- Isooctane
- 2,4,4-Trimethylpentane
- TMP