Substance code 0000
2-Hexanone; CASRN 591-78-6; 00/00/0000

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review 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 at http://www.epa.gov/iris/backgr-d.htm.

STATUS OF DATA FOR 2-HEXANONE

File First On-Line__/__/__

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)		00/00/0000
Chronic Inhalation RfC Assessment (I.B.)		00/00/0000
Carcinogenicity Assessment (II.)		00/00/0000

_I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

2-Hexanone
CASRN -- 591-78-6
Section I.A. Last Revised -- 00/00/0000

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/backgr-d.htm 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.

___I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Axonal swelling of the peripheral nerve Chronic drinking water study in rats O'Donoghue et al., 1978	BMDL: 5 mg/kg-day	1,000	5×10^{-3} mg/kg-day

*Conversion Factors and Assumptions – Animals were administered 2-hexanone in drinking water 24 hours/day, 7 days/weeks for 13 months, thus duration adjustment was not required.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES

O'Donoghue et al. (1978) conducted a 13-month study in male COBS/CD(SD) rats. The animals' drinking water contained 0, 0.25, 0.5, or 1.0% 2-hexanone (96% pure, containing 3.2% methyl isobutyl ketone (MiBK) and 0.7% unknown contaminants). The critical endpoint selected from this study was the incidence of swollen axons in peripheral nerves of male rats. This endpoint was chosen because peripheral neuropathy is the most consistent and relevant effect, identified in occupationally exposed humans and experimental animals, that occurs following low-level exposures to 2-hexanone. Axonal swelling was observed with high incidence in the peripheral nerve at the lowest dose tested (Table 1) and is the most sensitive endpoint observed in this study. Although some studies have suggested that axonal swelling may occur without progression to nerve dysfunction, in the study by O'Donoghue et al. (1978), myofibrillar atrophy, an effect observed subsequent to axonal swelling, displays a dose-dependent response.

Table 1. Summary of neuropathological findings in male rats

Treatment (dose)	Animals with axonal swelling				Animals with myofibrillar atrophy	
	Brain	Spinal cord	Dorsal root ganglia	Peripheral nerve[a]	Quadriceps muscle	Calf muscle
Control	0/10	0/5	0/5	0/10	0/10	0/10
0.25% 2-Hexanone (143 mg/kg-day)	2/10	7/10	0/7	8/10	1/10	2/10
0.5% 2-Hexanone (266 mg/kg-day)	4/10	5/5	0/5	10/10	5/10	6/10
1.0% 2-Hexanone (560 mg/kg-day)	8/10	5/5	3/5	10/10	10/10	10/10

[a]Data evaluated for RfD derivation.
Source: O'Donoghue et al. (1978).

Five other available subchronic studies are considered as supporting studies. Of these five studies, Krasavage et al. (1980) and Eben et al. (1979) both observed neurotoxicity after administration of single doses of 2-hexanone via gavage. These two studies were not considered as principal studies because only single, relatively high doses were administered. Abou-Donia et al. (1982) observed mild ataxia, which progressed to severe ataxia, in hens treated daily by gavage with 100 mg/kg 2-hexanone. Although the hen is a sensitive model for some neurotoxic effects, this study was not chosen as the principal study because doses contained high levels of MiBK (30%). Finally, two subchronic drinking water studies that utilized multiple doses of 2-hexanone and identified neurotoxicological outcomes were considered. The first study, conducted by Homan et al. (1977), utilized doses that were higher than those used by O'Donoghue et al. (1978), and the purity of 2 hexanone was not stated. The second study, by Abdel-Rahman et al. (1978), utilized doses of 97 and 243 mg/kg-day; however, the authors did not include complete data sets; that is, only data from the first 4 weeks of the study were presented. Although the 97 mg/kg-day dose used by Abdel-Rahman et al. (1978) is lower than the lowest dose in the chronic study by O'Donoghue et al. (1978), the data from the 97 mg/kg-day group were not reported. Further, the purity of the compound used was not stated.

___I.A.3. UNCERTAINTY FACTORS

UF = 1,000

An intraspecies uncertainty factor (UF_H) of 10 was applied to adjust for potentially sensitive human subpopulations. A default value is warranted because insufficient information is currently available to assess human-to-human variability in 2-hexanone toxicokinetics or toxicodynamics.

A default interspecies uncertainty factor (UF_A) of 10 was applied for extrapolation from animals to humans. No data on the toxicity of 2-hexanone to humans exposed by the oral route only were identified. Insufficient information is currently available to assess rat-to-human differences in 2-hexanone toxicokinetics or toxicodynamics.

A UF of 10 was applied to account for database deficiencies (UF_D). The database includes subchronic animal studies in rats and hens and a chronic study in rats but does not

include a multigenerational reproductive study or developmental studies. Additionally, there are inhalation studies that suggest the possibility of reproductive and immunological toxicity following exposure to 2-hexanone.

An UF for LOAEL-to-NOAEL extrapolation was not used because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 10% extra risk of axonal swelling of the peripheral nerve was selected under an assumption that it represents a minimal biologically significant change.

A subchronic-to-chronic UF (UF_S) was not applied because the principal study involved a chronic exposure.

___I.A.4. ADDITIONAL STUDIES/COMMENTS

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

Study -- Medium
Data Base – Low to Medium
RfD -- Medium

The overall confidence in this RfD assessment is medium. The application of BMD modeling to the available data influences the overall confidence of the RfD. Although BMD modeling may be a preferred method to the NOAEL/LOAEL approach, in this case a high incidence of peripheral nerve axonopathy was observed at the LOAEL. This observation left uncertainty surrounding the BMD model in the region of interest. Confidence in the principal study (O'Donoghue et al., 1978) is medium. The study uses 10 animals per group and reports clinical neurological deficits and neuropathological effects within a dose range in which LOAEL could be identified for the critical effect. Animal studies in two additional species (guinea pigs and hens) corroborate the primacy of the neurological endpoint and confirm the validity of peripheral neuropathy as the critical effect. Confidence in the database is medium. The database lacks information on multigenerational, developmental, and reproductive toxicity studies and developmental neurotoxicity. Reflecting medium confidence in the principal study and low to medium confidence in the database, confidence in the RfD is medium.

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

Source Document -- U.S. EPA, 2009

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 2-Hexanone* (U.S. EPA, 2009).

Agency Completion Date -- __/__/__

___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

2-Hexanone
CASRN -- 591-78-6
Section I.B. Last Revised -- 00/00/0000

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/m^3) 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.

___I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Sciatic-tibial motor nerve conduction velocity Subchronic inhalation study in monkeys (and rats) Johnson et al., 1977	$BMCL_{HEC}$: 90 mg/m^3	3,000	3×10^{-2} mg/m^3

*Conversion Factors and Assumptions -- molecular weight of 2-hexanone = 100.16 (at 25°C and 760 mm Hg) and 1 ppm = 100.16/24.45 = 4.1 mg/m^3. Duration adjustment of exposure concentrations and conversion to mg/m^3 was accomplished as follows: $BMCL_{ADJ}$ = 121 ppm × 6 hours/24 hours × 5 days/7 days = 22 ppm × 4.1 = 90 mg/m^3. The $BMCL_{HEC}$ was calculated for an extrarespiratory effect of a category 3 gas. The blood:gas partition coefficient ($H_{b/g}$) value

for 2-hexanone in humans is 127 (Sato and Nakajima, 1979); however, no value has been reported for monkeys or rats. According to EPA's RfC methodology (U.S. EPA, 1994), when the ratio of animal to human blood:gas partition coefficients $[(H_{b/g})_A/(H_{b/g})_H]$ is greater than one or the values are unknown, a value of one is used for the ratio by default. Thus, $BMCL_{HEC} = 90 \times [(H_{b/g})_A/(H_{b/g})_H] = 90$ mg/m^3.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES

The study by Johnson et al. (1977) was performed in monkeys and rats, with 8 and 10 animals per dose group, respectively. Two concentrations of commercial grade 2-hexanone were employed (100 and 1,000 ppm in air), with exposures occurring 6 hours per day, 5 days per week for a duration of 10 months. Concurrent control groups were used in both species. As part of this study, Johnson et al. (1977) conducted four neurological tests in each species (usually once per month) to identify effects in treated versus control animals. These four tests were (1) motor conduction velocity (MCV) of the right sciatic-tibial nerve, (2) MCV of the right ulnar nerve, (3) absolute refractory period of these two nerves, and (4) muscle action potentials in response to both sciatic and ulnar nerve stimulation.

Data from Johnson et al. (1977) on both sciatic-tibial and ulnar nerve MCVs in 2-hexanone-exposed monkeys and rats were considered for use in deriving the RfC. Studies in humans have provided insight into the relationship between decreased MCV and functional effects in humans. Sobue et al. (1978) observed a reduction in MCV among workers with severe polyneuropathy in a cross-sectional study of 1,662 shoe workers that were exposed to n-hexane, a parent compound of 2-hexanone. Passero et al. (1983) also noted an association between slowing MCV and disease severity among 98 polyneuropathy cases in a cohort of workers exposed to n-hexane. Both monkeys and rats exhibited significant decrements in sciatic-tibial nerve MCVs at the lowest administered concentration of 2-hexanone beginning at 9 and 7 months of exposure, respectively. A neuropathy similar to that observed for the sciatic-tibial nerves occurred in the ulnar nerves of both monkeys and rats. Monkeys in the low-exposure group exhibited statistically significant decreases in ulnar nerve MCVs relative to control values at 1 and 3 months, although, beginning at 6 months, this decline was not statistically significant. Since monkeys have a similar respiratory tract and breathing patterns to humans and the 2,5-hexanedione (the primary metabolite of 2-hexanone) typically affects long axons such as the sciatic-tibial nerve prior to other nerves, the sciatic-tibial nerve MCV in monkeys is used to derive the RfC. For comparison purposes, both sciatic-tibial MCV and ulnar MCV for both monkeys and rats were modeled.

Several studies of workers in a coated fabrics plant (Allen et al., 1975; Billmaier et al., 1974; Gilchrist et al., 1974) provide evidence in humans of a concentration-dependent neurotoxic response to 2-hexanone exposure. Although personal air samples were not collected in these studies, the available measures of exposure were sufficient to produce quantitative estimates of 2-hexanone inhalation exposure for two groups of workers (i.e., print operators and print helpers, both of whom exhibited peripheral neuropathy). In these workers, exposure to 2-hexanone also occurred via oral and dermal routes, since the study authors noted that individuals frequently ate at the work site and were accustomed to washing their hands with 2-hexanone. Because the magnitude of exposure to 2-hexanone from these two other exposure routes (i.e., oral and dermal), which could have been considerable, was not quantified by the study authors and the workers were also coexposed to MEK, which can potentiate the toxicity of 2-hexanone,

this study was not considered for use in RfC derivation.

___I.B.3. UNCERTAINTY FACTORS

UF = 3,000

A default intraspecies UF (UF_H) of 10 was applied to adjust for potentially sensitive human subpopulations (intraspecies variability). A 10-fold UF is warranted because insufficient information is currently unavailable to assess human-to-human variability in 2-hexanone toxicokinetics or toxicodynamics.

A default subchronic-to-chronic UF (UF_S) of 10 was applied to account for use of data following 6 months of exposure to 2-hexanone for the derivation of a chronic RfC.

A factor of 3 was selected to account for uncertainties in extrapolating from monkeys to humans. This value is adopted by convention where an adjustment from an animal-specific $BMCL_{ADJ}$ to a $BMCL_{HEC}$ has been incorporated. Application of a full UF of 10 would depend on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic component is mostly addressed by the determination of a HEC as described in the RfC methodology (U.S. EPA, 1994). The toxicodynamic uncertainty is also accounted for to a certain degree by the use of the applied dosimetry method and a UF of 3 is retained to fully address this component.

A UF of 10 was applied to account for database deficiencies (UF_D). The database includes a human occupational exposure study (with coexposure to MEK), subchronic animal studies in rats and hens, and a chronic study in cats. One postnatal development and behavior study on 2-hexanone in F344 rats (Peters et al., 1981) exists, identifying a LOAEL of 1,000 ppm (no NOAEL reported). The database does not include a multigenerational reproductive study or prenatal developmental studies. Additionally, Katz et al. (1980) observed a reduction in total white blood cell counts to 60% of control values in rats exposed to 2-hexanone in a subchronic inhalation study, suggesting that further study of immunotoxicity may be warranted. Because of the absence of a two-generation reproductive study and studies evaluating the possible developmental toxicity and immunotoxicity of 2-hexanone following exposure via inhalation, a UF_D of 10 is warranted.

A UF for LOAEL-to-NOAEL extrapolation was not used because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 5% change in nerve conduction velocity from the control mean was selected under an assumption that it represents a minimal biologically significant change.

___I.B.4. ADDITIONAL STUDIES/COMMENTS

Of the available animal studies on 2-hexanone, six subchronic studies (Abdo et al., 1982; Katz et al., 1980; Duckett et al., 1979, 1974; Saida et al., 1976; Mendell et al., 1974) and four chronic studies (Egan et al., 1980; Duckett et al., 1979; Krasavage and O'Donoghue, 1977; Spencer et al., 1975) were not selected for use in deriving the RfC. For many of these studies, purity of 2-hexanone was not stated (Duckett et al., 1979, 1974; Krasavage and O'Donoghue, 1977; Saida et al., 1976; Spencer et al., 1975; Mendell et al., 1974). Without more information on the purity of the 2-hexanone administered, it is difficult to ascertain if MiBK, a potential inducer of CYP450, impacted the toxicity of 2-hexanone. Abdo et al. (1982) did specify purity

and reported that the 2-hexanone used contained 30% MiBK. Other studies did not reported the sex of the experimental animals (Duckett et al., 1979, 1974; Saida et al., 1976) or provided limited data (Krasavage and O'Donoghue, 1977; Mendell et al., 1974) for the derivation of the RfC. The animal studies by Katz et al. (1980) and Egan et al. (1980) consisted of exposure to 2-hexanone (purity > 96%) at a single concentration for a period of 6 months or less, using only one strain and sex of rats.

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

Study -- Medium
Data Base -- Low to medium
RfC -- Low to medium

The overall confidence in this RfC assessment is low to medium. The application of BMD modeling on the available data does influence the overall confidence of the RfC; in this case, assumptions were applied to derive the estimate variance values that were used in the RfC calculations. Confidence in the principal study is medium; it involves exposures in two species via the inhalation route and sensitive diagnostic tests for determining treatment-related neurotoxicity. In addition, animal studies in four different species (monkeys, rats, cats, and hens) and occupational exposures corroborate the primacy of the neurological endpoint and confirm the relevance of the critical effect for decreased MCV values. Confidence in the database is low to medium. The database lacks multigenerational developmental and reproductive toxicity studies and a developmental neurotoxicity study. In addition the observation of a reduction in total white blood cell count suggests the need for further information on immunotoxicity. Therefore, the confidence in the database is low to medium.

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

Source Document -- U.S. EPA, 2009

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 2-Hexanone* (U.S. EPA, 2009).

Agency Completion Date -- __/__/__

___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

2-Hexanone
CASRN -- 591-78-6
Section II. Last Revised -- 00/00/0000

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 a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). 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.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for 2-hexanone is "inadequate to assess human carcinogenic potential." Specifically, there are no animal carcinogenicity studies available that examine exposure to 2-hexanone, and there are no studies available that assert a genotoxic potential of 2-hexanone. The available occupational studies do not present evidence for carcinogenic action of 2-hexanone, although these are limited by frequent coexposure to other chemicals (e.g., MEK).

___II.A.2. HUMAN CARCINOGENICITY DATA

The available occupational studies do not present evidence for carcinogenic action of 2-hexanone and are limited by frequent coexposure to other chemicals (e.g., MEK).

___II.A.3. ANIMAL CARCINOGENICITY DATA

There are no animal carcinogenicity studies available that examine exposure to 2-hexanone.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Not applicable.

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

Not applicable. Data are inadequate for an assessment of carcinogenic potential.

__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, 2009

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 2-Hexanone* (U.S. EPA, 2009).

___II.D.2. EPA REVIEW

Agency Completion Date -- __/__/__

___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

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CASRN -- 591-78-6
Section VI. Last Revised -- 00/00/0000

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__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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U.S. EPA (Environmental Protection Agency). (2005b) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available online at http://www.epa.gov/cancerguidelines.

U.S. EPA (Environmental Protection Agency). (2009) Toxicological review of 2-hexanone. Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC; EPA/635/R-03/002. Available online at http://www.epa.gov/iris.

_VII. REVISION HISTORY

2-Hexanone
CASRN -- 591-78-6
File First On-Line __/__/__

Date	Section	Description
__/__/__	All	IRIS Summary first posted

_VIII. SYNONYMS

2-Hexanone
CASRN -- 591-78-6
Section VIII. Last Revised -- 00/00/0000

2-Oxohexane
Butyl methyl ketone
Hexanone-2
Ketone, butyl methyl
Methyl butyl ketone
Methyl n-butyl ketone
Propylacetone
n-Butyl methyl ketone