2-Hexanone; CASRN 591-78-6

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-HEXANONE

File First On-Line 09/25/2009

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/25/2009
Inhalation RfC (I.B.)	yes	09/25/2009
Carcinogenicity Assessment (II.)	yes	09/25/2009

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 — 09/25/2009

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 (presumed 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.

An RfD assessment for 2-hexanone was not previously available on IRIS.

I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Axonal swelling of the peripheral nerve **13-Month drinking water study in rats** **O'Donoghue et al., 1978**	$BMDL_{10}$: 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 in the peripheral nerve with high incidence 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, myofibrillar atrophy, an effect observed subsequent to axonal swelling, displayed a dose-dependent response in the study by O'Donoghue et al. (1978).

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 set used for RfD derivation.
Source: O'Donoghue et al. (1978).

Methods of analysis: U.S. EPA's benchmark dose (BMD) software (BMDS), version 1.4.1c, was used to estimate a point of departure (POD) for deriving an RfD for 2-Hexanone from data on axonal swelling of the peripheral nerve. The POD was defined as the 95% lower confidence limit on the BMD (BMDL) associated with a benchmark response (BMR) of 10% extra risk of axonal swelling. A BMR of 10% is generally used in the absence of information regarding what level of change is considered biologically significant, and also to facilitate a consistent basis of comparison across assessments (U.S. EPA, 2000). All of the available dichotomous models in BMDS were fit to the axonal swelling incidence data. The multistage model, which provided the best fit of the data, yielded a BMD_{10} and $BMDL_{10}$ of 36.1 and 5.1 mg/kg-day, respectively. Modeling details are provided in the *Toxicological Review of 2-Hexanone* (U.S. EPA, 2009), Section 5.1.2 and Appendix B-1.

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%). Two subchronic drinking water studies, one in the rat and a second in the guinea pig, that utilized multiple doses of 2-Hexanone and identified neurotoxicological outcomes were considered as candidate principal studies. The rat study 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 study in the guinea pig by Abdel-Rahman et al. (1978) utilized doses of 97 and 243 mg/kg-day; however, 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 13-month 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

A default 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 were identified. Insufficient information is currently available to assess rat-to-human differences in 2-hexanone toxicokinetics or toxicodynamics.

An UF of 10 was applied to account for database deficiencies (UF_D). The database includes subchronic animal studies in rats and hens and a 13-month 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-NOAELextrapolation (UF_L) 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 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. Although the principal study (O'Donoghue et al., 1978) was not a standard 2-year bioassay, rats were exposed for 13 months, or more than half of their life span. Therefore, the exposure period used in the principal study was considered to be of chronic duration.

I.A.4. ADDITIONAL STUDIES/COMMENTS

No studies of the possible association between oral exposure to 2-Hexanone and noncancer health effects in humans are available. There are six oral toxicity studies of 2-Hexanone in experimental animals with exposures ranging from 3 to 13 months in duration. These include a 90-day gavage study in hens, 90-day and 40-week gavage studies in rats, 120-day and 13-month drinking water studies in rats, and a 24-week drinking water study in guinea pigs. These studies demonstrate that the nervous system is the target organ for 2-Hexanone toxicity following oral exposure.

Available data suggest that the principal metabolite of 2-Hexanone, 2,5 hexanedione, is responsible for the neurotoxicity associated with oral exposure to 2-Hexanone. For example, Krasavage et al. (1980) compared the neurotoxicity of 2-Hexanone with that of n-hexane, 5-hydroxy-2-Hexanone, 2,5-hexanediol, and 2-hexanol by administering equimolar doses of each chemical by gavage to five male COBS CD(SD)BR rats/group, 5 days/week for 90 days. Judged by the time required for the rats to develop hind-limb paralysis, 2,5-hexanedione had a higher neurotoxic potency than 2-Hexanone.

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

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. Confidence in the principal study (O'Donoghue et al., 1978) is medium. The study used 10 animals per group and reported 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) lend support to the choice of neurological effects as an endpoint of

concern. Confidence in the database is low to medium. The database lacks information on developmental, reproductive, and immune system toxicity. Reflecting medium confidence in the principal study and low to medium confidence in the database, confidence in the RfD is medium.

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, 2009

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, 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). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

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 — 09/25/2009

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 (presumed 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.

An RfC assessment for 2-hexanone was not previously available on IRIS.

I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfC
Motor conduction velocity of the sciatic-tibial nerve **Subchronic inhalation study in monkeys** **Johnson et al., 1977**	$BMCL_{05[HEC]}$: 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 $BMCL_{05[HEC]}$ 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, $BMCL_{05[HEC]} = 90 \times [(H_{b/g})_A/(H_{b/g})_H] = 90$ 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/day, 5 days/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. After approximately 6 months of exposure, monkeys and rats in the 1,000 ppm exposure group were removed from the study because neuropathy (characterized as hind-limb drag) had developed in these animals.

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.

In Johnson et al. (1977), 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. Similarly, MCVs were reduced 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 ulnar nerve MCVs were reduced relative to controls throughout the remainder of the study, these reductions were not statistically significant. Rats exhibited statistically significant decreases in ulnar nerve MCVs at 4 and 7 months exposure to 100 ppm 2-hexanone. Because monkeys have a similar respiratory tract and breathing patterns to humans and it is known that 2,5 hexanedione (the primary metabolite of 2-hexanone) typically affect long axons such as the sciatic-tibial nerve prior to other nerves, the sciatic-tibial nerve MCV in monkeys was identified as the critical effect to derive the RfC. For comparison purposes, sciatic-tibial MCV in rats and ulnar MCV in both monkeys and rats were also considered potential critical effects for RfC derivation.

Methods of analysis: The available continuous models in U.S. EPA's BMDS, version 2.0, were used to estimate a POD for deriving an RfC for 2-Hexanone from data on nerve MCV. Because the magnitude of variation in nerve MCVs between the 6- and 10-month data was similar and because more treatment groups were available for the 6-month exposure duration (i.e., two exposure groups plus control at 6 months versus one exposure group plus control at 10 months), the data at 6 months were used for BMD modeling. See the *Toxicological Review*

of 2-Hexanone (U.S. EPA, 2009), Section 5.2.2, for further discussion of the selection of the data set used for RfC derivation.

Statistically significant decreases in nerve conduction velocity are indicative of a neurotoxic effect; however, as noted in EPA's *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998) normal conduction velocity may be maintained for some time after the onset of axonal degeneration. Therefore, EPA determined that small changes in mean sciatic-tibial nerve MCV are biologically significant. A BMR of 5% extra risk was selected based on the following considerations: (1) this effect level is considered to be a minimal biologically significant change; (2) the potential for nerve fiber damage (i.e., axonal degeneration) with little to no change in MCV; and (3) the $BMDL_{05}$ falls within the low end of the range of the observable data.

The 1st-degree polynomial model provided the best fit for sciatic-tibial nerve MCV in the monkey. Because animals were exposed to 2-hexanone intermittently (i.e., 6 hours/day, 5 days/week), the $BMCL_{05}$ was adjusted to continuous exposure by multiplying by 6/24 × 5/7. The $BMCL_{05[ADJ]}$ was calculated to be 90.2 mg/m^3. Finally, the $BMCL_{05[ADJ]}$ was converted to a human equivalent concentration (HEC) using the methods in U.S. EPA (1994). Using an adjustment factor of one, the $BMCL_{05[HEC]}$ was determined to be 90 mg/m^3. Detailed discussion of BMD modeling and derivation of the HEC are provided in the *Toxicological Review of 2-Hexanone* (U.S. EPA, 2009), Sections 5.2.2 and 5.2.3 and Appendix B-2.

Several studies of workers in a coated fabrics plant (Allen et al., 1974; 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. Workers were also co-exposed to methyl ethyl ketone (MEK), which can potentiate the toxicity of 2-Hexanone. Because the magnitude of exposure to 2-hexanone from oral and dermal exposure routes was not quantified by the study authors and because of co-exposure to MEK, 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 available 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 an RfC.

A factor of 3 was selected to account for uncertainties in extrapolating from monkeys to humans (UF_A). This value is adopted by convention where an adjustment from an animal-specific $BMCL_{ADJ}$ to a $BMCL_{HEC}$ has been incorporated. Application of an 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 address this component.

An UF of 10 was applied to account for database deficiencies (UF_D). The database includes a human occupational exposure study (with co-exposure to MEK), subchronic animal studies in rats and hens, and a chronic study in cats. One postnatal development and behavior study (Peters et al., 1981) on 2-hexanone in F344 rats exists, identifying a LOAEL of 1,000 ppm (no NOAEL reported). The database does not include a multigenerational reproductive study or developmental studies. The database also lacks information regarding axonal degeneration at concentrations similar to those inducing minimal reductions in nerve MCV. 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, an UF_D of 10 is warranted.

An UF for LOAEL-to-NOAEL extrapolation (UF_L) 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, the 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 contaminant and inducer of CYP450, impacted the toxicity of 2-hexanone. Abdo et al. (1982) specified 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) that could be used 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.

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

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

Study — Medium
Data Base — Low
RfC — Low

The overall confidence in this RfC assessment is low. Confidence in the principal study is medium. The study included 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 lend support for the choice of neurologic effects as an endpoint of concern. Confidence in the database is low. The database lacks multigenerational developmental and reproductive toxicity studies. In addition, the observation of a reduction in total white blood cell count suggests the need for further information on immunotoxicity.

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 (2009)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, 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). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

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 — 09/25/2009

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.

A cancer assessment for 2-hexanone was not previously available on IRIS.

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 mutagenic potential of 2-hexanone. The available occupational studies do not present evidence for carcinogenic action of 2-hexanone, although these are limited by frequent co-exposure to other chemicals (e.g., MEK).

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.A.2. HUMAN CARCINOGENICITY DATA

The available occupational studies do not present evidence for carcinogenic action of 2-Hexanone and are limited by frequent co-exposure 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 White House offices, 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). ***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

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

2-Hexanone
CASRN — 591-78-6

VI.A. ORAL RfD REFERENCES

Abdel-Rahman, MS; Saladin, JJ; Bohman, CE; et al. (1978) The effect of 2-Hexanone and 2-Hexanone metabolites on pupillomotor activity and growth. Am Ind Hyg Assoc J 39(2):94–99.

Abou-Donia, MB; Makkawy, HA; Graham, DG. (1982) The relative neurotoxicities of n hexane, methyl n-butyl ketone, 2,5 hexanediol, and 2,5 hexanedione following oral or intraperitoneal administration in hens. Toxicol Appl Pharmacol 62(3):369–389.

Eben, A; Flucke, W; Mihail, F; et al. (1979) Toxicological and metabolic studies of methyl n-butyl ketone, 2,5 hexanedione, and 2,5 hexanediol in male rats. Ecotoxicol Environ Saf 3(2):204–217.

Homan, ER; Weil, CS; Cox, ER. (1977) Comparative pathology on rats given methoxyacetone and five other aliphatic ketones in drinking water (detone neurotoxicity). Produced by the Carnegie-Mellon Institute of Research, Pittsburgh, PA for the Union Carbide Corporation, Danbury, CT. Submitted under TSCA Section 8D; EPA Document No. 878212141; NTIS No. OTS0206068.

Krasavage, WJ; O'Donoghue, JL; DiVincenzo, GD; et al. (1980) The relative neurotoxicity of methyl-n-butyl ketone, n hexane and their metabolites. Toxicol Appl Pharmacol 52(3):433–441.

O'Donoghue, JL; Krasavage, WJ; Terhaar, CJ. (1978) A comparative chronic toxicity study of methyl n-propyl ketone, methyl n-butyl ketone, and hexane by ingestion. Eastman Kodak Company, Rochester, NY; Report No. 104657Y. Submitted under TSCA Section 8ECP; EPA Document No. 88-920008233; NTIS No. OTS0555051. [An external peer review was conducted by EPA in December 2007 to evaluate the accuracy of experimental procedures, results, and interpretation and discussion of the findings presented. A report of this peer review is available through the EPA's IRIS Hotline, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (e-mail address) and on the IRIS website (www.epa.gov/iris).]

U.S. EPA (Environmental Protection Agency). (2000b) Benchmark dose technical guidance document [external review draft]. Risk Assessment Forum, Washington, DC; EPA/630/R-00/001. Available online at

http://cfpub.epa.gov/ncea/cfm/nceapublication.cfm?ActType=PublicationTopics&detype=DOCUMENT&subject= BENCHMARK+DOSE&subjtype=TITLE&excCol=Archive.

U.S. EPA. (2009) Toxicological Review of 2-Hexanone in support of Summary Information on Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. Available online from http://www.epa.gov/iris.

VI.B. INHALATION RfC REFERENCES

Abdo, KM; Graham, DG; Timmons, PR; et al. (1982) Neurotoxicity of continuous (90 days) inhalation of technical grade methyl butyl ketone in hens. J Toxicol Environ Health 9(2):199–215.

Allen, N; Mendell, JR; Billmaier, JD; et al. (1975) Toxic polyneuropathy due to methyl n-butyl ketone. Arch Neurol 32(4):209–218.

Billmaier, D; Allen, N; Craft, B; et al. (1974) Peripheral neuropathy in a coated fabrics plant. J Occup Med 16(10):665–671.

Duckett, S; Williams, N; Francis, S. (1974) Peripheral neuropathy associated with inhalation of methyl-n-butyl ketone. Experientia 30(11):1283–1284.

Duckett, S; Streletz, LJ; Chambers, RA; et al. (1979) 50 ppm MnBK subclinical neuropathy in rats. Experientia 35:1365–1367.

Egan, G; Spencer, P; Schaumburg, H; et al. (1980) n Hexane-"free" hexane mixture fails to produce nervous system damage. Neurotoxicology 1:515–524.

Gilchrist, M; Hunt, W; Allen, N; et al. (1974) Toxic peripheral neuropathy. MMWR 23:9–10.

Johnson, BL; Setzer, JV; Lewis, TR; et al. (1977) Effects of methyl n-butyl ketone behavior and the nervous system. Am Ind Hyg Assoc J 38(11):567–579.

Katz, GV; O'Donoghue, JL; DiVincenzo, GD; et al. (1980) Comparative neurotoxicity and metabolism of ethyl n-butyl ketone and methyl n-butyl ketone in rats. Toxicol Appl Pharmacol 52(1):153–158.

Krasavage, WJ; O'Donoghue, JL. (1977) Chronic inhalation exposure of rats to methyl n-butyl ketone (MnBK). Eastman Kodak Company, Rochester, New York, NY. Submitted under TSCA Section 8ECP; EPA Document No. 88-920009282; NTIS No. OTS0571036. TSCA Docket/EPA TL-77-1.

Mendell, JR; Saida, K; Ganansia, MF; et al. (1974) Toxic polyneuropathy produced by methyl N-butyl ketone. Science 185(153):787–789.

Passero, S; Battistini, N; Cioni, R; et al. (1983) Toxic polyneuropathy of shoe workers in Italy. A clinical, neurophysiological and follow-up study. Ital J Neurolog Sci 4:463-472.

Peters, MA; Hudson, PM; Dixon, RL. (1981) The effect totigestational exposure to methyl n-butyl ketone has on postnatal development and behavior. Ecotoxicol Environ Saf 5(3):291–306.

Saida, K; Mendell, JR; Weiss, HS. (1976) Peripheral nerve changes induced by methyl n-butyl ketone and potentiation by methyl ethyl ketone. J Neuropathol Exp Neurol 35(3):207–225.

Sato, A; Nakajima, T. (1979) Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br J Ind Med 36(3):231–234.

Sobue, I; Iida, M; Yamamura, Y; et al. (1978) n-Hexane polyneuropathy. Int J Neurol 11:317–330.

Spencer, PJ; Schaumburg, HH; Raleigh, RL; et al. (1975) Nervous system degeneration produced by the industrial solvent methyl n-butyl ketone. Arch Neurol 32:219–222.

U.S. EPA (Environmental Protection Agency). (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH; EPA/600/8-90/066F. Available from the National Technical Information Service, Springfield, VA, PB2000-500023, and online at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=71993.

U.S. EPA. (1998) Guidelines for neurotoxicity risk assessment. Federal Register 63(93):26926–26954. Available online at http://www.epa.gov/raf/publications/guidelines-neurotoxicity-risk-assessment.htm.

U.S. EPA. (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.

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

U.S. EPA (Environmental Protection Agency). (2005a) Guidelines for carcinogen risk assessment. Federal Register 70(66):17765–18717. Available online at http://www.epa.gov/cancerguidelines/.

U.S. EPA. (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. (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 — 09/25/2009

Date	Section	Description
09/25/2009	All	IRIS Summary first posted

VIII. SYNONYMS

2-Hexanone
CASRN — 591-78-6
File First On-Line — 09/25/2009

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