n-Hexane; CASRN 110-54-3

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 n-Hexane

File First On-Line 07/01/90

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	qualitative discussion	12/23/2005
Inhalation RfC (I.B.)	yes	12/23/2005
Carcinogenicity Assessment (II.)	yes	12/23/2005

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — n-Hexane
CASRN — 110-54-3
Section I.A. Last Revised — 12/23/2005

In general, the oral Reference Dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily 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 based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis and 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. Since 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. Oral RfD Summary

Not available at this time.

No epidemiology or case report studies examining health effects in humans or chronic laboratory studies evaluating potential health effects in animals following oral exposure to n-hexane are available. An RfD for n-hexane cannot be derived in the absence of a suitable oral study of sufficient duration that evaluates an array of endpoints. The only study identified for oral exposure to n-hexane was of subchronic duration, utilized gavage exposure, and evaluated a small number (five/group) of animals (Krasavage et al., 1980). Several animals died in each dose group (two in the mid-dose and one in the high-dose groups, respectively) during the course of the study.

Krasavage et al. (1980) exposed five male COBS CD(SD) BR rats/group to doses of 0, 6.6, 13.2, and 46.2 mmol/kg (570 mg/kg) n-hexane by gavage, 5 days/week, for 90 days. The period of treatment and observation was extended to 120 days for those animals receiving 46.2 mmol/kg n-hexane to ensure that an overt neuropathological endpoint was detected. The onset of neuropathy was assessed by the initial appearance of hindlimb paralysis, at which point the animal was sacrificed and examined histopathologically. The appearance of hindlimb paralysis and giant axonal swellings were observed in the high-dose group (3/4 and 4/4, respectively). The Krasavage et al. (1980) study provided data on neurotoxicity only; lacked data on an adequate number of animals in the various dose groups; and lacked clear dose-response preventing the use of these data to develop an oral RfD.

A route-to-route extrapolation using available inhalation data is currently not possible since limited PBTK models are available for n-hexane (Fisher et al., 1997; Perbellini et al., 1986). The Fisher et al. (1997) lactational transfer model was developed using rodent tissue solubility and allometrically-scaled metabolic rate constants available in the published literature to estimate human tissue metabolic parameters. In addition, the authors suggested that the absence of exposure and toxicokinetic data on lactation transfer of chemicals such as n-hexane to nursing infants is a disadvantage of this model. The PBTK model by Perbellini et al. (1986) is also inappropriate for use in route-to-route extrapolation. The dose metric for the critical effect in this model is a function of the concentration of 2,5-hexanedione in circulation. The concentration-duration-response function for 2,5-hexanedione is unknown. In addition, the oral dose of n-hexane necessary to yield the same blood-concentration-time profile for 2,5-hexanedione, taking into account gastrointestinal uptake of the compound, is not accounted for

by Perbellini et al. (1986). Furthermore, studies indicate that the major metabolite of n-hexane in humans is 2,5-hexanedione, but in laboratory animals is 2-hexanol. Thus, using a PBTK model based on information from laboratory animal studies may not be appropriate.

I.A.2. Principal and Supporting Studies (Oral RfD)

Not applicable.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

Not applicable.

I.A.4. Additional Studies/Comments (Oral RfD)

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the 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 Oral RfD

Source Document — U.S. EPA, 2005a

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 n-Hexane (U.S. EPA, 2005a). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Panel Peer Review and Public Comments and Disposition (PDF)***

Agency Completion Date -- 12/23/2005

I.A.7. EPA Contacts (Oral RfD)

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 for Chronic Inhalation Exposure (RfC)

Substance Name — n-Hexane
CASRN — 110-54-3
Section I.B. Last Revised — 12/23/2005

In general, the Reference Concentration (RfC) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of 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 likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis.

Inhalation RfCs are derived according to the *Interim Methods for Development of Inhalation Reference Doses* (U.S. EPA, 1989) and subsequently, according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Since 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 of 2E-1 mg/m^3 was previously entered on the IRIS database in 1990. This value was based on a LOAEL of 204 mg/m^3 for neurotoxicity (electrophysical alterations) in humans (Sanagi et al., 1980). A total uncertainty factor of 300 was applied to the LOAEL (uncertainty factors of 10 for intraspecies variability, 10 for the use of a LOAEL, and 3 for limited reproductive and chronic respiratory toxicity data). The subchronic National Toxicology Program (NTP, 1991) study (published in the literature as Dunnick et al., 1989) in which B6C3F1 mice were exposed to 0, 500, 1000, 4000, and 10,000 ppm n-hexane 6 hours/day, 5 days/week, or 1000 ppm n-hexane 22 hours/day, 5 days/week, via inhalation for 13 weeks was used as a coprincipal study. The critical effect in the subchronic study was epithelial lesions in the nasal cavity. The change in the principal study from the previous IRIS assessment is due primarily to the identification of new literature. The Sanagi et al. (1980) occupational

exposure study reported co-exposure to acetone at a mean concentration of 39 ppm. More recent data suggest that co-exposure to acetone potentiates n-hexane metabolism and n-hexane-induced neurotoxicity (Cardona et al., 1996; Ladefoged et al., 1994, 1989; Larsen et al., 1991). Therefore, it is possible that the incidence or severity of the neurological changes observed by Sanagi et al. (1980) may have been a result of co-exposure to both solvents. Dunnick et al. (1989) was not retained as the coprincipal study for the derivation of the RfC in the current assessment because the study authors did not perform neurological histopathology at the mid-concentrations (500, 1000, 4000 ppm for 6 hours/day). The lack of histopathology is considered to be a significant deficiency in the Dunnick et al. (1989) study, since the nervous system appears to be the primary target of n-hexane-induced neurotoxicity (see Section 4.5.2 of the Toxicological Review of n-Hexane [U.S. EPA, 2005a]).

I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	RfC
Peripheral neuropathy (decreased MCV at 12 weeks) **Rat subchronic inhalation study** **Huang et al., 1989**	BMC: 550 mg/m^3 BMCL: 430 mg/m^3 $BMCL_{ADJ}$: 215 mg/m^3 $BMCL_{HEC}$: 215 mg/m^3	300	7E-1 mg/m^3

* Conversion Factors and Assumptions — MW = 86.18. Assuming 25°C and 760 mm Hg, 1 ppm = 86.18/24.45 = 3.52 mg/m^3. Duration adjustment of exposure concentrations was employed (12 hours/day, 7 days/week): $BMCL_{ADJ}$ = 430 mg/m^3 x 12h/24h = 215 mg/m^3. The $BMCL_{HEC}$ was calculated for an extrarespiratory effect of a category 3 gas. The blood:gas (air) partition coefficient ($H_{b/g}$) value for n-hexane in humans (H) is 0.8 (Perbellini et al., 1985) whereas a value of 2.29 has been reported in rats (A) (Gargas et al., 1989). According to the RfC methodology (U.S. EPA, 1994), where the ratio of animal to human blood:air partition coefficients $[(H_{b/g})_A/(H_{b/g})_H]$ is greater than one, a value of one is used for the ratio by default. Thus, $BMCL_{HEC}$ = 215 x $[(H_{b/g})_A/(H_{b/g})_H]$ = 215 mg/m^3.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Huang, J; Kato, K; Shibata, E; et al. (1989) Effects of chronic n-hexane exposure on nervous system-specific and muscle-specific proteins. Arch Toxicol 63:381-385.

Male Wistar rats (eight/group) were exposed to 0, 500, 1200, or 3000 ppm (0, 1762, 4230, 10,574 mg/m^3) n-hexane (>99% pure) for 12 hours/day, 7 days/week for 16 weeks (Huang et al., 1989). The authors measured motor nerve conduction velocity (MCV) in the tail nerve along with body weight before exposure and after 4, 8, 12, and 16 weeks of exposure to n-hexane. One animal from each group was sacrificed at 16 weeks exposure for histopathological evaluation of the nerve fibers in the tail. In addition, Huang et al. (1989) measured the levels of neuron-specific enolase and beta-S-100. These nervous system-specific proteins are a family of calcium binding proteins that are involved in processes such as cell-to-cell communication, cell growth, intracellular signal transduction, and development and maintenance of the central nervous system. A dose-dependent, statistically significant reduction in body weight gain was observed in the mid- (at 12 weeks) and high-dose (at 8 weeks) rats. Additionally, there were some neurological deficits in mid- and high-dose rats, including a reduction in grip strength and a comparative slowness of motion from week 12 of exposure. However, no hindlimb paralysis was observed by the termination of the experiment. Rats exposed to the mid and high doses of n-hexane showed a reduction in MCV. This reduction was statistically significant during weeks 8-16 of the exposure period compared with controls. Increased incidence of paranodal swellings, along with some evidence of demyelination and remyelination, was present in the peripheral nerves at both mid and high doses. However, these histopathological findings were more severe in the high dose group. Among biochemical changes, there were dose-dependent reductions in nervous system specific proteins, particularly the beta-S-100 proteins from tail nerve fibers, which were significantly reduced by approximately 75% at all dose levels. The neurophysiological deficits and histopathological effects that were evident in mid- and high-dose rats indicate a NOAEL of 500 ppm.

The Huang et al. (1989) study was selected as the principal study with peripheral neuropathy (decreased MCV at 12 weeks) in male rats as the critical effect. The available human and animal n-hexane inhalation exposure data suggest that the nervous system is the primary target of n-hexane toxicity (Sections 4.1.2 and 4.2.1 of the Toxicological Review of n-Hexane [U.S. EPA, 2005a]). In addition, Huang et al. (1989) evaluated a comprehensive array of neurological endpoints and an adequate number of animals and exposure groups and was of the appropriate quality for the derivation of the RfC. The Huang et al. (1989) data set provided an adequate dose response for BMD modeling with an estimated point of departure of a $BMCL_{HEC}$ of 215 mg/m^3 (Section 5.2.2 and Appendix B of the Toxicological Review of n-Hexane [U.S. EPA, 2005a]).

As described in Section 4.2.2 of the Toxicological Review of n-Hexane (U.S. EPA, 2005a), the toxic effects in laboratory animals following inhalation exposure to n-hexane support the nervous system as the primary target of toxicity. A number of studies identified a variety of effects on the nervous system, kidney, liver, and developing fetus at doses between 125-500 ppm (IRDC, 1992a, b; NTP, 1991; Dunnick et al., 1989; Huang et al., 1989; Mast et al., 1988a; Mast, 1987; Ono et al., 1982). These studies were considered for the selection of the principal study and are described below. Benchmark dose (BMD) modeling, where the data were amenable, was performed and is discussed in detail in Section 5.2.2 and Appendix B of the Toxicological Review of n-Hexane (U.S. EPA, 2005a).

Neurological deficits and respiratory lesions (mild epithelial lesions) were observed when B6C3F1 mice were exposed subchronically to 0, 500, 1000, 4000, and 10,000 ppm n-hexane, 6 hours/day, 5 days/week for 90 days or to 1000 ppm n-hexane for 22 hours/day, 5 days/week for 90 days (NTP, 1991; Dunnick et al., 1989). Dunnick et al. (1989) reported decreased locomotor activity and increased axonal swellings in the paranodal nerve in the 1000 ppm continuous exposure group (22 hours/day) and the 10,000-ppm exposure group (6 hours/day). Histopathology of the spinal cord and tibial nerve was performed in four animals/sex from the 0, 1000 ppm continuous exposure, and 10,000 ppm exposure groups only. The NOAEL (500 ppm) was based on the appearance of mild epithelial lesions in the nasal cavity. The authors suggested that this effect was more severe in the 1000 ppm continuous exposure group (22 hours/day) than in the 4000 ppm exposure group (6 hours/day). They also considered these effects to be nonspecific and indicative of inflammatory and regenerative changes secondary to the effects of the inhaled irritant. The authors were unclear as to whether the altered morphology was due to inflammation or direct action of n-hexane. Thus, the study authors stated that the nasal irritation was most likely secondary to the inhaled irritant. In addition, the absence of sufficient neuropathological information from the mid-concentration groups (i.e., 500, 1000, 4000 ppm for 6 hours/day) is considered to represent a significant deficiency in the interpretation of the Dunnick et al. (1989) study. Therefore, the NTP (1991)/Dunnick et al. (1989) study was not selected as the principal study for the derivation of the RfC.

The International Research and Development Corporation (IRDC, 1992a) exposed male Sprague Dawley rats to 0, 125, and 500 ppm n-hexane subchronically for 6 months (22 hours/day, 7 days/week). n-Hexane exposure resulted in a significant decrease in mean absolute and relative liver and kidney weights at both doses. These changes in organ weights were not accompanied by any histopathological evidence of liver or kidney toxicity. In the second phase of this study, IRDC (1992b) demonstrated an increased incidence of chronic nephritis in 6/11 controls and 10/10 rats exposed to 500 ppm n-hexane. This response is considered equivocal due to the high incidence of kidney nephropathy in the control animals. Axonal degeneration and muscle atrophy were also observed but only at the high dose. The data on axonal degeneration and muscle atrophy are not amenable to BMD modeling because

each effect lacks an adequate dose response for modeling (i.e., effects were seen at only the high dose). For example, 0/10, 0/10, and 7/10 animals showed tibial/sciatic nerve axonal degeneration and 0/10, 0/10, and 9/10 animals showed skeletal muscle atrophy at 0, 125, and 500 ppm, respectively. Finally, the results of this study are potentially compromised by possible co-exposure to a phthalate ester-type compound. The authors indicated that during exposure a brown oily material collected on the glass beads of the inhalation system for each exposure group. Samples of this brown material were subjected to infrared spectroscopy, which confirmed the presence of a phthalate ester-type compound. While the observed axonal degeneration at the high dose could constitute a LOAEL, the noted contamination compromises the results. Therefore, the IRDC (1992a, b) study was not selected as the principal study for the derivation of the RfC.

Ono et al. (1982) observed subchronic effects of n-hexane on the nervous system in male Wistar rats (eight/group) exposed to 0, 200, and 500 ppm n-hexane, 12 hours/day for 24 weeks. Only one animal from each group was examined histopathologically in an attempt to link any functional deficits to morphological changes that may have taken place over the duration of the experiment. The authors stated that they did not observe any definite clinical signs of neuropathy in any of the exposed groups. MCV and mixed MCVs (distal and both proximal and distal combined) were statistically significantly decreased in rats exposed to n-hexane at both 200 and 500 ppm. Distal latency and proximal mixed MCV were statistically significantly decreased at the low dose but not at the high dose. Degeneration of the myelinated axons was evident in the peripheral nerves at both exposures (histopathology in one animal). While the observed decreases in MCV could constitute a LOAEL, the lack of observed clinical neuropathy and failure to evaluate nerve histopathology on a larger number of animals are limitations of this study. In addition, BMD modeling of the data produced poor goodness of fit values estimated from the data (Appendix B of the Toxicological Review for n-Hexane [U.S. EPA, 2005a]). Therefore, the Ono et al. (1982) study was not selected as the principal study for the derivation of the RfC.

Mast et al. (1988a) exposed pregnant CD-1 mice (30/group) to 0, 200, 1000, and 5000 ppm n-hexane for 20 hours/day on gestational days (GDs) 6-17. The authors reported a significant increased number of late resorptions in mice exposed to 5000 ppm n-hexane. The effects noted are at only the high dose. The Mast et al. (1988a) study was not selected as the principal study for the derivation of the RfC because effects were noted only at a dose higher than doses where effects were observed in other studies.

Mast (1987) exposed pregnant Sprague-Dawley rats (30/group) to 0, 200, 1000, or 5000 ppm n-hexane for 20 hours/day on GDs 6-19. The authors observed a statistically significant reduction in fetal body weight gain in males at 1000 and 5000 ppm n-hexane exposure. A statistically significant increased incidence of reduced skeletal ossification of sternebrae 1-4

was also observed at 5000 ppm. This study identifies a developmental NOAEL of 200 ppm from these effects, but the range between the NOAEL and the next highest dose (1000 ppm) is considerable. This uncertainty in the dose response makes the selection of this study as the principal study questionable. Several additional studies have evaluated the effect of n-hexane exposure on the reproductive system and the developing fetus (Linder et al., 1992; Mast et al., 1988a, b; De Martino et al., 1987; Marks et al., 1980; Bus et al., 1979; Litton Bionetics Inc., 1979). In contrast to the studies by Mast (1987) and Mast et al. (1988a), these studies do not indicate that n-hexane exposure produces adverse reproductive and developmental effects. Nevertheless, BMD modeling was performed on the Mast (1987) data set. The results of the BMD modeling can be found in Section 5.2.2 and Appendix B of the Toxicological Review of n-Hexane (U.S. EPA, 2005a).

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 300.

A total uncertainty factor (UF) of 300 was applied to the point of departure of 215 mg/m^3: 10 for intraspecies variation (UF_H: human variability); 3 for interspecies differences (UF_A); 3 to extrapolate to chronic exposure from data in a less-than lifetime study (UF_S); and 3 to account for database deficiencies (UF_D).

An UF_H of 10 was applied to account for variations in susceptible subpopulations. One animal study suggests that weanling rats may be less susceptible to n-hexane-induced neurotoxicity than adult rats (Howd et al., 1983). Howd et al. (1983) compared the neurotoxicity of n-hexane in weanling versus young adult F344 rats, which were exposed to 0 or 1000 ppm n-hexane (95% pure) 24 hours/day, 6 days/week for 11 weeks. The authors observed significantly decreased grip strength and increased incidence of hindlimb paralysis in both weanling and adult rats. However, both endpoints appeared earlier and were of greater severity in adults compared to weanlings. The authors suggested that these differences in n-hexane-induced neurotoxicity may be due to smaller diameter and shorter axons in weanling compared to adult rats.

The CYP2E1 enzyme is responsible for metabolism of various aliphatic and aromatic hydrocarbons, solvents, and industrial monomers including n-hexane and acetone. Polymorphisms in CYP2E1 could possible lead to interindividual differences in the toxicity of chemicals metabolized by this enzyme. n-Hexane-induced neurotoxic effects are believed to be the result of metabolism of n-hexane to its toxic metabolite, 2,5-hexanedione, by the enzyme CYP2E1. In addition, differences in the development and maturity of phase I and phase II metabolic enzymes (specifically CYP2E1) between adults and children have been shown in several studies (Johnsrud et al., 2003; Ginsberg et al., 2002). Taken together, these

data suggest that differences in metabolism of n-hexane may exist within the human population and between adults and children.

Only one study with one dose group is available that directly observed susceptibility differences between adult and weanling animals (Howd et al., 1983). Several mode of action studies provide some evidence supporting the hypothesis that this increased susceptibility is because of differences in axonal length between adults and weanling rats. These studies did not directly observe effects of n-hexane on neurofilaments in weanling or young animals. Given the paucity of studies directly observing susceptibility differences between weanling and adult animals and the possibility of altered metabolic enzyme activity among individual humans and between adults and children, an UF_H of 10 was applied to account for variations in susceptible subpopulations.

An UF_A of 3 was applied to account for uncertainty in extrapolating from laboratory animals to humans. This value is adopted by convention where an adjustment from an animal-specific $BMCL_{ADJ}$ to a $BMCL_{HEC}$ already has been incorporated. Application of a full uncertainty factor 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 human equivalent concentration 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.

A UF_S of 3 was applied to extrapolate from subchronic to chronic exposure. A subchronic (16 weeks) study was used for the derivation of the RfC. However, 16 weeks is half of the time required for a newly synthesized neurofilament protein to be transported from the neuronal cell body to the axon terminal in the longest axons of the central nervous system and the peripheral nervous system of an adult rat (Griffin et al., 1984). The rate of neurofilament transport down an adult rat axon is 1 mm/day. The longest axons extend from the lumbar spinal cord to the hind foot and measure no more than 22 cm in the adult rat. Thus, transport for the full length of the axon would take approximately 32 weeks in an adult rat. Since the lifetime of neurofilaments (target of toxicity of n-hexane) is shorter than the lifetime of an adult rat, extrapolation from subchronic to chronic exposure is not necessary and an UF_S of 3 was applied.

A UF_D of 3 was applied to account for database deficiencies. The database includes many human occupational exposure studies (all with co-exposure to other potentially neurotoxic chemicals), subchronic animal studies in rats and mice, neurotoxicity studies in both humans and laboratory animals, and developmental studies in rats and mice following inhalation exposure to pure n-hexane. The database lacks a developmental neurotoxicity study and a multigeneration reproductive and developmental toxicity study following inhalation exposure

to pure n-hexane alone. Prenatal exposure to pure n-hexane induced skeletal anomalies, decreased fetal body weight, and increased resorptions, suggesting that the fetus may be affected by n-hexane inhalation exposure (Mast et al., 1988a; Mast 1987; Bus et al., 1979). One of these studies indicated a developmental NOAEL of 200 ppm for reduced fetal body weight gain (Mast, 1987). However, it remains unclear whether these developmental effects occur at doses lower than those that cause neurotoxicity. Studies investigating the reproductive and developmental effects of commercial hexane, a mixture containing approximately 50% n-hexane, are also available (see Section 4.4.2.2.3 of the Toxicological Review for n-Hexane [U.S. EPA, 2005a]). The studies with commercial hexane mixtures evaluated reproductive and developmental effects following exposure to doses of >= 500 ppm commercial hexane and resulted in marginal decreases in pup body weights and increased skeletal variations (BRRC, 1989a, b). Given the lack of a multigeneration reproductive and developmental studies following exposure to pure n-hexane and the uncertainty associated with low-dose developmental effects of exposure to n-hexane, an UF_D of 3 was applied.

An UF to account for the extrapolation from a LOAEL to a NOAEL was not applied because BMD modeling was used to determine the point of departure for derivation of the RfC.

I.B.4. Additional Studies/Comments (Inhalation RfC)

Several studies provide support for the selection of Huang et al. (1989) as the principal study and peripheral neuropathy as the critical effect. Specifically, studies in humans exposed to n-hexane levels in the workplace in a range of approximately 30-200 ppm (130-690 mg/m^3) n-hexane show effects associated with peripheral neuropathy, such as decreased MCV (Yucesoy et al., 1999; Karakaya et al., 1996; Chang et al., 1992; Huang et al., 1991; Yokoyama et al., 1990; Huang and Chu, 1989; Mutti et al., 1982a, b; Sanagi et al., 1980). No human studies are available where exposure was to n-hexane alone.

Sanagi et al. (1980) monitored the neurophysiological performance of 14 workers exposed to n-hexane and other solvents in the mixing and drying jobs at a factory producing tungsten carbide alloy. The workers were examined for signs of neurological deficits compared to 14 workers who were not exposed to any solvents in the same factory (Sanagi et al., 1980). The 22 breathing zone monitoring samples taken biannually over a 2-year period had an 8-hour time weighted average (TWA) of 58 ppm for n-hexane and 39 ppm for acetone. No other solvent concentrations were reported by the study authors. Compared to controls, exposed workers reported a significantly increased occurrence of headache, hearing deficits, dysesthesia in limbs, and muscle weakness. Exposed workers also showed an increased incidence of neurological signs relating to muscle strength and reduced vibration sensation of the radial nerve. Neurophysiological findings suggested a delayed recovery from a slowing of motor nerve conduction in the posterior tibial nerve.

Mutti et al. (1982a) compared MCVs in a group of 95 shoe factory workers exposed to a mixture of hydrocarbons containing n-hexane and 52 unexposed workers from the same factory. Exposed workers were divided into two groups based on hydrocarbon exposure. The mean TWA for n-hexane of the 108 breathing zone samples taken was 243 mg/m^3 (69 ppm) in the mid-exposure group and 474 mg/m^3 (134 ppm) in the high-exposure group. When the severity of neurological symptoms was compared, there was a gradation in response between the exposed groups, both of which displayed more severe symptoms than the controls.

Numerous additional occupational exposure studies involved exposure to other solvents including n-hexane. These studies indicate neurological symptoms predominate, including the impairment of color vision (Gobba and Cavalleri, 2003; Iregren et al., 2002; Issever et al., 2002; Seppalainen et al., 1979; Raitta et al., 1978) and the onset of symptoms similar to Parkinson's disease (Canesi et al., 2003; Vanacore et al., 2000; Hageman et al., 1999; Pezzoli et al., 1996, 1995, 1989).

Despite the large number of human inhalation exposure studies for n-hexane, these studies are considered inappropriate for dose-response assessment. The available occupational exposure studies and case reports contain insufficient data on the duration or concentration of n-hexane exposure and are confounded by co-exposure to other solvents including solvents that may potentiate n-hexane-induced toxicity. A variety of solvents such as toluene, methyl ethyl ketone, acetone, and xylene have been shown to potentiate n-hexane-induced neurotoxicity (see Section 4.4.3 of the Toxicological Review of n-Hexane [U.S. EPA, 2005a]). For example, it is possible that the incidence or severity of the neurological changes observed by Sanagi et al. (1980) may have been a result of co-exposure to both n-hexane and acetone. Supporting evidence for such an association comes from studies indicating that acetone may affect n-hexane metabolism, neurotoxicity, and reproductive toxicity following exposure to 2,5-hexanedione (Cardona et al., 1996; Ladefoged et al., 1994; Larsen et al., 1991; Ladefoged et al., 1989). A study in humans showed that acetone concentrations in the workplace significantly correlated with the ratio of urinary n-hexane metabolites (specifically 2,5-hexanedione) to n-hexane air concentrations (Cardona et al., 1996). It has been suggested that induction of n-hexane metabolism by acetone may potentiate neurotoxicity by decreasing the elimination of 2,5-hexanedione. For example, studies in rodents have shown that co-exposure to acetone and 2,5-hexanedione increases the concentration of 2,5-hexanedione in the sciatic nerve compared to administration of 2,5-hexanedione alone (Zhao et al., 1998; Ladefoged and Perbellini, 1986). In addition, acetone has been shown to induce CYP2E1, one of the enzymes showed to be involved in the metabolism of n-hexane to its toxic metabolite 2,5-hexanedione in rats (see Section 3.3 of the Toxicological Review of n-Hexane [U.S. EPA, 2005a]; Patten et al., 1986). Thus, co-exposure to acetone may induce CYP450 enzymes and increase the production of the neurotoxic metabolite, 2,5-hexanedione.

Oral co-exposure studies in rats further support acetone potentiation of n-hexane neurotoxicity (see Section 4.4.3 of the Toxicological Review of n-Hexane [U.S. EPA, 2005a]). Ladefoged et al. (1994, 1989) exposed male rats to 2,5-hexanedione alone and 2,5-hexanedione plus acetone in drinking water for 6 weeks and evaluated neurological and behavioral endpoints. Rats exposed to 2,5-hexanedione alone and 2,5-hexanedione plus acetone showed decreased balance time on a rotating rod, altered behavior (ambulation, grip strength, and rearing), decreased MCV, and increased giant axonal swelling of the sciatic nerve. The authors stated that these effects were greater in severity in the rats co-exposed to 2,5-hexanedione plus acetone compared with those exposed to 2,5-hexanedione. In addition, Larsen et al. (1991) suggested that co-exposure to acetone and 2,5-hexanedione may contribute to irreversible damage to the testis and male infertility in rats. Taken together, the data suggest that acetone may alter n-hexane metabolism and potentiate n-hexane-induced neurotoxicity and reproductive toxicity. Accordingly, a reliable effects level cannot be identified from the available reports of occupational exposure.

Studies in animals also provide support for the selection of Huang et al. (1989) as the principal study. In a follow-up study, Huang et al. (1992) observed an overall reduction in MCV in rats exposed to 2000 ppm n-hexane, 12 hours/day, 6 days/week for a total of 24 weeks, with the onset of neurophysiological deficits most evident in the distal segment of the sciatic nerve. Other sections of the central and peripheral nervous systems were comparatively unaffected.

Altenkirch et al. (1982) exposed male Wistar rats (five/group) to 0, 500, or 700 ppm n-hexane for up to 9 weeks. Clinical signs included excessive salivation and an increase in paralysis of the hind limbs. The time for this condition to develop was shorter in those rats exposed to the higher concentrations of n-hexane and to the mixtures. Histopathological examinations of the peripheral nerves showed the presence of axonal swellings, especially at the branches of the tibial and ischiatic nerves. A breakdown of axons and myelin developed distal to the axonal swellings, with an apparent intra-axonal accumulation of neurofilaments. Other morphological findings included axonal swellings of the gracile tract of the spinal cord, especially at the level of the gracile nucleus in the medulla oblongata.

Howd et al. (1983), Pryor et al. (1983), and Ichihara et al. (1998) all used single concentrations of n-hexane in the 1000-2000 ppm range to induce neurophysiological deficits and/or behavioral changes in F344 or Wistar rats exposed to n-hexane. Data from the Chemical Industry Institute of Toxicology's 13-week toxicological study in F344 rats exposed to n-hexane (0, 3000, 6500, 10,000 ppm, respectively) confirmed the neuropathological responses to the n-hexane based on the appearance of paranodal swellings of the tibial nerves in mid- and high-dose males (Cavender et al., 1984a, b).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Data Base — Medium
RfC — Medium

The overall confidence in this RfC assessment is medium. Confidence in the principal study (Huang et al., 1989) is medium; it involves a comparatively low but acceptable number of animals per group (eight/sex) and reports behavioral deficits, neurophysiological changes, and neuropathological effects within a dose range in which both a NOAEL and LOAEL could be identified. Numerous studies both in humans and laboratory animals support the selection of the nervous system as the target of n-hexane-induced toxicity. Confidence in the database is medium. The database lacks chronic exposure information on the pure compound via any route of exposure, a multigenerational developmental and reproductive toxicity study, and a developmental neurotoxicity study. The subchronic inhalation study of Huang et al. (1989) satisfies the minimum inhalation database requirements for deriving an RfC for n-hexane. Reflecting medium confidence in the principal study and medium confidence in the database, confidence in the RfC is medium.

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 Inhalation RfC

Source Document — U.S. EPA, 2005a

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 n-Hexane (U.S. EPA, 2005a). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Panel Peer Review and Public Comments and Disposition (PDF)***

Agency Completion Date -- 12/23/2005

I.B.7. EPA Contacts (Inhalation RfC)

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 — n-Hexane
CASRN — 110-54-3
Section II. Last Revised — 12/23/2005

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, 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 (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, 2005b), there is *inadequate information to assess the carcinogenic potential of n-hexane*. Specifically, there are no available animal carcinogenicity studies examining exposure to n-hexane and there is a single human study (Beall et al., 2001) where workers were chronically exposed to mixtures containing n-hexane along with other chemicals. A 2-year carcinogenicity bioassay in mice

and rats exposed to a mixture containing various hydrocarbons, including n-hexane, showed an increased incidence of liver tumors in female mice (Daughtrey et al., 1999; Biodynamics, 1993a, b). Daughtrey et al. (1999) observed an increased incidence of combined hepatocellular adenomas and carcinomas in female mice exposed to the highest dose of a mixture containing n-hexane (commercial hexane). In addition, the study authors identified a statistically significant trend for increased incidence of pituitary adenomas in female mice exposed to commercial hexane. Studies indicate that n-hexane is mostly nongenotoxic in short-term testing protocols. n-Hexane showed a minimal response in *Saccharomyces cerevisiae* D61.M (Mayer and Goin, 1994) and induced an increased incidence in the number of chromosomal mutations in albino rat bone marrow cells (Hazleton Laboratories, 1992). Also, the low pKa of exocyclic amino functional groups of DNA (<5) would preclude reaction with 2,5-hexanedione to yield pyrrole adducts. Thus, these data suggest a lack of mutagenic potential of n-hexane. The available studies in humans as well as laboratory animals are inadequate for cancer risk assessment. The 1990 IRIS assessment did not contain a characterization of the carcinogenic potential of n-hexane in humans.

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 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Only one of the occupational exposure studies on n-hexane has inferred a possible association between n-hexane and increased cancer incidence (Beall et al., 2001). Beall et al. (2001) conducted a nested case control study evaluating the relationship between the occurrence of intracranial tumors among employees at a petrochemical plant and exposure to various chemicals including n-hexane. The study authors selected subjects from approximately 2595 plant workers. The workers were mailed questionnaires that evaluated work history in the plant, and a total of 12 cases of intracranial tumors, which developed after hire dates at the plant, were identified from the respondents. All cases were confirmed by review of medical records and pathology specimens by four neuropathologists.

The authors showed that the odds ratio (OR) for self-reported exposure to n-hexane was statistically significantly elevated (OR, infinity), with a confidence interval (CI) of 1.4-infinity (6 cases and 26 controls evaluated) for gliomas. The OR for potential exposure to n-hexane based on job-related exposure estimates was 2.3 (CI, 0.4-13.7; 4 cases and 26 controls evaluated) for gliomas. Analyses by duration indicated a statistically significantly elevated OR of 16.2 (CI, 1.1-227.6; 2 cases and 2 controls evaluated) for potential long-term use of n-

hexane (> 48 months) for gliomas. No relationship was found between exposure to n-hexane and the occurrence of intracranial tumors. While the results of this study indicated that exposure to n-hexane may have contributed to the occurrence of brain tumors, specifically gliomas, the small number of cases, the large number of chemicals to which the employees were potentially exposed, and the high correlation between some of the parameters because of co-exposure to several other chemicals do not permit a conclusion about carcinogenicity from exposure to n-hexane alone.

II.A.3. Animal Carcinogenicity Data

In laboratory animals exposed for 2 years via inhalation to a commercial hexane mixture containing n-hexane (0, 900, 3000, 9000 ppm), there was a statistically significant increase in hepatocellular combined adenomas and carcinomas (7/50, 8/50, 9/49, 16/50, respectively) in female B6C3F1 mice (Daughtrey et al., 1999; Biodynamics, 1993a, b). This increase was not observed in male mice or in either sex of F344 rats exposed to commercial hexane under the same conditions.

Because commercial hexane is a variable mixture of hydrocarbons of which only about 52% is n-hexane, the use of commercial hexane as a toxicological surrogate for the qualitative and quantitative effects of pure n-hexane may be unjustified.

II.A.4. Supporting Data for Carcinogenicity

n-Hexane has shown little evidence of mutagenic activity in a number of short-term test systems. In vitro tests showed that n-hexane was not genotoxic in the salmonella (Ames) assay (with or without activation), did not cause DNA damage of *Escherichia coli* or *Bacillus subtilis*, and was negative for chromosomal aberrations in Chinese hamster ovary cells and forward mutations in the mouse lymphoma L5178 $tk^{+/-}$ assay (Daughtrey et al., 1994; Hazleton Laboratories, 1992; NTP, 1991; Houk et al., 1989; Mortelmans et al., 1986; Ishidate et al., 1984; McCarroll et al., 1981a, b). n-Hexane was marginal for inducing chromosome loss in the DNA of *S. cerevisiae* D61M (Mayer and Goin, 1994). In *in vivo* tests, n-hexane was negative for inducing dominant lethal mutations in CD-1 mice (Mast et al., 1988b; Litton Bionetics, 1980). Furthermore, n-hexane was unable to induce chromosomal aberrations and micronuclei in bone marrow cells of B6C3F1 mice injected intraperitoneally with n-hexane (Shelby and Witt, 1995). n-Hexane did not increase the incidence of sister chromatid exchanges in mouse bone marrow cells (NTP, 1991). Hazleton Laboratories (1992) recorded a slight, but significant, increase in the number of chromosomal mutations due to n-hexane exposure in albino rat bone marrow cells.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not applicable.

II.B.1. Summary of Risk Estimates

Not applicable.

II.B.2. Dose-Response Data

Not applicable.

II.B.3. Additional Comments

Not applicable.

II.B.4. Discussion of Confidence

Not applicable.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

Not applicable.

II.C.2. Dose-Response Data

Not applicable.

II.C.3. Additional Comments

Not applicable.

II.C.4. Discussion of Confidence

Not applicable.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2005a

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 n-Hexane (U.S. EPA, 2005a). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Panel Peer Review and Public Comments and Disposition (PDF)***.

II.D.2. EPA Review

Agency Completion Date -- 12/23/2005

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 — n-Hexane
CASRN — 110-54-3

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

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U.S.EPA. (2005b) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001F. Available from: http://www.epa.gov/iris/backgrd.html.

VII. Revision History

Substance Name — n-Hexane
CASRN — 110-54-3
File First On-Line 07/01/1990

Date	Section	Description
07/01/1990	I.B.	Inhalation RfC summary on-line
12/03/2002	I.B.6.	Screening-Level Literature Review Findings message has been added.
12/23/2005	I., II, VI	New RfD, RfC and cancer assessment.

VIII. Synonyms

Substance Name — n-Hexane
CASRN — 110-54-3
Section VIII. Last Revised — 12/23/2005

- 110-54-3
- n-Hexane
- Hexyl hydride
- Skellysolve B
- NCI-C60571