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## **n-Hexane**

**CAS Registry Number: 110-54-3**

Prepared by  
Bernard J. Kadlubar, M.S.  
Toxicology Section

## **Revision History**

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Revised DSD September 14, 2015: the odor-based value was withdrawn because n-hexane does not have a pungent, disagreeable odor (TCEQ 2015).

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## Chapter 1 Summary Table

Table 1 provides a summary of health- and welfare-based values based on an acute and chronic evaluation of n-hexane. Table 2 provides summary information on n-hexane's physical/chemical data.

**Table 1 Health- and Welfare-Based Values**

Short-Term Values	Concentration	Notes
<sup>acute</sup> ESL <sub>generic</sub> [1 h]	6,200 µg/m <sup>3</sup> (1,800 ppb)* <b>Short-Term ESL for Air Permit Reviews</b>	Tier II Generic Health-Based ESL.
Acute ReV	---	A generic ESL was developed since the minimum database for an acute ReV was not met.
<sup>acute</sup> ESL <sub>veg</sub>	---	No data of sufficient quality available.
<sup>acute</sup> ESL <sub>odor</sub>	---	Gasoline-like odor.
Long-Term Values	Concentration	Notes
<sup>chronic</sup> ESL <sub>nonlinear(nc)</sub> (HQ = 0.3)	200 µg/m <sup>3</sup> (57 ppb) <b>Long-Term ESL for Air Permit Reviews</b>	Critical Effect: Peripheral neuropathy in occupational workers from an offset printing factory.
Chronic ReV (HQ = 1)	670 µg/m <sup>3</sup> (190 ppb)*	Critical Effect: Peripheral neuropathy in occupational workers from an offset printing factory.
<sup>chronic</sup> ESL <sub>linear(c)</sub> <sup>chronic</sup> ESL <sub>nonlinear(c)</sub>	---	There is insufficient evidence that hexane has carcinogenic potential.
<sup>chronic</sup> ESL <sub>veg</sub>	---	No data found.

\* Values that may be used for evaluation of air monitoring data

Abbreviations used: **ppm**, parts per million, **ppb**, parts per billion; **µg/m<sup>3</sup>**, micrograms per cubic meter; **h**, h; **ESL**, Effects Screening Levels; **ReV**, Reference Value; <sup>acute</sup>ESL<sub>generic</sub>, Tier II generic health-based ESL; <sup>acute</sup>ESL<sub>odor</sub>, acute odor-based ESL; <sup>acute</sup>ESL<sub>veg</sub>, acute vegetation-based ESL; <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub>, chronic health-based ESL for nonlinear dose-response noncancer effects; <sup>chronic</sup>ESL<sub>linear(c)</sub>, chronic health-based ESL for linear dose-response cancer effect; <sup>chronic</sup>ESL<sub>nonlinear(c)</sub>, chronic health-based ESL for nonlinear dose-response cancer effect; and <sup>chronic</sup>ESL<sub>veg</sub>, chronic vegetation-based ESL

**Table 2 Chemical and Physical Data**

Parameter	Value	Reference
Molecular Formula	C <sub>6</sub> H <sub>14</sub>	Chemfinder, 2004
Chemical Structure		Chemfinder, 2004
Molecular Weight	86.1766	TRRP, 2006
Physical State	Liquid	TRRP, 2006
Color	Colorless	Chemfinder, 2004
Odor	Gasoline type	Chemfinder, 2004
CAS Registry Number	110-54-3	TRRP, 2006
Synonyms	Hexane/mixed isomers, Hexanes, n-Hexane, dipropyl, gettysolve-b, Hex, Hexyl hydride, n-Hexane ; Normal hexane, skellysolve B	Chemfinder, 2004
Solubility in water, mg/L	13.0 mg/L	TRRP, 2006
Log P <sub>ow</sub> or K <sub>ow</sub>	3.9	Chemfinder, 2004
Vapor Pressure	153 mm Hg at 25°C	HSDB, 2005
Relative Vapor Density	0.2 cm <sup>2</sup> /s	TRRP, 2006
Density	0.670 at 25°C	HSDB, 2005
Melting Point	-95°C to -100°C	Chemfinder, 2004
Boiling Point	69°C	Chemfinder, 2004
Conversion Factors	1 µg/m <sup>3</sup> = 0.284 ppb 1 ppb = 3.52 µg/m <sup>3</sup>	Toxicology Section

## **Chapter 2 Major Uses or Sources**

n-Hexane (hexane) is a solvent that has many uses in the chemical and food industries, either in pure form or as a component of the commercial hexane mixture. Highly purified hexane is primarily used as a reagent for chemical or chromatographic separations. Commercial hexane is a mixture that contains approximately 52% hexane; the balance is made up of varying amounts of structural isomers and related chemicals, such as methylpentane and methylcyclopentane. Mixtures containing hexane are also used in the extraction of edible fats and oils in the food industry, as cleaning agents in textile and furniture manufacturing, and in the printing industry. Hexane is the solvent base for many commercial products, such as glues, cements, paint thinners, and degreasers. The chemical is a minor constituent of crude oil and natural gas and, therefore, represents a variable proportion of different petroleum distillates. For example, hexane comprises about 11.6% of unleaded gasoline and about 2% of JP-4 aviation fuel (ATSDR, 1993b, 1999, USEPA 2005).

The most probable route of human exposure to hexane is by inhalation. Individuals are most likely to be exposed to hexane in the workplace; however, monitoring data indicate that hexane is a widely occurring atmospheric pollutant. Exposure from contact with vapors or emissions from heating and motor fuels refined from petroleum products is the most widespread form of low-level exposure for the general population. Most hexane in these fuels is oxidized, or destroyed, as part of the combustion process to provide heat or drive internal combustion engines. Small amounts of hexane, along with other petroleum compounds, volatilize to the atmosphere during handling, storage in fuel tanks, or through incomplete combustion. Recent research suggests that certain fungi may be able to produce hexane. These fungi may be common in older buildings, and in some parts of the country may provide exposures from previously unsuspected indoor sources. (ATSDR 1993a, 1999, NSC 2003).

## **Chapter 3 Acute Evaluation**

### ***3.1 Health-Based Acute ESL***

A narcotic effect was observed in mice after 10 minutes of inhalation exposure to 30,000 ppm hexane (Swann et al. 1974). In another study, a no-observed-adverse-effect-level (NOAEL) of 500 ppm was reported after a 5-minute inhalation exposure in an unidentified test species (Wayne and Orcutt 1960). Iba and Bird (2007) reported that rats exposed to 1,000 ppm for 6 h experienced no adverse health effects when compared to other treatment groups. This study did not clearly identify a NOAEL for hexane exposure as the purpose of the study was to examine the effects of co-exposure of rats to hexane and the 1,3-butadiene metabolite, 3-butene-1,2-diol. However, the findings of the Iba and Bird (2007) study add further evidence to the relatively nontoxic nature of hexane. None of the aforementioned studies were suitable to determine a point-of-departure (POD) that could be utilized for the derivation of an acute reference value (ReV). The minimum data requirement for the estimation of an acute ReV was not met; therefore

the protocol outlined in Section 3.6.2 of the ESL guidance document entitled *Tier II Generic ESL: Threshold of Concern and LC<sub>50</sub> Data Approaches* was implemented to estimate a Tier II generic ESL (TCEQ 2006).

### 3.1.1. Threshold of Concern (TOC) Approach

Hexane is a colorless liquid with a moderately high vapor pressure and is classified as a vapor for inhalation exposure. If the Threshold of Concern (TOC) categorization scheme outlined in Section 3.6.2.3 of the ESL guidelines were to be used, hexane would be classified as a Category V compound based on the Globally Harmonized System of Classification and Labeling of Chemicals (UN 2005) and be assigned a Tier II <sup>acute</sup>ESL<sub>generic</sub> of 1,000 µg/m<sup>3</sup>.

### 3.1.2. NOAEL-to-LC<sub>50</sub> (N-L) Ratio Approach

Studies that determined a concentration lethal to 50% of the study specimens (LC<sub>50</sub>) were used in this method. The following acute hexane toxicity data acquired from the Registry of Toxic Effects of Chemical Substances (RTECS) database were used:

- 4 h LC<sub>50</sub> in rats = 170,000 mg/m<sup>3</sup>
- 2 h LC<sub>50</sub> in mice = 150,000 mg/m<sup>3</sup>

As stated in Section 3.2.2 of the ESL guidelines (TCEQ 2006), a duration adjustment of LC<sub>50</sub> data is required for exposure durations less than 4 h. The mode of action is unknown, therefore in accordance with the ESL guidelines (TCEQ 2006), a default factor of n=1 was used for the acute exposure duration adjustment of the 2 h LC<sub>50</sub> data in mice using the following formula:

$$\begin{aligned}C_1 \times T_1 &= C_2 \times T_2 \\150,000 \text{ mg/m}^3 \times 2 \text{ h} &= C_2 \times 4 \text{ h} \\C_2 &= (150,000 \text{ mg/m}^3) \times (2/4) \\C_2 &= 75,000 \text{ mg/m}^3\end{aligned}$$

In order to calculate a generic ESL below which there would not be expected to be an appreciable risk for adverse health effects, a LC<sub>50</sub> value that has been adjusted to a 4-h exposure was multiplied by a N-L ratio of 8.3x10<sup>-5</sup> that was developed by Grant et al. (2007). See the formula below:

#### 4 h LC<sub>50</sub> in rats:

Tier II generic ESL = 4- h LC<sub>50</sub> x N-L ratio

Tier II generic ESL = 170,000 mg/m<sup>3</sup> x (8.3x10<sup>-5</sup>)

Tier II generic ESL = 14 mg/m<sup>3</sup> = 14,000 µg/m<sup>3</sup> = 4,000 ppb

#### Adjusted 4-h LC<sub>50</sub> in mice:

Tier II generic ESL = 4- h LC<sub>50</sub> x N-L ratio

Tier II generic ESL = 75,000 mg/m<sup>3</sup> x (8.3x10<sup>-5</sup>)

Tier II generic ESL = 6.2 mg/m<sup>3</sup> = 6,200 µg/m<sup>3</sup> = 1,800 ppb

The generic ESL of 6,200 µg/m<sup>3</sup> based on the adjusted 4-h LC<sub>50</sub> in mice will be used as the N-L ratio generic ESL because it is more conservative than the generic ESL of 14,000 µg/m<sup>3</sup> based on the rat 4-h LC<sub>50</sub> data.

### 3.1.3. Final Tier II Generic ESL

The TOC generic ESL is 1,000 µg/m<sup>3</sup> whereas the N-L ratio generic ESL is 6,200 µg/m<sup>3</sup>. A weight-of-evidence approach was used to determine which generic ESL was best supported by the experimental data. The experimental methods for the lethality studies reported in RTECS are unknown which makes the confidence in the validity of these values low. However, the toxicity studies of Swann et al. (1974), Wayne and Orcutt (1960), and Iba and Bird (2007) indicate hexane is relatively non-toxic. In addition, the chemical structure of hexane indicates that it is relatively non-toxic based on the Cramer classification scheme. The Cramer classification scheme is a well-known approach for classifying chemical toxicity based on chemical structure and recognized pathways for metabolic activation and deactivation (Cramer 1978). Although this classification scheme was originally developed for oral toxicity, it does contribute to the weight-of-evidence to indicate whether or not the chemical structure presents a potential concern regarding toxicity. The Cramer classification scheme places a particular substance, or chemical, in one of three classes. Class I substances have simple chemical structure with known metabolic pathways and produce innocuous end products. Class II contains substances with chemical structures associated with intermediate toxicity. Class III substances possess structural features associated with significant toxicity. Based on the Cramer classification scheme, hexane is classified as a Cramer Class I chemical (Toxtree v1.20).

Therefore, based on the weight-of-evidence, the N-L Ratio <sup>acute</sup>ESL<sub>generic</sub> of 6,200 µg/m<sup>3</sup> (1,800 ppb) was identified as the health-based <sup>acute</sup>ESL. This generic ESL will also be utilized during evaluation of air monitoring data in lieu of a ReV until data are available to derive a hexane-specific ReV, or a sufficient database of related chemicals has been developed under the new ESL guidelines to use a relative potency approach (TCEQ 2006).

## 3.2. Welfare-Based Acute ESLs

### 3.2.1 Odor Perception

Hexane is a colorless liquid that has an associated gasoline-like odor. A 50% odor detection threshold value of 5,300 µg/m<sup>3</sup> (1,500 ppb) was reported for hexane by Nagata (2003) utilizing the triangular odor bag method. Since hexane does not have a pungent or disagreeable odor, an <sup>acute</sup>ESL<sub>odor</sub> was not developed (TCEQ 2015).

### 3.2.2 Vegetation Effects

Haagen-Smit et al (1952) conducted a screening study on the effects of hexane on spinach (*Spinacia oleracea*), endive (*Cichorium endivia*), beets (*Beta vulgaris*), oats (*Avena sativa*), and alfalfa (*Medicago sativa*). Fumigations in this study were conducted in a small glass chamber with a 353 L capacity at concentrations of 25 ppm or greater for a minimum exposure duration of five h. No damage was observed as a result of exposure to hexane at 25 ppm and was designated as a NOAEL. According to the ESL guidelines (TCEQ 2006), TS determined an acute-vegetation ESL of 25 ppm as a threshold concentration from the study. However, as the reported vegetative effects were significantly above other health- and odor-based concentrations and the study was of insufficient quality, an  $^{\text{acute}}\text{ESL}_{\text{veg}}$  was not developed for hexane.

### 3.3 Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following acute value:

- $^{\text{acute}}\text{ESL}_{\text{generic}} = 6,200 \mu\text{g}/\text{m}^3$  (1,800 ppb)

The short-term ESL for air permit evaluations is the  $^{\text{acute}}\text{ESL}_{\text{generic}}$  of  $6,200 \mu\text{g}/\text{m}^3$  (1,800 ppb) (Table 1). The  $^{\text{acute}}\text{ESL}_{\text{generic}}$  of  $6,200 \mu\text{g}/\text{m}^3$  (1,800 ppb) is used for the evaluation of air monitoring data (Table 1).

## Chapter 4 Chronic Evaluation

### 4.1. Noncarcinogenic Potential

#### 4.1.1 Physical/Chemical Properties and Key Studies

Hexane is a colorless liquid with a moderately high vapor pressure and is classified as a vapor for inhalation exposure. The main chemical and physical properties are summarized in Table 2. There is not sufficient data to link exposure of hexane to a carcinogenic endpoint. In addition, inconclusive data exists regarding the exact nature of the dose-response relationship associated with hexane and its toxic endpoints in regards to the dose-response relationship. Therefore, hexane is classified as a noncarcinogen and the default nonlinear approach was used.

Based on reports from both human and animal studies, the most sensitive toxic endpoint resulting from hexane exposure is peripheral neuropathy, which is a condition characterized by loss of sensation and muscular control (Yamada S. 1967, Yamamura Y. 1969, Schaumberg and Spencer 1976, Seppalainen et al. 1979, Sanagi et al. 1980, Dunnick et al. 1989, Huang et al. 1989, Daughtrey et al. 1999). The human occupational inhalation study by Chang et al. (1993) was selected as the key study used for the derivation of the  $^{\text{chronic}}\text{ESL}$  and the rodent inhalation study by Miyagaki (1967) was selected as a supporting study. Both studies were well-conducted and hexane-induced peripheral neuropathy was the toxic-endpoint of interest in each study. However, the Chang et al. (1993) study was chosen as the key study because it was of sufficient

quality and was conducted in humans, thus removing the uncertainty involved with extrapolating from animal to human.

In the Chang et al (1993) study, symptomatic peripheral neuropathy was reported in 20 of 56 workers (36% of workers) in an offset printing factory and another 26 workers (approximately 46%) had evidence of subclinical neuropathy. Other reported effects included reductions in both sensory and action potentials, decreases in motor nerve conduction velocity and increased distal latency. In one severe case, a sural nerve biopsy revealed giant axonal swellings with accumulation of 10 nm neurofilaments, myelin sheath attenuation, and widening of nodal gaps. Optic neuropathy and CNS impairment were not common among the 56 workers evaluated in this study. Personal air samples were used to determine a range of hexane exposure concentrations of 80 to 210 ppm, with a mean of 132 ppm. At this particular factory, the workers worked 12 hs/day, 6 days/wk, and the mean duration of employment was 2.6 years, with a range of 1 month to 30 years. The range of employment duration provided sufficient exposure durations to classify the Chang et al. (1993) study as a chronic study. The mean hexane exposure concentration of 132 ppm determined in this study was designated as a lowest-observed-adverse-effect-level (LOAEL).

In the Miyagaki (1967) study, 6 groups of 10 male SM mice, a transgenic strain of mice, were housed in a gas-chamber and were exposed to 0, 100, 250, 500, 1,000, or 2,000 ppm hexane for 24 hs/day, 6 days/wk for one year. The purity level of the hexane used in this study, which is approximately 70%, is comparable to the composition used in most industry applications. It was determined that animals exposed to 250 ppm of hexane or higher for one year exhibited symptoms of peripheral neuropathy, such as abnormal posture, muscular atrophy, and various endpoints resulting from electrophysiological tests assessed nerve conductivity and muscle responses in mice. Based on the findings of this study by Miyagaki (1967), the 100 ppm treatment group showed no signs of physical impairment; therefore, this was designated as the NOAEL for this study.

#### **4.1.2 Mode-of-Action (MOA) Analysis and Dose Metric**

The metabolism of hexane takes place in the liver. The initial reaction is oxidation of hexane by cytochrome P-450 2E1 (CYP2E1) to hexanols, predominantly 2-hexanol. Further reactions convert 2-hexanol to 2-hexanone, 2,5-hexanediol, 5-hydroxy-2-hexanone, 4,5-dihydroxy-2-hexanone and the neurotoxicant 2,5-hexanedione. Hydroxylation at the 1- and 3- positions can be considered detoxification pathways; hydroxylation at the 2- position is a bioactivation pathway (ATSDR 1999). The proposed toxic moiety of hexane that induces peripheral neuropathy is 2,5-hexanediol. However, the precise mechanism by which hexane induces its critical effect as well as its complete metabolic pathway has not been clearly defined.

Data on exposure concentration of the parent chemical is available in both the Chang et al. (1993) study and the Miyagaki (1967) study. Since the MOA of the toxic response is not fully understood and data on other more specific dose metrics are not available (e.g. blood

concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue), exposure concentration of parent chemical will be used as the default dose metric.

### 4.1.3 Points-of-Departure (PODs) for Key and Supporting Studies and Dosimetric Adjustment

The LOAEL of 132 ppm reported in the Chang et al. (1993) key study and the NOAEL of 100 ppm reported in the Miyagaki (1967) supporting study were used to derive <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub>.

#### 4.1.3.1 Chang et al. (1993) Study

The occupational POD (POD<sub>oc</sub>) from the Chang et al. (1993) study was adjusted to a POD that is representative of a human equivalent concentration applicable to the general population (POD<sub>HEC</sub>) according to section of 4.2.1 of the ESL guidelines (TCEQ 2006) by using the following dosimetric adjustment formula:

$$\text{POD}_{\text{HEC}} = \text{POD}_{\text{OC}} \times (\text{VE}_{\text{ho}}/\text{VE}_{\text{h}}) \times (\text{days per week}_{\text{oc}}/\text{days per week}_{\text{res}})$$

where: VE<sub>ho</sub> = occupational ventilation rate for an eight-hr day (10 m<sup>3</sup>/day)

VE<sub>h</sub> = non-occupational ventilation rate for a 24-hr day (20 m<sup>3</sup>/day)

days per week<sub>oc</sub> = occupational weekly exposure frequency (study specific)

days per week<sub>res</sub> = residential weekly exposure frequency (7 days per week)

In the formula listed above, the default occupational ventilation rate of 10 m<sup>3</sup>/day was determined for an eight- h work day, and the workers in the Chang et al. (1993) study worked 12- h per day. However, based on scientific judgment, use of the default ventilation rate based on an eight- h work day was considered conservative for use in the derivation of POD<sub>HEC</sub>.

$$\text{Chang et al. (1993) POD}_{\text{HEC}} = 132 \text{ ppm} \times (10/20) \times (6/7) = 57 \text{ ppm}$$

#### 4.1.3.2 Miyagaki (1967) Study

The animal POD from the Miyagaki (1967) study was adjusted to a POD associated with continuous exposure scenario, or POD<sub>ADJ</sub>, as outlined in section 4.2.2 of the guidelines (TCEQ 2006) by using the following formula:

$$\text{POD}_{\text{ADJ}} = \text{POD} \times (\text{D}/24 \text{ h}) \times (\text{F}/\text{days})$$

where: D = Exposure duration, h per day

F = Exposure frequency, days per week

$$\text{Miyagaki (1967) POD}_{\text{ADJ}} = 100 \text{ ppm} \times (24/24) \times (6/7) = 86 \text{ ppm}$$

Hexane is insoluble in water and produces remote effects. Therefore, hexane is treated as a Category 3 vapor. The  $POD_{ADJ}$  was then adjusted to a  $POD_{HEC}$  in accordance with section 2.9.1 of the guidelines (TCEQ 2006) by using the following formula:

$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H)$$

where:  $H_{b/g}$  = ratio of the blood:gas partition coefficient

A = animal

H = human

For hexane, the blood:gas partition coefficients for rats and humans are 2.29 (Gargas et al. 1989) and 0.8 (Perbellini et al., 1985), respectively. According to the RfC methodology (USEPA, 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 (USEPA 1994).

$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H) = 86 \text{ ppm} \times 1 = 86 \text{ ppm}$$

Miyagaki (1967)  $POD_{HEC} = 86 \text{ ppm}$

#### 4.1.4 Selection of Critical Effect and Adjustment of $POD_{HEC}$

The MOA by which hexane produces peripheral neuropathy is not understood (Section 4.1.2), so the default for noncarcinogenic effects is to determine a POD and apply UFs to extrapolate from the POD to lower concentrations (i.e., assume a nonlinear MOA) in order to calculate a ReV.

To calculate chronic ReVs using both the Chang et al. (1993) and Miyagaki (1967) study, the  $POD_{HEC}$  calculated from each study was divided by the appropriate uncertainty factors (UFs). The Chang et al. (1993)  $POD_{HEC}$  was divided by: 1) LOAEL-to-NOAEL UF ( $UF_L$ ) of 10 to account for the uncertainty of extrapolating from a LOAEL to a NOAEL 2) an intraspecies UF ( $UF_H$ ) of 10 to account for variation in sensitivity among the members of the human population and 3) a database UF ( $UF_D$ ) of 3 to account for deficiencies in the available database (e.g. lack of two-generation reproductive/developmental studies):

$$ReV = POD_{HEC} / (UF_L \times UF_H \times UF_D) = 57 \text{ ppm} / (10 \times 10 \times 3) = 0.19 \text{ ppm}$$

$$ReV = 0.19 \text{ ppm} = 190 \text{ ppb} = 670 \mu\text{g}/\text{m}^3$$

The Miyagaki (1967)  $POD_{HEC}$  was divided by: 1) an interspecies uncertainty factor ( $UF_A$ ) of 3 for extrapolation from animals to humans because default dosimetric adjustments from animal-to-human exposure were conducted which accounts for toxicokinetic differences but not toxicodynamic differences, 2) a  $UF_H$  of 10 to account for variation in sensitivity among the members of the human population and 3) a  $UF_D$  of 3 to account for inconsistencies in the available database (e.g. lack of two-generation reproductive/developmental studies):

$$ReV = POD_{HEC} / (UF_A \times UF_H \times UF_D) = 86 \text{ ppm} / (3 \times 10 \times 3) = 0.86 \text{ ppm}$$

ReV = 0.86 ppm = 860 ppb

The ReV of 190 ppb based on the Chang et al. (1993) human study is used as the key study because it is more conservative than the ReV of 860 ppb based on the Miyagaki (1967) mice study.

#### **4.1.5 Health-Based Chronic ReV and <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub>**

The chronic ReV of 190 ppb ( $670 \mu\text{g}/\text{m}^3$ ) was rounded to two significant figures in accordance with our ESL guidelines (TCEQ 2006). The rounded chronic ReV was then used to calculate the <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub> by using the following formula and a hazard quotient (HQ) of 0.3 (Table 3):

$$\text{chronic ESL}_{\text{nonlinear(nc)}} = \text{chronic ReV} \times \text{HQ}$$

$$\text{chronic ESL}_{\text{nonlinear(nc)}} = 190 \text{ ppb} \times 0.3 = 57 \text{ ppb} \text{ (} 200 \mu\text{g}/\text{m}^3 \text{)}$$

**Table 3 Derivation of the Chronic ReV and <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub>**

Parameter	Summary
Study	Chang et al. (1993), supported by Miyagaki (1967)
Study Population	56 workers from an offset printing factory
Study Quality	High
Exposure Method	Inhalation
Critical Effects	Peripheral neuropathy
POD <sub>oc</sub>	132 ppm (LOAEL)
Exposure Duration	12 h/day, 6 days/wk, 2.6 years (mean)
POD <sub>HEC</sub> Dosimetric adjustment from occupational to general population	57 ppm
Total UFs	300
<i>Interspecies UF</i>	NA
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	10
<i>Subchronic to chronic UF</i>	NA
<i>Incomplete Database UF</i> <i>Database Quality</i>	3 medium
Chronic ReV (HQ = 1)	670 µg/m <sup>3</sup> (190 ppb)
<sup>chronic</sup> ESL <sub>nonlinear(nc)</sub> (HQ = 0.3)	200 µg/m <sup>3</sup> (57 ppb)

#### ***4.2. Carcinogenic Potential***

There is insufficient data to establish a carcinogenic endpoint as a result of chronic exposure to hexane.

#### ***4.3. Welfare-Based Chronic ESL***

There is insufficient data to establish an effect on vegetation as a result of chronic exposure to hexane.

#### ***4.4 Long-Term ESL and Values for Air Monitoring Evaluation***

The chronic evaluation resulted in the derivation of the following chronic values:

- chronic ReV = 670 µg/m<sup>3</sup> (190 ppb )
- <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub> = 200 µg/m<sup>3</sup> (57 ppb)

The long-term ESL for air permit evaluations is  $200 \mu\text{g}/\text{m}^3$  (57 ppb) (Table 1). The chronic ReV of  $670 \mu\text{g}/\text{m}^3$  (190 ppb) is used for evaluation of monitoring data (Table 1). The  $\text{chronic ESL}_{\text{nonlinear(nc)}}$  (HQ = 0.3) is not used to evaluate ambient air monitoring data.

## Chapter 5 References

### 5.1 References Cited in DSD

Agency for Toxic Substances and Disease Registry (ATSDR). 1993a. Toxicological profile for automotive gasoline. Available from ATSDR, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. Available from: [www.atsdr.cdc.gov/toxprofiles](http://www.atsdr.cdc.gov/toxprofiles).

Agency for Toxic Substances and Disease Registry (ATSDR). 1993b. Toxicological profile for jet fuels JP-4 and JP-7. Available from ATSDR, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. Available from: [www.atsdr.cdc.gov/toxprofiles](http://www.atsdr.cdc.gov/toxprofiles).

Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Toxicological profile for n-hexane. Available from ATSDR, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. [www.atsdr.cdc.gov/toxprofiles](http://www.atsdr.cdc.gov/toxprofiles).

Chang, CM, CW Yu, KY Fong, et al. 1993. N-hexane neuropathy in offset printers. *J. Neurol Neurosurg Psychiatry* 56(5):538-42.

ChemFinder.com. 2004. n-Hexane. ChemFinder.com Database and Internet Searching. <http://chemfinder.cambridgesoft.com/result.asp>. (accessed February 12, 2007).

Cramer, GM, RA Ford, and RL Hall. 1978. Estimation of toxic hazard-a decision tree approach. *Food Cosmet Toxicol* 16:255-76.

Daughtrey, W, P Newton, R Rhoden, et al. 1999. Chronic inhalation carcinogenicity study of commercial hexane solvent in F-344 rats and B6C3F1 mice. *Toxicol Sci* 48(1):21-29.

Dunnick, JK, DG Graham, RS Yang, et al. 1989. Thirteen-week toxicity study of n-hexane in B6C3F1 mice after inhalation exposure. *Toxicology* 57(2):163-172.

Gargas, M, R Burgess, and D Voisard. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. *Toxicol Appl Pharmacol* 98(1):87-89.

Grant, RL, BJ Kadlubar, NK Erraguntla, et al. 2007. Evaluation of acute inhalation toxicity for chemicals with limited toxicity information. *Reg Toxicol Pharm* 47(3):261-273.

- Haagen-Smit AJ, EF Darley, M Zaitlin, et al. 1952. Investigation on injury to plants from air pollution in the Los Angeles area. *Plant Physiology* 27(1): 18-34.
- Hazardous Substance Data Bank (HSDB). 2005. n-Hexane. TOXNET - Databases on toxicology, hazardous chemicals, environmental health, and toxic releases. <http://toxnet.nlm.nih.gov/>. (accessed March 15, 2007)
- Huang, J, K Kato, E Shibate, et al. 1989. Effects of chronic n-hexane exposure on nervous system-specific and muscle-specific proteins. *Arch Toxicol* 63(5):381-85.
- Iba, MM and MG Bird. 2007. Effect of n-hexane on the disposition and toxicity of the 1,3-butadiene metabolite 3-butene-1,2-diol. *Chem Biol Interact* 166(1-3):232-38.
- Miyagaki, H. 1967. Electrophysiological studies on the peripheral neurotoxicity of n-hexane. *Jap J Ind Health* 9(12-23):670-671.
- Nagata, Y. 2003. Measurement of odor threshold by triangle odor bag method. Odor Measurement Review, Japan Ministry of the Environment. Pp. 118-127.
- National Safety Council (NSC). 2003. n-Hexane. Chemical Background. National Safety Council, Itasca, IL. [www.nsc.org/library/chemical/n-hexane.htm](http://www.nsc.org/library/chemical/n-hexane.htm).
- Perbellini, L, F Brugnone, D Caretta, et al. 1985 Partition coefficients of some industrial aliphatic hydrocarbons (C5-C7) in blood and human tissues. *Br J Ind Med* 42(3):162-167.
- Registry of Toxic Effects of Chemical Substances Database 2006. Canadian Centre for Occupational Health and Safety, <http://ccinfoweb.ccohs.ca/rtecs/search.html>. (accessed May 15, 2007)
- Sanagi, S, Y Seki, K Sugimoto, et al. 1980 Peripheral nervous system function of workers exposed to n-hexane at low levels. *Int Arch Occup Env Hlth* 47(1):69-79.
- Schaumburg, HH and PS Spencer. 1976. Degeneration in central and peripheral nervous systems produced by pure n-hexane: an experimental study. *Brain* 99(2):183-192.
- Seppalainen, AM, C Raitta, and MS Huuskonen. 1979. n-Hexane-induced changes in visual evoked potentials and electroretinograms of industrial workers. *Electroencephal Clin Neurophysiol* 47:492-498.
- Swann, HE, BK Kwon, GK Hogan, et al. 1974. Acute inhalation toxicology of volatile hydrocarbons. *Am Ind Hyg Assoc J* 356:511-518.

Texas Commission on Environmental Quality (TCEQ). 2006. Guidelines to develop effects screening levels, reference values, and unit risk factors. RG-442. Chief Engineer's Office, Austin, TX.

Texas Commission on Environmental Quality (TCEQ). (2015). Approaches to Derive Odor-Based Values. Texas Commission on Environmental Quality. Office of the Executive Director, Austin, TX.

Texas Risk Reduction Program (TRRP). 2006. Chemical/physical properties table. [www.tceq.state.tx.us/assets/public/remediation/trrp/trrptoxchph\\_2006.xls](http://www.tceq.state.tx.us/assets/public/remediation/trrp/trrptoxchph_2006.xls). (accessed March 15, 2007)

United Nations. (UN). 2005. Globally harmonized system of classification and labeling of chemicals (GHS) First revised edition. ST/SG/AC.10/30/Rev.1 United Nations, New York and Geneva.

United States Environmental Protection Agency (USEPA). 2005. Toxicological review of n-hexane. Integrated Risk Information System. <http://www.epa.gov/iris/toxreviews/0486-tr.pdf>.

United States Environmental Protection Agency (USEPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington, DC: U.S. Environmental Protection Agency. EPA/600/8-90/066F.

Wayne, LG and JA Orcutt. 1960. Common organic solvents as precursors of eye-irritants in urban atmospheres. *J Occp Med* 2:383-89.

Yamada, S. 1967. Intoxication polyneuritis in the workers exposed to n-hexane. *Jap J Ind Health* 9:651-59.

Yamamura, Y. 1969. n-Hexane polyneuropathy. *Folia Psychiatr Neurol Jap* 23(1):45-57.

## ***5.2 References of Other Studies Reviewed by the TS***

Amoore, JE and E Hautala. 1983. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3(6):272-290.

Bio Dynamics Inc. 1978. 26 Week inhalation toxicity study of n-hexane in the rat. US EPA; Document #FYI-AX-1081-0137.

Cavender, FL, HW Casey, H Salem, et al. 1984. A 13-week vapor inhalation study of n-hexane in rats with emphasis on neurotoxic effects. *Fundam Appl Toxicol* 4(2 Pt1):191-201.

- Ladefoged, O, K Roswall, and JJ Larsen. 1994. Acetone potentiation and influence on the reversibility of 2,5-hexanedione-induced neurotoxicity studied with behavioral and morphometric methods in rats. *Pharmacol Toxicol* 74:294-99.
- Ladefoged, O, U Hass, and L Simonsen. 1989. Neurophysiological and behavioural effects of combined exposure to 2,5-hexanedione and acetone or ethanol in rats. *Pharmacol Toxicol* 65:372-75.
- NTP 1991. Toxicity studies of *n*-hexane in B6C3F1 (inhalation studies) National Toxicology Program. Research Triangle Park, NC. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. Publication No. 91-3121.
- Van Gemert, LJ and AH Nettenbreijer. 2003. Compilation of Odour Threshold Values in Air and Water. National Institute for Water supply, Voorburg, Netherlands.
- Wang, JD, YC Chang, KP Kao, et al. 1986. An outbreak of *n*-hexane induced polyneuropathy among press proofing workers in Taipei. *Am J Ind Med* 10(2):111-18.
- Zhao, WY, J Misumi, T Yasui, et al. 1998. Effects of methyl ethyl ketone, acetone, or toluene coadministration on 2,5-hexanedione concentration in the sciatic nerve, serum, and urine of rats. *Int Arch Occup Environ Health* 71:236-244.