APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *n*-Hexane
CAS Number: 110-54-3
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Acute
***MRL*:** 6 ppm (21 mg/m^3)
Critical Effects: Decreased fetal body weight
Reference: NIEHS 1987
Point of Departure: NOAEL of 200 ppm ($NOAEL_{HEC}$ of 167 ppm)
Uncertainty Factor: 30
LSE Graph Key: 9
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 6 ppm was derived for *n*-hexane based on a NOAEL of 200 ppm and a LOAEL of 1,000 ppm for developmental effects (7.5% decrease in male fetal body weight) in rats exposed on GDs 6–19 (14 days) for 20 hours/day (NIEHS 1987). The NOAEL was adjusted to continuous duration exposure, converted to a human equivalent concentration ($NOAEL_{HEC}$) of 167 ppm, and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: Several studies examined the acute-duration inhalation toxicity of *n*-hexane. A summary of the identified LOAELs is presented in Table A-1. Exposure to 1,000 ppm resulted in developmental effects, while exposure to 5,000 ppm resulted in body weight, neurological, developmental, and reproductive effects. The lowest LOAELs were 1,000 ppm for decreased litter weight and fetal body weight (Bus et al. 1979; NIEHS 1987).

Selection of the Principal Study: Bus et al. (1979) and NIEHS (1987) both identified LOAELs of 1,000 ppm for decreased fetal/litter weights. In the Bus et al. (1979) study, a 13.9% decrease in mean litter weight at 3 weeks after birth was observed in the offspring of rats exposed to 1,000 ppm *n*-hexane 6 hours/day on GDs 8–16. No differences were observed in birth weight or pup body weight 7 weeks after birth. In the NIEHS (1987) study, a 7.5% decrease in male fetal body weight was observed in the offspring of rats exposed to 1,000 ppm 20 hours/day on GDs 6–19; a NOAEL of 200 ppm was also identified.

Adjusting the durations to continuous exposure results in a $LOAEL_{ADJ}$ of 250 ppm for Bus et al. (1979) study and a $NOAEL_{ADJ}$ of 167 ppm and $LOAEL_{ADJ}$ of 833 ppm for NIEHS (1987) study. The NIEHS (1987) study was selected as the principal study because it identified a NOAEL for the most sensitive endpoint, used multiple doses, exposed animals for 20 hours/day (close to a continuous exposure), and examined a larger number of litters (23–28/group versus 8–14/group in the Bus et al. [1979] study).

Table A-1. Summary of NOAEL and LOAEL Values Following Acute-Duration Inhalation Exposure to *n*-Hexane

Species (strain, sex)	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Developmental effects					
Rats (Fischer-344, F)	9 days (GDs 8–16) 6 hours/day	ND	1,000 (250)	Decreased litter weight (13.9% at 3 weeks after birth)	Bus et al. 1979
Rats (Sprague-Dawley, F)	14 days (GDs 6–19) 20 hours/day	200 (167)	1,000 (833)	Decreased fetal body weight (7.5% in male offspring)	NIEHS 1987
Mice (Swiss, F)	12 days (GDs 6–17) 20 hours/day	ND	5,000 (4,167)	Decreased number of live fetuses per litter, increased incidence of late resorptions	NIEHS 1988c
Reproductive effects					
Rats (Sprague-Dawley, M)	2 weeks 6 days/week 16 hours/day	ND	5,000 (2,857)	Testicular lesions (spermatocyte necrosis, exfoliation of spermatids, and Sertoli cell vacuolization)	De Martino et al. 1987
Rats (Sprague-Dawley, M)	8 days 16 hours/day	ND	5,000 (3,333)	Testicular lesions (degeneration of spermatocytes, exfoliation of elongated spermatids, and Sertoli cell vacuolization)	De Martino et al. 1987
Rats (Sprague-Dawley, M)	24 hours Continuous	ND	5,000	Testicular lesions (focal degeneration of spermatocytes and mild exfoliation of elongated spermatids)	De Martino et al. 1987
Neurological effects					
Rats (Sprague-Dawley, M)	2 weeks 6 days/week 16 hours/day	ND	5,000 (2,857)	Decreased motor conduction velocity	De Martino et al. 1987
Body weight effects					
Rats (Sprague-Dawley, M)	2 weeks 6 days/week 16 hours/day	ND	5,000 (2,857)	Decreased body weight (20–30%) (serious LOAEL)	De Martino et al. 1987
Rats (Sprague-Dawley, F)	14 days (GDs 6–19) 20 hours/day	1,000 (833)	5,000 (4,167)	Decreased body weight (10% in pregnant dams, 12% in virgin females)	NIEHS 1987

ADJ = adjusted for continuous exposure; F = females; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level

Summary of the Principal Study:

NIEHS. 1987. Inhalation developmental toxicology studies: Teratology study of n-hexane in rats: Final report. Washington, DC: National Institute of Environmental Health Sciences. DE88006812. PNL-645. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/DE88006812.xhtml. October 20, 2022.

Timed-pregnant (30/group) and virgin (10/group) Sprague-Dawley rats were exposed to 0, 200, 1,000, or 5,000 ppm *n*-hexane vapor for 20 hours/day for 14 days (GDs 6–19 for pregnant females). All animals were observed daily for mortality, morbidity, and overt signs of toxicity. Adult body weights were monitored throughout the study and at sacrifice (GD 20 for pregnant rats). Uterine, placental, and fetal body weights were measured from pregnant females. Reproductive/developmental parameters evaluated included number of implants, early or late resorptions, number of live fetuses, number of dead fetuses, sex ratios, fetal weight, and malformations.

No maternal deaths or clinical signs of toxicity were observed. Statistically significantly decreased body weights were observed in pregnant and virgin females at 5,000 ppm. Extra-gestational body weight gain (weight gain minus the weight of the gravid uterus) was also statistically significantly decreased at 5,000 ppm. Exposure to *n*-hexane had no effect on the number of implantations, live pups per litter, resorptions per litter, fetal sex ratio, intrauterine death rate, or fetal or skeletal malformations. Fetal body weights were decreased at 1,000 ppm (7.5% for male offspring). At 5,000 ppm, decreased body weights were observed in males and females combined (15%), in males only (15%) and in females only (14%) (Table A-2).

Table A-2. Average Fetal Weights Following Maternal Inhalation Exposure to *n*-Hexane

Exposure concentration	0	200 ppm	1,000 ppm	5,000 ppm
Fetuses examined	339	350	392	408
Sex ratio (M/F)	0.53±0.14[a]	0.48±0.11	0.46±0.17	0.54±0.14
Fetal body weight (g)	3.48±0.37	3.54±0.36	3.27±0.32[b]	2.97±0.38[b]
Male fetal body weight (g)	3.60±0.39	3.66±0.39	3.33±0.33[b]	3.05±0.41[b]
Female fetal body weight (g)	3.33±0.37	3.43±0.37	3.23±0.32	2.86±0.36[b]

[a]Mean±standard deviation.
[b]Statistically significantly different from controls at p<0.05.

F = female; M = male

Source: NIEHS 1987

Selection of the Point of Departure for the MRL: Benchmark dose (BMD) modeling of the male fetal body weight data could not be attempted because the number of male fetuses was not reported. The NOAEL of 200 ppm for developmental effects (decreased male fetal body weights) in rats exposed for 20 hours/day on GDs 6–19 (NIEHS 1987) was selected as the point of departure (POD) for the MRL.

Adjustment for Intermittent Exposure: The intermittent 20 hours/day NOAEL of 200 ppm was adjusted to a 24-hour continuous exposure using the following equation:

$$NOAEL_{ADJ} = NOAEL \times \frac{20\ hours}{24\ hours} = 200\ ppm \times \frac{20\ hours}{24\ hours} = 167\ ppm$$

Human Equivalent Concentration: The human equivalent concentration (HEC) was calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of the *n*-hexane air:blood partition coefficient for humans and rats. The reported blood:gas (air) partition coefficient ($H_{b/g}$) values for *n*-hexane are 2.29 for rats (Gargas et al. 1989) and 0.8 for humans (Perbellini et al. 1985). Since the ratio of the rat to human blood:gas (air) partition coefficients is >1, a default value of 1 was used.

$$NOAEL_{HEC} = NOAEL_{ADJ} \times \frac{(H_{b/g})_A}{(H_{b/g})_H} = 167\ ppm \times 1 = 167\ ppm$$

Uncertainty Factor: The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

$$MRL = NOAEL_{HEC} \div UFs$$
$$167\ ppm \div 30 = 5.56\ ppm \approx 6\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of decreased fetal weight in rats as the critical effect is supported by several other studies using similar or higher concentrations or longer durations that also observed effects on fetal weight (Bus et al. 1979; Stoltenburg-Didinger et al. 1990). Additionally, a positive association was observed between ambient *n*-hexane exposure (represented as a unitless exposure intensity) and low birth weight (OR 1.06) in a case-control study in Texas (Gong et al. 2018).

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *n*-Hexane
CAS Number: 110-54-3
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Intermediate
***MRL*:** 0.4 ppm (1.4 mg/m^3)
Critical Effects: Lesions in the nasal cavity (multifocal regeneration and metaplasia in olfactory epithelium)
Reference: NTP 1991
Point of Departure: LOAEL of 1,099 ppm ($LOAEL_{HEC}$ of 111 ppm)
Uncertainty Factor: 300
LSE Graph Key: 43
Species: Mouse

MRL Summary: An intermediate-duration inhalation MRL of 0.4 ppm was derived for *n*-hexane based on a LOAEL of 1,099 ppm for respiratory effects (nasal cavity lesions) in mice exposed for 22 hours/day, 5 days/week for 13 weeks (NTP 1991). The LOAEL was duration adjusted to continuous duration exposure, converted to a human equivalent concentration ($LOAEL_{HEC}$) of 111 ppm, and divided by a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

Selection of the Critical Effect: Several studies have evaluated the intermediate-duration toxicity of inhaled *n*-hexane. A summary of the identified LOAELs is presented in Table A-3. The lowest LOAELs were identified for renal, neurological, musculoskeletal, body weight, and developmental effects with respiratory and reproductive effects observed at higher concentrations. One of the lowest LOAELs identified was 500 ppm for increased relative kidney weights and chronic nephritis in male rats exposed for 22 hours/day, 7 days/week for 6 months (API 1981). The study authors were unable to determine whether exposure to *n*-hexane exacerbated the normal age-related process observed in controls or caused a unique injury. High background rates of chronic nephropathy are commonly observed in male Sprague-Dawley rats and complicate its use as the critical effect. Additionally, the renal system is not a known target of *n*-hexane exposure, and several other rat and mouse studies have failed to identify a similar response (API 1978; Cavender et al. 1984; NTP 1991). Therefore, the renal effects were not selected as the critical effect for derivation of an intermediate-duration inhalation MRL.

The next lowest LOAELs identified were for neurological endpoints, which are a common outcome following inhalation exposure to *n*-hexane. Rats (sex not specified) exposed to 400–600 ppm *n*-hexane continuously for 42–162 days developed central and peripheral neuropathy, footdrop, waddling gait, and limb weakness, while histopathology revealed swollen axons and axonal degeneration (Schaumburg and Spencer 1976). Male rats exposed to 500 ppm for 22 hours/day, 7 days/week for 9 weeks presented with clinical signs of neurotoxicity (narcosis, paralysis) and histopathology (axonal swellings, myelin degradation), while rats exposed to 700 ppm for 8 hours/day, 7 days/week for 40 weeks only had axonal swelling (Altenkirch et al. 1982). Other studies have also shown neurological effects at 500 ppm, with abnormal gait and peripheral neuropathy in male rats exposed for 22 hours/day, 7 days/week for 6 months (API 1981), and decreased grip strength in male rats exposed for 24 hours/day, 5 days/week for 10 weeks (Rebert and Sorenson 1983). While there is consistent evidence of neurological effects, the calculated HECs for these effects were higher than those for respiratory nasal effects; thus, neurological effects were not selected as the critical effect for MRL derivation.

Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to *n*-Hexane

Species (strain, sex)	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Renal effects					
Rats (Sprague-Dawley, M)	6 months 7 days/week 22 hours/day	ND	500 (458)	Increased kidney weight, chronic nephropathy	API 1981
Respiratory effects					
Mice (B6C3F1, B)	13 weeks 5 days/week 22 hours/day	ND	1,099 (719)	Lesions in the nasal cavity (multifocal regeneration and metaplasia in olfactory epithelium)	NTP 1991
Rabbit (New Zealand)	24 weeks 5 days/week 8 hours/day	ND	3,000 (714)	Upper respiratory tract irritation (nasal discharge and salivation), respiratory difficulties (gasping, lung rales, mouth breathing), histopathology (centrilobular emphysema, pulmonary fibrosis, goblet cell metaplasia, epithelial desquamation)	Lungarella et al. 1984
Mice (B6C3F1, B)	13 weeks 5 days/week 6 hours/day	1,109 F (198) 4,421 M (789)	4,421 F (789) 10,000 M (1,786)	Lesions in the nasal cavity (multifocal regeneration and metaplasia in the olfactory epithelium)	NTP 1991
Neurological effects					
Rats (Wistar, M)	40 weeks 7 days/week 8 hours/day	ND	700 (233)	Axonal swelling in the spinal cord	Altenkirch et al. 1982
Rats (Fischer-344, M)	11 weeks 5 days/week 24 hours/day	ND	500 (357)	Decreased grip strength	Rebert and Sorenson 1983
Rats (Sprague-Dawley, NS)	45 days continuously	ND	400–600	Central and peripheral neuropathy, footdrop, waddling gait, limb weakness, swollen axons, axonal degeneration	Schaumburg and Spencer 1976

Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to *n*-Hexane

Species (strain, sex)	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Rats (Wistar, M)	9 weeks 7 days/week 22 hours/day	ND	500 (458)	SLOAEL: Clinical signs (narcosis, paralysis), multifocal giant axonal swellings, primarily in the calf muscles, breakdown of axons, and myelin degradation	Altenkirch et al. 1982
Rats (Sprague-Dawley, M)	6 months 7 days/week 22 hours/day	ND	500 (458)	Abnormal gait, peripheral nerve atrophy	API 1981
Rats (Wistar, M)	16 weeks 7 days/week 12 hours/day	500 (250)	1,200 (600)	Decreased grip strength and motor nerve conduction velocity, paranodal swelling, demyelination, and remyelination of the peripheral nerve	Huang et al. 1989
Mice (B6C3F1, B)	13 weeks 5 days/week 22 hours/day	ND	1,099 (719)	Decreased locomotor activity (females), paranodal swellings in tibial nerve	NTP 1991
Rats (Wistar, F)	63 days (GD 1–PND 42) 7 days/week 23 hours/day	ND	800 (767)	Hindlimb weakness	Stoltenburg-Didinger et al. 1990
Rats (Wistar, M)	20 weeks 6 days/week 12 hours/day	ND	2,000 (857)	Decreased motor conduction velocity	Ichihara et al. 1998
Rats (Sprague-Dawley, M)	30 weeks 6 days/week 10 hours/day	500 (179)	2,500 (892)	Tibial nerve axonal degeneration	Frontali et al. 1981
Rats (Fischer-344, M)	11 weeks 7 days/week (4 weeks) 6 days/week (7 weeks) 24 hours/day	ND	1,000 (914)	Decreased hindlimb and forelimb strength, and ataxia, increased action potential latency, and increased brainstem auditory-evoked response	Howd et al. 1983
Rats (Fischer-344, M)	13 weeks 5 days/week 6 hours/day	3,000 (536)	6,500 (1,160)	Axonopathy in the sciatic nerve	Cavender et al. 1984

Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to *n*-Hexane

Species (strain, sex)	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Rats (Fischer-344, M)	14 weeks 7 days/week 14 hours/day	ND	2,000 (1,167)	Decreased limb grip strength, startle response, and motor activity; increased evoked potential latencies	Pryor et al. 1983
Rats (Sprague-Dawley, M)	14 weeks 5 days/week 9 hours/day	1,500 (402)	5,000 (1,339)	Tibial nerve axonal degeneration	Frontali et al. 1981
Rats (Wistar, M)	16 weeks 7 days/week 12 hours/day	ND	3,040 (1,520)	Gait disturbances, decreased motor and mixed nerve conduction velocity, axonal swelling, neurofilament accumulation, denervated neuromuscular junctions	Takeuchi et al. 1980
Mice (B6C3F1, B)	13 weeks 5 days/week 6 hours/day	4,421 (789)	10,000 (1,785)	Decreased locomotor activity (females), paranodal swellings in tibial nerve	NTP 1991
Rats (Wistar, F)	20 days (GD 1-20) 4 hours/day	2,500 (417)	12,500 (2,083)	Irritability, aggression	Li et al. 2014
Rats (Sprague-Dawley, M)	6 weeks 6 days/week 16 hours/day	ND	5,000 (2,857)	SLOAEL: Decreased motor conduction velocity, peripheral neuropathy, and paralysis	De Martino et al. 1987
Musculoskeletal effects					
Rats (Sprague-Dawley, M)	6 months 7 days/week 22 hours/day	ND	500 (458)	Skeletal muscle atrophy	API 1981
Rats (Sprague-Dawley, M)	61 days 7 days/week 18 hours/day	ND	1,000 (750)	Hindlimb muscular atrophy	Nylen et al. 1989
Rats (Sprague-Dawley, M)	28 days 7 days/week 21 hours/day	ND	1,000 (875)	Hindlimb muscular atrophy	Nylen et al. 1989

Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to *n*-Hexane

Species (strain, sex)	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Rats (Wistar, M)	16 weeks 7 days/week 12 hours/day	ND	3,040 (1,520)	Muscular atrophy, denervation, irregular fibers, and disordered myofilaments	Takeuchi et al. 1980
Reproductive effects					
Rats (Sprague-Dawley, M)	61 days 7 days/week 18 hours/day	ND	1,000 (750)	Testicular atrophy	Nylen et al. 1989
Rats (Sprague-Dawley, M)	28 days 7 days/week 21 hours/day	ND	1,000 (875)	Testicular atrophy	Nylen et al. 1989
Rats (Sprague-Dawley, M)	6 weeks 6 days/week 16 hours/day	ND	5,000 (2,857)	Testicular lesions (spermatocyte necrosis, exfoliation of spermatids, and Sertoli cell vacuolization)	De Martino et al. 1987
Developmental effects					
Rats (Wistar, F)	21 days (GDs 1–21) 7 days/week 23 hours/day	ND	500 (479)	Decreased fetal body weight (22% at 9 days after birth), delayed histogenesis of the cerebellar cortex	Stoltenburg-Didinger et al. 1990
Rats (Wistar, F)	20 days (GDs 1–20) 7 days/week 4 hours/day	2,500 (417)	12,500 (2,083)	SLOAEL: Decreased live pups/litter, decreased percentage of secondary follicles, increased atretic follicles, and alterations in oestrus cycle in female offspring	Li et al. 2014, 2015

ADJ = adjusted for continuous exposure; B = both sexes; F = females; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; PND = postnatal day; SLOAEL = serious LOAEL

Decreased fetal body weights were observed following maternal exposure to 500 ppm (Stoltenburg-Didinger et al. 1990). Body weight and musculoskeletal effects were also observed at exposures between 500 and 1,000 ppm, but these effects were not considered critical effects for MRL derivation because they are thought to be secondary outcomes following injury to the primary neurological targets of *n*-hexane. Muscular atrophy and limb weakness have been shown to result from denervation in the extremities (Nylen et al. 1989; Takeuchi et al. 1980), and loss of body weight is often observed along with decreased food intake, possibly due to an underlying effect resulting in the animal's refusal or inability to eat normally. At concentrations of 1,000 ppm, respiratory effects have been observed. In male and female mice, exposure to 1,099 ppm *n*-hexane for 22 hours/day, 5 days/week for 13 weeks resulted in nasal cavity lesions, including multifocal regeneration, and metaplasia in olfactory epithelium (NTP 1991). Similar results were not observed in two rat studies, suggesting that mice may be more susceptible than rats to point-of-entry effects from *n*-hexane inhalation.

Taken together, the data suggest that respiratory, developmental, and neurological effects are the most sensitive targets following intermediate-duration inhalation exposure to *n*-hexane. A comparison of the HECs of the LOAELs ($LOAEL_{HEC}$) for these endpoints is presented in Table A-4. The lowest $LOAEL_{HEC}$ value is 111 ppm for nasal lesions in mice exposed for 22 hours/day (NTP 1991). Thus, nasal lesions were selected as the critical effect.

Table A-4. Potential PODs Following Intermediate-Duration Inhalation Exposure to *n*-Hexane

Species	Exposure	LOAEL (ppm)	$LOAEL_{ADJ}$ (ppm)	$LOAEL_{HEC}$ (ppm)	Effect (Reference)
Respiratory effects					
Mice	22 hours/day 5 days/week	1,099	719	111	Nasal cavity lesions (NTP 1991)
Mice	6 hours/day 5 days/week	4,421	789	122	Nasal cavity lesions (females only) (NTP 1991)
Neurological effects					
Rats	8 hours/day 7 days/week	700	233	233	Axonal swelling in the spinal cord (Altenkirch et al. 1982)
Rats	24 hours/day 5 days/week	500	357	357	Decreased grip strength (Rebert and Sorenson 1983)
Developmental effects					
Rats	23 hours/day 7 days/week	500	479	479	Decreased pup body weight (Stoltenburg-Didinger et al. 1990)

ADJ = adjusted; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure

Selection of the Principal Study: Few studies have evaluated respiratory effects following intermediate-duration inhalation exposure to *n*-hexane. Although rats appear to be more sensitive to *n*-hexane-induced neurotoxicity than mice, inhalation exposure studies in rats have failed to produce respiratory effects, suggesting that mice may be more sensitive to respiratory effects than rats. Male and female mice exposed to 1,099 ppm *n*-hexane for 22 hours/day, 5 days/week for 13 weeks presented with nasal cavity lesions (NTP 1991). In contrast, no histopathology was observed in the nasal cavity of male and female rats exposed up to 10,000 ppm for 6 hours/day, 5 days/week for 13 weeks (Cavender et al. 1984), or in male rats exposed to 500 ppm for 22 hours/day, 7 days/week for 6 months (API 1981).

Summary of the Principal Study:

NTP. 1991. Toxicity studies of n-hexane in B6C3F1 (inhalation studies). Research Triangle Park, NC: National Toxicology Program. PB91185322. NIH Publication No. 91-3121 https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox002.pdf. July 25, 2022.

Dunnick JK, Graham DG, Yang RS, et al. 1989. Thirteen-week toxicity study of n-hexane in B6C3F1 mice after inhalation exposure. Toxicology 57(2):163-172. https://doi.org/10.1016/0300-483x(89)90162-5.

Male and female $B6C3F_1$ mice (18/sex/group) were exposed to *n*-hexane for 6 hours/day, 5 days/week for 13 weeks at concentrations of 0, 500, 1,000, 4,000, or 10,000 ppm (mean analytical concentrations of 0, 580, 1,109, and 4,421 ppm; analytical concentration not reported for the 10,000-ppm exposure level). An additional group of mice (18/sex/group) was exposed to 1,000 ppm *n*-hexane for 22 hours/day, 5 days/week for 13 weeks (mean analytical concentration of 1,099 ppm). The core set of animals (10/sex/group) were evaluated for body weights, clinical signs of toxicity, and a complete histopathological assessment. The remaining animals (8/sex/group) were evaluated in a series of neurobehavior and neuropathology studies, including undifferentiated motor activity, forelimb and hindlimb grip strengths, thermal sensitivity, startle response, and foot splay. Four males and four females were randomly selected from the 0, 1,099 (22 hours/day), and 10,000 ppm groups for evaluation of spinal cord and tibial nerve.

Core group: Exposure up to 10,000 ppm for 6 hours/day or 1,099 ppm for 22 hour/day had no effect on survival or clinical signs of toxicity. Body weights were decreased in male mice exposed to either 10,000 ppm *n*-hexane for 6 hours/day (17% decrease) or to 1,099 ppm for 22 hours/day (10% decrease), but not in female mice comparably exposed. Sneezing was seen in males and females exposed to 10,000 ppm beginning at week 4 and continuing until the end of the study. Histopathologic evaluations revealed exposure-related lesions in the nasal cavities of male and female mice at 1,099 ppm (22 hours/day) and in female mice at 4,421 ppm. Multifocal regeneration and metaplasia of the olfactory epithelium were the most common lesions observed in both male and female mice. Higher concentrations resulted in more significant damage, including epithelial erosion, subacute inflammation, and focal fibrosis of the submucosa. No other histopathological effects outside of the nasal cavity were observed.

Neurological group: The only neurobehavioral finding observed was a decrease in locomotor activity in female mice at 1,099 (22 hours/day) and 10,000 ppm. Paranodal swellings in the tibial nerve were observed in 6/8 mice exposed to 1,099 (22 hours/day) and 10,000 ppm. Nerve damage at 1,099 ppm for 22 hours/day was similar to that observed at 10,000 ppm for 6 hours/day, suggesting that continuous exposure to *n*-hexane is more toxic than intermittent exposure.

Selection of the Point of Departure for the MRL: Lesions in the nasal cavity were observed in male and female mice at 1,099 ppm (22 hours/day) and in female mice at 4,421 ppm (6 hours/day), with continuous-adjusted $LOAEL_{ADJ}$ values of 719 and 789 ppm, respectively. The LOAEL value was selected as the POD. BMD modeling was not conducted because only one concentration was evaluated at this exposure duration.

Adjustment for Intermittent Exposure: The intermittent 22-hours/day, 5 days/week LOAEL of 1,000 ppm was adjusted to a 24-hour, 7 day/week continuous exposure using the following equation:

$$LOAEL_{ADJ} = LOAEL \times \frac{22\ hours}{24\ hours} \times \frac{5\ days}{7\ days}$$

$$1{,}099\ ppm \times \frac{22\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 719\ ppm$$

Human Equivalent Concentration: The HEC was calculated by multiplying the $LOAEL_{ADJ}$ by the regional gas dose ratio (RGDR). The RGDR for extrathoracic respiratory tract effects was calculated using the following equation:

$$RGDR_{ET} = \frac{(\frac{V_E}{SA_{ET}})_A}{(\frac{V_E}{SA_{ET}})_H}$$

Where:

$RGDR_{ET}$ = extrathoracic regional gas dose ratio (animal: human)
V_E = minute volume (based on body weight)
SA_{ET} = surface area of the extrathoracic region
A = animal
H = human

The human minute volume (13,800 mL/minute) and extrathoracic surface area (200 cm^2) are provided in EPA (1994b) along with the extrathoracic surface area in mice (3 cm^2). The mouse minute volume (32 mL/minute) was calculated based on the body weights reported in the study (males 30 g, females 25.4 g, average 27.7 g) (NTP 1991).

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RGDR_{ET}$$

$$LOAEL_{HEC} = 719\ ppm \times \frac{(\frac{32\ ml/min}{3\ cm^2})}{(\frac{13{,}800\ ml/min}{200\ cm^2})} = 719\ ppm \times 0.1546 = 111\ ppm$$

Uncertainty Factor: The $LOAEL_{HEC}$ was divided by a total uncertainty factor of 300:

- 10 for extrapolation from a LOAEL
- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

$$MRL = LOAEL_{HEC} \div UFs$$
$$111\ ppm \div 300 = 0.37\ ppm \approx 0.4\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The principal study (NTP 1991) was the only study located that examined respiratory histopathology in mice following *n*-hexane exposure. No histopathological effects have been observed in the nasal cavities of rats exposed to *n*-hexane at concentrations up to 10,000 ppm for 6 hours/day or 500 ppm for 22 hours/day (API 1981; Cavender et al. 1984), although the exposure duration or concentration may not have been high enough to elicit a response. Pulmonary effects have also been observed. Relative lung weights were increased in

male rats exposed to 1,000 ppm for 24 hours/day, 6–7 days/week for 11 weeks. However, histology was not performed on the lungs nor the nasal cavity (Howd et al. 1983). Male rabbits exposed to 3,000 ppm for 8 hours/day, 5 days/week for 24 weeks showed signs of respiratory irritation, breathing difficulties, and respiratory track histopathology (centrilobular emphysema, pulmonary fibrosis, goblet cell metaplasia, epithelial desquamation) (Lungarella et al. 1984). Since the NTP (1991) mouse study had the lowest $LOAEL_{HEC}$ for respiratory effects, it was chosen as the principal study.

Neurological effects are the most sensitive outcome evaluated and identified following inhalation exposure to *n*-hexane; however, the MRL based on neurological effects would be higher due to the dosimetric adjustment for systemic effects. Therefore, the MRL based on nasal effects is protective of neurological effects.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *n*-Hexane
CAS Numbers: 110-54-3
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: The database was not considered adequate for derivation of a chronic-duration inhalation MRL for *n*-hexane. Although there is a large database describing neurological effects in occupational workers resulting from inhalation exposure to *n*-hexane, these studies lack exposure information, or the exposure is confounded by additional compounds that exacerbate *n*-hexane-induced neurological effects. Only a single chronic-duration animal study was located that examined the reproductive toxicity of inhaled *n*-hexane (Leydig cell hyperplasia), but the study did not evaluate other potential sensitive targets such as neurological or respiratory outcomes, so it was not considered sufficient for deriving a chronic-duration MRL.

Rationale for Not Deriving an MRL: The neurotoxicity of *n*-hexane was first observed in the shoe industries of Japan and Italy in the 1960s and early 1970s. A number of epidemiological studies were initiated in response to outbreaks of apparent peripheral neuropathy in shoe workers. While the clinical course of the disease was well described, elucidation of a dose-response relationship has been difficult. In most cases, concentrations of *n*-hexane in the workplace air were not measured until after disease developed. Also, in almost all cases, workers were concurrently exposed to other chemicals which may have affected their response to *n*-hexane.

Few human studies are available that have the exposure and duration information needed to identify a point of departure. Sanagi et al. (1980) evaluated motor nerve conduction velocity in 14 occupationally exposed workers employed in a factory producing tungsten carbide alloys. Personal monitors reported mean 8-hour time weighted concentrations of *n*-hexane (58 ppm) and acetone (39 ppm); no other "solvent vapors" were detected. Chang et al. (1993) reported alterations in motor and sensory nerve amplitudes and latencies in printing press workers diagnosed with peripheral neuropathy. Mean concentrations of *n*-hexane were 63 ppm (background, 30–110 ppm) and 132 ppm (personal samplers, 80–210 ppm), although toluene and isopropyl alcohol were also measured, and additional exposures to lead, toluene, mercury, and diesel were also possible from the solvents used. Mutti et al. (1982a, 1982b) also identified electroneurographic abnormalities in shoe factory workers exposed to *n*-hexane near the recommended threshold limit value, but additional contaminants measured in the breathing zone included cyclohexane, MEK, and ethyl acetate. A study of oil spill workers found an association between cumulative *n*-hexane exposure and vibrotactile threshold (Chen et al. 2023a, 2023b); as with the other studies, the workers were exposed to other contaminants including benzene, toluene, ethylbenzene, and xylenes.

Several studies suggest that co-exposures to chemicals including acetone, toluene, and MEK may enhance *n*-hexane metabolism and neurotoxicity (Altenkirch et al. 1977, 1982; Ladefoged et al. 1989, 1994; Ladefoged and Perbellini 1986; Nylen et al. 1994; Nylen and Hagman 1994; Patten et al. 1986; Robertson et al. 1989; Zhao et al. 1998). Due to the known co-exposure to and potential interactions with acetone, the available human studies were not considered adequate for the development of a chronic-duration inhalation MRL. A single chronic-duration animal study examined the male reproductive toxicity of inhaled *n*-hexane (Imai and Omoto 1999). Leydig cell hyperplasia and benign Leydig cell tumors were observed in male rats exposed to 1,000 ppm *n*-hexane for 60 weeks, but this study was not considered adequate due to poor reporting and the lack of supporting studies suggesting that Leydig cells are a target of *n*-hexane exposure. Additionally, this study did not evaluate any other potential targets of *n*-hexane

exposure such as neurotoxicity or respiratory effects. Therefore, a chronic-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *n*-Hexane
CAS Numbers: 110-54-3
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: The database was not considered adequate for derivation of an acute-duration oral MRL for *n*-hexane. There is limited information on the toxicity of *n*-hexane following acute oral exposure. The only nonlethal effect is developmental toxicity (decreased fetal weight); however, increased maternal mortality has been observed at lower doses.

Rationale for Not Deriving an MRL: Three studies have evaluated the acute oral toxicity of *n*-hexane (Kimura et al. 1971; Linder et al. 1992; Marks et al. 1980). A LOAEL of 7,920 mg/kg/day was identified in mice for decreased fetal weight following oral exposure 3 times/day on GDs 6–15 (10 days) (Marks et al. 1980). In this same dosing regime, a non-statistically significant increase in dam mortality (9%) was observed at 2,830 mg/kg/day. The remaining two studies evaluated the potential reproductive toxicity of oral *n*-hexane exposure but did not identify an effect for any outcome. None of the acute-duration oral studies examined non-reproductive or developmental endpoints, particularly potential neurotoxicity, which is a known sensitive target of *n*-hexane.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *n*-Hexane
CAS Number: 110-54-3
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Intermediate
***MRL*:** 0.1 mg/kg/day
Critical Effects: Neurological effects (impaired performance on a test of memory)
Reference: Gao et al. 2019
Point of Departure: LOAEL of 43.5 mg/kg/day
Uncertainty Factor: 300
LSE Graph Key: 12
Species: Mouse

MRL Summary: An intermediate-duration oral MRL of 0.1 mg/kg/day was derived for *n*-hexane based on neurobehavioral effects (impaired performance on a test of memory) in mice administered via gavage 43.5 mg/kg/day for 20 consecutive days (Gao et al. 2019). The minimal LOAEL of 43.5 mg/kg/day was divided by a total uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Several intermediate-duration studies examining the oral toxicity of *n*-hexane are available. A summary of the identified LOAELs is presented in Table A-5. Exposure to 43.5 mg/kg/day resulted in neurobehavioral effects and neuromuscular effects were observed at ≥1,000 mg/kg/day. Other observed adverse effects include decreased body weight gain at ≥570 mg/kg/day and reproductive effects at 4,000 mg/kg/day. Neurological effects were chosen as the critical effect because they occurred at the lowest adverse effect level and the endpoint is well supported by epidemiological and animal studies involving inhalation exposure.

Selection of the Principal Study: Several studies are available that evaluated neurological effects following intermediate-duration oral exposure to *n*-hexane. The lowest adverse effect level of 43.5 mg/kg/day was identified in the Gao et al. (2019) mouse study. At higher doses, signs of clinical neurotoxicity (transient paralysis, abnormal gait, decreased rotarod latency) and decreased motor nerve conduction velocity were observed (Krasavage et al. 1980; Li et al. 2018, 2020a, 2020b; Ono et al. 1981; Wang et al. 2017). The Gao et al. (2019) study was selected as the principal study because it identified the lowest LOAEL for neurological effects.

Table A-5. Available NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to *n*-Hexane

Species (strain, sex)	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Body weight effects					
Rats (COBS, M)	90 days 5 times/week	ND	570	Decreased body weight (15%)	Krasavage et al. 1980
Rats (Wistar, M)	24 weeks 7 times/week	500	1,000	Decreased body weight (19%)	Li et al. 2020b
Rats (Wistar, M)	10 weeks 6 times/week	1,000	2,000	Decreased body weight (19%)	Li et al. 2018
Rats (Wistar, M)	7 weeks 7 times/week	ND	3,000	SLOAEL: Decreased body weight (23%)	Li et al. 2020a
Neurological effects					
Mice (Kunming, M, F)	20 days 7 times/week	ND	43.5	Impaired response on test of learning and memory (Y-maze)	Gao et al. 2019
Rats (Wistar, M)	24 weeks 7 times/week	500	1,000	Transient paralysis, abnormal gait, decreased ability to stay on a rotating rod and motor nerve conduction velocity	Li et al. 2020b
Rats (Wistar, M)	8 weeks 7 times/week	ND	1,000	Decreased motor and mixed nerve conduction velocity	Ono et al. 1981
Rats (Wistar, M)	10 weeks 6 times/week	1,000	2,000	Abnormal gait, decreased ability to stay on rotating rod	Li et al. 2018
Rats (Wistar, M)	7 weeks 7 times/week	ND	3,000	SLOAEL: Paralysis	Li et al. 2020a
Rats (Wistar, M)	8 weeks 7 times/week	ND	3,000	Decreased grip strength, abnormal gait	Wang et al. 2017
Rats (COBS, M)	90 days 5 times/week	1,140	4,000	SLOAEL: Hindlimb paralysis, axonal swelling, myelin retraction	Krasavage et al. 1980
Reproductive effects					
Rats (COBS, M)	90 days 5 times/week	1,140	4,000	SLOAEL: Testicular atrophy of the germinal epithelium	Krasavage et al. 1980

F = females; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

Summary of the Principal Study:

Gao J, Zhang X, Lin Q, et al. 2019. Changes to learning and memory ability and the expression of NGF/NGF-R mRNA in the brain tissue of mice exposed to *n*-hexane. Chin J Ind Hyg Occup Dis. 37:217-221.

Groups of 10 Kunming mice (presumably 5 males and 5 females) were administered *n*-hexane via gavage at 0, 43.5, 86.5, or 173.0 mg/kg/day for 20 days. Learning and memory were evaluated using a Y-maze test. The test was conducted on 2 consecutive days (the day after exposure completion and 24-hours later), the first day to assess learning and the second day to assess memory recall ability.

The investigators noted that decreased activity and reduced food intake were observed in the exposed groups beginning after exposure day 4; more pronounced symptoms were observed in the 173.0 mg/kg/day group. However, no incidence or frequency data were provided. The investigators also noted that the mean body weight, presumably in the 173.0 mg/kg/day group, was decreased by 2.1 g; no additional information was provided. On the first test (learning), significant decreases in the correct response rate were observed in the 86.5 and 173.0 mg/kg/day groups; no statistically significant alterations in total electric shock time or total training sessions were observed. In the second test (memory), significant increases in total electric shock time and decreases in correct response rate were observed in all three groups. Significant decreases in nerve growth factor (NGF) and nerve growth factor receptor (NGF-R) concentrations were observed at 173.0 and 86.5 mg/kg/day, respectively. Decreased levels of NGF messenger ribonucleic acid (mRNA) and NGF-R mRNA levels were also observed at 43.5 and 86.5 mg/kg/day, respectively.

Selection of the Point of Departure for the MRL: The minimal LOAEL of 43.5 mg/kg/day for impaired performance on a test of memory in mice administered *n*-hexane for 20 days was selected as the POD for the MRL. BMD modeling was not conducted because it is unclear whether values presented in Table 2 of the paper are the mean±standard deviation or mean±standard error of the mean. Therefore, the NOAEL/LOAEL approach was used.

Uncertainty Factor: The NOAEL is divided by a total uncertainty factor of 300:

- 3 for the use of a minimal LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

$$MRL = LOAEL \div UFs$$
$$43.5\ mg/kg/day \div 300 = 0.1\ mg/kg/day$$

The 43.5 mg/kg/day dose was considered a minimal LOAEL because overt signs of neurotoxicity were not observed at this dose level.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Several studies are available with similar LOAELs and critical effects (Li et al. 2018; Ono et al. 1981), while more serious neurological signs including lasting paralysis have been observed at higher concentrations (Krasavage et al. 1980; Li et al. 2020a). Additionally, body weight changes occurred at the same dose as the selected LOAEL, so this MRL is protective against decreased body weight as well.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *n*-Hexane
CAS Numbers: 110-54-3
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: The database was not considered adequate for derivation of a chronic-duration oral MRL for *n*-hexane.

Rationale for Not Deriving an MRL: No studies were located that describe the effects of chronic-duration oral exposure to *n*-hexane in humans or animals.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR *n*-HEXANE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to *n*-hexane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for *n*-hexane. ATSDR primarily focused on peer-reviewed articles without language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of *n*-hexane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of *n*-hexane are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

[a]Physical-chemical properties are not generally obtained from literature searches, but rather from curated governmental databases such as PubChem.

B.1.1 Literature Search

The literature search was conducted to update the Toxicological Profile for *n*-Hexane released in 1999. All literature cited in the previous (1999) toxicological profile were considered for inclusion in the updated profile. The initial literature search, which was performed in July 2022, was restricted to studies added to databases since January 1997. An updated literature search was performed after the Toxicological Profile for *n*-Hexane Draft for Public Comment was released in May 2024 to identify any additional studies added to databases between July 2022 and June 2024.

APPENDIX B

The following main databases were searched in July 2022 and June 2024:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for *n*-hexane. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to *n*-hexane were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
06/2024	((110-54-3[rn] AND (2022:3000[crdt] OR 2022:3000[edat] OR 2022:3000[dp] OR 2022/07/01:3000[mhda])) AND (("hexanes/toxicity"[mh] OR "hexanes/adverse effects"[mh] OR "hexanes/poisoning"[mh] OR "hexanes/pharmacokinetics"[mh] OR ("hexanes"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh]))) OR ("hexanes"[mh] AND toxicokinetics[mh:noexp]) OR ("hexanes"[mh] AND (indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR ((antagonist*[tw] OR inhibitor*[tw]) AND ("humans"[mh] OR "animals"[mh])) OR "blood"[tw] OR "serum"[tw] OR ("plasma"[tw] NOT spectromet*[tw]) OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])) OR ("hexanes/blood"[mh] OR "hexanes/cerebrospinal fluid"[mh] OR "hexanes/urine"[mh] OR "hexanes/antagonists and inhibitors"[mh]) OR ("hexanes"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("hexanes"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene

Table B-2. Database Query Strings

Database search date	Query string
	expression profiling"[mh])) OR ("hexanes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("hexanes/pharmacology"[majr]) OR ("hexanes"[mh] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))) OR ((110-54-3[rn] NOT Hexanes[mh]) AND (2022:3000[crdt] OR 2022:3000[edat] OR 2022:3000[dp] OR 2022/07/01:3000[mhda])) OR ((((110-54-3[rn] OR "Gettysolve-B"[tw] OR "Hexane, n-"[tw] OR "Hexyl hydride"[tw] OR "Skellysolve B"[tw] OR "n-Hexan"[tw] OR "n-Hexane"[tw] OR "hexanes"[tw]) NOT medline[sb]) AND (toxicity[ti] OR death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR "LC 50" OR LD50* OR "LD 50" OR "body weight" OR "body mass index" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhala* OR "inhale" OR "inhaled" OR "inhalent" OR "inhales" OR "inhaling" OR respiratory OR "pulmonary" OR airway OR trachea OR tracheobronchial OR lung OR lungs OR nose OR nasal OR nasopharyngeal OR larynx OR laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR "asthma" OR cilia OR mucocilliary OR cardio OR vascular OR cardiovascular OR "circulatory system" OR "circulatory function" OR "circulatory effect" OR "circulatory effects" OR "circulatory toxicity" OR "cardiac" OR "coronary" OR "heart rate" OR "heart failure" OR "heart attack" OR "heart muscle" OR "heartbeat" OR "myocardial-infarction" OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR "gastro-intestinal" OR gastrointestinal OR "digestive system" OR "digestive organs" OR "digestive function" OR "digestive effect" OR "digestive effects" OR "intestinal" OR intestine* OR "gi tract" OR "gi disorder" OR abdominal OR esophagus OR esophageal OR stomach OR pancreas OR pancreatic OR diarrhea OR nausea OR vomit OR ulcer* OR constipation OR emesis OR "gut microbes" OR "gut flora" OR "gut microflora" OR anorexia OR hematological OR hematology OR hemato OR haemato OR blood OR anemia OR anaemia OR cyanosis OR "cyanotic" OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "limb pain" OR hepatic OR "liver" OR hepatocytes OR gallbladder OR cirrhosis OR jaundice OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR hepatomegaly OR hepatotox* OR renal OR "kidney" OR "kidneys" OR "urinary" OR "bladder" OR "urine" OR "blood urea nitrogen" OR bun OR nephropath* OR nephrotox* OR dermal OR "cutaneous application" OR "skin contact" OR "skin rash" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin effects" OR "skin exposure" OR "skin contact" OR acanthosis OR dermatitis OR psoriasis OR edema OR acne OR eczema OR ocular OR "retinal" OR "eye function" OR "eye effects" OR "eye effect" OR "eye irritation" OR "blurred vision" OR blindness OR myopia OR cataracts OR "auditory system" OR "hearing loss" OR ototoxic* OR endocrine OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone secretion" OR "hormone toxicity" OR "hormone levels" OR "sella turcica" OR thyroid OR thyroxine OR adrenal OR pituitary OR immunological OR immunologic OR immune OR immunotox* OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR lymphocyt* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR

Table B-2. Database Query Strings

Database search date	Query string
	neurotoxicity OR "neuropathy" OR neurodegenerat* OR "neurodevelopment" OR "nervous system" OR "nerve" OR brain OR "cerebrovascular" OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR tremor OR behavior-change* OR behavioral-change* OR sensory-change* OR cognitive OR "cognition" OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR "reproduction system" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR "infertility" OR "maternal toxicity" OR developmental OR "in utero" OR placenta OR pregnan* OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR weanling* OR elderly OR oocyte OR ovary OR ovarian OR uterus OR uterine OR testes OR testicular OR sperm OR estrogen* OR androgen* OR "human milk" OR "breast milk" OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR fever OR cytotox* OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR "micronuclei" OR "micronucleus" OR "chromosomal aberrations" OR "chromosome aberrations" OR mutagenicity OR mutagenic OR "mechanism of action"[tiab:~0] OR "mode of action"[tiab:~0] OR "mechanism of toxicity"[tiab:~0] OR "adverse effect" OR "adverse effects" OR "health effects" OR noncancer OR poisoning OR morbidity OR inflammation OR "inflammatory response" OR histopathology OR antagonist OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "pbpk" OR "gene expression" OR "adverse outcome pathway" OR metabolom* OR proteom* OR genomic* OR transcriptom* OR epigenom* OR epigene* OR "transcription factor" OR "transcriptional activation" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR "population health" OR occupation* OR worker* OR workmen* OR workplace* OR "volunteers" OR "human health" OR "dietary" OR "oral intake" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR biomarker* OR biomonitor* OR "biological monitoring" OR "environmental fate" OR NHANES OR "Nutrition Examination Survey" OR (cvd NOT "chemical vapor deposition") OR (human AND (risk OR toxic* OR safety)) OR "in vitro" OR "cell line" OR "cell lines" OR "cultured" OR "3T3" OR "A549" OR "BEAS-2B" OR "CACO-2" OR "CHO cells" OR "HELA" OR "HepG2" OR "HepaRG" OR "Jurkat" OR "MCF-7" OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR leontopithecus OR longevans OR macaque* OR marmoset* OR medaka OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR

Table B-2. Database Query Strings

Database search date	Query string
	pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR wistar OR wood-mouse OR zebra-fish OR zebrafish)) AND (2022:3000[crdt] OR 2022:3000[edat] OR 2022:3000[dp]))
07/2022	((110-54-3 [rn] OR (("hexanes/toxicity"[mh] OR "hexanes/adverse effects"[mh] OR "hexanes/poisoning"[mh] OR "hexanes/pharmacokinetics"[mh] OR ("hexanes"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("hexanes"[mh] AND toxicokinetics[mh:noexp]) OR "hexanes/blood"[mh] OR "hexanes/cerebrospinal fluid"[mh] OR "hexanes/urine"[mh] OR ("hexanes"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("hexanes"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR "hexanes/antagonists and inhibitors"[mh] OR ("hexanes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("hexanes/pharmacology"[majr]) OR ("hexanes"[mh] AND ("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))))) AND (1997:3000[mhda] OR 1997:3000[crdt] OR 1997:3000[edat] OR 1997:3000[dp])) OR ((("Gettysolve-B"[tw] OR "Hexane, n-"[tw] OR "Hexyl hydride"[tw] OR "Skellysolve B"[tw] OR "n-Hexan"[tw] OR "n-Hexane"[tw] OR "hexanes"[tw]) NOT medline[sb]) AND (1997:3000[crdt] OR 1997:3000[edat] OR 1997:3000[dp]))))
NTRL	
06/2024	Limited to 2021 to present "Hexane" OR "Hexanes" OR "n-Hexane" OR "Hexane, n-" OR "Hexyl hydride" OR "n-Hexan" OR "Gettysolve-B" OR "Skellysolve B"
07/2022	Limited to title or keyword (1997-present) "Hexane" OR "Hexanes" OR "n-Hexane" OR "Hexyl hydride" OR "Hexane, n-" OR "n-Hexan" OR "Gettysolve-B" OR "Skellysolve B"
Toxcenter	
06/2024	FILE 'TOXCENTER' ENTERED AT 13:58:46 ON 28 JUN 2024 L1 28310 SEA FILE=TOXCENTER 110-54-3 L2 20623 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 2652 SEA FILE=TOXCENTER L2 AND ED>=20220701 ACT TOXQUERY/Q

Table B-2. Database Query Strings

Database search date	Query string

	L4 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L5 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,IT)
	L6 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L7 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L8 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L9 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L10 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L11 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L12 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L13 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L14 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L15 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L16 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L17 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L18 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L19 QUE (ENDOCRIN? AND DISRUPT?)
	L20 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L21 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L22 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L23 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L24 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L25 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L26 QUE (NEPHROTOX? OR HEPATOTOX?)
	L27 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L28 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L29 QUE L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28
	L30 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L31 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)

Table B-2. Database Query Strings

Database search date	Query string
	L32 QUE L29 OR L30 OR L31 L33 QUE (NONHUMAN MAMMALS)/ORGN L34 QUE L32 OR L33 L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L36 QUE L34 OR L35 --------- L38 1332 SEA FILE=TOXCENTER L3 AND L36 L39 52 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L40 1280 SEA FILE=TOXCENTER L38 NOT MEDLINE/FS L41 1292 DUP REM L39 L40 (40 DUPLICATES REMOVED) D SCAN L41
07/2022	FILE 'TOXCENTER' ENTERED AT 12:36:27 ON 25 JUL 2022 CHARGED TO COST=EH038.15.04.LB.04 L1 24545 SEA FILE=TOXCENTER 110-54-3 L2 24386 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 17710 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 14126 SEA FILE=TOXCENTER L3 AND PY>=1997 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)

Table B-2. Database Query Strings

Database search date	Query string
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L27 QUE (NEPHROTOX? OR HEPATOTOX?) L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (NONHUMAN MAMMALS)/ORGN L35 QUE L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 5842 SEA FILE=TOXCENTER L4 AND L37 L39 5090 SEA FILE=TOXCENTER L4 AND L30 L40 257 SEA FILE=TOXCENTER L39 AND MEDLINE/FS L41 709 SEA FILE=TOXCENTER L39 AND BIOSIS/FS L42 8 SEA FILE=TOXCENTER L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L43 4116 SEA FILE=TOXCENTER L39 AND CAPLUS/FS L44 4809 DUP REM L40 L41 L42 L43 (281 DUPLICATES REMOVED) D SCAN L44

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2024; 07/2022	Compound searched: 110-54-3
NTP	
06/2024	Limited 2020 to present or not dated Hexane n-Hexane Hexanes Hexane, n- Hexyl hydride n-Hexan Gettysolve-B Skellysolve B
07/2022	"Hexane" "Hexanes" "n-Hexane" "Hexyl hydride" "Hexane, n-" "n-Hexan" "Gettysolve-B" "Skellysolve B"
Regulations.gov	
06/2024	Notices limited to posted 1/1/2022 to present] 110-54-3 Hexane Hexanes Hexane, n- n-Hexane n-Hexan Hexyl hydride Gettysolve-B Skellysolve B
07/2022	Hexane n-Hexane Hexyl hydride Gettysolve-B Skellysolve B
NIH RePORTER	
09/2024	Search Criteria: Fiscal Year: Active Projects Text Search: "Hexane" OR "Hexanes" OR "n-Hexane" OR "Hexane, n-" OR "Hexyl hydride" OR "n-Hexan" OR "Gettysolve-B" OR "Skellysolve B" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
01/2023	Search Criteria--Fiscal Year: Active Projects, Text Search: "Hexane" OR "Hexane, n-" OR "Hexanes" OR "Hexyl hydride" OR "n-Hexan" OR "n-Hexane" OR "Gettysolve" OR "Skellysolve" (advanced), Limit to: Project Title, Project Terms, Project Abstracts
Other	Includes additional reference identified throughout the assessment process, which may include studies found by tree searching; recommended by intraagency, interagency, peer, or public reviewers; or published more recently than the date of literature search(es). Additional references include those for specific regulations or guidelines and publications found by targeted searches for specific information (e.g., searches for reviews of general [not chemical-specific] mechanisms of toxicity).

The 2022 pre-public comment search results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 7,402
- Number of records identified from other strategies: 87
- Total number of records to undergo literature screening: 7,489

The 2024 post-public comment search results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 1,555
- Number of records identified from other strategies: 23
- Total number of records to undergo literature screening: 1,578

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on *n*-hexane during the pre- and post-public comment drafts:

- Title and abstract screen
- Full text screen

Pre-Public Comment Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

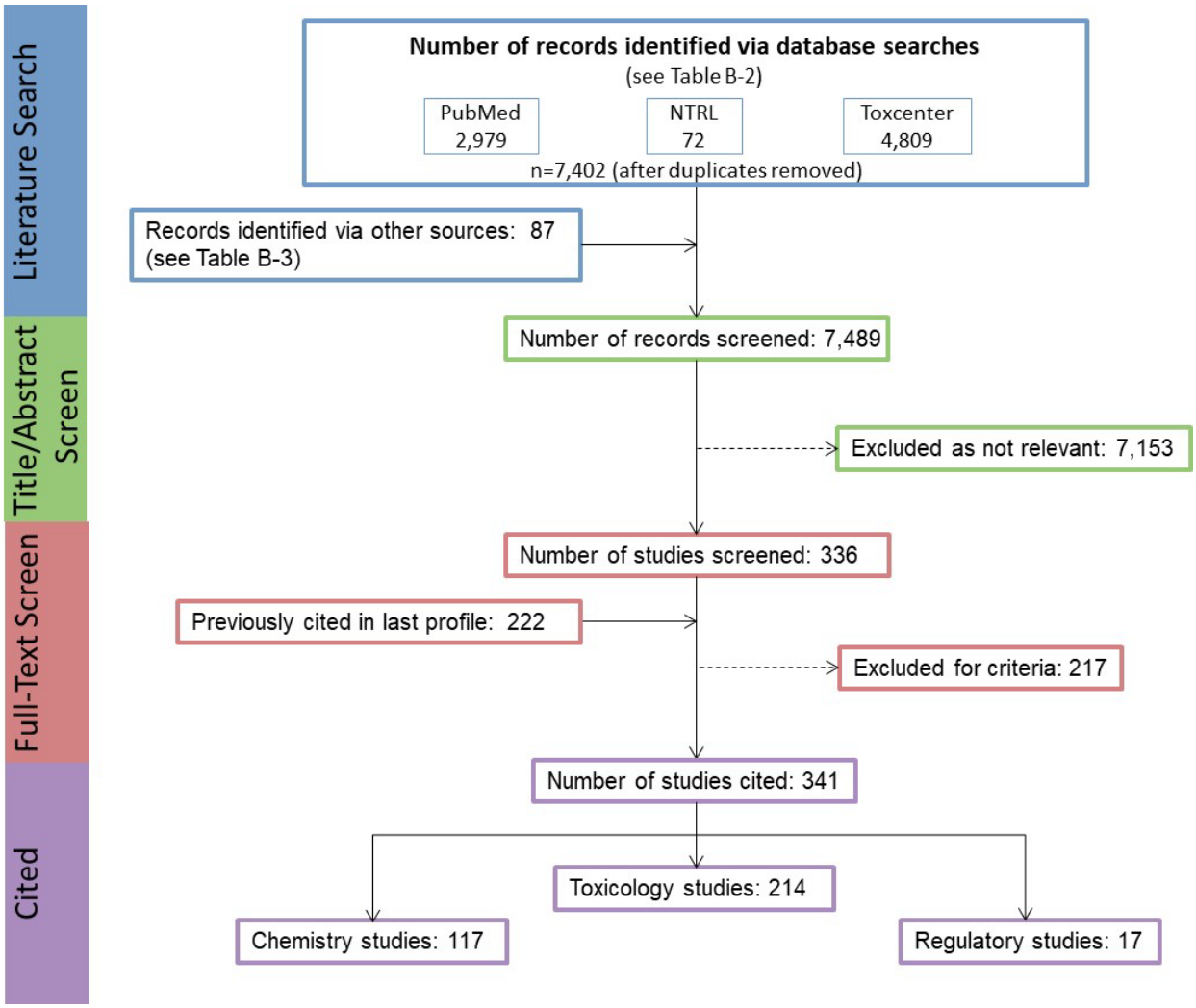
- Number of titles and abstracts screened: 7,489
- Number of studies considered relevant and moved to the next step: 336

Pre-Public Comment Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 336
- Number of studies cited in the previous toxicological profile: 222
- Total number of studies cited in the profile: 341

A summary of the results of the pre-public literature search and screening is presented in Figure B-1.

Figure B-1. July 2022 Pre-Public Comment Literature Search Results and Screen for *n*-Hexane*



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7. There may be references cited in more than one category.

Post-Public Comment Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

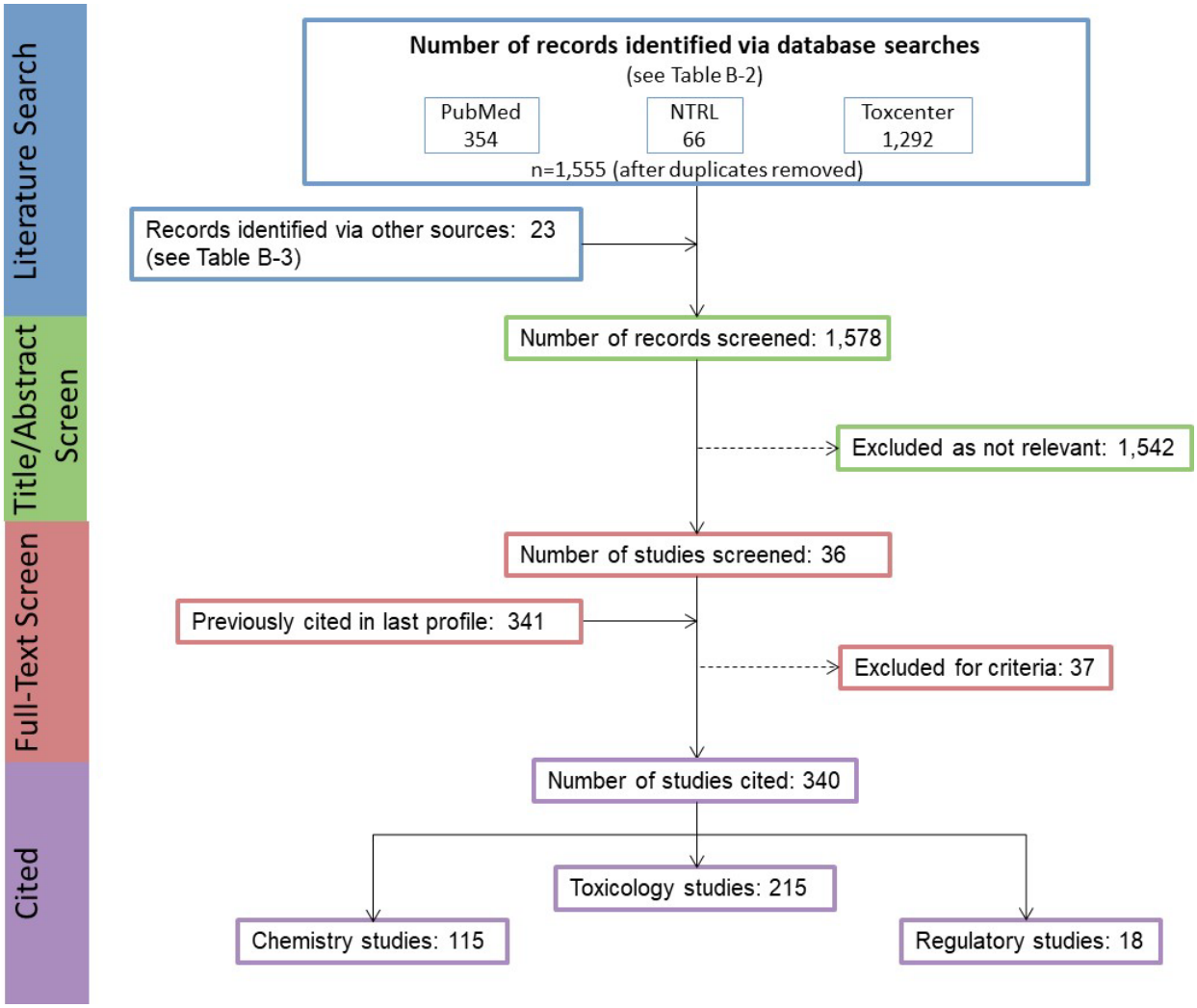
- Number of titles and abstracts screened: 1,578
- Number of studies considered relevant and moved to the next step: 36

Post-Public Comment Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 36
- Number of studies cited in the pre-public draft of the toxicological profile: 341
- Total number of studies cited in the profile: 340

A summary of the results of the post-public comment literature search and screening is presented in Figure B-2.

Figure B-2. June 2024 Post-Public Comment Literature Search Results and Screen for *n*-Hexane*



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7. There may be references cited in more than one category.

APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR *n*-HEXANE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to *n*-hexane, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to *n*-hexane:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to *n*-hexane. The inclusion criteria used to identify relevant studies examining the health effects of *n*-hexane are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of *n*-hexane. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the literature searches were intended to update the Toxicological Profile for *n*-Hexane. See Appendix B for the databases searched and the search strategy.

A total of 7,489 and 1,578 records relevant to all sections of the toxicological profile were identified in the initial and update literature search, respectively.

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of *n*-hexane.

Title and Abstract Screen. In the Title and Abstract Screen step, 101 documents (inclusive of all literature searches) were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 101 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 101 documents (114 studies), 69 documents (75 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted from Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for *n*-Hexane and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.19 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1, 2-2, and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for *n*-hexane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Both human and animal studies indicate that the nervous system is the primary target of *n*-hexane exposure. Additionally, the available animal studies suggest that the developmental and respiratory systems may also be sensitive targets of *n*-hexane exposure. Although numerous case reports evaluating *n*-hexane-induced neurotoxicity were available, these studies were not included in this review (discussed in Section 2.15). The remaining epidemiological and animal experimental studies examining these neurological, developmental, and respiratory outcomes were carried through to Steps 4–8 of the systematic review. There were 38 human and 52 animal studies (published in 70 documents) examining these outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for *n*-Hexane Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort															1 1		
Cross-sectional	2 2	6 3			5 1	1 1	4 2	4 1		1 1		3 2	25 22	2 2		1 0	
Case-control													5 2	3 3	1 1		1 1
Controlled		1 0								1 0							
Case series						2 2			1 1		1 0		≥10[a] ≥10[a]			2 0	
Oral studies																	
Cohort																	
Case-control																	
Controlled																	
Case series																	
Dermal studies																	
Cohort																	
Case-control																	
Controlled									1 1								
Case series																	
Number of studies examining endpoint				0	1	2	3	4	5–9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5–9	≥10							

[a]Due to the abundant database, case series examining neurological endpoints were not included in the systematic review

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Table C-4. Overview of the Health Outcomes for *n*-Hexane Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	6												6	5	6		
	2												1	3	3		
Intermediate-duration	16	7	3	3	6	3	8	8	3	3	3	4	24	9	3	4	1
	11	3	0	0	1	3	0	2	0	1	0	0	22	2	3	0	1
Chronic-duration	1													1			
	0													1			
Oral studies																	
Acute-duration	2													2	2		
	1													0	1		
Intermediate-duration	6				1								7	1			
	5				1								7	1			
Chronic-duration																	
Dermal studies																	
Acute-duration	1								1								
	0								1								
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of *n*-hexane health effects studies (observational epidemiology, human-controlled exposure, and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

Table C-8. Summary of Risk of Bias Assessment for *n*-Hexane—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Developmental							
Cohort							
Lehmann et al. 2002	++	+	+	+	+	++	First
Case-control							
Gong et al. 2018	++	+	++	+	+	++	First
Outcome: Respiratory							
Cross-sectional							
Buchdahl et al. 2000	+	+	+	+	+	++	First
Mustajbegovic et al. 2000	+	+	++	+	+	++	First
Nijem et al. 2000	–	–	++	–	–	+	Third
Nijem et al. 2001	–	–	++	–	–	+	Third
Paciencia et al. 2020	–	–	–	–	–	–	Third
Wichmann et al. 2009	+	+	++	–	++	++	Second
Outcome: Neurological							
Case-control							
Boggess et al. 2016	++	+	++	+	++	++	First
Goldman et al. 2012	+	–	+	–	+	+	Second
Issever et al. 2002	–	–	+	–	–	+	Third

Table C-8. Summary of Risk of Bias Assessment for *n*-Hexane—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Talbott et al. 2015	++	++	++	+	+	++	First
Verberk et al. 2004	–	–	+	–	+	+	Third
Cross-sectional							
Bates et al. 2016, 2019	+	–	–	–	+	++	Third
Beckman et al. 2016	+	+	+	–	+	++	Second
Chang and Yip 1987	–	–	+	–	–	+	Third
Chang 1987	–	–	+	–	–	+	Third
Chang et al. 1993	–	–	+	+	–	+	Third
Gong et al. 2003	+	+	+	+	+	++	First
Governa et al. 1987	–	–	–	+	–	–	Third
Huang et al. 1991	–	–	–	+	–	–	Third
Ithnin et al. 2011	–	–	–	–	–	–	Third
Juarez-Perez et al. 2014	–	–	–	+	–	+	Third
Murata et al. 1994	+	+	–	+	–	+	Second
Mutti et al. 1982a	+	–	–	+	+	+	Second
Mutti et al. 1982b	+	–	+	+	+	+	Second
Neghab et al. 2012	+	+	+	++	+	++	First
Nijem et al. 2000	–	–	+	–	+	+	Second

Table C-8. Summary of Risk of Bias Assessment for *n*-Hexane—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Nijem et al. 2001	–	–	+	–	+	+	Third
Park et al. 2009	+	–	+	+	–	+	Third
Pastore et al. 1994	+	–	–	+	+	+	Second
Raitta et al. 1978; Seppalainen et al. 1979	–	–	+	–	+	+	Third
Sanagi et al. 1980	+	+	–	++	+	+	First
Sliwinska-Kowalska et al. 2005	+	++	+	+	+	+	First
Tsai et al. 1997	+	++	+	–	+	++	Second
Wang et al. 1986	–	–	–	–	–	+	Third
Yokoyama et al. 1997	+	–	+	–	+	+	Third

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key questions used to assign risk of bias tier

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Table C-9. Summary of Risk of Bias Assessment for *n*-Hexane – Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings							Risk of bias tier
	Selection bias		Performance bias	Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Respiratory								
Inhalation acute exposure								
Nelson et al. 1943	–	–	–	–	– –	–	–	Third

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier

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Table C-10. Summary of Risk of Bias Assessment for *n*-Hexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Developmental Effects									
Inhalation acute exposure									
API 1979	–	–	+	+	+	–	+	++	First
Bus et al. 1979 (GDs 8–12)	–	–	+	+	+	+	+	++	First
Bus et al. 1979 (GDs 12–16)	–	–	+	+	+	+	+	++	First
Bus et al. 1979 (GDs 8–16)	–	–	+	+	+	+	+	++	First
NIEHS 1987	+	–	++	+	+	++	+	++	First
NIEHS 1988c	+	–	++	+	+	++	+	++	First
Inhalation intermediate exposure									
Li et al. 2014, 2015	–	–	–	–	–	–	–	+	Third
Stoltenburg-Didinger et al. 1990 (21 days)	–	–	– –	–	–	–	+	–	Third
Stoltenburg-Didinger et al. 1990 (63 days)	–	–	– –	–	–	–	+	–	Third
Oral acute exposure									
Marks et al. 1980 (1 dose/day)	+	–	+	+	+	+	+	+	Second
Marks et al. 1980 (3 doses/day)	+	–	+	+	+	+	+	+	Second
Outcome: Respiratory Effects									
Inhalation intermediate exposure									
API 1981	++	–	++	+	+	++	++	++	First
Cavender et al. 1984	+	–	+	+	++	++	++	++	First

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Table C-10. Summary of Risk of Bias Assessment for *n*-Hexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Howd et al. 1983 (21 days old)	+	–	+	+	++	–	+	++	First
Howd et al. 1983 (80 days old)	+	–	+	+	++	–	+	++	First
Lungarella et al. 1984	–	–	+	–	– –	+	+	+	Third
NTP 1991 (6 hours/day)	++	++	+	+	+	++	++	++	First
NTP 1991 (22 hours/day)	++	++	+	+	+	++	++	++	First
Outcome: Neurological Effects									
Inhalation acute exposure									
Chalansonnet et al. 2013	–	–	++	+	–	++	–	+	Third
De Martino et al. 1987 (1–2 weeks)	+	–	–	+	–	+	–	++	Third
NIEHS 1987	+	–	++	+	+	++	+	++	First
NIEHS 1988a	+	–	++	+	+	++	+	++	First
NIEHS 1988b	+	–	++	+	+	++	+	++	First
NIEHS 1988c	+	–	++	+	+	++	+	++	First
Inhalation intermediate exposure									
Altenkirch et al. 1982 (9 weeks)	–	–	++	–	+	+	++	++	Second
Altenkirch et al. 1982 (40 weeks)	–	–	++	–	+	+	++	++	Second
API 1981	++	–	++	–	+	++	++	++	First
Cavender et al. 1984	+	–	+	–	++	++	++	++	First

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Table C-10. Summary of Risk of Bias Assessment for *n*-Hexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
De Martino et al. 1987 (3–6 weeks)	+	–	–	–	–	+	–	++	Third
Frontali et al. 1981 (9 hours/day, 5 days/week)	++	–	+	–	–	+	–	+	Third
Frontali et al. 1981 (10 hours/day, 6 days/week)	++	–	+	–	–	+	–	+	Third
Howd et al. 1983 (21 days old)	+	–	+	–	++	–	+	++	Second
Howd et al. 1983 (80 days old)	+	–	+	–	++	–	+	++	Second
Huang et al. 1989	+	–	+	–	+	+	+	++	Second
Ichihara et al. 1998	+	–	+	+	+	+	+	++	First
Li et al. 2014, 2015	–	–	–	–	–	–	–	+	Third
Lungarella et al. 1984	–	–	+	–	– –	+	+	+	Third
NTP 1991 (6 hours/day)	++	++	+	–	+	++	++	++	First
NTP 1991 (22 hours/day)	++	++	+	–	+	++	++	++	First
Pryor et al. 1983	+	+	+	–	–	+	+	+	Second
Rebert and Sorenson 1983	–	–	+	–	+	–	+	+	Third
Schaumburg and Spencer 1976	–	–	– –	–	–	– –	–	–	Third
Stoltenburg-Didinger et al. 1990 (21 days)	–	–	–	–	–	–	+	+	Third
Takeuchi et al. 1980	–	–	–	–	–	+	+	+	Third
Oral intermediate exposure									
Gao et al. 2019	+	-	+	-	+	–	+	+	First

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Table C-10. Summary of Risk of Bias Assessment for *n*-Hexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Krasavage et al. 1980	+	–	+	–	+	++	+	++	First
Li et al. 2018	+	–	+	–	–	–	+	++	Second
Li et al. 2020a	+	–	+	++	–	–	+	++	Second
Li et al. 2020b	+	–	+	++	–	–	+	+	Second
Ono et al. 1981	–	–	+	–	–	– –	+	–	Third
Wang et al. 2017	+	–	+	–	+	–	+	+	Third

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to *n*-hexane and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to *n*-hexane and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-11, C-12, and C-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-11. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-12. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-13. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining developmental, respiratory, and neurological outcomes observed in the observational epidemiology, human-controlled exposure, and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

Table C-14. Presence of Key Features of Study Design for *n*-Hexane—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Developmental					
Cohort					
Lehmann et al. 2002	No	No	Yes	Yes	Low
Case-control					
Gong et al. 2018	No	No	Yes	Yes	Low
Outcome: Respiratory					
Cross-sectional					
Buchdahl et al. 2000	No	No	Yes	Yes	Low
Mustajbegovic et al. 2000	No	Yes	Yes	Yes	Moderate
Nijem et al. 2000	No	Yes	Yes	No	Low
Nijem et al. 2001	No	Yes	Yes	No	Low
Paciencia et al. 2020	No	No	Yes	No	Very low
Wichmann et al. 2009	No	No	Yes	Yes	Low
Outcome:					
Case-control					
Boggess et al. 2016	No	No	Yes	Yes	Low
Goldman et al. 2012	No	Yes	Yes	Yes	Moderate
Issever et al. 2002	No	Yes	Yes	Yes	Moderate
Talbott et al. 2015	No	No	Yes	Yes	Low
Verberk et al. 2004	No	Yes	Yes	Yes	Moderate
Cross-sectional					
Bates et al. 2016, 2019	No	Yes	Yes	Yes	Moderate
Beckman et al. 2016	No	Yes	Yes	Yes	Moderate
Chang and Yip 1987	No	Yes	Yes	Yes	Moderate
Chang 1987	No	Yes	Yes	Yes	Moderate
Chang et al. 1993	No	Yes	Yes	Yes	Moderate
Gong et al. 2003	No	Yes	Yes	Yes	Moderate
Governa et al. 1987	No	Yes	Yes	No	Low
Huang et al. 1991	No	Yes	Yes	Yes	Moderate
Ithnin et al. 2011	No	Yes	Yes	No	Low
Juarez-Perez et al. 2014	No	Yes	Yes	Yes	Moderate
Murata et al. 1994	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for *n*-Hexane—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Mutti et al. 1982a	No	Yes	Yes	Yes	Moderate
Mutti et al. 1982b	No	Yes	Yes	Yes	Moderate
Neghab et al. 2012	No	Yes	Yes	Yes	Moderate
Nijem et al. 2000	No	Yes	Yes	No	Low
Nijem et al. 2001	No	Yes	Yes	No	Low
Park et al. 2009	No	Yes	Yes	Yes	Moderate
Pastore et al. 1994	No	Yes	Yes	Yes	Moderate
Raitta et al. 1978; Seppalainen et al. 1979	No	Yes	Yes	Yes	Moderate
Sanagi et al. 1980	No	Yes	Yes	Yes	Moderate
Sliwinska-Kowalska et al. 2005	No	Yes	Yes	Yes	Moderate
Tsai et al. 1997	No	Yes	Yes	Yes	Moderate
Wang et al. 1986	No	Yes	Yes	No	Low
Yokoyama et al. 1997	No	Yes	Yes	Yes	Moderate

Table C-15. Presence of Key Features of Study Design for *n*-Hexane—Human-Controlled Exposure

Reference	Key Features				Initial study confidence
	Comparison group or served as own controls	Sufficient number of subjects tested	Appropriate outcome assessment	Appropriate statistical analysis	
Outcome: Respiratory effects					
Inhalation acute exposure					
Nelson et al. 1943	No	No	Yes	No	Very low

Table C-16. Presence of Key Features of Study Design for *n*-Hexane—Experimental Animal Studies

Reference	Key features				
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Developmental Effects					
Inhalation acute exposure					
API 1979	Yes	Yes	Yes	Yes	High
Bus et al. 1979 (GDs 8–12)	Yes	No	Yes	Yes	Moderate
Bus et al. 1979 (GDs 12–16)	Yes	No	Yes	Yes	Moderate
Bus et al. 1979 (GDs 8–16)	Yes	No	Yes	Yes	Moderate
NIEHS 1987	Yes	Yes	Yes	Yes	High
NIEHS 1988c	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Li et al. 2014, 2015	Yes	No	Yes	Yes	Moderate
Stoltenburg-Didinger et al. 1990 (21 days)	Yes	No	Yes	No	Low
Stoltenburg-Didinger et al. 1990 (63 days)	Yes	No	Yes	No	Low
Oral acute exposure					
Marks et al. 1980 (1 dose/day)	Yes	No	Yes	Yes	Moderate
Marks et al. 1980 (3 doses/day)	Yes	No	Yes	Yes	Moderate
Outcome: Respiratory Effects					
Inhalation intermediate exposure					
API 1981	Yes	Yes	Yes	Yes	High
Cavender et al. 1984	Yes	Yes	Yes	Yes	High
Howd et al. 1983 (21 days old)	Yes	Yes	Yes	Yes	High
Howd et al. 1983 (80 days old)	Yes	Yes	Yes	Yes	High
Lungarella et al. 1984	Yes	Yes	Yes	No	Moderate
NTP 1991 (6 hours/day)	Yes	Yes	Yes	Yes	High
NTP 1991 (22 hours/day)	Yes	Yes	Yes	Yes	High
Outcome: Neurological Effects					
Inhalation acute exposure					
Chalansonnet et al. 2013	Yes	No	Yes	No	Low
De Martino et al. 1987 (1–2 weeks)	Yes	No	Yes	No	Low
NIEHS 1987	Yes	Yes	Yes	No	Moderate
NIEHS 1988a	Yes	Yes	Yes	No	Moderate

Table C-16. Presence of Key Features of Study Design for *n*-Hexane—Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
NIEHS 1988b	Yes	Yes	Yes	No	Moderate
NIEHS 1988c	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
Altenkirch et al. 1982 (9 weeks)	Yes	No	Yes	No	Low
Altenkirch et al. 1982 (40 weeks)	Yes	No	Yes	No	Low
API 1981	Yes	Yes	Yes	Yes	High
Cavender et al. 1984	Yes	Yes	Yes	Yes	High
De Martino et al. 1987 (3–6 weeks)	Yes	No	Yes	No	Low
Frontali et al. 1981 (9 hours/day, 5 days/week)	Yes	No	Yes	No	Low
Frontali et al. 1981 (10 hours/day, 6 days/week)	Yes	No	Yes	No	Low
Howd et al. 1983 (21 days old)	Yes	Yes	Yes	Yes	High
Howd et al. 1983 (80 days old)	Yes	Yes	Yes	Yes	High
Huang et al. 1989	Yes	No	Yes	Yes	Moderate
Ichihara et al. 1998	Yes	No	Yes	Yes	Moderate
Li et al. 2014, 2015	Yes	No	Yes	Yes	Moderate
Lungarella et al. 1984	Yes	Yes	Yes	No	Moderate
NTP 1991 (6 hours/day)	Yes	Yes	Yes	Yes	High
NTP 1991 (22 hours/day)	Yes	Yes	Yes	Yes	High
Pryor et al. 1983	Yes	Yes	Yes	Yes	High
Rebert and Sorenson 1983	Yes	No	Yes	Yes	Moderate
Schaumburg and Spencer 1976	No	No	Yes	No	Low
Stoltenburg-Didinger et al. 1990 (21 days)	Yes	No	Yes	No	Low
Stoltenburg-Didinger et al. 1990 (63 days)	Yes	No	Yes	No	Low
Takeuchi et al. 1980	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Gao et al. 2019	Yes	Yes	Yes	Yes	High
Krasavage et al. 1980	Yes	No	Yes	No	Low
Li et al. 2018	Yes	Yes	Yes	Yes	High
Li et al. 2020a	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for *n*-Hexane—Experimental Animal Studies

Reference	Key features: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Li et al. 2020b	Yes	No	Yes	Yes	Moderate
Ono et al. 1981	Yes	No	Yes	Yes	Moderate
Wang et al. 2017	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-17.

Table C-17. Initial Confidence Rating for *n*-Hexane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Developmental Effects		
Inhalation acute exposure		
Animal studies		
Bus et al. 1979 (GDs 8–12)	Moderate	High
Bus et al. 1979 (GDs 12–16)	Moderate	
Bus et al. 1979 (GDs 8–16)	Moderate	
API 1979	High	
NIEHS 1987	High	
NIEHS 1988c	High	
Inhalation intermediate exposure		
Animal studies		
Li et al. 2014, 2015	Moderate	Moderate
Stoltenburg-Didinger et al. 1990 (21 days)	Low	
Stoltenburg-Didinger et al. 1990 (63 days)	Low	
Inhalation chronic exposure		
Human studies		
Lehmann et al. 2002	Low	Low
Gong et al. 2018	Low	

Table C-17. Initial Confidence Rating for *n*-Hexane Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral acute exposure		
Animal studies		
Marks et al. 1980 (1 dose/day)	Moderate	Moderate
Marks et al. 1980 (3 doses/day)	Moderate	
Outcome: Respiratory Effects		
Inhalation acute exposure		
Human studies		
Nelson et al. 1943	Very Low	Very Low
Inhalation intermediate exposure		
Animal studies		
API 1981	High	High
Cavender et al. 1984	High	
Howd et al. 1983 (21 days old)	High	
Howd et al. 1983 (80 days old)	High	
Lungarella et al. 1984	Moderate	
NTP 1991 (6 hours/day)	High	
NTP 1991 (22 hours/day)	High	
Inhalation chronic exposure		
Human studies		
Buchdahl et al. 2000	Low	Low
Mustajbegovic et al. 2000	Moderate	
Nijem et al. 2000	Low	
Nijem et al. 2001	Low	
Paciencia et al. 2020	Very low	
Wichmann et al. 2009	Low	
Nelson et al. 1943	Very low	
Outcome: Neurological Effects		
Inhalation acute exposure		
Animal studies		
Chalansonnet et al. 2013	Low	Moderate
De Martino et al. 1987 (1–2 weeks)	Low	
NIEHS 1987	Moderate	
NIEHS 1988a	Moderate	
NIEHS 1988b	Moderate	
NIEHS 1988c	Moderate	
Inhalation intermediate exposure		
Animal studies		
API 1981	High	High
Altenkirch et al. 1982 (9 weeks)	Low	
Altenkirch et al. 1982 (40 weeks)	Low	

Table C-17. Initial Confidence Rating for *n*-Hexane Health Effects Studies

	Initial study confidence	Initial confidence rating
Cavender et al. 1984	High	
De Martino et al. 1987 (3–6 weeks)	Low	
Frontali et al. 1981 (9 hours/day, 5 days/week)	Low	
Frontali et al. 1981 (10 hours/day, 6 days/week)	Low	
Howd et al. 1983 (21 days old)	High	
Howd et al. 1983 (80 days old)	High	
Huang et al. 1989	Moderate	
Ichihara et al. 1998	Moderate	
Li et al. 2014, 2015	Moderate	
Lungarella et al. 1984	Moderate	
NTP 1991 (6 hours/day)	High	
NTP 1991 (22 hours/day)	High	
Pryor et al. 1983	High	
Rebert and Sorenson 1983	Moderate	
Schaumburg and Spencer 1976	Low	
Stoltenburg-Didinger et al. 1990 (21 days)	Low	
Takeuchi et al. 1980	Moderate	
Inhalation chronic exposure		
Human studies		
Boggess et al. 2016	Low	
Goldman et al. 2012	Moderate	
Issever et al. 2002	Moderate	
Talbott et al. 2015	Low	
Verberk et al. 2004	Moderate	
Bates et al. 2016, 2019	Moderate	
Beckman et al. 2016	Moderate	
Chang and Yip 1987	Moderate	
Chang 1987	Moderate	
Chang et al. 1993	Moderate	
Gong et al. 2003	Moderate	Moderate
Governa et al. 1987	Low	
Huang et al. 1991	Moderate	
Ithnin et al. 2011	Low	
Juarez-Perez et al. 2014	Moderate	
Murata et al. 1994	Moderate	
Mutti et al. 1982a	Moderate	
Mutti et al. 1982b	Moderate	
Neghab et al. 2012	Moderate	
Nijem et al. 2000	Low	
Nijem et al. 2001	Low	

Table C-17. Initial Confidence Rating for *n*-Hexane Health Effects Studies

	Initial study confidence	Initial confidence rating
Park et al. 2009	Moderate	
Pastore et al. 1994	Moderate	
Raitta et al. 1978; Seppalainen et al. 1979	Moderate	
Sanagi et al. 1980	Moderate	
Sliwinska-Kowalska et al. 2005	Moderate	
Tsai et al. 1997	Moderate	
Wang et al. 1986	Low	
Yokoyama et al. 1997	Moderate	
Oral intermediate exposure		
Animal studies		
Gao et al. 2019	High	
Krasavage et al. 1980	Low	
Li et al. 2018	High	
Li et al. 2020a	High	High
Li et al. 2020b	Moderate	
Ono et al. 1981	Moderate	
Wang et al. 2017	High	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for developmental, respiratory, and neurological effects are presented in Table C-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with *n*-hexane exposure is presented in Table C-19.

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Developmental Effects			
Human studies	Low	-1 indirectness	Very low
Animal studies	High	+1 consistency	High
Outcome: Respiratory Effects			
Human studies	Low	-1 risk of bias	Very low
Animal studies	High		High
Outcome: Neurological Effects			
Human studies	Moderate	-1 risk of bias +1 consistency +1 large magnitude of effect +1 Residual bias	High
Animal studies	High	+1 consistency +1 dose response +1 large magnitude of effect	High

Table C-19. Confidence in the Body of Evidence for *n*-Hexane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Developmental	Very low	High
Respiratory	Very low	High
Neurological	High	High

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8, C-9, and C-10). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
    - No downgrade if none of the factors are considered indirect
    - Downgrade one confidence level if one of the factors is considered indirect

- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure

scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:

- Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for *n*-hexane, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for *n*-hexane is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for *n*-Hexane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Developmental	Very low	Health effect	Inadequate
Respiratory	Very low	Health effect	Inadequate
Neurological	High	Health effect	High
Animal studies			
Developmental	High	Health effect	High
Respiratory	High	Health effect	High
Neurological	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

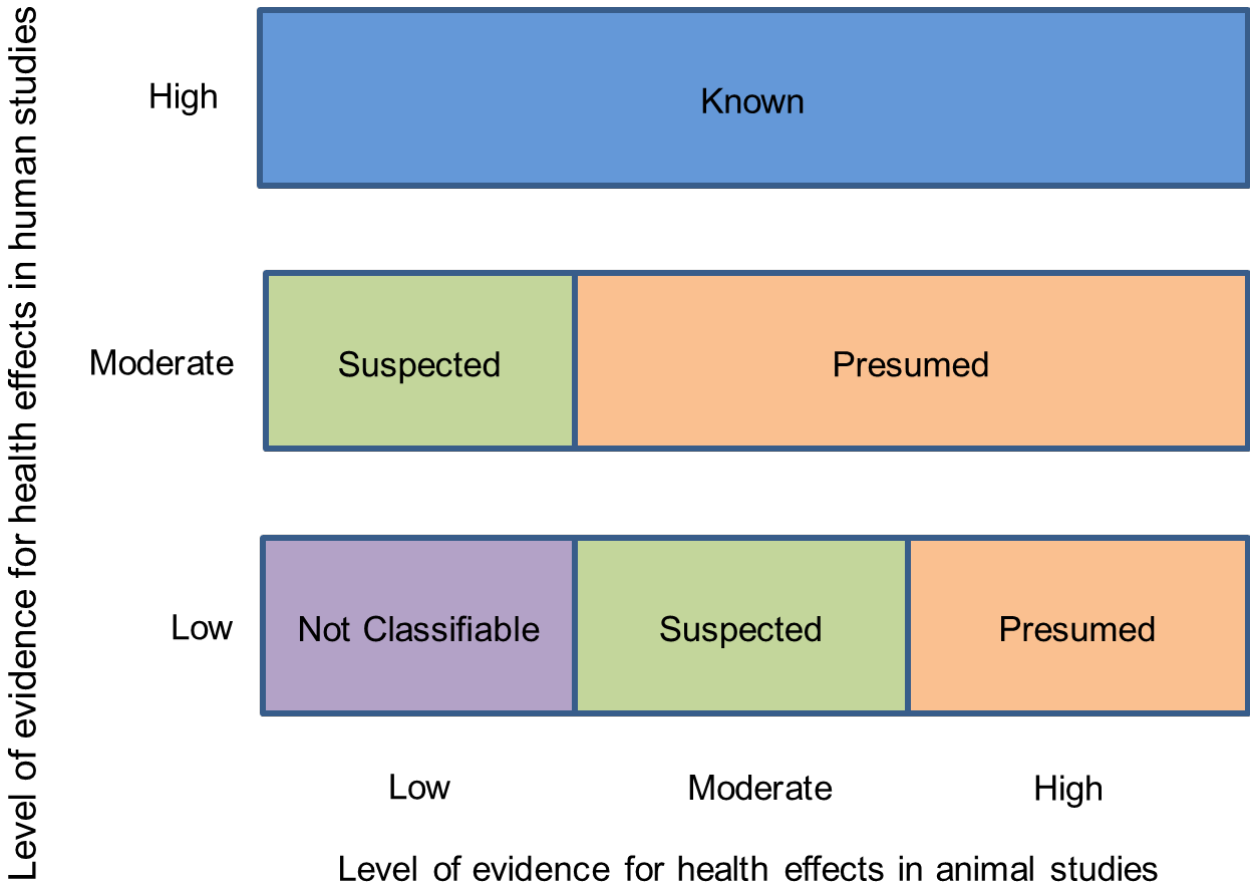
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
    - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
    - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
    - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
    - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
    - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
    - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for *n*-hexane are listed below and summarized in Table C-21.

Known Health Effects

- Neurological
  - High level of evidence from human studies: numerous human studies are available that establish the neurotoxicity of *n*-hexane (Chang et al. 1993; Gong et al. 2003; Huang et al. 1991; Murata et al. 1994; Mutti et al. 1982a, 1982b; Pastore et al. 1994; Raitta et al. 1978; Seppalainen et al. 1979; Sanagi et al. 1980; Wang et al. 1986; Yokoyama et al. 1997).
  - High level of evidence from animal studies: abundant data are available demonstrating the neurological effects of *n*-hexane inhalation (Altenkirch et al. 1982; API 1981; Cavender et al. 1984; De Martino et al. 1987; Frontali et al. 1981; Howd et al. 1983; Huang et al. 1989; Ichihara et al. 1998; NTP 1991; Schaumburg and Spencer 1976; Takeuchi et al. 1980) and oral exposure (Gao et al. 2019; Krasavage et al. 1980; Li et al. 2018, 2020a, 2020b; Ono et al. 1981; Wang et al. 2017) in rodents.

Suspected Health Effects

- Developmental
  - Inadequate evidence from human studies: A case-control study showed a positive association between ambient *n*-hexane exposure and low birth weight (Gong et al. 2018), while a cohort study reported an association between maternal *n*-hexane exposure and alterations of the neonatal immune system (Lehmann et al. 2002). No other developmental studies were available.
  - High level of evidence from animal studies: several rodent studies have reported decreased fetal/litter weights following inhalation (Bus et al. 1979; NIEHS 1987, 1988c; Stoltenburg-Didinger et al. 1990) or oral exposure (Marks et al. 1980) to *n*-hexane.
- Respiratory
  - Inadequate evidence from human studies: human survey studies have identified higher incidences of self-reported respiratory symptoms (i.e., cough, phlegm, bronchitis, chest tightness) in solvent-exposed workers (Mustajbegovic et al. 2000; Nijem et al. 2001). In a study evaluating the effects of ambient *n*-hexane exposure in children, reduced lung function was observed in children living near point sources (Wichmann et al. 2009); however, two additional studies found no associations between *n*-hexane exposure and hospital visits for breathing problems (Buchdahl et al. 2000) or the incidence of rhinitis (Paciencia et al. 2020) in children.
  - High level of evidence from animal studies: an inhalation study observed nasal lesions in mice following intermediate-duration exposure (NTP 1991); two similar studies did not find lesions in the nasal turbinates of rats (API 1981; Cavender et al. 1984). Additional studies have observed increased lung weights and lung lesions (Howd et al. 1983; Lungarella et al. 1984; NTP 1991).

Table C-21. Hazard Identification Conclusions for *n*-Hexane

Outcome	Hazard identification
Developmental	Suspected
Respiratory	Suspected
Neurological	Known

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX D

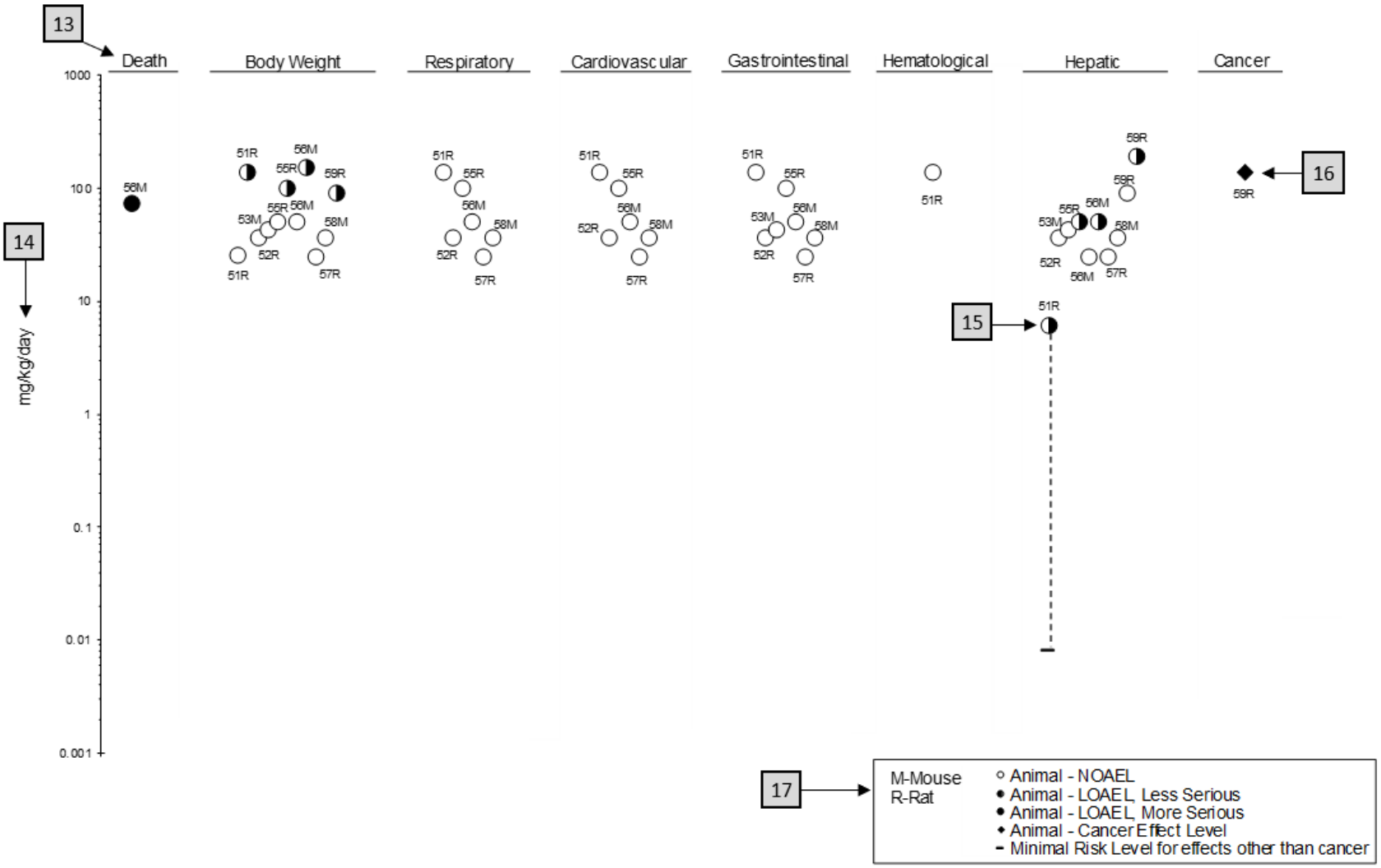
Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

(11)
[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/environmental-medicine/hcp/emhsis/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsLanding.aspx).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at https://www.pehsu.net/.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—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 noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result