UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
LAND AND EMERGENCY
MANAGEMENT

MEMORANDUM

SUBJECT: Recommendations on the Use of Chronic or Subchronic Noncancer Values for Superfund Human Health Risk Assessments

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TO: Superfund Emergency Management Divisions Directors, Regions 1 - 10

PURPOSE

The purpose of this memorandum is to provide recommendations from the Office of Land and Emergency Management (OLEM) regarding the use of the subchronic toxicity value rather than the chronic value for 19 specific chemicals as noted in the attachment.

This recommendation is based on OLEM's Human Health Regional Risk Assessment Forum's (OHHRRAF) Toxicity Workgroup evaluation of the toxicity of 32 chemicals. The OHHRRAF recommended using subchronic values in place of chronic values for 19 of the 32 chemicals OLEM concurs with the OHHRRAF recommendation. The Forum's recommendations may be applicable to EPA regional offices' activities to evaluate and address hazardous waste releases under the Comprehensive Environmental Response, Compensation and Liability Act, as amended (e.g., Hazard Ranking System scoring, remedial investigation and feasibility study process, and five-year reviews), and other OLEM risk evaluation efforts.

BACKGROUND

The Office of Solid Waste and Emergency Response[1] (OSWER) Directive 9285.7-53 **(***Human Health Toxicity Values in Superfund Risk Assessments*; December 5, 2003; commonly referred to as "the 2003 hierarchy guidance"), identifies an updated source hierarchy for human health toxicity values to consider when carrying out Superfund site risk assessments. It also states that "[t]his revised hierarchy recognizes that EPA should use the best science available on which to base risk assessments." Furthermore, the 2003 hierarchy guidance states that, "EPA and state personnel may use and accept other technically sound approaches," acknowledging "that there may be other sources of toxicological information," referring specifically to OSWER Directive

[1] The former name of what is now EPA's Office of Land and Emergency Management.

9285.7-16 (*Use of IRIS Values in Superfund Risk Assessment*; December 21, 1993), which offers similar guidance.[2]

The OHHRRAF Toxicity Workgroup identified 21 oral and 11 inhalation toxicity values where a subchronic toxicity value was lower than its corresponding chronic toxicity value. After review of relevant information, the Forum recommends use of the subchronic toxicity value rather than the chronic value for 19 of the 32. For the remaining 13 chemical toxicity values, the Forum recommends the chronic toxicity values be used.

The recommendations in the memorandum will be re-evaluated in the future as toxicity values are updated.

Please contact Michele Burgess (703-603-9003) or Laurence Libelo (703-603-8815) if you have any questions or require additional information.

Attachment
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[2] See OSWER Directive 9285.7-53, page 2, quoting OSWER Directive 9285.7-16: "...IRIS is not the only source of toxicology information, and in some cases more recent, credible and relevant data may come to the Agency's attention. In particular, toxicological information other than that in IRIS may be brought to the Agency by outside parties. Such information should be considered along with the data in IRIS in selecting toxicological values; ultimately, the Agency should evaluate risk based upon its best scientific judgement and consider all credible and relevant information available to it."

Selected Chronic Toxicity Values[a]						
Chemical (CASRN)	**Chronic Value**	**Source (Year)**	**Subchronic Value**	**Source (Year)**	**Selected Value**	**Date**
Inhalation (mg/m^3)						
*Acrylic acid (79-10-7)	0.001	IRIS (1994)	0.0002	PPRTV (2010)	0.0002	04/18/19
Ammonia (7664-41-7)	0.5	IRIS (2016)	0.1	PPRTV (2005)	0.5	04/18/19
Chlordane (12789-03-6)	0.0007	IRIS (1998)	0.0002	ATSDR (1994)	0.0007	04/18/19
1,1-Dichloroethylene (75-35-4)	0.2	IRIS (2002)	0.08[b]	ATSDR (1994)	0.2	04/18/19
*2-Ethoxyethanol (110-80-5)	0.2	IRIS (1991)	0.04	PPRTV (2013)	0.04	12/12/2019
*Ethyl chloride (75-00-3)	10	IRIS (1991)	4	PPRTV (2007)	4	04/18/19
*2-Methoxyethanol (109-86-4)	0.2	IRIS (1991)	0.007	PPRTV (2011)	0.007	04/18/19
Methyl tert-butyl ether (1634-04-4)	3	IRIS (1993)	2.5[c]	ATSDR (1996)	3	06/25/2020
Nitromethane (75-52-5)	0.005	PPRTV (2013)	0.004	PPRTV (2013)	0.005	04/18/19
Vinyl acetate (108-05-4)	0.2	IRIS (1990)	0.05[d]	ATSDR (2001)	0.2	06/25/2020
*Vinyl chloride (75-01-4)	0.1	IRIS (2000)	0.08[e]	ATSDR (2006)	0.08	08/27/2020
Oral (mg/kg-day)						
Acrylamide (79-06-1)	0.002	IRIS (2010)	0.001	ATSDR (2012)	0.002	06/27/2019
Acrylic acid (79-10-7)	0.5	IRIS (1994)	0.2	PPRTV (2010)	0.5	03/05/2020
*Acrylonitrile (107-13-1)	0.04	ATSDR (1990)	0.01	ATSDR (1990)	0.01	06/27/2019
*Allyl alcohol (107-18-6)	0.005	IRIS (1987)	0.004	PPRTV (2009)	0.004	04/18/19
*Atrazine (1912-24-9)	0.035	IRIS (1993)	0.003	ATSDR (2003)	0.003	06/27/2019
1,1-Biphenyl (92-52-4)	0.5	IRIS (2013)	0.1	PPRTV (2011)	0.5	04/18/19
*Bromodichloromethane (75-27-4)	0.02	IRIS (1987)	0.008	PPRTV (2009)	0.008	04/18/19
*Cadmium (7440-43-9)	0.0005/0.001f	IRIS (1989)	0.0001[f]	ATSDR (2012)	0.0001	04/18/19
*p-Chloroaniline (106-47-8)	0.004	IRIS (1988)	0.0005	PPRTV (2008)	0.0005	04/18/19
*p-Cresol (106-44-5)	0.1	ATSDR (2008)	0.02	PPRTV (2010)	0.02	04/18/19
Cyclohexanone (108-94-1)	5	IRIS (1987)	2	PPRTV (2010)	5	08/27/2020
Endosulfan (115-29-7)	0.006	IRIS (1994)	0.005	ATSDR (2015)	0.006	06/27/2019
*Ethyl acetate (141-78-6)	0.9	IRIS (1987)	0.7	PPRTV (2013)	0.7	04/18/19
*Ethylbenzene (100-41-4)	0.1	IRIS (1987)	0.05	(PPRTV (2009)	0.05	04/18/19
*Ethylene glycol (107-21-1)	2	IRIS (1987)	0.8	ATSDR (2010)	0.8	04/18/19
Ethylene glycol monobutyl ether (111-76-2)	0.1	IRIS (2010)	0.07	ATSDR (2010)	0.1	04/18/19
*Hepatchlor (76-44-8)	0.0005	IRIS (1987)	0.0001	ATSDR (2007)	0.0001	06/27/2019
*Hexachlorobenzene (118-74-1)	0.0008	IRIS (1988)	0.00001	PPRTV (2010)	0.00001	04/18/19
*Hexachlorocyclohexane, gamma (58-89-9)	0.0003	IRIS (1987)	0.00001	ATSDR (2005)	0.00001	08/27/2020
Pentachlorophenol (87-86-5)	0.005	IRIS (2010)	0.001	ATSDR (2001)	0.005	08/27/2020
*1,2,4,5-Tetrachlorobenzene (95-94-3)	0.0003	IRIS (1987)	0.00003	PPRTV (2013)	0.00003	04/18/19

[a]Decisions regarding the most appropriate toxicity value when the subchronic value was more conservative than the chronic value in the Regional Screening Levels (RSLs).
[b]Intermediate-duration MRL = 0.02 ppm
[c]Intermediate-duration MRL = 0.07 ppm
[d]Intermediate-duration MRL = 0.01 ppm
[e]Intermediate-duration MRL = 0.03 ppm
[f]Values for food/water.
[g]Chronic-duration MRL; an intermediate-duration MRL of 0.0005 mg/kg-day was also available (ATSDR 2012).
*Indicates that selection of the subchronic value.

1. Decisions that Require a Change in the RSLs (Inhalation).

Acrylic Acid (CASRN 79-10-7). The IRIS chronic RfC (1994) and the PPRTV subchronic p-RfC (2010) are based on the same study (Miller et al. 1981). However, the PPRTV used BMD modeling and dosimetric conversion factors to account for pharmacokinetics differences between mice and people. The PPRTV value is selected based on the use of updated methodology.

Summary Table for Acrylic Acid (CASRN 79-10-7)		
Source (Year)	**IRIS (1994)**	**PPRTV (2010)**
Toxicity Value	Chronic RfC	Subchronic p-RfC
Critical Study	Miller et al. 1981	
Species/Strain/Sex	B6C3F1 mice (15/sex/group)	
Study Duration	6 hours/day, 5 days/week, for 13 weeks	
Critical Effect(s)	Focal degeneration of the nasal olfactory epithelium	
POD	$LOAEL_{[HEC]}$ = 0.33 mg/m^3	$BMDL10_{[HEC]}$ = 0.02 mg/m^3
Composite UF	300[a]	100[b]
Toxicity Value (mg/m^3)	0.001	0.0002
Selected Value (mg/m^3)	0.0002	
Rationale	Updated methodology	

[a]The composite UF of 300 is based on 10 for UF_H, 3 for UF_S, 3 for UF_A, and 3 for UF_L.
[b]The composite UF of 100 if based on 3 for UF_A, 10 for UF_H, and 3 for UF_D

References:

- Miller, RR; Ayres, JA; Jersey GC; et al. (1981) Inhalation toxicity of acrylic acid. Fund. Appl. Toxicol. 1:271–277.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0002_summary.pdf#nameddest=rfc
- U.S. EPA. (2010) Provisional peer-reviewed toxicity values for acrylic acid (CASRN 79-10-7). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/AcrylicAcid.pdf

2-Ethoxyethanol (2-EE) (CASRN 110-80-5). The subchronic p-RfC (PPRTV 2013) is based on a developmental toxicity study. The PPRTV determined that, based on duration-adjusted concentrations, minor and major skeletal defects in the offspring of Dutch rabbits (Doe 1984b) is a more sensitive endpoint than testicular (and hematological) effects in adult New Zealand White rabbits (Barbee et al. 1984a), which was the critical effect identified by IRIS (1991). In support, fetal effects (minor skeletal defects) were also observed in a developmental toxicity study using Wistar rats (Doe 1984b). BMD modeling (i.e., updated methodology) was used in the PPRTV assessment to determine the POD (compared to the IRIS $NOAEL_{HEC}$). A benchmark response (BMR) of 5% extra risk was used; it is standard EPA practice to use a BMR of 5% for developmental endpoints. Although the data from Doe (1984b) were provided on a per pup basis (rather than a per-litter basis), the sample size of each exposure group was calculated from the data provided. The PPRTV also noted that BMD modeling could not be applied to the less sensitive endpoints from the Barbee et al. (1984a) study because an abnormally large standard deviation was reported for one of the testis weights values, and no quantitative data for seminiferous tubule degeneration were provided. The PPRTV value is selected based on the evaluation of sensitive (developmental) endpoints and the use of updated methodology.

Summary Table for 2-Ethoxyethanol (CASRN 110-80-5)		
Source (Year)	**IRIS (1991)**	**PPRTV (2013)**
Toxicity Value	Chronic RfC	Subchronic p-RfC
Critical Study	Barbee et al. 1984a	Doe 1984b
Species/Strain/Sex	New Zealand White rabbits (10/sex/group)	Dutch rabbits (24 females/group)
Study Duration	6 hours/day, 5 days/week for 13 weeks	6 hours/day on GDs 6-18
Critical Effect(s)	Decreased hemoglobin, decreased testis weight, and seminiferous tubule degeneration	Fetal skeletal effects
POD	$NOAEL_{[HEC]}$ of 68 mg/m^3	$BMDL_{[5\%HEC]}$ of 4.23 mg/m^3
Composite UF	300[a]	100[b]
Toxicity Value (mg/m^3)	0.2	0.04
Selected Value (mg/m^3)	0.04	

Rationale	Different study; updated methodology

[a]The composite UF of 300 is based on 3 for UF_A, 10 for UF_H, and 10 for UF_S.
[b]The composite UF of 100 if based on 3 for UF_A, 3 for UF_D, and 10 for UF_H

References:

- Barbee, S.J., J.B. Terrill, D.J. DeSousa and C.C. Conaway. 1984a. Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. Environ. Health Perspect. 57: 157-163.
- Doe, JE. (1984b) Ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate teratology studies. Environ Health Perspect 57:33−41.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0513_summary.pdf#nameddest=rfc
- U.S. EPA. (2013) Provisional peer-reviewed toxicity values for 2-ethoxyethanol (CASRN 110-80-5). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Ethoxyethanol2.pdf.

Ethyl Chloride (CASRN 75-00-3). The IRIS chronic RfC (1991) and the PPRTV subchronic p-RfC (2007) are based on the same study (Scortichini et al. 1986). However, the PPRTV Assessment used BMD modeling to determine the POD (i.e., updated methodology). The PPRTV value is selected based on the use of updated methodology.

Summary Table for 2-Ethyl Chloride (CASRN 75-00-3)		
Source (Year)	**IRIS (1991)**	**PPRTV (2007)**
Toxicity Value	Chronic RfC	Subchronic p-RfC
Critical Study	Scortichini et al. 1986	
Species/Strain/Sex	CF-1 mice (30 females/group)	
Study Duration	6 hours/day on GDs 6-15	
Critical Effect(s)	Delayed ossification of the skull bones	
POD	$NOAEL_{[HEC]}$ = 4000 mg/m^3	$LEC_{10[ADJ]}$ = 1078 mg/m^3
Composite UF	300[a]	300[b]
Toxicity Value (mg/m^3)	10	4
Selected Value (mg/m^3)	4	
Rationale	Updated methodology	

[a]The composite UF of 300 is based on 3 for UF_A, 10 for UF_H, and 10 for UF_D.
[b]The composite UF of 300 is based on 3 for UF_A, 10 for UF_H, and 10 for UF_D.

References:

- Scortichini, B.H., K.A. Johnson, J.J. Momany-Pfruender, and T.R. Hanley, Jr. 1986. Ethyl chloride: Inhalation teratology study in CF-1 mice. Dow Chemical Co. EPA Document #86- 870002248.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0523_summary.pdf#nameddest=rfc
- U.S. EPA. (2007) Provisional peer-reviewed toxicity values for chloroethane (CASRN 75-00-3). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Chloroethane.pdf

2-Methoxyethanol (CASRN 109-86-4). The IRIS chronic RfC (1991) and the PPRTV subchronic p-RfC (2011) are based on the same study (Miller et al. 1983). However, the PPRTV Assessment used BMD modeling to determine the POD (i.e., updated methodology). The PPRTV value is selected based on the use of updated methodology.

Summary Table for 2-Methoxyethanol (CASRN 109-86-4)		
Source (Year)	**IRIS (1991)**	**PPRTV (2011)**
Toxicity Value	Chronic RfC	Subchronic p-RfC
Critical Study	Miller et al. 1983	
Species/Strain/Sex	New Zealand White rabbits (5/sex/group)	
Study Duration	6 hours/day, 5 days/week, for 13 weeks	
Critical Effect(s)	Reduction in testis size	
POD	$NOAEL_{[HEC]}$ = 17 mg/m^3	$BMDL_{[10HEC]}$ = 0.73 mg/m^3
Composite UF	1000[a]	100[b]
Toxicity Value (mg/m^3)	0.02	0.007
Selected Value (mg/m^3)	0.007	
Rationale	Updated methodology	

[a]The composite UF of 1000 is based on 3 for UF_A, 3 for UF_D, 10 for UF_H, and 10 for UF_S.
[b]The composite UF of 300 is based on 3 for UF_A, 10 for UF_H, and 3 for UF_D.

References:

- Miller, R.R., J.A. Ayres, J.T. Young and M.J. McKenna. 1983. Ethylene glycol monomethyl ether. I. Subchronic vapor inhalation study with rats and rabbits. Fund. Appl. Toxicol. 3(1): 49- 54.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0525_summary.pdf#nameddest=rfc
- U.S. EPA. (2011) Provisional peer-reviewed toxicity values for 2-methoxyethanol (CASRN 109-86-4) and 2-methoxyethanol acetate (CASRN 110-49-6). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/MethoxyethanolAcetate2.pdf

Vinyl Chloride (CASRN 75-01-4). The IRIS assessment is based on a dietary study that used PBPK modeling for route-to-route (R2R) extrapolation. The ATSDR assessment is based on a study (Thornton et al., 2002) that was not available when the IRIS assessment was completed (2000). Other differences between the ATSDR intermediate-duration MRL (2006) and the IRIS chronic RFC (2000) were due to rounding. IRIS divided the POD of 2.5 mg/m^3 by the composite uncertainty factor (UF_C) of 30 to arrive at 0.08 mg/m^3, which was rounded to 0.1 mg/m^3. ATSDR identified a POD of 1.25 ppm, which was rounded to 1 ppm prior to the application of uncertainty factors. The POD divided by the UF_C of 30 generated an intermediate-duration MRL of 0.03 ppm; using the conversion factor 1 ppm = 2.56 mg/m^3 resulted in a toxicity value of 0.08 mg/m^3. Differences in the toxicity values is an artifact of the derivation process used by each agency. The ATSDR value is selected based on new information.

Summary Table for Vinyl Chloride (CASRN 75-01-4)		
Source (Year)	**IRIS (2000)**	**ATSDR (2006)**
Toxicity Value	Chronic RfC	Intermediate-duration MRL
Critical Study	Til et al. 1983, 1991	Thornton et al. 2002
Species/Strain/Sex	Wistar rats (50 to 100/sex/group)	Sprague-Dawley rats (30/sex/group)
Study Duration	Lifetime dietary	4 hours/day for two generations
Critical Effect(s)	Liver cell polymorphism	Centrilobular hypertrophy (F1 females)
POD	$NOAEL_{[HEC]}$ = 2.5 mg/m^3 (based on PBPK model R2R extrapolation)	$LEC_{[10HEC]}$ = 1 ppm
Composite UF	30[a]	30[b]
Toxicity Value	0.1 mg/m^3	0.03 ppm (0.08 mg/m^3)
Selected Value (mg/m^3)	0.08	
Rationale	New study	

[a]The composite UF of 30 is based on 3 for UF_A, and 10 for UF_H.
[b]The composite UF of 30 is based on 3 for UF_A, and 10 for UF_H.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (2006). Toxicological profile vinyl chloride. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp20.pdf
- Thornton SR, Schroeder RE, Robison RL, et al. 2002. Embryo-fetal developmental and reproductive toxicology of vinyl chloride in rats. Toxicol Sci 68:207-219.
- Til, HP; Feron, VJ; Immel, HR. (1991) Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. Food Chem Toxicol 29:713-718.
- Til, HP; Immel, HR; Feron, VJ. (1983) Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes. TNO Report No. V 83.285/291099, TSCATS Document FYI-AX-0184-0353, Fiche No. 0353.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/1001_summary.pdf#nameddest=rfc

2. Decisions that Require a Change in the RSLs (Oral).

Acrylonitrile (CASRN 107-13-1). The study used to derive the intermediate-duration MRL (Tandon, 1988) identified a serious LOAEL for decreased sperm count and testicular tubule degeneration at 10 mg/kg-day and used a UF_C of 1000 to derive a chronic-duration MRL of 0.01 mg/kg-day (see footnote f of Table 2-2 in the ATSDR Toxicological Profile). According to the same table, the chronic-duration MRL was derived from Biodynamics (1980) based on a NOAEL of 4.2 mg/kg-day for decreased red blood cells (footnote h). Figure 2-2 erroneously shows that the chronic-duration MRL was derived from Biodynamics (1980) using a NOAEL based on decreased red blood cells of 0.14 mg/kg-day. The intermediate-duration ATSDR value is selected because it is more protective than the chronic-duration MRL.

Summary Table for Acrylonitrile (CASRN 107-13-1)		
Source (Year)	**ATSDR (1990)**	**ATSDR (1990)**
Toxicity Value	Chronic-duration MRL	Intermediate-duration MRL
Critical Study	Biodynamics 1980	Tandon 1988
Species/Strain/Sex	F344 rats	Mice
Study Duration	24 months	60 days
Critical Effect(s)	Decreased red cells	Decreased sperm count and testicular tubule degeneration
POD	NOAEL = 4.2 mg/kg-day	LOAEL = 10 mg/kg-day
Composite UF	100[a]	1000[b]
Toxicity Value (mg/kg-day)	0.04	0.01
Selected Value (mg/kg-day)	0.01	
Rationale	Different methodology	

[a]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.
[b]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_L.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (1996). Toxicological profile for acrylamide. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp125.pdf
- Bio/dynamics. 1980b. A twenty-four month oral toxicity/carcinogenicity study of acrylonitrile administered in the drinking water to Fischer 344 rats. Biodynamics, Inc., Division of Biology and Safety Evaluation, East Millstone, NJ. Project No. BDN-77-27.
- Tandon R, Saxena DK, Chandra SV, et al. 1988. Testicular effects of acrylonitrile in mice. Toxicol Lett 42:55-63.

Allyl Alcohol (CASRN 107-18-6). The PPRTV (2009) assessment used a new study (NTP 2006) that was not available when the IRIS assessment was completed (1987) and used the BMD modeling to determine the POD (i.e., updated methodology). The PPRTV is selected based on new information and the use of updated methodology.

Summary Table for Allyl Alcohol (CASRN 107-18-6)		
Source (Year)	**IRIS (1987)**	**PPRTV (2009)**
Toxicity Value	Chronic RfD	Subchronic p-RfD
Critical Study	Carpanini et al. 1978	NTP 2006
Species/Strain/Sex	Wistar rats (15/sex/group)	F344/N rats (10/sex/group)
Study Duration	15 weeks	5 days/week for 14 weeks
Critical Effect(s)	Impaired renal function and kidney weights	Squamous hyperplasia of the forestomach epithelium (females)
POD	NOEL = 4.8 mg/kg-day	BMDL = 1.3 mg/kg-day
Composite UF	1000[a]	300[b]
Toxicity Value (mg/kg-day)	0.005	0.004
Selected Value (mg/kg-day)	0.004	
Rationale	New study; updated methodology	

[a]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_S.
[b]The composite UF of 300 is based on 10 for UF_A, 10 for UF_H, and 3 for UF_D.

References:

- Carpanini, F.M.B., I.F. Gaunt, J. Hardy, S.D. Gangalli, K.R. Butterworth and H.G. Lloyd. 1978. Short-term toxicity of allyl alcohol in rats. Toxicology. 9: 29-45.
- NTP (National Toxicology Program). 2006. NTP technical report on the comparative toxicity studies of allyl acetate, allyl alcohol and acrolein administered by gavage to F344/N rats and B6C3F1 mice. National Toxicology Program Toxicity Report Series Number 48. July 2006. Online. http://ntp.niehs.nih.gov/files/TS48_Web.pdf.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0004_summary.pdf#nameddest=rfd.U.S. EPA. (2009) Provisional peer-reviewed toxicity values for allyl alcohol (CASRN107-18-6). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/AllylAlcohol.pdf

Atrazine (CASRN 1912-24-9). The intermediate-duration MRL from ATSDR (2003) is based on a study (Gojmerac et al. 1999) that was not available at the time of the IRIS assessment (1993). The critical effect identified by ATSDR is indicative of the potential for endocrine disruption, and results in a lower toxicity value than the chronic RfD. The ATSDR value is selected based on new information.

Summary Table for Atrazine (CASRN 1912-24-9)		
Source (Year)	**IRIS (1993)**	**ATSDR (2003)**
Toxicity Value	Chronic RfD	Intermediate-duration MRL
Critical Study	Ciba-Geigy Corp. 1986	Gojmerac et al. 1999
Species/Strain/Sex	Sprague-Dawley rats (20/sex/group)	Swedish Landance/Large Yorkshire pigs (9 young females/group)
Study Duration	2 years	19 days
Critical Effect(s)	Decreased body weight gain	Delayed estrus
POD	NOAEL = 3.5 mg/kg-day	LOAEL = 1 mg/kg-day
Composite UF	100[a]	300[b]
Toxicity Value (mg/kg-day)	0.035	0.003
Selected Value (mg/kg-day)	0.003	
Rationale	New study	

[a]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.
[b]The composite UF of 300 is based on 10 for UF_A, 3 for UF_H, and 10 for UF_L.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (2003). Toxicological profile for atrazine. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp153.pdf
- Ciba-Geigy Corporation. 1986. MRID No. 00141874, 00157875, 00158930, 40629302. HED Doc. No. 005940, 006937. Available from EPA. Write to FOI, EPA, Washington, DC 20460.
- Gojmerac T, Uremovic M, Uremovic Z, et al. 1999. Reproductive disturbance caused by an s-triazine herbicide in pigs. Acta Vet Hung 47(1):129-135.
- U.S. EPA. (1993). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0209_summary.pdf

Bromodichloromethane (CASRN 75-27-4). The subchronic p-RfD (PPRTV 2009) is based on a study (Bielmeier et al. 2001) that was not available at the time of the IRIS assessment (1987). The PPRTV value is selected based on new information.

Summary Table for Bromodichhloromethane (CASRN 75-27-4)		
Source (Year)	**IRIS (1987)**	**PPRTV (2009)**
Toxicity Value	Chronic RfD	Subchronic p-RfD
Critical Study	NTP 1986	Bielmeier et al. 2001
Species/Strain/Sex	B6C3F1 mice (50/sex/group)	F344 rats (8-11 females/group)

Study Duration	102 weeks	GD 9
Critical Effect(s)	Renal cytomegaly	Full litter resorption
POD	LOAEL = 17.9 mg/kg-day	$BMDL_{05}$ = 0.76 mg/kg-day
Composite UF	1000[a]	100[b]
Toxicity Value (mg/kg-day)	0.02	0.008
Selected Value (mg/kg-day)	0.008	
Rationale	New study	

[a]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, 3 for UF_L, and 3 for UF_D.
[b]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.

References:

- Bielmeier, S.R., D.S. Best, D.L. Guidici et al. 2001. Pregnancy loss in the rat caused by bromodichloromethane. Toxicol. Sci. 59:309−315.
- NTP (National Toxicology Program). 1986. Toxicology and Carcinogenesis Studies of Bromodichloromethane in F344/N Rats and B6C3F1 Mice (gavage studies). NTP Technical Report, Ser. No. 321, NIH Publ. No. 87-2537.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0213_summary.pdf
- U.S. EPA. (2009) Provisional peer-reviewed toxicity values for bromodichloromethane (CASRN 75-27-4). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Bromodichloromethane.pdf

Cadmium (CASRN 7440-43-9). The chronic-duration MRL was derived from a meta-analysis of several studies assessing the effect of dietary cadmium on renal function in humans. The chronic-duration ATSDR value is selected based on new information (i.e., meta-analysis data).

Summary Table for Cadmium (CASRN 7440-43-9)			
Source (Year)	**IRIS (1989)**	**ATSDR (2012)**	**ATSDR (2012)**
Toxicity Value	Chronic RfD	Chronic-duration MRL	Intermediate-duration MRL
Critical Study	U.S. EPA 1985	Buchet et al. 1990; Järup et al. 2000; Suwazono et al. 2006	Brzóska et al. 2005a, 2005b; Brzóska and Moniuszko-Jakoniuk 2005
Species/Strain/Sex	Human studies involving chronic exposures	General population and residents of cadmium-polluted and non-polluted areas	Wistar rats (40 females/group)
Study Duration	Various	Various	12 months
Critical Effect(s)	Significant proteinuria	Renal dysfunction (proteinuria)	Decreased bone mineral density
POD	NOAEL (water) = 0.005 mg/kg-day NOAEL (food = 0.01 mg/kg-day	$UCDL_{10}$ = 0.00033 mg/kg-day (females)	$BMDL_{1SD}$ = 0.05 mg/kg-day
Composite UF	10[a]	3[b]	100[c]
Toxicity Value (mg/kg-day)	0.0005 (water) 0.001 (food)	0.0001	0.0005
Selected Value (mg/kg-day)	0.0001		
Rationale	New study		

[a]The composite UF of 10 is on 10 for UF_H.
[b]The composite UF of 3 is based on 3 for UF_H.
[c]The composite UF of 100 is based on 10 for UF_A and 10 for UF_H.
UCDL = lower limit on urinary cadmium dose

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (2003). Toxicological profile for cadmium. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp5.pdf
- Brzóska MM, Majewska K, Moniuszko-Jakoniuk J. 2005a. Bone mineral density, chemical composition and biomechanical properties of the tibia of female rats exposed to cadmium since weaning up to skeletal maturity. Food Chem Toxicol 43(10):1507-1519.

- Brzóska MM, Majewska K, Moniuszko-Jakoniuk J. 2005b. Weakness in the mechanical properties of the femur of growing female rats exposed to cadmium. Arch Toxicol 79(5):277-288.
- Brzóska MM, Moniuszko-Jakoniuk J. 2005. Disorders in bone metabolism of female rats chronically exposed to cadmium. Toxicol Appl Pharmacol 202(1):68-83.
- Buchet JP, Lauwerys R, Roels H, et al. 1990. Renal effects of cadmium body burden of the general population. Lancet 336:699-702.
- Järup L, Hellstrom L, Alfven T, et al. 2000. Low level exposure to cadmium and early kidney damage: The OSCAR study. Occup Environ Med 57(10):668-672.

p-Chloroaniline (CASRN 106-47-8). The subchronic p-RfD (PPRTV 2008) is based on a study (NTP 1989) that was not available when the IRIS assessment was completed (1988). The PPRTV value is selected based on new information.

Summary Table for p-Chloroaniline (CASRN 106-47-8)		
Source (Year)	**IRIS (1988)**	**PPRTV (2008)**
Toxicity Value	Chronic RfD	Subchronic p-RfD
Critical Study	NCI 1979	NTP 1989
Species/Strain/Sex	F344 rats (20 to 50/sex/group)	F344 rats (15/sex/group)
Study Duration	78 weeks (24 weeks observation)	6 months (interim)
Critical Effect(s)	Non-neoplastic lesions of splenic capsule	Methemoglobin formation
POD	LOAEL = 12.5 mg/kg-day	$LOAEL_{[ADJ]}$ = 1.4 mg/kg-day
Composite UF	3000[a]	3000[b]
Toxicity Value (mg/kg-day)	0.004	0.0005
Selected Value (mg/kg-day)	0.0005	
Rationale	New study	

[a]The composite UF of 3000 is based on 10 for UF_A, 10 for UF_H, 10 for UF_L, and 3 for UF_D.
[b]The composite UF of 3000 is based on 10 for UF_A, 10 for UF_H, 3 for UF_L, and 10 for UF_D.

References:

- NCI (National Cancer Institute). 1979. Bioassay of p-chloroaniline for possible carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 189. NTIS PB 295896.
- NTP (National Toxicology Program). 1989. Toxicology and carcinogenesis studies of parachloroaniline hydrochloride (CAS No. 20265-96-7) in F344/N rats and B6C3F1 mice (gavage studies). NTP-TR-351. NIH Pub. No. 89-2806.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0320_summary.pdf#nameddest=rfd
- U.S. EPA. (2008) Provisional peer-reviewed toxicity values for p-chloroaniline (CASRN 106-47-8). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Chloroanilinep.pdf

p-Cresol (CASRN 106-44-5). The chronic-duration MRL (ATSDR 2008) was based on a 2-year study that used a mixture of p- and m-cresols (CASRNs 95-48-7, 108-39-4, 1319-77-3, and 106-44-5); ATSDR considers the BRRC (1998) study, used in the PPRTV assessment to derive a subchronic p-RfD, an acute toxicity study (as per ATSDR policy). The PPRTV value is selected based on new information (i.e., data from a study not considered relevant to the ATSDR chronic-duration MRL).

Summary Table for p-Cresol (CASRN 106-44-5)		
Source (Year)	**ATSDR (2008)**	**PPRTV (2010)**
Toxicity Value	Chronic-duration MRL	Subchronic p-RfD
Critical Study	NTP 2008	BRRC 1988
Species/Strain/Sex	B6C3F1 mice (50/sex/group)	New Zealand White rabbits (14 females/group)
Study Duration	2 years	GDs 6-18
Critical Effect(s)	Bronchiolar hyperplasia of the lung and thyroid follicular degeneration	Mortality and clinical signs

POD	LOAEL = 100 mg/kg-day	NOAEL = 5 mg/kg-day
Composite UF	1000[a]	300[b]
Toxicity Value (mg/kg-day)	0.1	0.02
Selected Value (mg/kg-day)	0.02	
Rationale	Different study	

[a]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_L
[b]The composite UF of 300 is based on 10 for UF_A, 10 for UF_H, and 3 for UF_D.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (2003). Toxicological profile for cresols. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp34.pdf
- BRRC (Bushy Run Research Center). (1988) Developmental toxicity evaluation of o-, m- or p-cresol administered by gavage to rabbits and rats with cover letter dated 07/06/88. Final Project Report 51-508. TSCA Section 4 Submission. U.S. EPA Doc. No. 40-8860253. Fiche No. OTS0517695.
- NTP. 2008. Toxicology and carcinogenesis studies of cresols (CAS No. 1319-77-3) in male F344/N rats and female B6C3F1 mice (feed studies). Research Triangle Park, NC: National Toxicology Program. TR-550. Draft technical report.
- U.S. EPA. (2010) Provisional peer-reviewed toxicity values for 4-methylphenol (p-cresol) (CASRN 106-44-5). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Methylphenol4.pdf

Ethyl Acetate (CASRN 141-78-6). The IRIS assessment and the PPRTV are based on the same study (American Biogenics 1986), but the PPRTV assessment (2013) used body weight$^{3/4}$ to calculate a human equivalent dose and reduced the interspecies UF to 3. The PPRTV value is selected based on updated methodology.

Summary Table for Ethyl Acetate (CASRN 141-78-6)		
Source (Year)	**IRIS (1987)**	**PPRTV (2013)**
Toxicity Value	Chronic RfC	Subchronic p-RfC
Critical Study	American Biogenics 1986	
Species/Strain/Sex	Sprague-Dawley rats (30/sex/group)	
Study Duration	90 days	
Critical Effect(s)	Mortality and body weight loss	Clinical signs
POD	NOAEL = 900 mg/kg-day	$NOAEL_{[HED]}$ = 216 mg/kg-day
Composite UF	1000[a]	300[b]
Toxicity Value (mg/m^3)	0.9	0.7
Selected Value (mg/m^3)	0.7	
Rationale	Updated methodology	

[a]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_S.
[b]The composite UF of 300 is based on 3 for UF_A, 10 for UF_H, and 10 for UF_D.

References:

- American Biogenics Corporation. (1986) Rat oral subchronic study with ethyl acetate. Office of Solid Waste, U.S. Environmental Protection Agency, Washington, DC. 699273 (Cited in IRIS as: U.S. EPA. 1986. Rat oral subchronic study with ethyl acetate. Office of Solid Waste, Washington, DC.)
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0157_summary.pdf
- U.S. EPA. (2013) Provisional peer-reviewed toxicity values for ethyl acetate (CASRN 141-78-6) a. Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/EthylAcetate.pdf

Ethylbenzene (CASRN 100-41-4). The PPRTV assessment (2009) used BMD methodology and a toxicity study that was not available at the time of the IRIS assessment (1987). The PPRTV value is selected based on new information and the use of updated methodology.
*Note: The IRIS program is updating this assessment.

Summary Table Ethylbenzene (CASRN 100-41-4)

Source (Year)	IRIS (1987)	PPRTV (2009)
Toxicity Value	Chronic RfD	Subchronic p-RfD
Critical Study	Wolf et al. 1956	Mellert et al. 2007
Species/Strain/Sex	Albino rats (10 females/group and 20 female controls)	Wistar rats (10/sex/group)
Study Duration	5 days/week for 182 days	7 days/week for 13 weeks
Critical Effect(s)	Liver and kidney toxicity	Centrilobular hepatocyte hypertrophy (males)
POD	NOAEL = 97.1 mg/kg-day	$BMDL_{10}$ = 48 mg/kg-day
Composite UF	1000[a]	1000[b]
Toxicity Value (mg/kg-day)	0.1	0.05
Selected Value (mg/kg-day)	0.05	
Rationale	New study; updated methodology	

[a]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_S.
[b]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_D.

References:

- Mellert, W., K. Deckardt, W. Kaufmann et al. 2007. Ethylbenzene: 4- and 13-week rat oral toxicity. Arch. Toxicol. 81:361–370.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0051_summary.pdf
- U.S. EPA. (2009) Provisional peer-reviewed toxicity values for ethylbenzene (CASRN 100-41-4). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Ethylbenzene.pdf
- Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

Ethylene Glycol (CASRN 107-21-1). ATSDR (2010) used a new study (Neeper-Bradley et al. 1995) that was not available when the IRIS assessment was completed (1987). In addition, the ATSDR assessment used BMD modeling to determine the POD (i.e., updated methodology). The ATSDR value is selected based on new information and the use of updated methodology.

Summary Table Ethylene Glycol (CASRN 107-21-1)		
Source (Year)	**IRIS (1987)**	**ATSDR (2010)**
Toxicity Value	Chronic RfD	Intermediate-duration MRL
Critical Study	DePass et al. 1986	Neeper-Bradley et al. 1995; Tyl 1989
Species/Strain/Sex	F344 rats (30/sex/group)	CD-1 mice (30 females/group)
Study Duration	2 years	GDs 6-15
Critical Effect(s)	Kidney toxicity	Bilateral extra lumbar ribs (offspring)
POD	NOEL = 200 mg/kg-day	$BMDL_{10}$ = 75.59 mg/kg-day
Composite UF	100[a]	100[b]
Toxicity Value (mg/kg-day)	2	0.8
Selected Value (mg/kg-day)	0.8	
Rationale	New study; updated methodology	

[a]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.
[b]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (2010). Toxicological profile for ethylene glycol. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp96.pdf
- DePass, L.R., R.H. Garman, M.D. Woodside, et al. 1986a. Chronic toxicity and oncogenicity studies of ethylene glycol in rats and mice. Fund. Appl. Toxicol. 7: 547-565.
- Neeper-Bradley TL, Tyl RW, Fisher LC, et al. 1995. Determination of a no-observed-effect level for developmental toxicity of ethylene glycol administered by gavage to CD rats and CD-1 mice. Fundam Appl Toxicol 27:121-130.
- Tyl RW. 1989. Developmental toxicity evaluation of ethylene glycol administrated by gavage to CD-1 mice:

Determination of a "no-observed-effect-level" (NOEL). Bushy Run Research Center, CMA Project Report 51-591.

- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0238_summary.pdf

Heptachlor (CASRN 76-44-8). The ATSDR assessment derived a toxicity value based on developmental toxicity studies (Smialowicz et al. 2000; Moser et al. 2001) that evaluated sensitive endpoints and were not available when the IRIS assessment was completed (1987). The ATSDR value is selected based on the evaluation of sensitive (developmental) endpoints and new information.

Summary Table Heptachlor (CASRN 76-44-8)		
Source (Year)	**IRIS (1987)**	**ATSDR (2007)**
Toxicity Value	Chronic RfD	Intermediate-duration MRL
Critical Study	Velsicol Chemical 1955	Smialowicz et al. 2001†; Moser et al. 2001*
Species/Strain/Sex	CF white rats (20/sex/group)	Sprague-Dawley rats (15 to 20 females/group)
Study Duration	2 years	†GD 12-PND 71; pups exposed to day 42 *GD 12-PND 7 (dams); *PND 7-PND 21 or 42 (pups)
Critical Effect(s)	Increased liver weight (males)	†Immunological and *neurological effects
POD	NOEL = 0.15 mg/kg-day	LOAEL = 0.03 mg/kg-day
Composite UF	300[a]	300[b]
Toxicity Value (mg/kg-day)	0.0005	0.0001
Selected Value (mg/kg-day)	0.0001	
Rationale	New study	

[a]The composite UF of 300 is based on 10 for UF_A, 10 for UF_H, and 3 for UF_D.
[b]The composite UF of 300 is based on 10 for UF_A, 10 for UF_H, and 3 for UF_L.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (2007). Toxicological profile for heptachlor and heptachlor epoxide. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp12.pdf
- Moser VC, Shafer TJ, Ward TR, et al. 2001. Neurotoxicological outcomes of perinatal heptachlor exposure in the rat. Toxicol Sci 60(2):315-326.
- Smialowicz RJ, Williams WC, Copeland CB, et al. 2001. The effects of perinatal/juvenile heptachlor exposure on adult immune and reproductive system function in rats. Toxicol Sci 61(1):164-175.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0243_summary.pdf
- Velsicol Chemical Corporation. 1955a. MRID No. 00062599. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Hexachlorobenzene (CASRN 118-74-1). The PPRTV (2010) derived a toxicity value from a study (Bourque et al. 1995) that was not available when the IRIS assessment was completed (1988). The PPRTV value is selected based on new information.

Summary Table Hexachlorobenzene (CASRN 118-74-1)		
Source (Year)	**IRIS (1988)**	**PPRTV (2010)**
Toxicity Value	Chronic RfD	Subchronic p-RfD
Critical Study	Arnold et al. 1985	Bourque et al. 1995
Species/Strain/Sex	Sprague-Dawley rats (50/sex/group)	Cynomolgus monkeys (4 females/group)
Study Duration	130 weeks	13 weeks
Critical Effect(s)	Liver effects	Degenerative changes in primary and growing ovarian follicles

POD	NOAEL = 0.08 mg/kg-day	LOAEL = 0.01 mg/kg-day
Composite UF	100[a]	1000[b]
Toxicity Value (mg/kg-day)	0.0008	0.00001
Selected Value (mg/kg-day)	0.00001	
Rationale	New study	

[a]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.
[b]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_L.

References:

- Arnold, D.L., C.A. Moodie, S.M. Charbonneau, et al. 1985. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary Vitamin A. Fd. Chem. Toxic. 23(9): 779- 793.
- Bourque, AC; Singh, A; Lakhanpal, N; et al. (1995) Ultrastructural changes in ovarian follicles of monkeys administered hexachlorobenzene. Am J Vet Res 56:1673–1677.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0374_summary.pdf
- U.S. EPA. (2010) Provisional peer-reviewed toxicity values for hexachlorobenzene (CASRN 118-74-1). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Hexachlorobenzene.pdf

Hexachlorocyclohexane, gamma (CASRN 58-89-9). The ATSDR assessment (2005) derived a toxicity value based on a study (Meera et al. 1992) that was not available when the IRIS assessment was completed (1987). The ATSDR value is based on the use of a newer and longer study (24-week study). Despite the use of fewer animals (6 females/group), the study is of higher quality than the principal study used for the IRIS assessment (Zoecon Corp. 1983) and identified a lower POD. The ATSDR value is selected based on new information.

Summary Table Hexachlorocyclohexane (CASRN 58-89-9)		
Source (Year)	**IRIS (1987)**	**ATSDR (2005)**
Toxicity Value	Chronic RfD	Intermediate-duration MRL
Critical Study	Zoecon Corp. 1983	Meera et al. 1992
Species/Strain/Sex	Wistar KFM-Han rats (20/sex/group)	Swiss mice (6 females/group)
Study Duration	12 weeks; 5/sex/group maintained on control diet for an additional 6 weeks	Up to 24 weeks
Critical Effect(s)	Liver and kidney toxicity (females)	Reduced activity of lymphoid follicles with prominent megakaryocytes and delayed hypersensitivity to immune challenge
POD	NOAEL = 0.33 mg/kg-day	LOAEL = 0.012 mg/kg-day
Composite UF	1000[a]	1000[b]
Toxicity Value (mg/kg-day)	0.0003	0.00001
Selected Value (mg/kg-day)	0.00001	
Rationale	New study	

[a]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_S.
[b]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_L.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (2005). Toxicological profile for alpha-, beta-, gamma-, and delta-hexachlorocyclohexane. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp43.pdf
- Meera P, Rao PR, Shanker R, et al. 1992. Immunomodulatory effects of γ-HCH (lindane) in mice. Immunopharmacol Immunotoxicol 14:261-282.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0065_summary.pdf
- Zoecon Corporation. 1983. MRID No. 00128356. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

1,2,4,5-Tetrachlorobenzene (CASRN 95-94-3). The PPRTV (2013) derived a toxicity value from a 28-day study that identified a LOAEL (0.041 mg/kg-day for thyroid effects) lower than the NOAEL (0.34 mg/kg-day for liver effects) in a chronic study used in the IRIS assessment (1987). The Chu et al. (1983) study, while mentioned in the IRIS assessment summary, was not considered for the derivation of a chronic RfD (duration < 90 days). In addition, the PPRTV assessment used body weight$^{3/4}$ to derive the POD. The PPRTV value is selected based on the use of updated methodology.

Summary Table 1,2,4,5-Tetrachlorobenzene (CASRN 95-94-3)		
Source (Year)	**IRIS (1987)**	**PPRTV (2013)**
Toxicity Value	Chronic RfD	Subchronic p-RfD
Critical Study	Chu et al. 1984	Chu et al. 1983
Species/Strain/Sex	Weanling Sprague-Dawley rats (15/sex/group)	Sprague-Dawley rats (10/sex/group)
Study Duration	13 weeks	28 days
Critical Effect(s)	Kidney lesions	Thyroid toxicity (males)
POD	NOAEL = 0.34 mg/kg-day	$LOAEL_{[HED]}$ = 0.0098 mg/kg-day
Composite UF	1000[a]	300[b]
Toxicity Value (mg/kg-day)	0.0003	0.00003
Selected Value (mg/kg-day)	0.00003	
Rationale	Different study; updated methodology	

[a]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_S.
[b]The composite UF of 300 is based on 3 for UF_A, 10 for UF_H, and 10 for UF_L.

References:

- Chu, I; Villeneuve, D; Secours, V; Valli, VE. (1983) Comparative toxicity of 1,2,3,4-, 1,2,4,5-, and 1,2,3,5-tetrachlorobenzene in the rat: results of acute and subacute studies. J Toxicol Environ Health 11(4−6):663−677. 677338.

- Chu, I., D.C. Villeneuve, V.E. Valli and V.E. Secours. 1984. Toxicity of 1,2,3,4-, 1,2,3,5- and 1,2,4,5-tetrachlorobenzene in the rat: Results of a 90- day feeding study. Drug Chem. Toxicol. 7: 113-127.

- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0107_summary.pdf

3. Decisions that Require No Change in the RSLs (Inhalation).

Ammonia (CASRN 7664-41-7). The IRIS chronic RfC (2016) and the PPRTV subchronic p-RfC (2005) are based on the same study (Holness et al. 1989). However, the IRIS assessment included more details with respect to the occupational cohort and used a different approach to select the POD. The IRIS assessment also indicated that, although there are no developmental toxicity studies and studies of reproductive and other systemic endpoints are limited, the likelihood of effects at the RfC is small because: 1) ammonia is endogenously produced in humans and animals, and changes in blood ammonia levels at the POD would be small relative to normal blood ammonia levels; and 2) EPA is not aware of any mechanisms by which ammonia can exert effects at the point of contact (the respiratory system) that could directly or indirectly affect tissues distal to the point of contact. The more recent and highly-peer reviewed IRIS value (2016) is chosen as a Tier 1 value using standard EPA methods (e.g., application of UFs). The IRIS value is retained based on updated methodology.

Summary Table for Ammonia (CASRN 7664-41-7)		
Source (Year)	**IRIS (2016)**	**PPRTV (2005)**
Toxicity Value	Chronic RfC	Subchronic p-RfC
Critical Study	Holness et al. 1989	
Species/Strain/Sex	52 humans; occupationally exposed	
Study Duration	Average = 12.2 years	
Critical Effect(s)	Decreased lung function and respiratory symptoms	
POD	$NOAEL_{[HEC]}$ = 4.9 mg/m^3	$NOAEL_{[HEC]}$ = 2.3 mg/m^3
Composite UF	10[a]	30[b]
Toxicity Value (mg/m^3)	0.5	0.1
Selected Value (mg/m^3)	0.5	
Rationale	Updated IRIS assessment (including methodology and application of UFs)	

[a]The composite UF of 10 is based on 10 for UF_H.
[b]The composite UF of 30 if based on 10 for UF_H, and 3 for UF_D.

References:

- Holness, D.L., J.T. Purdham and J.R. Nethercott. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. Am. Ind. Hyg. Assoc. J. 50: 646-650.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0422_summary.pdf#nameddest=rfc
- U.S. EPA. (2005) Provisional peer-reviewed toxicity values for ammonia (CASRN 7664-41-7). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Ammonia.pdf

Chlordane (CASRN 12789-03-6). Minor hepatic effects (hepatocellular vacuolization and hypertrophy) identified as adverse by ATSDR (1994) were not considered biologically significant in the IRIS assessment (1998). The IRIS assessment considered the NOAEL to be 1.0 mg/m^3 (rather than 0.1 mg/m^3), adjusted for continuous exposure, applied the regional deposited dose ratio (RDDR) to extrapolate from rats to humans, lowered the UF for interspecies extrapolation (UF_A) from 10 to 3, and accounted for the lack of a reproduction study (UF_D). The IRIS value is retained based on the use of updated methodology.

Summary Table for Chlordane (CASRN 12789-03-6)		
Source (Year)	**IRIS (1998)**	**ATSDR (1994)**
Toxicity Value	Chronic RfC	Intermediate-duration MRL
Critical Study	Khasawinah et al. 1989	
Species/Strain/Sex	Wistar rats (35 to 47/sex/group)	
Study Duration	8 hours/day, 5 days/week, for 13 weeks	
Critical Effect(s)	Increased liver weight and changes in blood chemistry	Mild liver lesions and changes in blood chemistry
POD	$NOAEL_{[HEC]}$ = 0.65 mg/m^3	NOAEL[ADJ] = 0.024 mg/m^3
Composite UF	1000[a]	100[b]

Toxicity Value (mg/m^3)	0.0007	0.0002
Selected Value (mg/m^3)	0.0007	
Rationale	Updated methodology	

[a]The composite UF of 1000 is based on 3 for UF_A, 3 for UF_D, 10 for UF_H, and 10 for UF_S.
[b]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (1994). Toxicological profile for chlordane. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp31.pdf
- Khasawinah, A., C. Hardy, and G. Clark. 1989. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J. Toxicol. Environ. Health 28(3): 327-347. (The 90-day rat study.)
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0142_summary.pdf#nameddest=rfc

1,1-Dichloroethylene (CASRN 75-35-4). Compared to the ATSDR intermediate-duration MRL (1994), the IRIS chronic RfC (2002) was based on a later study that evaluated a more comprehensive set of endpoints, used the 1994 Inhalation Dosimetry approach to calculate the HEC, and used BMD methodology. Chronic-duration studies (e.g., Quast et al. 1986) were not considered in the derivation of an intermediate-duration MRL. ATSDR did not derive a chronic-duration MRL based on the Quast et al. (1986) study because a serious LOAEL was identified for developmental effects following acute-duration exposure at a lower exposure concentration, precluding the derivation of a chronic-duration MRL. The IRIS value is retained based on new information (i.e., a study not considered for the derivation of the intermediate-duration MRL) and the use of updated methodology.

Summary Table for 1,1-Dichloroethylene (CASRN 75-35-4)		
Source (Year)	**IRIS (2002)**	**ATSDR (1994)**
Toxicity Value	Chronic RfC	Intermediate-duration MRL
Critical Study	Quast et al. 1986	Prendergast et al. 1967
Species/Strain/Sex	Sprague-Dawley rats (86 animals/group)	Hartley guinea pigs (15/group)
Study Duration	6 hours/day, 5 days/week, for up to 18 months	24 hours/day for 90 days
Critical Effect(s)	Liver toxicity (fatty change)	Liver effects (increased ALT and AP; decreased lipid content)
POD	$BMDL_{[10HEC]}$ = 6.9 mg/m^3	NOAEL = 5 ppm
Composite UF	30[a]	300[b]
Toxicity Value	0.2 mg/m^3	0.02 ppm (0.08 mg/m^3)
Selected Value (mg/m^3)	0.2	
Rationale	Different study and updated methodology	

[a]The composite UF of 30 is based on 3 for UF_A, and 10 for UF_H.
[b]The composite UF of 300 if based on 10 for UF_H, 10 for UF_A, and 3 as a modifying factor to account for the close proximity of serious effects observed at the range of 10-25 ppm.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (1994). Toxicological profile for 1,1-dichloroethene. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp39.pdf
- Prendergast JA, Jones RA, Jenkins LJ, et al. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol Appl Pharmacol 10:270-289.
- Quast, JF; Mckenna, MJ; Rampy, LW; et al. (1986) Chronic toxicity and oncogenicity study on inhaled vinylidene chloride in rats. Fundam Appl Toxicol 6:105-144.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0039_summary.pdf#nameddest=rfc

Methyl *tert*-Butyl Ether (MTBE) (CASRN 1634-04-4). The IRIS chronic RfC (1993) is based on a chronic inhalation study (Chun et al. 1992); the ATSDR intermediate-duration MRL (1996) is based on a reproductive study (Neeper-Bradley 1991). Each study was evaluated in both assessments; dosimetric conversion factors were used in the IRIS assessment. The other difference between the two toxicity values is the conversion of the ATSDR MRL from ppm to mg/m^3. Rounded to one significant figure, the two reference values are identical. The RSL tables round to two digits and values; however, values are added as shown in the source document. The IRIS value is retained based on a different study (that results in a similar toxicity value as the intermediate-duration MRL) and the use of updated methodology.

Summary Table for MTBE (CASRN 1634-04-4)		
Source (Year)	**IRIS (1993)**	**ATSDR (1996)**
Toxicity Value	Chronic RfC	Intermediate-duration MRL
Critical Study	Chun et al. 1992	Neeper-Bradley 1991
Species/Strain/Sex	F344 rats (50/sex/group)	CD Sprague-Dawley rats (25/sex/group)
Study Duration	6 hours/day, 5 days/week, for 24 months	6 hours/day, 5 days/week, for up to 19 weeks
Critical Effect(s)	Increased liver and kidney weights; increased severity of renal lesions; clinical signs	Hypoactivity, lack of startle response, blepharospasm
POD	$NOAEL_{[HEC]}$ = 259 mg/m^3	$NOAEL_{[ADJ]}$ = 71 ppm
Composite UF	100[a]	100[b]
Toxicity Value	3 mg/m^3	2.5 mg/m^3 (0.7 ppm)
Selected Value (mg/m^3)	3	
Rationale	Different study; updated methodology	

[a]The composite UF of 100 is based on 3 for UF_A, 3 for UF_D, and 10 for UF_H.
[b]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (1996). Toxicological profile for methyl *tert*-butyl ether. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp91.pdf
- Chun, J.S., H.D. Burleigh-Flayer, and W.J. Kintigh. 1992. Methyl tertiary butyl ether: vapor inhalation oncogenicity study in Fischer 344 rats (unpublished material). Prepared for the MTBE Committee by Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc. Docket No. OPTS- 42098.
- Neeper-Bradley TL. 1991. Two-generation reproduction study of inhaled methyl tert-butyl ether in CD Sprague-Dawley rats. Project ID 53-594. Bushy Run Research Center, Export, PA.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0545_summary.pdf#nameddest=rfc

Nitromethane (CASRN 75-52-5). The PPRTV subchronic and chronic p-RfC (2013) are based on the same study (NTP 1997). However, to derive the chronic p-RFC, the PPRTV used the phase of the study that was longer and used more animals (50/group rather than 10/group). The larger number of animals reduces the confidence limits when the BMD methodology is used. The chronic p-RfC value is retained based on new information (i.e., consideration of the longer/more robust phase of the same principal study).

Summary Table for Nitromethane (CASRN 75-52-5)		
Source (Year)	**PPRTV (2013)**	**PPRTV (2013)**
Toxicity Value	Chronic p-RfC	Subchronic p-RfC
Critical Study	NTP 1997	
Species/Strain/Sex	B6C3F1 mice (50/sex/group)	B6C3F1 mice (10/sex/group)
Study Duration	6.2 hours/day, 5 days/week, for 103 weeks	6.2 hours/day, 5 days/week, for 13 weeks
Critical Effect(s)	Hyaline degeneration of the respiratory epithelium	Hyaline droplets of the respiratory epithelium
POD	$BMDL_{[10HEC]}$ = 1.60 mg/m^3	$BMDL_{[10HEC]}$ = 1.31 mg/m^3
Composite UF	300[a]	300[b]

Toxicity Value (mg/m^3)	0.005	0.004
Selected Value (mg/m^3)	0.005	
Rationale	Same study	

[a]The composite UF of 300 is based on 3 for UF_A, 10 for UF_H, and 10 for UF_D.
[b]The composite UF of 300 is based on 3 for UF_A, 10 for UF_H, and 10 for UF_D.

References:

- NTP (National Toxicology Program). (1997) Toxicology and carcinogenesis studies of nitromethane in F344/N rats and B6C3F1 mice (inhalation studies). U.S. Department of Health and Human Services, Public Health Service, Research Triangle Park, NC; Technical Report Series No 461. Available online at http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr461.pdf.
- U.S. EPA. (2013) Provisional peer-reviewed toxicity values for nitromethane (CASRN 75-52-5). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://hhpprtv.ornl.gov/issue_papers/Nitromethane.pdf

Vinyl Acetate (CASRN 108-05-4). IRIS (1990) and ATSDR (1992) used 104-week and 90-day studies, respectively. The NOAEL/LOAEL and the toxicological endpoint are the same in both studies. IRIS applied the regional gas dose to respiratory region (RGDR) to extrapolate from rats to humans and lowered the UF for interspecies extrapolation (UF_A) from 10 to 3. ATSDR also applied the RGDR conversion but retained the UF_A at 10. The difference between the toxicity values is the selection of UFs. The decision about the most appropriate value to use does not consider the UFs used (which is subjective) but rather evaluates whether new information was available and/or updated methodology was used. The IRIS value is retained because the intermediate-duration MRL is not based on new information or updated methodology.

Summary Table for Vinyl Acetate (CASRN 108-05-4)		
Source (Year)	**IRIS (1990)**	**ATSDR (1992)**
Toxicity Value	Chronic RfC	Intermediate-duration MRL
Critical Study	Owen 1988; Beems 1988, Dreef-van der Meulen 1988	Hazleton 1980
Species/Strain/Sex	(Crl:CD-1[ICR]BR) mice (90/sex/group)	CD-1 mice (10/sex/group)
Study Duration	6 hours/day, 5 days/week, for 104 weeks	6 hours/day, 5 days/week, for 90 days
Critical Effect(s)	Nasal epithelial lesions	Respiratory effects (inflammation of nasal turbinate epithelium; mild multifocal bronchitis)
POD	$NOAEL_{[HEC]}$ = 5 mg/m^3	$NOAEL_{[HEC]}$ = 5 mg/m^3
Composite UF	30[a]	100[b]
Toxicity Value	0.2 mg/m^3	0.05 mg/m^3 (0.01 ppm)
Selected Value (mg/m^3)	0.2	
Rationale	Different methodology (selection of UFs)	

[a]The composite UF of 30 is based on 3 for UF_A, and 10 for UF_H.
[b]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (1992). Toxicological profile vinyl acetate. Available online at https://www.atsdr.cdc.gov/ToxProfiles/tp59.pdf
- Beems, R.B. 1988. Report No. V 88.133: Histopathology of the respiratory tract of mice used in a 104-week inhalation study (Owen, 1988) with vinyl acetate. (TNO-CIVO Institutes, April 1988).
- Dreef-van der Meulen, H.C. 1988. Report No. V 88.033/270836: Histopathology of the respiratory tract of rats used in a 104 week inhalation study (Owen, 1988) with vinyl acetate: Revised version. (TNO-CIVO Institutes, October 1988).
- Hazleton. 1980. Vinyl acetate: 3 month inhalation toxicity study in the mouse. U.S. EPA/OTS public files. Hazleton Labs Europe Ltd. Document no. FYI-OTS-0184-0278.
- Owen, P.E. 1988. Vinyl acetate: 104 week inhalation combined chronic toxicity and carcinogenicity study in the rat and mouse. Report prepared by Hazleton Laboratories Europe Ltd., Harrogate, England for the Society of the Plastics Industry, Inc., New York. Report No.: 5547-51/15. November 1988.

- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0512_summary.pdf#nameddest=rfc

4. Decisions that Require No Change in the RSLs (Oral).

Acrylamide (CASRN 79-06-1). The ATSDR (2012) assessment identified a study with a lower HED than the study used by IRIS (2010). The ATSDR assessment calculated the HED using a PBPK rat model (Sweeney et al. 2010). The rat PBPK model was used to estimate rat dose metrics to predict the rat blood time-weighted average (TWA) acrylamide dose associated with the rat NOAEL of 0.2 mg/kg/day, resulting in an HED of 0.038 mg acrylamide/kg/day The IRIS assessment used BMD modeling to characterize the dose-response relationship and determine the POD, resulting in a $BMDL_{05HED}$ of 0.27 mg/kg/day. A different method (using ADME data) was used to calculate the HED in the IRIS assessment. An internal dose in the rat (area under a time-concentration curve, AUC) was derived from the external exposure to acrylamide based on methods and data that characterize the relationship between hemoglobin adducts, serum levels, and administered dose as reported in several rat studies. The studies were used to estimate the internal dose in rats, to extrapolate to an internal dose in humans, and to estimate the daily human intake of acrylamide needed to produce that internal human dose. Advantages to the IRIS value include 1) effects observed at the LOAEL in Burek et al. (1980) were slight and reversible, 2) the identification of a NOAEL for the Burek et al. (1980) study was limited by the selection of dose levels, 3) the IRIS assessment considered Burek et al. (1980) and other chronic-duration studies and used updated methodology when the toxicity value was updated in 2010, and 4) the selection of the IRIS value adheres to the toxicity hierarchy (and there is no overwhelming evidence to switch to a similar toxicity value based on subchronic exposure). The IRIS value was retained based on a different study and updated methodology.

Summary Table for Acrylamide (CASRN 79-06-1)		
Source (Year)	**IRIS (2010)**	**ATSDR (2012)**
Toxicity Value	Chronic RfD	Intermediate-duration MRL
Critical Study	Johnson et al. 1986	Burek et al. 1980
Species/Strain/Sex	F344 rats (90/sex/group)	F344 rats (10/sex/group)
Study Duration	Up to 2 years	Up to 93 days
Critical Effect(s)	Degenerative nerve changes	Neurological effects (ultrastructural degeneration in sciatic nerve fibers)
POD	$BMDL_{[05HED]}$ = 0.053 mg/kg-day	$NOAEL_{[HED]}$ = 0.038 mg/kg-day
Composite UF	30[a]	30[b]
Toxicity Value (mg/kg-day)	0.002	0.001
Selected Value (mg/kg-day)	0.002	
Rationale	Updated methodology	

[a]The composite UF of 30 is based on 3 for UF_A, and 10 for UF_H.
[b]The composite UF of 30 is based on 3 for UF_A, and 10 for UF_H.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (1996). Toxicological profile for acrylamide. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp203.pdf
- Burek JD, Albee RR, Beyer JE, et al. 1980. Subchronic toxicity of acrylamide administered to rats in the drinking water followed by up to 144 days of recovery. J Environ Pathol Toxicol 4(5- 6):157-182.
- Johnson KA; Gorzinski SJ; Bodner KM; Campbell RA; Wolf CH; Friedman MA; Mast RW (1986). Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. Toxicol Appl Pharmacol, 85: 154-168.
- Sweeney LM, Kirman CR, Gargas ML, et al. 2010. Development of a physiologically-based toxicokinetic model of acrylamide and glycidamide in rats and humans. Food Chem Toxicol 48(2):668- 685.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0286_summary.pdf#nameddest=rfd

Acrylic Acid (CASRN 79-10-7). The PPRTV (2010) and IRIS (1994) assessments used the same study. However, the PPRTV included a UF_D of 3 to account for the lack of a developmental study by oral exposure. The PPRTV assessment noted that BMD modeling could not be performed because of the lack of measured variation for the critical endpoint. The assessment relied heavily on the published version of the study (Hellwig et al. 1997); additional data are available in the unpublished version (BASF 1993). The IRIS assessment indicated that an uncertainty factor for database inadequacy was not considered necessary owing to evidence from bioavailability studies (oral and intravenous routes) that there is no difference in the rate of elimination of acrylic acid in rats and mice. The IRIS value was retained because the PPRTV value is not based on new information or updated methods.

Summary Table for Acrylic Acid (CASRN 79-10-7)		
Source (Year)	**IRIS (1994)**	**PPRTV (2010)**
Toxicity Value	Chronic RfD	Subchronic p-RfD
Critical Study	BASF 1993, Hellwig 1997	
Species/Strain/Sex	Wistar rats (25/sex/group)	
Study Duration	Two generations	
Critical Effect(s)	Reduced pup weight	
POD	NOAEL = 53 mg/kg-day	
Composite UF	100[a]	300[b]
Toxicity Value (mg/kg-day)	0.5	0.2
Selected Value (mg/kg-day)	0.5	
Rationale	Retain IRIS based upon application of UFs	

[a]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.
[b]The composite UF of 300 is based on 10 for UF_A, 10 for UF_H, and 3 for UF_D.

References:

- BASF (Badische Anilin- und Sodafabrik). 1993. Reproduction toxicity study with acrylic acid in rats: Continuous administration in the drinking water over 2 generations (1 litter in the first and 1 litter in the second generation). Project No. 71R0114/92011. BASF Aktiengesellschaft, Dept. of Toxicology, Rhein, FRG.
- Hellwig, J; Gembardt, C; Murphy, SR. (1997) Acrylic acid: Two-generation reproduction toxicity study in Wistar rats with continuous administration in the drinking water. Food Chem. Toxicol. 35(9):859–868.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0002_summary.pdf#nameddest=rfd
- U.S. EPA. (2010) Provisional peer-reviewed toxicity values for acrylic acid (CASRN 79-10-7). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/AcrylicAcid.pdf

1-1'-Biphenyl (CASRN 92-52-4). IRIS (2013) selected a different study to derive the RfD. In the IRIS assessment, the $BMDL_{10HEC}$ for kidney effects (Umeda et al. 2002) was lower than the $BMDL_{05}$ for developmental effects from Khera et al. (1979). The BMDL value selected by IRIS (2013) for Khera et al. (1979) was different than the BMDL value selected for the PPRTV due to differences in the critical endpoints selected. IRIS modeled the litter incidence of missing or unossified sternabrae (as the only anomaly that exhibited a dose-related increase when considered individually), whereas the PPRTV (2009) modeled the litter incidence of skeletal anomalies (combined). The PPRTV did not derive a chronic p-RfD; the PPRTV indicated that, "IRIS has derived a chronic value of 0.05 mg/kg-day based on a chronic-duration toxicity study of albino rats by Ambrose et al. (1960) with kidney damage as the critical effect. The IRIS database (U.S. EPA, 2010) should be checked to determine if any changes have been made" (the assessment has since been updated). The IRIS value was retained because the PPRTV value is not based on new information or updated methods.

Summary Table for 1,1'-Biphenyl (CASRN 92-52-4)		
Source (Year)	**IRIS (2013)**	**PPRTV (2011)**

Toxicity Value	Chronic RfD	Subchronic p-RfD
Critical Study	Umeda et al. 2002	Khera et al. 1979
Species/Strain/Sex	F344 rats (50/sex/group)	Wistar rats (18-20 females/group)
Study Duration	2 years	GDs 6-15
Critical Effect(s)	Renal papillary mineralization (males)	Increased incidence of litters with fetal skeletal anomalies
POD	$BMDL_{10HED}$ = 13.9 mg/kg-day	$BMDL_{05}$ = 9.59 mg/kg-day
Composite UF	30[a]	100[b]
Toxicity Value (mg/kg-day)	0.5	0.1
Selected Value (mg/kg-day)	0.5	
Rationale	Different study	

[a]The composite UF of 30 is based on 3 for UF_A, and 10 for UF_H.
[b]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.

References:

- Khera, KS; Whalen, C; Angers, G; et al. (1979) Assessment of the teratogenic potential of piperonyl butoxide, biphenyl, and phosalone in the rat. Toxicol Appl Pharmacol 47(2):353−358.
- Umeda, Y; Arito, H; Kano, H; Ohnishi, M; Matsumoto, M; Nagano, K; Yamamoto, S; Matsushima, T. (2002). Two-year study of carcinogenicity and chronic toxicity of biphenyl in rats. J Occup Health 44: 176-183.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0013_summary.pdf
- U.S. EPA. (2009) Provisional peer-reviewed toxicity values for 1,1'-biphenyl (CASRN 92-52-4). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Biphenyl11.pdf

Cyclohexanone (CASRN 108-94-1). The PPRTV included a UF_D of 3 whereas the IRIS assessment did not because it was not EPA practice at that time. BMD modeling could not be conducted because the body weight data were not provided in the principal study. The PPRTV value is based on a pilot study for the longer study (by the same authors) that forms the basis for the IRIS assessment. The PPRTV study was based on smaller group numbers (5/sex/group compared to 52/sex/group) and over a shorter duration (25 weeks compared to 2 years). The IRIS value was retained because the PPRTV value is not based on new information or updated methods.

Summary Table for Cyclohexanone (CASRN 108-94-1)		
Source (Year)	**IRIS (1987)**	**PPRTV (2010)**
Toxicity Value	Chronic RfD	Subchronic p-RfD
Critical Study	Lijinsky and Kovatch 1986	
Species/Strain/Sex	F344 rats (52/sex/group)	F344 rats (5/sex/group)
Study Duration	2 years	25 weeks
Critical Effect(s)	Depression in body-weight gain (both sexes)	Decreased weight gain (males)
POD	NOAEL = 462 mg/kg-day	NOAEL = 731 mg/kg-day
Composite UF	100[a]	300[b]
Toxicity Value (mg/kg-day)	5	2
Selected Value (mg/kg-day)	5	
Rationale	Different (phase of) study	

[a]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.
[b]The composite UF of 300 is based on 10 for UF_A, 10 for UF_H, and 3 for UF_D.

References:

- Lijinsky, W. and M. Kovatch. 1986. A chronic toxicity study of cyclohexanone in rats and mice (NCI study). J. Natl. Cancer Inst. 77(4): 941-949.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0219_summary.pdf#nameddest=rfd

- U.S. EPA. (2010) Provisional peer-reviewed toxicity values for cyclohexanone (CASRN 108-94-1). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. Available online at https://cfpub.epa.gov/ncea/pprtv/documents/Cyclohexanone.pdf

Endosulfan (CASRN 115-29-7). ATSDR (2015) used a lower NOAEL from a study (Banerjee and Hussain 1986) showing depressed immune response that was presumably not considered in the IRIS assessment (i.e., not mentioned in the IRIS summary documentation). Advantages to the IRIS value include 1) it is not known why the principal study used for derivation of the ATSDR MRL was not evaluated by the IRIS program, 2) data for depressed immune response in rats are not amenable to benchmark dose modeling (i.e., updated methodology was not used); and 3) selection of the IRIS value adheres to the toxicity hierarchy (and there is no overwhelming evidence to switch to a similar toxicity value based on subchronic exposure). The IRIS value was retained because the ATSDR value is not based on new information or updated methods.

Summary Table for Endosulfan (CASRN 115-29-7)		
Source (Year)	**IRIS (1994)**	**ATSDR (2015)**
Toxicity Value	Chronic RfD	Intermediate-duration MRL
Critical Study	Hoechst Celanese Corp 1989	Banerjee and Hussain 1986
Species/Strain/Sex	Sprague-Dawley rats (50/sex/group)	Wistar rats (10 to 12 males/group)
Study Duration	2 years	Up to 22 weeks
Critical Effect(s)	Decreased body weight gain; increased incidence of marked progressive glomerulonephrosis and blood vessel aneurysms (males)	Depressed immune response
POD	NOAEL = 0.6 mg/kg-day	NOAEL = 0.45 mg/kg-day
Composite UF	100[a]	100[b]
Toxicity Value (mg/kg-day)	0.006	0.005
Selected Value (mg/kg-day)	0.006	
Rationale	Retain IRIS value	

[a]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.
[b]The composite UF of 100 is based on 10 for UF_A, and 10 for UF_H.

References:

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Ethylene Glycol Monobutyl Ether (CASRN 111-76-2). IRIS (2010) derived a toxicity value from a chronic inhalation study (NTP 2000) using a PBPK model and BMD methodology to calculate the HED. The ATSDR assessment derived a toxicity value from a 13-week study (NTP 1993) with no NOAEL. The IRIS value was retained based on updated methodology.

Summary Table Ethylene Glycol Monobutyl Ether (CASRN 111-76-2)		
Source (Year)	**IRIS (2010)**	**ATSDR (2010)**
Toxicity Value	Chronic RfD	Intermediate-duration MRL
Critical Study	NTP 2000	NTP 1993
Species/Strain/Sex	F344/N rats and B6C3F1 mice (50/sex/group)	F344/N rats (10/sex/group)
Study Duration	6 hours/day, 5 days/week, for 2 years (inhalation)	13 weeks

Critical Effect(s)	Hemosiderin deposition in the liver	Hepatic effects
POD	BMDL[HED] = 1.4 mg/kg-day	LOAEL = 69 mg/kg-day
Composite UF	10[a]	1000[b]
Toxicity Value (mg/kg-day)	0.1	0.07
Selected Value (mg/kg-day)	0.1	
Rationale	Different study; updated methodology	

[a]The composite UF of 10 is based on 10 for UF_H.
[b]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_L.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (2010). Toxicological profile for 2-butoxyethanol and 2-butoxyethanol acetate. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp118.pdf
- NTP (National Toxicology Program) (2000) NTP technical report on the toxicology and carcinogenesis studies of 2 butoxyethanol (CAS No. 111 76 2) in F344/N rats and B6C3F1 mice (inhalation studies).
- NTP. 1993. Ethylene glycol ethers, 2-ethoxyethanoI, 2-butoxyethanol administered in drinking water to F344/N rats and B6C3Fl mice. NTP toxicity report series no. 26. National Toxicology Program, National Institutes of Health, Public Health Services, U.S. Department of Health and Human Services. NIH publication 93-3349.
- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0500_summary.pdf

Pentachlorophenol (CASRN 87-86-5). ATSDR (2001) derived chronic and intermediate-duration toxicity values based on a two-generation and one-generation reproduction studies in mink that only used one dose. The studies in mink were not well-conducted and observations in the one-generation study could not be replicated in the two-generation study (as mentioned in the IRIS assessment). The IRIS value was retained because the ATSDR value is not based on new information or updated methodology; the principal study is not considered reliable.

Summary Table Pentachlorophenol (CASRN 87-86-5)		
Source (Year)	**IRIS (2010)**	**ATSDR (2001)**
Toxicity Value	Chronic RfD	Intermediate-duration MRL
Critical Study	Mecler 1996	Beard et al. 1997
Species/Strain/Sex	Beagle dogs (4/sex/dose)	Mink (10 females/group)
Study Duration	52 weeks	3 weeks prior to mating and throughout pregnancy and lactation
Critical Effect(s)	Hepatotoxicity	Reproductive effects
POD	LOAEL = 1.5 mg/kg-day	LOAEL = 1 mg/kg-day
Composite UF	300[a]	1000[b]
Toxicity Value (mg/kg-day)	0.005	0.001
Selected Value (mg/kg-day)	0.005	
Rationale	Different study and methodology	

[a]The composite UF of 300 is based on 10 for UF_A, 10 for UF_H, and 3 for UF_L.
[b]The composite UF of 1000 is based on 10 for UF_A, 10 for UF_H, and 10 for UF_L.

References:

- Agency for Toxic Substances and Disease Registry (ATSDR) (2001). Toxicological profile pentachlorophenol. Available online at https://www.atsdr.cdc.gov/toxprofiles/tp51.pdf
- Beard AP, McRae AC, Rawlings NC. 1997. Reproductive efficiency in mink (Mustela vison) treated with the pesticides lindane, carbofuran, and pentachlorophenol. J Reprod Fertil 111:21-28.
- Mecler, F. (1996) Fifty-two week repeated dose chronic oral study of pentachlorophenol administered via capsule to dogs. Study conducted by TSI Mason Laboratories, Worcester, MA; TSI Report #ML-PTF-J31-95-94. Submitted to the Pentachlorophenol Task Force, c/o SRA International, Inc., Washington, DC. U.S. Environmental Protection Agency, Washington, DC; MRID 439827-01. Unpublished report.

- U.S. EPA. (2018). Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0086_summary.pdf