MICHIGAN DEPARTMENT OF
ENVIRONMENT, GREAT LAKES, AND ENERGY

VOLATILIZATION TO INDOOR AIR

Recommendations for Interim Action Screening Levels and Time-Sensitive Interim Action Screening Levels

Recommendations from the Toxics Steering Group
Volatilization to Indoor Air Workgroup
Revised December 2020

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1. BACKGROUND AND PURPOSE

This document is intended to provide recommended interim action screening levels for indoor air and to serve as guidance to staff of the Michigan Department of Environment, Great Lakes, and Energy (EGLE) using these screening levels to evaluate indoor air concentrations associated with volatilization to indoor air that may require actions (interim response activity or corrective actions) for protection of public health. The appendices of this document provide the process, basis, and chemical-specific justifications for the recommended interim action screening levels for indoor air.

The volatilization to indoor air pathway (VIAP) (i.e. vapor intrusion) is the migration of volatile substances from the subsurface media (soil, soil gas, and groundwater) into the indoor air of overlying structures. The VIAP is a highly complex and complicated exposure pathway. This pathway is relevant when a vapor source, a migration route, and human receptors are present. A pathway is relevant even if receptors are not currently occupying a site but can be expected to in the future. When receptors are present and concentrations of a volatile substance is or is likely to be above interim action indoor air screening levels, the VIAP is a substantial concern for public health and generally short-term exposure control may require evacuation/relocation or immediate mitigation to reduce concentrations to acceptable levels. For groundwater (drinking water) contamination, an alternate drinking water supply (e.g., bottled water) can be provided quickly or for soil (direct contact) contamination, measures to prevent contact with contaminated soils (e.g., covering, fencing, keeping children away) are rapidly available mitigation measures. Occupants of a building affected by contaminated vapors may require relocation to prevent breathing hazardous concentrations of volatile substances before a mitigation system can be completed. As with other exposure pathways, source control, removal measures, in-situ treatment, or other response activities may be needed to complete a cleanup while interim measures may be needed to control or mitigate exposure in the short term.

The cleanup programs under Part 111 (Hazardous Waste Management), Part 115, Part 201 (Environmental Remediation), and Part 213 (Leaking Underground Storage Tanks), of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended, require interim actions as necessary to protect public health and safety. In addition, the Public Health Code PA 368 of 1978 requires public health protection including control of environmental health hazards. See Appendix D for details of these authorities.

In 2016, the **Toxics Steering Group (TSG) VIAP Workgroup** was tasked by then MDEQ (now EGLE) and the Michigan Department of Health and Human Services (MDHHS) to evaluate and develop indoor air screening levels for volatile substances that are protective against human health effects that may result from ongoing VIAP exposures. Two sets of screening levels were requested, those requiring expedited mitigation as interim actions and those requiring immediate mitigation or evacuation. The request was to develop screening levels that are supported by both EGLE and the MDHHS, consistent with the Memorandum of Understanding between the agencies.

The set of recommended interim action screening levels (RIASLs) and time-sensitive recommended interim action screening levels (TS RIASLs) for residential and nonresidential indoor air exposure scenarios are presented in Tables 1 and 2, respectively. These screening levels are health-based values that represent best available science that, when exceeded, may result in an unacceptable risk to indoor air and a public health concern. The screening levels have been developed and evaluated by the TSG VIAP Workgroup using the decision framework presented in Appendix A. This set of chemicals includes hazardous substances frequently detected at sites subject to cleanup requirements under Parts 111, 115, 201, or 213 (Appendix D).

A well-developed conceptual site model (CSM), as it relates to the potential for VIAP, is critical for a thorough receptor evaluation and the identification of data gaps that need to be filled in order to make response decisions (MDEQ, 2013; U.S. EPA, 2012a, 2012b, 2015). Investigation of the VIAP is conducted using various types of data including the concentrations of contaminants in groundwater, soil, soil gas, sub-slab vapor, and modeled and/or measured analytical indoor air data. Without measured indoor air data, concentrations reported in the other datasets that are greater than the applicable media specific interim action screening levels could indicate a potential unacceptable health risk and require collection of indoor air data to more fully characterize current risk to human receptors and sensitive subpopulations. Indoor air data collection should be paired with sub-slab vapor data to assist in determining that concentrations detected in indoor air are resulting from the VIAP and not from other sources (e.g., consumer products). Evaluation of the VIAP may result in expedited mitigation efforts or, in some instances, coordination with the MDHHS for further action. If available data and the CSM warrant building-specific investigations (e.g., sub-slab soil vapor and indoor air samples), sampling plans should be reviewed with MDHHS toxicologists, when possible, prior to collecting indoor air samples. Collection of indoor air data for comparison to the TSG recommended interim action screening levels for indoor air is usually necessary for the MDHHS to make time-sensitive health-based decisions regarding human exposure at or near a contaminated VIAP site.

The hazardous substances identified in Tables 1 and 2 include developmental toxicants and substances with an Agency for Toxic Substances and Disease Registry (ATSDR) acute or intermediate inhalation minimal risk levels (MRL) or United States Environmental Protection Agency (U.S. EPA) acute or short-term reference concentrations (RfC), as well as those with chronic cancer and noncancer MRLs, RfCs or other health-based values (Appendix B). Since indoor air concentration data and health-based values are reported in different units (e.g., $\mu g/m^3$, ppb_{vol}), the RIASLs and TS RIASLs are provided in both units. The TSG VIAP Workgroup will develop and recommend indoor air interim action screening levels for additional volatile hazardous substances, with priority given to chemicals of concern, that are identified by field staff during review and investigation of sites with VIAP concerns.

The TSG VIAP Workgroup updated the 2017 report to address requests to develop new screening levels and correct or update values for some chemicals. The new and updated RIASLs and TS RIASLs in Tables 1 and 2 are identified by footnotes. In addition, other areas of this report were revised for

clarity and accuracy using the best available information. The process and approach for selecting toxicity values and developing screening levels were generally consistent with the 2017 report. As the need arises, based on vapor intrusion investigations and identification of additional hazardous substances of concern, this document will be updated periodically to include those additional hazardous substances and their associated RIASLs and TS RIASLs.

2. GUIDANCE AND IMPLEMENTATION OF RECOMMENDED INTERIM ACTION SCREENING LEVELS FOR INDOOR AIR AND TIME-SENSITIVE RECOMMENDED INTERIM ACTION SCREENING LEVELS

2.1 GUIDANCE

Two sets of interim action screening levels for indoor air are recommended by the TSG VIAP Workgroup: RIASL and TS RIASL for both residential and nonresidential exposure scenarios. As mentioned above, these interim action screening levels represent a scientifically defensible, health-based protective value that, when exceeded, may result in an unacceptable risk from chemical concentrations in indoor air and a public health concern.

Sites are reviewed by the EGLE-MDHHS VIAP review team by completion of an awareness/screening form and a presentation of the site data and CSM (consult your supervisor for guidance on filling out a VIAP Site Screening and Evaluation Form in the VIAP Database, prioritization, and further evaluation, as appropriate.). If available data and the CSM warrant building-specific investigations (e.g., sub-slab soil vapor and indoor air samples), sampling plans should be reviewed with MDHHS toxicologists, when possible, prior to collecting indoor air samples. The exceedance of an indoor air RIASL(s) from a VIAP source may require interim response activity or interim measures to be initiated expeditiously to mitigate the exposure(s). The exceedance of an indoor air TS RIASL(s) will require more rapid exposure mitigation, such as immediately increased ventilation, and/or may require a decision to evacuate building occupants in collaboration with the MDHHS. Immediately inform your supervisor for expedited review, action, and/or notification to the MDHHS, as appropriate. If an immediate concern for public health is indicated by any other available data and the CSM, immediately inform your supervisor for guidance on prioritization to proceed with further sampling (i.e., sub-slab vapor and/or indoor air sampling), taking other actions, and/or for MDHHS notification, as appropriate. The MDHHS, with EGLE support, will coordinate with the respective local public health agency for public health decisions and can provide assistance in gaining site access in time-sensitive situations.

The EGLE program contacts are:

- For Remediation and Redevelopment Division (RRD), Field Operations Section Managers
- For Materials Management Division (MMD), Hazardous Waste Section Manager

The RIASLs were developed consistent with the acceptable risk levels from Part 201 (MCL 324.20120a(4)); i.e., acceptable air concentrations that represent an upper bound cancer risk of one in 100,000 or a hazard quotient (HQ) of one for the most sensitive adverse effect were calculated for each hazardous substance. The RIASLs may be different than the acceptable indoor air concentration that served as the basis of the 2002/2013 cleanup criteria for volatilization to indoor air or any future updates to the Part 201 cleanup criteria, as TSG evaluations may include updated toxicity information when available for a hazardous substance and are not limited by statutory constraints. The TS RIASLs have been developed to be consistent with U.S. EPA guidance for time-sensitive actions (e.g., removal actions). These RIASLs and TS RIASLs are recommended screening levels to initiate interim actions. These RIASLs and TS RIASLs **are not** meant to define protective levels for all potential indoor air exposures and are not de facto cleanup levels or criteria. Nonresidential screening levels are calculated based on a healthy adult worker with potential exposure during a workday and potential intermittent exposure of adults and children who are customers, patrons, or visitors to commercial or industrial establishments during a portion of the workday. Residential screening levels are intended to address places where people live and/or children or other sensitive populations are present on a regular basis [greater than intermittent]. Residential screening levels may be more appropriate and protective for certain exposure scenarios (e.g., daycares, churches, schools, doctor's offices, hospitals, recreational areas, etc.).

Indoor air concentrations of volatile hazardous substances can vary substantially (10 to 1,000 times) within a single building over time due to varying conditions, including weather, building ventilation, diurnal or seasonal conditions (Holton *et al.*, 2013; U.S. EPA, 2012a, 2015). Because of the significant variation in indoor air concentrations, continued sampling and further evaluation is necessary for sites where indoor air concentrations are measured below RIASLs when soil vapor or groundwater concentrations and the CSM indicate there is likely to be a risk. One sampling event resulting in values below a RIASL does not exempt the building from further consideration when other information indicates that the VIAP is relevant (ATSDR, 2016; MDEQ, 2013). Further evaluation, including the collection of samples that represent the range of conditions expected at the facility, including worse case scenarios, and/or interim actions may need to be considered. Consult your supervisor for guidance on filling out a VIAP Site Screening and Evaluation Form in the VIAP Database, further evaluation (e.g., sampling), prioritization, response action, and notification/coordination with the MDHHS.

In some cases where a building is not currently occupied but soil vapor, groundwater, or soil concentrations indicate it is highly likely that indoor air concentrations will exceed RIASLs or measured indoor air concentrations exceed RIASLs, interim actions such as presumptive mitigation, a restrictive covenant, or some other reliable exposure control mechanism should be employed to assure public health is protected before the building is reoccupied. Acceptable uses (e.g., nonconforming residential or mixed use) under existing zoning may also require a restrictive covenant or other reliable exposure control be implemented as an interim action if residential RIASLs

are exceeded, but nonresidential RIASLs are not exceeded.

2.2 IMPLEMENTATION

When a VIAP exposure is discovered, in most cases, exposures have been occurring for the building occupants for a long period of time (months to many years). Some exposures have occurred for decades by the time a VIAP assessment has been conducted. Chronic health-based exposure values are appropriate for screening levels if they are lower than acute or short-term inhalation toxicity values. The RIASL for a hazardous substance is based on the Acceptable Air Concentration (AAC), which is the lowest of the calculated developmental, noncancer, cancer, or mutagenic acceptable air values (AAVs) as determined by the equations for cancer, noncancer, or developmental effects presented in Appendix A, unless an acute, short-term, or intermediate inhalation toxicity value is lower (such as Agency for Toxic Substances and Disease Registry (ATSDR) acute or intermediate inhalation Minimal Risk Levels (MRLs) or a U.S. EPA acute or short-term reference concentration (RfC)). The TS RIASLs are developed by multiplying the calculated chronic exposure AAVs for noncancer and developmental endpoints by three (3x). For the chronic exposure AAVs for cancer and mutagenic endpoints, the TS RIASLs are calculated by multiplying by 10 (10x). These chronic exposure AAVs are compared against available acute, short-term, or intermediate inhalation toxicity values. The lowest of the adjusted AAVs or acute, short-term, or intermediate inhalation toxicity values becomes the AAC for the TS RIASL; which due to the added adjustment factors, could be different than the AAC for the RIASL.

For nonresidential RIASLs and TS RIASLs, the assumption of a continuous 24-hour per day exposure time is used in the calculation of nonresidential health-based AAVs (Appendix A, equations 6-8). To reflect a more typical, reasonable maximum worker exposure, these values were adjusted to reflect a 12-hour per day exposure at a workplace by multiplying the calculated AAV by an additional factor of two (Table A-1); this modifying factor is not shown in the equations. Other adjustment factors for the number of hours per day at the workplace may be proposed based on a nonresidential land use that by its nature would only allow activities for limited exposure time. If adjustments to the residential or nonresidential RIASLs or TS RIASLs in Table 1 and 2 are proposed, consult an EGLE or MDHHS toxicologist.

The adjusted value remains the nonresidential $AAC_{adj,}$ used as above, for determining the nonresidential RIASLs and TS RIASLs. The modifying factor or adjustment is not applied for acute MRLs or RfCs based on exposures lasting less than 12 hours. For example, the nonresidential AACs and RIASLs for toluene and 1,1,1-trichloroethane incorporate acute inhalation reference values and are, therefore, not to be adjusted. For acute MRLs or RfCs that are based on or adjusted for continuous (24-hour) exposure, the AACs are adjusted for a 12-hour workday exposure. AACs based on intermediate ATSDR MRLs adjusted for continuous exposure are adjusted for 12-hour per day at the workplace (see Appendix A for details).

When the VIAP is identified as a potential unacceptable exposure risk to public health, indoor air data is a necessary line of evidence for MDHHS to evaluate whether there is a clear public health hazard. If soil vapor and/or other vapor source (e.g., groundwater and/or soil) concentrations in combination with a CSM indicate there is likely to be an unacceptable risk for indoor air exposures for an occupied building (e.g., exceedance of appropriate VIAP media-specific screening levels for soil vapor, groundwater, and/or soil), it is essential to collect indoor air data as soon as possible to determine if there are unacceptable levels of human exposure. Indoor air samples should be paired with sampling data of environmental medium (e.g., sub-slab vapor) in order to evaluate contributions from household chemical sources. If soil or groundwater data slightly exceed an appropriate media-specific screening level, it may be acceptable to collect only sub-slab vapor samples to determine if indoor air samples are necessary. Local public health departments make decisions about building occupancy; therefore, it is necessary for EGLE to inform MDHHS of indoor air sampling activities in homes and businesses. As stated in Section 2.1, EGLE staff should review all plans to collect indoor air with MDHHS toxicologists prior to collecting samples to allow appropriate preparations to take public health actions, when necessary. In addition, the MDHHS can coordinate with the local health department to facilitate site access and provide public health education.

Typically, indoor air samples are 24-hour samples. In some cases, other sampling times may be appropriate depending on chemical-specific and site-specific considerations (e.g., 12-hour samples to evaluate workplace exposure scenarios). Prior to collecting samples that are not 24-hour samples, consult with an appropriate toxicologist, the RRD Vapor Intrusion (VI) Technical and Program Support team and/or the MMD VI Work Group to confirm the acceptability of the indoor air and sub-slab vapor sampling strategies.

Summary of Guidance for Comparing Indoor Air Data to the RIASLs and TS RIASLs:

1. **Indoor air concentrations are detected but below the RIASLs:** This indicates that immediate action may not be necessary. However, detected indoor air concentrations below the RIASLs indicate that people are being exposed to chemicals in the indoor air. As noted above, indoor air concentrations can vary significantly over time, and be 10 to 1,000 times higher or lower than measured levels from a single sampling event (U.S. EPA, 2012a, 2015; Holton *et al.*, 2013). Additional sampling and evaluation may need to be conducted based on measured values in multiple media (e.g., indoor air, soil vapor, and groundwater), the long- and short-term toxicity considerations of the hazardous substance(s) present, and the CSM, to determine the need for mitigation or other exposure control measures. Consult your supervisor for guidance to follow your division's process for filling out a VIAP Site Screening and Evaluation Form in the VIAP Database, different prioritization, further evaluation (e.g.,

sampling), response action, and/or notification/coordination with the MDHHS. It may not be necessary to generate an official VIAP Awareness Form in all cases. Although the indoor air concentrations measured at this time are not likely to be an immediate public health threat, the MDHHS may be able to assist with public health education, access for continued monitoring, and coordination with the local public health agency.

2. **Indoor air concentrations above the RIASL but below the TS RIASL:** Mitigation of people's exposure should begin **as soon as possible**, as levels could vary over time and possibly be higher. Continued sampling will be needed until the mitigation is complete and documented to be effective in reducing and maintaining the chemical levels in the indoor air below the RIASL(s). Consult your supervisor for guidance to follow your division's process for filling out a VIAP Site Screening and Evaluation Form in the VIAP Database, prioritization, further evaluation, response action and/or notification to the MDHHS, as appropriate.
3. **Indoor air concentrations above the TS RIASL:** VIAP mitigation should begin **immediately**. Immediately inform your supervisor for expedited review, response action, and/or notification to the MDHHS, as appropriate. The MDHHS may determine occupants should not be in the buildings. Continued sampling will be needed until mitigation is complete and documented to be effective in reducing and maintaining the chemical levels in the indoor air below the RIASL(s) as occupants' actual exposure could have already been months to years. For chemicals where the RIASL has the same numerical value as the TS RIASL, the "TS RIASL" term is put in place of the numerical value to direct the staff to evaluate the chemical's air concentrations using the appropriate response timeframe.

2.3 LIMITATIONS

As stated previously, these RIASLs and TS RIASLs are not intended to define protective levels for all potential indoor air exposures and are not *de facto* cleanup levels or criteria.

These screening levels are generally for exposure to a single chemical only. At certain sites, volatilization to indoor air of more than one chemical could be occurring. Lower, more protective screening levels may need to be developed for those sites when the toxicity values of co-occurring chemicals are based on the same endpoint (target organ or critical effect(s)) (U.S. EPA 2015; ATSDR 2016). The MDHHS or U.S. EPA may determine and recommend different screening levels to address human exposure to multiple chemicals and multiple exposure pathways.

Additionally, the MDHHS may recommend different screening levels when addressing sites with sensitive populations or exposure scenarios where additional protections are needed. Sensitive populations include, but are not limited to, elderly, women who are or may become pregnant, infants and children, people with chronic illness, or those populations with multiple sources of exposure to chemicals (e.g., environmental justice considerations) (U.S. EPA 2012, 2015). Exposure scenarios that require further evaluation may be due to chemical-specific acute effects that were not

considered in the acute effects protected by the RIASL or TS RIASL (e.g., acetone and ammonia).

Table 1 Residential (Res) Recommended Interim Action Screening Levels (RIASLs) and Time-Sensitive Recommended Interim Action Screening Levels (TS RIASLs) (Revised List January 2020)

Hazardous Substance	Chemical Abstract Service Number	Molecular Weight g/mol	Res RIASL µg/m³[3,a]	Res RIASL ppb_{vol}[1,b]	Basis for Res RIASL	Res TS RIASL µg/m³	Res TS RIASL ppb_{vol}	Basis for Res TS RIASL
Acetone	67641	58.08	TS RIASL	TS RIASL	ATSDR MRL[c] Intermed	31,000	13,000	ATSDR MRL Intermed
Acetophenone[2]	98862	120.15	3,200	650	Res AAC[d] Dev (SE)	9,600	2,000	3× Res AAC Dev (SE)
Ammonia	7664417	17.03	520[3]	750[3]	Res AAC Noncancer	1,200[3]	1,700[3]	ATSDR MRL Acute
Benzene	71432	78.11	3.3	1.0	Res AAC Cancer	19	6.0	ATSDR MRL Intermed
2-Butanone (MEK)[2]	78933	72.11	5,000	1,700	Res AAC Dev (SE)	15,000	5,100	3× Res AAC Dev (SE)
Carbon Tetrachloride[2]	56235	153.82	4.5	0.72	Res AAC Cancer	45	7.2	10× Res AAC Cancer
Chlordane	57749	409.78	TS RIASL	TS RIASL	ATSDR MRL Intermed	0.20	0.012	ATSDR MRL Intermed
Chlorobenzene[2]	108907	112.56	52	11	Res AAC Noncancer	160	34	3× Res AAC Noncancer
Chloroethane[2]	75003	64.52	4,200	1,600	Res AAC Noncancer	13,000	4,700	3× Res AAC Noncancer
Chloroform	67663	119.38	1.1	0.23	Res AAC Cancer	11	2.3	10× Res AAC Cancer
Chloromethane[2]	74873	50.49	94	45	Res AAC Noncancer	280	140	3× Res AAC Noncancer
2-Chlorophenol[2]	95578	128.56	18	3.4	Res AAC Dev (SE)	54	10	3× Res AAC Dev (SE)

Hazardous Substance	Chemical Abstract Service Number	Molecular Weight g/mol	Res RIASL µg/m³[3,a]	Res RIASL ppb$_{vol}$[1,b]	Basis for Res RIASL	Res TS RIASL µg/m³	Res TS RIASL ppb$_{vol}$	Basis for Res TS RIASL
1,3-Dichlorobenzene[2]	541731	147	3.1	0.52	Res AAC Noncancer	9.4	1.6	3× Res AAC Noncancer
1,4-Dichlorobenzene	106467	147	6.5	1.1	Res AAC Cancer	65	11	10× Res AAC Cancer
1,1-Dichloroethane	75343	98.96	16	4.0	Res AAC Cancer	160	40	10× Res AAC Cancer
1,1-Dichloroethylene	75354	96.94	210	53	Res AAC Noncancer	630	160	3× Res AAC Noncancer
cis-1,2-Dichloroethylene	156592	96.94	8.3	2.1	Res AAC Noncancer	25	6.3	3× Res AAC Noncancer
trans-1,2-Dichloroethylene[2]	156605	96.94	83	21	Res AAC Noncancer	250	63	3× Res AAC Noncancer
1,2-Dichloropropane[2]	78875	112.99	4.2	0.90	Res AAC Noncancer	13	2.7	3× Res AAC Noncancer
Diisopropyl Ether[2]	108203	102.18	700	170	Res AAC Dev (SE)	2,100	500	3× Res AAC Dev (SE)
1,4-Dioxane[2]	123911	88.11	5.1	1.4	Res AAC Cancer	51	14	10× Res AAC Cancer
Ethanol	64175	46.07	TS RIASL	TS RIASL	AQD Acute ITSL[e]	19,000	10,000	AQD Acute ITSL
Ethylbenzene	100414	106.17	10	2.3	Res AAC Cancer	100	23	10× Res AAC Cancer
n-Hexane	110543	86.18	730	210	Res AAC Noncancer	2,200	620	3× Res AAC Noncancer
Mercury, elemental[2]	7439976	200.59	0.31	0.038	Res AAC Noncancer	0.94	0.11	3× Res AAC Noncancer
Methanol[2]	67561	32.05	20,000	15,000	Res AAC Dev (SE)	60,000	46,000	3× Res AAC Dev (SE)

Hazardous Substance	Chemical Abstract Service Number	Molecular Weight g/mol	Res RIASL µg/m³[3,a]	Res RIASL ppb$_{vol}$[1,b]	Basis for Res RIASL	Res TS RIASL µg/m³	Res TS RIASL ppb$_{vol}$	Basis for Res TS RIASL
4-Methyl-2-pentanone[2] (MIBK)	108101	100.2	TS RIASL	TS RIASL	AQD Acute ITSL[e]	820	200	AQD Acute ITSL[e]
Methylene chloride[2]	75092	84.93	630	180	Res AAC Noncancer	1,000	290	ATSDR MRL Intermed
Methyl tert-butyl ether (MTBE)	1634044	88.15	98	27	Res AAC Cancer	980	270	10× Res AAC Cancer
Propyl alcohol[2]	71238	60.10	TS RIASL	TS RIASL	AQD Acute ITSL	2,500	1,000	AQD Acute ITSL
n-Propylbenzene[2]	103651	120.20	1,000	200	Res AAC Dev (SE)	3,000	610	3× Res AAC Dev (SE)
Tetrachloroethylene (PCE)	127184	165.83	TS RIASL	TS RIASL	ATSDR MRL Acute	41	6.0	ATSDR MRL Acute
Toluene	108883	92.14	5,200	1,400	Res AAC Noncancer	7,500	2,000	ATSDR MRL Acute
Triallate[2]	2303175	304.66	200	16	Res AAC Dev (SE)	600	48	3× Res AAC Dev (SE)
1,2,4-Trichlorobenzene[2]	120821	181.45	2.1	0.28	Res AAC Noncancer	6.3	0.84	3× Res AAC Noncancer
1,1,1-Trichloroethane	71556	133.41	TS RIASL	TS RIASL	IRIS RfC[f] Short-term	5,000	920	IRIS RfC Short-term
Trichloroethylene (TCE)	79016	131.39	2.0	0.37	Res AAC Dev (SE)	6.0	1.1	3× Res AAC Dev (SE)
Trimethylbenzenes[2]	95636	120.2	63	13	Res AAC Noncancer	190	38	3× Res AAC Noncancer
Vinyl acetate[2]	108054	86.09	210	59	Res AAC Noncancer	630	180	3× Res AAC Noncancer
Vinyl chloride[2]	75014	62.5	1.6	0.64	Res AAC Cancer	16	6.4	10× Res AAC Cancer

Hazardous Substance	Chemical Abstract Service Number	Molecular Weight g/mol	Res RIASL µg/m³[3,a]	Res RIASL ppb$_{vol}$[1,b]	Basis for Res RIASL	Res TS RIASL µg/m³	Res TS RIASL ppb$_{vol}$	Basis for Res TS RIASL
Xylenes	1330207	106.17	230	53	Res AAC Noncancer	690	160	3× Res AAC Noncancer

[1] RIASL ppb$_{vol}$ = [RIASL (µg/m³) ×24.45] ÷ (Molecular Weight) at standard temperature and pressure

[2] 2020 additional or updated RIASLs

Acronyms:

[a] **µg/m³** – microgram per meter cubed

[b] **ppb$_{vol}$** – part per billion by volume

[c] **ATSDR MRL** – Agency for Toxic Substances and Disease Registry Inhalation Minimum Risk Level for Acute Inhalation (**Acute**) or Intermediate Inhalation (**Intermed**) exposure durations

[d] **Res AAC** – Residential Acceptable Air Concentration calculated from equations in Appendix A, based on **Cancer**, **Mutagenic** cancer, **Noncancer**, single event **(SE)** developmental **(Dev)** or full-term **(FT)** developmental toxicity

[e] **AQD Acute ITSL** – EGLE Air Quality Division Acute Initial Threshold Screening Level

[f] **IRIS RfC Short-term** –U.S. Environmental Protection Agency Integrated Risk Information System Reference Concentration for short-term exposure

Table 2 Nonresidential (NR) Recommended Interim Action Screening Levels (RIASLs) and Time-Sensitive Recommended Interim Action Screening Levels (TS RIASLs) (Revised List January 2020)

Hazardous Substance	Chemical Abstract Service Number	Molecular Weight g/mol	NR RIASL (24-hour exposure day) µg/m³	NR RIASL (12-hour exposure day) µg/m³[3,a]	NR RIASL (12-hour exposure day) ppb_{vol}[1,b]	Basis for NR RIASL	NR TS RIASL (12-hour exposure day) µg/m³	NR TS RIASL (12-hour exposure day) ppb_{vol}	Basis for NR TS RIASL
Acetone	67641	58.08	TS RIASL	TS RIASL	TS RIASL	ATSDR MRL[c] Intermed	31,000	13,000	ATSDR MRL Intermed
Acetophenone[2]	98862	120.15	3,200	6,400	1,300	NR AAC_{adj} Dev (SE)	19,000	4,000	3× NR AAC_{adj} Dev (SE)
Ammonia	7664417	17.03	TS RIASL	TS RIASL	TS RIASL	ATSDR MRL Acute	1,200	1,700	ATSDR MRL Acute
Benzene[2]	71432	78.11	7.7	15	4.8	NR AAC_{adj} Cancer	54	17	ATSDR MRL $Intermed_{adj}$
2-Butanone (MEK)[2]	78933	72.11	5,000	10,000	3,400	NR AAC_{adj} Dev (SE)	30,000	10,000	3× NR AAC_{adj} Dev (SE)
Carbon Tetrachloride[2]	56235	153.82	11	21	3.4	NR AAC_{adj} Cancer	210	34	10× NR AAC_{adj} Cancer
Chlordane	57749	409.78	TS RIASL	TS RIASL	TS RIASL	ATSDR MRL $Intermed_{adj}$	0.56	0.033	ATSDR MRL $Intermed_{adj}$
Chlorobenzene	108907	112.56	77	150	33	NR AAC_{adj} Noncancer	460	100	3× NR AAC_{adj} Noncancer
Chloroethane[2]	75003	64.52	6,100	12,000	4,600	NR AAC_{adj} Noncancer	37,000	14,000	3× NR AAC_{adj} Noncancer
Chloroform	67663	119.38	2.6	5.2	1.1	NR AAC_{adj} Cancer	52	11	10× NR AAC_{adj} Cancer

Hazardous Substance	Chemical Abstract Service Number	Molecular Weight g/mol	NR RIASL (24-hour exposure day) µg/m³	NR RIASL (12-hour exposure day) µg/m³[3,a]	NR RIASL (12-hour exposure day) ppb_{vol}[1,b]	Basis for NR RIASL	NR TS RIASL (12-hour exposure day) µg/m³	NR TS RIASL (12-hour exposure day) ppb_{vol}	Basis for NR TS RIASL
Chloromethane	74873	50.49	140	280	140	NR AAC_{adj} Noncancer	410	200	ATSDR MRL Intermed
2-Chlorophenol[2]	95578	128.56	18	36	6.8	NR AAC_{adj} Dev (SE)	110	21	3× NR AAC_{adj} Dev (SE)
1,3-Dichlorobenzene[2]	541731	147	4.6	9.2	1.5	NR AAC_{adj} Noncancer	28	4.6	3× NR AAC_{adj} Noncancer
1,4-Dichlorobenzene[2]	106467	147	15	31	5.1	NR AAC_{adj} Cancer	310	51	10× NR AAC_{adj} Cancer
1,1-Dichloroethane[2]	75343	98.96	37	75	18	NR AAC_{adj} Noncancer	750	180	10× NR AAC_{adj} Cancer
1,1-Dichloroethylene[2]	75354	96.94	310	610	150	NR AAC_{adj} Noncancer	1,800	460	3× NR AAC_{adj} Noncancer
cis-1,2-Dichloroethylene[2]	156592	96.94	12	25	6.2	NR AAC_{adj} Noncancer	74	19	3× NR AAC_{adj} Noncancer
trans-1,2-Dichloroethylene[2]	156605	96.94	120	250	62	NR AAC_{adj} Noncancer	740	190	3× NR AAC_{adj} Noncancer
1,2-Dichloropropane[2]	78875	112.99	6.1	12	2.6	NR AAC_{adj} Noncancer	37	8.0	3× NR AAC_{adj} Noncancer
Diisopropyl Ether[2]	108203	102.18	700	1,400	340	NR AAC_{adj} Dev (SE)	4,200	1,000	3× NR AAC_{adj} Dev (SE)
1,4-Dioxane[2]	123911	88.11	12	24	6.7	NR AAC_{adj} Cancer	240	66	10× NR AAC_{adj} Cancer

Hazardous Substance	Chemical Abstract Service Number	Molecular Weight g/mol	NR RIASL (24-hour exposure day) µg/m³	NR RIASL (12-hour exposure day) µg/m³[a]	NR RIASL (12-hour exposure day) ppb_{vol}[1,b]	Basis for NR RIASL	NR TS RIASL (12-hour exposure day) µg/m³	NR TS RIASL (12-hour exposure day) ppb_{vol}	Basis for NR TS RIASL
Ethanol	64175	46.07	TS RIASL	TS RIASL	TS RIASL	AQD Acute ITSL[e]	19,000	10,000	AQD Acute ITSL
Ethylbenzene	100414	106.17	24	48	11	NR AAC_{adj} Cancer	480	110	10× NR AAC_{adj} Cancer
n-Hexane[2]	110543	86.18	1,100	2,100	610	NR AAC_{adj} Noncancer	6,400	1,800	3× NR AAC_{adj} Noncancer
Mercury, elemental	7439976	200.59	0.46	0.92	0.11	NR AAC_{adj} Noncancer	2.8	0.34	3× NR AAC_{adj} Noncancer
Methanol[2]	67561	32.05	20,000	40,000	31,000	NR AAC_{adj} Dev (SE)	120,000	92,000	3× NR AAC_{adj} Dev (SE)
4-Methyl-2-pentanone (MIBK)[2]	108101	100.2	TS RIASL	TS RIASL	TS RIASL	AQD Acute ITSL[e]	820	200	AQD Acute ITSL[e]
Methylene chloride	75092	84.93	920	1,800	530	NR AAC_{adj} Noncancer	2,900	830	ATSDR MRL Intermed
Methyl tert-butyl ether (MTBE)	1634044	88.15	230	460	130	NR AAC_{adj} Cancer	4,600	1,300	10× NR AAC_{adj} Cancer
Propyl alcohol[2]	71238	60.10	TS RIASL	TS RIASL	TS RIASL	AQD Acute ITSL	2,500	1,000	AQD Acute ITSL
n-Propylbenzene[2]	103651	120.20	1,000	1,000	200	NR AAC Dev (SE)	3,000	610	3× NR AAC Dev (SE)
Tetrachloroethylene (PCE)	127184	165.83	41	TS RIASL	TS RIASL	ATSDR MRL Acute	82	12	ATSDR MRL Acute
Toluene	108883	92.14	TS RIASL	TS RIASL	TS RIASL	ATSDR MRL	7,500	2,000	ATSDR MRL

Hazardous Substance	Chemical Abstract Service Number	Molecular Weight g/mol	NR RIASL (24-hour exposure day) µg/m³	NR RIASL (12-hour exposure day) µg/m³[a]	NR RIASL (12-hour exposure day) ppb_{vol}[1,b]	Basis for NR RIASL	NR TS RIASL (12-hour exposure day) µg/m³	NR TS RIASL (12-hour exposure day) ppb_{vol}	Basis for NR TS RIASL
						Acute			Acute
Triallate[2]	2303175	304.66	200	200	16	NR AAC Dev (SE)	600	48	3× NR AAC Dev (SE)
1,2,4-Trichlorobenzene[2]	120821	181.45	3.1	6.1	0.83	NR AAC_{adj} Noncancer	18	2.5	3× NR AAC_{adj} Noncancer
1,1,1-Trichloroethane[2]	71556	133.41	TS RIASL	TS RIASL	TS RIASL	IRIS RfC[f] Acute 8-hour	7,000	1,300	IRIS RfC Acute 8-hour
Trichloroethylene (TCE)	79016	131.39	2.0	4.0	0.74	NR AAC_{adj} Dev (SE)	12	2.2	3× NR AAC_{adj} Dev (SE)
Trimethylbenzenes[2]	95636	120.2	92	180	37	NR AAC_{adj} Noncancer	550	110	3× NR AAC_{adj} Noncancer
Vinyl acetate[2]	108054	86.09	310	610	170	NR AAC_{adj} Noncancer	1,800	520	3× NR AAC_{adj} Noncancer
Vinyl chloride[2]	75014	62.5	14	27	11	NR AAC_{adj} Cancer	270	110	10× NR AAC_{adj} Cancer
Xylenes[2]	1330207	106.17	340	670	160	NR AAC_{adj} Noncancer	2,000	470	3× NR AAC_{adj} Noncancer

[1] RIASL ppb_{vol} = [RIASL (µg/m³) ×24.45] ÷ (Molecular Weight) at standard temperature and pressure

[2] 2020 additional or updated RIASLs

Acronyms:

[a] **µg/m³** – microgram per meter cubed

[b] **ppb_{vol}** – part per billion by volume

[c] **ATSDR MRL** – Agency for Toxic Substances and Disease Registry Inhalation Minimum Risk Level for Acute (**Acute**), Intermediate (**Intermed**), or Intermediate adjusted (**Intermed$_{adj}$**) exposure durations

[d] **NR AAC** –Nonresidential Acceptable Air Concentration calculated from equations in Appendix A, based on Cancer, Noncancer, single event (**SE**) developmental (**Dev**) or full-term (**FT**) developmental toxicity

[e] **AQD Acute ITSL** – EGLE Air Quality Division Acute Initial Threshold Screening Level **IRIS RfC Acute 8-hour** – U.S. Environmental Protection Agency Integrated Risk Information System Reference Concentration for acute 8-hour exposure duration

REFERENCES

ATSDR. 2016. Evaluating Vapor Intrusion Pathways: Guidance for the ATSDR's Division of Community Health Investigations. ATSDR. October 31, 2016. www.atsdr.cdc.gov/docs/svi_guidance_508.pdf

Holton, C., H. Luo, P. Dahlen, K. Gorder, E. Dettenmaier, and P. C. Johnson. 2013. Temporal variability of indoor air concentrations under natural conditions in a house overlying a dilute chlorinated solvent groundwater plume. *Environmental Science & Technology* 47:13347-13354.

MDEQ. 2013. Guidance Document: For the Vapor Intrusion Pathway. Michigan Department of Environmental Quality, Remediation and Redevelopment Division. www.michigan.gov/documents/deq/deq-rrd-VIGuidanceDoc-May2013_422550_7.pdf

MDEQ. 2016. Process to Address Developmental and/or Reproductive Toxicity in the Derivation of Generic Cleanup Criteria. Toxics Steering Group, Children's Environmental Health Subcommittee, Lansing, Michigan. (unpublished).

U.S. EPA. 2012a. EPA's Vapor Intrusion Database: Evaluation and Characterization of Attenuation Factors for Chlorinated Volatile Organic Compounds and Residential Buildings. EPA-530-R-10-002. March. Currently available online at: www.epa.gov/oswer/vaporintrusion/documents/OSWER_2010_Database_Report_03-16-2012_Final.pdf

U.S. EPA. 2012b. Conceptual Model Scenarios for the Vapor Intrusion Pathway.

EPA-530-R-10-003. February. Currently available online at: www.epa.gov/oswer/vaporintrusion/documents/vi-cms-v11final-2-24-2012.pdf

U.S. EPA. 2015. OSWER Technical Guide for Assessing and Mitigating the Vapor Intrusion Pathway from Subsurface Vapor Sources to Indoor Air. OSWER Publication 9200.2-154. June. Currently available online at: www.epa.gov/sites/production/files/2015-09/documents/oswer-vapor-intrusion-technical-guide-final.pdf

APPENDIX A: PROCESS FOR DEVELOPING RECOMMENDED INTERIM ACTION SCREENING LEVELS (RIASLS) AND TIME-SENSITIVE RECOMMENDED INTERIM ACTION SCREENING LEVELS (TS RIASLS) FOR VOLATILIZATION TO INDOOR AIR SITES

This process presumes that most volatilization to indoor air sites, at the time of the evaluation with these recommended screening levels, will have buildings that have been occupied by residents or workers for an extended period of time (years to decades). Therefore, in most cases, chronic inhalation health-based values are appropriate for public health risk decisions. Recent VIAP evaluations have demonstrated that for a few hazardous substances there are some short-term health benchmarks (e.g., ATSDR intermediate and acute inhalation MRLs, U.S. EPA acute and short-term RfCs) that are lower than the lowest calculated health-based Acceptable Air Values (AAVs) based on chronic health benchmarks. To make sure the RIASLs and the TS RIASLs are adequately protective of public health for both short-term and long-term exposures, the recommended screening levels will typically use the lower of the short-term health benchmark and the lowest AAV. The lowest AAV or short-term health benchmark becomes the basis for the Acceptable Air Concentration (AAC) that is used to establish the RIASL or TS RIASL for a hazardous substance. Health benchmarks may be provided in mg/m^3, $\mu g/m^3$, ppm_{vol}, or ppb_{vol}. Both $\mu g/m^3$, and ppb_{vol} values are provided as final RIASLs and TS RIASLs. These values are developed using the steps below with any exposure adjustments (e.g., nonresidential exposure hours/day) applied to the original value before unit conversion.

Step 1. Determine the health-based residential and nonresidential AAVs and identify acute, short-term, or intermediate health benchmarks. The **lowest** of the values identified below becomes the AAC and the basis for the residential and nonresidential **RIASLs**. Adjustments of the nonresidential AAC and RIASL may be used to account for workday exposures or exposure time described below. The health-benchmark that becomes the AAC or adjusted AAC (AAC_{adj}) is rounded to two significant figures. Exposure time-based adjustment is not applicable to residential AACs and RIASLs.

- Acceptable Air Values (AAVs):
  - Determine the calculated health-based AAVs for non-carcinogenic, developmental, carcinogenic, and mutagenic health effects developed by RRD or TSG VIAP Workgroup using the inhalation toxicity endpoints (reference concentration (RfC) and Inhalation Unit Risk Factor (IURF)) and algorithms presented below (*See Determination of AAVs*). These AAVs are based on a noncancer hazard quotient (HQ) of one or a cancer target risk (TR) of 1 in 100,000 (10^{-5}).
  - For AACs based on nonresidential AAVs**, the AAC may be adjusted for a workday exposure, if appropriate**, by multiplying the unrounded AAC value by two to adjust for a 12 hour/day exposure at the workplace (NR AAC_{adj}). Other adjustment factors for the

number of hours per day at the workplace may be proposed based on a nonresidential land use that by its nature would only allow activities for limited exposure time.

- ATSDR acute inhalation MRL (MRL_{acute})
  - For nonresidential AAC based on the acute inhalation MRL, adjustment to account for a 12 hour/day exposure at the workplace is appropriate ($MRL_{acute,adj}$) if the MRL_{acute} is based on or has been adjusted for continuous exposure.
- ATSDR intermediate inhalation MRL (MRL_{int})
  - For nonresidential AAC based on intermediate inhalation MRL, adjustment to account for a 12-hour/day exposure at the workplace is appropriate if the MRL_{int} is based on or has been adjusted for continuous exposure. Additional adjustment may be applied to account for a five out of seven-day work week ($MRL_{int,adj}$) as the MRL_{int} addresses exposure greater than two weeks to less than a year.
- U.S. EPA acute RfC (RfC_{acute}) or short-term RfC (RfC_{short})
  - For nonresidential AAC based on acute or short-term RfC, adjustment to account for a 12-hour exposure at the workplace may be applied using the following considerations:
    - If RfC_{acute} or RfC_{short} is based on a duration of exposure in the critical study of 12 hours or less, no adjustment is applied.
    - If RfC_{acute} or RfC_{short} is based on a study with exposure duration greater than 12 hours or adjusted for continuous exposure, adjustment, ($RfC_{acute,adj}$ or $RfC_{short,adj}$) is appropriate.
    - If RfC_{short} is based on a study with exposure duration greater than two weeks and adjusted for continuous exposure, adjustment is appropriate. Additional adjustment to account for a five out of seven day work week ($RfC_{short,adj}$) may also be appropriate.
- Other acute or short-term health-based inhalation value (e.g., EGLE acute Initial Threshold Screening Level (ITSL) as determined and justified by the TSG VIAP workgroup. This includes acute ITSLs derived from occupational exposure limits (OELs). OELs include the Occupational Safety and Health Administration (OSHA) permissible exposure limits (PEL), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), and National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limit (REL). OELs were previously evaluated for their applicability to the Air Pollution Control Rules used by the AQD (MDNR, 1989). Recognizing the limitations associated with applying OELs to exposure of the general public, ITSLs derived from OELs are applied a total uncertainty factor (UF) of 100, 10 to extrapolate for occupational exposure durations and 10 to account for human variability.

Step 2. Determine the **TS RIASLs**. The **lowest** of the available values identified below is the basis for the TS RIASL for residential and nonresidential land use:

- 3x the chronic exposure noncancer or developmental Res AAV, NR AAV, or NR AAV_{adj} calculated in Step 1.
- 10x the cancer or mutagenic Res AAV, NR AAV, or NR AAV_{adj} calculated in Step 1.
- Acute inhalation MRL (MRL_{acute} or $MRL_{acute,adj}$) as identified in Step 1.
- Intermediate inhalation MRL (MRL_{int} or $MRL_{int,adj}$) as identified in Step 1.
- Acute or short-term RfC identified in Step 1.
- Other appropriate short-term health-based value as determined and justified by the TSG VIAP workgroup.

Step 3. Convert µg/m³ to ppb_{vol}. Insert the unrounded concentration in µg/m³ into the below equation:

$$\frac{\mu g}{m^3} = ppbv \times \frac{MW}{24.45}$$

Where MW = molecular weight in grams per mole (g/mole) and 24.45 is at standard temperature and pressure (25°C and 1 atmosphere). Round the ppb_{vol} concentration to 2 significant figures.

Other Considerations

Considerations when evaluating the health-based chronic AAVs, acute and intermediate MRLs, and acute and short-term RfCs for use as RIASLs and TS RIASLs include:

- The duration of exposure and effects/endpoint in the critical study are evaluated to determine whether adjustment for nonresidential hours/day and days/week exposure is appropriate and if the use of 3x or 10x the chronic exposure based-AAV as TS RIASLs will protect for acute or short-term toxicity.
- For developmental toxicants, it is important to note if a critical effect may be a result of a single exposure event. For nonresidential RIASL and TS RIASL based on a developmental toxicant classified as a single exposure event, adjustment for work-related exposure may be appropriate if the developmental toxicity value is based on a continuous (24-hour) exposure. Consider the current EGLE approach and policy and best available information when evaluating for single exposure events.
- Additional available literature and various health outcomes are evaluated to determine if confidence level on the benchmark concentration (BMCL) is evaluated. The BMCL is preferred, when appropriate. Other methods are also evaluated including estimation of the human equivalent dose or continuous exposure dose.
- The uncertainty factors (UFs) applied and level of confidence in the toxicity endpoint are examined to understand the limitation of or degree of uncertainty in the toxicity or risk estimate.

Calculation of the AAVs:

The following equations were used in calculating the AAVs in this report. Changes to the equation or a different value for the parameters in the equation may be proposed for evaluation by the TSG VIAP workgroup. Recommended revisions/changes will require TSG approval.

Considerations for Developmental Effects

The determination that a hazardous substance is a developmental chemical that can be based on a single event exposure or a full-term exposure is based on the TSG recommendations detailed in the Recommendations from the Toxics Steering Group Children's Environmental Health Subcommittee: Process to Address Developmental and/or Reproductive Toxicity in the Derivation of Generic Cleanup Criteria (MDEQ, 2015).

There is sufficient data for many hazardous substances that demonstrates that adverse endpoints can result from a single day or shorter exposure during prenatal development. Mortality, structural, or functional abnormalities are adverse effects that are most likely to occur from an acute or single event exposure (U.S. EPA, 1991; U.S. EPA, 1995; U.S. EPA, 1996; U.S. EPA, 1998). Developmental or reproductive toxicity that manifests as only altered growth (e.g., reduced birth weight, delayed ossification) without structural or functional changes is most likely to occur from repeated exposures during development. Based on chemical-specific developmental or reproductive adverse effects information, the exposure of pregnant receptors (residents and workers) to hazardous substances with developmental or reproductive toxicity is classified into either a single event exposure (SE) for mortality, structural or functional abnormalities; or a full-term exposure (FT) for altered growth. For those categorized as SE, the screening level will be developed assuming a single exposure to a pregnant receptor. For those hazardous substances categorized with FT developmental or reproductive toxicity, the exposure is assumed to occur over the full duration of the pregnancy. The environmental data used to determine compliance with these screening level must represent the exposure assumptions

Developmental toxicity and reproductive toxicity are defined as follows:

- "Developmental toxicity means adverse outcomes induced during exposure at any early- life stage from preconception through adolescence (U.S. EPA, 2006; WHO, 2011). This toxicity can occur at any point in the life span and may include: (1) death; (2) structural abnormality; (3) altered growth; and/or (4) functional deficiency (U.S. EPA, 1991; U.S. EPA, 2006; WHO, 2011)."
- "Reproductive toxicity manifests as harmful effects on sexual function and fertility. This can include changes to the female or male reproductive organs, the related endocrine system, and/or pregnancy outcomes. For reproductive effects, the process is intended to address those that occur as a result of early life exposures (i.e., from preconception through adolescence)."

Refer to the MDEQ (2015) Report for details on the approach for developing developmental or reproductive-based values.

RESIDENTIAL:

1. Equation for carcinogenic effects:

$$AAV_{ca} = \frac{TR \times AT_{ca}}{IURF \times ED_{res} \times EF_{res}}$$

where,

AAV_{ca}	(Acceptable air value)	=	chemical-specific, µg/m^3
TR	(Target risk level)	=	10^{-5}
AT_{ca}	(Averaging time)	=	28,470 days
IURF	(Inhalation unit risk factor)	=	chemical-specific, (µg/m^3)$^{-1}$
ED_{res}	(Exposure duration)	=	32 years
EF_{res}	(Exposure frequency)	=	350 days/year

2. Equation for Carcinogens with mutagenic EFFECTS:

$$AAV_{mut} = \frac{TR \times AT_{ca}}{IURF \times EF_{res} \times \left[\left(ED_{<2} \times ADAF_{<2}\right) + \left(ED_{2-6} \times ADAF_{2-6}\right) + \left(ED_{6-16} \times ADAF_{6-16}\right) + \left(ED_{16-32} \times ADAF_{16-32}\right)\right]}$$

where,

AAV_{mut}	(Acceptable air value)	=	chemical-specific, µg/m^3
TR	(Target risk level)	=	10^{-5}
AT_{ca}	(Averaging time)	=	28,470 days
IURF	(Inhalation unit risk factor)	=	chemical-specific, (µg/m^3)$^{-1}$
EF_{res}	(Exposure frequency)	=	350 days/year
$ED_{age\ <2}$	(Exposure duration, age <2 years)	=	2 years
$ADAF_{<2}$	(Age-dependent adjustment factor for cancer potency, age <2 years)	=	10
$ED_{age\ 2\text{-}6}$	(Exposure duration, age 2-6 years)	=	4 years
$ADAF_{2\text{-}6}$	(Age-dependent adjustment factor for cancer potency, age 2-6 years)	=	3
$ED_{age\ 6\text{-}16}$	(Exposure duration, age 6-16 years)	=	10 years
$ADAF_{6\text{-}16}$	(Age-dependent adjustment factor for cancer potency, age 6-16 years)	=	3
$ED_{age\ 16\text{-}32}$	(Exposure duration, age 16-32 years)	=	16 years
$ADAF_{16\text{-}32}$	(Age-dependent adjustment factor for cancer potency, age 16-32 years)	=	1

3. Equation for Non-carcinogenic EFFECTS:

$$AAV_{nc} = \frac{THQ \times AT_{res} \times RfC \times RSC}{ED_{res} \times EF_{res}}$$

where,

AAV_{nc}	(Acceptable air value)	=	chemical-specific, µg/m^3
THQ	(Target hazard quotient)	=	1
AT_{res}	(Averaging time)	=	11,680 days
RfC	(Reference concentration)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
ED_{res}	(Exposure duration)	=	32 years
EF_{res}	(Exposure frequency)	=	350 days/year

4. EQUATION FOR DEVELOPMENTAL EFFECTS - CHILD:

$$AAV_{dev} = \frac{THQ \times AT_{child} \times RfC_{dev} \times RSC}{ED_{child} \times EF_{child}}$$

where,

AAV_{dev}	(Acceptable air value)	=	chemical-specific, µg/m^3
THQ	(Target hazard quotient)	=	1
AT_{child}	(Averaging time)	=	2,190 days
RfC_{dev}	(Reference concentration, developmental)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
ED_{child}	(Exposure duration)	=	6 years
EF_{child}	(Exposure frequency)	=	350 days/year

5. Equation for developmental EFFECTS – pregnant resident (Single event [SE] or full-term [FT] exposure):

$$AAV_{dev} = \frac{THQ \times AT_{preg} \times RfC_{dev} \times RSC}{ED_{preg} \times EF_{preg}}$$

where,

AAV_{dev}	(Acceptable air value)	=	chemical-specific, µg/m^3
THQ	(Target hazard quotient)	=	1
$AT_{preg,FT}$	(Averaging time, full-term pregnancy)	=	280 days or chemical-specific
$AT_{preg,SE}$	(Averaging time, single event exposure during pregnancy)	=	1 day or chemical-specific
RfC_{dev}	(Reference concentration, developmental)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	chemical-specific or 1
$ED_{preg,FT}$	(Exposure duration, full-term pregnancy)	=	40 weeks or chemical-specific
$ED_{preg,SE}$	(Exposure duration, single event exposure during pregnancy)	=	1 day or chemical-specific
$EF_{preg,FT}$	(Exposure frequency, full-term pregnancy)	=	6.7125 days/week or chemical-specific
$EF_{preg,SE}$	(Exposure frequency, single event exposure during pregnancy)	=	1 day/day or chemical-specific

NONRESIDENTIAL:

Note: The following equations assume an exposure time of 24 hours per day. To adjust for a 12 hour/day exposure at the workplace, multiply the AAC (lowest of calculated AAVs and acute/short-term health benchmarks) by a factor of two, as appropriate.

6. equation for Carcinogenic EFFECTS:

$$AAV_{ca} = \frac{TR \times AT_{ca}}{IURF \times ED_{nr} \times EF_{nr}}$$

where,

AAV_{ca}	(Acceptable air value)	=	chemical-specific, µg/m^3
TR	(Target risk level)	=	10^{-5}
AT_{ca}	(Averaging time)	=	28,470 days
IURF	(Inhalation unit risk factor)	=	chemical-specific, (µg/m^3)$^{-1}$
ED_{nr}	(Exposure duration)	=	20 years
EF_{nr}	(Exposure frequency)	=	238 days/year

7. equation for NON-Carcinogenic EFFECTS:

$$AAV_{nc} = \frac{THQ \times AT_{nr} \times RfC \times RSC}{EF_{nr} \times ED_{nr}}$$

where,

AAV_{nc}	(Acceptable air value)	=	chemical-specific, µg/m^3
THQ	(Target hazard quotient)	=	1
AT_{nr}	(Averaging time)	=	7,300 days
RfC	(Reference concentration)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
EF_{nr}	(Exposure frequency)	=	238 days/year
ED_{nr}	(Exposure duration)	=	20 years

8. Equation for developmental EFFECTS – PREGNANT WORKER:

$$AAV_{dev} = \frac{THQ \times AT_{dev} \times RfC_{dev} \times RSC}{ED_{dev} \times EF_{dev}}$$

where,

AAV_{dev}	(Acceptable air value)	=	chemical-specific, µg/m^3
THQ	(Target hazard quotient)	=	1
$AT_{dev,FT}$	(Averaging time, pregnant worker, full-term pregnancy)	=	280 days or chemical-specific
$AT_{dev,SE}$	(Averaging time, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
RfC_{dev}	(Reference concentration)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	chemical-specific or 1
$ED_{dev,FT}$	(Exposure duration, pregnant worker, full-term pregnancy)	=	40 weeks or chemical-specific
$ED_{dev,SE}$	(Exposure duration, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
$EF_{dev,FT}$	(Exposure frequency, pregnant worker, full-term pregnancy)	=	4.575 days/week or chemical-specific
$EF_{dev,SE}$	(Exposure frequency, pregnant worker, single event exposure during pregnancy)	=	1 day/day or chemical-specific

REFERENCES

Michigan Department of Environmental Quality (MDEQ). 2015. Recommendations from the Toxics Steering Group Children's Environmental Health Subcommittee: Process to Address Developmental and/or Reproductive Toxicity in the Derivation of Generic Cleanup Criteria. December 2015. www.michigan.gov/documents/deq/deq-aqd-tox-dev_rep_tox_cleanup_criteria_618442_7.pdf

Michigan Department of Natural Resources (MDNR). 1989. Final Report of the Michigan Air Toxics Policy Committee, a Proposed Strategy for Processing Air Quality Permit Applications for New Emission Sources of Toxic Air Pollutants. September 1989.

United States Environmental Protection Agency (USEPA). 1991. Guidelines for Developmental Toxicity Risk Assessment. Federal Register 56(234):63798-63826. www.epa.gov/risk/guidelines-developmentaltoxicity-risk-assessment

USEPA. 1995. Policy on evaluating health risks to children. Office of the Administrator, Washington, DC. http://www.epa.gov/osa/spc/2poleval.htm

USEPA. 1996. Guidelines for Reproductive Toxicity Risk Assessment. Risk Assessment Forum, Washington, DC; EPA/630/R-96/009. http://cfpub.epa.gov/ncea/raf/pdfs/repro51.pdf

USEPA. 1998. Guidelines for Neurotoxicity Risk Assessment. Federal Register 63(93):26926-26954. EPA/630/R-95/001F. www.epa.gov/risk/guidelines-neurotoxicity-riskassessment

USEPA. 2006. Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. National Center for Environmental Assessment, Washington, DC; EPA/630/P-30/003F. http://www2.epa.gov/sites/production/files/2013-09/documents/agegroups.pdf

World Health Organization. 2011. Summary of Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals. World Health Organization, Geneva, Switzerland. http://www.who.int/ceh/health_risk_children.pdf?ua=1

APPENDIX B: BASIS FOR DEVELOPING THE RIASLS AND TS RIASLS

Pursuant to Part 201 (MCL 324.20120a(4)) of the Michigan Natural Resources and Environmental Protection Act, 1994 PA 451 as amended, unacceptable human exposure is indicated when chemical levels represent cancer risks greater than 10^{-5} or a HQ greater than one. The RIASLs and TS RIASLs are developed to evaluate continued exposure related to the VIAP when indoor air concentrations of hazardous substances exceed these unacceptable risk levels. The acceptable air concentrations that exceed unacceptable risk levels are determined for residential and nonresidential[1] land use using the process outlined in Appendix A. In general, the U.S. EPA considers unacceptable human exposures as occurring when chemical levels result in cancer risks greater than 10^{-4} to 10^{-6} or a HQ of one for noncancer effects (U.S. EPA, 2015).

As many of the sites potentially have had contamination for multiple decades and complete remediation may take additional months to years, people may have had unacceptable indoor air exposure for an extended period of time. To address this potential exposure, interim action levels are necessary to ensure that when unacceptable exposures are identified, they are stopped as soon as possible. This is especially important when short-term exposure could result in health effects, such as in the case of developmental toxicants or mutagenic carcinogens.

Since many of these ongoing exposures are already chronic, the TS RIASLs in this document were patterned after levels recommended for the U.S. EPA removal activities (Regional Removal Management Levels or RMLs; U.S. EPA, 2016). These generic RMLs correspond to a cancer risk level of 10^{-4} or HQ of three for noncancer effects.

The U.S. EPA vapor intrusion site guidance includes the need for prompt action due to human health risks at certain VI sites (U.S. EPA, 2015). Specifically, the U.S. EPA VI Guidance states:

EPA has emphasized the importance of interim actions and site stabilization in the Resource Conservation and Recovery Act (RCRA) corrective action program to control or abate "ongoing risks" to human health and the environment while site characterization is underway or before a final remedy is selected (see the *Federal Register* of May 1, 1996 [61 FR 19446]). Interim actions encompass a wide range of institutional and physical corrective action activities to achieve stabilization and can be implemented at any time during the corrective action process. EPA recommends that interim actions, including PEM *{presumptive mitigation}*, be employed as early in

[1] Nonresidential screening levels are calculated based on a healthy adult **worker with potential exposure during a workday and potential intermittent exposure of adults and children who are customers, patrons, or visitors to commercial or industrial establishments during a portion of the workday**. Residential screening levels are intended to address places where people live and/or children or other sensitive populations are present **on a regular basis [greater than intermittent]. Residential screening levels may be more appropriate and protective for certain exposure scenarios** (e.g., daycares, **churches,** schools, doctor's offices, **hospitals, recreational areas, etc.**).

the corrective action process as possible, consistent with the human health and environmental protection objectives and priorities for the site. EPA recommends that, as further information is collected, program implementers continue to look for opportunities to conduct additional interim response actions.

The 2015 U.S. EPA VI Guidance document addresses situations when indoor air concentrations are higher than health-protective screening levels for acute or short-term exposure. Therefore, to determine when urgent action is needed, time-sensitive interim action levels are required. In an U.S. EPA memo, the recommended response action at sites with trichloroethylene, a hazardous substance linked to developmental health effects after a short-term exposure, is accelerated response when indoor air concentrations are above a HQ of one. Completion of mitigation measures are recommended within a few weeks. An urgent response is recommended when indoor air concentrations are above a HQ of three. For urgent response, mitigation measures were recommended within a few days, with the possibility of temporary relocation for the residents (U.S. EPA, 2014).

TOXICITY VALUE SELECTION

Best available information in selecting toxicity values is represented by 1) knowledge gained through research and studies; 2) best practices from other states; 3) sound science; and 4) available new information. In order to make the determination of what toxicity information represents the best available, toxicity values and relevant information was obtained from multiple sources and compared. Data sources were categorized in Tiers as follows:

1. Tier 1 Sources
    a. U.S. EPA Integrated Risk Information System (IRIS)
    b. U.S. EPA Office of Pesticide Programs (OPP)
2. Tier 2 Sources
    a. Agency for Toxic Substances and Disease Registry (ATSDR)
    b. U.S. EPA Provisional Peer Reviewed Toxicity Values (PPRTV)
3. Tier 3 Sources
    a. Other States that derive or publish their own toxicity values including Texas, New York, Minnesota, Massachusetts, California, and Michigan. States such as Ohio, Indiana and Wisconsin use the EPA Regional Screening Levels (RSL) and therefore the RSL's hierarchy of sources. Search sources included websites and environmental databases from the following state, federal, and international agencies:
        i. Michigan Department of Environmental Quality Chemical Criteria Database (CCD)

ii. California Environmental Protection Agency (CalEPA)
iii. Massachusetts Department of Environmental Protection
iv. Minnesota Department of Health
v. New Jersey Department of Environmental Protection
vi. New York State Department of Environmental Conservation
vii. Texas Commission on Environmental Quality
viii. U.S. EPA Health Effects Summary Tables (HEAST) database
ix. National Toxicology Program Report on Carcinogens (RoC)
x. World Health Organization International Agency for Research on Cancer (IARC)
xi. World Health Organization International Programme on Chemical Safety (IPCS)
xii. Health Canada
xiii. National Institute for Public Health and the Environment, RIVM
xiv. European Chemicals Agency REACH database
xv. Organization for Economic Co-Operation and Development (OECD)

LIMITATIONS OF THESE SCREENING LEVELS

The RIASLs and TS RIASLs are not intended to define protective levels under all conditions and are not *de facto* cleanup levels or criteria. They generally address exposure to a single chemical only. At certain sites, volatilization to indoor air of more than one chemical could be occurring. Different screening levels may need to be developed for those sites when the toxicity values of co-occurring hazardous substances are based on the same health endpoint, target organ, or system (U.S. EPA 2015, 2016). The MDHHS may recommend different screening levels to address human exposure to multiple chemicals.

Additionally, the MDHHS may recommend different screening levels when addressing sites with sensitive and vulnerable populations. These populations include, but are not limited to elderly, women who are or may become pregnant, infants and children, people with chronic illness, or those populations with multiple sources of exposure to chemicals (e.g., environmental justice considerations) (U.S. EPA 2012, 2015).

REFERENCES:

U.S. Environmental Protection Agency (U.S. EPA). December 3, 2012 memorandum transmits OSWER Directive 9200.2-84, entitled "Assessing Protectiveness at Sites for Vapor Intrusion. Supplement to the Comprehensive Five-Year Review Guidance."
https://semspub.epa.gov/work/HQ/176385.pdf

U.S. EPA. July 9, 2014 memorandum EPA Region 9 Response Action Levels and Recommendations to Address Near-Term Inhalation Exposures to TCE in Air from Subsurface Vapor Intrusion.
https://yosemite.epa.gov/r9/sfund/r9sfdocw.nsf/3dc283e6c5d6056f88257426007417a2/6a24ed351efe25b888257d16007659e8/$FILE/R9%20TCE%20Action%20Levels%20and%20Recs%20Memo%207_14.pdf

U.S. EPA. 2015. OSWER Technical Guide For Assessing And Mitigating The Vapor Intrusion Pathway From Subsurface Vapor Sources To Indoor Air. OSWER Publication 9200.2-154. June 2015.
www.epa.gov/sites/production/files/2015-09/documents/oswer-vapor-intrusion-technical-guide-final.pdf

U.S. EPA. 2016. Regional Removal Management Levels (RMLs) User's Guide.
www.epa.gov/risk/regional-removal-management-levels-rmls-users-guide Last Updated 25 May 2016.

APPENDIX C: CHEMICAL-SPECIFIC JUSTIFICATIONS FOR RIASLS AND TS RIASLS

The justifications for the RIASLs and TS RIASLs of each hazardous substance include a summary table of the residential and nonresidential screening levels in two different units ($\mu g/m^3$ and ppb_{vol}), the basis of these screening levels, the sources and basis for the toxicity values, and a discussion of uncertainties related to the toxicity estimates. The basis for exposure adjustment (<24 hr/workday) for nonresidential RIASL and TS RIASL is included. Also presented at the end of each justification is a summary of the toxicity assessment for each inhalation toxicity value considered in developing the RIASLs and TS RIASLs.

ACETONE (CAS #67-64-1) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	Residential TS RIASL
Action Level	31,000 µg/m³ (13,000 ppb_{vol})	31,000 µg/m³ (13,000 ppb_{vol})
Basis	Change in visual evoked response (ATSDR MRL Intermediate)	Change in visual evoked response (ATSDR MRL Intermediate)

Nonresidential RIASLs

	Nonresidential RIASL	Nonresidential TS RIASL
Action Level	31,000 µg/m³ (13,000 ppb_{vol})	31,000 µg/m³ (13,000 ppb_{vol})
Basis	Change in visual evoked response (ATSDR MRL Intermediate)	Change in visual evoked response (ATSDR MRL Intermediate)

Discussion of Basis

The basis of the RIASLs and TS RIASLs is the ATSDR intermediate inhalation MRL of 31,000 µg/m³. This MRL is the same value as the chronic inhalation MRL used to develop the risk-based residential and nonresidential AAVs of 32,000 and 95,000 µg/m³, respectively. The intermediate MRL is selected over the AAVs to appropriately protect for less than chronic inhalation exposures. The nonresidential RIASL and TS RIASLs were not adjusted to a 12-hour exposure time as the intermediate MRL's point of departure (POD) or lowest observed adverse effect level (LOAEL) was not adjusted to a continuous exposure.

The intermediate MRL is based on humans exposed to acetone for four weeks or less, up to four days per week and 1, 3, or 7.5 hours per day. A LOAEL of 1,250 ppm (2,969 mg/m³) was identified based on changes in the visual evoked response, a measure of neurological effects. The LOAEL was not adjusted to a continuous exposure. ATSDR (1994) derived an acute MRL of 62 mg/m³ (62,000 µg/m³) based on a study of human volunteers (11 men and 11 women) exposed to 237 ppm acetone for 4 hours on one day (Dick *et al.*, 1989). The LOAEL of 237 ppm for neurobehavioral effects (increases in response and percent false negatives in auditory discrimination; increased anger, hostility) was applied a total uncertainty factor of 9, 3 each for use of a minimal LOAEL and human variability.

MDEQ AQD (1992) established an acute ITSL of 5,900 µg/m³, 8-hour averaging time, to protect against neurobehavioral effects and sensory irritation. Based on information identified in this report, AQD is currently reevaluating the 1992 ITSL and will likely adopt ATSDR assessment. Therefore, the RIASLs and TS RIASLs will remain based on the ATSDR intermediate MRLs because it is based on a repeated dose and longer exposure study and lower than the acute MRL.

Uncertainties in the toxicity estimate:

The intermediate inhalation MRL is not adjusted to a continuous exposure but has a total uncertainty factor (UF) of 100 for use of a LOAEL (10) and human variability (10). The studies used to develop the MRLs are intermittent exposures for less than one week. Humans exposed to the LOAEL had changes in their visual evoked response after less than an exposure of 7.5 hours for four days. This is the best available information, but it is unclear if exposures at or over a year could result in a more sensitive endpoint. The UFs may be protective for this.

Source of the Toxicity Values

ATSDR Chronic and intermediate MRL = 13 ppm or 30.9 mg/m^3 (3.1E+4 µg/m^3); (13 ppm*58.08 g/mol) /24.45 = 30.9 mg/m^3.
Critical Study: Stewart, RD; Hake, CL; Wu, A; *et al*. (1975) Acetone: development of a biologic standard for the industrial worker by breath analysis. Medical College of Wisconsin, Inc., Milwaukee. Dept. of Environmental Medicine. U.S Dept. of Commerce. NTIS PB82172917. (Stewart *et al*. 1975)
Method(s): human volunteers were exposed to acetone <1,250 ppm for <7.5 hours/day, 2-5 days/week for 6 weeks.
Critical effect: neurological effects (increased visual evoked response)
End point or Point of Departure (POD): LOAEL = 1,250 ppm
Note: Supporting studies identified additional neurological and behavioral effects in humans exposed to 250 ppm acetone for a single day (5.25 hours) or for six days (6 hours a day) in humans exposed to 237 ppm.
Uncertainty Factors: UF = 100, 10-fold for use of a LOAEL and 10-fold for human variability
Source and Date: ATSDR, 5/1994
ATSDR Acute MRL = 26 ppm or 61.76 mg/m^3 (61,762 µg/m^3); (26 ppm*58.08 g/mol) /24.45 = 61.76 mg/m^3.
Critical Study: Dick RB, Brown WD, Setzer JV, et al. 1989. Neurobehavioral effects of short duration exposures to acetone and methyl ethyl ketone. Br. J. Ind. Med. 46: 1(1):l-12.
Method(s): human volunteers (11 men and 11 women) were exposed to 237 ppm acetone 4 hours on one day.
Critical effect: neurobehavioral effects (increases in response and percent false negatives in auditory discrimination; increased anger, hostility)
End point or Point of Departure (POD): LOAEL = 237 ppm
Uncertainty Factors: UF = 9, 3 each for use of a minimal LOAEL and human variability
Source and Date: ATSDR, 5/1994
EGLE: AQD (1992) ITSL = 5.9E+03 µg/m^3 with 8-hour averaging time.
Basis: ITSL is based upon a NIOSH REL of 590 mg/m^3. ITSL = 590 mg/m^3 x 1,000 µg/mg = 590,000 µg/m^3 x 1% = 5900 µg/m^3.
Method: NIOSH established an REL of 250 ppm (or 590 mg/m^3) to protect against irritant and neurobehavioral effects observed at doses lower than the TLV and PEL. Specific toxicity data used to derive the NIOSH REL is not summarized by AQD; the screening level documentation does describe

human exposure data to justify using the NIOSH REL instead of the ACGIH TLV and OSHA PEL. The total UF of 100 was applied to the REL to extrapolate from worker exposure and to account for human variability. AQD applies a default total UF of 100 to occupational exposure limits (OELs) to account for human variability (10) and exposure time between the worker and the general population (10).

REL Critical studies: Dick *et al*. 1989. Neurobehavioral effects of short duration exposures to acetone and methyl ethyl ketone. Br J Ind Med 46:111-121.

AQD's Uncertainty Factors: Per Air Pollution Control Rules used by the AQD (MDNR, 1989), ITSLs derived from RELs are derived by applying a total UF of 100, 10 to extrapolate for occupational exposure durations and 10 to account for human variability.

Source and date: MDEQ-AQD, 6/18/1992

Cancer:

Carcinogen Weight-of-Evidence (WOE) Class: data are inadequate for an assessment of the human carcinogenic potential of acetone

IRIS WOE Basis: based on the availability of one human study of limited utility, no chronic animal studies, and no additional information on structural analogues with known carcinogenic potential. Acetone has tested negative in almost all genotoxicity studies.

Source and Date: IRIS, 7/31/2003.

ACETOPHENONE (CAS #98-86-2) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	3,200 µg/m³ (650 ppb_{vol})	9,600 µg/m³ (2,000 ppb_{vol})
Basis	Neurotoxicity, reproductive and developmental toxicity (Res AAC SE Developmental– EGLE RfC)	3 × Res AAC SE Developmental

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	6,400 µg/m³ (1,300 ppb_{vol})	19,000 µg/m³ (4,000 ppb_{vol})
Basis	Neurotoxicity, reproductive and developmental toxicity (NR AAC_{adj} SE Developmental – EGLE RfC)	3 × NR AAC_{adj} SE Developmental

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for acetophenone are based on the MDEQ (2015) RfC of 3.2E+03 per µg/m³. Both residential and nonresidential AACs are based on developmental effects that may result from a single event exposure during pregnancy. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the toxicity value was based on a repeated-dose study (see Source of the Toxicity Values below for study details).

The RfC is based on route extrapolation of the modified PPRTV RfD which comes from a combined repeated-dose reproductive and developmental toxicity screening study (ATF, 2003). This study observed neurological and reproductive/developmental effects. PPRTV (2011) derived a screening subchronic RfD of 8.0E-01 mg/kg-day, which was used to calculate the EGLE RfC = (8.0E-01 x 80)/20 = 3.2E+03 µg/m³ (assumes 20 m³/day air rate and 80 kg adult body weight).

No Tier 1 or Tier 2 sources had available values. EGLE prefers repeated dose toxicity as basis for toxicity endpoints; therefore, the RfC value of 3.2E+03 per µg/m³ based on a route to route extrapolation of the 2011 PPRTV RfD is recommended as it is based on a repeated dose, reproductive and developmental toxicity study and a more recent assessment. Note that MDEQ (1994) developed an 8-hour averaging time ITSL of 4.9E+02 µg/m³ based on ACGIH TLV of 49 mg/m³ for eye irritation, which is an acute effect.

Uncertainties in the toxicity estimate:

A total uncertainty factor of 300 was used to derive the subchronic screening RfD, where 10 was

used for interspecies extrapolation, 3 was used for database deficiencies, and 10 was used for intraspecies variability. An additional uncertainty factor is not used for subchronic to chronic based on the developmental effects and EPA guidance for developmental effects. The ATF (2003) study is reported as proprietary data: only the text was available for review (no data summary tables were available). Per PPRTV, the study was stated to be a combined repeated dose toxicity test and reproductive/developmental screening test conducted according to the Organization for Economic Co-operation and Development (OECD) Guideline No. 422 and was GLP compliant. The ATF (2003) study provides a lower POD for endpoints not tested in the Hagan *et al*. (1967) study. However, the subchronic value derived from the ATF (2003) study was relegated to a screening value because the study was not peer reviewed and the data were not available for review. Additionally, the RfC was determined by route extrapolation from an RfD, which uses an oral route of exposure instead of an inhalational route of exposure. There is limited data regarding the health effects of inhalational exposure to acetophenone in animals and humans.

The published Hagan *et al.* (1967) study limitations included insufficient presentation of data, absence of effects even at the highest dose tested, and neither neurological nor reproductive/developmental effects were evaluated.

Source of the Toxicity Values

Noncancer:
PPRTV RfC/MDEQ = 3.2E+03 µg/m^3
Basis: EGLE as a Tier 3 source. No Tier 1 or Tier 2 available.
Critical Study: Environmental Protection Agency (2011). Provisional Peer-Reviewed Toxicity Values for Acetophenone. (EPA Publication No. 690-R-11-002F). Cincinnati, OH: U.S. EPA Office of Research and Development.
Method: Sprague-Dawley rats were exposed to adjusted doses of 0, 75, 225, or 750 mg/kg-day acetophenone (98.8% pure) in corn oil daily via gavage for a minimum of 28 days during the toxicity phase. Males from the toxicity phase were mated with females in the reproduction phase. In the reproductive/developmental phase of the ATF (2003) study, male and female rats were treated for a minimum of 14 days before mating, and female rats were treated through Lactation Day (LD) 3. Detailed clinical observations were conducted at least weekly until evidence of mating, and then females were checked daily through gestation and lactation. Males were processed as part of the repeated dose toxicity study detailed above. After at least 14 days of treatment, a single male was cohabitated with a single female for a maximum of 14 days. Females with no evidence of mating were sacrificed 19 days after mating began, females that failed to deliver were sacrificed on GD 25, and F0 females and their offspring were sacrificed on LD 4.
Critical effect: Neurotoxicity, reproductive and developmental toxicity (decreased mean forelimb grip strength and motor activity in male rats, decreased live birth index, decreased number of F1 pups surviving to LD 4, and decreased pup body weight)
End point or Point of Departure (POD): adjusted NOAEL = 225 mg/kg-day

Uncertainty Factors: 300, 10 each for interspecies extrapolation and intraspecies variability and 3 for database deficiency
Source and Date: PPRTV, 6/15/2011

Tier 1 and 2 Sources:
IRIS: Per IRIS (02/01/1991), no value at this time
PPRTV: Per PPRTV (6/15/2011), no RfC value at this time.
MRL: No MRL record available at this time.

Tier 3 Sources:
EGLE: AQD (1994) ITSL = 4.9E+02 µg/m^3 with 8-hour averaging time. ITSL = 49 mg/m^3 x 1,000 µg/mg = 49,000 µg/m^3 x 1% = 490 µg/m^3.
Basis: The MDEQ (1994) ITSL of 4.9E+02 µg/m^3 is based on ACGIH TLV of 49 mg/m^3 for eye irritation, which is an acute effect. ECHA (REACH) extrapolated an inhalation DNEL of 1.8E+04 µg/m^3 based on a NOEL = 750 mg/kg day from a subchronic oral study (Hagan, 1967) with a UF of 10; therefore, oral DNEL = 75 mg/kg day. The IRIS (1989) RfD relied on the Hagan *et al*. (1967) studies, which observed no effects, but did not include neurological or reproductive/developmental screening.
Method: ACGIH adopted a TLV for acetophenone based on a recommendation to reduce eye irritation. Application of acetophenone to the eyes of rabbits as two drops of saturated aqueous solution caused discomfort; however, the effects were limited to a transient optical irregularity of the corneal epithelium, with no opacity, and the eyes returned to normal by the next day. Additionally, one study reported that instillation of 771 mg of undiluted acetophenone into the eyes of rabbits produced moderate irritation and transient corneal injury. Per AQD, although these studies indicate a low degree of eye irritation, data on long term safety is limited. **Reference:** ACGIH (1993). Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. 1993-1994. American Conference of Governmental Industrial Hygienists, Cincinnati, p.12.
Source and Date: MDEQ/AQD, 6/08/1994
ECHA (REACH): Derived No Effect Level (DNEL) = 18.4 mg/m^3 (1.8E+04 µg/m^3):
Basis: NOAEC: 184 mg/m^3
Justification for route-to route-extrapolation: 1.15 m^3/kg body weight (default), 0.5 absorption via inhalation factor 2 higher compared to oral (default)
Critical Study: Hagan EC, Hansen WH, Fitzhugh OG, Jenner PM, Jones WI, Taylor JM, Long EL, Nelson AA, Brouwer JB. 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity, Food Cosmet. Toxicol. 5:141-157
Methods: Groups of 10 male and 10 female weanling Osborne-Mendel rats were exposed to 0, 1,000, 2,500 and 10,000 ppm acetophenone in food for 17 weeks. NOEL: 10,000 ppm in food (750 mg/kg body weight/day) report. A NOAEL of 423 mg/kg was estimated by U.S. EPA IRIS, accounting for the loss by evaporation from food.
Critical Effect: No effect at the highest dose
Overall assessment factor (AF) = 10, 2 for differences in duration of exposure and 5 for interspecies

differences.
Source: ECHA Reach Database Acetophenone
Additional Note: ECHA considered a combined repeated dose toxicity study and reproduction/developmental screening study as a second key study (Kapp *et al*., 2003). See Tier 3 Data Worksheet for details.
Other Tier 3: No value is available at this time from these Tier 3 sources/databases: HEAST, NTP ROC, health and environmental agencies of California, Massachusetts, Minnesota, New Jersey, New York, and Texas, WHO (IARC), WHO (IPCS/INCHEM), Canada, The Netherlands (RIVM) and OECD HPV.
Cancer:
Carcinogen Weight-of-Evidence (WOE) Class: Class D - "Inadequate Information to Assess Carcinogenic Potential"
IRIS WOE Basis: No human or animal data are available to assess the carcinogenicity of oral exposure.
Source and Date: IRIS, 2/01/1991
Tier 1 and 2 Sources:
IRIS: Per IRIS (02/01/1991), no value at this time
PPRTV: Per PPRTV (6/15/2011), no value at this time.
MRL: NA; MRLs are for non-cancer effects only.

AMMONIA (CAS #7664-41-7) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	520 µg/m³ (750 ppb_{vol})	1,200 µg/m³ (1,700 ppb_{vol})
Basis	Respiratory effects from worker exposure (Res AAC Noncancer – U.S. EPA IRIS RfC)	Eye, nose, and throat irritation (ATSDR MRL Acute)

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	1,200 µg/m³ (1,700 ppb_{vol})	1,200 µg/m³ (1,700 ppb_{vol})
Basis	Eye, nose, and throat irritation (ATSDR MRL Acute)	Eye, nose, and throat irritation (ATSDR MRL Acute)

Discussion of Basis

The residential RIASL is based on the 2016 IRIS RfC of 520 µg/m³ based on a duration adjusted (continuous exposure) NOAEL of 4.9 mg/m³ for respiratory effects in an occupational exposure study (Holness *et al*., 1989). Holness *et al*. (1989) identified three exposure groups amongst the entire group of exposed workers: low (< 6.25 ppm), medium (6.25-12.5 ppm), and high (>12.5 ppm). No statistically significant differences were seen between the control group and any of the exposure groups (either the subgroups or the overall exposed group). While a LOAEL was not identified in this study, the larger body of evidence supports the findings identified therein (Ali, 1989; Ballal, 1998; Rahman, 2007; U.S. EPA, 2016).

ATSDR has also derived a chronic MRL of 70 µg/m³ for ammonia using the Holness *et al*. (1989) study as the key study (ATSDR, 2004). The Holness *et al*. (1989) study was used to derive both the U.S. EPA IRIS RfC and the ATSDR chronic MRL (ATSDR, 2004; EPA, 2016). Differences in benchmark values reside within the POD, and application of different modifying factors and exposure duration adjustment factors. The U.S. EPA RfC value will be used for deriving the ammonia residential RIASL for the following reasons:

1) It is the most recent peer-reviewed health benchmark evaluation for ammonia. With this, it has a comprehensive review of the toxicological literature.
2) Although ATSDR (2004) applied a modifying factor of 3, the U.S. EPA (2016) provides adequate reasoning for why a modifying factor was not used for the lack of reproductive and developmental studies (see the source information below for details).
3) ATSDR used an estimate of the time weighted average (TWA) of the overall exposed group as the POD. However, U.S. EPA used an estimate of the NOAEL identified by Holness *et al*. (1989) from the most highly exposed subgroup within that study (EPA, 2016; Holness *et al*.,

1989). It is more appropriate to use an exposure estimate from the NOAEL identified from the most highly exposed subgroup as the POD. Therefore, U.S. EPA's POD is preferred.

The risk-based AAV based on the IRIS RfC was not chosen for the basis of the nonresidential RIASL or the TS RIASLs because the ATSDR acute inhalation MRL is lower. There is an AQD acute ITSL also based on acute respiratory irritation. It should be noted that short-term health effects are possible after an acute exposure to levels lower than values based on the RfC, possibly due to people's adaptation during longer exposure times and healthy worker considerations.

The residential TS RIASL and nonresidential RIASL and TS RIASL are based on the ATSDR acute inhalation MRL of 1.7 ppm or 1,200 µg/m^3. It is based on a human study where 16 volunteers were exposed for a maximum of two hours to 50, 80, 110, and 140 ppm ammonia (Verberk, 1977; ATSDR, 2004). Subjects were surveyed for sensitivity to ammonia every 15 minutes, and 50 ppm was identified as the LOAEL where eye, nose and throat irritation and general discomfort were considered the critical effects.

The MDEQ AQD (2017) established an acute ITSL of 350 µg/m^3 based on a LOAEL of 5 ppm (≈3.5 mg/m^3) for eye irritation and central nervous symptoms, like headaches, after acute exposure to 5 and 25 ppm ammonia of twelve healthy volunteers on three separate occasions for three hours each time in a controlled human study (Sundblad *et al*., 2004). The AQD acute ITSL for ammonia is lower than the ATSDR acute MRL and used a more recent study that was not considered in the ATSDR assessment. However, because the 2004 acute MRL is based on a robust toxicity assessment (with external reviews), the acute MRL is selected as the basis for the RIASL.

Uncertainties in the toxicity estimates:
The U.S. EPA RfC has an UF of 10 for human variability, since the studies were conducted on healthy adult workers. The ATSDR acute MRL has a total UF of 30 applied to the LOAEL, 10 for human variability, and 3 for the use of a LOAEL. For the AQD acute ITSL, the total UF applied is 10, 3 each for human variability and LOAEL to NOAEL extrapolation.

Source of the Toxicity Values

Noncancer:
Basis: The IRIS RfC was selected as the basis for the noncancer AAC, because it is a Tier 1 source, and a more recent assessment of ammonia.
IRIS: RfC = 5.0E-1 mg/m^3 (500 µg/m^3).
Critical Study: Holness, DL; Purdham, JT; Nethercott, JR. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. The Am. Ind. Hyg. Assoc. 50(12):646-650.
Supporting Studies:

1) Ali, BA; Ahmed, HO; Ballal, SG; Albar, AA. 2001. Pulmonary function of workers exposed to ammonia: A study in the Eastern Province of Saudi Arabia. Int. J. Occup. Environ. Health 7: 19-22.

2) Ballal, SG; Ali, BA; Albar, AA; Ahmed, HO; Al-Hasan, AY. 1998. Bronchial asthma in two chemical fertilizer producing factories in eastern Saudi Arabia. Int. J. Tuberc. Lung Dis. 2: 330-335.
3) Rahman, MH; Bråtveit, M; Moen, BE. 2007. Exposure to ammonia and acute respiratory effects in a urea fertilizer factory. Int. J. Occup. Environ. Health 13:153-159.

Methods: A cross sectional epidemiology study of soda ash plant workers. Male workers exposed to ammonia (n=58) and controls (n=31 from stores and office areas of plant).
Average exposure was 12.2 yrs. Exposure was measured using personal samples, one work-shift/person for an average of 8.4 hours. Two analytical methods were used for measuring ammonia concentrations in workplace air. The American Thoracic Society questionnaire was used to identify respiratory symptoms. Average exposure for exposed workers was 6.5 mg/m^3.
Critical effect: Decreased lung function and respiratory effects (cough, wheezing, and other asthma-related symptoms) in workers
End point or Point of Departure (POD): NOAEL = 13.6 mg/m^3; NOAEL$_{adj}$ = 4.9 mg/m^3
Uncertainty Factors: UF = 10 for intraspecies variability
Source and Date: IRIS, 9/20/2016
Note: Although ATSDR (2004) applied a modifying factor of 3, the U.S. EPA (2016) provides adequate reasoning for why a modifying factor was not used for the lack of reproductive and developmental studies. Their justification is as follows:

> "The inhalation ammonia database includes one limited study of reproductive and developmental toxicity in pigs that did not examine a complete set of reproductive or developmental endpoints. Normally, confidence in a database lacking reproductive and developmental toxicity studies is considered to be lower… However, the likelihood of reproductive, developmental, and other systemic effects at the RfC is considered small because it is well documented that ammonia is endogenously produced in humans and animals, and any changes in blood ammonia levels at the POD would be small relative to normal blood ammonia levels. Further, EPA is not aware of any mechanisms by which effects at the point of contact (i.e., respiratory system) could directly or indirectly impact tissues or organs distal to the point of contact."

MRL: **ATSDR** (9/2004) chronic inhalation MRL = 0.1 ppm = 0.07 mg/m^3 = 70 µg/m^3 based on respiratory effects.
Critical Study: Holness DL, Purdham JT, Nethercott JR. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. Am. Ind. Hyg. Assoc. 50:646-650.
Methods: Workers exposed for an average of 12.2 years in a soda ash plant were evaluated for sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, and others), eye and throat irritation, and lung function parameters (FVC, FEV1, FEV1/FVC, FEF50, and FEF75). The cohort consisted of 52 workers and 35 controls. The subjects were assessed on two workdays: on the first workday of their workweek and on the last workday of their workweek; the average sample collection period was 8.4 hours. All of the participants in the study were males.
Critical effect: No significant alterations in lung function in chronically exposed workers

End point or Point of Departure (POD): NOAEL = 9.2 ppm (mean TWA exposure concentration); NOAEL adjusted for continuous exposure (9.2 x 8/24 hours x 5/7 days) =2.2 ppm
Uncertainty Factors: UF = 30, 10 for intraspecies variability and 3 for database deficiencies – lack of reproductive and developmental studies
Source and Date: ATSDR, 9/2004

ATSDR (9/2004) **acute inhalation MRL** = 1.7 ppm=1.2 mg/m^3=1200 µg/m^3 based on respiratory effects.
Critical Study: Verberk MM. 1977. Effects of ammonia in volunteers. Int. Arch. Occup. Environ. Health 39:73-81.
Methods: Male and female volunteers (N=16) were exposed to 50, 80, 110, and 140 ppm ammonia for up to two hours. Exposure related differences were determined using lung function testing as measured by VC, FEV1 and FIV1; subjective reports of respiratory symptoms; and airway hyper-responsiveness as measured by the DeVries (1971) method for histamine threshold.
Critical effect: respiratory symptoms
End point or Point of Departure (POD): LOAEL = 50 ppm
Uncertainty Factors: UF = 30, 10 for intraspecies variability and 3 for use of a LOAEL
Source and Date: ATSDR, 9/2004

EGLE:
AQD acute ITSL = 350 µg/m^3
Critical Study: Sundblad, B.M., F. Acevedo, L. Ernstgård, G. Johanson, K. Larsson, L. Palmberg. 2004. Acute respiratory effects of exposure to ammonia on healthy subjects. Scand. J. Work Environ. Health 4: 313-321.
Method(s): 12 male and female, healthy volunteers were exposed to a sham exposure or ammonia exposure (5 and 25 ppm) for three hours. Lung spirometry, methacholine challenge provocation testing, inflammatory cell count and complement factor C3 and C3b in peripheral blood, cytokines in nasal lavage, exhaled nitric oxide, and self-reported respiratory symptoms were evaluated.
Critical effect: respiratory symptoms of irritation
End point or Point of Departure (POD): LOAEL = 5 ppm
Uncertainty Factors: UF = 10, 3 for intraspecies variability and 3 for LOAEL to NOAEL extrapolation. A factor of 3 was used for human variability based on guidance that indicates "for direct-acting chemicals whose site of action is the point of first contact…√10 may be sufficient" (Office of Environmental Health Hazard Assessment (OEHHA), 2008). Similarly, for their derivation of an acute health benchmark for ammonia, an UF of 3 for human variability was used by both the Texas Commission on Environmental Quality (TCEQ) and the Office of Environmental Health Hazard Assessment or OEHHA (OEHHA, 1999; TCEQ, 2016). The UF of 3 for a LOAEL to NOAEL extrapolation was used for minimal adverse effects of irritation. The low exposure group (5 ppm) was regarded as a LOAEL for slight severity.
Source and Date: MDEQ/AQD, 1/2017

Cancer:

Carcinogen Weight-of-Evidence (WOE) Class: Inadequate for an assessment of human carcinogenic potential.

WOE Basis: Human data are not available. Among animals, no evidence for carcinogenicity was observed in two strains of mice administered ammonium hydroxide in drinking water for two years or in a urethane-sensitive strain of mice administered ammonia in water by gavage for four weeks. There is some indication that ammonia contributes to the development of cancer when co-administered with diethyl pyrocarbonate (via formation of urethane) or N-methyl-N'-nitro-N-nitrosoguanidine (via stimulation of cell proliferation in the gastric mucosa). Limited genotoxicity testing has produced mixed results.

Source and Date: PPRTV, 2/02/2005

IRIS: Per IRIS (9/20/2016), no value at this time.

PPRTV: Per PPRTV (2/02/2005), no value at this time.

MRL: Per ATSDR (9/2004), no value at this time.

EGLE: Per EGLE-CCD, no value at this time.

BENZENE (CAS #71-43-2) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	3.3 µg/m³ (1.0 ppb_{vol})	19 µg/m³ (6.0 ppb_{vol})
Basis	Increased incidence of human leukemia (Res AAC Cancer – U.S. EPA IRIS IURF)	Delayed reaction of mouse splenic lymphocytes to foreign antigens (ATSDR MRL Intermediate Inhalation)

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	15 µg/m³ (4.8 ppb_{vol})	54 µg/m³ (17 ppb_{vol})
Basis	Increased incidence of human leukemia (NR AAC_{adj} Cancer – U.S. EPA IRIS IURF)	Delayed reaction of mouse splenic lymphocytes to foreign antigens (ATSDR MRL $Intermediate_{adj}$ Inhalation)

Discussion of Basis

The U.S. EPA's IRIS IURF is the basis of the residential and nonresidential AACs and RIASLs for benzene. Benzene is a "known" human carcinogen (U.S. EPA Category A) for all routes of exposure. The U.S. EPA's IURF is based on leukemia development in exposed workers. The AAVs calculated for carcinogenic effects is lower than those calculated for non-carcinogenic effects, based on immunotoxicity (decreased mouse B cell count for the ATSDR chronic inhalation MRL and decreased human lymphocyte count for the U.S. EPA IRIS RfC) which have been identified as the most sensitive non-carcinogenic effects. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour exposure time as the IURF and intermediate MRL, respectively are based on continuous exposure.

The residential and nonresidential TS RIASLs are developed from the ATSDR intermediate inhalation MRL of 6.0 ppbv (19 µg/m³) as this value is lower than ten times the cancer risk based AAVs. The MRL is based on delayed reaction of mouse splenic lymphocytes to foreign antigens. A LOAEL of 10 ppm was identified for that reaction, and with adjustment for a continuous human equivalent concentration results in a LOAEL (HEC_{adj}) of 1.8 ppm. This is slightly lower, but similar, to the continuous human equivalent concentration calculated for the ATSDR chronic inhalation MRL (LOAEL [HEC_{adj}] of 2.55 ppm) and the BMCL (8.2 mg/m³ [2.57 ppm]) for the U.S. EPA IRIS RfC. The intermediate MRL (19 µg/m³) was adjusted to account for a five out of seven-day work week as the intermediate MRL addresses exposure greater than two weeks to less than a year. The adjusted

intermediate MRL = 27 µg/m^3.

Uncertainties in the toxicity estimate:

The U.S. EPA IURF was estimated using linear extrapolation of occupational data from Rinsky *et al*. (1981, 1987). The U.S. EPA published a range of risk estimates, 2.2E-6 to 7.8E-6 (µg/m^3)$^{-1}$. EGLE used the high end of the range of IURFs (i.e., 7.8E-6). The U.S. EPA indicated that at the time of their assessment "the true cancer risk from exposure to benzene cannot be ascertained, even though dose-response data are used in the quantitative cancer risk analysis, because of uncertainties in the low-dose exposure scenarios and lack of clear understanding of the mode of action."

The ATSDR intermediate inhalation MRL has a total UF of 300, 10 for human variability, 3 for animal to human dosimetric conversion, and 10 for use of a LOAEL.

Source of the Toxicity Values
Chronic Inhalation Noncancer:
Basis: ATSDR is based on a more current study than IRIS.
ATSDR chronic inhalation MRL = 0.01 mg/m^3 (1.0E+1 µg/m^3)
MRL: ATSDR (08/2007), chronic inhalation MRL = 0.003 ppm or 0.01 mg/m^3:
Critical Study: Lan Q, Zhang L, Li G, *et al*. 2004a. Hematotoxicity in workers exposed to low levels of benzene. Science 306:1774-1776.
Method(s): A cross-sectional study on 250 workers (approximately two-thirds female) exposed to benzene at two shoe manufacturing facilities in Tianjin, China, and 140 age- and gender-matched workers in clothing manufacturing facilities that did not use benzene. The benzene exposed workers had been employed for an average of 6.1±2.9 years. Benzene exposure was monitored by individual organic vapor monitors (full shift) 5 or more times during 16 months prior to phlebotomy.
Critical effect: decreased B cell count
End point or Point of Departure (POD): $BMCL_{0.25sdadj}$ = 0.03 ppm
Uncertainty Factors: UF = 10 for intraspecies (human) variability
Source and date: ATSDR, 08/2007. From 12/2014 MRL list.

Intermediate Inhalation Noncancer
Basis: ATSDR intermediate (subchronic) MRL.
MRL: ATSDR (08/2007) intermediate inhalation MRL = 0.006 ppm or 0.019 mg/m^3 (1.9E+1 µg/m^3)
Critical Study: Rosenthal GJ, Snyder CA. 1987. Inhaled benzene reduces aspects of cell-mediated tumor surveillance in mice. Toxicol Appl Pharmacol 88:35-43.
Method(s): A 20 exposure day (6 hr/day, 5 days/week) inhalation study in male C57Bl/6 mice. Mice were exposed to 10, 30, or 100 ppm benzene and had number of lymphocytes and functional capacity of splenic lymphocytes evaluated by mixed-lymphocyte culture (capacity to mount an immune response against foreign antigens) and 51Cr-release cytotoxicity assay.

Critical effect: delayed MLC activity and lysing capacity of splenic lymphocytes
End point or Point of Departure (POD): $LOAEL_{adj}$ = 1.8 ppm
Uncertainty Factors: UF = 300 (10 for use of a LOAEL, 3 for animal to human dosimetric conversion, 10 for intraspecies [human] variability)
Source and Date: ATSDR, 08/2007. From 3/2016 MRL list.

Cancer:
Basis: IRIS is a Tier 1 value and a more recent review than EGLE.
IRIS IURF: Ranges from 2.2E-6 to 7.8E-6 $(\mu g/m^3)^{-1}$. EGLE applied the high end of the range of IURFs (i.e., 7.8E-6) to both the residential and nonresidential risk-based values calculation.

Critical Studies:

1) Rinsky, RA; Young, RJ; Smith, AB. 1981 Leukemia in benzene workers. Am. J. Ind. Med. 2:217-245;
2) Rinsky, RA; Smith, AB; Horning, R; *et al*. 1987 Benzene and leukemia: an epidemiologic risk assessment. N. Engl. J. Med. 316:1044-1050; and
3) Crump, KS. (1994) Risk of benzene-induced leukemia: a sensitivity analysis of the Pliofilm cohort with additional follow-up and new exposure estimates. J. Toxicol. Environ. Health 42:219-242.

Method(s):

1) *Dose response data*: *Tumor Type* - leukemia; *Test Species* - human; *Route* - inhalation, occupational exposure
2) *Extrapolation method*: Low-dose linearity utilizing maximum likelihood estimates (Crump, 1992, 1994).

Carcinogen Weight-of-Evidence (WOE) Class: A known human carcinogen for all routes of exposure
Basis: IRIS WOE: convincing human evidence as well as supporting evidence from animal studies
Source and Date: IRIS, 1/19/2000. IRIS Toxicological Review (U.S. EPA, 04/2003) is available.

2-BUTANONE; METHYL ETHYL KETONE (MEK) (CAS #78-93-3) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	5,000 µg/m³ (1,700 ppb_{vol})	15,000 µg/m³ (5,100 ppb_{vol})
Basis	Developmental toxicity – skeletal variations (Res AAC SE Developmental – IRIS RfC)	3 × Res AAC Developmental

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	10,000 µg/m³ (3,400 ppb_{vol})	30,000 µg/m³ (10,000 ppb_{vol})
Basis	Developmental toxicity – skeletal variations (NR AAC_{adj} SE Developmental – IRIS RfC)	3 × NR AAC_{adj} Developmental

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for 2-butanone are based on the U.S. EPA IRIS (2003) chronic RfC (RfC = 5.0 mg/m³).

Both residential and nonresidential AACs are based on developmental effects that may result from a single event exposure during pregnancy. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was derived for chronic and continuous exposure (24 hr/day). No ATSDR acute or intermediate inhalation MRL values are available at this time.

The critical study (Schwetz *et al*., 1991) exposed virgin Swiss CD-1 mice and sperm plug-positive (gestation day 0) females to MEK concentrations of 0, 398±9, 1,010±28, or 3,020±79 ppm (0, 1,174±27, 2,980±83, or 8,909±233 mg/m³) by inhalation for 7 hr/day on gestation days 6-15. Dams were sacrificed on gestation day 18. The exposure concentration of 5,202 mg/m³ was reported as the lowest effective concentration (LEC_{10}). The critical response was skeletal variations, a developmental toxicity effect. After adjusting the LOAEL for continuous exposure (24 hr/day), and a dosimetric adjustment to a human equivalent concentration, the LEC_{HEC} of 1,517 mg/m³ was used to calculate the chronic RfC.
Uncertainties in the toxicity estimate:
The total uncertainty factor (UF) of 300 is composed of a factor of 10 for intraspecies variability, a factor of 3 for interspecies extrapolation, and a factor of 10 for database inadequacies. The interspecies extrapolation of 3 is used because the adjusted LEC_{HEC} had addressed the

pharmacokinetic component of this uncertainty factor. Per IRIS, the database is insufficient because neurotoxicity was noted in adult animals but not in developing animals. Reproductive toxicity, developmental neurotoxicity, and chronic toxicity studies are lacking. Confidence in the key study is high, confidence in the database is medium, and confidence in the RfC is medium.
Source of the Toxicity Values
Noncancer:
Basis: IRIS is a Tier 1 source. No Tier 2 available.

IRIS RfC = 5.0E+0 mg/m^3.
Critical Study: Schwetz, BA; Mast, TJ; Weigel, R.J; *et al*. (1991) Developmental toxicity of inhaled methyl ethyl ketone in mice. Fund Appl Toxicol 16:742-748.
Methods: Mouse developmental study; Groups of 10 virgin Swiss CD-1 mice and 33 sperm plug-positive (gestation day 0) females were exposed to mean MEK concentrations of 0, 398±9, 1,010±28, or 3,020±79 ppm (0, 1,174±27, 2,980±83, or 8,909±233 mg/m^3) by inhalation for 7 hr/day on gestation days 6-15. Dams were then sacrificed on gestation day 18.
Critical effect: developmental toxicity (skeletal variations)
End point or Point of Departure (POD): LEC = 5,202 mg/m^3; LEC_{HEC} = 1,517 mg/m^3
Uncertainty Factors: UF = 300, 10 each for intraspecies variability and database deficiencies and 3 for interspecies extrapolation
Source and Date: IRIS, 9/26/2003

Tier 2 Sources:
PPRTV: No PPRTV record is available at this time.
MRL: No MRL record is available at this time.

Tier 3 Source:
MDEQ: Per MDEQ (9/26/2003), AQD adopted the IRIS RfC as their ITSL. Averaging time is 24-hour. AQD did not apply an additional UF to account for subchronic to chronic extrapolation to derive the chronic RfC because the point of departure is a developmental effect from a critical window of exposure (gestational period). The developmental-based RfC is therefore expected to be protective of chronic exposures.
Developmental or Reproductive Effects:
For inhalation, the RfC is based on reproductive-developmental effects.
Inhalation Exposure Pathways - Single Exposure.

Cancer:
Carcinogen Weight-of-Evidence (WOE) Class: “data are inadequate for an assessment of human carcinogenic potential".
IRIS WOE Basis: Studies of humans chronically exposed to MEK are inconclusive, and MEK has not been tested for carcinogenicity in animals by the oral or inhalation routes.
Source and Date: IRIS, 9/26/2003

Tier 1 and 2 Sources:
IRIS: Per IRIS (9/26/2003), no value at this time.
PPRTV: No PPRTV record is available at this time.
MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Source:
MDEQ: Per MDEQ-AQD, no value at this time.

CARBON TETRACHLORIDE (CAS #56-23-5) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	Residential TS RIASL
Action Level	4.5 µg/m³ (0.72 ppb_{vol})	45 µg/m³ (7.2 ppb_{vol})
Basis	Increased incidence of hepatocellular carcinomas (Res AAC Cancer – IRIS IURF)	10 × Res AAC Cancer

Nonresidential RIASLs

	Nonresidential RIASL	Nonresidential TS RIASL
Action Level	21 µg/m³ (3.4 ppb_{vol})	210 µg/m³ (34 ppb_{vol})
Basis	Increased incidence of hepatocellular carcinomas (NR AAC_{adj} Cancer – IRIS IURF)	10 × NR AAC_{adj} Cancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for carbon tetrachloride are based on the IRIS (2010) IURF of 5.6E-06 per µg/m³. Both residential and nonresidential AACs are based on cancer effects. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the IURF represented continuous exposure.

The IURF is based on two critical studies. The first study exposed BDF1 mice and F344 rats to carbon tetrachloride for 6 hr/day for 5 days/week for 104 weeks. An increased incidence of hepatocellular adenomas and carcinomas in rats and mice, and adrenal pheochromocytomas in mice was observed (Nagano et al 2007). The second study used an extrapolation method which involved using a log-probit model with linear extrapolation from the POD (LEC_{10}). The IURF was derived by dividing the exposure risk by the LEC_{10} (1.78 × 104 µg/m³) (the 95% lower bound on the exposure associated with a 10% extra cancer risk). The IURF represents an upper bound, continuous lifetime exposure risk estimate.

Uncertainties in the toxicity estimate:

There is a lack of data on the health effects of human exposure to carbon tetrachloride. The IURF is based on sufficient evidence from animal data (multiple species), which represents extrapolated continuous lifetime exposure risk estimate.

Source of the Toxicity Values

Noncancer:
Tier 1 Source:

IRIS:

Basis: IRIS RfC, is selected because it is a Tier 1 value and more current than the ATSDR MRL, a Tier 2.

IRIS – RfC = 0.1 mg/m^3 (1.0E+2 µg/m^3)

Critical Studies: Nagano *et al*., 2007b; JBRC, 1998

1) Nagano, K; Sasaki, T; Umeda, Y; *et al*. 2007b. Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhal. Tox. 19:1089-1103
2) JBRC (Japan Bioassay Research Center). 1998. Sub chronic inhalation toxicity and carcinogenicity studies of carbon tetrachloride in F344 rats and BDF1 mice (Studies Nos. 0020, 0021, 0043, and 0044). Kanagawa, Japan Industrial Safety and Health Association, Japan Bioassay Research Center, Kanagawa, Japan. Unpublished report to the Ministry of Labor. Hirasawa Hadano Kanagawa, 257 Japan.

Method(s): F344/DuCrj rats (50/sex/group) were exposed (whole-body) to 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m^3) of carbon tetrachloride (99.8% pure) vapor for 6 hr/day, 5 days/week for 104 weeks.

Critical effect: Fatty changes in the liver.

End point or Point of Departure (POD): $BMCL_{10[HEC]}$: 14.3 mg/m^3

Uncertainty Factors: UF = 100, 10 for intraspecies variability and 3 each for interspecies extrapolation and database insufficiency

Source and Date: IRIS, 3/31/2010

Tier 2 Sources:

PPRTV: No PPRTV record available at this time.

MRL: ATSDR (8/2005) inhalation chronic MRL = 0.03 ppm (189 µg/m^3)

Critical Studies: Japan Bioassay Research Center. 1998. Subchronic inhalation toxicity and carcinogenicity studies of carbon tetrachloride in F344 rats and BDF1 mice (Studies Nos. 0020, 0021, 0043, and 0044). Kanagawa, Japan Industrial Safety and Health Association, Japan Bioassay Research Center (Unpublished report to the Ministry of Labor). Hirasawa Hadano Kanagawa, 257 Japan. (In 2001, T. Matsushima provided to SRC organ weight data tables for these studies.) (Methods published in Nagano K, Nishizawa T, Yamamoto S, *et al*. 1998. Inhalation carcinogenesis studies of six halogenated hydrocarbons in rats and mice. In: Chiyotani K, Hosoda Y, Aizawa Y, eds. Advances in the prevention of occupational respiratory diseases. Elsevier Science B.V., 741-746.)
Note: Per ATSDR, the 2-year bioassay in rats is selected as the principal study for the chronic inhalation MRL since it provided a NOAEL and a LOAEL for hepatic effects without increased mortality.

Method(s): F344/DuCrj rats (50/sex/group) were exposed (whole-body) to vapors of carbon tetrachloride (>99% pure) at concentrations of 0, 5, 25, or 125 ppm, 6 hr/day, 5 days/week for 104 weeks.

Critical effects: increased liver weight, serum enzymes, and liver histopathology (fatty change, granulation, foci, and deposition of ceroid, fibrosis, and cirrhosis).

End point or Point of Departure (POD): NOAEL = 5 ppm

Uncertainty Factors: UF = 30, 10 for interspecies variability and 3 for interspecies extrapolation with dosimetric adjustment
Source and Date: ATSDR, 8/2005

MRL: ATSDR (8/2005) inhalation intermediate MRL = 0.03 ppm (189 µg/m^3)
Critical Studies: Adams EM, Spencer HC, Rowe VK, *et al*. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Arch. Ind. Hyg. Occup. Med. 6:50-66.
Method(s): Wistar rats (15–25 males, 15–23 females) were exposed carbon tetrachloride (5, 10, 25, 50, 100, 200, and 400 ppm) for 173–205 days (5 days/week, 7 hr/day).
Critical effects: fatty degeneration and increased liver weights.
End point or Point of Departure (POD): NOAEL = 5 ppm; LOAEL = 10 ppm. $NOAEL_{adj}$ is 0.9 ppm (5 ppm x 7 hr/24 hr x 5 days/7 days)
Uncertainty Factors: UF = 30, 10 for interspecies variability and 3 for interspecies extrapolation with dosimetric adjustment
Additional information: Hepatotoxicity is identified as the critical effect of intermediate-duration inhalation exposure to carbon tetrachloride since it was noted at the lowest LOAELs of other toxicity studies. The study by Adams *et al*. (1952) is selected as the principal study because it identified the lowest LOAEL and the highest NOAEL for the critical effect.
Source and Date: ATSDR, 8/2005

Tier 3 Source:
MDEQ: Per MDEQ, AQD adopted IRIS value.

Cancer:
Tier 1 Source:
IRIS:
Basis: IRIS IURF = 5.6E-6 $(\mu g/m^3)^{-1}$ is the only value available.
Critical Studies:

1) Nagano, K; Sasaki, T; Umeda, Y; *et al*. (2007b) Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhal. Tox. 19:1089-1103
2) JBRC (Japan Bioassay Research Center). (1998) Sub-chronic inhalation toxicity and carcinogenicity studies of carbon tetrachloride in F344 rats and BDF1 mice (Studies Nos. 0020, 0021, 0043, and 0044). Kanagawa, Japan Industrial Safety and Health Association, Japan Bioassay Research Center, Kanagawa, Japan. Unpublished report to the Ministry of Labor. Hirasawa Hadano Kanagawa, 257 Japan.

Method(s):

1) *Dose response data*: *Tumor Type* - pheochromocytoma; *Test Species* - male BDF1 mouse; *Route* - vapor (inhalation) for 6 hr/day, 5 days/week for 104 weeks
2) *Extrapolation method*: Log-probit model with linear extrapolation from the POD (LEC_{10}).

The IUR is derived from the LEC_{10} (1.78 × 104 µg/m^3), the 95% lower bound on the exposure associated with a 10% extra cancer risk, by dividing the risk (as a fraction) by the LEC_{10}, and

represents an upper bound, continuous lifetime exposure risk estimate.

Carcinogen Weight-of-Evidence (WOE) Class: "likely to be carcinogenic to humans"
IRIS WOE Basis: (1) inadequate evidence of carcinogenicity in humans and (2) sufficient evidence in animals by oral and inhalation exposure, i.e., hepatic tumors in multiple species (rat, mouse, and hamster) and pheochromocytomas (adrenal gland tumors) in mice.
Source and Date: IRIS, 3/31/2010

Tier 2 Sources:
PPRTV: No PPRTV record available at this time.
MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Source:
MDEQ: AQD adopted IRIS (2010) value.

CHLORDANE (CAS #57-74-9; 12789-03-6) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	0.20 µg/m^3 (0.012 ppb$_{vol}$)	0.20 µg/m^3 (0.012 ppb$_{vol}$)
Basis	Centrilobular hypertrophy, hepatocellular vacuolization, increased P450, decreased albumin, decreased albumin/globulin ratio (ATSDR MRL Intermediate Inhalation)	ATSDR MRL Intermediate Inhalation

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	0.56 µg/m^3 (0.033 ppb$_{vol}$)	0.56 µg/m^3 (0.033 ppb$_{vol}$)
Basis	ATSDR MRL Intermediate$_{adj}$ Inhalation	ATSDR MRL Intermediate$_{adj}$ Inhalation

Discussion of Basis

The basis of the residential and nonresidential RIASLs and TS RIASLs is the ATSDR intermediate inhalation MRL. The intermediate inhalation MRL is based on hepatic effects (centrilobular hypertrophy, hepatocellular vacuolization, increased P450, decreased albumin, decreased albumin/globulin ratio) exposed to chlordane for 90 days (5 days a week for 8 hours a day). The NOAEL (0.1 mg/m^3) for hepatic effects is also a NOAEL for hematopoietic/immunological effects (increased leukocyte count, decreased platelet count in females). For the residential RIASLs, the intermediate inhalation MRL is a more protective value than AAVs calculated with an U.S. EPA IRIS RfC or IURF. It should be noted that the RfC is based on the same study selected by ATSDR. The NOAEL selected by ATSDR is the lowest exposure group, 0.1 mg/m^3, while the U.S. EPA RfC is based on a NOAEL of 1.0 mg/m^3.

The nonresidential RIASL and TS RIASL were adjusted to a 12-hour exposure time as the intermediate inhalation MRL was adjusted for an occupational exposure (12/24 hours and 5/7 days). The adjusted MRL is approximately half of the nonresidential AAVs based on the U.S. EPA RfC or IURF.

Uncertainties in the toxicity estimate:

The intermediate inhalation MRL had a total UF of 100 (10 to account for animal model and 10 to account for human variability).

Source of the Toxicity Values

Noncancer:
IRIS RfC = 7.0E-4 mg/m^3.
Critical Study: Khasawinah, A., C. Hardy, and G. Clark. 1989b. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J. Toxicol. Environ. Health 28(3): 327-347. (The 90-day rat study.)
Method(s): Wistar rats (35 47/sex/group) were exposed to 0, 0.1, 1.0, or 10 mg/m^3 technical chlordane, 8 hours/day, 5 days/week, for 13 weeks, followed by a 13-week recovery period.
Critical effect: hepatic effects
End point or Point of Departure (POD): NOAEL = 1.0 mg/m^3; NOAEL (HEC) = 0.65 mg/m^3.
Uncertainty Factors: UF = 1,000, 10 each for interspecies variability, interspecies extrapolation, and use of a subchronic study
Source and Date: IRIS, 2/07/1998

MRL: ATSDR (5/1994) chronic inhalation MRL = 2.0E-5 mg/m^3. An intermediate-duration inhalation MRL = 2.0E-4 mg/m^3 is available based on the same studies used for the chronic MRL.
Critical Study: Khasawinah, A., C. Hardy, and G. Clark. 1989a. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J. Toxicol. Environ. Health 28(3): 327-347. (The 90-day rat study.)
Method(s): Wistar rats (35-47/sex/group) were exposed to 0, 0.1, 1.0, or 10 mg/m^3 technical chlordane, 8 hr/day, 5 days/week, for 13 weeks (90 days), followed by a 13-week recovery period.
Critical effect: hepatic effects (hepatocellular hypertrophy and increased cytochrome P-450)
End point or Point of Departure (POD): NOAEL = 0.1 mg/m^3
Uncertainty Factors for the Chronic MRL: UF = 1,000, 10 each for intraspecies variability, interspecies extrapolation, and use of a sub chronic study
Uncertainty factors for the intermediate MRL: UF = 100, 10 for interspecies variability, 10 for interspecies extrapolation
Source and Date: ATSDR, 5/1994 (Toxicological Profile); ATSDR Addendum 12/2013a.

Cancer:
IRIS IURF = 1.0E-4 (µg/m^3)$^{-1}$.
IRIS IURF Basis: IRIS used the oral cancer slope factor (CSF) to estimate an IURF as no chronic inhalation bioassays are available. The estimation assumed 100% absorption of inhaled chlordane and a breathing rate of 20 m^3/day. IRIS is the only available value.
Oral CSF Critical Studies:
1) Khasawinah, A.M. and J.F. Grutsch. 1989a. Chlordane: 24-month tumorigenicity and chronic toxicity test in mice. Reg. Toxicol. Pharmacol. 10: 244-254.
2) Velsicol Chemical Corporation. 1983. Twenty-four-month chronic toxicity and tumorigenicity test in mice by chlordane technical. Unpublished study by Research Institute for Animal Science in Biochemistry and Toxicology, Japan. MRID No. 00144312, 00132566. Available from U.S. EPA.

Method(s): ICR mice (80/sex/group) were given 0, 1, 5, or 12.5 ppm (0, 0.15, 0.75, and 1.875 mg/kg-day) chlordane in the diet for 104 weeks.

1) *Dose response data*: *Tumor Type* - hepatocellular carcinoma; *Test Species* - mouse/CD-1 (IRDC), mouse/B6C3F1 (NCI), mouse/ICR (Khasawinah and Grutsch); *Route* - diet
2) *Extrapolation method*: Linearized multistage procedure, extra risk

Carcinogen Weight-of-Evidence (WOE) Class: B2; probable human carcinogen

IRIS WOE Basis: Human carcinogenicity data: inadequate. Animal carcinogenicity data: sufficient

Source and Date: IRIS, Last revision date: 2/07/1998. IRIS literature review in 2001 did not identify any significant new studies.

CHLOROBENZENE (CAS #108-90-7) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	52 µg/m³ (11 ppb_{vol})	160 µg/m³ (34 ppb_{vol})
Basis	Renal tubule dilation (Res AAC Noncancer – PPRTV RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	150 µg/m³ (33 ppb_{vol})	460 µg/m³ (100 ppb_{vol})
Basis	Renal tubule dilation (NR AAC_{adj} Noncancer– PPRTV RfC)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for chlorobenzene are developed from the PPRTV (2006) RfC (RfC = 50 µg/m³). This RfC was based on a two-generation reproduction study (Nair *et al.*, 1987) exposing rats to chlorobenzene for 6 hr/day, 7 days/week for 10 weeks prior to mating, through mating, gestation and lactation. The critical effect observed was renal tubular dilation in male rats. A $LED_{10\ HEC}$ = 4 6 mg/m³ was calculated based on this effect. Liver effects were also seen at the same doses. Similar kidney effects were also seen in dogs, male and female rats, and male and female mice. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on a repeated-dose study and continuous exposure. See details below.

Uncertainties in the toxicity estimate:

For the chronic p-RfC derivation, PPRTV divided the $BMCL_{[HEC]}$ by a UF of 1,000, including: 10 for human variability, 3 for extrapolation from rats-to-humans using dosimetric adjustments, 10 for use of a subchronic study, and 3 for database deficiencies. PPRTV identifies the confidence in the database as low based on the absence of well-documented studies evaluating the full respiratory tract and neurotoxicity after exposure to chlorobenzene. Available human data indicates neurotoxicity may be a sensitive endpoint for chlorobenzene. PPRTV assigned the confidence in the key study as high.

Source of the Toxicity Values
Noncancer:
Basis: PPRTV RfC
PPRTV (10/12/2006): RfC = 5.0E-2 mg/m³ (5.0E+1 µg/m³.) derived as follows:
Critical Study:

Nair, R.S., J.A. Barter, R.E. Schroeder *et al*. 1987. A two-generation reproduction study with monochlorobenzene vapor in rats. Fund. Appl. Toxicol. 9:678-686.

Method(s): Two-generation reproductive study in rats: CD Sprague-Dawley rats (30/sex/group) were exposed by inhalation (dynamic air chamber) at 0, 50, 150, or 450 ppm (0, 230, 691, or 2,072 mg/m^3) chlorobenzene for 6 hr/day, 7 days/week for 10 weeks before mating, and during mating, gestation, and lactation. The male and female F0 rats were sacrificed after the lactation period. F1 rats (30/sex/group) were exposed to the same concentrations of chlorobenzene (beginning 1-week post-weaning) for 11 weeks before mating and during mating, gestation, and lactation. The F1 rats were also sacrificed after the lactation period. The F2 pups were sacrificed after weaning.

Critical effect: renal tubular dilation

End point or Point of Departure (POD): $LED_{10\ HEC}$ = 46 mg/m^3

Uncertainty Factors: UF = 1,000, 10 each for intraspecies variability and use of subchronic study and 3 each for interspecies extrapolation using dosimetric adjustments and database uncertainties

Source and Date: PPRTV, 10/2006

Cancer:

IRIS (1991): Carcinogen Weight-of-Evidence (WOE) Class: D; not classifiable as to human carcinogenicity.

Basis: IRIS WOE: No human data, inadequate animal data and predominantly negative genetic toxicity data in bacterial, yeast, and mouse lymphoma cells.

Source and Date: IRIS, 3/01/1991

CHLOROETHANE (CAS #75-00-3) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	4,200 µg/m³ (1,600 ppb_{vol})	13,000 µg/m³ (4,700 ppb_{vol})
Basis	Delayed fetal ossification (foramina of the skull bones) (Res AAC Noncancer –PPRTV RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	12,000 µg/m³ (4,600 ppb_{vol})	37,000 µg/m³ (14,000 ppb_{vol})
Basis	Delayed fetal ossification (foramina of the skull bones) (NR AAC_{adj} Noncancer –PPRTV RfC)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential noncancer AACs, RIASLs and TS RIASLs for chloroethane are based on the U.S. EPA PPRTV subchronic RfC of 4,000 µg/m³. The 2007 PPRTV subchronic RfC is based on a human equivalent concentration of the lower 95% confidence limit of the Effect Concentration ($LEC_{10(HEC)}$) of 1,078 mg/m³ for delayed fetal ossification (foramina of the skull bones) in female mice exposed to chloroethane for 6 hr/day on days 6 through 15 of gestation (Scortichini *et al*., 1986). The PPRTV subchronic RfC was adjusted for intermittent exposure. An IRIS (1991) RfC of 1.0E+7 µg/m³ is also based on the Scortichini *et al*. study and critical effect but used a NOAEL = 4,000 mg/m³ to derive a chronic RfC. The PPRTV RfC was selected as it is a newer evaluation than IRIS and was established using a benchmark dose analysis approach. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on a human equivalent concentration (HEC) for continuous exposure. See details below.

The 1998 ATSDR acute Inhalation MRL is 15 ppm (40 mg/m³) based on the study of Scortichini *et al*. (1986). The MRL was based on a NOAEL of 1,504 ppm (4,000 mg/m³) and per ATSDR (1998), no adjustment for intermittent exposure was used since fetotoxic effects may be due to peak concentrations. Compared to the ATSDR, the PPRTV used dosimetric adjustments to derive a HEC. The developmental AAC based on the PPRTV RfC is protective of subchronic and acute exposures and therefore selected as basis for the RIASL and TS RIASL.

Uncertainties in the toxicity estimate:

The total UF applied is 300 for the PPRTV subchronic RfC. A UF of 10 is used to account for intraspecies variability, 3 for interspecies extrapolation because of the use of dosimetric

adjustments, and 10 for database deficiencies. No additional UF to account for subchronic to chronic extrapolation was applied since the critical effect is developmental and the exposure was during gestation. The confidence assigned to the RfC estimate is medium although the critical study is considered a well-conducted one due to lack of longer exposure toxicity and reproductive studies and the absence of a strong exposure-response relationship and maternal toxicity level. For the ATSDR acute inhalation MRL the total UF applied is 100, 10 each to account for human variability and interspecies extrapolation.

Source of the Toxicity Values

Non-cancer:

Tier 2 Source:

Basis: PPRTV subchronic p-RfC = 4.0E+0 mg/m^3. No additional UF to account for subchronic extrapolation is applied since the critical effect is developmental effect from gestational exposure (developmental study). The IRIS (1991) RfC = 1.0E+4 µg/m^3 is based on the same study (Scortichini *et al*., 1986) using the NOAEL approach. PPRTV used benchmark dose modeling to generate the POD.

Critical Study: 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.

Method(s): 30 CF-1 mice were exposed to 0, 491 +/-37 ppm (1.3 g/m^3), 1,504 +/- 84 ppm (4,000 mg/m^3), and 4,946 +/- 159 ppm (13,000 mg/m^3) ethyl chloride for 6 hr/day on days 6 through 15 of gestation. The animals were sacrificed on the 18th day of gestation.

Critical effect: delayed fetal ossification (foramina of the skull bones)

End point or Point of Departure (POD): $LEC_{10(HEC)}$ = 1,078 mg/m^3 derived using benchmark dose (BMDS) analysis and adjusted for intermittent exposure.

Uncertainty Factors: UF = 300, 10 each for interspecies variability and database deficiencies; and 3 for interspecies extrapolation

Source and date: PPRTV, 7/24/2007

Tier 1 Source:

IRIS: IRIS (1991) RfC = 1.0E+1 mg/m^3

Critical Study: 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.

Method(s): 30 CF-1 mice were exposed to 0, 491 +/- 37 ppm (1.3 g/m^3), 1504 +/- 84 ppm (4000 mg/m^3), and 4,946 +/- 159 ppm (13,000 mg/m^3) ethyl chloride for 6 hr/day on days 6 through 15 of gestation. The animals were sacrificed on the 18th day of gestation.

Critical effect: delayed fetal ossification

End point or Point of Departure (POD): NOAEL = 4,000 mg/m^3 (1504 ppm); $NOAEL_{HEC}$ = 4,000 mg/m^3 not adjusted for intermittent exposure.

Uncertainty Factors: UF = 300, 10 each for interspecies variability and database deficiencies; and 3 for interspecies extrapolation
Source and Date: IRIS, 4/01/1991

MRL: Per ATSDR (12/1998), no inhalation chronic or intermediate MRL at this time.
ATSDR acute MRL = 15 ppm (40 mg/m^3) is available based on the study of Scortichini *et al*. (1986):
Critical Study: 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.
Method(s): 23-26 pregnant mice were exposed to 0, 491 +/-37 ppm (1.3 g/m^3), 1504 +/- 84 ppm (4000 mg/m^3), and 4,946 +/- 159 ppm (13,000 mg/m^3) ethyl chloride for 6 hr/day on days 6 through 15 of gestation. The animals were sacrificed on the 18th day of gestation.
Critical effect: very slight fetotoxicity (delayed ossification)
End point or Point of Departure (POD): NOAEL = 1,504 ppm or 4,000 mg/m^3
"Because fetotoxic effects may result from peak concentrations rather than total duration of exposure, the NOAEL was not adjusted for intermittent exposure".
Uncertainty Factors: UF = 100 (10 each for intraspecies variability and interspecies extrapolation)
Source and date: ATSDR, 12/1998

Cancer:
Carcinogen Weight-of-Evidence (WOE) Class: likely to be carcinogenic to humans
IRIS WOE Basis: increased incidences of uterine carcinomas in chloroethane-exposed mice are considered relevant to human health but marginally suitable for quantitative cancer assessment of chloroethane. The only available inhalation carcinogenicity bioassay (NTP, 1989) used a single chloroethane exposure level (15,000 ppm) at which a high proportion (86%) of female mice developed uterine tumors. Because a mutagenic mode of action cannot be discounted and no other mode of action has been proposed, a linear non-threshold dose-response model would be appropriate.
Source and Date: PPRTV, 7/24/2007.

CHLOROFORM (CAS #67-66-3) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	1.1 µg/m³ (0.23 ppb_{vol})	11 µg/m³ (2.3 ppb_{vol})
Basis	Hepatocellular carcinoma (Res AAC Cancer – U.S. EPA IRIS IURF)	10 × Res AAC Cancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	5.2 µg/m³ (1.1 ppb_{vol})	52 µg/m³ (11 ppb_{vol})
Basis	Hepatocellular carcinoma (NR AAC_{adj} Cancer – U.S. EPA IRIS IURF)	10 × NR AAC_{adj} Cancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs and TS RIASLs for chloroform are based on the IRIS IURF of 2.3E-5 per µg/m³. The IURF is based on a cancer study by the National Cancer Institute (NCI, 1976). The risk-based cancer AAVs are lower than the chronic, intermediate and acute noncancer MRLs and are therefore more appropriate. The ATSDR chronic MRL of 98 µg/m³ is based on hepatic effects (hepatomegaly) observed in 68 workers exposed to chloroform for one to four years. The Intermediate Inhalation MRL of 240 µg/m³ is based on liver toxicity in mostly female workers exposed to chloroform for 6 months. The acute MRL of 490 µg/m³ is based on hepatic effects in female mice exposed to chloroform for one week. The AAC for cancer effects also protects for subchronic and acute exposure noncancer effects. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the IURF was based on continuous exposure. See details below.

Uncertainties in the toxicity estimate:

Per IRIS (2001), chloroform is likely to be carcinogenic to humans **by all routes of exposure** (emphasis added) under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues. The IURF is derived using a gavage cancer study. However, inhalation studies used in determining the noncancer MRLs support the high likelihood of hepatic effects including cytotoxicity resulting from inhalation of chloroform.

Source of the Toxicity Values

Cancer:
IRIS IURF = 2.4E-6 $(\mu g/m^3)^{-1}$
Basis: IRIS is a Tier 1 source.
Critical Study: National Cancer Institute (NCI) (1976) Report on carcinogenesis bioassay of

chloroform. Bethesda, MD: National Cancer Institute.
Methods: This IURF is based on data from a gavage study. The incidence data for both male and female mice were used to derive slope factors of 3.3E-2 and 2.0E-1 per (mg/kg)/day, respectively.

1) *Dose response data*: *Tumor Type* — hepatocellular carcinoma; *Test Species* - mouse, B6C3F1, female; *Route* - oral, gavage
2) *Extrapolation method*: linearized multistage procedure, extra risk.

Carcinogen Weight-of-Evidence (WOE) Class: Chloroform is likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues (U.S. EPA, 1998a,b). Chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration.
IRIS WOE Basis: Based on: 1) observations in animals exposed by both oral and inhalation pathways which indicate that sustained or repeated cytotoxicity with secondary regenerative hyperplasia precedes, and is probably required for, hepatic and renal neoplasia; 2) there are no epidemiological data specific to chloroform and, at most, equivocal epidemiological data related to drinking water exposures that cannot necessarily be attributed to chloroform amongst multiple other disinfection byproducts; and 3) genotoxicity data on chloroform are essentially negative.
Source and Date: IRIS, 10/19/2011

Noncancer:
ATSDR chronic MRL = 9.8E+1 µg/m^3
Basis: ATSDR is a Tier 2 source, no Tier 1 available. Inhalation chronic MRL = 0.02 ppm or 9.8E-2mg/m^3 (at 25°C and 1 atm). An intermediate-duration inhalation MRL = 0.05 ppm (2.4E-1 mg/m^3) is available based on a LOAEL of 14 ppm for toxic hepatitis in workers exposed to up to 400 ppm for less than 6 months (Phoon *et al*., 1983).

ATSDR Chronic MRL:
Critical Study: Bomski H, Sobolewska A, Strakowski A. 1967. Toxic damage of the liver by chloroform in chemical industry workers. Int Arch F Gewerbepathologie u. Gewerbehygiene 24: 127- 134 (German)
Methods: A group of 68 workers were occupationally exposed to chloroform for one to four years. Doses ranged from 2 to 205 ppm and air concentrations ranged from 0.01 to 1.0 mg/L.
Critical effect: hepatomegaly
End point or Point of Departure (POD): LOAEL = 2 ppm
Uncertainty Factors: UF = 100, for interspecies variability and LOAEL to NOAEL extrapolation
Source and Date: ATSDR, 9/1997. A Toxicological Profile is available.

ATSDR Intermediate and Acute MRLs:
Intermediate MRL = 0.05 ppm (2.4E-1 mg/m^3)

Critical Study: Phoon WH, Goh KT, Lee LT, *et al*. 1983. Toxic jaundice from occupational exposure to chloroform. Med J Malaysia 38:31-34.
Methods: Workers in two outbreaks of toxic hepatitis, in workers occupationally exposed to chloroform, were studied. The workers were mostly women. Blood chloroform levels of workers and workplace concentrations were measured. All workers were exposed for at less six months.
Critical effect: hepatic effects
End point or Point of Departure (POD): LOAEL = 14 ppm
Uncertainty Factors: UF = 100, for interspecies variability and LOAEL to NOAEL extrapolation and modifying factor (MF) of 3 for insufficient data to determine the seriousness of the hepatic effects.
Source and Date: ATSDR, 9/1997. A Toxicological Profile is available.

Acute MRL = 0.1 ppm or 4.9E-2 mg/m^3 (at 25°C and 1 atm).
Critical Study: Larso JL, Wolf DC, Morgan KT, *et al*., 1994. The toxicity of 1-week exposures to inhaled chloroform in female B6C3F1 mice and male F-344 rats. Fund. Appl. Toxicol. 22:431-446.
Methods: Animals (5/group) were exposed to 0, 1, 3, 30, 100 or 300 chloroform via inhalation for 6 hours a day for 7 consecutive days. Actual concentrations were 1.2, 3, 10, 29.5, 101 and 228 ppm for mice and 1.5, 3.1, 10.4, 29.3, 100 and 271 ppm for rats. Cell proliferation was quantitated as the % cells in S-phase using immunohistochemical detection of BrdU-labeled nuclei.
Critical effect: hepatic effects in mice
End point or Point of Departure (POD): NOAEL = 3 ppm; NOAEL$_{HEC}$ = 3 ppm
Uncertainty Factors: UF = 30, 10 for human variability and 3 for interspecies variability
Source and Date: ATSDR, 9/1997. A Toxicological Profile is available.

CHLOROMETHANE (CAS #74-87-3) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	94 µg/m³ (45 ppb_{vol})	280 µg/m³ (140 ppb_{vol})
Basis	Cerebellar lesions (Res AAC Noncancer – U.S. EPA IRIS RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	280 µg/m³ (140 ppb_{vol})	410 µg/m³ (200 ppb_{vol})
Basis	Cerebellar lesions (NR AAC_{adj} Noncancer – U.S. EPA IRIS RfC)	Hepatic toxicity - increased ALT levels (ATSDR Intermediate Inhalation MRL)

Discussion of Basis

The U.S. EPA's IRIS RfC of 90 µg/m³ is the basis of the AAC, residential RIASL and TS RIASL, and nonresidential RIASL for chloromethane. The RfC was derived from two critical studies (Landry *et al*. 1983, 1985) where female mice were intermittently (5.5 hr/day) or continuously (22 hr/day) exposed to methyl chloride (chloromethane) over 11 days. The critical effect was determined to be cerebellar lesions with a NOAEL of 50 ppm (103 mg/m³) and $NOAEL_{HEC}$ of 95 mg/m³. The nonresidential RIASL was adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure.

The nonresidential TS RIASL was developed from the ATSDR intermediate inhalation MRL of 0.2 ppm (410 µg/m³). This MRL was based on a LOAEL of 51 ppm (24,700 µg/m³) for the critical effect of hepatic toxicity (increased alanine aminotransferase (ALT) levels) in mice at 12, 18, and 24 months. Rats and mice were exposed for two years to chloromethane (CIIT, 1981 unpublished study). The intermediate MRL was selected over the 3x AAC value of 828 µg/m³ to be protective of time-sensitive shorter exposure of nonresidential receptors to chloromethane. The POD was not adjusted for continuous exposure based on the toxicokinetics of chloromethane. The nonresidential TS RIASL was not adjusted to a 12-hour work exposure time as the endpoint (LOAEL) was not adjusted for continuous 24-hour exposure. See details below.

Uncertainties in the toxicity estimate:

The IRIS RfC contained a total UF of 1000. A UF of 10 was used to protect sensitive human subpopulations (intraspecies variability), 10 to extrapolate from an 11-day continuous exposure to a lifetime inhalation exposure study, and 3 ($10^{1/2}$) each for a total of 10 to account for interspecies

variability and database insufficiency.

The ATSDR intermediate inhalation MRL has a total uncertainty of 300, 3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability.

Source of the Toxicity Values

Chronic Inhalation Noncancer:
IRIS:
Basis: IRIS (7/17/2001) is a tier 1 source. RfC = 9.0E-2 mg/m^3 (9.0E+1 µg/m^3).
Critical Studies:

1) Landry, TD; Quast, JF; Gushow, TS; *et al*. 1983. Methyl chloride: inhalation toxicity in female C57BL/6 mice continuously or intermittently exposed for 11 days. EPA/OTS Doc #878213687, NTIS/OTS0206357. (unpublished)
2) Landry, TD; Quast, JF; Gushow, TS; *et al*. 1985. Neurotoxicity of methyl chloride in continuously versus intermittently exposed female C57BL/6 mice. Fundam. Appl. Toxicol. 5(1): 87-98.

Method(s): Female C57BL/6 mice (12/group) were exposed continuously (22-22.5 hr/day for 11 days) to 15, 50, 100, 150, or 200, ppm methyl chloride. Mice were also exposed intermittently (5.5 hr/day) for 11 days to 0, 150, 400, 800, 1,600, or 2,400 ppm.
Critical effect: cerebellar lesions
End point or Point of Departure (POD): NOAEL = 50 ppm (103.2 mg/m^3) $NOAEL_{HEC}$ = 94.6 mg/m^3
Uncertainty Factors: UF = 1,000, 10 each for intraspecies variability, and 11 day to chronic exposure extrapolation and 3 ($10^{1/2}$) each for a total of 10 to account for interspecies extrapolation and database deficiency
Source and Date: IRIS, 7/17/2001

Tier 2 Sources:
PPRTV: PPRTV (12/4/2012) refers to the IRIS chronic RfC. A sub chronic p-RfC = 3.0 mg/m^3 is available:
Critical Studies: Landry *et al*. (1983, 1985)
Method(s): Female C57BL/6 mice (12/group) were "continuously" (22−22.5 hr/day) exposed to 0, 15, 50, 100, 150, or 200ppm (0, 28.4, 94.6, 189.3, 283.9, or 378.6mg/m^3), or "intermittently" (5.5 hr/day) to 0, 150, 400, 800, 1,600, or 2,400 ppm (0, 71.0, 189.3, 378.6, 757.2, or 1,135.8 mg/m^3) of chloromethane (purity = 99.5%) for whole body during 11 days. Neurofunctional testing was conducted during the study.
Critical effect: cerebellar lesions in female C57BL/6 mice
End point or Point of Departure (POD): NOAEL = 50 ppm; $NOAEL_{adj}$ = 94.6 mg/m^3; $NOAEL_{HEC}$ = 94.6 mg/m^3
Uncertainty Factors: UF = 30, 10 for interspecies variability and 3 for interspecies extrapolation
MRL: ATSDR (12/1998) inhalation chronic MRL = 0.05 ppm. The 2009 ATSDR Addendum for

chloromethane reported that very little new information was found that is relevant to the Toxicological Profile.
Critical Study: CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Unpublished study prepared by Battelle-Columbus Laboratories, Columbus, OH. OTS Submission Document ID 40-8120717
Method(s): F344 rats and B6C3F1 mice (120/sex/species/concentration) were exposed to 0, 50, 225, or 1000 ppm (0, 18, 83, or 368 mg/m^3) chloromethane 6 hr/day, 5 days/week, for up to 24 months. Interim sacrifices and toxicological evaluations were scheduled for 6, 12, and 18 months after initiation of the study. Due to high mortality in the 1000-ppm mice, this group was euthanized after 21 or 22 months of exposure. A 6-month interim report of this study was prepared by Mitchell *et al*. (1979b). The results of the chronic-duration study were presented in the unpublished final report by CIIT (1981).
Critical effect: neurological effects (swelling and degeneration of the axons of the spinal cord) in male and female mice
End point or Point of Departure (POD): NOAEL = 50 ppm
Uncertainty Factors: UF = 100, 10 each for intraspecies variability and interspecies extrapolation
Source and Date: ATSDR, 12/1998

MRL: ATSDR (12/1998) intermediate inhalation MRL = 0.2 ppm. The 2009 ATSDR Addendum for chloromethane reported that very little new information was found that is relevant to the Toxicological Profile.
Critical Study: CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Unpublished study prepared by Battelle-Columbus Laboratories, Columbus, OH. OTS Submission Document ID 40-8120717
Method(s): Fischer 344 rats and B6C3F1 mice. Animals (120 per sex per exposure level) were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hr/day, 5 days/week for up to two years.
Critical effect: increased ALT levels
End point or Point of Departure (POD): LOAEL = 51 ppm
Uncertainty Factors: UF = 300, 3 for use of a LOAEL, 10 each for intraspecies variability and interspecies extrapolation
Source and Date: ATSDR, 12/1998

MRL: ATSDR (12/1998) acute inhalation MRL = 0.5 ppm. The 2009 ATSDR Addendum for chloromethane reported that very little new information was found that is relevant to the Toxicological Profile.
Critical Study: Landry DL, Quast JF, Gushow TS, Mattsson. 1985. Neurotoxicity of methyl chloride in continuously versus intermittently exposed female C57BL/6 mice. Fundam. Appl. Toxicol. 5:87-98.
Method(s): Groups of 12 mice each were exposed to chloromethane in whole body inhalation chambers for 11 days either continuously 22 hr/day at 0, 15, 50, 100, 150, 200, or 400 ppm or intermittently 5.5 hr/day at 0, 150, 400, 800, 1,600, or 2,400 ppm. The mice were subjected to

neurofunctional testing (ability to stay on a rotating 4 cm diameter rod) on days 4, 8, and 11.
Critical effect: no neurological effects or histopathologic damage observed
End point or Point of Departure (POD): NOAEL = 50 ppm
Uncertainty Factors: UF = 100, 10 each for intraspecies variability and interspecies extrapolation
Source and Date: ATSDR, 12/1998

Tier 3 Source:
EGLE: EGLE-CCD-AQD (09/03/2013) adopted IRIS RfC of 90 µg/m^3.
Cancer:
Carcinogen Weight-of-Evidence (WOE) Class: "Inadequate Information to Assess Carcinogenic Potential"
IRIS WOE Basis: Little pertinent information and/or conflicting evidence. In animals, only a single 2-year study (CIIT, 1981) was conducted, resulting in tumors in the kidneys of male mice but no tumors at any other site or in female mice or rats of either sex. Human studies were limited to an epidemiological study in which pancreatic cancer was not associated with chloromethane exposure (Kernan *et al*., 1999), along with other studies either confounded by exposure to other chemicals (Dow Corning Corporation, 1992; Olsen *et al*., 1989), by demonstrating a "healthy worker" effect (Holmes *et al*., 1986), or by having wide variability (Rafnsson and Gudmundsson, 1997), thus precluding meaningful conclusions.
Source and Date: PPRTV, 12/14/2012; IRIS, 2001

2-CHLOROPHENOL (CAS #95-57-8) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	18 µg/m³ (3.4 ppb_{vol})	54 µg/m³ (10 ppb_{vol})
Basis	Increase in stillbirths and decrease in litter size (Res AAC SE Developmental – EGLE ITSL)	3 × Res AAC SE Developmental

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	36 µg/m³ (6.8 ppb_{vol})	110 µg/m³ (21 ppb_{vol})
Basis	Increase in stillbirths and decrease in litter size (NR AAC_{adj} SE Developmental – EGLE ITSL)	3 × NR AAC_{adj} SE Developmental

Discussion of Basis

The residential and nonresidential AACs, RIASLs and TS RIASLs are based on the MDEQ (2006) ITSL of 18 µg/m³, 24-hour averaging time. The MDEQ (2006) ITSL is extrapolated from the U.S. EPA RfD (U.S. EPA, 1988). The RfD is based on a NOAEL of 50 ppm (≈5 mg/kg per day) from a rat reproductive study (Exon and Koller, 1982). In this study, groups of weanlings, female Sprague-Dawley rats were administered 0, 5, 50, or 500 ppm of 2-chlorophenol in drinking water for 10 weeks. After the 10 weeks, the rats were bred. Dosing continued through parturition and weaning. The critical effects, decreased litter size and increased percentage of stillborn pups, were observed in the 500-ppm dose group. These critical effects are developmental effects that may be due to a single exposure event during pregnancy. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time since the ITSL was for a 24-hour averaging and extrapolated from a chronic oral RfD that was based on exposures during breeding, pregnancy, and weaning.

There are no Tier 1 and 2 sources and no short-term MRL values available.

Uncertainties in the toxicity estimate:

The ITSL is based on extrapolation from an oral toxicity value assuming a 70 kg body weight and breathing rate of 20 m³/day (MDEQ, 2006). The total uncertainty factor (UF) applied is 1,000, where 10 accounts for interspecies extrapolation, 10 accounts for intraspecies variability, and 10 accounts for subchronic to chronic duration extrapolation. The confidence assigned by IRIS to the RfD estimate is low because the confidence in the study and the database are low.

Source of the Toxicity Values

Non-cancer:

Basis: The MDEQ (2006) ITSL was selected as the best available inhalation developmental toxicity value because sufficient derivation details are available. No Tier 1 and 2 sources were available. The MDEQ (2006) value and other Tier 3 sources, California EPA (2015) and New Jersey (2008), were based on route extrapolation of the U.S. EPA IRIS (1993) RfD.

IRIS: RfC has not been derived (8/22/1988)
ATSDR: MRL has not been derived (7/03/2007)

EGLE:
MDEQ/AQD (2006) ITSL=1.8E+1 µg/m^3, 24-hour averaging time, derived from U.S. EPA's IRIS oral RfD pursuant to R232 (1) b (assumes 70 kg body weight and 20 m3/day air breathing rate.
The IRIS (1993) RfD of 0.005 mg/kg-day is derived as follows:
Critical Study: Exon, J.H. and L.D. Koller. 1982. Effects of trans placental exposure to chlorinated phenols. Environ Health Perspect 46:137-140.
Methods: Weanling female Sprague-Dawley rats (12-20/dose group) were exposed to 0, 5, 50, or 500 ppm of 2-chlorophenol in drinking water for 10 weeks. The rats were bred after treatment. Treatment was continued during breeding, gestation, and weaning. IRIS assumed for rats a daily intake of water equal to 10% of its body weight or 0.1 L/kg/day.
Critical effect: Reproductive effects (increased conception rate, increased number of stillbirths, and decreased litter size) in the 500-ppm dose group.
End point or Point of Departure (POD): NOAEL = 5 mg/kg-day (50 ppm)
Uncertainty Factors: UF = 1,000,10 each for intraspecies variability, interspecies extrapolation, and subchronic to chronic interpolation
Source and date: MDEQ/AQD, 6/02/2006

California DTSC: RfC = 2.0E+1 µg/m^3 based on route extrapolation from an IRIS (1993) oral toxicity value (5.0E-3 mg/kg-day) to an inhalation toxicity value:
RfC (µg/m^3) = RfD (mg/kg-day) × 80 kg × (1 day/20 m^3) × 1000 µg/mg
Source: DTSC MSL, 2015

New Jersey DEP: Per DEP (2008), RfC = 1.8E+1 µg/m^3 based on IRIS RfD of 5.0E-3 mg/kg-day (assumes 70 kg body weight and 20 m^3/day air breathing rate).
Source: New Jersey DEP - Toxicity Factors, 9/23/2008

Cancer:
Carcinogen Weight-of-Evidence (WOE) Class: inadequate for an assessment of human carcinogenic potential
WOE Basis: In accordance with current U.S. EPA cancer guidelines (EPA, 2005), the available data

are inadequate for an assessment of human carcinogenic potential.
Source and Date: U.S. EPA PPRTV, 7/03/2007

IRIS: Per U.S. EPA IRIS (1988), no value at this time.
PPRTV: Per U.S. EPA PPRTV (2007), no value at this time.
MRL: N/A; MRLs are for non-cancer effects only.
MDEQ: Per MDEQ/AQD (2006), no value at this time.

1,3-DICHLOROBENZENE (CAS #541-73-1) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	3.1 µg/m³ (0.52 ppb_{vol})	9.4 µg/m³ (1.6 ppb_{vol})
Basis	Decreased density of thyroid colloid from 90-day oral administration (Res AAC Noncancer – EGLE ITSL)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	9.2 µg/m³ (1.5 ppb_{vol})	28 µg/m³ (4.6 ppb_{vol})
Basis	Decreased density of thyroid colloid from 90-day oral administration (NR AAC_{adj} Noncancer – EGLE ITSL)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs and TS RIASLs for 1,3-dichlorobenzene are based on the EGLE AQD's chronic ITSL, 3.0 µg/m³ (MDEQ, 2006). The ITSL is based on a 90-day oral rat study in which the critical effect was thyroid reduction of follicular colloidal density in male rats given 1,3-dichlorobenzene at 9 mg/kg per day (McCauley *et al*., 1995b). The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous oral exposure. See details below.

There are very few studies on the toxicity of 1,3-dichlorobenzene. Other state agencies have also derived screening levels for chronic exposure to 1,3-dichlorobenzene at 10 µg/m³ (NYSDEC, 2005) and 27 µg/m³ (TCEQ, 2015), but they are either derived via route extrapolation, as well, or they are derived from another compound (1,4-dichlorobenzene). As a result, the basis for these other health benchmarks are not more appropriate than the EGLE ITSL. Furthermore, the values are higher than the EGLE ITSL, so they may not be as health protective.

Uncertainties in the toxicity estimate:

The AAC is based on route extrapolation from a 90-day oral rat study, where the LOAEL was 9 mg/kg per day. The ratio of body weight to daily inhalation volume was assumed to be 1 kg/0.9 m³, the ratio of oral absorption to inhalation absorption was assumed to be 1/1 and a total UF of 3,000 was used, where a UF of 3 was used for LOAEL to NOAEL extrapolation, a UF of 10 was used for subchronic to chronic extrapolation, a UF of 10 was used for interspecies extrapolation and a UF of 10 was used for intraspecies extrapolation.

Source of the Toxicity Values

Noncancer:

Basis: EGLE AQD derived its value by route extrapolation from a 90-day oral study in rats. No IRIS RfC, U.S. EPA PPRTVs, or ATSDR MRLs were available.

EGLE: chronic ITSL = 3.0 µg/m^3 with annual averaging time. This screening level is based on oral rat 90-day study (McCauley *et al*., 1995). Calculated using R232(1)(e) equation and default rat inhalation rate.

Critical Study: McCauley, P.T., M. Robinson, F.B. Daniel, and G.R. Olson 1995b. Toxicity studies of 1,3-dichlorobenzene in Sprague-Dawley rats. Drug Chem. Toxicol. 18(2&3):201-221.

Method(s): Groups of 10 male and 10 female Sprague-Dawley rats were administered 1,3-Dichlorobenzene in gavage doses of 0, 9, 37, 147, or 588 mg/kg per day in corn oil for 90 consecutive days.

Critical effect: thyroid pathology even at lowest dose tested

End point or Point of Departure (POD): LOAEL = 9 mg/kg

Uncertainty Factors: UF=3,000 (3 for LOAEL-to-NOAEL, 100 for inter and intra-species extrapolation and 10 for subchronic to chronic exposure).

Source and date: MDEQ/AQD, 8/02/2006

Cancer:

Carcinogen Weight-of-Evidence (WOE) Class: not classifiable as to human carcinogenicity (classification D)

Basis: IRIS WOE: no human data, no animal data and limited genetic data

Source and Date: Per IRIS (9/01/1990) and IRIS external review draft (2004) no value at this time.

1,4-DICHLOROBENZENE (CAS #106-46-7) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	6.5 µg/m³ (1.1 ppb_{vol})	65 µg/m³ (11 ppb_{vol})
Basis	Increased incidence of hepatocarcinoma and adenoma (Res AAC Cancer - EGLE IURF)	10 × Res AAC Cancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	31 µg/m³ (5.1 ppb_{vol})	310 µg/m³ (51 ppb_{vol})
Basis	Increased incidence of hepatocarcinoma and adenoma (NR AAC_{adj} Cancer, EGLE IURF)	10 × NR AAC_{adj} Cancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for 1,4-dichlorobenzene are based on the IURF developed by MDEQ (2016) based on a carcinogenicity study in mice and rats exposed to para-dichlorobenzene for approximately two years (NTP, 1987), resulting in increased incidence of hepatocarcinoma and adenoma in male mice. The ATSDR chronic, intermediate, and acute MRLs for 1,4-dichlorobenzene (60, 1,200, and 12,000 µg/m³, respectively) are based on noncancer effects and higher than the residential and nonresidential risk-based cancer AAVs; therefore, the cancer AACs are used as basis for the RIASLs and TS RIASLs. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the IURF was based on continuous exposure.

Uncertainties in the toxicity estimate:

The EGLE IURF of 3.9E-6 $(\mu g/m^3)^{-1}$ is based on the hepatocarcinoma and adenoma incidence data in male mice (NTP, 1987) and using the U.S. EPA Benchmark Dose Software using the cancer multistage model. California (OEHHA, 2009) has an inhalation unit risk = 1.1 E-05 $(ug/m^3)^{-1}$. The difference is due to differing methods: 1) They used a linearized multistage procedure developed by Crump *et al*., (1982); EGLE used the U.S.EPA's Benchmark Dose Software using the cancer multistage model and 2) OEHHA used a scaling factor of $q_{human} \times q_{animal} \times (bw_h/bw_a)^{1/3}$; EGLE used an U.S. EPA method which uses an exponent of (¼) in the calculation.

Source of the Toxicity Values

Noncancer:
Basis: This value is based on more current studies compared to the IRIS RfC basis.

ATSDR (7/2006), chronic inhalation MRL = 0.01 ppm or 0.06 mg/m^3: (Molecular weight = 147 g/mol).

Critical Studies:

1) Aiso S, Takeuchi T, Arito H, *et al*. 2005b. Carcinogenicity and chronic toxicity in mice and rats exposed by inhalation to para-dichlorobenzene for two years. J Vet Med Sci 67(10):1019-1029.
2) Japan Bioassay Research Center. 1995. Toxicology and carcinogenesis studies of p-dichlorobenzene in 344/DuCrj rats and Crj:BDF1 mice. Two-year inhalation studies. Japan Industrial Safety and Health Association. Study carried under contract with the Ministry of Labour of Japan.

Method(s): F344/DuCrj rats and Crj:BDF1 mice (50/sex/dose) were exposed to 1,4-dichlorobenzene in target concentrations of 0, 20, 75, or 300 ppm for 6 hr/day, 5 days/week for 104 weeks.
Critical effect: increased incidences of nasal lesions in female rats
End point or Point of Departure (POD): $BMCL_{10}$ = 9.51 ppm; $BMCL_{adj}$ = 1.7 ppm; $BMCL_{HEC}$ = 0.27 ppm (1.62 mg/m^3; MW = 147 g/mol)
Uncertainty Factors: UF = 30, 10 for intraspecies variability and 3 for interspecies extrapolation
Source and Date: ATSDR, 7/2006

Cancer:
EGLE AQD
Basis: EGLE IURF = 3.9E-6 (µg/m^3)$^{-1}$.
Critical Study: NTP (National Toxicology Program). 1987. Toxicology and carcinogenesis studies of 1,4-dichlorobenzene in F344/N rats and B6C3F1 mice (gavage studies). NTP TR 319. NIH Publ.
Method(s): Groups of 50 male and female F344/N rats and B6C351 mice were exposed in corn oil by gavage to 1,4-DCB 5 days/week at doses of 0, 150, or 300 mg/kg-day for two years.

1) *Dose response data: Tumor Type* – male mouse hepatocarcinoma and adenoma data (see AQD justification, 11/2016)
2) *Extrapolation method:* U.S. EPA benchmark dose software

Carcinogen Weight-of-Evidence (WOE) Class:
IRIS WOE Basis: This substance/agent has not undergone a complete evaluation and determination under the U.S EPA's IRIS program for evidence of human carcinogenic potential.
Source and Date: EGLE AQD Screening Level for 1,4-dichlorobenzene dated December 1, 2016.

1,1-DICHLOROETHANE (CAS #75-34-3) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	Residential TS RIASL
Action Level	16 µg/m³ (4.0 ppb_{vol})	160 µg/m³ (40 ppb_{vol})
Basis	mammary gland adenocarcinomas observed in female rats (Res AAC Cancer; CalEPA)	10 × Res AAC Cancer

Nonresidential RIASLs

	Nonresidential RIASL	Nonresidential TS RIASL
Action Level	75 µg/m³ (18 ppb_{vol})	750 µg/m³ (180 ppb_{vol})
Basis	mammary gland adenocarcinomas observed in female rats (NR AAC_{adj} Cancer; CalEPA)	10 × NR AAC_{adj} Cancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for 1,1-dichloroethane are based on cancer risk. The IURF used in the AAV calculation was a California EPA (CalEPA, 2020) IURF value of 1.6E-6 $(µg/m^3)^{-1}$ extrapolated from an oral cancer slope factor established using a 1977 National Cancer Institute study that exposed male and female rats and mice to 1,1-dichloroethane by gavage. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the IURF was based on continuous exposure.

EGLE AQD calculated a noncancer inhalation initial threshold screening level (ITSL) based on an annual averaging time equal to 500 µg/m³ (EGLE, 1997) based on Hoffman *et al.*'s (1971) subchronic mammalian inhalation study. The cancer AAVs are considered health-protective for noncancer adverse effects as they are lower than the ITSL. No ATSDR MRL is available at this time.

Uncertainties in the toxicity estimate:

Per CalEPA, an expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor from an NCI bioassay (1977). The IURF was then extrapolated from the oral cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m³/day.

Source of the Toxicity Values
Noncancer:

EGLE:
Basis: CalEPA, a Tier 3 source. No Tier 1 or Tier 2 sources at this time.
Agencies that adopted CalEPA IURF without modification include New Jersey, New York, Texas, and U.S. EPA RSL (see details below).

IRIS: Per IRIS (12/01/1996), no value at this time.
PPRTV: Per PPRTV (9/27/2006), no value at this time. Hofmann *et al*. (1971) identified renal effects in the cat as the most sensitive species for 1,1-dichloroethane in a subchronic study. However, the data are inadequate to identify the 500 ppm level as either a LOAEL or a NOAEL. No effects on the kidneys or other organs were found in other species tested in this study or in other repeated exposure inhalation studies (Dow Chemical, 1990; AIHA, 1986; Union Carbide, 1947).
MRL: Per ATSDR April 2015 list, no MRL at this time.

EGLE: MDEQ/AQD (1997) ITSL = 5.0E+2 µg/m^3: Averaging time = annual.
Critical Study: Hofmann, H.T., H. Birnstiel and P. Jobst. 1971. Inhalation toxicity of 1,1- and 1,2-dichloroethane. Arch. Toxicol. 27: 248-265.
Methods: Sprague-Dawley rats, Pirbright-White guinea pigs, "colored" rabbits and cats were exposed to 0 or 500 ppm of 1,1-dichloroethane (2024 mg/m^3) for 6 hr/day, 5 days/week for 13 weeks. Each species was composed of an equal number of males and females (2 each for cats and rabbits, 5 each for guinea pigs and rats).
Critical effect: increased BUN and abnormal kidney histopathology
End point or Point of Departure (POD): NOAEL = 2025 µg/m^3; duration adjusted NOAEL = 138 mg/kg/day (based on a cat inhalation rate and body weight of 1.26 m^3/day and 3.3 kg, respectively).
Uncertainty Factors: UF = 1,000 (10 each for intraspecies variability, interspecies extrapolation and use of a subchronic study)
Source and Date: MDEQ/AQD, 8/25/1997

HEAST: RfC= 5E-1 µg/m^3 based on HEAST Summary, 1997.

California DTSC: RfC= 8.0E+02 µg/m^3 based on RfD and route extrapolation.

New York DEC: RfC= 500 µg/m^3 based on a POD of 5E+5 µg/m^3 (NOEL) and UF = 1000. Based on kidney damage in cats exposed by inhalation six hr/day, 5 days/week for 13 weeks. Study LOEL = 1E+6 µg/m^3. (U.S. EPA HEAST, 1997)

Texas CEQ: RfC= 2.4E+03 µg/m^3. TCEQ adopted the ATSDR MRL of 2.4 mg/m^3 for 1,2-dichloroethane, a surrogate chemical for 1,1-dichloroethane (TCEQ Justification, 2011).

Other Tier 3: No value is available at this time from these Tier 3 sources/databases: NTP ROC, health and environmental agencies of Massachusetts, Minnesota and New Jersey, WHO (IARC), WHO (IPCS/INCHEM), Canada, The Netherlands (RIVM), ECHA (REACH) and OECD HPV.

Cancer:

CalEPA: CSF = 1.6E-06 $(\mu g/m^3)^{-1}$

Critical Studies: National Cancer Institute (NCI, 1977). Bioassay of 1,1-Dichloroethane for Possible Carcinogenicity. Carcinogenesis Technical Report Series No. 66. NTIS Publication No. P:B 283345. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Beth, MD.

Methods: Gavage studies in male and female B6C3F1 mice and Osborne Mendel rats. Dosing was performed once/day, 5 days/week. Additionally, the low- and high-dose mouse treatment groups was performed cyclically in the latter part of the experimental period; one exposure-free week was followed by 4 weeks of exposure.

Cancer potency is based on mammary gland adenocarcinomas observed in female rats, the most sensitive of the species/sex combinations tested. Because survival was poor for the female rats, the potency was derived using a time-to-tumor analysis (Crump *et al*., 1991).

Route-to-route extrapolation was used to develop IURF from the cancer potency factor using a reference human body weight of 70 kg and an inhalation rate of 20 m^3/day.

Source: CalEPA: Office of Environmental Health Hazard Assessment OEHHA 2009. Air Toxics Hot Spots Program Technical Support Document for Cancer Potencies. Appendix B. Chemical-specific summaries of the information used to derive unit risk and cancer potency values (page B-245). Updated 2011.

U.S. EPA RSL: IURF = 1.6E-06 $(\mu g/m^3)^{-1}$ based on CalEPA 2009 (RSL, 2017)

New Jersey DEP: IURF = 5.7E-03 $(\mu g/m^3)^{-1}$ based on CalEPA 2009 (NJDEP Toxicity Values for Inhalation Exposure, 2011)

New York DEC: IURF = 1.6E-06 $(\mu g/m^3)^{-1}$ based on CalEPA 2002/2009 (NYDOH, 2004)

Texas CEQ: IURF = 1.6E-06 $(\mu g/m^3)^{-1}$ based on CalEPA 2009 (TCEQ, 2014)

Other Tier 3 sources: No value is available at this time from these Tier 3 sources/databases: HEAST, NTP ROC, health and environmental agencies of Massachusetts, Minnesota, WHO (IARC), WHO (IPCS/INCHEM), Canada, The Netherlands (RIVM), OECD HPV, and ECHA (REACH).

1,1-DICHLOROETHYLENE (CAS #75-35-4) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	210 µg/m³ (53 ppb_{vol})	630 µg/m³ (160 ppb_{vol})
Basis	Liver toxicity, fatty change (Res AAC Noncancer – U.S. EPA IRIS RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	610 µg/m³ (150 ppb_{vol})	1,800 µg/m³ (460 ppb_{vol})
Basis	Liver toxicity, fatty change (NR AAC_{adj} Noncancer – U.S. EPA IRIS RfC)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs and TS RIASLs for 1,1-dichloroethylene are based on the U.S. EPA IRIS chronic RfC of 200 µg/m³. The IRIS RfC of 200 µg/m³ is based on a NOAEL of 25 ppm ($NOAEL_{HEC}$ = 17.7 mg/m³, $BMCL_{10[HEC]}$ = 6.9 mg/m³) and LOAEL of 75 ppm for fatty liver change in female rats after 18 months of exposure for 6 hr/day and 5 days/week (Quast *et al*., 1986). The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on a human equivalent concentration adjusted for continuous exposure. See details below.

The ATSDR Intermediate Inhalation MRL is based on hepatic effects (increased liver enzymes and mottled livers) reported at a NOAEL of 5 ppm and a LOAEL of 15 ppm after 90 days of continuous exposure in guinea pigs (Prendergast *et al*., 1967). A review of Prendergast *et al*., 1967 identifies that the biochemical evaluations were only conducted at 2 doses, 20 mg/m³ (5 ppm) and 189 mg/m³ (48 ppm), with significant increases in liver enzymes only observed at 189 mg/m³ continuous exposure. Liver histological changes were observed at 189 mg/m³ in multiple species, but not at lower doses. The LOAEL for this study for 1,1-dichloroethylene is 189 mg/m³ (48 ppm) and the NOAEL is 101 mg/m³ (25 ppm). Although there is evidence that continuous exposure results in adverse effects at lower doses, the similarities in the NOAELs and LOAELs for both studies indicate use of the IRIS RfC is appropriate for 1,1-dichloroethylene for the RIASLs and TS RIASLs.

Uncertainties in the toxicity estimate:

For the IRIS RfC, the total UF applied is 30. A UF of 10 is used to account for intraspecies variability and a UF of 3 for interspecies variability because of the use of dosimetric adjustments. The confidence assigned by IRIS to the RfC estimate is high due to an adequate number of animals in a chronic 2-year study that identified both a NOAEL and LOAEL and was thorough in reporting experimental and exposure details. The animal database provides sufficient supporting data for the RfC.

For the ATSDR intermediate inhalation MRL the total UF applied is 100. A UF of 10 each was used for human variability and interspecies extrapolation.

Source of the Toxicity Values
Noncancer:
Basis: IRIS is the only available chronic value and a Tier 1 source.
IRIS RfC = 2.0E-1 mg/m^3.
Critical Study: 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.
Method(s): Sprague-Dawley rats (Spartan sub strain, 86 animals/sex/dose) to 1,1-dichloroethylene by inhalation 6 hr/day, 5 days/wk., for up to 18 months. Rats were exposed to 1,1- dichloroethylene concentrations of 10 ppm and 40 ppm for the first 5 weeks of the study. Based on the absence of observable treatment-related effects among rats sacrificed after 1 month of exposure, the concentrations were increased to 25 and 75 ppm through the 18th month of the study. The surviving animals were then held without exposure to 1,1-dichloroethylene until 24 months.
Critical effect: liver toxicity (fatty change) in rats
End point or Point of Departure (POD): $NOAEL_{HEC}$ = 17.7 mg/m^3; $BMCL_{10HEC}$ = 6.9 mg/m^3
Uncertainty Factors: UF = 30, 10 for intraspecies variability and 3 for interspecies extrapolation.
Source and Date: IRIS, 8/13/2002
MRL: ATSDR (5/1994; 7/2009) intermediate inhalation MRL = 0.02 ppm
Critical Study: Prendergast, JA; Jones, RA; Jenkins, JR Jr, *et al*. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethene. Toxicol. Appl. Pharmacol. 10:270-289.
Method(s): Long-Evans or Sprague-Dawley rats, Hartley guinea pigs, beagle dogs, New Zealand albino rabbits, and squirrel monkeys (15 rats/group, 15 guinea pigs/group, 3 rabbits/group, 2 dogs/group, or 3 or 9 monkeys/group) were exposed continuously for 90 days to 1,1-DCE vapors at 189 ± 6.2, 101 ± 4.4, 61 ± 5.7, or 20 ± 2.1 mg/m^3. The concurrent controls included 304 rats, 314 guinea pigs, 48 rabbits, 34 dogs, and 57 monkeys. The age of the animals was not specified.
Critical effect: hepatic effects in guinea pigs (increased SGPT and alkaline phosphatase activity and decreased lipid content)
End point or Point of Departure (POD): NOAEL = 5 ppm
Uncertainty Factors: UF = 300, 10 each for intraspecies variability and interspecies extrapolation, and 3 as modifying factor for the close proximity of serious effects at 10-25 ppm range
Source and date: ATSDR, 5/1994. Addendum for 1,1-Dichloroethene Supplement to the 1994 Toxicological Profile for 1,1-Dichloroethene (7/2009)
Cancer:
Carcinogen Weight-of-Evidence (WOE) Class: C (Possible human carcinogen); Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential (Inhalation route). Not assessed under the IRIS Program
Source and Date: IRIS, 8/13/2002

CIS-1,2-DICHLOROETHYLENE (CAS #156-59-2) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	8.3 µg/m³ (2.1 ppb_{vol})	25 µg/m³ (6.3 ppb_{vol})
Basis	Increased relative kidney weight from 90-day oral administration (Res AAC Noncancer – California DTSC RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	25 µg/m³ (6.2 ppb_{vol})	74 µg/m³ (19 ppb_{vol})
Basis	Increased relative kidney weight from 90-day oral administration (NR AAC_{adj} Noncancer – California DTSC RfC)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs and TS RIASLs for cis-1,2-dichloroethylene are based on the California Department of Toxic Substances Control's (DTSC's) RfC of 8.0 µg/m³. The DTSC's RfC is based on route extrapolation from the U.S. EPA IRIS's reference dose (RfD) derived from an oral, rat study in which increased relative kidney weight was observed in male rats (CA DTSC, 2015; McCauley *et al*., 1995a; U.S. EPA, 2010). There are very few studies on the toxicity of cis-1,2-dichloroethylene. As a result, U.S. EPA's RfD provided the most appropriate benchmark with which to derive an RfC. Benchmark dose modeling was performed to determine the dose at which a 10% change in relative kidney weight would be expected to occur in exposed rats as compared to the control counterparts. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure. See details below.

No acute or intermediate inhalation health benchmarks values are available.

Uncertainties in the toxicity estimate:
The AACs are based on an RfC that was derived from extrapolation of the oral toxicity value (IRIS RfD of 2.0E-03 mg/kg-day) assuming an 80 kg body weight and breathing rate of 20 m³/day (CA DTSC, 2015). In the absence of inhalation exposure studies, route to route extrapolation is generally an alternative method by which a toxicity endpoint could be developed. The IRIS oral RfD is based on an endpoint benchmark dose level (BMDL) that is preferred by U.S. EPA and ATSDR. The total UF applied

is 3,000 to account for intraspecies variability (10), interspecies extrapolation (10), use of a subchronic study (10), and database deficiencies (3). The confidence assigned by IRIS to the RfD estimate is low due to lack of chronic, reproductive and developmental studies. By extension, the uncertainties in the RfC estimate are high for the same reasons and the assumption that the toxicity resulting from oral exposure is the same for that from inhalation exposure.

Source of the Toxicity Values
Noncancer:
Basis: Both EGLE and CalEPA derived their values by extrapolating the IRIS RfD. However, the CalEPA value assumed an 80 kg body weight (BW), the recent U.S. EPA OSWER recommended BW while EGLE used 70 kg. NY, TX and RIVM use surrogates. See details below.

California DTSC-EPA: RfC = 8.0E+00 µg/m³. EGLE also used route extrapolation of the same IRIS value; however, California used a body weight of 80 kg (OSWER, 2013) while EGLE used 70 kg. RIVM (2009) used the surrogate method.
Source: HHRA Note Number: 3, DTSC Modified Screening Levels, 5/2015

Cancer:
Carcinogen Weight-of-Evidence (WOE) Class: "inadequate information to assess the carcinogenic potential"
IRIS WOE Basis: absence of epidemiological studies in humans and lack of animal studies
Source and Date: IRIS, 9/30/2010

Tier 3 Source:
MDEQ/AQD
The EGLE AQD has also derived an RfC using route extrapolation from the same RfD. However, the EGLE AQD RfC is 18 µg/m³ because the database UF of 3 that was used by U.S. EPA was removed, and 70 kg body weight for a person was used in the route conversion. Given U.S. EPA guidance to use 80 kg body weight, and the lack of studies provided on cis-1,2-dichloroethylene, the California DTSC will be used for the residential and nonresidential AACs (U.S. EPA, 2011).

TRANS-1,2-DICHLOROETHYLENE (CAS #156-60-5) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	83 µg/m³ (21 ppb_{vol})	250 µg/m³ (63 ppb_{vol})
Basis	Decreased number of antibody-forming cells (Res AAC Noncancer – CalEPA RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	250 µg/m³ (62 ppb_{vol})	740 µg/m³ (190 ppb_{vol})
Basis	Decreased number of antibody-forming cells (NR AAC_{adj} Noncancer – CalEPA RfC)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for trans-1,2-dichloroethylene are based on the California EPA's (CalEPA, 2015) RfC of 80 µg/m³. The ATSDR (1996), a Tier 2 source, derived an intermediate inhalation MRL of 7.9E-1 mg/m³, based on a subchronic inhalation study (Freundt *et al*., 1977). However, per EPA-NCEA (2014) and IRIS (2010), the use of the Freundt study is not appropriate due to several limitations of the study. Therefore, MDEQ proceeded to identifying Tier 3 sources of toxicity values in accordance with CSA Framework for establishing toxicity value (MDEQ, 2015). Among available Tier 3 values, CalEPA is preferred as it is based on extrapolated IRIS RfD of 0.02 mg/kg-day (U.S. EPA, 2010) and the OSWER (2013) recommended body weight (80 kg).

The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure.

New Jersey and New York adopted the RIVM (2001) value, which is based on the Freundt *et al*. (1977) study and uncertainty factor of 3000. MDEQ AQD (2016) ITSL is based on IRIS RfD that has been modified by excluding the UF for database insufficiency from the total UF used by IRIS. The modified IRIS RfD and body weight of 70 kg were used to derive the ITSL.

There is an acute MRL based on the 8-hour exposure studies published as part of the same overall project from Freundt *et al*. (1977). The acute MRL is the same value as the intermediate MRL. Per

EPA-NCEA and IRIS, several limitations of the Freundt study preclude its use in deriving the RfC.

Uncertainties in the toxicity estimate:

The RfC is a route-to-route extrapolated estimate and assumes that inhalation toxicity is approximately similar to oral toxicity. The point of departure, $BMDL_{1SD}$ of 65 mg/kg-day, is applied a total uncertainty factor of 3000 to account for human variability (10), interspecies extrapolation (10), use of a subchronic study (10), and database deficiency (3). Per IRIS, the database deficiencies are: 1) missing studies of reproductive toxicity, including a two-generation reproductive toxicity study. 2) one inhalation study (DuPont, 1988a) showed developmental toxicity only in high-dose groups.

Sources Toxicity Values
Tier 3 Source:
CALEPA:
Basis: No Tier 1 available. ATSDR (1996), a Tier 2 source, derived an intermediate inhalation MRL of 7.9E-1 mg/m^3, based on a subchronic inhalation study (Freundt *et al*., 1977). Per EPA-NCEA (2014) and IRIS (2010), the use of the Freundt study is not appropriate due to several limitations of the study. Therefore, MDEQ proceeded to Tier 3 sources evaluation in accordance with CSA Framework for establishing toxicity value (MDEQ, 2015). Among available Tier 3 values, CalEPA is preferred as it is based on extrapolated IRIS RfD and used the OSWER (2013) recommended body weight (80 kg). MDEQ (2016) is based on IRIS RfD that has been modified. New Jersey and New York adopted the RIVM (2001) value, which is based on the Freundt *et al*. (1977) study and uncertainty factor of 3000. ECHA did not present details of the unpublished study used to derive the DNEL. See details below.

Tier 1 and 2 Sources:
IRIS: Per IRIS (9/30/2010), no value at this time.
PPRTV: No PPRTV record available at this time.

ATSDR (1996) MRL: Per ATSDR, no inhalation chronic MRL value at this time. Inhalation intermediate MRL = 0.2 ppm (0.79 mg/m^3) was derived as follows:
Critical Study: Freundt, KI, Liebaldt, GP, and Lieberwirth, E. 1977. Toxicity Studies on Trans-1, 2-Dichloroethylene. Toxicology, 7, pp. 141-153.
Methods: Female, mature SPF Wistar rats (6/group) were exposed 5 days per week, for either 8 or 16 weeks, at or 200 ppm of trans-1,2-dichloroethene by inhalation.
Critical effect: fatty degeneration of liver cells
End point or Point of Departure (POD): LOAEL = 200 ppm
Uncertainty Factors: UF = 1,000, 10 each for intraspecies variability, interspecies extrapolation and LOAEL to NOAEL extrapolation. MDEQ applied an additional UF = 3 for subchronic to chronic extrapolation; the total UF is 3,000. The adjusted chronic inhalation RfC = 2.6E-1 mg/m^3 (2.6E+2 µg/m^3.

Source and Date: ATSDR, 8/1996

ATSDR: ATSDR (8/1996) acute inhalation MRL = 0.2 ppm = 0.79 mg/m^3 (790 µg/m^3) is derived as follows:
The acute MRL was based on the 8-hour exposure studies published as part of the same overall project from Freundt *et al*. (1977), where the critical effect was observed to be fatty degeneration of liver cells with exposure to ≥200 ppm trans-1,2-dichloroethylene. The endpoint LOAEL was not adjusted for continuous exposure due to acute effect after 8 hours of exposure. Since the same UFs were applied, the acute MRL is the same value as the intermediate MRL, 0.2 ppm (790 µg/m^3). See Intermediate MRL derivation above.

Tier 3 Source:
MDEQ: MDEQ/AQD updated ITSL = 7.0E+1 µg/m^3. The value is based on the 9/30/2010 IRIS RfD of 0.02 mg/kg-day
Critical Study: Shopp, GM, Jr; Sanders, VM; White, KL, Jr; *et al*. (1985) Humoral and cell-mediated immune status of mice exposed to trans-1, 2-dichloroethylene. Drug Chem. Toxicol. 8:393–407.
Method(s): CD-1 mice (10/sex/group) were exposed to trans-1, 2-DCE at concentrations of 0.1, 1.0, and 2.0 mg/mL in drinking water containing 1% emulphor for 90 days. The equivalent doses are 17, 175, and 387 mg/kg-day in male mice and 23, 224, 452 mg/kg-day in female mice.
Critical effect: Decreased number of antibody-forming cells (AFCs) against sheep red blood cells (sRBCs) in male mice
End point or Point of Departure (POD): $BMDL_{1SD}$ = 65 mg/kg-day
Uncertainty Factors: UF = 3,000, 10 each for intraspecies variability, interspecies extrapolation and use of a subchronic study, and 3 for database deficiencies
Source and Date: MDEQ/AQD, 9/30/2010

MDEQ: AQD (2016) revised ITSL = 200 µg/m^3 (annual averaging time) using a modified 2010 IRIS RfD of 6.5E-2 mg/kg-day. MDEQ used a total UF = 1000, which excluded the UF for database insufficiency. IRIS RfD is based on a total UF = 3,000 that includes a UF of 3 for database deficiencies. Per IRIS, an UF of 3 was used to account for database deficiencies for the following reasons: 1) missing studies of reproductive toxicity, including a two-generation reproductive toxicity study. 2) one inhalation study (DuPont, 1988a) showed developmental toxicity only in high-dose groups. However, oral range-finding studies of the developmental toxicity of a mixture of 1,2-DCE isomers (composition of isomers unknown) (NTP, 1991a,b,c) observed no evidence of developmental toxicity in mice or rats. Per AQD, the UF for database deficiency was "determined to be unnecessary because there was no chemical-specific or toxicity-specific reason that a database UF was justified and appropriate".

CalEPA: RfC = 80 µg/m^3 based on route-to-route extrapolation of the IRIS chronic RfD = 2.0E-2 mg/kg-day assuming an 80 kg body weight and breathing rate of 20 m^3/day:
IRIS (2010) RfD basis:

Critical Study: Shopp, GM, Jr; Sanders, VM; White, KL, Jr; *et al*. 1985. Humoral and cell-mediated immune status of mice exposed to trans-1, 2-dichloroethylene. Drug Chem. Toxicol. 8:393–407.
Methods: CD-1 mice (10/sex/group) were exposed to trans-1, 2-DCE at concentrations of 0.1, 1.0, and 2.0 mg/mL in drinking water containing 1% emulphor for 90 days. The equivalent doses are 17, 175, and 387 mg/kg-day in male mice and 23, 224, 452 mg/kg-day in female mice.
Critical effect: Decreased number of antibody-forming cells (AFCs) against sheep red blood cells (sRBCs) in male mice
End point or Point of Departure (POD): $BMDL_{1SD}$ = 65 mg/kg-day
Uncertainty Factors: UF = 3,000 (10 each for intraspecies variability, interspecies extrapolation, and use of a subchronic study, and 3 for database deficiencies)
Source and Date: CalEPA DTSC, May 2015

New Jersey DEP: RfC = 60 µg/m³ The RfC is a route to route extrapolation of the RfD = 0.017 mg/kg-day (NJDWQI).
Source: New Jersey Dept. of Environmental Protection - Toxicity Factors 9/23/2008

New York DEC: RfC = 60 µg/m³ is based on an RIVM (2001) value: LOEL; UF = 3000; Critical effect = lung and liver effects in rates exposed by inhalation for 8 or 16 weeks. No other study details are available.
Source: Appendix A. Fact Sheets Containing a Summary of Data Used to identify Toxicity Values (Reference Dose, Reference Concentration, Oral Potency Factor, and Inhalation Unit Risk) Used in the Calculation of Soil Cleanup Objectives Based on the Potential for Chronic Toxicity in Adults and Children from Chronic Exposures to Soil Contaminants.
http://www.dec.ny.gov/docs/remediation_hudson_pdf/appendixa.pdf (2005)

TERA/ITER Database and RIVM: RfC = 60 µg/m³. RIVM derived a provisional tolerable concentration in air (TCA) of 0.060 mg/m³ based on a LOAEL of 780 mg/m³ (equivalent to 185 mg/m³ after adjustment for continuous exposure) for liver and lung effects observed in rats exposed to trans-1,2-dichloroethylene in a subchronic study (Freundt *et al*., 1977). RIVM used an uncertainty factor of 3000 (10 each for inter- and intraspecies variation, 10 for use of a LOAEL, and 3 for limited study duration). The TCA is provisional because of the use of the LOAEL from a study of limited duration.
Source: Tiesjema B and AJ Baars. 2009. Re-evaluation of some human-toxicological Maximum Permissible Risk levels earlier evaluated in the period 1991 - 2001. RIVM report no. 711701092. National Institute for Public Health and the Environment, Bilthoven, The Netherlands, p 40 [In Dutch]. Available at http://www.rivm.nl/bibliotheek/rapporten/711701092.html

ECHA (REACH): DNEL (Derived No Effect Level) Value: 198 mg/m³ based on a 90-day subchronic inhalation study.
Study Report. 1998 (Details on study and methods are limited)
Species: rat; Strain: other: Crl:CD®(SD) BR
Sex: male/female; Age at study initiation: 7 weeks

Type of inhalation exposure: whole body
Doses / Concentrations: 0, 200, 1000, and 4000 ppm for 6 hr/day, 5 days/week over a 90-day period
Critical effects: no observed adverse effect concentration - no effects on body weight, clinical observations, body weight gain, food consumption, clinical or anatomical pathology parameters, or liver cell proliferation.
POD: NOAEC - greater or equal 4,000 ppm (15859 mg/m^3) in rats. Correction of exposure duration (6 hr/day) to default general population exposure (24 hr/day).
Overall assessment factor (AF): 20 (10 for intraspecies variability, and 2 for subchronic exposure).
Source: ECHA (www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/16486/7/1) (accessed 3/26/2018)

Other Tier 3: No value is available at this time from these Tier 3 sources/databases: HEAST, NTP ROC, health and environmental agencies of Massachusetts and Minnesota, Texas, WHO (IARC), WHO (IPCS/INCHEM), Canada, and OECD

1,2-DICHLOROPROPANE (CAS #78-87-5) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	4.2 µg/m³ (0.90 ppb_{vol})	13 µg/m³ (2.7 ppb_{vol})
Basis	Hyperplasia of the nasal mucosa (Res AAC Noncancer – IRIS)	3 × Res AAC NC

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	12 µg/m³ (2.6 ppb_{vol})	37 µg/m³ (8.0 ppb_{vol})
Basis	Hyperplasia of the nasal mucosa (NR AAC_{adj} Noncancer – IRIS)	3 × NR AAC_{adj} NC

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for 1,2-dichloropropane are based on the IRIS (1991) RfC of 4.0E+0 per µg/m³. Both residential and nonresidential AACs are based on noncancer effects. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was adjusted for continuous human exposure.

The RfC is based on a 13-week inhalation toxicity study with rats, mice, and rabbits (Nitschke, *et al*., 1988). F344 and B6C3F1 mice (10/sex/group) were exposed to 0, 15, 50, or 150 ppm of 1,2-dichloropropane (0, 69.3, 231, or 693 mg/m³) for 6 hr/day, 5 days/week for 13 weeks (duration-adjusted concentrations = 0, 12.4, 41.3, and 124 mg/m³). New Zealand rabbits (7/sex/group) were exposed to 0, 150, 500, or 1000 ppm (0, 693, 2310, or 4621 mg/m³) according to the same regimen (duration-adjusted concentrations = 0, 124, 413, and 825 mg/m³). The LOAEL was 69.3 mg/m³ (15 ppm) and it was adjusted to $LOAEL_{ADJ\text{-}HEC}$ = 1.3 mg/m³.

The ATSDR (1989) Intermediate Inhalation MRL, 3.2E-2 mg/m³ (32 µg/m³), is also based on the Nitschke *et al*., study (1988). The 12-hour work exposure time adjusted MRL is higher than the 3x NR AAV_{adj}; therefore, the TS RIASL is based on the 3x NR AAC_{adj}.

Uncertainties in the toxicity estimate:

The total uncertainty factor (UF) of 300 is composed of a factor of 10 for intraspecies variability and 3 each for extrapolation from a subchronic study, use of a minimal LOAEL, and interspecies extrapolation due to the use of dosimetric adjustments. Based on the IRIS summary, there is high confidence in the key study, and medium confidence in both the database and RfC.

Source of the Toxicity Values

Noncancer:
RfC/ITSL = 4.0E+0 µg/m^3
Basis: IRIS as a Tier 1 source. Tier 2 source ATSDR (1989) intermediate MRL is based on an older assessment. Both used the same critical study.
Critical Study: Nitschke K.D., K.A. Johnson, D.L. Wackerle, J.E. Phillips and D.A. Dittenber. 1988. Propylene dichloride: A 13-week inhalation toxicity study with rats, mice, and rabbits. Dow Chemical Company, Mammalian and Environmental Toxicology Research Laboratory, Midland, MI. OTS Doc. #86-870001397.
Methods: F344 and B6C3F1 mice (10/sex/group) were exposed to 0, 15, 50, or 150 ppm 1,2-dichloropropane (0, 69.3, 231, or 693 mg/m^3) for 6 hr/day, 5 days/week for 13 weeks (duration-adjusted concentrations = 0, 12.4, 41.3, and 124 mg/m^3). New Zealand rabbits (7/sex/group) were exposed to 0, 150, 500, or 1000 ppm (0, 693, 2310, or 4621 mg/m^3) according to the same regimen (duration-adjusted concentrations = 0, 124, 413, and 825 mg/m^3).
Critical effect: hyperplasia of the nasal mucosa
End point or Point of Departure (POD): LOAEL = 69.3 mg/m^3 (15 ppm); LOAEL$_{adj\text{-}HEC}$ = 1.3 mg/m^3
Uncertainty Factors (UF): UF = 300, 10 for intraspecies variability and 3 each for extrapolation from a subchronic study, use of a minimal LOAEL, and interspecies extrapolation due to the use of dosimetric adjustments.
Source and Date: IRIS, 12/01/1991

Tier 2 Sources:
PPRTV: PPRTV (11/30/2003) did not evaluate RfC.
MRL: Per ATSDR (1989), no chronic inhalation MRL. Intermediate inhalation MRL = 0.007 ppm (3.2E-2 mg/m^3) (MW = 112.99 g/mol):
Critical Study: Nitschke K.D., K.A. Johnson, D.L. Wackerle, J.E. Phillips and D.A. Dittenber. 1988. Propylene dichloride: A 13-week inhalation toxicity study with rats, mice, and rabbits. Dow Chemical Company, Mammalian and Environmental Toxicology Research Laboratory, Midland, MI. OTS Doc. #86-870001397
Methods: F344 and B6C3F1 mice (10/sex/group) were exposed to 0, 15, 50, or 150 ppm 1,2-dichloropropane (0, 69.3, 231, or 693 mg/m^3) for 6 hr/day, 5 days/week for 13 weeks (duration-adjusted concentrations = 0, 12.4, 41.3, and 124 mg/m^3). New Zealand rabbits (7/sex/group) were exposed to 0, 150, 500, or 1,000 ppm (0, 693, 2310, or 4,621 mg/m^3) according to the same regimen (duration-adjusted concentrations = 0, 124, 413, and 825 mg/m^3).
Critical effect: upper respiratory lesions in rat
End point or Point of Departure (POD): LOAEL = 15 ppm
Uncertainty Factors: UF = 1,000, 10 each for intraspecies variability, interspecies extrapolation, and use of a LOAEL
Source and Date: ATSDR, 12/1989; ATSDR Toxicological Profile

Tier 3 Source:
EGLE: MDEQ, AQD (9/15/2015) adopted IRIS RfC = 4 µg/m^3, averaging time = annual.

Cancer:
CSF: 3.6E-02 $(mg/kg\text{-}day)^{-1}$
Tier 3 Sources:
CALEPA/EGLE:
Basis: No Tier 1 and 2 available. CalEPA (1999) value is based on a newer assessment that used new methodology based on the LED_{10} to derive the potency estimate. MDEQ (1997) used Global 82 method and revised species scaling factor to derive the value. Both used the NTP (1986) data. HEAST (1993) used the same study; however, estimation details are not available. New Jersey and Texas used the HEAST value. Minnesota adopted the CalEPA value. See details below.

Tier 1 and 2 Sources:
IRIS: Per IRIS (12/01/1991), no value at this time.
PPRTV: Per PPRTV (11/30/2003), no value at this time.
MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Sources:
EGLE: MDEQ/AQD (9/18/2013) IURF = 5.0E-6 $(\mu g/m^3)^{-1}$
Critical Study: Umeda Y1, Matsumoto M, Aiso S, Nishizawa T, Nagano K, Arito H, Fukushima S. 2010. Inhalation carcinogenicity and toxicity of 1,2-dichloropropane in male and female F344 rats. Inhalation Toxicology: International Forum for Respiratory Research. 22: 1116-1126.
Methods:
male and female F344 rats were exposed to DCP for either 13 wk or 2 years. In the 13-wk study, the DCP concentrations used were 125, 250, 500, 1000, or 2000 ppm (v/v), and in the 2-year study the DCP concentrations were 80, 200, or 500 ppm (v/v). Thirteen-week exposure to DCP induced hyperplasia in the respiratory epithelium and atrophy of the olfactory epithelium at 125 ppm and above. Two-year exposure to DCP significantly increased incidences of papilloma in the nasal cavity of male and female rats exposed to 500 ppm DCP. In addition, three cases of esthesioneuroepithelioma were observed in the DCP-exposed male rats.
Dose response data: Tumor Type – nasal tumors; Test Species - male rats
Source and Date: MDEQ/AQD, 9/18/2013

HEAST: CSF= 6.8E-2 $(mg/kg\text{-}day)^{-1}$:
Key Study: (005062). NTP. 1986. NTP Technical Report on the Carcinogenesis Studies of 1.2-Dichloropropane (Propylene Dichloride) In F344/N Rats and B6c3f1 Mice (Gavage Studies). Ntp-82-092. Nih Publ No 84-2519. Ntp Tr 263. Us Dhhs. Phs, Nih. August. 1986 Draft.
Methods: F344/N rats and B6CF1 mice, oral gavage. F344/N rats (50/sex/group) received 1,2-Dichloropropane in corn oil by gavage five days/week for 103 weeks. Male rats received 0, 62 or 125 mg/kg (averaged over seven days/week these doses equal 0, 44.3 and 89.3 mg/kg-day,

respectively). Female rats received 0, 125 or 250 mg/kg (0, 89.3 and 178.6 mg/kg-day, respectively).
Tumor type: liver tumors in mouse
Source: HEAST Summary 1997

California DTSC: CSF= 0.036 or 3.6E-2 $(mg/kg\text{-}day)^{-1}$.
Key study: NTP (1986). Toxicology and carcinogenesis studies of 1,2-dichloropropane (propylene dichloride) (CAS No. 78-87-5) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program Technical Report Series No. 263. NIH Publication No. 86-2519.
Method: 1,2-DCP was administered to F344/N rats (50/sex/group) in corn oil by gavage 5days/week for 103 weeks. Male rats received 0, 62, or 125 mg/kg (averaged over 7 days/week these doses equal 0, 44.3, and 89.3 mg/kg-day, respectively). Female rats received 0, 125, or 250 mg/kg (0, 89.3, and 178.6 mg/kg-day, respectively).
Calculation: The most sensitive site, gender and species for tumor development from 1,2-DCP was the combined incidence of hepatocellular adenomas and carcinomas observed in male mice in the NTP (1986) bioassay. The p-value of the least squares coefficient indicates a reasonable fit of the model polynomial to this experimental dataset. The CSF_{human} calculated from this dataset is $3.6x10^{-2}$ $(mg/kg\text{-}day)^{-1}$.
Note: Potency estimates were calculated using the LMS model and the new method based on the LED_{10}. The estimates from these two methodologies were consistent: 3.8×10^{-2} $(mg/kg\text{-}day)^{-1}$ and 3.6×10^{-2} $(mg/kg\text{-}day)^{-1}$.
Source: OEHHA 1999. Public Health Goal for 1,2-Dichloropropane in Drinking Water, 1999.
Minnesota PCA: CSF= 3.6E-2 (mg/kg-day)-1 based on CalEPA.
New Jersey DEP: CSF= 6.8E-2 (mg/kg-day)-1 based on HEAST.
Texas CEQ: CSF= 6.8E-02 (mg/kg-day)-1 based on HEAST.
Other Tier 3: No value is available at this time from these Tier 3 sources/databases: NTP ROC, health and environmental agencies of Massachusetts and New York, WHO (IARC), WHO (IPCS/INCHEM), Canada, The Netherlands (RIVM), ECHA (REACH) and OECD HPV.
Carcinogen Weight-of-Evidence (WOE) Class: Group C, possible human carcinogen
IRIS WOE Basis: based on hepatocellular carcinomas in male mice, with a positive trend and borderline significance in female mice; and increased incidence of renal tubular cell adenomas in rats.
Source and Date: Office of Pesticide Programs (OPP) Memorandum dated 8/08/2014: **Subject:** Triallate. Human Health Risk Assessment Scoping Document in Support of Registration Review, 8/08/2014.

Tier 1 and 2 Sources:
IRIS: Per IRIS (12/1/1991), no value at this time. IRIS has not evaluated triallate for evidence of human carcinogenic potential. Per IRIS (2015), this chemical is no longer being updated under the IRIS Program. The user is directed to the OPP for updates.
PPRTV: No PPRTV record available at this time.

MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Source:
EGLE: Per MDEQ/AQD, no value at this time.

DIISOPROPYL ETHER (CAS #108-20-3) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	700 µg/m³ (170 ppb_{vol})	2,100 µg/m³ (500 ppb_{vol})
Basis	Rib malformations (Res AAC SE Developmental – PPRTV RfC)	3 × Res AAC SE Developmental

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	1,400 µg/m³ (340 ppb_{vol})	4,200 µg/m³ (1,000 ppb_{vol})
Basis	Rib malformations (NR AAC_{adj} SE Developmental – PPRTV RfC)	3 × NR AAC_{adj} SE Developmental

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for diisopropyl ether are based on the U.S. EPA's PPTRV (2011) RfC of 700 µg/m³. Both residential and nonresidential AACs are based on developmental effects that may result from a single event exposure during pregnancy. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time because the RfC was based on continuous exposure (See details below).

The RfC is based on two critical studies. The first was a subchronic study which exposed rats to 0, 2,000, 13,800, or 29,700 mg/m³ of diisopropyl ether vapors for 6 hr/day, 5 days/week, for 13 weeks. The second was a developmental toxicity study which exposed rats to 0, 12, 940, or 28,000 mg/m³ of diisopropyl ether vapors for 6 hr/day on days 6-16 of gestation. Both rat studies found rudimentary and short 14th ribs in fetal rats exposed during gestation. The exposures in these studies were for 6 hr/day; however, the point of departure (POD), a $BMCL_5$, was adjusted to represent a continuous exposure. The rat $BMCL_5$ was adjusted to continuous exposure by multiplying the $BMCL_5$ by 6/24 hours resulting in the $BMCL_{adj}$ of 66 mg/m³. Additionally, the rat $BMCL_{adj}$ was adjusted to reflect the human equivalent concentration (HEC) by application of a default value of 1 for the dosimetric adjustment factor (DAF), resulting in the $BMCL_{HEC}$ of 66 mg/m³.

Uncertainties in the toxicity estimate:
A total uncertainty factor of 100 was used to derive the screening RfC, where 10 was used for intraspecies variability, and 3 each was used for interspecies extrapolation and database deficiencies. Confidence in the principal study (Dalbey and Feuston, 1996) is high. This study included an appropriate number of animals and exposure levels and investigated a suitable range of

endpoints. Confidence in the database is medium. Only one species has been evaluated (rat) in a subchronic study, a neurotoxicity study, and a developmental study. A multigeneration reproduction study is not available.

No subchronic-to-chronic extrapolation uncertainty factor was applied because the critical effect occurs at a critical stage of development, thus it is not considered exposure duration-dependent. Confidence in the subchronic RfC is medium.

Source of the Toxicity Values
Noncancer:
RfC = 7.0E+02 µg/m^3
Basis: PPRTV as a Tier 2 source. No Tier 1 available.
Critical Study:
Dalbey, W. and M. Feuston. 1996. Subchronic and developmental toxicity studies of vaporized diisopropyl ether in rats. J. Toxicology. Environ. Health 49:29–43.
Method:

1) Subchronic study: Sprague-Dawley rats (14/sex/group) were whole-body exposed to 0 (untreated), 0 (sham-exposed), 2000, 13,800, or 29,700 mg/m^3 (0, 480, 3300, or 7100 ppm) of diisopropyl ether 6 hr/day, 5 days/week, for approximately 13 weeks.
2) Developmental study: groups of 22 mated female Sprague-Dawley rats were whole-body exposed to 0 (untreated); 0 (sham-exposed); 1,800; 12,940; or 28,200 mg/m^3 (0; 430; 3,095; or 6,745 ppm) diisopropyl ether vapor for 6 hr/day on days 6–16 of gestation.

Critical effect: rudimentary and short 14th ribs in fetal rats exposed during gestation
End point or Point of Departure (POD): BMCL$_{HEC}$ = 66 mg/m^3
Uncertainty Factors: UF = 100, 10 for intraspecies variability and 3 each for interspecies extrapolation and database deficiencies. No subchronic-to-chronic extrapolation uncertainty factor was applied because the critical effect occurs at a critical stage in development, thus it is not considered exposure duration-dependent. Therefore, the subchronic RfC is the same as the chronic RfC.
Source and Date: PPRTV, 4/21/2011

Tier 1 and 2 Sources:
IRIS: No IRIS file available at this time.
MRL: No MRL record available at this time.

Tier 3 Source:
MDEQ: MDEQ/AQD RfC = 3.58E+02 µg/m^3. See Part 201 Value RfC details. Averaging time = 24 hours.

Cancer:
Tier 1 and 2 Sources:

IRIS: No IRIS file available at this time.
PPRTV: Per PPRTV (4/21/2011), no value at this time. The cancer assessment for diisopropyl ether is on hold until the completion of an EPA-NIEHS review of cancer data.
MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Source:
MDEQ: Per MDEQ/AQD, no value at this time.

1,4-DIOXANE (CAS #123-91-1) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	5.1 µg/m³ (1.4 ppb_{vol})	51 µg/m³ (14 ppb_{vol})
Basis	Increased incidence of multiple tumor types (Res AAC Cancer – IRIS IURF)	10 × Res AAC Cancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	24 µg/m³ (6.7 ppb_{vol})	240 µg/m³ (66 ppb_{vol})
Basis	Increased incidence of multiple tumor types (NR AAC_{adj} Cancer – IRIS IURF)	10 × NR AAC_{adj} Cancer

Discussion of Basis

The U.S. EPA's IRIS IURF is the basis of the residential and nonresidential AACs, RIASLs, and TS RIASLs for 1,4-dioxane (U.S. EPA, 2013). 1,4-Dioxane is classified by U.S. EPA as "likely to be carcinogenic to humans" by all routes of exposure. The IURF is based on increased incidence of multiple tumor types (nasal, liver, kidney, peritoneal, mammary gland, and Zymbal gland) from a whole-body 2-year inhalation study in rats (Kasai *et al*., 2009). The residential and nonresidential AACs for carcinogenic effects are lower than the ATSDR MRLs for acute and intermediate inhalation exposures (0.72 and 7.2 mg/m³, respectively). The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the IURF was based on continuous exposure.

Uncertainties in the toxicity estimate:
The U.S. EPA IURF was estimated using linear extrapolation (multistage, multi-tumor model) of data on tumor incidence at multiple sites in male rats (Kasai *et al*., 2009). Kasai *et al*. (2009) is considered a well-designed study. However, female mice were found to be the most sensitive gender and species between rats and mice in an oral study of 1,4-dioxane (Kano *et al*., 2009). Thus, it is suspected that an inhalation study with female mice may be more sensitive for cancer effects from 1,4-dioxane.

U.S. EPA noted that, "The available evidence in support of the hypothesized MOAs for 1,4-dioxane is not conclusive. In the absence of sufficient information to support a mechanism of action (MOA) for the observed tumor types associated with exposure to 1,4-dioxane, a linear low-dose extrapolation approach was used to estimate human carcinogenic risk associated with 1,4-dioxane exposure." U.S. EPA also noted that there is a "lack of understanding about the potential differences in metabolism and susceptibility across exposed populations."

Source of the Toxicity Values
Noncancer:
RfC = 3.0E+01 µg/m^3
Basis: IRIS is a Tier 1 source. Additionally, the assessment is similar to the assessment conducted by ATSDR (2012) except for the use of a database uncertainty factor.
Critical Study: Kasai, T; Kano, H; Umeda, Y; Sasaki, T; Ikawa, N; Nishizawa, T; Nagano, K; Arito, H; Nagashima, H; Fukushima, S. (2009). Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. Inhal. Toxicol. 21: 889-897.
Method: 6-week-old male F344/DuCrj rats (50/group) were exposed via inhalation to 0 (clean air), 50, 250, and 1,250 ppm (0, 180, 900, and 4,500 mg/m^3, respectively) of vaporized 1,4-dioxane (>99% pure) for 6 hr/day, 5 days/week, for 104 weeks (2 years) in whole body inhalation chambers.
Critical effect: Atrophy and respiratory metaplasia of the olfactory epithelium
End point or Point of Departure (POD): LOAEL = 50 ppm; LOAEL POD_{HEC} = 32.2 mg/m^3
Uncertainty Factors: UF = 1,000, 10 each for intraspecies variability and use of a LOAEL and 3 each for interspecies extrapolation and database deficiency
Source and Date: IRIS, 9/20/2013

Tier 2 Source:
PPRTV: No PPRTV record is available at this time.
MRL: ATSDR (2012) inhalation chronic MRL = 0.03 ppm or 0.11 mg/m^3 (MW = 88.11 g/mol); (mg/m^3 = (ppm x MW)/24.45)
Critical Study: Kasai T, Kano H, Umeda Y, *et al*. 2009. Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male. Inhal. Toxicol. 21:889-897.
Methods: Groups of male F344/DuCrj rats (50/group) were exposed whole-body to target concentrations of 0, 50, 250, or 1,250 ppm 1,4-dioxane vapors 6 hr/day, 5 days/week for 104 weeks; controls were exposed to clean air.
Critical effect: atrophy of the olfactory epithelium
End point or Point of Departure (POD): The lowest exposure concentration tested, 50 ppm 1,4-dioxane, is the LOAEL for nasal lesions (atrophy of the olfactory epithelium); a NOAEL was not defined in this study.
Uncertainty Factors: UF = 300, 10 each for human variability and use of a LOAEL, and 3 for extrapolation from animals to humans with dosimetric adjustment
Source and Date: ATSDR, 4/2012. A Toxicological Profile is available.

Intermediate inhalation MRL: Intermediate MRL = 0.2 ppm or 0.72 mg/m^3
Critical Study: Kasai T, Saito M, Senoh H, *et al*. (2008). Thirteen-week inhalation toxicity of 1,4-dioxane in rats. Inhalation Toxicol. 20:961-971.
Methods: Groups of male F344/DuCrj rats (50/group) were exposed whole-body to target concentrations of 0 (clean air), 100, 200, 400, 800, 1,600, 3,200, or 6,400 ppm 1,4-dioxane vapors 6 hr/day, 5 days/week, for 13 weeks.

Critical effect: lesions in the olfactory epithelium of the nasal cavity in male rats.
End point or Point of Departure (POD): $BMCL_{10}$ = 27.99 ppm; $BMCL_{[HEC]}$ = 4.998 ppm. Duration adjustment (6/24 hours x 5/7 days) and calculation method for Category 3 gas were applied to determine HEC.
Uncertainty Factors: UF = 30, 3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability.
Source and Date: ATSDR, 4/2012. A Toxicological Profile is available.

Acute inhalation MRL: The acute MRL = 2 ppm or 7.21 mg/m^3 is based on the 20 ppm NOAEL for eye and respiratory effects in humans.
Critical study: Ernstgård *et al*., 2006. Acute effects of exposure to vapours of dioxane in humans. Human Exp. Toxicol. 25:723-729.
Uncertainty factors: UF = 10 for human variability
Source and Date: ATSDR, 4/2012. A Toxicological Profile is available.

Tier 3 Source:
MDEQ: MDEQ-AQD ITSL = 1.0E+02 µg/m^3.
Basis: The annual ITSL is based on the IRIS RfC. The RfC was derived from Kasai *et al*. (2009), in which a LOAEL of 50 ppm for respiratory metaplasia and atrophy of the olfactory epithelium were identified as critical effects. The total UF for the RfC was 1000. The database UF of 3 was removed for derivation of the annual ITSL. The 1-hour ITSL was derived from the study by Ernstgard *et al*. (2006), in which a NOAEL of 20 ppm was identified from a study using human volunteers. A total UF of 10 was applied to this NOAEL.
Source and date: MDEQ/AQD, 2013

Cancer:
Basis: IRIS (2013) is a Tier 1 source. No Tier 2 available.

IRIS (2013) IURF = 5.0E-06 (µg/m^3)$^{-1}$
Critical Study: Kasai, T; Kano, H; Umeda, Y; Sasaki, T; Ikawa, N; Nishizawa, T; Nagano, K; Arito, H; Nagashima, H; Fukushima, S. (2009). Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. Inhal. Toxicol. 21: 889-897.
Methods: male 6-week-old F344/DuCrj rats (50/group) were exposed via inhalation to 0 (clean air), 50, 250, and 1,250 ppm (0, 180, 900, and 4,500 mg/m^3, respectively) of vaporized 1,4-dioxane (>99% pure) for 6 hr/day, 5 days/week, for 104 weeks (2 years) in whole body inhalation chambers.
1) *Dose response data: Tumor Type* - multiple (nasal, liver, kidney, peritoneal, mammary gland, and Zymbal gland); *Test Species* - male F344 rats; *Route* – inhalation.
2) *Extrapolation method:* Multi-tumor dose-response model with linear extrapolation from the POD ($(BMCL_{10})_{HEC}$) associated with a 10% increase in cancer risk.
Carcinogen Weight-of-Evidence (WOE) Class: "likely to be carcinogenic to humans" by all routes of exposure.

IRIS WOE Basis: based on the following findings: (1) inadequate evidence of carcinogenicity in humans, and (2) sufficient evidence in animals (i.e., hepatic tumors in multiple species [three strains of rats, two strains of mouse, and in guinea pigs]; mesotheliomas of the peritoneum, mammary tumors, and nasal tumors have also been observed in rats following 2 years of oral exposure to 1,4-dioxane).
Source and Date: IRIS, 9/20/2013. A Toxicological Review is available.

Tier 2 Sources:
PPRTV: No PPRTV record is available at this time.
MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Source:
MDEQ: MDEQ/AQD (1/29/2014) IURF = 5.0E-06 $(\mu g/m^3)^{-1}$
Basis: The inhalation potency was derived from the U.S. EPA IRIS IURF.

ETHANOL (CAS #64-17-5) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	Residential TS RIASL
Action Level	19,000 µg/m^3 (10,000 ppb$_{vol}$)	19,000 µg/m^3 (10,000 ppb$_{vol}$)
Basis	Worker eye and respiratory tract irritation (EGLE, AQD Acute ITSL)	EGLE, AQD Acute ITSL

Nonresidential RIASLs

	Nonresidential RIASL	Nonresidential TS RIASL
Action Level	19,000 µg/m^3 (10,000 ppb$_{vol}$)	19,000 µg/m^3 (10,000 ppb$_{vol}$)
Basis	Worker eye and respiratory tract irritation (EGLE, AQD Acute ITSL)	EGLE, AQD Acute ITSL

Discussion of Basis

The EGLE ITSL is the basis of the AAC and Residential and Nonresidential RIASLs. The EGLE ITSL is based on the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV). With an adjustment for an eight-hour averaging time, the ITSL is 19,000 µg/m^3. This value is based on worker complaints of irritation to the eyes and respiratory tract. Based on a comparison with human oral data (NOAEL = 23.3 grams/day), this is also considered protective against the most sensitive human endpoint, fetal alcohol syndrome. The nonresidential RIASL and TSRIASL were not adjusted to a 12-hour work exposure time since health effects from ethanol exposure have been observed within minutes (ACGIH, 2010).

The ACGIH considers ethanol a confirmed animal carcinogen, but the relevance to human health is unknown.

Uncertainties in the toxicity estimate:

The EGLE ITSL is based on the ACGIH Threshold Limit Value Short-Term Exposure Level (STEL; 15 minutes) of 1,000 ppm (1,880,000 µg/m^3). People exposed to 1,000 ppm resulted in no respiratory irritation, but levels between 100 and 1,920 ppm were reported as “annoying.”
A STEL was selected as irritant effects occur at levels lower than those that are associated with long-term health effects. The EGLE ITSL applied a default total UF of 100 to the TLV-STEL to account for human variability (10) and exposure time between the worker and the general population (10). The National Institute for Occupational Safety and Health Recommended Exposure Limit for a 10-hour time-weighted average is 1,000 ppm (1,900,000 µg/m^3).

Source of the Toxicity Values

EGLE: 1.9E+4 µg/m³
EGLE: AQD (1992) ITSL = 1.9E+4 µg/m³:
Basis: Best available data is EGLE ACGIH TLV (Browning [1956] and Lester & Greenberg [1951]). The use of one hundredth of the TLV of 1000 ppm (1900 µg/m³) is also sufficiently protective of the most sensitive human endpoint - Fetal Alcohol Syndrome. EGLE was chosen due to the availability of supporting information. Documents for MA, MN, RIVM and ECHA are not available.

ITSL Derivation and Justification: Per EGLE AQD (1992), the poor quality of inhalation toxicity data for animals makes identification of a NOAEL difficult, with little confidence for the derived number. The human oral data clearly identify Fetal Alcohol Syndrome as the most sensitive of human effects. However, there is no human inhalation data on fetal effects from this route. The bolus effect from drinking alcohol with resultant high short-term blood concentrations, plus questionable self-reporting of alcohol doses, makes use of this data of rather limited value for deriving an AAC [ITSL]. The use of one hundredth of the TLV for the AAC [ITSL] is considered the best available alternative at this time. From the one ounce per day alcohol consumption rate converted to an air concentration, an AAC [ITSL] based on the TLV should be sufficiently protective for fetal effects. Therefore, the ITSL is 19 mg/m³ with an eight-hour average.
Source and Date: EGLE-CCD/AQD, 4/16/1992

IRIS: No IRIS file is available at this time.
PPRTV: No PPRTV record is available at this time.
MRL: No MRL record is available at this time.

Massachusetts DEP: RfC= 51.24 µg/m³ based on 1990 Method. Supporting information could not be found.
Minnesota: RfC= 15000 µg/m³. Supporting information could not be found.
RIVM: RfC= 30800 µg/m³. Supporting information could not be found.
ECHA (REACH): RfC= 114 mg/m³. A critical study with supporting information could not be found.
Other Tier 3: No value is available at this time from these Tier 3 sources/databases: HEAST, NTP ROC, health and environmental agencies of California, New Jersey, New York, and Texas, WHO (IARC), WHO (IPCS/INCHEM), Canada, and OECD HPV.

ETHYLBENZENE (CAS #100-41-4) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	Residential TS RIASL
Action Level	10 µg/m^3 (2.3 ppb$_{vol}$)	100 µg/m^3 (23 ppb$_{vol}$)
Basis	Renal tubule neoplasms from chronic exposure (Res AAC Cancer – CalEPA IURF)	10 × Res AAC Cancer

Nonresidential RIASLs

	Nonresidential RIASL	Nonresidential TS RIASL
Action Level	48 µg/m^3 (11 ppb$_{vol}$)	480 µg/m^3 (110 ppb$_{vol}$)
Basis	Renal tubule neoplasms from chronic exposure (NR AAC$_{adj}$ Cancer – CalEPA IURF)	10 × NR AAC$_{adj}$ Cancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for ethylbenzene are derived from the IURF developed by the CalEPA (2011) of 2.50E-06 (µg/m^3)$^{-1}$. The CalEPA IURF is based on the renal tubule carcinoma or adenoma incidence data in male rats (NTP, 1999). The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the IURF was based on continuous exposure.

The U.S. EPA IRIS RfC (1000 µg/m^3) is based on rabbit and rat studies where developmental toxicity was suggested but not clearly evident (Hardin *et al*., 1981; U.S. EPA, 1991). Furthermore, the U.S. EPA's confidence in this RfC was classified as "low", and at the time of the IRIS RfC derivation, there was no human or animal carcinogenicity data available (U.S. EPA, 1991). The ATSDR's acute and intermediate inhalation MRLs (22,000 and 8700 µg/m^3, respectively) are based on ototoxicity in rats (Cappaert *et al*., 2000; Gagnaire *et al*., 2007), and the chronic MRL (260 µg/m^3) is based on nephropathy in female rats (NTP, 1999). As compared to the IRIS' RfC and ATSDR's acute, intermediate and chronic MRLs for ethylbenzene, the RIASLs and TS RIASLs derived from the CalEPA IURF are lower and would therefore be health protective for effects seen above these other health benchmarks.

Uncertainties in the toxicity estimate:

The 2011 CalEPA IURF of 2.50E-06 (µg/m^3)$^{-1}$ is based on the renal tubule carcinoma or adenoma incidence data in male rats (NTP, 1999) and using the linearized multistage (LMS) model methodology. The values and the process used to derive them have undergone public and peer review and were approved by the California Scientific Review Panel for Toxic Air Contaminants.

Therefore, the cancer potency estimate was well vetted in relation to use of available data and methodology and the value could be assigned medium level of confidence.

Source of the Toxicity Values
Noncancer:
Basis: ATSDR is a more current assessment than IRIS.
ATSDR inhalation chronic MRL = 0.06 ppm or 2.6E-1 mg/m^3.
Critical Study: NTP. 1999. NTP technical report on the toxicology and carcinogenesis studies of ethylbenzene in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services.
NTP TR 466.
Methods: F344/N rats (50/sex/ group) were exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation for 6 hr/day, 5 days/week for 104 weeks.
Critical effect: increased severity of chronic progressive nephropathy in female rats
End point or Point of Departure (POD): $LOAEL_{HEC}$ = 17.45 ppm
Uncertainty Factors: UF = 300, 10 each for intraspecies variability and use of a LOAEL and 3 for interspecies extrapolation
Additional data: ATSDR acute MRL (5ppm) and intermediate MRLs (2 ppm) are based on neurological effects (Cappaert *et al*., 1999 and Gagnaire *et al*., 2007, respectively).
Source and Date: ATSDR, 11/2010

Cancer:
Basis: CalEPA IUR is based on a 2011 assessment using different models and dose metrics. The final value is based on the most appropriate model. CalEPA, the EGLE, and NY used the same key study, but the models used to derive the values varied. Minnesota and New Jersey adopted the CalEPA value. See details below.
California DTSC (CALEPA): IURF= 0.0000025 or 2.5E-6 $(\mu g/m^3)^{-1}$
Using either the LMS or BMD with different dose metrics, the 95% upper confidence bound on the unit risk value for purposes of calculating cancer risks associated with exposure to ethylbenzene is in the range 5.5 x 10-4 to 6.6 x 10-3 (mg/m^3)-1, based on the incidence data from the NTP (1999). The unit risk value of 2.5 x10^{-3} $(mg/m^3)^{-1}$, or 2.5 x10^{-6} $(\mu g/m^3)^{-1}$, based on the renal tubule carcinoma or adenoma incidence data in male rats and using the LMS methodology applied to lifetime weighted average (LTWA) doses is considered most appropriate.
Key study: National Toxicology Program (NTP), 1999. Toxicology and Carcinogenesis Studies of Ethylbenzene (CAS No. 100-41-4) in F344/N Rats and in B6C3F1 Mice (Inhalation Studies). Technical Report Series No. 466. NIH Publication No. 99-3956. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP, Research Triangle Park, NC.
Carcinogen Weight-of-Evidence (WOE) Class: The IARC (Vol.: 77. 2000, p. 227) has concluded that there is inadequate evidence to classify ethylbenzene as a carcinogen in humans and sufficient evidence in experimental animals (Group 2B).

An NTP (1999) bioassay exposed male and female rats and mice to 0, 75, 250, or 750 ppm ethylbenzene for up to 2 years. NTP reported that ethylbenzene showed clear evidence of carcinogenic activity in male rats based on increased incidences of renal tubule neoplasms and testicular adenomas, some evidence of carcinogenic activity in female rats based on increased incidences of renal tubule adenomas, some evidence of carcinogenic activity in male mice based on increased incidences of alveolar/bronchiolar neoplasms, and some evidence of carcinogenic activity in female mice based on increased incidences of hepatocellular neoplasms.

N-HEXANE (CAS #110-54-3) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	730 µg/m³ (210 ppb_{vol})	2,200 µg/m³ (620 ppb_{vol})
Basis	Peripheral neuropathy (decreased MCV at 12 weeks) in male rats (Res AAC Noncancer – U.S. EPA IRIS RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	2,100 µg/m³ (610 ppb_{vol})	6,400 µg/m³ (1,800 ppb_{vol})
Basis	Peripheral neuropathy (decreased MCV at 12 weeks) in male rats (NR AAC_{adj} Noncancer – U.S. EPA IRIS RfC)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for n-hexane are based on the U.S. EPA IRIS RfC of 700 µg/m³. The RfC is based on 16-week subchronic rat inhalation study by Huang *et al*. 1989. The critical effect reported was peripheral neuropathy (decreased motor nerve conduction velocity (MCV)) in male rats. The U.S. EPA's Toxicological Review of n-Hexane (U.S. EPA, 2005) indicates that based on available human and animal n-hexane inhalation exposure, the nervous system is the primary target of toxicity. A 12 hr/day, 7 days/week duration adjustment of exposure concentration was applied by the U.S. EPA to the BMCL of 430 mg/m³, resulting in a POD $BMCL_{adj}$ of 215 mg/m³. There are no acute or intermediate MRLs currently available. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure.

An ATSDR chronic inhalation MRL of 2,115 µg/m³ (ATSDR, 1999) was derived from an epidemiology study of factory workers exposed to hexane over an average 6-year period (Sanagi *et al*. 1980). Generally, human exposure studies are preferable to animals; however, per IRIS (U.S. EPA, 2005) studies showed that solvents including toluene, methyl ethyl ketone, acetone, and xylene potentiate neurotoxicity resulting from the n-hexane exposure. From these findings, IRIS indicated that the severity of the neurological changes observed in Sanagi (1980) may be attributed to exposure to both n-hexane and acetone. IRIS also noted that studies had shown that n-hexane metabolism and neurotoxicity are affected by acetone.

Uncertainties in the toxicity estimate:

For the U.S. EPA IRIS value, a total UF of 300 was applied to the POD of 215 mg/m^3: 10 for intraspecies variation; 3 for interspecies differences; 3 to extrapolate to chronic exposure from data in a less-than lifetime study; and 3 to account for database deficiencies. The subchronic study used to derive the RfC is a 16-week study. Per IRIS, "16 weeks is half of the time required for a newly synthesized neurofilament protein to be transported from the neuronal cell body to the axon terminal in the longest axons of the central nervous system and the peripheral nervous system of an adult rat (Griffin *et al*. 1984)". Therefore, only a factor of 3 was used to extrapolate the POD to a chronic exposure dose.

Source of the Toxicity Values
Noncancer:
Basis: IRIS is a Tier 1 source.

Tier 1 Source
IRIS (12/ 23/2005)**:** RfC = 7E+2 µg/m^3
Critical Study: Huang, J; Kato, K; Shibata, E; *et al*. (1989) Effects of chronic n-hexane exposure on nervous system-specific and muscle-specific proteins. Arch. Toxicol. 63:381-385.
Methods: Male Wistar rats (8/group) were exposed to 0, 500, 1,200, or 3,000 ppm (0, 1,762, 4,230, 10,574 mg/m^3) n-hexane (>99% pure) for 12 hr/day, 7 days/week for 16 weeks. The authors measured MCV in the tail nerve along with body weight before exposure and after 4, 8, 12, and 16 weeks of exposure to n-hexane. One animal from each group was sacrificed at 16 weeks exposure for histopathological evaluation of the nerve fibers in the tail. In addition, Huang *et al*. (1989) measured the levels of neuron-specific enolase and beta-S-100. These nervous system-specific proteins are a family of calcium binding proteins that are involved in processes such as cell-to-cell communication, cell growth, intracellular signal transduction, and development and maintenance of the central nervous system.
Critical effect: Peripheral neuropathy (decreased MCV at 12 weeks) in male rats.
End point or Point of Departure (POD): POD = 215 mg/m^3. The neurophysiological deficits and histopathological effects that were evident in mid- and high-dose rats indicate a NOAEL of 500 ppm.
Uncertainty Factors: UF = 300, 10 for intraspecies variation, 3 each for interspecies extrapolation, extrapolation to chronic exposure, and database deficiencies. The subchronic study used for deriving the RfC is a 16-week study. However, 16 weeks is half of the time required for a newly synthesized neurofilament protein to be transported from the neuronal cell body to the axon terminal in the longest axons of the central nervous system and the peripheral nervous system of an adult rat (Griffin *et al*., 1984).
Source and Date: IRIS, 12/23/2005

Tier 2 Sources:
PPRTV: Per PPRTV (09/30/2009), a subchronic p-RfC of 2 mg/m^3 (2E+3 µg/m^3) was derived using

the same study and data as used by the U.S. EPA IRIS to derive the chronic RfC. A total UF of 100 was applied to derive the subchronic p-RfC (10 for intraspecies variability, 3 for intraspecies variability, and 3 for database deficiency). The critical effect was peripheral neuropathy. Updated literature searches did not reveal additional data beyond those that were evaluated in the previous IRIS assessment.

MRL: ATSDR (7/1999) chronic inhalation MRL = 0.6 ppm (= 2 mg/m^3 [based on 1 ppm = 3.52 mg/m^3] = 2E+3 µg/m^3)
Critical study: Sanagi, S. *et al*. (1980) Peripheral nervous system functions of workers exposed to n-hexane at a low level. Int. Arch. Occup. Environ. Health 47(1): 69-79.
Method(s): This is an epidemiology study on two age-matched groups consisting of 14 control workers and 14 exposed workers employed in a factory producing tungsten carbide alloys. Exposure was estimated with 22 personal samples taken from the breathing zones over a period of 2 years. The 8-hour time-weighted average exposure to solvent vapors consisted of n-hexane at 58±41 ppm and acetone at 39±30 ppm. The exposure duration ranged from 1 to 12 years, with an average of 6.2 years. Both groups completed questionnaires and underwent clinical neurological examinations and neurophysiological and nerve stimulation studies.
Critical Effect: neurotoxicity; reduced motor nerve conduction velocity in occupationally exposed workers
End point or point of departure (POD): The LOAEL was identified as 58 ppm.
Uncertainty factors: 100 (10 for LOAEL-to-NOAEL extrapolation, 10 for intraspecies variability).
Source and Date: ATSDR, 7/1999.

Tier 3 Source:
EGLE AQD: MDEQ, AQD ITSL = 700 ug/m^3 (24 hr. averaging time). Based on the U.S. EPAs RfC, from Huang *et al*. (1989) - a 16-week rat inhalation study that change motor nerve conduction velocity. BMDS methods were used to develop this RfC. AQD calculation date: 01/04/2006.

Cancer:
IRIS 12/23/2005:
WOE Characterization: There is inadequate information to assess the carcinogenic potential of n-hexane. Studies indicate that n-hexane is mostly nongenotoxic in short-term testing protocols. n-Hexane showed a minimal response in Saccharomyces cerevisiae D61.M (Mayer and Goin, 1994) and induced an increased incidence in the number of chromosomal mutations in albino rat bone marrow cells (Hazleton Laboratories, 1992). Also, the low pKa of exocyclic amino functional groups of DNA (<5) would preclude reaction with 2,5-hexanedione to yield pyrrole adducts. Thus, these data suggest a lack of mutagenic potential of n-hexane.

MERCURY, ELEMENTAL (CAS #7439-97-6) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	0.31 µg/m^3 (0.038 ppb$_{vol}$)	0.94 µg/m^3 (0.11 ppb$_{vol}$)
Basis	Hand tremor and increased memory disturbance, also considered protective for neurodevelopmental effects (Res AAC Noncancer – U.S. EPA IRIS RfC)	3 × Res AAC NC

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	0.92 µg/m^3 (0.11 ppb$_{vol}$)	2.8 µg/m^3 (0.34 ppb$_{vol}$)
Basis	Hand tremor and increased memory disturbance, also considered protective for neurodevelopmental effects (NR AAC$_{adj}$ NC)	3 × NR AAC$_{adj}$ NC

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs are based on the U.S. EPA's IRIS RfC of 0.3 µg/m^3, which is based on hand tremor and increased memory disturbance in workers. The U.S. EPA converted the LOAEL to a continuous exposure (LOAEL of 0.025 mg/m^3 x MVho/MVh x 5 days/7 days = 0.009 mg/ m^3 LOAEL$_{adj}$; where breathing volume for occupational exposure [MVho] = 10 m^3/day, breathing volume for a day [MVh] = 20 m^3/day). The RfC is very similar to the ATSDR chronic inhalation MRL of 0.2 µg/m^3, based on hand tremors in workers (LOAEL$_{adj}$ = 0.026 mg/m^3 x [8 hr/24 hr] x [5 days/7 days] = 0.0062 mg/m^3). The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure.

The RfC and chronic MRL values are basically equivalent; the only difference is how the U.S. EPA and ATSDR accounted for the less than 24-hour workday. Currently, the U.S. EPA adjusts based on inhalation volume and may be a more appropriate adjustment. It should be noted that elemental mercury is a developmental toxicant, and this value is protective of neurodevelopmental effects in fetuses and children. Additionally, these values also line up with screening levels used by MDHHS to respond to elemental mercury spills. Typically, after all elemental mercury sources are removed from a home, MDHHS typically considers that clean-up is complete when the source mercury has been removed and mercury levels in the indoor air drop below 1.0 µg/m^3. With all sources of elemental mercury removed, the air concentrations will drop to below the ATSDR chronic MRL within a few days. In occupational settings, cleanup is considered complete when all sources of mercury are

removed and the mercury levels in the indoor air are below 3 µg/m^3. In volatilization to indoor air scenarios, the indoor air concentrations may vary widely (see main text) with no mercury sources in the home to remove resulting in exposures that could be harmful to fetuses and children.

Uncertainties in the toxicity estimate:
The U.S. EPA RfC has an uncertainty factor of 10 for human variability and 3 for database deficiency (total of 30). The ATSDR chronic inhalation MRL includes an UF of 3 for a minimal LOAEL and a 10 for human variability (total of 30). Both the U.S. EPA and IARC have listed elemental mercury as not classifiable as to carcinogenicity.

Source of the Toxicity Values
IRIS: RfC = 3.0E-4 mg/m^3
Critical Studies:

1) Fawer, R.F., U. DeRibaupierre, M.P. Guillemin, M. Berode and M. Lobe. 1983. Measurement of hand tremor induced by industrial exposure to metallic mercury. J. Ind. Med. 40: 204-208.
2) Piikivi, L. and U. Tolonen. 1989. EEG findings in chlor-alkali workers subjected to low long-term exposure to mercury vapor. Br. J. Ind. Med. 46: 370-375.
3) Piikivi, L. and H. Hanninen. 1989. Subjective symptoms and psychological performance of chlorine-alkali workers. Scand. J. Work Environ. Health. 15: 69-74.
4) Piikivi, L. 1989. Cardiovascular reflexes and low long-term exposure to mercury vapor. Int. Arch. Occup. Environ. Health. 61: 391-395.
5) Ngim, C.H., S.C. Foo, K.W. Boey and J. Jeyaratnam. 1992. Chronic neurobehavioral effects of elemental mercury in dentists. Br. J. Ind. Med. 49: 782-790.
6) Liang, Y-X., R-K. Sun, Y. Sun, Z-Q. Chen and L-H. Li. 1993. Psychological effects of low exposure to mercury vapor: Application of a computer-administered neurobehavioral evaluation system. Environ. Res. 60: 320-327.

Method(s): Human occupational inhalation studies

1) Fawer *et al*. (1983) used a sensitive objective electronic measure of intention tremor (tremors that occur at the initiation of voluntary movements) in 26 male workers (mean age of 44 years) exposed to low levels of mercury vapor in various occupations: fluorescent tube manufacture (n=7), chloralkali plants (n=12), and acetaldehyde production (n=7). Controls (n=25; mean age of 44.6 years) came from the same factories but were not exposed occupationally. Personal air samples (two per subject) were used to characterize an average exposure concentration of 0.026 mg/m^3. It should be noted that it is likely that the levels of mercury in the air varied during the period of exposure and historical data indicate that previous exposures may have been higher. Exposure measurements for the control cohort were not performed. The average duration of exposure was 15.3 years.
2) Piikivi and Tolonen (1989) used electroencephalograms (EEGs) to study the effects of long-term exposure to mercury vapor in 41 chloralkali workers exposed for a mean of 15.6 +/- 8.9 years as compared with matched referent controls. They found that the exposed workers, who had mean blood Hg levels of 12 ug/L and mean urine Hg levels of 20 ug/L, tended to have an

increased number of EEG abnormalities when analyzed by visual inspection only.

3) Piikivi and Hanninen (1989) studied the subjective symptoms and psychological performances on a computer-administered test battery in 60 chloralkali workers exposed to mercury vapor for a mean of 13.7 ± 5.5 years as compared with matched referent controls. The exposed workers had mean blood Hg levels of 10 ug/L and mean urine Hg levels of 17 ug/L. Both subjective and objective symptoms of autonomic dysfunction were investigated in 41 chloralkali workers exposed to mercury vapor for a mean of 15.6 ± 8.9 years as compared with matched referent controls (Piikivi, 1989).
4) Ngim *et al*. (1992) assessed neurobehavioral performance in a cross-sectional study of 98 dentists (38 female, 60 male; mean age 32, range 24-49 years) exposed to TWA concentrations of 0.014 mg/m^3 (range 0.0007 to 0.042 mg/m^3) versus 54 controls (27 female, 27 male; mean age 34, range 23-50 years) with no history of occupational exposure to mercury. Air concentrations were measured with personal sampling badges over typical working hours (8-10 hours) and converted to an 8-hour TWA.
5) Liang *et al*. (1993) investigated workers in a fluorescent lamp factory with a computer-administered neurobehavioral evaluation system and a mood inventory profile. The exposed cohort (mean age 34.2 years) consisted of 19 females and 69 males exposed uninterruptedly for at least 2 years prior to the study. Exposure was monitored with area samplers and ranged from 0.008 to 0.085 mg/m^3 across worksites. No details on how the exposure profiles to account for time spent in different worksites were constructed. The average exposure was estimated at 0.033 mg/m^3 (range 0.005 to 0.19 mg/m^3). The average duration of working was 15.8 years for the exposed cohort.

Critical effect: Hand tremor, increases in memory disturbance, slight subjective and objective evidence of autonomic dysfunction

End point or Point of Departure (POD):

1) The TWA of 0.025 mg/m^3 was designated a LOAEL. Using the TWA and adjusting for occupational ventilation rates and workweek, the resultant LOAEL$_{HEC}$ is 0.009 mg/m^3.
2) The authors extrapolated an exposure level associated with these EEG changes of 0.025 mg/m^3 from blood levels based on the conversion factor calculated by Roels *et al*. (1987).
3) The authors extrapolated an exposure level associated with these subjective measures of memory disturbance of 0.025 mg/m^3 from blood levels based on the conversion factor calculated by Roels *et al*. (1987).
4) The authors extrapolated an exposure level associated with these subjective and objective measures of autonomic dysfunction of 0.030 mg/m^3 from blood levels based on the conversion factor calculated by Roels *et al*. (1987).
5) These neurobehavioral effects are consistent with central and peripheral neurotoxicity and the TWA is considered a LOAEL. Using the TWA and adjusting for occupational ventilation rates and the reported 6-day workweek, the resultant LOAEL$_{HEC}$ is 0.006 mg/m^3.
6) Based on these neurobehavioral effects, the TWA of 0.033 mg/m^3 is designated as LOAEL. Using the TWA and adjusting for occupational ventilation rates and workweek, the resultant LOAEL$_{HEC}$ is 0.012 mg/m^3.

CONCLUSION: The TWA level of 0.025 mg/m^3 was used to represent the exposure for the synthesis of the studies described above. Using this TWA and taking occupational ventilation rates and workweek into account results in a $LOAEL_{HEC}$ of 0.009 mg/m^3.
Uncertainty Factors: UF = 30, 10 for the protection of sensitive human subpopulations (including concern for acrodynia) and use of a LOAEL, and 3 for lack of database, particularly developmental and reproductive studies.
Source and Date: IRIS, 06/01/1995.

MRL: ATSDR (03/1999) MRL = 0.0002 mg/m^3 (= 0.2 µg/m^3)
Critical Study: Fawer RF, de Ribaupierre Y, Guillemin MP, *et al*. 1983. Measurement of hand tremor induced by industrial exposure to metallic mercury. Br. J. Ind. Med. 40:204-208.
Methods: Hand tremors were measured in 26 male workers exposed to metallic mercury and 25 control males working in the same facilities but not exposed to mercury. Workers had been exposed to mercury through the manufacture of fluorescent tubes, chloralkali, or acetaldehyde. Hg-exposed workers had a duration of exposure of 15.3 ± 2.6 years, blood Hg of 41.3 ± micromoles Hg/L, and urinary Hg of 11.3 ± 1.2 micromoles Hg/mole of creatinine. Mean Hg level measured using personal air monitors was 0.026± 0.0926 ± 0.004 mg/m^3 (3 subjects were exposed to greater than 0.05 mg/m^3.)
Critical Effects: Increased frequency of tremors
End Point or Point of Departure: LOAEL = 0.026 mg/m^3 (= 2.6E+1 µg/m^3).
Uncertainty Factors: UF = 30, 3 for use of a minimal LOAEL and 10 for human variability.
Source and Date: ATSDR, 03/1999

METHANOL (CAS #67-56-1) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	20,000 µg/m³ (15,000 ppb_{vol})	60,000 µg/m³ (46,000 ppb_{vol})
Basis	Reduced brain weight (Res AAC SE Developmental – U.S. EPA IRIS RfC)	3 × Res AAC Developmental

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	40,000 µg/m³ (31,000 ppb_{vol})	120,000 µg/m³ (92,000 ppb_{vol})
Basis	Reduced brain weight (NR AAC_{adj} SE Developmental – U.S. EPA IRIS RfC)	3 × NR AAC_{adj} Developmental

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for methanol are based on the chronic IRIS RfC of 2.0E+04 µg/m³. Both residential and nonresidential AACs are based on developmental effects that may result from a single event exposure during pregnancy. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on 20 hr/day exposures.

The IRIS RfC is based on two critical studies. The first study was a two-generational study conducted by NEDO which exposed F0 rats to 0, 10, 100, and 1,000 ppm of methanol vapor from 8 weeks of age for 20 hr/day. The F1 generation was exposed to the same concentrations from birth to the end of mating (males) or to weaning of F2 pups after delivery (females). The F2 generation were exposed from birth to 21 days old. There was a reduction in brain, pituitary, and thymus weights among F2 pups, and early testicular descent was observed in F0 and F1 males exposed to 1,000 ppm.

The second study explored the effects of inhalation exposure to methanol on pregnant mice. Pregnant CD-1 mice were exposed to 1,000, 2,000, 5,000, 7,500, 10,000, or 15,000 ppm of methanol vapors for 7 hr/day on days 6-15 of gestation. Significant increases in the incidence of exencephaly and cleft palate were observed at 5,000 ppm and above. A dose-related increase in cervical ribs or ossification sites lateral to the seventh cervical vertebra was significant at 2,000 ppm and above. The NOAEL for the developmental toxicity in this study was 1,000 ppm.

EGLE AQD (2013) derived a one-hour initial threshold screening level (ITSL) based on California acute REL of 28,000 µg/m³. The acute REL was derived from a free-standing NOAEL (a NOAEL

identified in a study that did not identify a LOAEL) of 250 mg/m^3 in which 12 volunteers were exposed to methanol vapor for 75 minutes (Cook, *et al*., 1991). Volunteers served as their own controls via sham exposures. The critical effect is neurological: sensory, behavioral, and reasoning performance were evaluated before, during, and after exposure. The acute ITSL is lower than the residential TS RIASL, nonresidential RIASL and TS RIASL. However, since the EGLE AQD ITSL is based on a free-standing NOAEL, it is not clear what exposure level causes adverse effects with acute exposures. As a result, the 1-hour ITSL should be referenced to be health protective of neurobehavioral effects from acute exposures of methanol, but it will not be the basis for the RIASLs.

Uncertainties in the toxicity estimate:
This calculation used animal data for the calculation of an RfC for the inhalational exposure pathway in humans, using UF = 100 (10 for human variability and 3 each for interspecies extrapolation and deficiencies in the toxicity database). The total UF of 100 was applied to the $POD_{internal}$ to obtain an $RfC_{internal}$, which was then converted to an RfC using the human PBPK model.

Source of the Toxicity Values
Noncancer:
IRIS RfC= 2.0E+04 µg/m^3
Basis: IRIS is a Tier 1 source. No Tier 2 available.
Critical Studies:

1) NEDO (New Energy Development Organization). 1987. Toxicological research of methanol as a fuel for power station: summary report on tests with monkeys, rats and mice. Tokyo, Japan.
2) Rogers, JM; Mole, ML; Chernoff, N; Barbee, BD; Turner, CI; Logsdon, TR; Kavlock, RJ. (1993b). The developmental toxicity of inhaled methanol in the CD-1 mouse, with quantitative dose-response modeling for estimation of benchmark doses. Teratology 47: 175-188.

Method(s):

1) F0, F1, and F2 rats were exposed to 0, 10, 100, or 1000 ppm of methanol during periods critical for gamete formation and fetal development. The brains of F2 rats were weighed and compared to unexposed weights.
2) Pregnant mice were exposed to 1,000, 2,000, 5,000, 7,500, 10,000, or 15,000 ppm of methanol vapors for 7 hr/day on days 6-15 of gestation. Cervical rib abnormalities were observed among the exposed pups.

Critical effect: Reduced brain weight
End point or Point of Departure (POD): $POD_{internal}$ = $BMDL_{1SD}$= $POD_{internal}$ = 858 mg-hr/L
Uncertainty Factors: UF = 100, 10 for human variability and 3 each for interspecies extrapolation and database deficiencies.
Source and Date: IRIS, 9/30/2013

Tier 3 source:
MDEQ: Per MDEQ-AQD (11/26/2013), the 24-hour AT ITSL is based upon the U.S. EPA inhalation RfC of 20 mg/m^3. The 1-hour ITSL is based on the California acute REL of 28,000 µg/m^3. The acute REL

was derived from a free-standing human NOAEL of 250 mg/m^3 in which volunteers were exposed to methanol vapor for 75 minutes (Cook, *et al*., 1991).

Tier 2 Sources:
PPRTV: No PPRTV record available at this time.
MRL: No MRL record available at this time.

Cancer:
Tier 1 and 2 Sources:
IRIS: Per IRIS (9/30/2013) no value available.
PPRTV: No PPRTV record available at this time.
MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Source:
EGLE: Per AQD, no value at this time.

4-METHYL-2-PENTANONE; METHYL ISOBUTYL KETONE (MIBK) (CAS #108-10-1) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	820 µg/m³ (200 ppb_{vol})	820 µg/m³ (200 ppb_{vol})
Basis	Central nervous system symptoms (EGLE, AQD Acute ITSL)	EGLE, AQD Acute ITSL

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	820 µg/m³ (200 ppb_{vol})	820 µg/m³ (200 ppb_{vol})
Basis	Central nervous system symptoms (EGLE, AQD Acute ITSL)	EGLE, AQD Acute ITSL

Discussion of Basis

The residential and nonresidential RIASLs and TS RIASLs for 4-methyl-2-pentanone are based on the EGLE, AQD acute ITSL of 820 µg/m³. The nonresidential RIASL and TS RIASL were not adjusted to a 12-hour work exposure time as the acute ITSL is based on an 8-hour averaging time.
No ATSDR acute or intermediate inhalation MRL values are available at this time.

The EGLE AQD ITSL is based on the ACGIH TLV for MIBK (MDEQ, 2016). In the ITSL documentation, it is noted that, "ACGIH (2010) summarized several human studies…to derive the TLV. One study found that at 200 mg/m³ (49 ppm) for two hours there was a statistical elevation in intensity of [central nervous system] CNS symptoms as reported on the 17-item questionnaire." Furthermore, the IRIS toxicological review indicates that the RfC may not be protective of health effects from acute exposures. To be health protective of both developmental effects and CNS effects, the acute ITSL is the basis for the RIASLs and TS RIASLs.

Uncertainties in the toxicity estimate:

The EGLE ITSL applies a default total UF of 100 to OELs to account for human variability (10) and exposure time between the worker and the general population (10). This default UF is used to derive the ITSL from a TLV, an occupational exposure limit (OEL).

Source(s) of the Toxicity Values

Tier 3 Source:
EGLE: AQD (2016) ITSL = 8.2E+02 µg/m³ with 8-hour averaging time.
Basis: While a Tier 1 source is available, the acute ITSL is protective of less than chronic exposures

and the IRIS (U.S. EPA 2003) toxicological review indicates that the RfC may not be protective of health effects from acute exposures.

Tier 1 Source:
Basis: IRIS is a Tier 1 source and based on a 1987 developmental study. No Tier 2 available.
IRIS RfC = 3 mg/m^3 (3.0E+3 µg/m^3)
Critical Study: Tyl, R.W. *et al*. (1987) Developmental toxicity evaluation of inhaled methyl isobutyl ketone in Fischer 344 rats and CD-1 mice. Fund. Appl. Toxicol. 8:310-327.
Methods: Developmental and maternal toxicity were evaluated in groups of 35 pregnant Fischer 344 rats and 30 pregnant CD-1 mice exposed by inhalational exposure to 0, 300, 1,000, or 3,000 ppm (0, 307, 1,026, 3,073 mg/m^3) MIBK for 6 hr/day on gestation days 6-15. Animals were sacrificed on gestation day 21 (rats) or day 18 (mice). Dams were evaluated for exposure-related changes in clinical signs, body weight, food consumption, organ weights (kidney, liver and gravid uterus), and reproductive parameters; fetuses were evaluated for exposure-related changes in body weight and viability and for external, skeletal, and thoracic and peritoneal visceral alterations.
Critical effect: Reduced fetal body weight, skeletal variations, and increased fetal death in mice, and skeletal variations in rats.
End point or Point of Departure (POD): NOAEL$_{HEC}$ = 1,026 mg/m^3 and LOAEL$_{HEC}$ = 3,073 mg/m^3.
Uncertainty Factors: UF = 300; 3 for interspecies extrapolation (10 not used because human equivalent concentration made);10 for intraspecies variability; and 10 for database deficiency based on the lack of developmental neurotoxicity data, definitive neurotoxicity data in , and the lack of any chronic toxicity data.
Source: IRIS, 04/25/2003

Tier 2 Sources:
PPRTV: No PPRTV value is available at this time.
MRL: No MRL record is available at this time.

Tier 3 Source:
EGLE: AQD (2016) ITSL = 8.2E+02 µg/m^3 with 8-hour averaging time.
Basis: ITSL is based upon an ACGIH TLV of 20 ppm (82 mg/m^3). ITSL = 82 mg/m^3 x 1,000 µg/mg = 82,000 µg/m^3 x 1% = 820 µg/m^3.
Method: ACGIH (2010) summarized several human studies used to derive the TLV. One study found that at 200 mg/m^3 (49 ppm) for two hours there was a statistical elevation in intensity of CNS symptoms as reported on the 17-item questionnaire.
Reference: ACGIH (2010). Methyl Isobutyl Ketone. Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Edition. Cincinnati, OH.
Source and Date: MDEQ-AQD, 5/31/2016

Developmental or Reproductive Effects:
For inhalation, the RfC is based on reproductive-developmental effects.

Inhalation Exposure Pathways - Single Exposure.

Cancer:
Tier 1 and 2 Sources:
IRIS: Per IRIS (04/25/2003), no quantitative estimate of carcinogenic risk from inhalation exposure was derived because no cancer epidemiology studies in humans and no carcinogenicity assays in animals were located.
PPRTV: No PPRTV value is available at this time.
MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Source:
MDEQ: Per MDEQ-AQD, no inhalation toxicity value available at this time.

METHYLENE CHLORIDE (CAS #75-09-2) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	630 µg/m³ (180 ppb_{vol})	1,000 µg/m³ (290 ppb_{vol})
Basis	Hepatic vacuolation in rats after chronic exposure (Res AAC Noncancer-U.S. EPA IRIS RfC)	Hepatic effects in rats after 90-day exposure (ATSDR MRL Intermediate Inhalation)

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	1,800 µg/m³ (530 ppb_{vol})	2,900 µg/m³ (830 ppb_{vol})
Basis	Hepatic vacuolation in rats after chronic exposure (NR AAC_{adj} Noncancer-U.S. EPA IRIS RfC)	Hepatic effects in rats after 90-day exposure (ATSDR MRL $Intermediate_{adj}$ Inhalation)

Discussion of Basis

The residential and nonresidential AACs and RIASLs for methylene chloride are based on the U.S. EPA's IRIS RfC of 600 µg/m³. The RfC was derived from a 2-year inhalation study, where male and female rats were exposed to 0, 50, 200 or 500 ppm methylene chloride for 6 hr/day, 5 days/week (U.S. EPA, 2011c). Physiologically based pharmacokinetic (PBPK) modeling was used to derive the point of departure for the critical effect of hepatic vacuolation. Methylene chloride is likely to be carcinogenic in humans and there is a U.S. EPA IRIS IURF based on hepatocellular or bronchoalveolar carcinomas and adenomas. However, the calculated cancer AAVs are higher than the noncancer AAVs.

The residential and nonresidential TS RIASLS are developed from the ATSDR intermediate inhalation MRL of 300 ppb (1,000 µg/m³). It is based on hepatic effects (cytoplasmic vacuolization and fatty infiltration in rats) and is also protective for kidney damage. A LOAEL of 25 ppm was identified from the continuous 90-day exposure study. For the purposes of developing nonresidential RIASLs for workplace scenarios, the intermediate MRL (1,000 µg/m³) was adjusted from continuous exposure to account for a five out of seven-day work week as the intermediate MRL addresses exposure greater than two weeks to less than a year. The adjusted intermediate MRL = 1,450 µg/m³.

The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC and intermediate inhalation MRL were based on continuous exposure concentration. No acute values are available at this time.

Uncertainties in the toxicity estimate:

The IRIS RfC is based on a PBPK model-derived point of departure, 17.2 mg/m^3 (U.S. EPA, 2011c). An UF of 3 ($10^{0.5}$) was used for interspecies extrapolation, an uncertainty factor of 3 ($10^{0.5}$) was used for interspecies extrapolation, and an UF of 3 was used for database deficiency.

The ATSDR intermediate inhalation MRL has a total uncertainty of 30, 10 for human variability and 3 for extrapolation from animals to human.

Source of the Toxicity Values

Chronic Inhalation Noncancer:
Basis: IRIS is a Tier 1 source.
IRIS: RfC = 6 x10^{-1} mg/m^3
Critical Study: Nitschke, KD; Burek, JD; Bell, TJ; *et al*. (1988a) Methylene chloride: a 2-year inhalation toxicity and oncogenicity study in rats. Fundam. Appl. Toxicol. 11:48–59.
Methods: Nitschke *et al*. (1988a) exposed groups of 90 male and 90 female Sprague-Dawley rats to 0, 50, 200, or 500 ppm dichloromethane (>99.5% pure) for 6 hr/day, 5 days/week for 2 years. Interim sacrifices were conducted at 6, 12, 15, and 18 months (five rats/sex/interval). A PBPK model for the rat (Andersen *et al*., 1991, modified by U.S. EPA) was used to estimate rat internal doses from the Nitschke *et al*. (1988a) study. The dose metric used to conduct the modeling was mg dichloromethane metabolized via the Cytochrome P450 (CYP) pathway/liter of liver tissue/day. Incidence data for hepatic effects (hepatic vacuolation) in the rat from Nitschke *et al*. (1988a) were fit to the available dichotomous models in BMDS version 2.0 (using internal dose as the dose measure) to obtain the rat internal $BMDL_{10}$. Because the dose metric is a rate of metabolism and the clearance of these metabolites may be slower per volume tissue in the human compared with the rat, this rodent internal dose metric was adjusted by dividing by a pharmacokinetic allometric scaling factor of body weight $(BW)^{0.75}$ (operationalized as $[BW_{human}/BW_{rat}]^{0.25} \approx 4.09$) to obtain a human equivalent internal $BMDL_{10}$.
Critical effect: Hepatic effects (hepatic vacuolation).
End point or Point of Departure (POD): $BMDL_{10}$(HEC) = 17.2 mg/m^3. The human equivalent internal $BMDL_{10}$ was then converted to the human equivalent concentration (HEC) using a human PBPK model (adapted from David *et al*., 2006) that provided a distribution of HECs. The 1st percentile of the distribution of HECs, 17.2 mg/m^3, was used as a POD for the RfC. See Section 5.2.3 of the Toxicological Review of Dichloromethane (U.S. EPA, 2011) for further details.
Uncertainty Factors: UF = 30, 3 for extrapolation from lab animals to humans, 3 for sensitive individuals, and 3 for database deficiencies.
Source and Date: IRIS, 11/18/2011

Intermediate Inhalation MRL:
Basis: ATSDR developed and intermediate (subchronic) inhalation MRL.
ATSDR intermediate inhalation MRL = 0.3 ppm (1.04 mg/m^3 [1.04E-03 µg/m^3])

Critical Study: Haun CC, Vernot EH, Darmer KI, *et al*. 1972. Continuous animal exposure to low levels of dichloromethane. AMRL-TR-72-130, paper no. 12.
Methods: Rats (20/group – no details on sex or strain) were exposed continuously for 14 weeks at 0, 25, or 100 ppm. Histopathological examination of the tissues was carried out and relative organ weights were determined at the end of the exposure. Cytoplasmic vacuolization and indication of fatty infiltration (positive-oil-red stain) were reported in animals exposed to 25 and 100 ppm.
Critical effect: hepatic effects - cytoplasmic vacuolization and fatty infiltration
End point or Point of Departure (POD): LOAEL(HEC) = 25 ppm
Uncertainty Factors: UF = 90, 3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, 10 for intraspecies [human] variability
Source and Date: ATSDR, 09/2000. From 3/2016 MRL list.

Cancer:
Basis: IRIS is a Tier 1 source.
Critical Studies:

1) Mennear, JH; McConnell, EE; Huff, JE; *et al*. 1988. Inhalation and carcinogenesis studies of methylene chloride (dichloromethane) in F344/n rats and B6C3F1 mice. Ann NY Acad. Sc. 534: 343–351.
2) NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of dichloromethane (methylene chloride) (CAS No. 75-09-2) in F344/N rats and B6C3F1 mice (inhalation studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR 306.

Methods: A 2-year inhalation exposure study in B6C3F1 mice, similar to that in F344/N rats, was also conducted by NTP. The mice (50/sex/exposure level) were exposed to dichloromethane (>99% pure) by inhalation at concentrations of 0, 2,000, or 4,000 ppm in exposure chambers 6 hr/day, 5 days/week for 2 years. As with the study in rats, mean daily concentrations in the mice never exceeded 110% of the target and were <90% of the target in only 23 of 1,476 analyses. Endpoints monitored included clinical signs, mortality, and gross and microscopic examinations of 32 tissues at study termination. Clinical examinations were conducted weekly for 3.5 months and biweekly until month 8. After 8 months, the animals were clinically examined and palpated monthly for tumors and masses until the end of the study.
Extrapolation Method: Multistage model with linear extrapolation from the point of departure ($BMDL_{10}$).
Tumor Types — Hepatocellular carcinomas or adenomas, bronchoalveolar carcinomas or adenomas
Carcinogen Weight-of-Evidence (WOE) Class: Likely to be carcinogenic in humans.
Basis: Following U.S. EPA (2005a) Guidelines for Carcinogen Risk Assessment, dichloromethane is "likely to be carcinogenic in humans," based predominantly on evidence of carcinogenicity at two sites in 2-year bioassays in male and female B6C3F1 mice (liver and lung tumors) with inhalation exposure (NTP, 1986) and at one site in male B6C3F1 mice (liver tumors) with drinking water exposure (Serota *et al*., 1986b; Hazleton Laboratories, 1983).
Source and Date: IRIS 11/18/2011

METHYL TERT-BUTYL ETHER (MTBE) (CAS #1634-04-4) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	98 µg/m³ (27 ppb_{vol})	980 µg/m³ (270 ppb_{vol})
Basis	Kidney adenomas and carcinomas, Leydig interstitial cell tumors, and leukemia and lymphomas (Res AAC Cancer – CalEPA IURF)	10 × Res AAC Cancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Levels	460 µg/m³ (130 ppb_{vol})	4,600 µg/m³ (1,300 ppb_{vol})
Basis	Kidney adenomas and carcinomas, Leydig interstitial cell tumors, and leukemia and lymphomas (NR AAC_{adj} Cancer – CalEPA IURF)	10 × NR AAC_{adj} Cancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for MTBE are based on the California EPA IURF. The IURF of 2.6E-07 per µg/m³ is based on an extrapolated CSF value of 2.6E-07 per µg/m³. This value was derived using the geometric mean of potency estimates for male rat kidney adenomas and carcinomas combined, male rat Leydig interstitial cell tumors, and leukemia and lymphomas in female rats from four oral and inhalation studies. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the IURF was based on continuous exposure concentration.

There is an ATSDR intermediate inhalation MRL for MTBE (2,500 µg/m³) based on neurotoxicity (central nervous system (CNS) sedation) in rats exposed to MTBE for 6 hr/day, 5-7 days/week for 14-19 weeks in a reproductive study (Neeper-Bradley, 1991).

Uncertainties in the toxicity estimate:

The CalEPA IURF was based on an oral CSF that used rat oral and inhalation data. The mode of action for MTBE carcinogenesis was not known and the parent compound MTBE was used for determining the dose metrics. The internal doses were estimated using a simplified PBPK model (Borghoff *et al*. 1996). For absorbed doses, 100% and 50% of oral and inhaled MTBE, respectively were the assumptions for uptake. A 70 kg human inhaling 20 m³ per day was used to extrapolate the IURF estimate. All these considerations and assumptions contribute to uncertainties in the cancer

potency estimate (OEHHA, 1999).

The ATSDR intermediate MRL is derived using a NOAEL for neurotoxicity (no CNS sedation) that was multiplied by 6 hour/24 hour/day and 5 days/7 days/week to yield an adjusted $NOAEL_{adj}$ of 71 ppm. A total uncertainty factor of 100 was applied to address interspecies extrapolation and intraspecies variability. A 13-week study (Dood, 1989) also showed neurotoxicity symptoms. In the absence of human data, developmental toxicity reported in animal studies indicates there may be a potential for developmental effects due to MTBE exposure.

Source of the Toxicity Values
Chronic Inhalation Noncancer:
IRIS (09/01/1993): RfC = 3.0E+0 mg/m^3 (3E+3 $\mu g/m^3$)
Critical Study: 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.
Method: Fischer 344 rats (50/sex/group) were exposed to analytical mean concentrations of 403, 3,023, or 7,977 ppm MTBE vapors (1,453, 10,899, or 28,760 mg/m^3) 6 hr/day, 5 days/week for 24 months (duration-adjusted values are 259, 1946, 5136 mg/m^3, respectively).
Critical effect: Increased absolute and relative liver and kidney weights and increased severity of spontaneous renal lesions (females), increased prostration (females) and swollen periocular tissue (males and females).
Point of Departure (POD): NOAEL = 1,453 mg/m^3 (403 ppm); $NOAEL_{adj}$ = 259 mg/m^3; NOAEL(HEC) = 259 mg/m^3.
Uncertainty Factors: UF = 100, 10 for intraspecies variability, 3 for interspecies extrapolation rather than 10 because dosimetric adjustments were made, and 3 for database deficiencies because of the lack of certain information from the chronic exposure bioassay.
Source: IRIS, 9/01/1993

PPRTV: No PPRTV record for MTBE is available at this time.

ATSDR chronic MRL (07/1996): Chronic inhalation MRL = 7E-1 ppm (= 2.5 mg/m^3 = 2.5E+3 $\mu g/m^3$)
Critical study: Chun *et al*., (1992) Methyl tertiary butyl ether: Vapor inhalation oncogenicity study in Fischer 344 rats. Bushy Run Research Center, Export, PA. Project No. 91N0013B.
Method: Fischer 344 rats (50/sex/group) were exposed to 0, 400, 3,000, or 8,000 ppm MTBE 6 hr/day, 5 days/week for up to 24 months. (Conversion: 1 ppm = 3.61 mg/m^3).
Critical effect: Chronic progressive nephropathy
Point of departure (POD): NOAEL = 400 ppm; The NOAEL was multiplied by 6 hour/24 hour/day and 5 days/7 days/week to yield a $NOAEL_{adj}$ of 71 ppm.
Uncertainty factors: 100, 10 each for interspecies extrapolation and intraspecies variability
Source and Date: ATSDR, 7/1996

Intermediate Inhalation Noncancer:
MRL (07/1996): Intermediate inhalation MRL = 7E-1 ppm (= 2.5 mg/m^3 = 2.5E+3 µg/m^3)
Critical study: Neeper-Bradley, (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.
Method: Rats (25/sex/group) were exposed to 0, 400, 3,000, or 8,000 ppm MTBE 6 hr/day, 5 days/week for 10 days prior to mating through gestation day 19.
Critical effect: Chronic progressive nephropathy
Point of departure (POD): NOAEL = 400 ppm; The NOAEL was multiplied by 6 hour/24 hour/day and 5 days/7 days/week to yield a $NOAEL_{adj}$ of 71 ppm.
Uncertainty factors: 100, 10 each for interspecies extrapolation and intraspecies variability
Source and Date: ATSDR, 7/1996

Acute Inhalation Noncancer:
MRL (1996): Acute inhalation MRL = 2 ppm (= 2.5 mg/m^3 = 7.21E+3 µg/m^3) based on neurological effects.
Critical study: Gill, 1989
Method: Fischer 344 rats (22/sex/group) were exposed to 0, 800, 4,000, or 8,000 ppm MTBE for six hr.
Critical effect: No CNS sedation
Point of departure (POD): NOAEL = 800 ppm; The NOAEL was multiplied by six hour/24 hr to yield a $NOAEL_{adj}$ of 200 ppm.
Uncertainty factors: 100, 10 each for interspecies extrapolation and intraspecies variability
Source and Date: ATSDR, 1996

Cancer:
IRIS (12/01/1991): A cancer assessment for MTBE is not available at this time.
PPRTV: No PPRTV record for MTBE is available at this time.
MRL: NA; MRLs are for noncancer effects only.

CalEPA: IURF = 2.6E-07 $(\mu g/m^3)^{-1}$. The IURF was extrapolated from an oral CSF value.
Critical Studies for CSF:

1) Belpoggi F, Soffritti M, Maltoni C. 1998. Pathological characterization of testicular tumours and lymphomas-leukaemias, and of their precursors observed in Sprague-Dawley rats exposed to methyl tertiary-butyl ether (MTBE). Eur. J. Oncol. 3(3): 201-206.
2) Belpoggi F, Soffritti M, Maltoni C (1995). Methyl tertiary-butyl ether (MtBE) - a gasoline additive - causes testicular and lymphohaematopoietic cancers in rats. Toxicol. Ind. Hlth. 11(2): 119-149. March.
3) Belpoggi F, Soffritti M, Filippini F, Maltoni C. 1997. Results of long-term experimental studies on the carcinogenicity of methyl tert-butyl ether. Annals N. Y. Acad. Sci. 837: 77-95.

December 26.
4) Chun JS, Burleigh-Flayer HD and Kintigh WJ. 1992. Methyl tertiary ether: vapor inhalation oncogenicity study in Fisher 344 rats. Bushy Run Research Center Report No. 91N0013B. Union Carbide Chemicals and Plastics Company, Inc. submitted to the United States Environmental Protection Agency under TSCA Section 4 Testing Consent Order 40 CFR 799.5000 with cover letter dated November 19, 1992. EPA/OPTS#42098.

Methods:
The CSF was the geometric mean of the potency estimates for the male rat kidney adenomas and carcinomas combined (1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$) (Chun *et al*. 1992), and the male rat Leydig interstitial cell tumors (1.55×10^{-3} $(mg/kg\text{-}day)^{-1}$) and the leukemia and lymphomas in female rats (2.09×10^{-3} $(mg/kg\text{-}day)^{-1}$) (Belpoggi *et al*. 1995, 1998). The combined data yielded a CSF of 1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$. Assuming a 70 kg human inhaling 20 m^3 per day, the oral CSF was converted to an inhalation cancer unit risk factor or URF of 9.3×10^{-7} ppb^{-1}, or 2.6E-7 $(\mu g/m^3)^{-1}$.
Source and Date: CalEPA OEHHA, 1999

New Jersey DEP: IURF = 2.6E-7 $(\mu g/m^3)^{-1}$. Based on OEHHA (CalEPA).
New York DEC: IURF = 2.6E-7 $(\mu g/m^3)^{-1}$. Based on OEHHA (CalEPA).
Texas CEQ: IURF = 2.6E-7 $(\mu g/m^3)^{-1}$. Based on OEHHA (CalEPA).

U.S. EPA RSL: IURF = 2.6E-7 $(\mu g/m^3)^{-1}$. Based on OEHHA (CalEPA).
Other Tier 3 Sources: No value is available at this time from these Tier 3 sources/databases: HEAST, NTP ROC, health and environmental agencies of Massachusetts, Minnesota, WHO (IARC), WHO (IPCS/INCHEM), Canada, The Netherlands (RIVM), OECD HPV, and ECHA (REACH).

PROPYL ALCOHOL (CAS #71-23-8) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	2,500 µg/m³ (1,000 ppb_{vol})	2,500 µg/m³ (1,000 ppb_{vol})
Basis	Sensory irritation (EGLE, AQD Acute ITSL)	(EGLE, AQD Acute ITSL)

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	2,500 µg/m³ (1,000 ppb_{vol})	2,500 µg/m³ (1,000 ppb_{vol})
Basis	Sensory irritation (EGLE, AQD Acute ITSL)	(EGLE, AQD Acute ITSL)

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for propyl alcohol are based on the EGLE (2019) acute ITSL of 2.5E+3 µg/m³. Since the averaging time for the acute exposure is 8 hours, less than 12 hours, the nonresidential RIASL and TS RIASL were not adjusted to a 12-hour work exposure time.

The acute ITSL is based on the Threshold Limit Value (TLV) of 246 mg/m³ pursuant to AQD Rule 336.1232 (1)(c). The TLV is "based on animal models of sensory irritation and on the structure activity relationship to 2-propanol" (ACGIH, 2007).

Uncertainties in the toxicity estimate:

The EGLE ITSL applied a default total UF of 100 to account for human variability (10) and exposure time between the worker and the general population (10). This default uncertainty factor is used to derive the initial threshold screening level from a TLV, an occupational exposure limit (OEL).

Source of the Toxicity Values

Noncancer:
EGLE:
Basis: No Tier 1 or Tier 2 values available. The EGLE (2019) value, a Tier 3 source, is selected because it represents the most current assessment. The value is based on acute effects, which is also protective of systemic effects including developmental effects. Massachusetts is a 1990 assessment and Minnesota source and basis are not available. See details below:

Tier 3 Sources:

EGLE: AQD (5/8/2019) updated ITSL = 2,500 or 2.5E+3 µg/m³ (8-hour averaging) based on the Threshold Limit Value (TLV) of 246 mg/m³ pursuant to AQD Rule 336.1232 (1)(c). The TLV is based on acute toxicity data.

Justification and ITSL Derivation: Per AQD (2019), the unadjusted TLV is expected to be health protective for developmental effects, because the TLV documentation states, "Based on comparisons of n-propanol studies in rats, Nelson *et al*. concluded that n-propanol was neither a selective developmental toxin nor would exposure to this material place human females at risk for alcohol-induced birth defects who are occupationally exposed at concentrations no greater than 200 ppm 8-hour TWA" (Nelson *et al*., 1990; ACGIH, 2007). While the derivation for the TLV itself is not known, the TLV support documentation further states that the TLV is "based on animal models of sensory irritation and on the structure activity relationship to 2-propanol" (ACGIH, 2007). This has been previously noted as a major limitation of the TLV, since it is based on acute toxicity data and a chemical structure comparison instead of a chemical-specific repeated study (MDNR, 1992). Especially considering the differences in relative potencies and critical effects, use of chemical structure comparisons without clear, detailed documentation of the rationale is a limitation of the TLV. *However, protection against the acute effects seems most appropriate given the potential for portal of entry effects, irritancy, and developmental effects.*

$$\text{ITSL} = \frac{\text{OEL}}{100}$$

$$\text{potential ITSL} = \frac{246\ {}^{\text{mg}}/_{\text{m}^3}}{100} \times \frac{10^3 \mu\text{g}}{\text{mg}} = 2{,}460\ \frac{\mu\text{g}}{\text{m}^3} \approx 2{,}500\ \frac{\mu\text{g}}{\text{m}^3}\text{, 8 hour averaging time}$$

Source and Date: EGLE/AQD, 5/8/2019

Massachusetts DEP: TEL/AAL = 133.63 µg/m³. The Ambient Air Limits (AAL) and Threshold Effect Exposure Limit (TEL) for propyl alcohol were last updated in 1990.
Source and date: Massachusetts Ambient Air Guidelines Table, January 2015

Minnesota PCA/DH: Noncancer chronic air concentration = 1200 µg/m³. The source and basis are not available.

ECHA (REACH): Inhalation DNEL = 80 mg/m³. The Derived No Effect Level is based on a 90-day repeated toxicity study.
Critical Study: OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day) 1981
Methods: Wistar rats were exposed to propyl alcohol vapors via nose-only inhalation. A NOAEL of 8000 mg/m³ air (nominal) was observed. There were no significant adverse effects at the highest tested concentration (8000 mg/m³).
Source and Date: EU Risk Assessment Report, CAS No. 71-23-8: Propan-1-ol, Vol. 82 (2008).

Tier 1 and 2 Sources:
IRIS: No IRIS file is available at this time.
PPRTV: Per PPRTV (5/1/2007), there are no chronic inhalation toxicity studies of n-propyl alcohol available. Derivation of a chronic RfC is precluded by the lack of suitable data.
MRL: No MRL record is available at this time.

Other Tier 3: No value is available at this time from these Tier 3 sources/databases: HEAST, NTP ROC, health and environmental agencies of California, New Jersey, New York, and Texas, and WHO (IARC), WHO (IPCS/INCHEM), Canada, The Netherlands (RIVM) and OECD HPV.

Cancer:
Carcinogen Weight-of-Evidence (WOE) Class: available data are inadequate for an assessment of human carcinogenic potential Source and Date: PPRTV, 5/1/2007

Tier 1 and 2 Sources: IRIS: No IRIS file is available at this time.
PPRTV: Per PPRTV (5/1/2007), no value at this time.
MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Sources:
EGLE: Per AQD, no value at this time.

N-PROPYLBENZENE (CAS # 103-65-1) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	1,000 µg/m³ (200 ppb_{vol})	3,000 µg/m³ (610 ppb_{vol})
Basis	Reduced number of live fetuses and skeletal malformations (Res AAC SE Developmental – PPRTV)	3 × Res AAC Developmental

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Levels	1,000 µg/m³ (200 ppb_{vol})	3,000 µg/m³ (610 ppb_{vol})
Basis	Reduced number of live fetuses and skeletal malformations (NR AAC SE Developmental – PPRTV)	3 × NR AAC Developmental

Discussion of Basis

The residential and nonresidential AACs, RIASL, and TS RIASL for n-propylbenzene are based on a 2009 PPRTV chronic RfC.

The RfC of 1.0+03 µg/m³ is based on U.S. EPA IRIS ethylbenzene RfC surrogate from developmental toxicity studies (Andrew *et al*. 1981; Hardin *et al*. 1981). Because the IRIS RfC (for ethylbenzene) is based on developmental studies, the same value is recommended as a screening subchronic RfC. The first study exposed Wistar rats (n=78-107/concentration) and New Zealand white rabbits (n=29/concentration) via inhalation to concentrations of 0, 100, or 1,000 ppm (434 or 4,342 mg/m³) for 6-7 hr/day, 7 days/week during days 1-19 and 1-24 of gestation. The second study exposed groups of female rats pregestationally for 3 weeks prior to mating and exposure was continued into the gestational period. All pregnant animals were sacrificed 1 day prior to term (21 days for rats; 30 days for rabbits). Maternal organs were histopathologically examined and fetuses were sexed, measured, and checked for internal and skeletal abnormalities.

The nonresidential RIASL and TS RIASL were not adjusted to a 12-hour work exposure time as the developmental NOAEL (basis for RfC) was not adjusted for continuous exposure.

Uncertainties in the toxicity estimate:
No chronic, subchronic, developmental, or reproductive toxicity studies conducted by the inhalation route of exposure were located for *n*-propylbenzene. Evaluation of available data for ethylbenzene and isopropyl benzene supported the former as a stronger surrogate for n-propyl benzene (PPRTV

2009). The total uncertainty factor is 300, where 10 accounts for intraspecies variation, 3 accounts for interspecies extrapolation, and 10 for database deficiencies (lack of multigenerational reproductive and chronic studies).

Source of the Toxicity Values

Noncancer:
RfC/ITSL = 1E+03 µg/m^3
Basis: PPRTV as a Tier 3 source. No Tier 1 and 2 available. MDEQ (1994) is based on a LD_{50} value. Minnesota also adopted the PPRTV screening value. Both New York and Texas used isopropylbenzene (cumene) as chemical surrogate. See details below.

Per PPRTV (2009), due to a lack of data, no chronic or subchronic RfCs are developed. Based on their analysis, PPRTV determined that ethylbenzene is the stronger surrogate candidate:

- For ethylbenzene, IRIS provides a chronic RfC of 1E+0 mg/m^3 (1E+3 µg/m^3) based on Andrews *et al*. (1981) and Hardin *et al*. (1981) for developmental toxicity. Subsequent developmental toxicity studies support the results of these earlier studies. Because the IRIS RfC (for ethylbenzene) is based on developmental studies, the same value (1E+0 mg/m^3) is recommended as a subchronic RfC. A chronic screening value RfC of 1E+0 mg/m^3 is recommended for n-propylbenzene.
- The subchronic ototoxicity study by Gagnaire *et al*. (2007) suggests that ototoxicity may be the most sensitive endpoint for inhalation exposure to ethylbenzene. However, at this time, the best available information supports utilization of the existing IRIS values.

Source and Date: PPRTV, 2/4/2009

IRIS (3/1/1991) RfC = 1E+0 mg/m^3 (1E+03 µg/m^3) for ethylbenzene:
Critical Studies:

1) Andrew, F.D., R.L. Buschbom, W.C. Cannon, R.A. Miller, L.F. Montgomery, D.W. Phelps, *et al*. 1981. Teratologic assessment of ethylbenzene and 2- ethoxyethanol. Battelle Pacific Northwest Laboratory, Richland, WA. PB 83- 208074, 108.
2) Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(Suppl 4):66–75.

Methods: Wistar rats (n=78-107/concentration) and New Zealand white rabbits (n=29-30/concentration) were exposed 6-7 hr/day, 7 days/week during days 1-19 and 1-24 of gestation, respectively, to nominal concentrations of 0, 100, or 1,000 ppm (434 or 4,342 mg/m^3) by inhalation. A separate group of rats was exposed pregestationally for 3 weeks prior to mating and exposure was continued into the gestational period. Actual concentrations were within 10% of target concentrations. All pregnant animals were sacrificed 1 day prior to term (21 days for rats; 30 days for rabbits).
Critical Effect: Developmental toxicity

End point or Point of Departure (POD): NOAEL = 434 mg/m^3 (100 ppm)
Uncertainty Factors: UF = 300, 10 for intraspecies variability, 3 for interspecies extrapolation, and 10 for database deficiencies (absence of multigenerational reproductive and chronic studies)
Source and Date: IRIS, 3/1/1991 for ethylbenzene (100-41-4)

Tier 1 and 2 Sources:
IRIS: No IRIS file available for n-propylbenzene at this time.
PPRTV (2/4/2009): Per PPRTV, no chronic or subchronic RfD at this time. A screening value is available.
MRL: No MRL record available at this time.

Other Tier 3 Sources:
MDEQ-AQD (1994): MDEQ/AQD ITSL = 20 µg/m^3. ITSL based on rat LD_{50} of 6,040 mg/kg reported by Jenner *et al*. (1964). The ITSL was calculated from this LD_{50} by the equation from Rule 232(1)(h) with annual averaging.
Critical study: Jenner *et al*. 1964. Food flavoring and compounds of related structure. Acute oral toxicity. Food Cosmet. Toxicol. 2:327-343.
Methods:
End point: LD_{50} = 6,040 mg/kg
Source and Date: MDEQ-AQD, 11/10/1994

Minnesota PCA: RfC= 1.00E+00 mg/m^3 based on PPRTV 2/7/2009.
New York DEC: RfC= 400 µg/m^3 based on based on the IRIS 2004 value for isopropylbenzene as a surrogate. A reference concentration is available for isopropylbenzene, which is structurally and chemically similar to n-propylbenzene. The similarity between the two chemicals provides a basis for using toxicity data for isopropylbenzene to represent n-propylbenzene. (Toxicity value recommendation: July 2004)
Source and Date: New York State Brownfield Cleanup Program, Development of Soil Cleanup Objectives: Technical Support Document, 2006, Appendix A p2 p.A-644.
Texas CEQ: RfC= 4.0E-01 mg/m^3 (4.0E+2 µg/m^3)
Justification: N-Propylbenzene is structurally similar to Cumene, which has an IRIS RfC. Cumene is used as a surrogate for n-propylbenzene.
Source and Date: TCEQ 7/22/2003 Assessment of n-Propylbenzene (In TCEQ Communication, 2015)

Other Tier 3: No value is available at this time from these Tier 3 sources/databases: HEAST, NTP ROC, health and environmental agencies of California, Massachusetts and New Jersey, Canada, The Netherlands (RIVM), WHO (IARC), WHO (IPCS/INCHEM), ECHA (REACH) and OECD HPV.

TETRACHLOROETHYLENE, PERCHLOROETHYLENE (PCE) (CAS #127-18-4) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	41 µg/m^3 (6.0 ppb$_{vol}$)	41 µg/m^3 (6.0 ppb$_{vol}$)
Basis	Neurotoxicity (reaction time, cognitive effects; color vision) in occupationally exposed adults (ATSDR MRL Acute Inhalation, U.S. EPA IRIS RfC)	ATSDR MRL Acute Inhalation

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Levels	82 µg/m^3 (12 ppb$_{vol}$)	82 µg/m^3 (12 ppb$_{vol}$)
Basis	Neurotoxicity (reaction time, cognitive effects; color vision) in occupationally exposed adults (ATSDR MRL Acute$_{adj}$ Inhalation)	ATSDR MRL Acute$_{adj}$ Inhalation

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for PCE are based on the ATSDR acute inhalation MRL (41 µg/m^3). The intermediate and chronic MRL are also equal to 41 µg/m^3. The acute MRL is based on a human occupational study (Cavalleri, *et al*., 1994). Per ATSDR (2014), color vision was evaluated in 35 PCE-exposed workers (22 dry cleaners and 13 ironers) with an average of 106 months of exposure. There also is an U.S. EPA IRIS RfC available (40 µg/m^3) based on two studies, one of which was the study used to derive the acute MRL (Cavalleri, *et al*.,1994; Echeverria, *et al*., 1995). The midpoint from the two studies' candidate RfCs was used as the final RfC (IRIS, 2012). The critical effects are neurotoxicity (reaction time, cognitive effects, and color vision) in occupationally exposed adults.

The calculated 24-hour residential and nonresidential risk-based AAVs based on the IRIS RfC (42 and 62 µg/m^3, respectively) are higher than the acute MRL. Therefore, the PCE residential RIASL and TS RIASL are based on the acute MRL of 41 µg/m^3.

Although the IRIS RfC and acute MRL are the same, it is important to use the acute MRL as the basis for the action levels as it represents a 1-14 day short-term exposure. Further studies supporting an acute MRL value include three human exposure studies (Hake and Stewart, 1977; Altmann 1990,

1992) that reported neurological deficiencies following PCE exposures ranging from 4 – 7.5 hours for 4 – 5 days (see PCE Tox Profile MRLs for further detail). Furthermore, although the critical effect is neurotoxicity, information concerning neurological, developmental, and immunological effects is lacking to provide evidence that a more susceptible population is indeed not at risk of short-term effects. Per IRIS (2012), immunotoxicity is associated with other chemicals that are structurally similar to PCE, and therefore this adds a layer of concern for short-term exposures of susceptible subpopulations (e.g., children, pregnant women).
The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the point of departure (LOAEL) was adjusted to a continuous exposure concentration. See below.

Uncertainties in the toxicity estimate:

The ATSDR acute inhalation MRL was estimated using a LOAEL (Cavalleri, 1994) and total UFs of 100 for human variability and for use of a LOAEL. Altman (1990) identified a NOAEL of 2 ppm, which is almost equal to the LOAEL of 1.7 ppm; however, ATSDR indicated the uncertainty of this NOAEL in adequately protecting for longer exposures (up to two weeks) as other studies indicated that continuous or repeated exposures over durations longer than four days may yield higher blood levels. Therefore, ATSDR concluded that "the chronic-duration LOAEL of 1.7 ppm (continuous equivalent exposure concentration) from Cavalleri (1994) may represent a better basis for acute and intermediate-duration MRLs. "In addition, simulation demonstrated that steady-state is reached at about 2 weeks of continuous exposure and 99% of steady-state at 90 days and the blood concentration-time values are "very similar" for acute and chronic exposure, therefore, ATSDR used the chronic MRL as the acute-duration MRL.

Source of the Toxicity Values

Chronic Inhalation Noncancer:
IRIS:
Basis: IRIS is a Tier 1 source.
IRIS tetrachloroethylene RfC= 4.0E+1 µg/m^3.
Critical Studies:

1) Echeverria, D; White, RF; Sampaio, C. 1995. A behavioral evaluation of PCE exposure in patients and dry cleaners: A possible relationship between clinical and preclinical effects. J Occup Environ Med 37: 667-680.
2) Cavalleri, A; Gobba, F; Paltrinieri, M; Fantuzzi, G; Righi, E; Aggazzotti, G. 1994. Perchloroethylene exposure can induce color vision loss. Neurosci Lett 179: 162-166. http://dx.doi.org/10.1016/0304-3940 (94)90959-8.

Methods:

1) Echeverria *et al*. (1995) examined 65 dry cleaners in Detroit, MI, using a standardized neurobehavioral battery.
2) Cavalleri *et al*. (1994) tested the color vision among 35 dry cleaning and laundry workers compared to 35 controls matched on age, alcohol consumption, and smoking. The candidate

RfCs from these two studies ranged from 0.015 to 0.056 mg/m^3. The RfC, 0.04 mg/m^3, is the midpoint of this range rounded to one significant figure.

Critical effect: 1) neurotoxicity (reaction time, cognitive effects) in occupationally exposed adults, and 2) neurotoxicity (color vision) in occupationally exposed adults

End point or Point of Departure (POD): 1) $LOAEL_{HEC}$ = 56 mg/m^3, 2) $LOAEL_{HEC}$ = 15 mg/m^3

Uncertainty Factors: UF = 1, 000, 10 each for intraspecies variability, LOAEL to NOAEL extrapolation and database deficiencies

Source and Date: IRIS, 02/10/2012. An IRIS Toxicological Review is available.

MRL: ATSDR List (12/2014) chronic inhalation MRL = 6.0E-3 ppm (41 µg/m^3)

Critical Studies:

1) Cavalleri A; Gobba F; Paltrinieri M; *et al*. 1994. Perchloroethylene exposure can induce color vision loss. Neurosci. Lett. 179:162-166.
2) Gobba F; Righi E; Fantuzzi G; *et al*. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. Arch. Environ. Health 53:196-198.

Methods: Color vision was evaluated in 35 tetrachloroethylene-exposed workers (22 dry cleaners and 13 ironers) with an average of 106 months of exposure. Concentrations were measured in the breathing zone by personal passive samplers. The TWA concentrations for all workers ranged from 0.38–31.19 ppm, with mean exposures of 6.23, 7.27, and 4.80 ppm for all workers, dry cleaners, and ironers, respectively. Controls included an equal number (35) of workers without occupational exposure to solvents, and were matched for sex, age, alcohol consumption, and cigarette smoking. The subjects were reexamined 2 years later using the same test; results were reported by Gobba *et al*. (1998).

Critical effect: increased CCI scores (decreased color vision)

End point or Point of Departure (POD): LOAEL = 1.7 ppm. The 7.3 ppm concentration was multiplied by 8/24 hours and 5/7 days to yield an equivalent continuous exposure concentration of 1.7 ppm.

Uncertainty Factors: UF = 100, 10 each for intraspecies variability and use of a LOAEL; MF = 3 for database deficiencies

Source and date: ATSDR, 2019 from 4/2015 MRL list.

Acute Inhalation Noncancer:

MRL: ATSDR (12/2014) acute inhalation MRL = 6.0E-3 ppm

Critical Study: Cavalleri A; Gobba F; Paltrinieri M; *et al*. 1994. Perchloroethylene exposure can induce color vision loss. Neurosci. Lett. 179:162-166.

Methods: Color vision was evaluated in 35 tetrachloroethylene-exposed workers (22 dry cleaners and 13 ironers) with an average of 106 months of exposure. Concentrations were measured in the breathing zone by personal passive samplers. The TWA concentrations for all workers ranged from 0.38–31.19 ppm, with mean exposures of 6.23, 7.27, and 4.80 ppm for all workers, dry cleaners, and ironers, respectively. Controls included an equal number (35) of workers without occupational exposure to solvents, and were matched for sex, age, alcohol consumption, and cigarette smoking. Color vision was evaluated by the Lanthany 15 Hue desaturated panel (D-15d) test, which is designed for early detection of acquired dyschromatopsia. The results of the test were expressed as

color confusion index (CCI). The subjects were reexamined 2 years later using the same test; results were reported by Gobba
et al. (1998).
Critical effect: increased CCI scores (decreased color vision)
End point or Point of Departure (POD): LOAEL = 1.7 ppm. The 7.3 ppm concentration was multiplied by 8/24 hours and 5/7 days to yield an equivalent continuous exposure concentration of 1.7 ppm.
Uncertainty Factors: UF = 100, 10 each for intraspecies variability and use of a LOAEL; MF = 3 for database deficiencies
Source and date: ATSDR, 10/14 from 2019 MRL list

Cancer:
IRIS:
Basis: IRIS is a Tier 1 source.
IRIS tetrachloroethylene IURF= 3.0E-7 $(\mu g/m^3)^{-1}$
Critical Studies: JISA (Japan Industrial Safety Association). 1993. Carcinogenicity study of tetrachloroethylene by inhalation in rats and mice. Hadano, Japan.
Method(s): 2-year (104-week) carcinogenicity study; F344DuCrj (Fischer) rats and Crj:BDF1 mice (400 rats and 400 mice) were used in a total of four groups, three study sample treatment groups and one control group, of 50 males and females each. Based on two-week and 13-week preliminary studies, the concentration was set at 600 ppm, 200 ppm and 50 ppm in rats and 250 ppm, 50 ppm, and 10 ppm in mice, and administered for 6 hr/day, 5 days a week for 104 weeks.

1) *Dose response data*: *Tumor Type* - Hepatocellular adenomas or carcinomas; *Test Species* - Male Crj:BDF1 mice; *Route* – inhalation
2) *Extrapolation method*: Multistage model (with linear extrapolation from the point of departure ($BMCL_{10}$), followed by extrapolations to humans using the PBPK model of Chiu and Ginsberg (2011)

Carcinogen Weight-of-Evidence (WOE) Class: "likely to be carcinogenic in humans by all routes of exposure."
Basis: IRIS WOE: based on suggestive evidence of carcinogenicity in epidemiologic studies and conclusive evidence that the administration of PCE, either by ingestion or by inhalation to sexually mature rats and mice, increases tumor incidence.
Source and Date: IRIS, 02/10/2012. An IRIS Toxicological Review is available.

TOLUENE (CAS #108-88-3) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	5,200 µg/m³ (1,400 ppb_{vol})	7,500 µg/m³ (2,000 ppb_{vol})
Basis	Neurological impairments from multiple occupational studies with chronic exposure (Res AAC Noncancer – U.S. EPA IRIS RfC)	Cognitive impairments in toluene sensitive people after 20 minutes (ATSDR MRL Acute Inhalation)

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Levels	7,500 µg/m³ (2,000 ppb_{vol})	7,500 µg/m³ (2,000 ppb_{vol})
Basis	Cognitive impairments in toluene sensitive people after 20 minutes (ATSDR MRL Acute Inhalation)	ATSDR MRL Acute Inhalation

Discussion of Basis

The residential AAC and RIASL for toluene is based on the U.S. EPA IRIS RfC of 5,000 µg/m³. The residential TS RIASL and nonresidential AAC, RIASL, and TS RIASL are based on the ATSDR acute inhalation MRL.

The U.S. EPA IRIS RfC of 5 mg/m³ (5,000 µg/m³ or 2,000 ppb_v is derived from ten occupational studies demonstrating deficits in neurological function after years (1-21 years) of worker exposure.

The ATSDR chronic inhalation MRL is based on a single series of occupational studies that had a NOAEL of 45 ppm determined but no adverse effects observed. The NOAEL used by ATSDR is higher than the NOAEL of 34 ppm used for the U.S. EPA IRIS RfC that is based on an average NOAEL from a number of occupational studies that observed a number of neurological impairments. Although the NOAEL is higher, the ATSDR chronic inhalation MRL is lower since the conversion to continuous exposure uses 8 hours per workday/24 hours and 5 days/7 days. The U.S. EPA IRIS RfC uses 10 m³ per workday out of 20 m³ per day inhalation rate to adjust for continuous exposure and 5 days/7 days. The U.S. EPA IRIS RfC accounts for a higher breathing rate during working hours as compared to nonworking hours that includes sleeping hours at a lower breathing rate and is the best available information for the residential RIASL.

The ATSDR acute inhalation MRL of 2 ppm or 7,500 µg/m³ is based on a study of 20 human subjects with a history of solvent exposure with adverse reactions to toluene (i.e., clinically sensitive

to toluene) (Little *et al.*, 1999). Statistically significant cognitive impairments were measured after a 20-minute exposure to 15 ppm of toluene as compared to pre-exposure scores for three of six tests. Another test had a near-significant increase in reaction time. No adjustment was made for continuous exposure for this acute value.

The ATSDR acute inhalation MRL is lower than the IRIS RfC-based residential TS RIASL (15,600 µg/m^3), RfC-based nonresidential AAC (7,700 µg/m^3), and RfC-based nonresidential adjusted RIASL and TS RIASL (15,000 and 46,000 µg/m^3, respectively). Therefore, the acute inhalation MRL is recommended for the residential TS RIASL and the nonresidential AAC, RIASL, and TS RIASL. No adjustment to a 12-hour work exposure time is needed as the MRL (NOAEL) was not based on continuous exposure.

Uncertainties in the toxicity estimate:

The U.S. EPA IRIS RfC had a total UF of ten applied to account for human variability. The ATSDR acute inhalation MRL had a total UF of 9, 3 for human variability and 3 for extrapolating from a LOAEL to a NOAEL.

Source of the Toxicity Values

Chronic Inhalation Noncancer:
IRIS:
Basis: IRIS is a Tier 1 source.
IRIS RfC= 5.0E+3 µg/m^3
Critical Study: Multiple occupational human studies: Abbate *et al*. (1993); Boey *et al*. (1997); Cavalleri *et al*. (2000); Eller *et al*. (1999); Foo *et al*. (1990); Murata *et al*. (1993); Nakatsuka *et al*. (1992); Neubert *et al*. (2001); Vrca *et al*. (1995) and; Zavalic *et al*. (1998).
Methods: An arithmetic mean of the NOAEL values derived from the principal studies (refer to Table 1 of IRIS Toxicological Review) was chosen to represent an average point of departure. The highest NOAEL was identified as 44 ppm (Nakatsuka *et al*., 1992). The lowest LOAELs were identified as 40-42 ppm (Vrca *et al*., 1995, 1997; Cavalleri *et al*., 2000). The average exposure level of 34 ppm is used as POD for the RfC.
Critical effect: neurological effects in occupationally exposed workers
End point or Point of Departure (POD): NOAEL (average) = 34 ppm (128 mg/m^3); $NOAEL_{adj}$ = 46 mg/m^3
Uncertainty Factors: UF = 10 for intraspecies variability
Source and Date: IRIS, 9/23/2005

MRL: ATSDR (9/2015), inhalation chronic MRL = 1 ppm (3.8 mg/m^3)
Critical Studies: Series of human occupational studies: Schäper *et al*. (2003), Schäper *et al*. (2004), Schäper *et al*. (2008), Seeber *et al*. (2004), Seeber *et al*. (2005), Zupanic *et al.* (2002).
Method(s): A NOAEL was determined from a series of studies that assessed subjective neurological

symptoms, performance on psychomotor tasks, color vision, and hearing in groups of German photogravure printers employed for an average duration of 13.5 years (Schäper *et al*. 2003, 2004, 2008; Seeber *et al*. 2004, 2005; Zupanic *et al*. 2002). These studies compared neurological end points in workers with high exposure to toluene (printers, n=106–181) with workers with low exposure to toluene (end-processors, n=86–152). Using job history and current exposure and historical exposure levels, individual TWA exposure levels were calculated. The average TWA levels for printers and end-processors were calculated to be 45 and 10 ppm for subjects included in analyses by Schäper *et al*. (2003, 2008), 45 and 9 ppm for subjects included in analyses by Seeber *et al*. (2004, 2005) and Zupanic *et al*. (2002), and 43 and 9 ppm for subjects included in analyses by Schäper *et al*. (2004)

Critical effect: neurological effects

End point or Point of Departure (POD): NOAEL = 45 ppm; $NOAEL_{adj}$ = 45 ppm x 5 days/7 days x 8 hours/24 hours

Uncertainty Factors: UF = 10 for human variability

Source and Date: ATSDR, 9/2017

Acute Inhalation Noncancer

MRL: ATSDR (9/2015), acute inhalation MRL = 2 ppm (7.5 mg/m^3) derived as follows:

Critical Study: Little CH, Georgiou GM, Shelton MJ, *et al*. 1999. Clinical and immunological responses in subjects sensitive to solvents. Arch. Environ. Health 54(1):6-14.

Method(s): Twenty subjects with a history of solvent exposure and adverse reactions to toluene (i.e., clinically sensitive to toluene) were assessed in a battery of neuropsychological tests prior to and after a 20-minute exposure to 15 ppm toluene. The battery of tests included immediate and delayed prose memory, reaction time, letter cancellations, digit symbol, focal length, and STROOP color and color-word tasks.

Critical effect: neurological effects

End point or Point of Departure (POD): LOAEL = 15 ppm

Uncertainty Factors: UF = 9, 3 each for human variability and LOAEL to NOAEL.

Source and Date: ATSDR, 9/2017

Cancer:

Carcinogen Weight-of-Evidence (WOE) Class: "inadequate information to assess the carcinogenic potential"

Basis: IRIS WOE: studies of humans chronically exposed to toluene are inconclusive, toluene was not carcinogenic in adequate inhalation cancer bioassays of rats and mice exposed for life (CIIT, 1980; NTP, 1990; Huff, 2003), and increased incidences of mammary cancer and leukemia were reported in a lifetime rat oral bioassay at a dose level of 500 mg/kg-day but not at 800 mg/kg-day (Maltoni *et al*., 1997).

Source and Date: IRIS, 9/23/2005

TRIALLATE (CAS #2303-17-5) – DEVELOPED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	200 µg/m³ (16 ppb_{vol})	600 µg/m³ (48 ppb_{vol})
Basis	Increased fetal skeletal variations (Res AAC SE Developmental – OPP/MDEQ RfC)	3 × Res AAC SE Developmental

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Levels	200 µg/m³ (16 ppb_{vol})	600 µg/m³ (48 ppb_{vol})
Basis	Increased fetal skeletal variations (NR AAC SE Developmental – OPP/MDEQ RfC)	3 × NR AAC SE Developmental

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs for triallate are based on the RfC of 2.0E+02 µg/m³, an MDEQ extrapolated value using U.S. EPA's Office of Pesticide Programs' (OPP) (U.S. EPA, 2014) inhalation toxicity assessment (see below). Both residential and nonresidential AACs are based on a developmental effect (increased fetal skeletal variations) that may result from a single event exposure during pregnancy. The nonresidential RIASLs and TS RIASLs were not adjusted for a 12-hour workday exposure time as the route-extrapolated RfC was not adjusted for continuous exposure and the critical effect (increased skeletal variations in the fetus) is "presumed to occur after a single exposure (dose)". See details below.

The RfC is based on an OPP inhalation short-term (1-30 days) and intermediate-term (1-6 months) exposure, derived from a rabbit oral developmental study. MDEQ-RRD extrapolated the RfC based on an oral NOAEL of 5 mg/kg-day, UF = 100, 80 kg body weight (BW), and 20 m³/day air inhalation rate.

Uncertainties in the toxicity estimate:

A total uncertainty factor of 100 was used to derive the screening RfC, where 10 each was used for interspecies extrapolation and intraspecies variability. Inhalation toxicity is assumed to be equivalent to oral toxicity.

Source of the Toxicity Values

Noncancer:
RfC/ITSL = 2.0E+02 µg/m³

Basis: OPP is a Tier 1 source with a more recent evaluation than IRIS. OPP (2014) inhalation short-term (1-30 days) and intermediate term (1-6 months). Level of Concern (LOC) = 100 is based on a rabbit oral developmental study. Based on NOAEL = 5 mg/kg-day, UF = 100, BW = 80 kg, and inhalation rate = 20 m^3/day, MDEQ-RRD derives an RfC = [(5.0/100)*80)/20] = 0.2 mg/m^3 = 2.0E+02 µg/m^3.

Critical Study:

1) Schardein, J.; Laughlin, K.; Blair, M.; *et al*. 1982. Teratology Study in Rabbits (IR-80-087): 401-146. (Unpublished study received Sep 8, 1982 under 524-124; prepared by International Research and Development Corp., submitted by Monsanto Co., Washington, DC; CDL:248293-B)
2) Li, A. 1994. Triallate Rabbit Teratology Study: Addendum: Individual Animal Observations: Lab Project Number: RD 1258: IR-80-087. Unpublished study prepared by International Research and Development Corp. 155 p.

Method(s): Rabbit developmental study.

Critical effect: increased skeletal variations in the fetus. Per OPP, this effect is "presumed to occur after a single exposure (dose) and thus are appropriate for this (acute) risk assessment." Inhalation toxicity is assumed to be equivalent to oral toxicity.

Uncertainty Factors: UF = 100, 10 each for intraspecies variability and interspecies extrapolation. The database for triallate was considered complete.

Source and Date: Office of Pesticide Programs (OPP) Memorandum dated 8/08/2014: Subject: Triallate. Human Health Risk Assessment Scoping Document in Support of Registration Review, 8/08/2014 (pp 3-7); OPP Reregistration Eligibility Decision (RED) for Triallate (RED), 3/2001

Tier 1 and 2 Sources:

IRIS: Per IRIS (1/1/1992), no value at this time. Per IRIS (EPA 2016), this chemical is no longer being updated under the IRIS Program. The user is directed to the EPA-OPP for updates. **PPRTV:** No PPRTV record available at this time.

MRL: No MRL record available at this time.

Tier 3 Source:

MDEQ: Per MDEQ-AQD, no value at this time.

Cancer:

IURF: no value available at this time

Carcinogen Weight-of-Evidence (WOE) Class: Group C, possible human carcinogen

IRIS WOE Basis: based on hepatocellular carcinomas in male mice, with a positive trend and borderline significance in female mice; and increased incidence of renal tubular cell adenomas in rats.

Source and Date: Office of Pesticide Programs (OPP) Memorandum dated 8/08/2014: Subject: Triallate. Human Health Risk Assessment Scoping Document in Support of Registration Review, 8/08/2014.

Tier 1 and 2 Sources:
IRIS: Per IRIS (1/1/1992), no value at this time. IRIS has not evaluated triallate for evidence of human carcinogenic potential. Per IRIS (2015), this chemical is no longer being updated under the IRIS Program. The user is directed to the OPP for updates.
PPRTV: No PPRTV record available at this time.
MRL: NA; MRLs are for non-cancer effects only.

Tier 3 Source:
MDEQ: Per MDEQ-AQD, no value at this time.

1,2,4-TRICHLOROBENZENE (CAS #120-82-1) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	2.1 µg/m³ (0.28 ppb_{vol})	6.3 µg/m³ (0.84 ppb_{vol})
Basis	increased urinary excretion of porphyrins (Res AAC Noncancer – PPRTV RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	6.1 µg/m³ (0.83 ppb_{vol})	18 µg/m³ (2.5 ppb_{vol})
Basis	increased urinary excretion of porphyrins (NR AAC_{adj} Noncancer – PPRTV RfC)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs and TS RIASLS for 1,2,4-trichlorobenzene are based on the PPRTV (2009) RfC of 2 µg/m³. The PPRTV RfC critical studies were two subchronic inhalation studies exposing rats to 1,2,4-trichlorobenzene for 6 hr/day, 5 days/week for three months (Watanabe *et al*., 1977; Watanabe *et al*.,1978). The critical effect observed was increased urinary excretion of porphyrins and a $BMCL_{HEC}$ = 4.6 mg/m³ was calculated. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure concentration.

The EGLE AQD also generated a 2006 ITSL. The ITSL = 4.0 µg/m³ based on rat NOAEL of 21 mg/m³ reported by Watanabe *et al*. (1977) for increased urinary porphyrins at 76 mg/m³.

Uncertainties in the toxicity estimate:

Per PPRTV, for the chronic p-RfC derivation, the $BMCL_{[HEC]}$ was divided by a UF of 3000, including 3 for extrapolation from rats-to-humans using dosimetric adjustments, 10 for protection of sensitive individuals and 10 for database deficiencies, as well as an additional UF of 10 for use of a subchronic study. The absence of a well-documented chronic study in a sensitive species (such as rat) is accounted for by the use of a full 10-fold UF for extrapolation from subchronic-to-chronic effects. PPRTV assigned the confidence in the key study as medium.

Source of the Toxicity Values

Noncancer:

Basis: PPRTV RfC

PPRTV (6/16/2009): RfC = 2E-3 mg/m^3 (2 µg/m^3)

Critical Studies:

1) Watanabe, P.G., H.O. Yankel and R.J. Kociba. 1977. Subchronic toxicity study of inhaled 1,2,4-trichlorobenzene in rats. Toxicology Research Center, Health and Environmental Research, Dow Chemical Company, Midland, MI. Produced 11/18/77. Submitted 12/20/82. TSCATS 20327. EPA Doc. #878221105.
2) Watanabe, P.G., R.J. Kociba, R.E. Hefner Jr. *et al*. 1978. Subchronic toxicity studies of 1,2,4-trichlorobenzene in experimental animals. Toxicol. Appl. Pharmacol. 45:332-333.

Method(s): Groups of 10 male and 26 female Sprague-Dawley rats were exposed by inhalation to 0, 2.8, or 10.2 ppm 1,2,4-trichlorobenzene (0, 21 or 76 mg/m^3) 6 hr/day, 5 days/week, for 3 months. Between four and five females/group were sacrificed after two weeks, one month, or two months of exposure, and 2- or 4-months post-exposure for assessment of total liver porphyrins. Urine was collected at these same intervals from the rats maintained for the entire experiment. The NOAELs and LOAELs from Watanabe *et al*. (1977, 1978) were first adjusted to an equivalent continuous exposure concentration, then converted to HECs.

Critical effect: increased urinary excretion of porphyrins

End point or Point of Departure (POD): $BMCL_{HEC}$ = 4.6 mg/m^3

Uncertainty Factors: UF = 3,000, 10 each for intraspecies variability, use of a subchronic study and database deficiencies, and 3 for interspecies extrapolation

Source and Date: PPRTV, 6/16/2009

Cancer:

PPRTV (2009): Carcinogen Weight-of-Evidence (WOE) Class: “Likely to Be Carcinogenic to Humans” by the oral route of exposure based on a finding of increased tumor incidence in mice. Only one chronic inhalation study is identified (Coate *et al*., 1977) and, in the study, the neoplastic changes are not reported.

Source and Date: PPRTV, 6/16/2009

1,1,1-TRICHLOROETHANE (CAS #71-55-6) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	5,000 µg/m³ (920 ppb_{vol})	5,000 µg/m³ (920 ppb_{vol})
Basis	Neurological effects in people from short-term exposures (24 hours - 30 days) (U.S. EPA IRIS Short-term RfC)	U.S. EPA IRIS Short-term RfC

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	7,000 µg/m³ (1,300 ppb_{vol})	7,000 µg/m³ (1,300 ppb_{vol})
Basis	Neurological effects in people from short-term exposures (8 hour) (U.S. EPA IRIS Acute 8-hour RfC)	U.S. EPA IRIS Acute 8-hour RfC

Discussion of Basis

The residential AAC, RIASL, and TS RIASL for 1,1,1-trichloroethane are based on the U.S. EPA IRIS RfC for short-term neurobehavioral effects (reaction time being most sensitive) in human volunteers in a controlled setting. Although the subchronic and chronic inhalation studies in rodents resulted in liver histopathologic changes at higher concentrations, the acute/short-term RfCs of 5-9 mg/m³ are lower than the calculated subchronic and chronic IRIS RfCs. Therefore, U.S. EPA has these longer-term RfCs default to the 5 mg/m³ short-term RfC (24 hours to 30 days) that is also protective of the liver effects observed in rodents after longer-term exposure. In addition, developmental toxicity studies in three species also indicated developmental toxicity occurred at higher concentrations. As such, the noncancer U.S. EPA short-term RfC of 5,000 µg/m³ is appropriate for the RIASL and the TS RIASL based on short-term neurobehavioral effects including reaction time.

There is an acute MRL of 6,300 µg/m³ based on the same studies and endpoints. The U.S. EPA short-term RfC is preferred since the acute MRL does not include the PBPK model adjustment for peak blood steady state used for the U.S. EPA IRIS short-term RfC of 5 mg/m³. An intermediate MRL of 3,800 µg/m³ is available based on increase in glial fibrillary acid protein in gerbils with a NOAEL of 70 ppm and a LOAEL of 210 ppm. The human studies LOAEL was at 175 ppm. Since the LOAELs of these neurological endpoints in both rodents and humans are similar, the human data-based value is an appropriately protective value for both endpoints and is based on data in the species of concern.

The nonresidential AAC, RIASL and TS RIASL for 1,1,1-trichlorethane are based on the acute U.S. EPA IRIS RfC for 8-hours of 7,000 µg/m³. This value is not adjusted for time duration for nonresidential

use since it represents an exposure period per day in the workplace with a typical range of 8-12 hours and is more reasonable than the short-term value for 24 hours or longer for most nonresidential scenarios. This value is more appropriate than the use of a calculated nonresidential AAV (7,700 µg/m^3) based on the short-term, subchronic, and chronic RfC. The acute 8-hour RfC is based on adverse neurological effects in people from a one-hour exposure to 1,1,1-trichloroethylene and has been predicted for an 8-hour exposure duration using a PBPK model. The nonresidential RIASL and TSRIASL were not adjusted to a 12-hour work exposure time as the RfC was based on an 8-hour acute exposure concentration.

Uncertainties in the toxicity estimate:
The IRIS acute and short-term RfCs are based on an acute study evaluating neurobehavioral effects (reaction time being most sensitive) in human volunteers in a controlled setting (Mackay 1987). The POD was derived using PBPK modeling to arrive at an extrapolated 8-hour and steady-state (14-day) air concentration that would result in the blood concentration resulting in adverse effects. A total UF of 100 was applied to the POD to account for intraspecies differences (UF=10) and extrapolation from LOAEL to NOAEL (UF=10). The latter is needed because the POD for the lowest exposure concentration examined was associated with adverse effects. A UF to extrapolate from a shorter to a longer exposure duration was not necessary because the acute RfC was derived from a study using an acute exposure protocol. A database UF was not applied because the acute database for this chemical was considered complete. Per IRIS, the neurological effects are well demonstrated in acute animal studies and are shown to be the most sensitive endpoints in these studies. The level of confidence assigned by IRIS to the acute RfC is medium. Overall, the uncertainties relating to the RfC and its basis are considered low.

Source of the Toxicity Values

Chronic Inhalation Noncancer:
Basis: IRIS is a Tier 1 value.
IRIS: IRIS (2007) chronic RfC= 5.0E+3 µg/m^3.
Critical Studies:

1) Quast, JF; Calhoun, LL; McKenna, MJ. 1984. Chlorothene VG: a chronic inhalation toxicity and oncogenicity study in rats and mice (part 1 and 2) with cover letter dated 082184. The Dow Chemical Company, Midland, MI. Submitted under TSCA Section 4; EPA Document No. 40-8424496; NTIS No. OTS0510656.
2) Quast, JF; Calhoun, LL; Frauson, LE. 1988. 1,1,1-Trichloroethane formulation: a chronic inhalation toxicity and oncogenicity study in Fischer 344 rats and B6C3F1 mice. Fundam. Appl. Toxicol. 11: 611-625.
3) McNutt, NS; Amster, RL; McConnell, EE; *et al*. 1975. Hepatic lesions in mice after continuous inhalation exposure to 1,1,1-trichloroethane. Lab Invest 32:642-654.

Methods:

1) Quast *et al*. (1988, 1984) exposed groups of 80 male and 80 female F344 rats and B6C3F1

mice to 0, 150, 500, or 1500 ppm (0, 820, 2730, or 8190 mg/m^3) production-grade (94%) 1,1,1-trichloroethane vapor for 6 hr/day, 5 days/week for 2 years. Ten rats and ten mice of each sex from each exposure group were scheduled for interim sacrifices after 6, 12, and 18 months of exposure, and the remaining 50 rats and 50 mice/sex/group were scheduled for sacrifice after 24 months of exposure.

2) McNutt *et al*. (1975) chamber-exposed male CF-1 mice to 0, 250, or 1000 ppm (0, 1370, or 5460 mg/m^3) technical grade 1,1,1-trichloroethane (94—97% pure, 2.4—3.0% dioxane, 0.12—0.30% butanol) continuously for up to 14 Serial sacrifices were performed on ten mice/concentration at weekly intervals during the exposure period and at post exposure weeks two and four.

Critical effect: Liver histopathologic changes
End point or Point of Departure (POD): $NOAEL_{HEC}$ = 1,553
Uncertainty Factors: UF = 100, 10 each for intraspecies variability and interspecies extrapolation.
Note: Because the chronic RfC based on liver histopathologic changes following repeated exposure (16 mg/m^3) was higher than the short-term RfC (5 mg/m^3), the chronic RfC was set at 5 mg/m^3 so as not to exceed the limiting reference value derived for short-term exposure. The short-term RfC applies to exposures for more than 24 hours up to 30 days. See below for more details.
Source and Date: IRIS, 9/28/2007. An IRIS Toxicological Review is available.

Short-term Inhalation Noncancer
IRIS:
Basis: IRIS is a Tier 1 value.
IRIS (2007) **short-term RfC**= 5.0E+3 µg/m^3
Critical Study: Mackay, CJ; Campbell, L; Samuel, AM; *et al*. 1987. Behavioral changes during exposure to 1,1,1-trichloroethane: time-course and relationship to blood solvent levels. Am. J. Ind. Med. 11: 223—239.
Methods: Mackay *et al*. (1987) chamber-exposed 12 adult male volunteers to 0, 950, and 1900 mg/m^3 (0, 175, and 350 ppm) of 1,1,1-trichloroethane (purity not reported) for 3.5 hours. Neurobehavioral tests were performed 25 minutes before exposure and four times during exposure, starting at 20, 60, 120, and 180 minutes. Each test battery took 20—25 minutes to complete. Testing included five psychomotor performance tests (simple reaction time, four-choice reaction time, Stroop test [a measure of susceptibility to distraction], syntactic reasoning [via analysis of grammatical statements], and digital step-input tracking [a measure of eye-hand coordination]) and a subjective measure of mood (stress-arousal checklist).
Critical effect: impaired psychomotor performance, especially increased reaction time
End point or Point of Departure (POD): $LOAEL_{pbpk\ adj}$ = 526 mg/m^3 adjusted based on PBPK modeling of inhaled concentration at steady-state to achieve blood level causing adverse effects (Yang, 2006; Reitz *et al*., 1988).
Uncertainty Factors: UF = 100, 10 each for human variability and LOAEL to NOAEL
Source and Date: IRIS, 9/28/2007. An IRIS Toxicological Review is available.

Acute Inhalation Noncancer
Basis: IRIS is a Tier 1 value.
IRIS: IRIS (2007) 8-hour Acute RfC = 7.0E+3 µg/m^3
Critical Study: Mackay, CJ; Campbell, L; Samuel, AM; *et al*. 1987. Behavioral changes during exposure to 1,1,1-trichloroethane: time-course and relationship to blood solvent levels. Am. J. Ind. Med. 11: 223—239.
Methods: Mackay *et al*. (1987) chamber-exposed 12 adult male volunteers to 0, 950, and 1900 mg/m^3 (0, 175, and 350 ppm) of 1,1,1-trichloroethane (purity not reported) for 3.5 hours. Neurobehavioral tests were performed 25 minutes before exposure and four times during exposure, starting at 20, 60, 120, and 180 minutes. Each test battery took 20—25 minutes to complete. Testing included five psychomotor performance tests (simple reaction time, four-choice reaction time, Stroop test [a measure of susceptibility to distraction], syntactic reasoning [via analysis of grammatical statements], and digital step-input tracking [a measure of eye-hand coordination]) and a subjective measure of mood (stress-arousal checklist).
Critical effect: impaired psychomotor performance, especially increased reaction time
End point or Point of Departure (POD): $LOAEL_{pbpk\ adj}$ = 693 mg/m^3
Uncertainty Factors: UF = 100, 10 each for human variability and use of LOAEL
Source and Date: IRIS, 9/28/2007. An IRIS Toxicological Review is available.

Cancer:
Carcinogen Weight-of-Evidence (WOE) Class: "inadequate information to assess carcinogenic potential."
Basis: Epidemiologic studies of humans chronically exposed to 1,1,1-trichloroethane are inconclusive. A 2-year inhalation bioassay showed no treatment-related increase in tumors in rats and mice at an exposure concentration below the maximum tolerated dose. The two available oral cancer bioassays in rats and mice are considered inadequate for evaluation of carcinogenic potential.
Source and Date: IRIS, 9/28/2007

TRICHLOROETHYLENE (TCE) (CAS #79-01-6) – DEVELOPED 2017

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	2.0 µg/m³ (0.37 ppb_{vol})	6.0 µg/m³ (1.1 ppb_{vol})
Basis	Immunotoxic and developmental effects from hours-days of exposure (Res AAC SE Developmental – U.S. EPA IRIS RfC)	3 × Res AAC SE Developmental

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	4.0 µg/m³ (0.74 ppb_{vol})	12 µg/m³ (2.2 ppb_{vol})
Basis	Immunotoxic and developmental effects from hours-days of exposure (NR AAC_{adj} SE Developmental – U.S. EPA IRIS RfC)	3 × NR AAC_{adj} SE Developmental

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLS for trichloroethylene (TCE) are based on the U.S. EPA IRIS chronic RfC (2 µg/m³). The RfC is based on two rodent studies. The first study is a 30-week drinking water study resulting in decreased thymus weight in female mice (immunotoxicity). The second is a developmental study where pregnant female rats were exposed to TCE in drinking water during gestation and resulted in fetal cardiac malformations. The ATSDR intermediate and chronic inhalation MRLs are available and are both 2 µg/m³ also. The MRLs are based on the same IRIS studies and endpoints. See details below.
The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure concentration.

Uncertainties in the toxicity estimate:
Two different studies with different adverse effects and UFs are the basis of the U.S. EPA IRIS RfC. Both are based on oral toxicity studies, but with PBPK modeling to extrapolate between routes, species and account for variability within species. The RfC calculation from the study that resulted in decreased thymus weight in female mice (Kiel *et al.*; 2009) used a total UF of 100, 3 each for human variability and mouse to human extrapolation based on PBPK modeling to account for toxicokinetic differences, and 10 for a LOAEL. This RfC has a medium to high confidence due to high confidence in the immunotoxic hazard coupled with quantitative uncertainties in the dose-response assessment. The RfC calculation based on cardiac malformations from prenatal exposure (Johnson *et al.*, 2003) includes a total uncertainty factor of 10, 3 each for human variability and rat to human extrapolation

based on PBPK modeling to account for toxicokinetic differences. The overall confidence in this RfC is medium due to important limitations with the study, overall weight of evidence supporting the adverse effect of TCE on cardiac development, and higher confidence in the dose-response analysis.

Source of the Toxicity Values

Noncancer:

Basis: IRIS is a Tier 1 source.

IRIS RfC = 2.0E-3 mg/m^3

Critical Studies and Methods:

1) 30-week drinking water study, Kiel *et al*., 2009 (immunotoxicity);
2) drinking water exposure from GD 1 to 22, Johnson *et al*., 2003 (heart malformations)

Multiple Critical effects, Point of Departure (POD), Uncertainty Factors (UF), and candidates RfCs:

1) Female B6C3F1 Mice: IMMUNOTOXICITY. Point of Departure: LOAEL (HEC99) = 0.19 mg/m^3 with UF of 100 yields candidate RfC of 0.0019 mg/m^3.
2) Fetal Sprague-Dawley Rats: INCREASED FETAL CARDIAC MALFORMATIONS. Point of Departure: BMDL01 (HEC99) = 0.021 mg/m^3 with UF of 10 yields candidate RfC of 0.0021 mg/m^3

Final RfC Basis: The average of these two candidate RfCs yields a final RfC of 0.002 mg/m^3 or 2 µg/m^3.

Source and Date: IRIS, 9/28/2011. An IRIS Toxicological Review is available.

Cancer:

Basis: IRIS is a Tier 1 Source.

IRIS IURF = 4.1E-6 (adult-based IURF); **IURF** = 3.1E-6 for liver and NHL tumors; and **IURF** = 1.0E-6 for kidney (mutagenic MOA).

Note: TCE is carcinogenic at multiple sites. For kidney tumors, TCE acts via a mutagenic mode of action (MOA). For liver and other TCE-induced tumors, the MOA is not clear. Increased early-life susceptibility is assumed for kidney cancer and, therefore, the age-dependent adjustment factors (ADAFs) should be applied to the kidney cancer component of the total cancer risk. For liver and non-Hodgkin lymphoma (NHL), the cancer risk is calculated without ADAF. The U.S. EPA (2015) Regional Screening Level (RSL) generated adjustment factors for cancer and cancer with mutagenic effects: CAF = 0.756 and MAF = 0.244, respectively to facilitate calculating inhalation exposure risk. These factors are based on the ratio of the NHL and liver-based IURF or kidney-based IURF to the adult-based IURF estimate. These factors should be applied in calculating the risk-based health values for TCE exposure via inhalation.

Critical Studies: Charbotel *et al*. (2006); U.S. EPA (2011); and Raaschou-Nielsen *et al*. (2003).

Methods:

1) *Dose response data*: *Tumor Type* - Renal cell carcinoma, non-Hodgkin's lymphoma, and liver tumors; *Test Species* - Human (epidemiological studies); *Route* - Inhalation
2) *Extrapolation method*: Low-dose linear extrapolation from the point of departure (LEC01) with a factor of 4 applied to include non-Hodgkin's lymphoma (NHL) and liver cancer risks, combined risk,

Carcinogen Weight-of-Evidence (WOE) Class: "carcinogenic to humans" by all routes of exposure; carcinogenic by a mutagenic MOA for induction of kidney tumors; Increased early-life susceptibility is assumed therefore, age-dependent adjustment factors (ADAFs) should be used for the kidney cancer component of the total cancer risk.
Basis: convincing evidence of a causal association between TCE exposure in humans and kidney cancer, but there is also human evidence of TCE carcinogenicity in the liver and lymphoid tissues.
Source and Date: IRIS, 9/28/2011. An IRIS Toxicological Review is available.

TRIMETHYLBENZENES – 1,2,3-TRIMETHYLBENZENE; 1,2,4-TRIMETHYLBENZENE; AND 1,3,5-TRIMETHYLBENZENE COMBINED (CAS #S 25551-13-7; 526-73-8; 95-63-6; 108-67-8) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	63 µg/m^3 (13 ppb$_{vol}$)	190 µg/m^3 (38 ppb$_{vol}$)
Basis	Decreased pain sensitivity from subchronic exposure (Res AAC Noncancer – U.S. EPA IRIS RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	180 µg/m^3 (37 ppb$_{vol}$)	550 µg/m^3 (110 ppb$_{vol}$)
Basis	Decreased pain sensitivity from subchronic exposure (NR AAC$_{adj}$ Noncancer – U.S. EPA IRIS RfC)	3 × NR AAC$_{adj}$ Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs, and TS RIASLs are based on the 2016 U.S. EPA IRIS RfC for all trimethylbenzene (TMB) isomers combined of 60 µg/m^3. The IRIS RfC was derived using benchmark dose modeling with PBPK modeling or default dosimetric methods. The critical study was a subchronic study with decreased pain sensitivity as the critical effect (Korsak and Rydzynski, 1996). The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure concentration.

An IRIS subchronic RfC for TMB was set to 200 µg/m^3 based on neurological effects. The subchronic RfC was derived using the same methods used for calculating the chronic RfCs except subchronic-to-chronic uncertainty factor was not applied.

Uncertainties in the toxicity estimate:

The IRIS chronic RfC is based on a developmental and four subchronic studies, which demonstrated neurological, hematological, respiratory, developmental and maternal toxicity endpoints. The neurological effect was the most sensitive effect and was used as basis for the overall RfC. An RfC value was derived for each of the subchronic studies using a composite UF of 300 to account for human variability (10), interspecies variability (3), database deficiency (3) and use of a subchronic study. The UF for subchronic to chronic extrapolation and lack of data increased the uncertainties in

the estimate. IRIS assigned a low to medium confidence on the chronic RfC.

Source of the Toxicity Values
Noncancer:
Basis: IRIS (9/9/2016):
IRIS: RfC = 5E-2 mg/m^3 (5E+1 µg/m^3)
Critical Study: Korsak, Z. and K. Rydzynski. 1996. Neurotoxic effects of acute and subchronic inhalation exposure to Trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. Int. J. Occup. Med. Environ. Health 9:341–349.
Method(s): Rats were exposed to 0, 123, 492, or 1,230 mg/m^3 1,2,4-TMB for 6 hr/day, 5 days/week, for 3 months. Neurobehavioral effects were assessed using performance testing.
Critical effect: Decreased pain sensitivity in male rats (neurotoxicity)
End point or Point of Departure (POD): A deterministic rat PBPK model was used to was used to convert non-continuous external inhalation concentrations (in mg/m^3) of 1,2,4-TMB to the internal blood dose metric of average weekly venous blood concentration (in mg/L) of 1,2,4-TMB. Internal doses were modeled using BMDS. The resulting POD was adjusted for the non-continuous exposures in this study, POD_{adj} = 0.099 mg/L, and then converted to HECs using a human PBPK model, POD_{HEC} = 18.15 mg/m^3.
Uncertainty Factors: UF = 300 (10 for intraspecies variability and 3 each for use of a subchronic study, interspecies extrapolation, and database deficiencies).
Source and Date: IRIS, 9/2016

IRIS (2016) Subchronic RfCs:
Subchronic overall RfC = 2.0E-1 mg/m^3 (2.0E+2 µg/m^3) based on neurological effects following exposure to 1,2,4-TMB. All of the studies used to calculate the chronic RfCs for TMBs were subchronic or gestational in duration. The subchronic RfC was derived using the same methods used for calculating the chronic RfCs except subchronic-to-chronic uncertainty factor was not applied.
Tier 2 Sources:
PPRTV (2007): chronic p-RfC = 7E-3 mg/m^3 (= 7E+0 µg/m^3):
Critical Study: Korsak, Z., J. Stetkiewicz, W Majcherek, I. Stetkiewicz, J. Jajte and K. Rydzyński. (2000) Subchronic inhalation toxicity of 1,2,4-trimethylbenzene (pseudocumene) in rats. Int. J. Occup. Med. Environ. Health 13(2):155-164.
Methods: Outbred Imp:WIST rats (10/sex/group; 20/sex/group at the highest exposure concentration) were exposed to 0, 123, 492 or 1,230 mg/m^3 of 1,2,4-trimethylbenzene vapors for 6 hr/day, 5 days/week for 3 months.
Critical effect: Decreased clotting time in female rats.
End point or Point of Departure (POD): A NOAEL of 123 mg/m^3 was identified and adjusted for non-continuous exposure, $NOAEL_{adj}$ = 21.8 mg/m^3. A human equivalent concentration was calculated from the adjusted value, $NOAEL_{HEC}$ = 21.8 mg/m^3.
Source and Date: PPRTV, 2007
Tier 3 Source:

MDEQ: MDEQ/AQD (1/26/2012) established 2 ITSLs: 1,200 µg/m^3 (8-hour averaging time) and 50 µg/m^3 (annual averaging time). These are applied to all 3 TMB isomers in combination. The acute value is protective of irritancy and other potential effects, based on human experimental studies and occupational experience. The annual value is partially consistent with the PPRTVs (chronic) of 5 µg/m^3 (1,2,3-TMB) and 7 µg/m^3 (1,2,4-TMB) which were based on rat studies and CNS effects. For the PPRTVs, EPA employed database UF of 10 which was not employed in the derivation of the chronic ITSL. The PPRTVs apply only to each specific isomer, and no PPRTV is available for 1,3,5-TMB; the AQD justified grouping the 3 isomers together. AQD does not routinely apply database UF =10 in their own risk assessments.

Cancer:

IRIS (9/9/2016): No IRIS file is available at this time. Per the September 2016 IRIS Toxicological Review of Trimethylbenzenes, the database for TMBs provides "inadequate information to assess carcinogenic potential". This characterization is based on the limited and equivocal genotoxicity findings, and the lack of data indicating carcinogenicity in experimental animal species via any route of exposure. Information available on which to base a quantitative cancer assessment is lacking, and thus, no cancer risk estimates for either oral or inhalation exposures are derived.

VINYL ACETATE (CAS #108-05-4) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	Residential TS RIASL
Action Level	210 µg/m³ (59 ppb_{vol})	630 µg/m³ (180 ppb_{vol})
Basis	Nasal epithelial lesions (Res AAC Noncancer – U.S. EPA IRIS RfC)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	Nonresidential TS RIASL
Action Level	610 µg/m³ (170 ppb_{vol})	1,800 µg/m³ (520 ppb_{vol})
Basis	Nasal epithelial lesions (NR AAC_{adj} Noncancer – U.S. EPA IRIS RfC)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs and TS RIASLs for vinyl acetate are based on the U.S. EPA IRIS chronic RfC of 200 µg/m³. The IRIS RfC of 200 µg/m³ is based on a NOAEL of 50 ppm (176 mg/m³; $NOAEL_{HEC}$ = 5 mg/m³) and LOAEL of 200 ppm (704 mg/m³) for nasal epithelial lesions in rats and mice after 104 weeks of exposure for 6 hr/day and 5 days/week (Owen *et al*. 1988). The ATSDR Intermediate Inhalation MRL is based on respiratory effects (respiratory distress, slight inflammation in the nasal turbinates and mild multifocal bronchitis) reported at a NOAEL of 50 ppm and a LOAEL of 200 ppm after 90 days of exposure in mice (Hazelton, 1979) from the same research group as the IRIS critical studies. Since the ATSDR and IRIS NOAELs and LOAELs are the same, the proposed RIASLs and TS RIASLs are based on the IRIS RfC. The IRIS RfC is based on a chronic study and includes dosimetric adjustment.
The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure concentration.

Uncertainties in the toxicity estimate:
For the IRIS RfC, the total UF applied is 30. A UF of 10 is used to account for intraspecies variability and a UF of 3 for interspecies variability because of the use of dosimetric adjustments. The confidence assigned by IRIS to the RfC estimate is high due to an adequate number of animals in a chronic 2-year study that identified both a NOAEL and LOAEL and was thorough in reporting experimental and exposure details. The animal database provides sufficient supporting data for the RfC.

For the ATSDR intermediate inhalation MRL the total UF applied is 100. A UF of 10 each was used for

human variability and interspecies extrapolation.

Source of the Toxicity Values

Noncancer:

Basis: The IRIS RfC was selected because it is based on a chronic inhalation study. IRIS is a **Tier 1 source.**

IRIS RfC = 2.0E-1 mg/m^3

Critical Studies:

1) 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.
2) 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).
3) 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).

Methods: Sprague-Dawley rats (Crl:CD[SD]BR) and mice (Crl:CD-1[ICR]BR) (90 animals/sex/dose, 60 for the main study and 30 for laboratory testing) were exposed to 0, 50, 200, or 600 ppm of 99.9% vinyl acetate for 6 hr/day, 5 days/week for 104 weeks. Interim sacrifices were done at 51 and 81 weeks and recovery. Values corresponded to 0, 176, 704, and 2113 mg/m^3, and duration-adjusted values were 0, 31, 126, and 378 mg/m^3.

Critical effect: nasal epithelial lesions

End point or Point of Departure (POD): NOAEL = 176 mg/m^3 (50 ppm); NOAEL$_{HEC}$ = 5 mg/m^3

Uncertainty Factors: UF = 30, 10 for interspecies variability and 3 for interspecies extrapolation

Source and Date: IRIS, 10/01/1990

MRL: Per ATSDR (7/1992), no chronic inhalation MRL at this time.

Intermediate inhalation MRL = 0.01 ppm

Critical Study: Hazleton. 1980b. 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.

Methods: Mice were exposed to vinyl acetate in drinking water at doses up to 950 mg/kg-day 6hr/day, 5days/week for 3 months.

Critical effect: inflammation of nasal turbinate epithelium; mild multi-focal bronchitis

End point or Point of Departure (POD): NOAEL = 50 ppm concentration corrected for intermittent exposure and HEC)

Uncertainty Factors: UF = 100, 10 each for interspecies variability and interspecies extrapolation

Source and Date: ATSDR, 7/1992

Cancer:

Carcinogen Weight-of-Evidence (WOE) Class: Not assessed under the IRIS Program

Source and Date: IRIS, 10/01/1990

VINYL CHLORIDE (CAS #75-01-4) - DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	1.6 µg/m³ (0.64 ppb_{vol})	16 µg/m³ (6.4 ppb_{vol})
Basis	mutagenic liver cancer risk from early-life exposure (Res AAC Mutagenic Cancer – U.S. EPA IRIS IURF)	10 x Res AAC Mutagenic Cancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	27 µg/m³ (11 ppb_{vol})	270 µg/m³ (110 ppb_{vol})
Basis	liver cancer risk from exposure during adulthood (NR AAC_{adj} Cancer – U.S. EPA IRIS IURF)	10 x NR AAC_{adj} Cancer

Discussion of Basis

The residential AAC, RIASL, and TS RIASL are based on the mutagenic cancer risk using the U.S. EPA IRIS's IURF for exposures beginning from birth. The nonresidential AAC, RIASL, and TS RIASL are based on the U.S. EPA IRIS IURF for exposures during adulthood. Both of the U.S. EPA IRIS IURFs are estimated from increased incidence of liver angiosarcomas, angiomas, hepatomas, and neoplastic nodules in female rats after inhalation exposure. These values are lower than any other health-based values for noncancer adverse effects.

Vinyl chloride has chemical-specific data showing that short-term early life exposures result in cancer risk greater or equivalent to that of long-term adult exposures. Combined with long-term exposure risk observed in adults, the cancer risk for young children is assumed to be twice that of adults (combined short-term exposure and long-term exposure risk). Human occupational studies have shown increased cancer risk from vinyl chloride is both dose- and time-dependent.

The carcinogenic health-based AAV for vinyl chloride are calculated using unique equations that consider lifetime averaging (prorated) of continuous exposure from birth to adulthood (age-adjusted segment) and no averaging (non-prorated) for childhood exposure (child segment) due to greater sensitivity to vinyl chloride exposure during early life. The equations are based on those currently used for deriving the EPA cancer RSL for vinyl chloride.

$$AAV_{ca,VC} = \frac{TR}{\left(\frac{IURF \times ED_{res} \times EF_{res}}{AT_{ca}}\right) + (IURF)}$$

where,

$AAV_{ca,VC}$	(Acceptable air value for vinyl chloride)	=	1.631 µg/m^3
TR	(Target risk level)	=	10^{-5}
AT_{ca}	(Averaging time)	=	28,470 days
IURF	(Inhalation unit risk factor)	=	4.4E-06 (µg/m^3)$^{-1}$
ED_{res}	(Exposure duration)	=	32 years
EF_{res}	(Exposure frequency)	=	350 days/year

The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the IURF was based on continuous exposure.

Uncertainties in the toxicity estimate:

The IRIS IURF is based on the 95% upper confidence limit on risk for female rats. Human equivalent doses are calculated for a gas: extra respiratory effect based on a PBPK model of Clewell (1995). The risk values based on the animal dose metric are assumed to correspond to the same risk for the same human dose metric. It is assumed that the linear relationship between the dose metric and the low concentrations demonstrated by PBPK modeling is valid. Per IRIS, confidence is high that "the steady-state concentration of the active metabolite in the liver is accurately modeled, although the possibility of cancer induction at sites other than the liver is of some concern". The values are recommended for lifetime exposure beginning at adulthood. To address vinyl chloride's genotoxicity, an additional twofold safety factor is added to address risk from early life exposures to vinyl chloride.

Source of the Toxicity Values

Noncancer:

Basis: ATSDR is the most current value and therefore the best available.

ATSDR intermediate-duration inhalation MRL = 0.03 ppm (7.67 E-2 mg/m^3 rounded off to 8.0E-2 mg/m^3). Per ATSDR, no chronic inhalation MRL at this time

Critical Study: 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.

Method(s): Sprague-Dawley rats (30/sex/group) were exposed to vinyl chloride vapor concentrations of 0, 10, 100, or 1,100 ppm, 6 hr/day for 10 weeks prior to mating and during a 3-week mating period. F0 males were exposed during the gestational period and sacrificed following the completion of parturition. F0 females were exposed during gestation and lactation (with the exception of a break in exposure from gestation day 21 through postnatal days 4 to allow for delivery of litters).

Critical effect: hepatic centrilobular hypertrophy

End point or Point of Departure (POD): LEC_{10} = 5 ppm; LEC_{10HEC} = 1 ppm

Uncertainty Factors: UF = 30 (10 for intraspecies variability and 3 for interspecies extrapolation)

Source and Date: ATSDR, 7/2006

Cancer:

Basis: IRIS is the only available IURF and a Tier 1 source. The EGLE AQD, a Tier source, adopted the

IRIS value.

IRIS presented two IURF values: 8.8E-6 per mg/kg-day for continuous lifetime exposure from birth (incorporates a 2-fold adjustment), and 4.4E-6 per mg/kg-day for continuous lifetime exposure during adulthood. IRIS recommends a twofold adjustment to account for greater responsiveness to VC exposure during early life. Per IRIS, animal evidence indicates age-dependent sensitivity and therefore, concern for young children potentially exposed to VC. The EGLE used IURF = 4.4E-6 per mg/kg-day for both residential and nonresidential inhalation criteria. As described above, a different equation is used for the residential cancer health-based value due to increased cancer risk for exposure during childhood.

Critical Studies:

1) Maltoni, C; Lefemine, G; Ciliberti, A; *et al*. 1981. Carcinogenicity bioassays of vinyl chloride monomer, a model of risk assessment on an experimental basis. Environ Health Perspect 41:3-29.
2) Maltoni, C; Lefemine, G; Ciliberti, A; *et al*. 1984. Experimental research on vinyl chloride carcinogenesis, Vol. 1 and 2. In: Archives of research on industrial carcinogenesis. Princeton, NJ: Princeton Scientific Publishers, Inc.

Method(s): Sprague-Dawley rats (30/sex/group) were exposed to 0, 1, 5, 10, 25, 50, 100, 150, 200, 250, 500, 2500, 6000, or 10,000 ppm VC by inhalation for 4 hr/day, 5 days/week for 52 weeks (Maltoni *et al*., 1981, 1984).

1) *Dose response data*: *Tumor Type* - liver angiosarcoma, hepatocellular carcinoma, and neoplastic nodules; *Test Species* – Female Sprague-Dawley rats; *Route* – Inhalation
2) *Extrapolation method*: a) Linearized multistage (b) LED 10/linear method

Carcinogen Weight-of-Evidence (WOE) Class: known human carcinogen by the inhalation route of exposure and the oral route by analogy because of positive animal bioassay data

Basis: (1) consistent epidemiologic evidence of a causal association between occupational exposure via inhalation and the development of angiosarcoma, an extremely rare tumor; (2) consistent evidence of carcinogenicity in rats, mice, and hamsters by both the oral and inhalation routes; (3) mutagenicity and DNA adduct formation by VC and its metabolites in numerous in vivo and in vitro test systems; and (4) efficient VC absorption via all routes of exposure tested, followed by rapid distribution throughout the body.

Note: The recommended slope factors should not be used if the water concentration exceeds 10+05 µg/L, because above this concentration the slope factor may differ.

Source and Date: IRIS, 8/7/2000. A Toxicological Review is available. An IRIS screening-level review in 2003 did not identify any critical new studies.

XYLENES (CAS #1330-20-7) – DEVELOPED 2017; REVISED 2020

Residential RIASLs

	Residential RIASL	**Residential** TS RIASL
Action Level	230 µg/m³ (53 ppb_{vol})	690 µg/m³ (160 ppb_{vol})
Basis	Subjective symptoms of neurotoxicity, respiratory toxicity, and eye irritation. (Res AAC Noncancer– ATSDR chronic MRL)	3 × Res AAC Noncancer

Nonresidential RIASLs

	Nonresidential RIASL	**Nonresidential** TS RIASL
Action Level	670 µg/m³ (160 ppb_{vol})	2,000 µg/m³ (470 ppb_{vol})
Basis	Subjective symptoms of neurotoxicity, respiratory toxicity, and eye irritation. (NR AAC_{adj} Noncancer – ATSDR chronic MRL)	3 × NR AAC_{adj} Noncancer

Discussion of Basis

The residential and nonresidential AACs, RIASLs and TS RIASLs for xylenes are developed from the 2007 ATSDR chronic MRL of 2.2E+2 µg/m³. The MRL is based on a study of workers exposed to mixed xylenes reporting adverse subjective symptoms of neurotoxicity (anxiety, forgetfulness, floating sensation), respiratory toxicity, (nasal irritation and sore throat) and eye irritation. The ATSDR acute and intermediate MRLs (2,600 and 8,700 µg/m³, respectively) are higher than the calculated noncancer residential and nonresidential AAVs for xylenes; therefore, the AAVs are the basis for the AACs, RIASLs, and TS RIASLs. The nonresidential RIASL and TS RIASL were adjusted to a 12-hour work exposure time as the RfC was based on continuous exposure concentration.

Uncertainties in the toxicity estimate:
The chronic MRL of 0.05 ppm was derived using a LOAEL from an occupational study (Uchida 1993) and a total UF of 300 to account for human variability (10), use of a LOAEL (10) and database deficiencies (3). The database deficiency uncertainty is due to the lack of supporting studies on the chronic neurotoxicity of xylenes and use of a LOAEL contributes to the uncertainty in the estimate. The neurotoxicity symptoms were supported by observations in a short exposure human study (Ernstgard, 2002). This study is the basis for the acute-duration inhalation MRL. A repeated intermediate-duration human exposure study (NIOSH, 1981) also reported the subjective symptoms for irritation of the nose and throat observed in the Uchida study. Studies in animals also confirm that the nervous system is a sensitive target of inhalation exposure to xylenes.

Source of the Toxicity Values

Noncancer:

Basis: ATSDR, is a Tier 1 source. The MRL was selected because it is based on human data.

ATSDR Chronic inhalation MRL = 0.05 ppm (2.2E+2 µg/m^3, where 1 ppm = 4.34 mg/m^3) is derived as follows:

Critical Study: Uchida Y, Nakatsuka H, Ukai H, *et al*. 1993. Symptoms and signs in workers exposed predominantly to xylenes. Int. Arch. Occup. Environ. Health 64:597-605.

Method(s): 175 workers (107 men, 68 women) were exposed to mixed xylenes in Chinese factories during the production of rubber boots, plastic coated wire, or in printing work. Nonexposed workers (116 men, 125 women) were recruited from the same or other factories as a comparison population. Exposures, measured with a diffusive sampler, indicated that xylenes accounted for >70% of total exposure, with m-xylene accounting for 50% of the xylene exposure, followed by p- and o-xylenes. Toluene exposure and ethylbenzene exposure were about 1 and 3 ppm, respectively, with no benzene exposure.

Critical effect: subjective symptoms of neurotoxicity (anxiety, forgetfulness, floating sensation) and respiratory toxicity (nasal irritation and sore throat) and eye irritation. These symptoms were observed in Ernstgard *et al.* (2002), the principal study used for deriving the acute-duration inhalation exposure MRL

End point or Point of Departure (POD): LOAEL = 14 ppm

Uncertainty Factors: UF = 300, 10 each for intraspecies variability and use of a LOAEL and 3 for database deficiencies

Additional note: A single chronic-duration inhalation MRL has been derived based on data for mixed xylenes that applies to mixed xylenes and all of the individual isomers. The justification for deriving a common value is that the isomers have similar toxicokinetic properties and elicit similar toxicological effects, with no isomer consistently exhibiting the greatest potency, depending on the end point.

Source and Date: ATSDR, 8/2007

Cancer:

Carcinogen Weight-of-Evidence (WOE) Class: inadequate for an assessment of the carcinogenic potential of xylenes.

Basis: Adequate human data on the carcinogenicity of xylenes are not available, and the available animal data are inconclusive as to the ability of xylenes to cause a carcinogenic response. Evaluations of the genotoxic effects of xylenes have consistently given negative results.

Source and Date: IRIS, 2/21/2003. An IRIS Toxicological Review is available.

REFERENCES:

Agency for Toxic Substances and Disease Registry (ATSDR). 1989. Toxicological Profile for 1,2-Dichloropropane. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. December 1989. www.atsdr.cdc.gov/toxprofiles/tp134.pdf

ATSDR. 1992. Toxicological Profile for Vinyl Acetate. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. July 1992. www.atsdr.cdc.gov/toxprofiles/tp59.pdf

ATSDR. 1994a. Toxicological Profile for Acetone. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. May 1994. www.atsdr.cdc.gov/ToxProfiles/tp21.pdf

ATSDR. 1994b. Toxicological Profile for Chlordane. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. May 1994. www.atsdr.cdc.gov/ToxProfiles/tp31.pdf

ATSDR. 1994c. Toxicological Profile for 1,1-Dichloroethene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. May 1994. www.atsdr.cdc.gov/toxprofiles/tp39.pdf

ATSDR. 1996. Toxicological Profile for Methyl tert-Butyl Ether. Atlanta, GA: U.S. Department of Health and Human Services. August 1996. www.atsdr.cdc.gov/toxprofiles/tp91.pdf

ATSDR. 1997. Toxicological Profile for Chloroform. Atlanta, GA: U.S. Department of Health and Human Services. September 1997. www.atsdr.cdc.gov/toxprofiles/tp6.pdf

ATSDR. 1998. Toxicological Profile for Chloromethane. Atlanta, GA: U.S. Department of Health and Human Services. December 1997. www.atsdr.cdc.gov/toxprofiles/tp106.pdf

ATSDR. 1999. Toxicological Profile for Mercury. Atlanta, GA: U.S. Department of Health and Human Services. March 1999. www.atsdr.cdc.gov/toxprofiles/tp.asp?id=115&tid=24

ATSDR. 2000. Toxicological Profile for Methylene Chloride. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. September 2000. www.atsdr.cdc.gov/ToxProfiles/tp14.pdf

ATSDR. 2004. Toxicological Profile for Ammonia. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. September 2004. www.atsdr.cdc.gov/toxprofiles/tp126.pdf

ATSDR. 2005. Toxicological Profile Carbon Tetrachloride. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. August 2005. www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=196&tid=35#information

ATSDR. 2006a. Toxicological Profile for Dichlorobenzenes. Atlanta, GA: U.S. Department of Health and Human Services. August 2006. www.atsdr.cdc.gov/toxprofiles/tp10.pdf

ATSDR. 2006b. Toxicological Profile for Vinyl Chloride. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. July 2006. www.atsdr.cdc.gov/ToxProfiles/tp20.pdf

ATSDR. 2007a. Toxicological Profile for Benzene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. August 2007. www.atsdr.cdc.gov/ToxProfiles/tp3.pdf

ATSDR. 2007b. Toxicological Profile for Xylene. Atlanta, GA: US Department of Health and Human Services. August 2007. www.atsdr.cdc.gov/toxprofiles/tp71.pdf

ATSDR. 2009a. Addendum to the Toxicological Profile for 1,1-Dichloroethene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. July 2009. www.atsdr.cdc.gov/toxprofiles/1_1_dichloroethene_addendum.pdf

ATSDR. 2009b. Addendum to the Toxicological Profile for Chloromethane. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. June 2009. www.atsdr.cdc.gov/toxprofiles/chloromethane_addendum.pdf

ATSDR. 2010a. Toxicological Profile for Ethylbenzene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. November 2010. www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=383&tid=66

ATSDR. 2010b. Addendum to the Toxicological Profile for Methylene Chloride. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. July 2010. www.atsdr.cdc.gov/toxprofiles/methylene_chloride_addendum.pdf

ATSDR. 2012. Toxicological Profile for 1,4-Dioxane. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. April 2012. www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=955&tid=199

ATSDR. 2013. Addendum to the Toxicological Profile for Chlordane. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. http://www.atsdr.cdc.gov/toxprofiles/chlordane_addendum.pdf

ATSDR. 2019. Toxicological Profile for Tetrachloroethylene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. June 2019. www.atsdr.cdc.gov/toxprofiles/tp18.pdf

ATSDR. 2017. Toxicological Profile for Toluene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. June 2017. www.atsdr.cdc.gov/toxprofiles/tp56.pdf

ATSDR. 2016. Addendum to the Toxicological Profile for Vinyl Chloride. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. January 2016. www.atsdr.cdc.gov/toxprofiles/VinylChloride_addendum_508.pdf

ATSDR. 2019. Toxicological profile for 1,2-Dichloropropane (Draft for Public Comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. September 2019. www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=831&tid=162

California Environmental Protection Agency (CalEPA). 2020a. 1,1-Dichloroethane. California Office of Environmental Health Hazard Assessment, California Government. https://oehha.ca.gov/chemicals/11-dichloroethane

CalEPA. 2020b. 1,2-Dichloroethylene, cis. California Office of Environmental Health Hazard Assessment, California Government. https://oehha.ca.gov/water/chemicals/12-dichloroethylene-cis

CalEPA. 2020c. 1,2-Dichloroethylene, trans. California Office of Environmental Health Hazard Assessment, California Government. https://oehha.ca.gov/water/chemicals/12-dichloroethylene-trans

Michigan Department of Environmental Quality (MDEQ). 1992a. Memo from Gary Butterfield to File for Ethanol (CAS #64-17-5). MDEQ, Air Quality Division. April 16, 1992.

MDEQ. 1992b. Memo from Gary Butterfield to File for n-Propanol (CAS #71-23-8). Michigan Department of Environmental Quality. July 22, 1992.

MDEQ. 1994. Memo from Marco Bianchi to File for Acetophenone (CAS #98-86-2). MDEQ. June 8, 1994.

MDEQ. 2006a. Memo from Margaret M. Sadoff to File for 2-Chlorophenol (CAS #95-57-8). Michigan Department of Environmental Quality. June 2, 2006.

MDEQ. 2006b. Memo from Gary Butterfield to File for 1,3-Dichlorobenzene (CAS #541-73-1). Michigan Department of Environmental Quality, Air Quality Division. August 4, 2006.

MDEQ. 2016. Memo from Michael Depa to File for Methyl Isobutyl Ketone (CAS #108-10-1). Michigan Department of Environmental Quality, Air Quality Division. May 31, 2016.

MDEQ. 2017. Chemical Update Worksheet for Toluene (CAS #108-88-3). Michigan Department of Environmental Quality, Remediation and Redevelopment Toxicology Unit. June 19, 2017.

United States Environmental Protection Agency (U.S. EPA). 1988. IRIS Database for 2-Chlorophenol, IRIS Summary for 2-Chlorophenol. U.S. Environmental Protection Agency. August 22, 1988. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=303

U.S. EPA. 1990a. IRIS Database for 1,3-Dichlorobenzene, IRIS Summary for 1,3-Dichlorobenzene. U.S. Environmental Protection Agency. September 1, 1990. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=399

U.S. EPA. 1990b. IRIS database for Vinyl Acetate, IRIS Summary for Vinyl Acetate. October 10, 1990. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=512

U.S. EPA. 1991a. IRIS Database for Chlorobenzene, IRIS Summary for Chlorobenzene. U.S. Environmental Protection Agency. March 1, 1991. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=399

U.S. EPA. 1991b. IRIS Database for Ethyl Chloride, IRIS Summary for Ethyl Chloride. April 1, 1991. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=523

U.S. EPA. 1991c. IRIS Database for 1,2-Dichloropropane, IRIS Summary for 1,2-Dichloropropane. December 1, 1991. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=601
U.S. EPA. 1991d. IRIS Database for Methyl tert-butyl ether, IRIS Summary for methyl tert-butyl ether. U.S. Environmental Protection Agency. December 1, 1991. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=545

U.S. EPA. 1991e. IRIS Database for Ethylbenzene, IRIS Summary for Ethylbenzene. U.S. Environmental Protection Agency. January 31, 1991. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=51

U.S. EPA. 1995. IRIS Database for Mercury, Elemental, IRIS Summary for Mercury, Elemental. June 1, 1995. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=370

U.S. EPA. 1998. IRIS Database for Chlordane, IRIS Summary for Chlordane. February 7, 1998. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=142

U.S. EPA. 2000. IRIS Database for Vinyl Chloride, IRIS Summary and Toxicological review for vinyl chloride. U.S. Environmental Protection Agency. August 7, 2000. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1001

U.S. EPA. 2001a. IRIS Database for Chloroform, IRIS Summary and Toxicological review for chloroform. U.S. Environmental Protection Agency. October 19, 2001. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=25

U.S. EPA. 2001b. IRIS Database for Methyl Chloride, IRIS Summary and Toxicological review for methyl chloride. U.S. Environmental Protection Agency. July 17, 2001. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1003

U.S. EPA. 2002. IRIS Database for 1,1-Dichloroethylene, IRIS Summary and Toxicological review for 1,1-Dichloroethylene. U.S. Environmental Protection Agency. August 13, 2002. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=39

U.S. EPA. 2003a. IRIS Database for Acetone, IRIS Summary and Toxicological Review for Acetone. U.S. Environmental Protection Agency. July 31, 2003. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=128

U.S. EPA. 2003b. IRIS Database for Benzene, CASRN: 71-43-2, IRIS Summary, Toxicological Review, and Supporting Documents for Benzene. April 17, 2003. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=276

U.S. EPA. 2003c. IRIS Database for Methyl Ethyl Ketone (MEK), CASRN: 78-93-3, IRIS Summary, Toxicological Review, and Supporting Documents for MEK. September 26, 2003. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=71

U.S. EPA. 2003d. IRIS Database for Xylenes, IRIS Summary and Toxicological Review for Xylenes. U.S. Environmental Protection Agency. February 21, 2003. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=270

U.S. EPA. 2004. IRIS Toxicological Review of Dichlorobenzenes (2004 External Review Draft). US Environmental Protection Agency, Cincinnati, OH, EPA/635/R-03/015, 2004.

U.S. EPA. 2005a. Provisional Peer Reviewed Toxicity Values for Ammonia (CASRN 7664-41-7). Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH. https://hhpprtv.ornl.gov/issue_papers/Ammonia.pdf

U.S. EPA. 2005b. IRIS Database for n-Hexane, CASRN: 110-54-3, IRIS Summary and Supporting Documents for n-Hexane. December 23, 2005. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=486

U.S. EPA. 2005c. IRIS Database for Toluene, IRIS Summary and Toxicological Review for Toluene. U.S. Environmental Protection Agency. September 23, 2005. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=118

U.S. EPA. 2006. Provisional Peer Reviewed Toxicity Values for 1,1-Dichloroethane. Superfund Health Risk Technical Support Center, U.S. Environmental Protection Agency. September 27, 2006. https://hhpprtv.ornl.gov/issue_papers/Dichloroethane11.pdf

U.S. EPA. 2007a. Provisional Peer Reviewed Toxicity Values for Chloroethane (CASRN 75-00-3). Superfund Health Risk Technical Support Center, U.S. Environmental Protection Agency. July 24, 2007. https://cfpub.epa.gov/ncea/pprtv/documents/Chloroethane.pdf

U.S. EPA. 2007b. IRIS Database for 1,1,1-Trichloroethane, IRIS Summary and Toxicological Review for 1,1,1-Trichloroethane. U.S. Environmental Protection Agency. September 28, 2007. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=197

U.S. EPA. 2009a. Provisional Peer Reviewed Toxicity Values for Commercial or Practical Grade Hexane (CASRN 110-54-3). Superfund Health Risk Technical Support Center, U.S. Environmental Protection Agency. September 30, 2009. https://cfpub.epa.gov/ncea/pprtv/documents/HexaneCommercial.pdf

U.S. EPA. 2009b. Provisional Peer Reviewed Toxicity Values for n-Propylbenzene (CASRN 103-65-1). Superfund Health Risk Technical Support Center, U.S. EPA. February 4, 2009. https://cfpub.epa.gov/ncea/pprtv/documents/Propylbenzenen.pdf

U.S. EPA. 2009c. Provisional Peer Reviewed Toxicity Values for 1,2,4-Trichlorobenzene. Superfund Health Risk Technical Support Center, U.S. Environmental Protection Agency. June 16, 2009. https://hhpprtv.ornl.gov/issue_papers/Trichlorobenzene124.pdf

U.S. EPA. 2010a. IRIS Database for Carbon Tetrachloride, IRIS Executive Summary, Toxicological Review, and Supporting Documents for Carbon Tetrachloride. March 31, 2010. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=20

U.S. EPA. 2010b. IRIS Database for trans-1,2-Dichloroethylene, IRIS Executive Summary, Toxicological Review, and Supporting Documents for trans-1,2-Dichloroethylene. September 30, 2010. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=314

U.S. EPA. 2010c. IRIS Database for cis-1,2-Dichloroethylene, IRIS Summary, Toxicological Review, and Supporting Documents for cis-1,2-Dichloroethylene. September 30, 2010. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=418

U.S. EPA. 2011a. IRIS Database for Trichloroethylene, IRIS Summary and Supporting Documents for Trichloroethylene. U.S. Environmental Protection Agency. September 28, 2011. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=199

U.S. EPA. 2011b. Provisional Peer Reviewed Toxicity Values for Diisopropyl ether. Superfund Health Risk Technical Support Center, U.S. Environmental Protection Agency. April 21, 2011. https://cfpub.epa.gov/ncea/pprtv/documents/DiisopropylEther.pdf

U.S. EPA. 2011c. IRIS Database for Dichloromethane (Methylene Chloride) CASRN: 75-09-2, IRIS Summary and Supporting Documents for Dichloromethane. November 18, 2011. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=70

U.S. EPA. 2011d. IRIS Database for Trichloroethylene, IRIS Summary and Supporting Documents for Trichloroethylene. U.S. Environmental Protection Agency. September 28, 2011. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=199

U.S. EPA. 2011e. IRIS Database for Trichloroethylene, IRIS Summary and Supporting Documents for Trichloroethylene. U.S. Environmental Protection Agency. September 28, 2011. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=199

U.S. EPA. 2012a. Provisional Peer Reviewed Toxicity Values for Chloromethane. Superfund Health Risk Technical Support Center, U.S. Environmental Protection Agency. December 4, 2012. https://hhpprtv.ornl.gov/issue_papers/Chloromethane.pdf

U.S. EPA. 2012b. IRIS Database for Tetrachloroethylene, IRIS Summary, Toxicological Review, and Supporting Documents for Tetrachloroethylene. U.S. Environmental Protection Agency. February 10, 2012. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=106

U.S. EPA. 2013a. IRIS Database for 1,4-Dioxane, IRIS Executive Summary and Supporting Documents for 1,4-Dioxane. U.S. Environmental Protection Agency. September 20, 2013. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=326

U.S. EPA. 2013b. IRIS Database for Methanol, IRIS Summary, Toxicological Review, and Supporting Documents for Methanol. U.S. Environmental Protection Agency. September 30, 2013. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=305

U.S. EPA. 2016a. IRIS Database for Ammonia, IRIS Executive Summary, Toxicological Review, and Supplemental Information for Ammonia, Noncancer Inhalation. U.S. Environmental Protection Agency. September 20, 2016. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=422

U.S. EPA. 2016b. IRIS Database for Triallate, IRIS Executive Summary. U.S. Environmental Protection Agency. July 15, 2016. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=195

U.S. EPA. 2016c. IRIS Database for Trimethylbenzenes, IRIS Summary, Toxicological Review, and Supporting Documents for Trimethylbenzenes. U.S. Environmental Protection Agency. September 9, 2016. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1039, https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1037, https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1038

APPENDIX D: AUTHORITIES

SUMMARY OF RESPONSE AUTHORITY

Public Health Code, PA 368 of 1978

In addition to the EGLE's responsibilities to the health and welfare of Michigan residents, the MDHHS has their own legal responsibilities to the health and welfare of Michigan residents. Under the Public Health Code, Act 368 of 1978, the state health department has a responsibility to "continually and diligently endeavor to prevent disease, prolong life, and promote the public health." Additionally, the department shall "have general supervision of the interests of the health and life of the people of this state" and "make investigations and inquiries as to the causes, prevention, and control of environmental health hazards, nuisances, and sources of illness." See below for citations of PA 368.

Part 201

Interim response activity is for actions taken prior to the implementation of a remedial action, as necessary to prevent, minimize, or mitigate injury to public health, safety, or welfare, or to the environment. Interim response activities can include temporary relocation of people and/or access limitations. See below for citations of Part 201 and the associated administrative rules.

Part 213

Requires immediate and expeditious identification and mitigation of acute vapor risks and any other action necessary to abate an immediate threat to public health, safety, or welfare, or the environment.

Part 111

Corrective action includes actions determined by the department as necessary to protect public health, safety, or welfare or the environment including temporary relocation of people. This includes requirements to meet environmental protection standards established by the director for indoor air. Resource Conservation and Recovery Act (RCRA) corrective action guidance includes interim actions to control or abate ongoing risks to human health and the environment in advance of the final remedy selection. See below for citations of Part 111, the associated administrative rules and RCRA corrective action guidance citations.

Part 115

Corrective action includes activities that may be necessary to prevent, minimize, or mitigate injury to public health, safety, or welfare. This includes requirements to meet environmental protection standards established by the director for indoor air.

Relevant sections of the Public Health Code PA 386, Part 201 and associated administrative rules, Part 213, Part 111 and associated administrative rules, Part 115, and RCRA corrective action guidance.

PUBLIC HEALTH CODE, PA 368 OF 1978

MCL 333.2221(1) ...The department shall continually and diligently endeavor to prevent disease, prolong life, and promote public health through organized programs, including prevention and control of environmental health hazards; prevention and control of diseases; prevention and control of health problems of particularly vulnerable population groups...

(2) The department shall:

(a) Have general supervision of the interests of the health and life of the people of this state...

(d) Make investigations and inquiries as to:

(i) The causes, prevention, and control of environmental health hazards, nuisances, and sources of illness.

(e) Plan, implement, and evaluate health education by the provision of expert technical assistance...

PART 201 CITATIONS FOR INTERIM RESPONSE ACTIVITIES RELATED TO VOLATILIZATION TO INDOOR AIR:

324.20101 Definitions.

Sec. 20101. (1) As used in this part:

(x) "Hazardous substance" means 1 or more of the following, but does not include fruit, vegetable, or field crop residuals or processing by-products, or aquatic plants, that are applied to the land for an agricultural use or for use as an animal feed, if the use is consistent with generally accepted agricultural management practices at the time of the application or stamp sands:

(i) Any substance that the department demonstrates, on a case by case basis, poses an unacceptable risk to the public health, safety, or welfare, or the environment, considering the fate of the material, dose-response, toxicity, or adverse impact on natural resources.

(ii) Hazardous substance as defined in the comprehensive environmental response, compensation, and liability act, 42 USC 9601 to 9675.

(iii) Hazardous waste as defined in part 111.

(iv) Petroleum as described as a regulated substance in section 21303.

(y) "Interim response activity" means the cleanup or removal of a released hazardous

substance or the taking of other actions, prior to the implementation of a remedial action, as may be necessary to prevent, minimize, or mitigate injury to the public health, safety, or welfare, or to the environment. Interim response activity also includes, but is not limited to, measures to limit access, replacement of water supplies, and temporary relocation of people as determined to be necessary by the department. In addition, interim response activity means the taking of other actions as may be necessary to prevent, minimize, or mitigate a threatened release.

324.20107a Duties of owner or operator having knowledge of facility; hazardous substances; obligations based on current numeric cleanup or site-specific criteria; liability for costs and damages; compliance with section; applicability of subsection (1)(a) to (c) to state or local unit of government; "express public purpose" explained.

Sec. 20107a. (1) A person who owns or operates property that he or she has knowledge is a facility shall do all of the following with respect to hazardous substances at the facility:

(b) Exercise due care by undertaking response activity necessary to mitigate unacceptable exposure to hazardous substances, mitigate fire and explosion hazards due to hazardous substances, and allow for the intended use of the facility in a manner that protects the public health and safety.

(2) The owner's or operator's obligations under this section shall be based upon the current numeric cleanup criteria under section 20120a(1) or site-specific criteria approved under section 20120b.

324.20114 Owner or operator of facility; duties; response activity without prior approval; easement; applicability of subsections (1) and (3); effect of section on authority of department to conduct response activities or on liability of certain persons; determination of nature and extent of hazardous substance; "available analytical method" defined.

Sec. 20114. (1) Except as provided in subsection (4), an owner or operator of property who has knowledge that the property is a facility shall do all of the following with respect to a release for which the owner or operator is liable under section 20126:

(e) Immediately identify and eliminate any threat of fire or explosion or any direct contact hazards.

(h) Upon written request by the department, take 1 or more of the following actions:

(i) Provide a response activity plan containing a plan for undertaking interim response activities and undertake interim response activities consistent with that plan.

(iv) Take any other response activity determined by the department to be technically sound and necessary to protect the public health, safety, welfare, or the environment.

324.20118 Response activity; remedial action; purposes; selection or approval; conditions.

Sec. 20118. (1) The department may take response activity or approve of response activity proposed by a person that is consistent with this part and the rules promulgated under this part relating to the selection and implementation of response activity that the department concludes is necessary and appropriate to protect the public health, safety, or welfare, or the environment.

(3) Remedial action undertaken under subsection (1) shall accomplish all of the following:

(a) Assure the protection of the public health, safety, and welfare, and the environment with respect to the environmental contamination addressed by the remedial action.

324.20119 Action to abate danger or threat; administrative order; noncompliance; liability; petition for reimbursement; action in court of claims; evidence.

Sec. 20119. (1) In accordance with this section, if the department determines that there may be an imminent and substantial endangerment to the public health, safety, or welfare, or the environment, because of a release or threatened release, the department may require persons who are liable under section 20126 to take necessary action to abate the danger or threat.

324.20120a Cleanup criteria.

(16) Remedial actions that rely on categorical cleanup criteria developed pursuant to subsection (1) shall also consider other factors necessary to protect the public health, safety, and welfare, and the environment as specified by the department, if the department determines based on data and existing information that such considerations are relevant to a specific facility. These factors include, but are not limited to, the protection of surface water quality and consideration of ecological risks if pertinent to the facility based on the requirements of this part.

R 299.28 Cleanup criteria for contaminated environmental media based on other injury which requires consideration.

Rule 28. (1) To assure that hazardous substances in contaminated environmental media do not pose unacceptable risks not accounted for by other rules in this part, the concentration of a hazardous substance in a given environmental medium shall meet cleanup criteria based on sound scientific principles and determined by the department to be necessary to protect the public health, safety, and welfare and the environment from any of the following:

(e) Nonsystemic or acute toxicity.

(h) Other injury that requires consideration.

(2) The basis for and information used by the department to develop cleanup criteria under this rule shall be made available to the public upon request.

PART 213

324.21303 Definitions; N to V.

(h) "Regulated substance" means any of the following:

(i) A substance defined in section 101(14) of title I of the comprehensive environmental response, compensation, and liability act of 1980, Public Law 96-510, 42 USC 9601, but not including a substance regulated as a hazardous waste under subtitle C of the solid waste disposal act, title II of Public Law 89-272, 42 USC 6921 to 6939e.

(ii) Petroleum, including crude oil or any fraction of crude oil that is liquid at standard conditions of temperature and pressure (60 degrees Fahrenheit and 14.7 pounds per square inch absolute). Petroleum includes but is not limited to mixtures of petroleum with de minimis quantities of other regulated substances and petroleum-based substances composed of a complex blend of hydrocarbons derived from crude oil through processes of separation, conversion, upgrading, or finishing such as motor fuels, jet fuels, distillate fuel oils, residual fuel oils, lubricants, and petroleum solvents.

(iii) A substance listed in section 112 of part A of title I of the clean air act, chapter 360, 84 Stat 1685, 42 USC 7412.

324.21304c Duty of owner or operator of property; basis; liability for corrective action activity costs and natural resource damages; applicability of subsection (1)(a) to (c) to state or local unit of government.

Sec. 21304c. (1) A person that owns or operates property that the person has knowledge is contaminated shall do all of the following with respect to regulated substances at the property:

(b) Exercise due care by undertaking corrective action necessary to mitigate unacceptable exposure to regulated substances, mitigate fire and explosion hazards due to regulated substances, and allow for the intended use of the property in a manner that protects the public health and safety.

324.21307 Report of release; initial response actions; duties of owner or operator liable under MCL 324.21323a.

(2) After a release has been reported under subsection (1), the owner or operator that is liable under section 21323a shall immediately begin and expeditiously perform all of the following initial actions:

(a) Identify and mitigate immediate fire, explosion hazards, and acute vapor hazards.

(e) Take any other action necessary to abate an immediate threat to public health, safety, or welfare, or the environment.

(3) Immediately following initiation of initial response actions under this section, the owner or operator that is liable under section 21323a shall do all of the following:

(b) Continue to monitor and mitigate any additional immediate fire and safety hazards posed by vapors or NAPL that have migrated from the underground storage tank system excavation zone and entered into subsurface structures.

324.21308a Initial assessment report; discovery of migrating or mobile NAPL; additional information; supporting documentation upon request.

Sec. 21308a. (1) Within 180 days after a release has been discovered, the owner or operator that is liable under section 21323a shall complete an initial assessment report and submit the report to the department on a form created pursuant to section 21316. The report shall include the following information:

(a) Results of initial actions taken under section 21307(2).

(b) Site information and site characterization results. The following items shall be included as appropriate given the site conditions:

(*xv*) Whether toxic or explosive vapors or migrating or mobile NAPL was found and what steps were taken to evaluate those conditions and the current levels of toxic or explosive vapors or migrating or mobile NAPL in nearby structures.

PART 111 CITATIONS FOR INTERIM ACTIONS/EARLY ACTIONS RELATED TO VOLATILIZATION TO INDOOR AIR:

324.11102 Definitions; B to F.

(2) “Contaminant” means any of the following:

(a) Hazardous waste as defined in R 299.9203 of the Michigan administrative code.

(b) Any hazardous waste or hazardous constituent listed in appendix VIII of part 261 or appendix IX of part 264 of title 40 of the code of federal regulations.

(3) “Corrective action” means an action determined by the department to be necessary to protect the public health, safety, or welfare, or the environment, and includes, but is not limited to, investigation, evaluation, cleanup, removal, remediation, monitoring, containment, isolation, treatment, storage, management, temporary relocation of people, and provision of alternative water supplies, or any corrective action allowed under title II of the solid waste disposal act or regulations promulgated pursuant to that act.

324.11103 Definitions; G to O.

(3) "Hazardous waste" means waste or a combination of waste and other discarded material including solid, liquid, semisolid, or contained gaseous material that because of its quantity, quality, concentration, or physical, chemical, or infectious characteristics may cause or significantly contribute to an increase in mortality or an increase in serious irreversible illness or serious incapacitating but reversible illness, or may pose a substantial present or potential hazard to human health or the environment if improperly treated, stored, transported, disposed of, or otherwise managed. Hazardous waste does not include material that is solid or dissolved material in domestic sewage discharge, solid or dissolved material in an irrigation return flow discharge, industrial discharge that is a point source subject to permits under section 402 of title IV of the federal water pollution control act, chapter 758, 86 Stat. 880, 33 U.S.C. 1342, or is a source, special nuclear, or by-product material as defined by the atomic energy act of 1954, chapter 1073, 68 Stat. 919.

R 299.9629 Corrective action.

Rule 629. (1) Owners or operators of facilities that treat, store, or dispose of hazardous waste shall conduct corrective action as necessary to protect the public health, safety, welfare, and the environment pursuant to a corrective action program approved by the director, unless otherwise specified in this rule. The corrective action program shall be conducted as follows:

(a) Owners or operators of facilities that apply for, or have been issued, an operating license pursuant to part 111 of the act shall institute corrective action for all releases of a contaminant from any waste management units at the facility, regardless of when the contaminant may have been placed in or released from the waste management unit.

(b) Owners or operators of facilities that are not included in subdivision (a) of this subrule and for which the owner or operator, or both, is or was subject to the interim status requirements defined in RCRA, except for facilities that have received formal written approval of the withdrawal of their EPA part A hazardous waste permit application from the director or the EPA, shall institute corrective action for all releases of hazardous waste from the facility, regardless of when the hazardous waste may have been placed in or released from the facility.

(2) Owners or operators shall implement corrective action beyond the facility boundary if the releases referenced in subrule (1) of this rule have or may have migrated, or otherwise have or may have been emitted, beyond the facility boundary, unless the owner or operator demonstrates, to the satisfaction of the director, that, despite the owner's or operator's best efforts, the owner or operator is unable to obtain the necessary permissions to undertake such actions. The owner or operator shall not be relieved of all responsibility to clean up a release that has migrated or been emitted beyond the facility boundary where off-site access is denied. On-site measures to address such releases shall be determined on a case-by-case basis. Assurances of financial responsibility for such corrective action shall be provided.

(3) The owners or operators who are required to establish a corrective action program pursuant to part 111 of the act and these rules shall, at a minimum, do the following, as applicable:

(a) For facilities that are specified in subdivision (a) of subrule (1) of this rule, the owner or operator, or both, shall take corrective action to ensure compliance with the groundwater protection standards, and, if necessary, other applicable environmental protection standards, established by the director....

(iii) The environmental protection standards which are necessary for the cleanup and

protection of soil, surface water, sediments, and ambient and indoor air that are established pursuant to part 201 of the act on the effective date of these rules if the limits are not less stringent than allowed pursuant to RCRA.

(b) For facilities that are specified in subdivision (b) of subrule (1) of this rule, the owner or operator, or both, shall take corrective action to ensure compliance with the groundwater protection standards, and, if necessary, other applicable environmental protection standards, established by the director....

(iii) The environmental protection standards which are necessary for the cleanup and protection of soil, surface water, sediments, and ambient and indoor air that are established pursuant to part 201 of the act on the effective date of these rules if the limits are not less stringent than allowed pursuant to RCRA.

R 299.9502 Operating licenses; applicability and general application requirements.

(12)... (a) If the director determines that even a short delay in the implementation of a remedy would adversely affect human health or the environment, the director may delay compliance with the public notice and public comment requirements of this subrule and implement the remedy immediately. However, the director shall assure involvement of the public at the earliest opportunity, and, in all cases, upon making the decision that additional remedial action is not needed at the facility.

R 299.9901 "Hazardous waste emergency" defined.

Rule 901. "Hazardous waste emergency" means an actual or potential escape of hazardous wastes or hazardous waste constituents into the environment for which the director, or his or her designee, determines that immediate corrective action to remove or contain the wastes or waste constituents is required to prevent or correct environmental damage.

R 299.9902 Declaration of hazardous waste emergency.

Rule 902. (1) The director, or his or her designee, shall declare a hazardous waste emergency based on the following criteria:

(a) The waste meets the criteria of section 3(3) of part 111 of the act.

(b) A determination and oral or written report by on-scene emergency response staff to the director, or his or her designee, that the hazardous wastes or hazardous waste constituents have entered the environment or might enter the environment without corrective action or that corrective action must be taken to eliminate a threat to the environment or public health, safety, and welfare.

(2) If a hazardous waste emergency is declared, it shall be declared ended by the director, or his or her designee, when the threat to the environment has ended.

R 299.9903 Report by the on-scene coordinator.

Rule 903. A written report shall be filed with the director, or his or her designee, by the on-scene coordinator summarizing the tasks accomplished, including an evaluation of the effectiveness of the action to control the hazardous waste emergency.

PART 115 CITATIONS FOR INTERIM ACTIONS/EARLY ACTIONS RELATED TO VOLATILIZATION TO INDOOR AIR:

324.11502 Definitions; A to C.

(23) "Corrective action" means the investigation, assessment, cleanup, removal, containment, isolation, treatment, or monitoring of constituents, as defined in a facility's approved hydrogeological monitoring plan, released into the environment from a disposal area, or the taking of other actions related to the release as may be necessary to prevent, minimize, or mitigate injury to the public health, safety, or welfare, the environment, or natural resources that is consistent with 42 USC 6941 to 6949a and regulations promulgated thereunder.

324.11505 Definitions; R, S.

(4) "Response activity" means an activity that is necessary to protect the public health, safety, welfare, or the environment, and includes, but is not limited to, evaluation, cleanup, removal, containment, isolation, treatment, monitoring, maintenance, replacement of water supplies, and temporary relocation of people.

R 299.4103 Definitions; F to L.

Rule 103. As used in these rules:

(j) "Hazardous substance" means a hazardous substance as defined in part 201 of the act.

R 299.4105 Definitions; S to W.

Rule 105. As used in these rules:

(a) "Sanitary landfill" means a type of disposal area consisting of 1 or more landfill units and the active work areas associated with these units. Sanitary landfills shall be classified as 1 of the following types of landfills:

(i) A type II landfill, which is a municipal solid waste landfill and includes a municipal solid waste incinerator ash landfill.

(ii) A type III landfill, which is any landfill that is not a municipal solid waste landfill or hazardous waste landfill and includes all of the following:

(A) Construction and demolition waste landfills.

(B) Industrial waste landfills.

(C) Landfills which accept waste other than household waste, municipal solid waste incinerator ash, or hazardous waste from conditionally exempt small quantity generators.

R 299.4318 Type III landfill operating requirements; groundwater monitoring.

Rule 318. (1) The requirements of this rule apply to all type III landfill units, except as provided in subrule (2) of this rule.

(9) If the owner or operator determine, pursuant to a statistical test specified in R 299.4908, that there is a statistically significant increase over background for 1 or more of the constituents or indicators listed in subrule (5) of this rule at any monitoring well at or within the solid waste boundary, or at other monitoring locations required by the director, then the owner and operator shall do all of the following:

(b) Within 30 days of the determination, the owner and operator may demonstrate to the director that a source other than a landfill unit or other source at the facility caused the contamination, that the statistically significant increase resulted from error in sampling, analysis, statistical evaluation, or natural variation in groundwater quality, or that the increase is authorized by a permit that is issued pursuant to the provisions of part 31 of the act. A report that documents this demonstration shall be certified by a qualified groundwater scientist, be submitted to the director within 30 days of the determination and be placed in the facility's files. If the director notifies the owner or operator that a successful demonstration has not been made, then within 15 days of the notification by the director the owner and operator shall submit a response action plan to the director as required in R 299.4319. ...

R 299.4319 Type III landfill operation; response action plan.

Rule 319. (1) The owner and operator of a type III landfill unit that is required to prepare a response action plan shall do all of the following:

(4) As part of a response action plan for a type III landfill, the owner or operator shall do both of the following:

(a) Establish groundwater protection standards for all constituents that are determined to be above background in accordance with part 201 of the act.

(b) If necessary, initiate a remedial investigation pursuant to part 201 of the act.

(6) If 1 or more hazardous substances are detected at statistically significant levels and are above the appropriate cleanup criteria for groundwater established by the department pursuant to section 20120a of the act in any sampling event, then the owner or operator shall do all of the following:

(a) Continue response actions to control the source of contamination.

(c) Characterize the nature and extent of any release by installing additional monitoring wells, as necessary.

(e) Initiate a feasibility study, as specified in part 201 of the act. The feasibility study shall be completed within a reasonable period of time approved by the director.

(7) Based on the results of the feasibility study, the owner and operator shall propose to the director a remedial action plan which is in compliance with the provisions of part 201 of the act.

R 299.4439 Type II landfill groundwater monitoring and corrective action; applicability.

Rule 439. (1) The requirements of R 299.4440 to R 299.4445 apply to all type II landfill units, except as provided in subrules (2) and (6) of this rule.

R 299.4440 Type II landfill groundwater monitoring; detection monitoring program.

(8) If the owner and operator determine, pursuant to a statistical test specified in R 299.4908, that there is a statistically significant increase over background for 1 or more of the constituents at any monitoring well at the solid waste boundary or at other monitoring locations required by the director, then the owner and operator shall do both of the following:

(b) Prepare and submit to the director an assessment monitoring plan that is in compliance with R 299.4441 and a response action plan that is in compliance with R 299.4442 within 45 days of the determination, or pursuant to an alternate schedule approved by the director, except as provided in subrule (9) of this rule.

R 299.4441 Type II landfill groundwater monitoring; assessment monitoring program.

Rule 441. (1) Assessment monitoring is required at a type II landfill if a statistically significant increase over background has been detected for 1 or more of the constituents listed in R 299.4440.

(4) After obtaining the results from the initial or subsequent sampling events required in subrule (2) of this rule, the owner and operator shall do all of the following:

(d) Establish groundwater protection standards consistent with section 20120a of the act for all constituents that are detected pursuant to this rule.

(7) If 1 or more constituent listed in R 299.4450 to R 299.4454 or appendix II constituents are detected at statistically significant levels and are above the groundwater protection standard established pursuant to subrule (9) of this rule, in any sampling event, then the owner or operator shall do all of the following:

(e) Characterize the nature and extent of the release by installing additional monitoring wells as necessary.

(g) Except as provided by subrule (8) of this rule, initiate an assessment of

corrective measures as required by R 299.4443 within 90 days of the detection.

R 299.4442 Type II landfill groundwater monitoring; response action plan.

Rule 442. (1) The owner and operator of a type II landfill unit that is required to prepare a response action plan shall identify all of the following:

(a) Possible sources of contamination.

(b) Interim response activities taken or to be taken to control possible sources of contamination.

(2) The director shall approve or deny a response action plan within 60 days of submittal. If the director denies a plan, the director shall specify schedules for closure and interim response necessary to protect human health and the environment.

R 299.4443 Type II landfill corrective action; assessment of corrective measures.

Rule 443. (1) Within 90 days of finding that any hazardous substances have been detected at a statistically significant level, and exceed the groundwater protection standards defined in R 299.4441, the owner and operator of a type II landfill shall initiate an assessment of corrective measures. Such an assessment shall be completed within a reasonable period of time approved by the director.

R 299.4444 Type II landfill corrective action; remedy selection and remedial action plan.

Rule 444. (1) Based on the results of the corrective measures assessment pursuant to R 299.4443, the owner and operator shall propose to the director a remedy that, at a minimum, meets the standards specified in subrule (2) of this rule. The owner and operator shall, within 14 days of selecting a remedy, submit to the director a proposed remedial action plan which is in compliance with part 201 of the act and which describes the selected remedy and how it meets the standards of part 201 of the act. The proposed remedial action plan shall be placed in the operating record.

(2) Remedies that are proposed by an owner or operator shall be in compliance with all of the following provisions:

(a) Be protective of human health and the environment.

(b) Be able to attain the groundwater protection standard as specified in R 299.4441.

R 299.4445 Type II landfill corrective action; implementation of remedial action plan.

Rule 445. (1) Based on the schedule established pursuant to R 299.4444 for the initiation and completion of remedial activities, the owner and operator shall do all of the following:

(b) Implement the remedial action plan approved pursuant to R 299.4444.

(c) Take any interim response activities which are required by the director or which are otherwise necessary to ensure the protection of human health and the environment.

Interim measures shall, to the greatest extent practicable, be consistent with the objectives, and contribute to the performance, of any remedy that may be required pursuant to R 299.4444. All of the following factors shall be considered by an owner or operator in determining whether interim measures are necessary:

RCRA – CA WEBSITE

www.epa.gov/hw/learn-about-corrective-action

While site characterization is underway or before a final remedy is selected, corrective action facilities often need interim actions. Interim actions are used to control or abate ongoing risks to human health and the environment in advance of the final remedy selection. For example, actual or potential contamination of drinking water supplies may necessitate an interim action to provide alternative drinking water sources. U.S. EPA issued **Interim Actions documents** to assist in this process.

2015 OSWER Technical Guide for Assessing and Mitigating the Vapor Intrusion Pathway from Subsurface Vapor Sources to Indoor Air

1.2.2 Taking Action with Limited Data under RCRA Corrective Action

EPA has emphasized the importance of interim actions and site stabilization in the RCRA corrective action program to control or abate “ongoing risks” to human health and the environment while site characterization is underway or before a final remedy is selected (see the *Federal Register* of May 1, 1996 [61 FR 19446]). Interim actions encompass a wide range of institutional and physical corrective action activities to achieve stabilization and can be implemented at any time during the corrective action process. EPA recommends that interim actions, including PEM, be employed as early in the corrective action process as possible, consistent with the human health and environmental protection objectives and priorities for the site. EPA recommends that, as further information is collected, program implementers continue to look for opportunities to conduct additional interim response actions.

APPENDIX E: ACRONYMS AND ABBREVIATIONS

µg/m^3 ..... micrograms per meter cubed
AAC ..... acceptable air concentration
AAV ..... acceptable air value
ACGIH ..... American Conference of Governmental Industrial Hygienists
adj ..... adjusted
AF ..... assessment factor
AQD ..... Air Quality Division
ATF ..... Bureau of Alcohol, Tobacco, Firearms, and Explosives
atm ..... atmosphere
ATSDR ..... Agency for Toxic Substances and Disease Registry
BMCL ..... benchmark concentration
BW ..... body weight
CalEPA ..... California Environmental Protection Agency
CCD ..... Chemical Criteria Database
CSF ..... cancer slope factor
CSM ..... conceptual site model
DCP 1,2-dichloropropane
dev ..... developmental effect
DNEL ..... derived no effect level
DTSC ..... California Department of Toxic Substances Control
ECHA ..... European Chemicals Agency
EGLE ..... Environment, Great Lakes, and Energy
FT ..... full term
GD ..... gestation day
HEAST ..... Health Effects Assessment Summary Tables
HEC ..... human equivalent concentration
HQ ..... hazard quotient
IARC ..... International Agency for Research on Cancer
int ..... intermediate
IPCS ..... International Programme on Chemical Safety
IRIS ..... Integrated Risk Information System

ITSL ..... initial threshold screening level
IURF..... inhalation unit risk factor
kg ..... kilogram
LD..... lactation day
LEC..... lowest effective concentration
LED..... lowest effective dose
LOAEL..... lowest observed adverse effect level
LOEL..... lowest observed effect level
LTWA ..... lifetime weighted average
MDEQ ..... Michigan Department of Environmental Quality
MDHHS..... Michigan Department of Health and Human Services
MEK..... methyl ethyl ketone/2-butanone
mg/kg-day ... milligrams per kilogram per day
mg/m^3 ..... milligrams per meter cubed
MIBK..... methyl isobutyl ketone
MMD..... Materials Management Division
MOA..... mechanism of action
MRL..... minimal risk level
MTBE..... methyl tert-butyl ether
mut..... mutagenic effect
MW..... molecular weight
NEDO..... New Energy Development Organization
NOAEC..... no observed adverse effect concentration
NOAEL ..... no observed adverse effect level
NOEL ..... no observed effect level
nr..... nonresidential
NTP..... National Toxicology Program
OECD ..... Organization for Economic Co-Operation and Development
OEL..... occupational exposure limit
OPP..... Office of Pesticide Programs
OSHA ..... Occupational Safety and Health Administration
OSWER ..... Office of Solid Waste and Emergency Response

PBPK ..... physiologically based pharmacokinetic modeling
PCE ..... tetrachloroethylene
PEL ..... permissible exposure limit
POD ..... point of departure
ppb ..... parts per billion
ppb_{vol} ..... parts per billion by volume
ppm ..... parts per million
ppm_{vol} ..... parts per million by volume
PPRTV ..... provisional peer-reviewed toxicity values
p-RfC ..... provisional reference concentration
RCRA ..... Resource Conservation and Recovery Act
REACH ..... Registration, Evaluation and Authorisation of Chemicals
REL ..... recommended exposure limit
res ..... residential
RfC ..... reference concentration
RfD ..... reference dose
RIASL ..... recommended interim action screening level
RML ..... removal management levels
RoC ..... Report on Carcinogens
RRD ..... Remediation and Redevelopment Division
RSL ..... regional screening level
SE ..... single exposure
TCE ..... trichloroethylene
TLV ..... threshold limit values
TMB ..... trimethylbenzene
TS RIASL ..... time-sensitive recommended interim action screening level
TSG ..... Toxics Steering Group
TWA ..... time weighted average
U.S. EPA ..... United States Environmental Protection Agency
UF ..... uncertainty factor
VI ..... vapor intrusion
VIAP ..... volatilization to indoor air pathway
WOE ..... weight-of-evidence