HSIA halogenated solvents industry alliance, inc.

August 16, 2018

Tyler Lloyd
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Docket No. EPA-HQ-OPPT-2016-0732 (PCE)

Dear Mr. Lloyd:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) represents producers, distributors, and users of perchloroethylene (also referred to as perc or PCE or tetrachloroethylene). We offer these comments on EPA's problem formulation for the risk evaluation of perchloroethylene under the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act enacted in June 2016. 83 Fed. Reg. 26998 (June 11, 2018). HSIA supports the condition of use proposed in the problem formulation document as being appropriate for the risk evaluation and is pleased that EPA is implementing systematic review approaches in all aspects of the risk evaluation.

Perchloroethylene is subject to transportation regulations by the Department of Transportation (DOT) and the Pipeline and Hazardous Materials Safety Administration (PHMSA).

Appendix A.1 of the problem formulation document lists the federal laws and regulations to which perchloroethylene are subject to. There are also specific transportation regulatory requirements for perchloroethylene by the DOT and PHMSA; these regulations need to be added to the list of Federal Laws and Regulations in Appendix A.1. The DOT regulations provide instructions on how perchloroethylene is to be transported by air, highway, rail or water. It defines the operational measures to ensure the health and safety of workers, as well as to ensure that no product is allowed to be released into the air, soil or water. PHMSA has the responsibility to maintain the hazardous material regulations.

Assessments for worker and consumer exposures should utilize all industry provided and publicly available information.

HSIA agrees with EPA's proposed conceptual models in the problem formulation document for perchloroethylene. Attached as Appendix 1 are occupational exposure data for various exposure scenarios that have been collected by HSIA. We encourage EPA to utilize all

available industry provided and publicly available information in its analysis of the exposure assessment in the risk evaluation.

A threshold approach should be used for evaluating cancer risk to perchloroethylene based on a non-genotoxic MOA for liver tumors in mice.

EPA's IRIS assessment concluded that perchloroethylene is "likely to be carcinogenic to humans" based primarily on evidence of increased liver tumors in mice (EPA, 2012).[1] In rats, the incidence of mononuclear cell leukemia (MCL) was also increased, but these tumors are not considered relevant to humans.[2] Evidence of cancer in humans is inadequate or limited at best, with few studies showing positive associations, and for those studies that do, exposure estimates are lacking and/or confounded by exposure to other potential carcinogens. For liver tumors, EPA concluded that the epidemiological data showed mixed results (EPA, 2012).

The mechanism for liver tumors in mice exposed to perchloroethylene is thought to involve the oxidative metabolites and not the GSH metabolites of perchloroethylene (EPA, 2012). Genotoxicity studies on perchloroethylene are generally negative, and trichloroacetic acid (TCA), the major urinary metabolite of perchloroethylene, exhibits little to no genotoxic potential *in vitro* or *in vivo* (EPA, 2012). However, some of the other oxidative metabolites have shown mixed results or weakly positive results at very high dose levels (EPA, 2012).

The weight of evidence for a mode-of-action (MOA) for liver tumors in perchloroethylene-exposed mice strongly favors the involvement of TCA, the major urinary metabolite of perchloroethylene, leading to peroxisome proliferator-activated receptor α (PPARα) activation and peroxisome proliferation. Because this MOA does not involve direct genotoxic activity from TCA, a threshold dose-response assessment should be considered appropriate when evaluating the cancer risk. EPA's IRIS assessment cites a review article by Melnick (2001)[3] as describing evidence of possible genotoxicity from PPARα- activation in addition to peroxisome proliferation; however, this is an incorrect interpretation of that article. Melnick (2001) does not discuss genotoxicity as a possible mechanism of PPARα-activation, but instead describes other mechanisms that would also have a threshold MOA (*e.g*., perturbation of cell growth control through cell proliferation and/or suppression of apoptosis).

The perchloroethylene IRIS assessment also concluded that the mouse liver tumors were not mediated solely by a PPARα-activation/peroxisome proliferation MOA because of data indicating that other mechanisms may be involved, and that the contribution of these other MOAs to the induction of liver tumors in unknown. It is questionable, however, whether these

[1] Environmental Protection Agency, Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in Support of Summary Information on the Integrated Risk Information System (IRIS) (EPA/635/R-08/011F) (2012).

[2] Ismael, J. and Dugard, P.H., A review of perchloroethylene and rat mononuclear leukemia, Regul. Toxicol. Pharmacol. 45: 178-199 (2006); Thomas, J., Haseman, J.K, Goodman, J.I., Ward, J.M., Loughran, Jr., T.P., and Spencer, P.J., A review of large granular lymphocytic leukemia in Fischer 344 rats as an initial step toward evaluating the implication of the endpoint to human cancer risk assessment, Toxicol. Sci. 99: 3-19 (2007).

[3] Melnick, R.L., Is peroxisome proliferation an obligatory precursor step in the carcinogenicity of di(2-ethylhexyl)phthalate (DEHP)?, Environ. Health Perspect. 109: 437-442 (2001).

other mechanisms involve a mutagenic MOA, particularly since there is no convincing evidence that tetrachloroethylene is genotoxic in vivo.

Even if there are multiple mechanisms for the hepatocarcinogenicity of perchloroethylene in mice, the data overall show a much stronger support for estimating cancer risk using a threshold MOA than for a linear low-dose extrapolation approach.

Current occupational exposure limits are adequately protective against cancer in workers.

Occupational exposure limits, such as threshold limit values (TLVs) derived by the American Conference of Governmental Industrial Hygienists (ACGIH), are considered to be protective for occupational exposures. An analysis by Gradient attached as Appendix 2 concludes that the ACGIH TLV of 25 ppm as an 8-hour time-weighted-average (TWA) is protective against cancer in workers at perchloroethylene manufacturing facilities. While this conclusion is based on the worker exposure data tabulated in Appendix 1 on Companies A and B, the data from the third perchloroethylene manufacturing company (Company C) also shows values that are below the ACGIH TLV. Gradient's assessment is that perchloroethylene is a non-genotoxic carcinogen, so that a non-linear dose-response is appropriate.

Integration of OPPT's Systematic Review Principles into TSCA Evaluations.

EPA's Office of Pollution Prevention and Toxics (OPPT) has released a guidance document that describes the general systematic review principles it will use to conduct risk evaluations under the amended TSCA.[4] As noted in its risk evaluation rule, EPA has concluded that systematic review is an integral part of a weight of the scientific evidence approach and that integrating systematic review into risk evaluations is critical to meet the statutory requirements of TSCA.[5] In the systematic review, HSIA supports the use of a numerical scoring system to inform the characterization of the data information sources during the data integration phase. We also see as critical the evaluation of data quality prior to incorporation of the information into the risk evaluation.

Conclusion

We hope that these comments and the Gradient review will be useful to EPA as it develops the risk evaluation for perchloroethylene.

Respectfully submitted,

Faye Graul

Faye Graul
Executive Director

[4] EPA, Application of systematic review in TSCA risk evaluations, Office of Chemical Safety and Pollution Prevention, EPA-740-P1-8001 (May 2018).

[5] Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act, 82 *Fed Reg* 33726, 33734 (July 20, 2017).

Attachments

Attachment 1

Exposure monitoring data of workers at perchloroethylene manufacturing facilities are presented in the tables below. Full shift data are listed in Tables I, III, and V; task samples are listed in Tables II, IV, and VI.

Table I. Worker Exposure Data (Full Shift Samples) from a Perchloroethylene Manufacturing Facility (Company A)

Exposure Group	Approx. Frequency/ Duration	Task Description	Sample Date	Sample Duration (minutes)	Perchloroethylene (ppm)
Operator	Full-shift	General 8-hour exposure	04/17/18	480	Not detected ≤0.065
Operator	Full-shift	General 8-hour exposure	04/19/18	480	Not detected ≤0.065
Operator	Full-shift	General 8-hour exposure	04/23/18	480	Not detected ≤0.065
Operator	Full-shift	General 8-hour exposure	04/24/18	480	Not detected ≤0.065
Operator	Full-shift	General 8-hour exposure	04/25/18	480	0.078
Operator	Full-shift	General 8-hour exposure	04/27/18	480	Not detected ≤0.065

Table II. Worker Exposure Data (Task Samples) from a Perchloroethylene Manufacturing Facility (Company A)

Exposure Group	Task description	Sample Date	Sample Duration (minutes)	Perchloroethylene (ppm)
Inside/outside operator	Catch samples – closed loop system	01/21/16	23	Not detected ≤ 1
Multicraft	Cleaning equipment with solvent	09/06/16	23	Not detected ≤ 0.5
Multicraft	Cleaning equipment with solvent	09/07/16	20	Not detected ≤ 1
Multicraft	Cleaning equipment with solvent	09/08/16	23	Not detected ≤ 0.5
Multicraft	Cleaning equipment with solvent	09/08/16	15	Not detected ≤ 1
Maintenance technician/technologist	Cleaning equipment with solvent	09/08/16	15	Not detected ≤ 1
Maintenance technician/technologist	Cleaning equipment with solvent	09/08/16	15	Not detected ≤ 1
Multicraft	Cleaning equipment with solvent	09/08/16	20	Not detected ≤ 1
Maintenance technician/technologist	Cleaning equipment with solvent	09/08/16	16	Not detected ≤ 1
Multicraft	Cleaning equipment with solvent	09/08/16	18	Not detected ≤ 1
Inside/outside operator	Catch samples – open loop system	02/21/17	45	Not detected ≤ 0.69
Inside/outside operator	Catch samples – open loop system	03/01/17	30	Not detected ≤ 2
Inside/outside operator	Catch samples – open loop system	03/01/17	25	Not detected ≤ 1.3

Table III. Worker Exposure Data (Full Shift Samples) from a Perchloroethylene Manufacturing Facility (Company B)

Exposure Group	Approximate Frequency/ Duration	Task Description	Sample Date	Sample Duration (minutes)	Perchloroethylene (ppm)
Analyzer Technician	Full-Shift	Perform maintenance on instrumentation	11/4/08	480	0.032
Analyzer Technician	Full-Shift	Perform maintenance on instrumentation	11/5/08	480	0.062
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	7/26/07	720	0.041
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	8/7/07	720	0.034
Electrician	Full-Shift	Full-Shift - worked in the utilities F1 area, worked in the 5CP unit and in the electrical shop.	11/4/08	480	0.1
Electrician	Full-Shift	Full-Shift - worked all day installing heaters on the PERC reactor.	11/5/08	480	0.085
Instrument Technician	Full-Shift	Perform maintenance on instrumentation	11/4/08	480	0.12
Instrument Technician	Full-Shift	Perform maintenance on instrumentation	11/5/08	480	0.037
Lab Day Technician	Full-Shift	Full-Shift - worked the 8 hr day job loading tank cars. Loade perc and carbon tetrachloride.	4/30/08	480	0.073
Lab Shift Technician	Full-Shift	Full-Shift - helped run organic samples. Dumped organic sample retains.	4/10/08	720	0.042
Lab Shift Technician	Full-Shift	Full-Shift - helped run organic samples and dumped retains.	4/14/08	720	0.029
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	8/6/07	720	0.036
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	8/7/07	720	0.037
Millwright	Full-Shift	Perform maintenance on compressors, rotating equipment, and pumps	9/30/08	480	0.19
Millwright	Full-Shift	Perform maintenance on compressors, rotating equipment, and pumps	10/1/08	480	0.053
Millwright	Full-Shift	Perform maintenance on compressors, rotating equipment, and pumps	10/2/08	480	0.3

Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	8/11/06	720	0.063
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	7/26/07	720	0.32
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	8/6/07	720	4.6
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	8/7/07	720	0.077
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	10/9/08	720	0.11
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	4/13/10	720	0.051
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	7/12/10	720	0.1
Shipping Day Technician	Full-Shift	Load product/locomotive and rail activities	4/4/06	480	0.2
Shipping Day Technician	Full-Shift	Load product/locomotive and rail activities	5/10/07	480	0.14
Shipping Day Technician	Full-Shift	Load product/locomotive and rail activities	4/29/08	480	0.4
Shipping Day Technician	Full-Shift	Load product/locomotive and rail activities	5/1/08	480	0.28
Shipping Day Technician	Full-Shift	Load product/locomotive and rail activities	5/10/10	480	0.069
	Full-Shift	Full-Shift	10/5/10		1.8
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	4/4/06	720	0.16
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	4/4/06	720	1
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	4/5/06	720	0.16
Utilities Boiler Technician	Full-Shift	Maintenance preparation	7/10/08	720	0.12

Utilities Boiler Technician	Full-Shift	Maintenance preparation	6/5/12	720	0.076
Utilities Boiler Technician	Full-Shift	Maintenance preparation	8/1/12	720	0.22
Utilities Boiler Technician	Full-Shift	Maintenance preparation	10/11/12	720	0.1
Utilities Incinerator Technician	Full-Shift	Maintenance preparation/filter changes/waste transfer/flushing and purging lines	8/25/06	720	0.054
Adminstration II (Process Supervisor)	Full-Shift	Full-Shift - routine Supervison of unit operations.	6/8/16	480	<0.065
Adminstration II (Process Supervisor)	Full-Shift	Full-Shift - routine Supervison of unit operations.	6/16/16	480	<0.063
Adminstration II (Process Supervisor)	Full-Shift	Full-Shift - routine Supervison of unit operations.	7/6/16	480	<0.065
Adminstration II (Process Supervisor)	Full-Shift	Full-Shift - routine Supervison of unit operations.	7/6/16	480	<0.063
Analyzer Technician	Full-Shift	Perform maintenance on instrumentation	12/4/06	480	<0.031
Analyzer Technician	Full-Shift	Perform maintenance on instrumentation	12/5/06	480	<0.032
Analyzer Technician	Full-Shift	Perform maintenance on instrumentation	10/1/07	480	<0.026
Analyzer Technician	Full-Shift	Perform maintenance on instrumentation	10/2/07	480	<0.028
Analyzer Technician	Full-Shift	Perform maintenance on instrumentation	10/3/07	480	<0.028
Analyzer Technician	Full-Shift	Perform maintenance on instrumentation	12/6/07	480	<0.032
Analyzer Technician	Full-Shift	Perform maintenance on instrumentation	11/10/08	480	<0.026
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	7/20/06	720	<0.044
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	7/21/06	720	<0.42
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	8/11/06	720	<0.042
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	7/26/07	720	<0.029
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	8/6/07	720	<0.051
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	10/1/07	720	<0.026
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	10/8/08	720	<0.022

EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	10/9/08	720	<0.022
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	10/13/08	720	<0.02
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	2/18/14	720	<0.047
EDC Outside Equipment Technician	Full-Shift	Maintenance preparation/sample collection/perform rounds	8/26/14	720	<0.032
Electrician	Full-Shift	Full-Shift - worked on the EDC reactor and compressor systems.	12/4/06	480	<0.03
Electrician	Full-Shift	Full-Shift - worked on monitor on F-1 deck, worked in the 230 yard and in the chlorine unit.	12/5/06	480	<0.031
Electrician	Full-Shift	Full-Shift - worked in the membrane chopper room and on the top of TK1801.	10/2/07	480	<0.027
Electrician	Full-Shift	Full-Shift - worked on electrical equipment for MCI unit and worked in the old MCFII unit.	10/3/07	480	<0.027
Electrician	Full-Shift	Full-Shift - worked on electrical systems.	12/6/07	480	<0.032
Electrician	Full-Shift	Full-Shift - worked on electrical problems in the caustic and in the chlorine unit.	11/10/08	480	<0.033
Instrument Technician	Full-Shift	Perform maintenance on instrumentation	12/4/06	480	<0.031
Instrument Technician	Full-Shift	Perform maintenance on instrumentation	12/5/06	480	<0.032
Instrument Technician	Full-Shift	Perform maintenance on instrumentation	12/6/06	480	<0.032
Instrument Technician	Full-Shift	Perform maintenance on instrumentation	10/1/07	480	<0.027
Instrument Technician	Full-Shift	Perform maintenance on instrumentation	10/2/07	480	<0.026
Instrument Technician	Full-Shift	Perform maintenance on instrumentation	10/3/07	480	<0.027
Instrument Technician	Full-Shift	Perform maintenance on instrumentation	11/10/08	480	<0.026
Lab Day Technician	Full-Shift	Full-Shift - made and shot standards.	3/7/06	480	<0.035
Lab Day Technician	Full-Shift	Full-Shift - helped run organic sample rounds and worked on lab instruments.	3/8/06	480	<0.033
Labor Day Technician	Full-Shift	Full-Shift - ran samples.	5/21/07	480	<0.047

Labor Day Technician	Full-Shift	Full-Shift - worked in the environmental lab and helped in the inorganic area.	5/22/07	480	<0.048
Labor Day Technician	Full-Shift	Full-Shift - made organic standards. Shot controls on instruments. Calibrated the IH instrument.	5/23/07	480	<0.048
Lab Day Technician	Full-Shift	Full-Shift - ran organic samples, ran RCL and wets.	4/10/08	480	<0.026
Lab Day Technician	Full-Shift	Full-Shift - ran organic samples all day and dumped retained samples under lab hood.	4/11/08	480	<0.028
Lab Day Technician	Full-Shift	Full-Shift - helped run organics samples most of the day, helped with caustic samples. Dumped organic retains.	4/11/08	480	<0.027
Lab Day Technician	Full-Shift	Full-Shift - ran organic samples, doing RCL and wet test analysis. Dumped the sample retains under lab hood.	4/14/08	480	<0.023
Lab Shift Technician	Full-Shift	Full-Shift - ran organics, made rounds, dumped lab retains. Ran organic samples.	3/7/06	720	<0.033
Lab Shift Technician	Full-Shift	Full-Shift - worked in the organics section of the lab running samples all day. Made 1 round in the plant to pick up samples.	3/8/06	720	<0.034
Lab Shift Technician	Full-Shift	Full-Shift - made rounds in plant to pick up samples and analyzed standard organic samples.	3/9/06	720	<0.034
Lab Shift Technician	Full-Shift	Full-Shift - worked in the environmental lab all day. Dumped lab retainer.	3/9/06	720	<0.034
Lab Shift Technician	Full-Shift	Full-Shift - made unit round to pick up samples. Ran organic samples all day.	5/21/07	720	<0.04
Lab Shift Technician	Full-Shift	Full-Shift - made round into plant to pick up samples. Ran organic samples all day.	5/22/07	720	<0.042
Lab Shift Technician	Full-Shift	Full-Shift - made round into plant to pick up samples. Ran organic samples all day. Dumped sample bottles.	5/23/07	720	<0.041
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	7/20/06	720	<0.039

MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	7/21/06	720	<0.042
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	8/11/06	720	<0.036
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	10/8/08	720	<0.021
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	10/9/08	720	<0.02
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	10/13/08	720	<0.023
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	2/25/10	720	<0.041
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	7/12/10	720	<0.04
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	9/16/10	720	<0.042
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	8/3/11	720	<0.016
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	9/7/11	720	<0.045
MCI Outside Equipment Technician	Full-Shift	Maintenance preparation of equipment/collect samples/perform rounds	10/6/11	720	<0.047
Millwright	Full-Shift	Perform maintenance on compressors, rotating equipment, and pumps	9/30/08	480	<0.037
Millwright	Full-Shift	Perform maintenance on compressors, rotating equipment, and pumps	10/1/08	480	<0.039
Millwright	Full-Shift	Perform maintenance on compressors, rotating equipment, and pumps	10/2/08	480	<0.038

Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	7/20/06	720	<0.04
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	7/21/06	720	<0.035
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	10/8/08	720	<0.21
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	11/3/08	720	<0.021
Perc Outside Equipment Technician	Full-Shift	Maintenance preparation of piping and equipment/collect samples/perform rounds/change filters and traps	9/16/10	720	<0.039
Shipping Day Technician	Full-Shift	Load product/locomotive and rail activities	4/6/06	480	<0.038
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	4/5/06	720	<0.039
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	4/6/06	720	<0.038
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	4/6/06	720	<0.041
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	5/5/07	720	<0.035
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	5/8/07	720	<0.035
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	5/10/07	720	<0.031
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	5/14/07	720	<0.04
Shipping Shift Technician	Full-Shift	Load/unload raw materials and product/sample collection	5/10/10	720	<0.042
Utilities Boiler Technician	Full-Shift	Maintenance preparation	7/8/08	720	<0.015
Utilities Boiler Technician	Full-Shift	Maintenance preparation	7/9/08	720	<0.02
Utilities Control Board Technician	Full-Shift	Full-Shift - worked control board.	8/22/06	720	<0.043
Utilities Control Board Technician	Full-Shift	Full-Shift - worked control board.	8/24/06	720	<0.045
Utilities Control Board Technician	Full-Shift	Full-Shift - worked control board.	8/25/06	720	<0.037

Utilities Incinerator Technician	Full-Shift	Maintenance preparation/filter changes/waste transfer/flushing and purging lines	8/22/06	720	<0.045
Utilities Incinerator Technician	Full-Shift	Maintenance preparation/filter changes/waste transfer/flushing and purging lines	8/24/06	720	<0.047
Utilities Incinerator Technician	Full-Shift	Maintenance preparation/filter changes/waste transfer/flushing and purging lines	8/31/07	720	<0.032
Utilities Incinerator Technician	Full-Shift	Maintenance preparation/filter changes/waste transfer/flushing and purging lines	9/5/07	720	<0.032
Utilities Incinerator Technician	Full-Shift	Maintenance preparation/filter changes/waste transfer/flushing and purging lines	9/21/07	720	<0.033
Utilities Incinerator Technician	Full-Shift	Maintenance preparation/filter changes/waste transfer/flushing and purging lines	7/8/08	720	<0.019
Utilities Incinerator Technician	Full-Shift	Maintenance preparation/filter changes/waste transfer/flushing and purging lines	7/9/08	720	<0.015
Utilities Incinerator Technician	Full-Shift	Maintenance preparation/filter changes/waste transfer/flushing and purging lines	7/10/08	720	<0.021

Table IV. Worker Exposure Data (Task Samples) from a Perchloroethylene Manufacturing Facility (Company B)

Exposure Group	Task Name	Approximate Frequency/Duration	Task Description	Sample Date	Sample Duration (minutes)	Perchloroethylene (ppm)
Shipping Day Tech	Connecting CTET railcar	STEL - 2 times/week - 5	Connecting Carbon Tetrachloride loading lines to railcar for loading.	10/14/10	40	<0.15
Chlorine Day Tech	Loading CTET Dump Buggy	STEL - 2 times/week - 5	Loading CTET Dump Buggy	11/8/12	15	<0.21
Chlorine Day Tech	Loading CTET Dump Buggy	STEL - 2 times/week - 5	Loading CTET Dump Buggy	11/27/12	15	<0.21
Chlorine Day Tech	Loading CTET Dump Buggy	STEL - 2 times/week - 5	Loading CTET Dump Buggy	12/28/12	15	<0.21
Chlorine Day Tech	Loading CTET Dump Buggy	STEL - 2 times/week - 5	Loading CTET Dump Buggy	12/31/12	15	<0.21
Shipping Day Tech	Connecting CTET railcar	STEL - 2 times/week - 5	Connecting Carbon Tetrachloride loading lines to railcar for loading.	12/28/12	15	<0.21
Shipping Day Tech	Disconnecting CTET Railcar	STEL - 2 times/week - 5	Disconnecting Carbon Tetrachloride loading lines after loading railcar.	11/29/11	15	<0.21
Shipping Day Tech	Disconnecting CTET Railcar	STEL - 2 times/week - 5	Disconnecting Carbon Tetrachloride loading lines after loading railcar.	11/29/11	15	<0.21
Shipping Shift Tech	Connecting CTET Truck	STEL - Weekly / 5	Connecting CTET loading Lines to load CTET Truck	12/31/12	15	<0.21
Shipping Shift Tech	Connecting CTET Truck	STEL - Weekly / 5	Connecting CTET loading Lines to load CTET Truck	12/28/12	15	<0.21
Shipping Shift Tech	Disconnecting CTET Truck	STEL - Weekly / 5	Disconnecting Carbon Tetrachloride loading lines after loading truck.	1/17/12	15	<0.21
Shipping Shift Tech	Disconnecting CTET Truck	STEL - Weekly / 5	Disconnecting Carbon Tetrachloride loading lines after loading truck.	8/24/11	11	<0.29
Shipping Day Tech	Connecting CTET railcar	STEL - Weekly / 5	Connecting Carbon Tetrachloride loading lines to railcar for loading.	10/12/10	17	<<0.35

Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from DR-215. Closed loop sampling station. Used sample pump with manifold splitter to collect sample for organics and HCL.	7/13/15	30	<0.4
Shippng Day Tech	Disconnecting CTET Railcar	STEL - 2 times/week - 5	Disconnecting Carbon Tetrachloride loading lines after loading railcar.	10/19/10	15	<0.4
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Dr 204 sample collection	9/22/10	15	<0.41
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Dr 204 sample collection	9/22/10	15	<0.41
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from DR 223 A/B. Closed loop sampling station.	7/14/15	30	<0.41
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from DR 223 A/B. Closed loop sampling station.	7/22/15	20	<0.41
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from DR 223 A/B. Closed loop sampling station.	8/20/15	30	<0.41
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Dr 204 sample collection	9/22/10	15	0.42
Shipping Shift Tech	Connecting CTET Truck	STEL - Weekly / 5	Connecting Carbon Tetrachloride loading lines to load CTET truck.	8/24/11	7	<0.46
Shipping Day Tech	Disconnecting CTET Railcar	STEL - 2 times/week - 5	Disconnecting Carbon Tetrachloride loading lines after loading railcar.	11/30/11	15	0.47
Shipping Day Tech	Disconnecting CTET Railcar	STEL - 2 times/week - 5	Disconnecting Carbon Tetrachloride loading lines after loading railcar.	10/13/10	15	0.48
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from DR-215. Closed loop sampling station.	8/31/15	25	<0.51
Perchloroethylene Outside Equipment	Sample Collection	STEL - Daily / 2	Collected process sample from D223 A/B. Closed loop sampling	9/3/15	25	<0.51

Technician			station.			
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Sample collection form T204 Draw	8/15/11	6	<0.53
Chlorine Day Tech	Unloading Dump Buggy	STEL - 2 times/week - 5	Unloading Dump Buggy into PERC unit process.	11/8/12	15	0.54
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from D207. Closed loop sampling station.	8/21/15	22	<0.51
Chlorine Day Tech	Unloading Dump Buggy	STEL - 2 times/week - 5	Unloading Dump Buggy into PERC unit process.	9/23/10	15	0.58
Chlorine Day Tech	Unloading Dump Buggy	STEL - 2 times/week - 5	Unloading Dump Buggy into PERC unit process.	9/28/10	20	<0.59
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from t-204 reflux. Closed loop sampling station.	9/10/15	20	<0.59
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from t-204 reflux. Closed loop sampling station.	7/22/15	20	<0.61
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from DR-207. Closed loop sampling station.	6/24/15	20	<0.62
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Sample collection form T204 Draw	10/11/11	5	<0.65
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from t-204 reflux. Closed loop sampling station.	7/2/15	18	<0.68
Chlorine Day Tech	Unloading Dump Buggy	STEL - 2 times/week - 5	Unloading Dump Buggy into PERC unit process.	5/3/10	15	<0.86
Shipping Shift Tech	Disconnecting CTET Truck	STEL - Weekly In plant Load - 5	Disconnecting Carbon Tetrachloride loading lines after loading truck.	1/11/12	15	0.95
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Collected process sample from DR-215. Closed loop sampling station.	10/8/15	15	<0.96
Shipping Day Tech	Disconnecting CTET Railcar	STEL - 2 times/week - 5	Disconnecting Carbon Tetrachloride loading lines after	10/19/10	15	1.5

			loading railcar.			
Perchloroethylene Outside Equipment Technician	Sample Collection	STEL - Daily / 2	Sample collection form T204 Draw	6/9/11	8	1.7
Chlorine Day Tech	Loading CTET Dump Buggy	STEL - 2 times/week - 5	Loading CTET Dump Buggy	12/19/11	15	5
Shipping Shift Tech	Connecting CTET Truck	STEL - 2 times/week - 5	Connecting CTET loading Lines to load CTET Truck	6/5/12	15	<2.1
Tank Area Loader	Solvent Loading	Infrequent / ≤ 15	Solvent Loading	6/29/06	15	6.4
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	12/6/06	12	0.824
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	12/6/06	15	2.69
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	12/6/06	16	3.957
Chloromethanes II Thermal Technician	0600 Sample Round	Daily / ≤ 15	0600 Sample Round	12/12/06	15	<0.048
Tank Area Loader	Trailer Sample	Infrequent / ≤ 15	Trailer Sample	3/21/07	15	1.9
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	5/8/07	15	3.4
Chloromethanes II Thermal Technician	0600 Sample Round	Daily / ≤ 15	0600 Sample Round	12/20/07	15	1.6
Tank Area Loader	Trailer Sample	Infrequent / ≤ 15	Trailer Sample	4/16/08	15	1.5
Chloromethanes II Thermal Technician	0600 Sample Round	Daily / ≤ 15	0600 Sample Round	7/31/08	15	28
Chloromethanes II Thermal Technician	0600 Sample Round	Daily / ≤ 15	0600 Sample Round	2/4/09	15	<1.2
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	6/24/09	15	6.5
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	5/12/09	15	1.5
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	5/14/09	15	10
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	8/25/10	15	80
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	8/25/10	15	4.6

VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	10/7/10	15	<0.31
Tank Area/Drum Fill Loader	Drum Sampling	Bi-weekly / ≤ 15	Drum Sampling	10/20/10	15	0.79
Tank Area/Drum Fill Loader	Drum Sampling	Bi-weekly / ≤ 15	Drum Sampling	10/20/10	15	0.3
Tank Area/Drum Fill Loader	Drum Sampling	Bi-weekly / ≤ 15	Drum Sampling	10/20/10	15	12
Tank Area/Drum Fill Loader	Drum Sampling	Bi-weekly / ≤ 15	Drum Sampling	11/10/10	15	1.1
Tank Area Loader	Sample Collection	Infrequent / ≤ 15	Sample Collection	12/10/10	15	1.9
Tank Area/Drum Fill Loader	Drum Sampling	Bi-weekly / ≤ 15	Drum Sampling	12/21/10	15	7.8
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	12/22/10	15	2
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	12/22/10	15	1.6
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	5/26/11	15	12
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	7/30/11	15	13
VCRU Technician	Special Samples	Infrequent / ≤ 15	Special Samples	8/2/11	21	1.3
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	9/19/11	15	10
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	9/28/11	15	4.9
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	10/7/11	15	4.6
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	10/17/11	15	0.73
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	10/19/11	15	4.3
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	10/18/11	15	2.6
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	10/25/11	15	1.4
Tank Area Loader	Special Samples	Infrequent / ≤ 15	Special Samples	11/28/11	15	2

Tank Area/Drum Fill Loader	Drum Sampling	Bi-weekly / ≤ 15	Drum Sampling	11/30/11	15	5.1
Tank Area/Drum Fill Loader	Drum Sampling	Bi-weekly / ≤ 15	Drum Sampling	11/30/11	15	3
Tank Area/Drum Fill Loader	Drum Sampling	Bi-weekly / ≤ 15	Drum Sampling	11/30/11	15	11
Tank Area/Drum Fill Loader	Drum Sampling	Bi-weekly / ≤ 15	Drum Sampling	11/30/11	15	10
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	12/1/11	15	6.5
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	12/12/11	15	4.1
Tank Area Loader	Special Samples	Infrequent / ≤ 15	Special Samples	12/12/11	15	5.4
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	12/13/11	15	2.2
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	12/16/11	15	7.5
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	12/22/11	15	2.7
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	4/2/12	15	2.5
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	10/25/12	20	3.7
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	5/13/13	20	1.6
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	5/28/13	15	1.6
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	5/28/13	16	<1.1
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	5/29/13	15	<1.2
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	6/26/13	23	8.5
Tank Area Loader	Special Samples	Infrequent / ≤ 15	Special Samples	7/30/13	15	200
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	8/15/13	15	7
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	6/27/13	18	12

Tank Area Loader	Special Samples	Infrequent / ≤ 15	Special Samples	11/13/13	19	1.9
Tank Area Loader	Special Samples	Infrequent / ≤ 15	Special Samples	11/20/13	15	4
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	12/4/13	15	3.9
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	6:00 am morning samples - T503 Bottoms, T504 bottoms, T503 Reflux, T504 Reflux, T505 Bottoms, T505 Reflux, T506 Reflux, T505 After, T506 After, and Trap. Took tower readings, checked levels and pressures in towers.	3/20/14	18	1.8
Control Lab Technician	Special Samples	Frequent / ≤ 15	Took bottles to chlorine plant to get sample, went with chlorine plant operator to pre-cooler trailer, rinsed sample line into rinse jar, then filled 2 sample bottles with sample from trailer. Took bottles and rinse jar back to lab. dumped rinse jar into solvent for recovery tote. brought samples into lab and put them on the stirrer.	3/21/14	15	<0.46
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Collected 6:00 am samples, which include: Trap, T505after, T506after, T504 bottoms, T505 bottoms, T503 bottoms, T503 reflux.	5/27/14	16	5.3

VCRU Technician	D530 Filter Change	Weekly / ≤ 15	Blocked filters in. drained excess chemical from bleed valve at bottom of filter housing, removed lid of filter with an impact wrench, removed filter, put it in the D530 filter drum, put a new filter in, replaced excess chemical into filter casing. replaced lid on filter casing. Dumped excess chemical from bucket into waste for recovery drum. Repeated this again for 2nd filter. Unblocked filters.	6/4/14	15	2.3
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Transferred jugs from cart to platform, opened solvent for recovery tote, dumped 6 jugs into tote, closed lid on tote, put jugs back on cart and took them back inside.	6/16/14	15	20
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Lab tech had the jugs already loaded on a cart. he took the cart outside to the solvents for recovery tote, dumped the jug contents into the tote, recapped them, put them back on the cart. He did this 5 times, then recapped the solvent for recovery tote. Then he took the cart and jugs back inside and put them away.	6/25/14	15	6.4

Control Lab Technician	Special Samples	Weekly / ≤ 15	Opened valve on trailer and drained sample line into waste jug. filled 2 sample bottles , then closed valve. drained the excess from the sample line into the waste jug. took sample bottles and waste jug back to lab. dumped waste jug contents into solvent for recovery tote and put sample bottles on magnetic stirrer to mix.	7/25/14	20	<0.32
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	10/22/14	15	3.9
Control Lab Technician	Special Samples	Weekly / ≤ 15	Put waste jug under sample tubing and purged sample line into waste jug. filled 2 sample bottles and capped them. drained sample tubing into waste jug. Took samples and waste jug back to lab. dumped waste jug into solvent for recovery tote and put it away.	11/6/14	15	2.5
Tank Area Loader	Special Samples	Infrequent / ≤ 15	Special Samples	12/15/14	19	1.2
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	12/17/14	16	25
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	12/17/14	17	18
Control Lab Technician	Special Samples	Varies / ≤ 15	Special Samples	12/20/14	15	<0.39
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	12/22/14	29	13
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	12/23/14	16	1.4
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	STEL - Dumped 4 (3 gal) solvent jugs into recovery tote.	1/12/15	15	5.8

VCRU Technician	D530 Filter Change	Weekly / ≤ 15	Closed valves to block in filter. opened drain valves at the bottom to drain off organic liquid into a bucket. closed drain valve, used air tools to remove lid from filter. removed filter from filter pot and placed it in the satellite drum. placed new filter in filter pot and put organics from bucket back into filter pot. placed lid back on top of filter pot and tightened it up with air tools. opened valves back up to filter pot. repeated this process on the 2nd filter pot.	1/28/15	20	2.4
Control Lab Technician	Special Samples	Weekly / ≤ 15	Purged sample line into waste bucket. filled 2 sample bottles with sample, then purged sample line again into waste jug. took all of that back to the lab and dumped the contents of the waste jug into the solvent for recovery tote. weighed sample bottles and put them on the stirrer for a second, then put them in the refrigerator.	2/3/15	15	0.81
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	0600 sample round - collected T503bottoms, T504bottoms, Trap, T505bottoms, T505product, T503 reflux. collected these samples, rinsing the bottles into a waste bucket. dumped contents of the waste bucket into a solvent for recovery tote.	2/25/15	19	<0.3
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	STEL-dumping lab waste jugs to recovery tote, using burpless recovery funnel. Some burping noted at end of 2nd jug dump.	4/17/15	15	5.8

Solvent Loader	Special Samples	Frequent / ≤ 15	Blew out product line, connected air hose to pressure up railcar, rinsed sample bottle 2 times, dumping rinsate into waste bucket. filled sample bottles. finished pressuring up railcar, then disconnected.	5/27/15	18	5
Solvent Loader	Special Samples	Frequent / ≤ 15	Disconnected VCRU hose, turned on air to blow out the load hose. Connected air hose to pressure up railcar. rinsed sample bottle 2 times, dumping rinsate into waste bucket, then filled the sample bottle and capped it. sniffed railcar down to pressure up car. Pressured it up, then disconnected it and sealed it. Dumped waste from waste bucket into solvent for recovery tote.	5/28/15	17	5.5
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	5/28/15	17	8.3
Control Lab Technician	Special Samples	Varies / ≤ 15	Communicated with chlorine plant operator to open and control valves so he could fill the 2 sample bottles. Then drained sample line into solvent for recovery jug. Dumped solvent for recovery jug contents into solvent for recovery tote.	6/10/15	20	3.7

VCRU Technician	D530 Filter Change	Weekly / ≤ 15	Employee drained out the filter pot into a waste bucket, then removed the lid from the filter pot. Took out the old filter and put it into the filter waste drum. Then he put a new filter in and poured the liquid from the waste bucket back into the filter casing and put the lid back on. Repeated this process for the 2nd filter, then dumped the contents of the waste jug into a solvent for recovery drum.	6/16/15	15	7.1
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Picked up the 0600 sample round - T503 bottoms, T503 reflux, T504 bottoms, T505 bottoms, T506 reflux, T505 after, T506 after and trap.	7/21/15	28	13
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	Closed 2 valves to block in filters. Drained excess carbon tetrachloride into a waste bucket. Removed lid from filter and removed filter from casing. Put a new filter in and poured the carbon tet from the waste bucket back into the filter casing. Placed lid back on filter and sealed. Repeated this process for the second filter.	7/22/15	16	15

Solvent Loader	Special Samples	Frequent / ≤ 15	Disconnected load hose and VCRU hose. Connected air hose to pressure up car. filled sample bottle with product, rinsed bottle and dumped it into a waste bucket. Filled the sample bottle again and capped it. Disconnected sample line from railcar. Filled another bucket with water and poured it over the dome of the railcar to leak check it.	8/17/15	17	5.5
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumped 3 solvent jugs into solvent for recovery tote.	8/17/15	15	5.7
Control Lab Technician	Special Samples	STEL	Purged line into waste jug. Filled 2 sample bottles with sample. purged line into waste jug. Took samples back to lab.	9/17/15	15	2.7
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Collected 0600 samples - T503 bottoms, T504 bottoms, T505 bottoms, T503 reflux, T504 reflux, T505 reflux, T506 reflux, TRAP, T505A, T506A.	11/19/15	25	0.56
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Took one jug from the lab to the tote outside. Opened the funnel, dumped the jug inside and closed it. Repeated this process for 3 jugs total.	11/20/15	15	1.7
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	Drained the first filter out into a waste bucket. Removed filter lid, then removed the filter into another waste bucket. Put a new filter in the casing. replaced the lid, then repeated this process for the second filter.	12/2/15	21	2.8

Control Lab Technician	Special Samples	Weekly / ≤ 15	Purged sample line into a waste jug. Filled sample bottles and put them in a carrier. Drained sample line into the waste jug and disconnected sample apparatus. Took back to lab and dumped the waste jug into the solvent for recovery tote.	12/3/15	17	4.6
Solvent Loader	Special Samples	Frequent / ≤ 15	Disconnected hose that goes to VCRU. Connected air hose to pressure up railcar. Disconnected load hose and fittings. Filled sample bottle and rinsed it, then dumped that into a waste bucket. Filled bottle again and capped it. Disconnected sampling apparatus and the rest of the hoses. Finished sealing up the railcar.	12/10/15	15	7
Solvent Loader	Special Samples	Frequent / ≤ 15	Disconnected load line. connected air line to pressure up car and turned air on. connected sample hose line and opened sample line and let sample line purge into waste bucket. Filled sample bottle a little ways, rinsed it and dumped the rinsate into the waste bucket. Filled sample bottle and capped it. Closed sample line valve and disconnected sample tubing. Disconnected load line fitting. Pressure checked railcar. Finished tightening everything up and sealed it up.	3/14/16	16	2.4
Solvent Loader	Special Samples	Frequent / ≤ 15	Special Samples	3/15/16	17	7.1
Solvent Loader	Special Samples	Frequent / ≤ 15	Special Samples	3/15/16	15	7.7

Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Collected 0600 samples - T503 bottoms, T504 bottoms, T505 bottoms, T505A, T506A, TRAP, T503 reflux and stabbed D517 with amylene stabilizer.	3/15/16	18	0.9
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	Blocked in first set of filters, drained excess carbon tetrachloride from filter casing into a waste bucket. Removed filter lid and removed excess carbon from around top of filter casing. pulled filter up and held it there to keep carbon tetrachloride in the filter casing. Pulled the filter out and put it in a waste bucket. Placed new filter in filter casing. Poured carbon tetrachloride from waste bucket back into filter casing. Put gasket back in place and replaced lid. Repeated this process for second filter. Dumped used filters into the satellite drum for filters. Dumped excess carbon tetrachloride that was in waste bucket, into a solvent for recovery drum.	3/16/16	25	5.1

Control Lab Technician	Special Samples	Weekly / ≤ 15	Went to pre-cooler trailer with chlorine plant operator. Put sample tubing into the waste jug and opened the valves. Closed valves and removed jug. Placed sample bottle under tubing, opened valves again to sample. Repeated for second sample bottle. Removed second sample bottle and put waste jug back under sample tubing. Purged sample line into jug. took bottles back to lab and poured waste from waste jug into the solvent for recovery tote.	3/30/16	15	<0.43
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Placed funnel in top of tote. Dumped 3 jugs into tote. Removed funnel and replaced cap on tote.	3/31/16	15	3.7
Solvent Loader	Special Samples	Frequent / ≤ 15	Blew out load line with air hose. disconnected load hose. Connected air hose to railcar to pressure up railcar and pressured it up. Disconnected the air hose and connected the sampling line fittings. Purged sample line into waste bucket, then filled sample bottle with some product and rinsed the bottle out into the waste bucket. Filled the sample bottle and capped it. Disconnected the rest of the load connections and sealed up the railcar.	5/24/16	16	0.95
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	6/7/16	15	<0.41

VCRU Technician	D530 Filter Change	Weekly / ≤ 15	Blocked filters in. drained excess carbon tetrachloride out of filter casing. Used impact to remove filter lid. Cleaned around the filter lid. Removed filter with pliers, draining excess carbon tetrachloride into casing before pulling it all the way out. Placed a new filter inside the casing and poured the excess carbon tetrachloride from the bucket under the drain back into the casing. Replaced filter lid and tightened it with the impact. Repeated this process on the 2nd filter. Put excess carbon tetrachloride that was in buckets into a solvent for recovery drum.	6/8/16	19	19
Control Lab Technician	Special Samples	Weekly / ≤ 15	Purged sample line into waste jug; filled 2 sample bottles, then drained sample line into waste jug.	6/28/16	17	<0.36
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Lab tech had jugs loaded onto a cart. Pushed the cart outside, dumped 7 jugs into the solvent for recovery tote, put empty jugs back on the cart and rolled it back into the lab.	7/11/16	15	5.4
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Collected 0600 samples - T503 bottoms, T503 reflux, T504 bottoms, T505 bottoms, T505 after, T506 after, Trap.	8/9/16	17	9.2

Solvent Loader	Special Samples	Frequent / ≤ 15	Connected air line to blow the load line out. disconnected load hose. Connected air line to pressure up railcar. Connected sampling apparatus to railcar. Started purging sample line into a waste bucket. Filled sample bottle and rinsed it. Dumped that into a waste bucket. Filled sample bottle and capped it. Disconnected sampling apparatus. Closed air line and finished disconnecting railcar and sealed it up.	9/8/16	15	2.6
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	Drained filter casing into a waste bucket. removed filter casing lid. Scraped excess carbon into filter. Pulled filter from casing and put it over a waste bucket. Transferred to D530 filter satellite drum. Placed a new filter in the casing and re-bolted the lid on. Repeated this process for the second filter casing.	9/21/16	15	2.6
Control Lab Technician	Special Samples	Weekly / ≤ 15	Took sample bottles to Chlorine plant to sample trailer. Went with chlorine plant operator to trailer. Filled 2 sample bottles, after purging sample line into a waste jug. Took samples and waste jug back to lab. Dumped contents of waste jug into solvent for recovery tote. Placed sample bottles on magnetic stirrer.	9/28/16	15	1.4
Control Lab Technician	Dumping jugs	Varies / ≤ 15	Screwed on the funnel for the solvent for recovery tote. Dumped 7 jugs into the tote. closed the funnel. Unscewed funnel from tote and capped the tote.	9/28/16	15	6.4

Solvent Loader	Special Samples	Frequent / ≤ 15	Opened drum. Inserted tube into drum. Filled sample bottle and capped it. Sealed drum back up.	11/16/16	15	4.2
Solvent Loader	Special Samples	Frequent / ≤ 15	Opened drum. Inserted sample tube into drum. Filled sample bottle, then sealed drum.	11/22/16	15	0.93
Solvent Loader	Special Samples	Frequent / ≤ 15	Connected sampling apparatus to railcar. Turned on air to pressure up railcar. Purged sample line into a waste bucket. Filled sample bottle, rinsed it into a waste bucket. Filled sample bottle again and capped it. Disconnected sampling apparatus and sealed up railcar.	12/1/16	17	5.5
Control Lab Technician	Special Samples	Weekly / ≤ 15	Sampled pre-cooler trailer, with the assistance of the chlorine plant operator. Purged sample line into a waste jug, then filled 2 sample bottles. Purged excess from sample line into waste jug and then took jug back to lab and put into the solvent for recovery tote.	12/2/16	15	4.1
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	12/28/16	15	3
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	Blocked in filter. Drained filter casing into waste jugs from bleed valves. Removed filter casing lid. Removed carbon and filter from filter casing. put a new filter in. Poured carbon tet from waste buckets into the filter casing. Replaced the lid of the filter casing. Repeated this process for second filter.	12/28/16	27	12
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	6/7/17	15	0.51
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	3/22/17	16	2.4

Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	8/3/17	22	2.1
Chloromethanes II Thermal Technician	Sample Collection	Daily / ≤ 15	Sample Collection	12/20/17	17	2.4
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	6/7/17	15	1.1
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	3/21/17	15	3
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	3/27/17	15	7.7
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	8/3/17	15	1.4
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	9/25/17	15	2.8
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	12/7/17	18	<0.3
Control Lab Technician	Special Samples	Frequent / ≤ 15	Special Samples	12/16/17	15	1.9
Control Lab Technician	Dumping Jugs	Varies / ≤ 15	Dumping Jugs	12/20/17	15	6.4
Solvent Loader	Special Samples	Frequent / ≤ 15	Special Samples	6/6/17	15	9.4
Solvent Loader	Special Samples	Frequent / ≤ 15	Special Samples	3/28/17	16	2.4
Solvent Loader	Special Samples	Frequent / ≤ 15	Special Samples	9/22/17	16	0.46
Solvent Loader	Special Samples	Frequent / ≤ 15	Special Samples	12/6/17	15	0.92
Solvent Loader	Special Samples	Frequent / ≤ 15	Special Samples	12/20/17	15	1.6
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	6/7/17	17	56
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	3/22/17	22	7.5
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	10/11/17	15	14
VCRU Technician	D530 Filter Change	Weekly / ≤ 15	D530 Filter Change	12/13/17	21	0.89
Solvent Loader	Special Samples	Frequent / ≤ 15	Special Samples	12/20/17	15	0.96

Table V. Worker Exposure Data (Full Shift Samples) from a Perchloroethylene Manufacturing Facility (Company C)

Exposure Group	Approximate Frequency/ Duration	Comment	Sample Date	Sample Duration (minutes)	Perchloroethylene (ppm)
B Operator	Full-Shift	-	2016	479	0.109
B Operator	Full-Shift	-	2016	484	0.115
Pipefitter	Full-Shift	Supplied air	2016	449	0.151
D Operator	Full-Shift	-	2016	483	1.15
D Operator	Full-Shift	-	2016	479	1.22
D Operator	Full-Shift	-	2016	489	1.44
B Operator	Full-Shift	-	2016	477	1.52
D Operator	Full-Shift	-	2016	489	2.67
Shipping Tankerman	Full-Shift	-	2016	475	3.42
Shipping Tankerman	Full-Shift	-	2016	476	4.76
C Operator	Full-Shift	-	2016	483	8.74
C Operator	Full-Shift	-	2016	504	BDL
B Operator	Full-Shift	-	2016	501	BDL
B Operator	Full-Shift	-	2016	478	BDL
C Operator	Full-Shift	-	2016	476	BDL
Pipefitter	Full-Shift	-	2016	452	BDL
Insulator	Full-Shift	-	2016	449	BDL
Pipefitter	Full-Shift	-	2016	447	BDL
Pipefitter	Full-Shift	-	2016	458	BDL
Welder	Full-Shift	-	2016	445	BDL

Insulator	Full-Shift	Dust mask-N95	2016	455	BDL
Welder	Full-Shift	-	2016	451	BDL
Machinist	Full-Shift	-	2016	472	BDL
Pipefitter	Full-Shift	APR	2017	435	0.213
B Operator	Full-Shift	-	2017	472	0.265
Pipefitter	Full-Shift	-	2017	460	0.274
Pipefitter	Full-Shift	APR/SAR	2017	439	0.301
D Operator	Full-Shift	-	2017	468	0.966
B Operator	Full-Shift	-	2017	474	2.62
B Operator	Full-Shift	-	2017	474	BDL
C Operator	Full-Shift	-	2017	474	BDL
Pipefitter	Full-Shift	Supplied air	2017	460	BDL
Welder	Full-Shift	-	2017	444	BDL
Welder	Full-Shift	Supplied air	2017	450	BDL
Insulator	Full-Shift	Dust mask-half face	2017	434	BDL

*Below the detection limit.

Table VI. Worker Exposure Data (Task Samples) from a Perchloroethylene Manufacturing Facility (Company C)

Exposure Group	Task description	Sample Date	Sample Duration (minutes)	Perchloroethylene (ppm)
D Operator	-	2016	26	1.52
D Operator	-	2016	29	2.11
Shipping Tankerman	-	2016	20	8.74
Shipping Tankerman	-	2016	18	11.2
C Operator	-	2016	22	BDL
C Operator	-	2016	23	BDL
B Operator	-	2016	22	BDL
C Operator	-	2016	28	BDL
B Operator	-	2016	21	BDL

Attachment 2

Evaluation of the Carcinogenic Mode of Action and Occupational Exposure Limits for Tetrachloroethylene

August 14, 2018

GRADIENT

www.gradientcorp.com
20 University Road
Cambridge, MA 02138
617-395-5000

Table of Contents

Executive Summary

In the following analysis, we provide an overview of the relevant scientific information for the carcinogenic endpoints that are the basis of several agency tetrachloroethylene (PCE) cancer toxicity value derivations. Our analysis is based on review of several PCE regulatory agency documents in addition to several key review articles. Based on the available information (*i.e.*, toxicity, epidemiology, and mode of action data), we propose an occupational exposure limit (OEL) for PCE that provides support for existing agency PCE OELs.

- PCE is classified by the United States Environmental Protection Agency (US EPA) as "likely to be carcinogenic in humans," based primarily on evidence of increased liver tumors in mice. The International Agency for Research on Cancer (IARC) classifies PCE as a Group 2A carcinogen ("probably carcinogenic to humans"), based on limited evidence for carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.
- PCE was found to cause increased incidence of liver tumors in mice, increased kidney toxicity in rats, but kidney tumor incidence was not significantly increased compared to controls. Increased incidence of mononuclear cell leukemia (MCL) was also observed in rats following chronic exposure to PCE.
- Evidence of a causal association between PCE exposure and cancer in humans is inadequate or limited at best, with few studies showing positive associations, and for those studies that do, exposure estimates are lacking and/or confounded by exposure to other potential carcinogens.
    - There is no evidence that PCE causes liver cancer or kidney cancer in humans.
    - Although an increase in bladder cancer has been observed in some occupational studies (laundry workers and dry-cleaners), a recent meta-analysis suggests uncertainty with respect to contribution from other exposures, including smoking (Vlaanderen *et al*., 2014).
    - Increases in non-Hodgkin's lymphoma and multiple myeloma have also been observed in some epidemiology studies of PCE-exposed workers; however, results are inconsistent across these studies.
- PCE metabolism yields multiple metabolites through two main pathways:
    - The "oxidative pathway" (*via* cytochrome P450 metabolism) that occurs predominantly in the liver and primarily yields the metabolite trichloroacetic acid (TCA).
    - The "glutathione (GSH) conjugation pathway" (*via* GSH transferase activity) that occurs in the liver or kidney to form trichlorovinyl glutathione (TCVG), which is further metabolized in the kidney to *S*-trichlorovinyl-L-cysteine (TCVC).
- PCE and its main oxidative metabolite (TCA) exhibit little, if any, genotoxicity. The GSH metabolites (TCVG and TCVC), however, have been shown to be genotoxic.
    - Although TCVG and TCVC, if generated, would predominantly be present in the kidney, the animal and epidemiology data provide limited evidence to suggest a causal association between PCE exposure and kidney cancer, suggesting there is little involvement of the genotoxic PCE-generated GSH metabolites as a primary contributor to PCE-induced cancer.

- The relevance of rat MCL to humans is unclear due to the high background rates of this tumor in aging rats. In addition, the specific PCE metabolite that may be responsible for increased MCL in rats is not known. Since it is very likely that the dose-response for MCL in rats reflects the pre-existing spontaneity of these tumors, the MCL rat data should not be used to reflect a potential mechanism of action and dose-response extrapolation to humans.
    - Based on these uncertainties, the NRC expert panel (2010) did not reach consensus regarding the use of the rat MCL data for human health risk assessment during its review of EPA's PCE IRIS evaluation.
- Based on our review of the key scientific information regarding the mode of action (MoA) for PCE-induced liver tumors in mice, it is our interpretation that the data strongly suggest mechanisms related to the non-genotoxic TCA metabolite generated from oxidative metabolism of PCE (*e.g.*, oxidative stress and cytotoxicity, PPARα-activation/peroxisome proliferation).
    - Since the most likely mechanisms for PCE-induced liver tumors in mice are not genotoxic, application of a linear genotoxic MoA to a point of departure (POD), based on oxidative metabolism in the liver, is not supported by the best available science.
    - Overall, a threshold MoA based on oxidative metabolism of PCE to TCA, which in turn leads to PPARα-activation and peroxisome proliferation (in addition to other possible non-genotoxic mechanisms, such as oxidative stress and cytotoxicity), is more consistent with the best available information for PCE carcinogenesis in mice.
- Although the PPARα-activation MoA in mice is generally not considered relevant to humans due to the much lower levels of PPARα in the human liver compared to the rodent liver, the involvement of other possible mechanisms (*e.g.*, oxidative stress and cytotoxicity) in potential PCE carcinogenesis in humans should be considered. Therefore, oxidative metabolism to TCA should be considered potentially relevant to humans (even if the PPARα-activation MoA is not).
    - Since the there is no strong evidence to support an assumption of genotoxicity for PCE and TCA (the major PCE metabolite in the liver), overall, the best available information for potential PCE liver carcinogenesis in humans suggests a threshold mode of action based on oxidative metabolism to TCA in the liver.
- Although not supported by the best available science for a possible PCE carcinogenic MoA, several agencies (US EPA, CalOEHHA, MADEP, and MDH)[6] derived PCE cancer toxicity values applying a genotoxic linear extrapolation. The US EPA value is based on liver tumors in mice, but several agencies derived values based on MCL incidence in rats (MADEP and MDH), or liver tumor and MCL incidence in rodents (CalOEHHA).
- More consistent with the current science for PCE, several non-US regulatory agencies (Health Canada and the Danish EPA) derived PCE toxicity values based on a non-genotoxic threshold MoA for cancer.
- Based on our interpretation of the best available science for PCE carcinogenesis, we propose a PCE OEL of 28 ppm, based on the US EPA (2012) point of departure (POD) for liver cancer (*i.e.* total TCA metabolism in the liver), that provides support for the existing ACGIH TLV of 25 ppm.
    - The US EPA PCE POD is a $BMDL_{10}$ of 58 ppm. Adjustment for occupational exposure (20/10 m^3 per day inhalation rate × 7/5 days per week) results in an upward adjustment of

[6] California Office of Environmental Health Hazard Assessment (CalOEHHA); Massachusetts Department of Environmental Protection (MADEP); and the Minnesota Department of Health (MDH).

2.8-fold, to 162 ppm. An adjustment for a worker exposure duration of 40 years *vs*. a lifetime is as follows: 162 ppm x 70/40 years = 284 ppm.

- We applied an uncertainty factor (UF) of 3 for pharmacodynamic differences between animals and humans, and an additional UF of 3 because PCE is considered a threshold carcinogen, to derive a PCE OEL of 28 ppm.

1 Introduction and Background

Tetrachloroethylene (PCE) is classified by the United States Environmental Protection Agency (US EPA) as "likely to be carcinogenic in humans," based primarily on evidence of increased liver tumors in mice (US EPA, 2012a). PCE was found to cause increased kidney toxicity in rats, but kidney tumor incidence was not significantly increased compared to controls (US EPA, 2012a). Increased incidence of mononuclear cell leukemia (MCL) was also observed in rats following chronic exposure to PCE (US EPA, 2012a).

Evidence of cancer in humans is inadequate or limited at best, with few studies showing positive associations, and for those studies that do, exposure estimates are lacking and/or confounded by exposure to other potential carcinogens. Overall, there is no evidence that PCE causes liver cancer or kidney cancer in humans (US EPA, 2012a; Christensen *et al*., 2013; Guyton *et al*., 2014; Cichocki *et al*., 2016).[7] Although an increase in bladder cancer has been observed in some occupational studies (laundry workers and dry-cleaners), a recent meta-analysis suggests uncertainty with respect to contribution from other exposures, including smoking (Vlaanderen *et al*., 2014).[1] Increases in non-Hodgkin's lymphoma and multiple myeloma have also been observed in some epidemiology studies of PCE-exposed workers; however, results are inconsistent across these studies (US EPA, 2012a; Cichocki *et al*., 2016). The International Agency for Research on Cancer (IARC) classifies PCE as a Group 2A carcinogen ("probably carcinogenic to humans"), based on limited evidence for carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals (IARC, 2014).

In the following analysis, we provide an overview of the relevant scientific information for the carcinogenic endpoints that are the focus of several agency PCE cancer toxicity value derivations (*i.e*., liver cancer and MCL). MCL was included in the California Office of Environmental Health Hazard Assessment (CalOEHHA) PCE cancer toxicity value derivation, and is used as the basis of two state agency PCE cancer toxicity values (for the Massachusetts Department of Environmental Protection [MADEP] and the Minnesota Department of Health [MDH]); therefore, we briefly describe this endpoint. Since liver cancer is the endpoint that is the basis of several other agency PCE cancer toxicity values, including US EPA (US EPA, 2012a), and given the scientific debate regarding whether MCL should be used for PCE human health risk assessment (NRC, 2010), for consideration of a possible PCE occupational exposure limits (OELs), we discuss only the liver cancer endpoint.

Based on the available scientific evidence for an association between PCE exposure and liver tumor incidence in animals, the possible modes of action for PCE-induced liver tumors in animals, and US EPA's recent dose-response evaluation for PCE and liver tumors and

[7] Gray highlighted references are studies not included in US EPA's Toxicological Review for PCE (2012a) or in the US EPA Problem Formulation Document for PCE (US EPA, 2018).

extrapolation to humans (US EPA, 2012a), we propose a liver-cancer-specific occupational exposure limit (OEL) for PCE that provides support for several existing OELs for PCE (including the American Conference of Governmental Industrial Hygienists [ACGIH] threshold limit value [TLV]). Therefore, the analysis described herein should be considered by US EPA in its risk evaluation for PCE under the new Toxic Substances and Control Act (US EPA 2017, 2018).

2 PCE Metabolism and Potential Genotoxicity of PCE Metabolites

The metabolism of PCE yields multiple metabolites through two main pathways: (1) the "oxidative pathway" *via* cytochrome P450 metabolism, and (2) the "glutathione (GSH) conjugation pathway" *via* GSH transferase activity. The oxidative pathway occurs predominantly in the liver and primarily yields the metabolite trichloroacetic acid (TCA). PCE GSH conjugation occurs in the liver or kidney to form trichlorovinyl glutathione (TCVG), which is further metabolized in the kidney to *S*-trichlorovinyl-L-cysteine (TCVC). The involvement of these metabolites in animal and potential human carcinogenesis has been extensively studied by researchers.

A physiologically based pharmacokinetic (PBPK) model for PCE toxicokinetics in mice, rats, and humans was recently developed (Chiu and Ginsberg, 2011) to try to gain a better understanding of the extent to which the two metabolic pathways might contribute to animal and potential human carcinogenesis from PCE exposure. As described by Chiu and Ginsberg (2011), the PBPK model for PCE identified a large range of uncertainty for PCE metabolic flux through the GSH conjugation pathway in humans (Chiu and Ginsberg, 2011), contributing to continued debate among researchers with respect to the relevance of the GSH conjugation pathway for humans.

PCE exhibits minimal (if any) genotoxicity potential as a parent compound *in vitro* or *in vivo* (US EPA, 2012a). Certain metabolites of PCE, however, have been shown to be genotoxic. The major PCE metabolite from the oxidative pathway (TCA) exhibits little to no genotoxic potential *in vitro* or *in vivo* (US EPA, 2012a). Genotoxicity studies of other metabolites from the oxidative pathway (*e.g.*, dichloroacetic acid [DCA]) have found mixed results with positive results occurring mostly at high doses (US EPA, 2012a). TCVG and TCVC from the GSH conjugation pathway, on the other hand, both yield positive results in *in vitro* and in *in vivo* genotoxicity assays (US EPA, 2012a). As discussed by US EPA (2012a), unscheduled DNA synthesis was found to increase in a dose-dependent manner in mammalian porcine kidney cells following exposure to TCVC (Vamvakas *et al.*, 1989). TCVC (in the presence of rat kidney S9 activation) and TCVG (with and without S9 activation) were also found to be mutagenic in bacterial assays (US EPA, 2012a).

2.1 Potential Involvement GSH Metabolites in Liver and Kidney Tumors

The extent to which the GSH metabolites contribute to the mode of action (MoA) for liver and kidney carcinogenesis in animals, and the relevance of the proposed animal MoA to potential human carcinogenesis, have been extensively studied by researchers, but are not fully understood. The current available evidence, however, suggests that the mechanism of PCE-

induced liver tumors in mice likely involves the oxidative PCE metabolites, and not the GSH metabolites (US EPA, 2012a). See further discussion in Section 4 regarding other proposed mechanisms for liver tumors.

Since the GSH metabolites are the main PCE metabolites generated in the kidney, scientific studies have investigated to what extent these metabolites might be involved in kidney carcinogenesis in animals and humans. As described by US EPA (2012a), the epidemiology data provide limited evidence to suggest a causal association between PCE exposure and kidney cancer in humans, with many studies finding no statistically significant associations and most finding no exposure-response relationships for kidney cancer and PCE. The epidemiologic studies do support an association between PCE and chronic kidney disease, as measured by urinary excretion of renal proteins and end-stage renal disease (ESRD) incidence US EPA (2012a). In animals studies, PCE has been found to cause kidney toxicity potentially mediated through the PCE GSH conjugation pathway, but no studies reported statistically significant associations between exposure to PCE and kidney tumors in rodents (US EPA, 2012a).

Therefore, the current scientific information provides little support for an association between PCE exposure and kidney cancer. Since the GSH metabolites would primarily be present in the kidney following high exposures to PCE, these results suggest there is little involvement of PCE-generated GSH metabolites as a primary contributor to PCE-induced cancer.

3 Mononuclear Cell Leukemia (MCL) and Potential Relevance to Human

Increased incidence of MCL was observed in F344 rats following chronic exposure to PCE (National Toxicology Program [NTP], 1986, and Japanese Industrial Safety Association [JISA], 1993, as cited within US EPA, 2012a). However, there were concerns raised by the NRC expert panel (without reaching consensus) during review of EPA's PCE IRIS evaluation (NRC, 2010) regarding the use of the rat MCL data for human health risk assessment.

The relevance of MCL to humans is unclear due to the high background rates of this tumor in aging F344 rats. As noted in the NRC's review of the draft IRIS PCE assessment (NRC, 2010) "NTP has decided to stop using its F344 rat colony in its bioassays for reasons that include the high background rate of MCL." In addition, the NRC indicated that "the use of the MCL data could be justified only if it is EPA's policy to choose the most conservative unit risk when considering options but that such justification should be distinguished as a policy decision, not a scientific one" (NRC, 2010).

In addition, the specific PCE metabolite that may be responsible for increased MCL in rats is not known (US EPA, 2012a). Therefore, the mechanism of action for MCL tumor formation in rats is uncertain, and an assumption that the GSH pathway is involved in rat MCL tumor formation, is also uncertain. The limited information on the MCL mechanism of action does not provide a strong scientific basis for a linear-no-threshold extrapolation from the point of departure for derivation of cancer toxicity values for this endpoint, as was applied by MADEP (2014), MDH (2014), and CalOEHHA (2016) in derivation of their PCE cancer inhalation toxicity values (see further discussion in Section 5 and Table 1).

In addition, given that there is a high background for this tumor type in rats, it is very likely that the dose-response for MCL in rats reflects the pre-existing spontaneity of these tumors and, therefore, should not be used to reflect a potential mechanism of action and dose-response extrapolation to humans.

4 Liver Tumor MoA in Animals and Potential Relevance to Humans

4.1 Liver Tumor MoA in Animals

Several mechanisms have been proposed for PCE-induced liver tumors in mice, including epigenetic changes (*i.e*., hypomethylation), cytotoxicity and oxidative stress, and PPARα-activation (US EPA 2012a). Although US EPA (US EPA 2012a) also discusses the possibility of mutagenicity induced by one or more of the PCE metabolites in the liver, there is little support for this proposed mechanism because there is little to no evidence for mutagenicity and genotoxicity by TCA, the major PCE metabolite produced in the liver, and limited evidence of genotoxicity for other oxidative metabolites (*e.g*. DCA).

There is scientific support for the involvement of cytotoxicity and oxidative stress by PCE and its metabolites in mouse liver tumors, as hepatotoxicity was observed in mice within the NTP (1986) bioassay that also observed hepatocellular carcinomas in mice. Several studies also suggest that TCA and DCA decrease global methylation and promoter hypomethylation in mouse liver (Ge *et al*., 2001 and Tao *et al*., 1998, as described in US EPA, 2012a).

The mechanism of action that has been investigated most extensively is PPARα-activation by TCA, which has been shown to lead to peroxisome proliferation and hepatocyte proliferation in mice and rats (US EPA 2012a). However, US EPA (2012a) describes experimental evidence suggesting that PCE-induced liver tumors in mice are not mediated solely by a PPARα-activation/peroxisome proliferation MoA, stating that "the modest peroxisome proliferation observed in response to tetrachloroethylene may lack specificity with respect to species, tissue, and dose," concluding that the available data are "insufficient to demonstrate a causative role of this effect in the induction of other key events posited for the PPARα-activation MOA hypothesis, and for hepatocarcinogenesis by tetrachloroethylene" in mice. Although it is possible that other mechanisms are involved, such as epigenetic changes (*i.e*., hypomethylation) and cytotoxicity and oxidative stress, it is still possible (if not, likely) that PPARα-activation is involved at least to some extent in the MoA, since TCA has been shown to activate PPARα to induce liver peroxisome proliferation and hepatocyte proliferation in rodents (US EPA, 2012a). In addition, currently the data do not point specifically to another more likely mechanism (or mechanisms).

There is little evidence, however, to suggest that other mechanisms would involve direct genotoxicity from PCE metabolites at concentrations less than those required for oxidative metabolism. US EPA (2012a) cites a review article by Melnick (2001) as describing evidence of possible genotoxicity from PPARα-activation in addition to peroxisome proliferation; however, this is an incorrect interpretation of that article. Melnick (2001) does not discuss genotoxicity as

a possible mechanism of PPARα-activation, but instead describes other mechanisms that would also have a threshold MoA (*e.g.*, perturbation of cell growth control through cell proliferation and/or suppression of apoptosis). In addition, the study by Bull *et al*. (2004) that US EPA (2012a) cites as part of the basis for evidence that other mechanisms are involved in addition to peroxisome proliferation provides evidence suggesting that any potential involvement from the more minor PCE oxidative metabolite (*i.e.*, dichloroacetic acid [DCA]), would likely be *via* suppression of apoptosis and increased cell proliferation, not genotoxicity. Therefore, the scientific evidence does not suggest genotoxicity as one of the potential mechanisms from the PPARα-activation pathway.

Since PPARα-activation, cytotoxicity and oxidative stress, hypomethylation, and/or other possible mechanisms of toxicity may be involved in liver tumor formation in mice, proposing a single mechanism is difficult. US EPA concluded that the MoA for PCE-induced carcinogenesis in animals likely involves a number of different mechanisms (US EPA, 2012a). Although a combination of mechanisms is a reasonable conclusion based on the available information, the weight of evidence more strongly supports a threshold non-genotoxic MoA than a non-threshold genotoxic MoA.

US EPA, however, conservatively concluded that because the contribution to genotoxicity from PCE metabolites could not be ruled out, a non-threshold genotoxic MoA was most appropriate. As described more in Section 5 and in Table 1, at least two non-US regulatory agencies (Danish EPA [2014] and Health Canada [2015]) recently derived toxicity values for PCE based on a threshold MoA for carcinogenesis.

4.1.1 Interpretation of Mouse Liver Tumor MoA Information

Based on our review of the key scientific information regarding the MoA for PCE-induced liver tumors in mice, within several PCE regulatory agency documents in addition to several review articles (Guyton *et al*., 2014; Cichocki *et al*., 2016; Corton *et al*., 2014),[1] it is our interpretation that:

- The data strongly suggest that the formation of PCE-induced liver tumors in mice involves mechanisms related to the non-genotoxic TCA metabolite generated from oxidative metabolism of PCE (*e.g.*, oxidative stress and cytotoxicity, PPARα-activation/peroxisome proliferation).
- Although there is uncertainty with respect to the degree to which other mechanisms in addition to the TCA-induced PPARα-activation/peroxisome proliferation MoA might be involved in the mouse liver tumors, the data suggest that the other possible mechanisms are not directly genotoxic. PCE is not genotoxic and the major metabolite (TCA) is also not genotoxic. Although some of the metabolites from the GSH pathway have been shown to be genotoxic, these are likely minor metabolites compared to TCA and generated only at high PCE exposure concentrations. In addition, GSH pathway metabolites are more likely to be associated with kidney toxicity than liver toxicity and cancer. Therefore, the overall genotoxic potential for PCE is weak, particularly in the liver.
- In addition, any mechanism other than PPARα-activation/peroxisome proliferation (*e.g.*, oxidative stress and cytotoxicity) may also not be the sole mechanism of carcinogenesis. In other words, there is no evidence to suggest that if other mechanisms are involved, that they act

independently from the toxicity generated through TCA-induced PPARα-activation/peroxisome proliferation. It is very possible that oxidative stress and cytotoxicity, PPARα-activation/peroxisome proliferation, and perhaps hypomethylation act in combination to generate mouse liver tumors, and that none of these mechanisms by themselves would be sufficient to cause tumors.

- Given that the evidence suggests there may be a combination of mechanisms involved in liver tumor formation in mice, but that the most likely mechanisms are not genotoxic, application of a linear genotoxic MoA to a point of departure (POD), based on oxidative metabolism in the liver, is not supported by the best available science. Overall, a threshold MoA based on oxidative metabolism of PCE to TCA, which in turn leads to PPARα-activation and peroxisome proliferation (in addition to other possible non-genotoxic mechanisms, such as oxidative stress and cytotoxicity), is more consistent with the best available information for PCE carcinogenesis in mice.

4.2 Potential Relevance of the Mouse Liver Tumor MoA to humans

The relevance of PPARα-activation/peroxisome proliferation to human hepatocellular carcinoma has been debated within the scientific community (Guyton *et al*., 2014; NRC, 2010; Corton *et al*., 2014). For example, NRC (2010), in its review of the draft IRIS toxicological profile for PCE, stated the following: "the weight of evidence strongly favors a key role of PPARα activation in tetrachloroethylene-induced hepatocarcinogenesis in mice; furthermore, this mode of action lacks relevance for human hepatocarcinogenesis." However, as described in a review by Guyton *et al*. (2014), several members of the NRC peer-review committee did not support this conclusion, indicating that many data gaps remain with regard to the mechanism of PCE-induced liver tumor formation in rats.

A recent review by Corton *et al*. (2014) applied a MoA framework to evaluate the weight of evidence relevant to the hypothesized MoA for PPARα activator-induced rodent hepatocarcinogenesis and its relevance to humans. The authors of the study were members of a PPARα case study panel that was organized by a steering committee to provide a multidisciplinary perspective on the MoA for PPARα-induced liver tumors and human relevance. The authors included experts from regulatory agencies (including US EPA), academia, industry, and private consultants. The analysis concluded that although the MoA is biologically plausible in humans, the hypothesized key events for a PPARα-activation MoA in humans is unlikely because of differences in toxicodynamic and biological responses between rodents and humans. Although the data clearly suggest quantitative differences between rats and humans for key events in the PPARα-activation MoA, the actual difference is not known. In addition, it is not clear if there are also qualitative differences between responses in rodents and humans in PPARα-activation that are related to the observed differences between species. Overall, the weight of evidence suggests that PPARα-activation is unlikely to be relevant to humans (Corton *et al*., 2014).

There is no strong evidence, however, to suggest that the other possible non-genotoxic mechanisms of liver tumor formation in mice (*i.e*., oxidative stress and cytotoxicity, hypomethylation) are not relevant to humans.

Based on the current state of the science, briefly described in this section, we conclude the following with regard to the potential relevance of PCE-induced mouse liver tumors to humans:

- Although the PPARα-activation MoA in mice is generally not considered relevant to humans due to the much lower levels of PPARα in the human liver compared to the rodent liver, given that mechanisms in addition to the PPARα-activation MoA may be necessary to cause liver tumors in mice (*e.g.*, oxidative stress and cytotoxicity), the involvement of these other mechanisms in potential PCE carcinogenesis in humans should be considered. Therefore, oxidative metabolism to TCA should be considered potentially relevant to humans (even if the PPARα-activation MoA is not).
- Since human occupational studies have found little association between PCE exposure and carcinogenesis, and the overall genotoxic potential for PCE and TCA (the major PCE metabolite in the liver) is weak, there is no strong evidence to support an assumption of genotoxicity and linear extrapolation from an oxidative metabolism POD down to lower levels of exposure.
- Therefore, overall, even though the data are uncertain with respect to a possible mechanism of action, the best available information for potential PCE liver carcinogenesis in humans suggests a threshold mode of action based on oxidative metabolism to TCA in the liver.

5 Regulatory Agency PCE Cancer Risk Evaluations for Human Health Risk Assessment

To provide perspective on agency application of the data summarized in sections 2-4, this section provides a summary of several recent agency PCE cancer toxicity values derived for general population risk assessment.

Three agencies were identified that applied the liver tumor endpoint to the toxicity value derivation (US EPA, 2012a; Danish EPA, 2014; Health Canada, 2015). We identified two state agencies (MADEP and MDH) that applied the MCL endpoint to the toxicity value derivation (MADEP, 2014; MDH, 2014). CalOEHHA considered multiple tumor endpoints, including liver tumors and MCL (CalOEHHA, 2016). The recommended MoA for PCE from each agency is briefly summarized in Table 1, in addition to the point of departure (POD) and health endpoint that was used as the basis of the inhalation toxicity value.

US EPA (2012a), CalOEHHA (2016), MADEP (2014), and MDH (2014) applied a genotoxic MoA and used a linear extrapolation method from the POD to derive inhalation unit risk (IUR) values for PCE. CalOEHHA based its derivation on total PCE metabolism and all tumor incidence in rats and mice (including liver tumors, MCL, kidney tumors, and other tumor endpoints), US EPA based its derivation on total oxidative metabolism in the liver and liver tumors incidence in mice, and MADEP and MDH based its derivation on total PCE metabolism and MCL incidence in rats. US EPA (2012a) and CalOEHHA (2016) indicated that given the limited understanding of the MoA for PCE, the data are insufficient to evaluate PCE primarily as a non-genotoxic carcinogen using a threshold MoA model. As discussed above, this approach is not consistent with the best available scientific information for PCE.

Given the inadequate evidence from occupational studies to suggest a causal association between PCE and cancer in humans, and that one of the mechanisms for PCE-induced mouse liver tumors is likely the non-genotoxic PPARα-activation MoA, or other non-genotoxic mechanism (*e.g.* oxidative stress and cytotoxicity), US EPA's, CalOEHHA's, MADEP's, and MDH's derivation of cancer risk values for quantification of PCE cancer risk (US EPA, 2012a) is overly conservative and inconsistent with the most current and scientifically robust information for PCE carcinogenesis.

It is noteworthy that US EPA indicates that the IUR value of 2×10^{-3} per parts per million (ppm):

> should not be used with exposures exceeding 60 ppm, or 400 mg/m^3 (the equivalent ambient exposures corresponding to the POD for male mouse hepatocellular tumors), because above this exposure level, the dose-response relationship is not linear, and the unit risk would tend to overestimate risk. (US EPA, 2012a)

This statement indicates that the dose-response information for the available data is not linear in the observable range.

In addition, US EPA chose to base the derivation only on the oxidative metabolism pathway, stating that with respect to liver carcinogenicity, the GSH pathway "is presumed to be less important than the role of oxidative metabolites" (US EPA, 2012a). Because oxidative metabolism is a major metabolic pathway for PCE in animals, and because there is little (if any) evidence for genotoxicity through the oxidative pathway (*i.e.*, the major metabolite for this pathway, TCA, is not genotoxic), it is scientifically inconsistent to use a POD based mostly on metabolism to TCA and then assume a genotoxic linear dose-response extrapolation to lower concentrations.

In deriving a PCE drinking water guideline, Health Canada also describes the uncertainty in the PCE-induced carcinogenic MoA in rodents, but concludes that "[a]lthough there is not absolute certainty regarding the MoA of tetrachloroethylene for hepatocellular tumors, there is a much stronger weight of evidence to support the threshold approach than for the use of linear low-dose extrapolation for the assessment of hepatocellular tumors" (Health Canada, 2015). Health Canada derived a PCE drinking water guideline based on liver tumors, applying a threshold MoA, and also derived a PCE drinking water guideline based on neurological effects. The agency indicated that the non-cancer health-based value (HBV) for neurological effects was more conservative than the HBV for liver tumors; thus the agency chose the neurological HBV for the drinking water guideline as protective of all health effects, including cancer (Health Canada, 2015). Although the Health Canada drinking water guideline is not directly relevant to an inhalation toxicity value, the threshold dose-response applied by Health Canada to the PCE MoA is relevant for all exposure pathways, because PCE metabolism in the liver and kidneys is the same regardless of the route of exposure.

The Danish Environmental Protection Agency (Danish EPA) also recently reviewed the scientific information for PCE health effects and concluded that although there is uncertainty regarding the PCE-induced MoA for liver tumors in mice, based on the weight of evidence, "[t]here is probably a threshold for the hepatocarcinogenicity of tetrachloroethylene and/or its metabolites in mice" (Danish EPA, 2014). Danish EPA derived a health-based PCE air concentration based on several health endpoints (liver cancer, kidney cancer, neurotoxicity, and developmental effects), assuming a threshold MoA for carcinogenesis, and chose the lowest of the concentrations (neurotoxicity – color visions changes) as the POD for the health-based PCE air concentration as protective of all health endpoints, including cancer.

6 Occupational Guidelines for PCE

Table 2 lists the occupational exposure limits (OELs) for PCE that we reviewed and the basis of their derivation, if provided. As shown in Table 2, we did not identify documentation supporting the derivation of the OELs from the United Kingdom, Denmark, Sweden, Finland, and Iceland.

As shown in Table 2, all of the existing PCE OELs for which derivation information is available are based on a non-genotoxic threshold MoA. The ACGIH TLV of 25 ppm (ACGIH, 2001) and the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) of 100 ppm (NIOSH and OSHA, 1978) are both based on neurological effects. Although both agency documents describe liver and kidney toxicity and carcinogenesis studies in animals following high levels of PCE exposure, both conclude that the relevance of these studies to humans is uncertain.

The most recent OEL we identified (20 ppm) was derived by the European Commission Scientific Committee on Occupational Exposure Limits (SCOEL, 2009). In derivation of its OEL, SCOEL conducted a thorough evaluation of the PCE epidemiological and animal carcinogenesis studies available, in addition to a review of available genotoxicity data, and concluded that:

> The limited evidence linking exposure to tetrachloroethylene to cancers in humans is not convincing, whereas results of animal experiments demonstrate a clear association with cancers of the liver in mice… so far no excess risk of cancers of the liver in humans could be identified. (SCOEL, 2009)

In addition, SCOEL concluded that the available data indicate that PCE is non-genotoxic *in vivo*. In accordance with SCOEL guidelines for OEL derivation, strong evidence of non-genotoxicity *in vivo* provides justification for PCE to be categorized as a non-genotoxic Group D carcinogen. Based on the available information for all health endpoints, SCOEL derived a PCE OEL of 20 ppm based on neurological effects, which it determined was the most sensitive health endpoint.

6.1 Conclusions and Proposed PCE OEL

Given that PCE is most likely a carcinogen in mice *via* a threshold MoA, and that oxidative metabolism in the liver is likely one of the key first steps in PCE metabolism that is necessary for tumor formation in mice, if there is potential for PCE to cause cancer in humans, an OEL that is based on oxidative metabolism in human liver would protect against cancer in workers. In addition, since kidney tumors were not statistically significantly increased in the rodent bioassays, and there is debate regarding application of rat MCL to PCE human health risk assessment, and since US EPA has chosen to derive its PCE cancer toxicity value based on the

liver tumor endpoint, here we propose an OEL based only on the liver tumor endpoint that supports application of the existing OELs for PCE.

We propose applying the $BMDL_{10}$ (*i.e*., the 95% lower confidence limit on the benchmark dose associated with a 10% extra risk) value of 58 ppm PCE (Table 1) derived by US EPA (2012a) as a threshold POD for carcinogenesis in humans for derivation of an inhalation concentration that is protective for workers. Based on application of the recent PBPK model (US EPA, 2012a), US EPA estimated that a human inhalation concentration of 58 ppm PCE would result in PCE oxidative metabolism in the human liver equal to the PCE oxidative metabolism in the mouse liver that resulted in only a 10% excess risk above controls. Consistent with US EPA guidelines for benchmark dose (BMD) modeling (US EPA, 2012b), a 10% excess risk is generally reflective of a no observed adverse effect level (NOAEL). As described by US EPA, "[t]he 10% response level has customarily been used for comparisons because it is at or near the limit of sensitivity in most cancer bioassays and in non-cancer bioassays of comparable size" (US EPA, 2012b).

Because the 58 ppm PCE value assumes continuous human exposure, an adjustment for occupational exposure (20/10 m^3 per day inhalation rate × 7/5 days per week) results in an upward adjustment of 2.8-fold, to 162 ppm. Note that adjustment from continuous exposure to a worker exposure would best be conducted within the PBPK model; however, the current approach provides a reasonable rough estimate. In addition, the POD is defined in units of lifetime average daily dose (*i.e*., a 70-year exposure duration). Therefore, an adjustment for a worker exposure duration of 40 years is appropriate (162 ppm x 70/40 years = 284 ppm).

The POD accounts only for pharmacokinetic differences between mice and humans (*via* application of the PBPK model). Therefore, consistent with standard risk assessment practice, an additional uncertainty factor of 3 is needed for possible pharmacodynamic differences between mice and humans. The 10-fold intraspecies uncertainty factor (UF) is typically not applied for derivation of OELs, such as ACGIH TLVs, because it is assumed that within a healthy worker population there is less variability than within the general population (*i.e*., small likelihood of sensitive subpopulations) (Pearce *et al*., 2007). As described by the European Food Safety Authority (EFSA) (2005), the default UFs for intraspecies and interspecies differences are sufficient for chemicals with a threshold mode of action, and additional uncertainty factors are applicable for chemicals that are "genotoxic and carcinogenic." EFSA (2005) does not address whether to apply additional UFs for non-genotoxic threshold carcinogens. However, as discussed by Ritter *et al*. (2007), and cited by Health Canada in derivation of its liver-tumor based portion of the PCE drinking water guideline[8] (Health Canada, 2015), application of an additional UF of 1-10 for threshold carcinogens is recommended. Health Canada applied a UF of 10 based on a threshold MoA for PCE carcinogenesis (Health Canada, 2015). Since we are deriving an OEL, and not a safe level for the general population, an additional UF of 3 for a threshold carcinogen for worker exposures seems appropriate.

[8] Note that as discussed earlier, the PCE Health Canada drinking water guideline is based on neurological effects since the value for this endpoint was lower than the PCE liver-tumor based drinking water guideline. As such, the Health Canada PCE drinking water guideline is protective of all endpoints, including cancer.

Application of the composite UF of 10 results in an inhalation concentration of 28 ppm PCE as an OEL protective against carcinogenesis in workers (284 ppm ÷ 10 = 28 ppm). This value is greater than the SCOEL PCE OEL of 20 ppm and the ACGIH TLV for PCE of 25 ppm.

Therefore, the best available scientific information for PCE carcinogenesis supports application of the SCOEL OEL and ACGIH TLV values for PCE (20-25 ppm) for protection against cancer in workers.

7 Comparison of PCE Exposure Data to OELs

We compared the OELs shown in Table 2 to PCE air concentration data provided to us in August 2018. As shown in Table 2, the 95% upper confidence limit on the mean [UCLM] and 90th percentile values for PCE are below the SCOEL OEL and the ACGIH TLV. Thus, monitored PCE concentrations do not represent a concern for adverse health effects.

Table 1 PCE Regulatory Toxicity Values for the General Population

Agency (Source)	Genotoxic MoA (Linear Extrapolation)	Non-genotoxic Threshold MoA	HEC Point of Departure (ppm)	Health Endpoint	Toxicity Value	Notes
US EPA IRIS (US EPA, 2012a)	Yes	–	$BMDL_{10}$ = 58	Total PCE hepatic oxidative metabolism (liver tumors)	IUR = 2 x 10^{-3} risk per ppm	$BMDL_{10}$ calculated from Table 5-18 in US EPA (2012a) and the inhalation dose metric conversion factor (DMCF) from the PBPK model ($BMDL_{10}$ of 2.1 internal dose units ÷ DMCF of 0.0363 dose units/ppm = 58 ppm)
CalOEHHA (CalOEHHA, 2016)	Yes	–	$BMDL_{05}$ = 0.47-1.83	Total PCE metabolism from oxidative and GSH pathways combined (multiple tumor endpoints)	URF = 4 x 10^{-2} risk per ppm	$BMDL_{05}$ values are from Table 6 in CalOEHHA (2016)
Massachusetts DEP (2014)	Yes	–	$BMDL_{10}$ = 4.8	Total PCE metabolism from oxidative and GSH pathways combined (MCL)	IUR = 2 x 10^{-2} risk per ppm	$BMDL_{10}$ of 2.26 internal dose units ÷ DMCF of 0.473 dose units/ppm = 4.8 ppm
Minnesota Department of Health (2014)	Yes	–	$BMDL_{10}$ = 4.8	Total PCE metabolism from oxidative and GSH pathways combined (MCL)	IUR = 2 x 10^{-2} risk per ppm	Based on MADEP (2014 215-7472)

Agency (Source)	Genotoxic MoA (Linear Extrapolation)	Non-genotoxic Threshold MoA	HEC Point of Departure (ppm)	Health Endpoint	Toxicity Value	Notes
Danish EPA (Danish EPA, 2014)	–	Yes	LOAEC = 2.2	Liver cancer, kidney cancer, neurotoxicity, developmental effects	Health-based air concentration for general population: 0.007 ppm	Value is ultimately based on neurotoxicity (color vision changes). The authors indicated that the neurotoxicity endpoint is protective for other health endpoints, including cancer.
Health Canada (Health Canada, 2015)	–	Yes	NA	Hepatic oxidative metabolism, neurotoxicity	NA	The regulatory value is for drinking water, so the point of departure is not relevant to inhalation risk. However, the MoA is relevant to all exposure pathways. The drinking water guideline is ultimately based on neurotoxicity (color vision changes). The authors indicated that the neurotoxicity endpoint is protective for other health endpoints, including cancer.

Notes:
$BMDL_{10}$ = 95% Lower Confidence Limit on the Benchmark Dose Associated with a 10% Extra Risk; $BMDL_{05}$ = 95% Lower Confidence Limit on the Benchmark Dose Associated with a 5% Extra Risk; DMCF = Dose Metric Conversion Factor; GSH = Glutathione; HEC = Human Equivalent Concentration; IUR = Inhalation Unit Risk; LOAEC = Lowest Observed Adverse Effect Concentration; MOA = Mode of Action; NA = Not Applicable; PBPK = Physiologically Based Pharmacokinetic; PCE = Tetrachloroethylene; ppm = Parts Per Million; URF = Unit Risk Factor.

Table 2 PCE 8-hour Occupational Exposure Limits – Comparison with Monitored PCE Exposure Concentrations

Agency or Country (Source)	Genotoxic MoA (Linear Extrapolation)	Non-genotoxic Threshold MoA	Health Endpoint	OEL (ppm)	MOE (95% ULCM = 0.061 ppm)[(a)]	MOE (90th Percentile = 0.13 ppm)[(b)]
ACGIH TLV (ACGIH, 2001)	–	Yes	Neurotoxicity (headaches, dizziness, sleepiness, incoordination)	25	410	192
OSHA PEL (NIOSH and OSHA, 1978)	–	Yes	Liver toxicity, nervous system disorders	100	1,639	769
European Commission SCOEL (SCOEL, 2009)	–	Yes	Liver and kidney toxicity, nervous system disorders	20	328	154
United Kingdom HSE, 2005 (HSE, 2011)	Quantitative bases not available			50	820	385
Denmark, Sweden, Finland, Iceland (NEG and DECOS, 2003)				10	164	77
Norway (NEG and DECOS, 2003)				6	98	46

Notes:
ACGIH = American Conference of Governmental Industrial Hygienists; SCOEL = Scientific Committee on Occupational Exposure Limits; HSE = Health and Safety Executive; MOA = Mode of Action; MOE = Margin of Exposure; OSHA = Occupational Safety and Health Administration; OEL = Occupational Exposure Limit; PCE = Tetrachloroethylene; PEL = Permissible Exposure Limit; ppm = Parts Per Million; TLV = Threshold Limit Value; UCLM = Upper Confidence Limit on the Mean.
MOE = OEL ÷ 95% UCLM, or OEL ÷ 90th percentile.
(a) The 95% UCLM values were calculated using US EPA' Pro UCL Software Version 5.1.
(b) The 90th Percentile values were calculated using one half of the detection limit for non-detects.

References

American Conference of Governmental Industrial Hygienists (ACGIH). 2001. "Documentation for tetrachloroethylene (CAS No. 127-18-4)." In *Documentation of the Threshold Limit Values and Biological Exposure Indices (Seventh Edition)*. 6p.

Bull, RJ; Sasser, LB; Lei, XC. 2004. "Interactions in the tumor-promoting activity of carbon tetrachloride, trichloroacetate, and dichloroacetate in the liver of male B6C3F1 mice." *Toxicology* 199(2-3):169-183. doi: 10.1016/j.tox.2004.02.018.

California Office of Environmental Health Hazard Assessment (CalOEHHA). 2016. "Perchloroethylene Inhalation Cancer Unit Risk Factor (Public Review Draft)." Air Toxics Hot Spots Program. 44p., February. Accessed at http://www.oehha.ca.gov/air/hot_spots/pdf/finalpublicreviewPCE_UR_TSD02162016.pdf.

Chiu, WA; Ginsberg, GL. 2011. "Development and evaluation of a harmonized physiologically based pharmacokinetic (PBPK) model for perchloroethylene toxicokinetics in mice, rats, and humans." *Toxicol. Appl. Pharmacol.* 253(3):203-234.

Christensen, KY; Vizcaya, D; Richardson, H; Lavoue, J; Aronson, K; Siemiatycki, J. 2013. "Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal." *J. Occup. Environ. Med.* 55(2):198-208.

Cichocki, JA; Guyton, KZ; Guha, N; Chiu, WA; Rusyn, I; Lash, LH. 2016. "Target organ metabolism, toxicity, and mechanisms of trichloroethylene and perchloroethylene: Key similarities, differences, and data gaps." *J. Pharmacol. Exp. Ther.* 359(1):110-123. doi: 10.1124/jpet.116.232629.

Corton, JC; Cunningham, ML; Hummer, BT; Lau, C; Meek, B; Peters, JM; Popp, JA; Rhomberg, L; Seed, J; Klaunig, JE. 2014. "Mode of action framework analysis for receptor-mediated toxicity: The peroxisome proliferator-activated receptor alpha (PPARa) as a case study." *Crit. Rev. Toxicol.* 44(1):1-49. doi: 10.3109/10408444.2013.835784.

Danish Environmental Protection Agency (Danish EPA). 2014. "Evaluation of Health Hazards by Exposure to Tetrachloroethylene and Proposal of a Health-Based Quality Criterion for Ambient Air." 58p.

European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Occupational Exposure Limits (SCOEL). 2009. "Recommendation of the Scientific Committee on Occupational Exposure Limits for Tetrachloroethylene (Perchloroethylene)." SCOEL/SUM/133. 45p., June.

European Food Safety Authority (EFSA). 2005. "Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic." *EFSA J.* 282:1-31.

Guyton, KZ; Hogan, KA; Siegel Scott, C; Cooper, GS; Bale, AS; Kopylev, L; Barone, S Jr; Makris, SL; Glenn, B; Subramaniam, RP; Gwinn, MR; Dzubow, RC; Chiu, WA. 2014. "Human health effects of tetrachloroethylene: Key findings and scientific issues." *Environ. Health Perspect.* 122(4):325-334. doi: 10.1289/ehp.1307359.

Health Canada. 2015. "Guidelines for Canadian Drinking Water Quality: Guideline Technical Document, Tetrachloroethylene." Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch. 94p.

International Agency for Research on Cancer (IARC). 2014. "Tetrachloroethylene." IARC Monograph No. 106. In IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 106: Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents. International Agency for Research on Cancer (IARC), World Health Organization (WHO). p219-352. Accessed at http://monographs.iarc.fr/ENG/Monographs/vol106/mono106-002.pdf.

Massachusetts Dept. of Environmental Protection (MADEP). 2014. "Summary of the Basis of Cancer Risk Values for Tetrachloroethylene." Office of Research and Standards. 8p., January 22. Accessed at http://www.mass.gov/eea/docs/dep/toxics/stypes/pcecan.pdf.

Melnick, RL. 2001. "Is peroxisome proliferation an obligatory precursor step in the carcinogenicity of di(2-ethylhexyl)phthalate (DEHP)?" *Environ. Health Perspect.* 109(5):437-442.

Minnesota Dept. of Health (MDH). 2014. "Toxicity Summary for Tetrachloroethylene (PCE) (CAS No. 127-18-4)." 9p., July 18

National Institute for Occupational Safety and Health (NIOSH); Occupational Safety and Health Administration (OSHA). 1978. "Occupational Health Guideline for Tetrachloroethylene." 5p., September.

National Research Council (NRC). 2010. Review of the Environmental Protection Agency's Draft IRIS Assessment of Tetrachloroethylene." Committee to Review EPA's Toxicological Assessment of Tetrachloroethylene. National Academies Press, 187p. Accessed at http://www.nap.edu/catalog/12863/review-of-the-environmental-protection-agencys-draft-iris-assessment-of-tetrachloroethylene.

National Toxicology Program. 1986. "Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) in F344/N rats and B6C3F(1) mice (inhalation studies)." Report to US Dept. of Health and Human Services, National Institutes of Health (Washington, DC) National Technical Information Service (NTIS) NTIS PB87-147054; NTP TR 311; NIH Publication No. 86-2567. 197p., August.

Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG); Health Council of the Netherlands, Dutch Expert Committee on Occupational Safety (DECOS). 2003. "133. Tetrachloroethylene (PER)." Arbete och Halsa; Vetenskaplig Skriftserie 2003:14. 116p.

Pearce, N; Checkoway, H; Kriebel, D. 2007. "Bias in occupational epidemiology studies." *Occup. Environ. Med.* 64(8):562-568.

Ritter, L; Totman, C; Krishnan, K; Carrier, R; Vezina, A; Morisset, V. 2007. "Deriving uncertainty factors for threshold chemical contaminants in drinking water." *J. Toxicol. Environ. Health B Crit. Rev.* 10(7):527-557.

United Kingdom, Health and Safety Executive (HSE). 2011. "EH40/2005 Workplace Exposure Limits: Containing the List of Workplace Exposure Limits for Use with the Control of Substances Hazardous to Health Regulations (As Amended) (Second Edition)." 74p., March. Accessed at http://www.hse.gov.uk/pubns/priced/eh40.pdf.

US EPA. 2012a. "Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in Support of Summary Information on the Integrated Risk Information System (IRIS) (Final)." EPA/635/R-08/011F, 1077p., February. Accessed at http://www.epa.gov/iris/toxreviews/0106tr.pdf.

US EPA. 2012b. "Benchmark Dose Technical Guidance." Risk Assessment Forum. EPA/100/R-12/001, 99p., June.

US EPA. 2017. "Procedures for chemical risk evaluation under the amended Toxic Substances Control Act (Final rule)." *Fed. Reg.* 82(138):33726-33753. 40 CFR 702. July 20. Accessed at https://www.gpo.gov/ fdsys/pkg/FR-2017-07-20/pdf/2017-14337.pdf.

US EPA. 2018. "Problem Formulation of the Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro) (CAS No. 127-18-4)." Office of Chemical Safety and Pollution Prevention, EPA-740-R1-7017, 167p., May.

Vamvakas, S; Dekant, W; Henschler, D. 1989. "Assessment of unscheduled DNA synthesis in a cultured line of renal epithelial cells exposed to cysteine S-conjugates of haloalkenes and haloalkanes." *Mutat. Res.* 222(4):329-335.

Vlaanderen, J; Straif, K; Ruder, A; Blair, A; Hansen, J; Lynge, E; Charbotel, B; Loomis, D; Kauppinen, T; Kyyronen, P; Pukkala, E; Weiderpass, E; Guha, N. 2014. "Tetrachloroethylene exposure and bladder cancer risk: A meta-analysis of dry-cleaning-worker studies." *Environ. Health Perspect.* 122(7):661-666.