Extracted from the TSCA Work Plan Chemical Risk Assessment for Trichloroethylene: Degreasing, Spot Cleaning and Arts and Craft Uses, CASRN: 70-01-6, [HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-chemical-risk-assessment"]

2.6 HAZARD/DOSE-RESPONSE ASSESSMENT

2.6.1 Approach and Methodology

2.6.1.1 Selection of TCE IRIS Assessment as the Source Document for the TCE TSCA Assessment

EPA/OPPT's work plan risk assessment for TCE is based on the hazard and dose-response information published in the toxicological review that the U.S. EPA's Integrated Risk Information System (IRIS) published in 2011. EPA/OPPT used the TCE IRIS assessment as the preferred data source for toxicity information, rather than developing a new toxicological assessment. The TCE IRIS assessment used a weight-of-evidence approach, the latest scientific information and physiologically-based pharmacokinetic (PBPK) modeling to develop hazard and dose-response assessments for TCE's carcinogenic and non-carcinogenic health effects resulting from lifetime oral or inhalation exposure.

Development of TCE's hazard and dose-response assessments considered the principles set forth by the various risk assessment guidelines issued by the National Research Council and the U.S. EPA. Primary, peer-reviewed literature identified through December 2010 was included where that literature was determined to be critical to the assessment (EPA, 2011e). Appendix K provides the guidelines that were considered when developing the TCE IRIS assessment. Some of these guidelines discussed the type of considerations that should be made when evaluating the quality of toxicity data and study reliability. Also Appendix K describes the study selection and data quality criteria that the U.S. EPA's IRIS program and OPPT used to evaluate the hazard data.

The TCE IRIS assessment underwent several levels of peer review including agency review, science consultation on the draft assessment with other federal agencies and the Executive Office of the President, public comment, external peer review by the EPA's Science Advisory Board (SAB) in 2002, scientific consultation by the U.S. National Academy of Sciences (NAS) in 2006 (NRC, 2006)[15], external peer review of the revised draft assessment by the EPA's Science Advisory Board (SAB) in January 2011 (EPA, 2011c)[16], followed by final internal agency review and EPA-led science discussion on the final draft.

Furthermore, EPA/OPPT consulted the EPA's Guidelines for Developmental Toxicity Risk Assessment when making the decision to use developmental toxicity studies in the acute risk assessment of commercial and consumer uses of degreasers and arts/crafts spray fixatives containing TCE (EPA, 1991). The basis for this decision relies on the presumption and EPA's

[15] NAS report, "Assessing the human health risks of trichloroethylene: Key scientific issues (2006)": [HYPERLINK "http://www.nap.edu/catalog.php?record_id=11707" \h]

[16] EPA's SAB peer review report for the 2009 EPA's Draft Assessment entitled "Toxicological Review of Trichloroethylene": [HYPERLINK "http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f648525742400690127/B73D5D39A8F184BD8525" \h] 7817004A1988/$File/EPA-SAB-11-002-unsigned.pdf

policy that a single exposure at a critical window of fetal development may produce adverse developmental effects (EPA, 1991). In other words, a single dose in a developmental toxicity study may be enough to cause developmental effects.

2.6.1.2 Aspects of the TCE IRIS Assessment that Were Adopted in the OPPT Risk Assessment

2.6.1.2.1 Carcinogenic Hazard and Dose-Response Assessment

TCE is carcinogenic to humans by all routes of exposures as documented in the TCE IRIS assessment. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer (EPA, 2011e). The human epidemiological evidence is strong for kidney and more limited for non-Hodgkin lymphoma (NHL) and liver cancer, and less convincing for biliary tract cancer. Less human evidence is found for an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia (EPA, 2011e). Further support for TCE's carcinogenic characterization comes from positive results in multiple rodent cancer bioassays in rats and mice of both sexes, similar toxicokinetics between rodents and humans, mechanistic data supporting a mutagenic mode of action for kidney tumors, and the lack of mechanistic data supporting the conclusion that any of the mode(s) of action for TCE-induced rodent tumors are irrelevant to humans (EPA, 2011e).

The cancer dose-response analysis used linear-dose extrapolation to derive an inhalation unit risk (IUR) of 2×10^{-2} per ppm (4.1×10^{-6} per $\mu g/m^3$) for various cancers[17]. The IUR for TCE was based on human kidney cancer risks that were reported by Charbotel et al. (2006) and adjusted for potential risk for NHL and liver cancer based on human epidemiological data (EPA, 2011e). The IUR is defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air (EPA, 2011b). The IUR was used in the EPA/OPPT risk assessment to estimate excess cancer risks for the inhalation occupational exposures scenarios. There is high confidence in the IUR because it was based on good quality human data, and was similar to unit risk estimates derived from multiple rodent bioassays (EPA, 2011e). Moreover, there was sufficient weight of evidence to conclude that TCE operates through a mutagenic mode of action for kidney tumors (EPA, 2011e).

EPA/OPPT decided not to use the IUR to calculate the theoretical cancer risk associated with a single (acute) exposure to solvent degreasers, arts/crafts fixative and spotting agent products containing TCE. NRC (2001) published methodology for extrapolating cancer risks from chronic to short-term exposures to mutagenic carcinogens. These methods were published with the caveat that extrapolation of lifetime theoretical excess cancer risks to single exposures has great uncertainties.

[17] The dose-response analysis for cancer endpoints can be found in Chapter 5 of the TCE IRIS assessment EPA (2011e).

As NRC (2001) explains, "*There are no adopted state or federal regulatory methodologies for deriving short-term exposure standards for workplace or ambient air based on carcinogenic risk, because nearly all carcinogenicity studies in animals and retrospective epidemiologic studies have entailed high-dose, long-term exposures. As a result, there is uncertainty regarding the extrapolation from continuous lifetime studies in animals to the case of once-in-a-lifetime human exposures. This is particularly problematical, because the specific biologic mechanisms at the molecular, cellular, and tissue levels leading to cancer are often exceedingly diverse, complex, or not known. It is also possible that the mechanisms of injury of brief, high-dose exposures will often differ from those following long-term exposures. To date, U.S. federal regulatory agencies have not established regulatory standards based on, or applicable to, less than lifetime exposures to carcinogenic substances* (NRC, 2001)." Thus, the final EPA/OPPT work plan risk assessment for TCE does not estimate excess cancer risks for acute exposures because the relationship between a single short-term exposure to TCE and the induction of cancer in humans has not been established in the current scientific literature.

2.6.1.2.2 Non-Cancer Hazard and Dose-Response Assessment

EPA/OPPT used margin of exposures (MOEs)[18] to estimate non-cancer risks based on the following:

1. the lowest PBPK-derived human equivalent concentrations (HECs) within each health effects domain reported in the TCE IRIS assessment;
2. the same endpoint/study-specific uncertainty factors (UFs) that the IRIS program applied to the PBPK-derived HECs; and
3. the exposure estimates calculated for the TCE uses examined in this risk assessment (see *Environmental Releases and Exposure Summary*).

MOEs allow for the presentation of a range of risk estimates rather than a single risk estimate based on the inhalation reference concentration (RfC). Given the different exposure scenarios considered (both acute and chronic for small commercial degreasers, and just acute for the two consumer exposure scenarios), different endpoints were used based on the expected exposure durations. For non-cancer effects, risks to developmental effects were evaluated for acute (short-term) exposures, whereas risks to other adverse effects (toxicity to the liver, kidney, nervous system, immune system, and the reproductive system) were evaluated for repeated (chronic) exposures to TCE.

Table 2-18 lists the studies and corresponding HECs and UFs that EPA/OPPT used in the work plan risk assessment for TCE. Key studies in Table 2-18 are briefly described in the *Human Health Hazard Summary* along with other toxicity and epidemiological studies, with detailed descriptions provided in the TCE IRIS assessment (EPA, 2011e). Appendix L contains the complete list of oral and inhalation non-cancer studies within each health effects domain that the TCE IRIS assessment considered suitable for dose-response analysis.

[18] Margin of Exposure (MOE) = (Non-cancer hazard value, POD) ÷ (Human Exposure). See equation in Table 2-29. The benchmark MOE is used to interpret the MOEs and consists of the total UF set by the IRIS program for each study in Table 2-18. See section 2.7.1 for an explanation of the benchmark MOE.

The TCE IRIS assessment used a series of steps to generate the PBPK-derived HECs that OPPT used in its risk assessment (Table 2-19). EPA/OPPT did not rely on those steps that were associated with the derivation of candidate RfCs (cRfC) or final RfC value (Table 2-19). Below is a brief discussion of those steps that EPA/OPPT adopted in this risk assessment.

The non-cancer dose-response analysis in the TCE IRIS assessment commenced with the review and selection of high quality epidemiological and toxicity studies that reported both adverse non-cancer health effects and quantitative dose-response data[19] (Table 2-19). Subsequently, *point of departures (PODs)*[20] were identified for those studies that had suitable data for dose- response analysis. PODs can be a NOAEL[21] or LOAEL[22] for an observed incidence, or change in level of response, or the lower confidence limit on the dose at the benchmark dose (BMD)[23].

The dose-response assessment was organized in five health effects domains: (1) neurotoxicity; (2) systemic (body weight) and organ toxicity (liver and kidney effects); (3) immunotoxicity; (4) reproductive; and (5) developmental effects. PBPK modeling was used to estimate internal dose PODs (idPOD) and subsequently HECs based on the oral and inhalation PODs identified in earlier steps. The PBPK modeling integrated internal dose-metrics based on TCE's mode of action and the role of different TCE metabolites in toxicity (EPA, 2011e). Note that the effects within the same health effect domain were generally assumed to have the same relevant internal dose- metrics (EPA, 2011e).

Furthermore, the PBPK model was used to estimate the interspecies and within-human pharmacokinetic variability (or just within-human variability for the human-based PODs) corresponding to each idPOD for each candidate critical effect. The results of this calculation were 50th, 95th and 99th percentile HEC estimates for POD analyzed within each health effects domain. Also, the PBPK model integrated a Bayesian population analysis to characterize pharmacokinetic uncertainties and variability (EPA, 2011e). More information on the PBPK modeling is provided in the next section below, including how the HECs were calculated.

EPA/OPPT used the endpoint/study-specific UFs from the TCE IRIS assessment as the benchmark MOEs for the risk calculations. These UFs were applied to the PBPK-derived PODs to account for (1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL (EPA, 2011b).

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[19] Non-cancer toxicological and epidemiological studies are described in Chapter 4 of the TCE IRIS assessment. [20] A point of departure (POD) is a dose or concentration that can be considered to be in the range of observed responses, without significant extrapolation. A POD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures EPA (2011b).

[21] NOAEL=No-observed-adverse-effect level

[22] LOAEL= Lowest-observed-adverse-effect level

[23] The benchmark dose (BMD) is a dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background EPA (2011b).

Table 2-18. Lowest PBPK-derived HECs for different effects domains based on analysis in TCE IRIS assessment

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm)[3]	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) for Benchmark MOE[4]	Reference
CHRONIC	Liver	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures, variable time periods for 30-120 days	$BMDL_{10}$ = 21.6 ppm	Increased liver/body weight ratio	25	12	9.1	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Kidney	Rat (female)	Oral (gavage)	500 to 1,000 mg/kg-bw/day	5 days/week for 104 weeks	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.042	0.0085	0.0056	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	NTP (1988)
	Nervous System	Rat (male)	Inhalation	50 to 300 ppm	8 hrs/day, 5 days/weeks for 6 weeks	LOAEL = 12 ppm	Significant decreases in wakefulness	13	6.4	4.8	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; *Total UF=300*	Arito et al. (1994)
	Immune System	Mouse (female)	Oral (drinking water)	0.001 to 14 ppm (0.001 to 14 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*[5]	Keil et al. (2009)
		Mouse (female)	Oral (drinking water)	0.001 to 14 ppm (0.001 to 14 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=3; *Total UF=30*[5]	Keil, D. E. et al. (2009)
	Reproductive System	Human (male)	Inhalation	29.6 ppm (mean exposure)	Measured values after an 8-hour work shift; mean 5.1 years on job	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	1.4	0.7	0.5	UF_S=10; UF_A= 1; UF_H=3; UF_L=1; *Total UF=30*	Chia et al. (1996)

Table 2-18. Lowest PBPK-derived HECs for different effects domains based on analysis in TCE IRIS assessment

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm)[3]	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) for Benchmark MOE[4]	Reference
ACUTE OR CHRONIC	Developmental effects	Rat (female)	Oral (drinking water)	2.5 to 1,100 ppm (2.5 to 1,100 mg/kg-bw/day)	22 days throughout gestation (gestational days 0 to 22)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.012	0.0051	0.0037	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Johnson et al. (2003)

Notes:
1 Control concentrations were not included in the table, but discussed in the study summaries in section 2.6.2.
2 POD type can be NOAEL, LOAEL, or BMDL; the IRIS program adjusted all values to continuous exposure.
3 1 ppm = 5.374 mg/m^3
4 UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF. UF values were those used in the TCE IRIS assessment (EPA, 2011e).
5 Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UF (EPA, 2011e).

Table 2-19. Steps of the Non-Cancer TCE IRIS Process that Were Considered in OPPT's Non-Cancer Hazard/Dose-Response Approach [1]

Step#	NON-CANCER IRIS APPROACH	NON-CANCER OPPT APPROACH *Considered (+) / Not Considered (—)*
1	Evaluation of all studies (inhalation and oral) that provided (1) non-cancer adverse health effects and (2) quantitative dose-response data	+
2	Identification of the Points of Departure (POD) based on applied dose	+
3	Adjustment of each POD by endpoint/study-specific uncertainty factors (UFs)	—
4	Derivation of candidate reference concentrations (cRfCs) and selection of the lowest values within each health endpoint domain taking into account the confidence of the estimate	—
5	Application of PBPK modeling to estimate internal dose PODs (i.e., HECs) for those candidate critical effects selected from inhalation and oral studies based on applied dose	+
6	Estimation of interspecies and within-human pharmacokinetic variability for the internal dose PODs by PBPK modeling	+
7	Adjustment of each internal dose POD by endpoint/study-specific UFs [2]	—
8	Derivation of PBPK model-based candidate RfCs (p-cRfC) for each candidate critical effect	—
9	Characterization of the uncertainties of the cRfCs derived by applied dose and PBPK modeling (p-cRfC) by using quantitative uncertainty analyses of pharmacokinetic uncertainty and variability from the Bayesian population analysis [3]	—
10	Evaluation of the most sensitive cRfCs and set final RfC value.	—

Notes:

1 Table 2-19 is an adaptation of Figure 5-1 (Chapter 5) in the TCE IRIS assessment (EPA, 2011e).

2 Endpoint/study-specific UFs were used as benchmark MOEs in the OPPT's TCE risk assessment.

3 EPA/OPPT consulted the characterization of the uncertainties in the TCE IRIS assessment and those aspects related to the uncertainties of the individual studies and the generation of PBPK-derived HECs were discussed in the OPPT's TCE risk assessment.

APPENDIX L. LIST OF ORAL AND INHALATION STUDIES SUITABLE FOR NON-CANCER DOSE-RESPONSE ANALYSIS IN THE TCE IRIS ASSESSMENT

L-1 Liver Effects

Target Organ	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Liver	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures, variable time periods for 30-120 days	$BMDL_{10}$= 21.6 ppm	Increased liver/body weight ratio	25	12	9.1	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Mouse (male)	Oral (gavage)	100 to 3,200 mg/kg-bw/day	6 weeks	$BMDL_{10}$= 82 mg/kg-bw/day		32	15	11	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Buben and O'Flaherty (1985)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hr/day, 5 days/week for 4 weeks	$BMDL_{10}$= 25 ppm		53	24	19	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Woolhiser et al. (2006)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-2 Kidney Effects

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Kidney	Rat (female)	Oral (gavage)	500 to 1,000 mg/kg-bw/day	5 days/week for 104 weeks	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.042	0.0085	0.0056	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	NTP (1988)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hr/day, 5 days/week for 4 weeks	$BMDL_{10}$= 15.7 ppm	Increased kidney weight/body weight ratio	0.099	0.020	0.013	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Woolhiser et al. (2006)
	Rat (male)	Oral (gavage)	50 to 250 mg/kg-bw/day	4-5 days/week for 52 weeks	$BMDL_{10}$ = 34 mg/kg-bw/day	Pathology changes in renal tubule	0.19	0.038	0.025	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Maltoni and Cotti (1986)
	Rat (male)	Inhalation	100 to 600 ppm	7 hrs/day, 5 days/week for 2 years	$BMDL_{10}$= 40.2 ppm	Pathology changes in renal tubule	0.28	0.057	0.038	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Maltoni and Cotti (1986)
	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures for 30-120 days	$BMDL_{10}$ = 34.7 ppm	Increased kidney weight/body weight ratio	0.88	0.18	0.12	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Mouse (female)	Oral (gavage)	869 to 1,739 mg/kg-bw/day	5 days/week, TWA during exposure period (78 weeks), animals observed for 90 weeks	LOAEL = 620 mg/kg-bw/day	Pathology changes in renal tubule (toxic nephrosis)	3.9	0.77	0.5	UF_S=1; UF_A= 3; UF_H=3; UF_L=30; *Total UF=300*	NCI (1976)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-3 Neurotoxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Nervous system	Rat (male)	Inhalation	50 to 300 ppm	8 hrs/day, 5 days/weeks for 6 weeks	LOAEL = 12 ppm	Significant decreases in wakefulness	13	6.4	4.8	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; *Total UF=300*	Arito et al. (1994)
	Human (both sexes)	Inhalation	704 ppm × years of exposure (mean cumulative exposure)	Mean of 16 years	LOAEL = 14 ppm	Trigeminal nerve effects (increased latency in masseter reflex)	14	7.0	5.3	UF_S=1; UF_A= 1; UF_H=3; UF_L=3; *Total UF=10*	Ruijten et al. (1991)
	Rat (male)	Oral (drinking water)	24 to 47 mg/kg-bw/day	8 weeks	LOAEL = 47 mg/kg-bw/day	Cognitive effects (demyelination of hippocampus)	18	9.2	7.1	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Isaacson et al. (1990)
	Rat (male)	Oral (gavage)	1,000 mg/kg-bw/day	5 days/week for 6 weeks	LOAEL = 710 mg/kg-bw/day	Degeneration of dopamine-containing neurons in substantia nigra	126	62	47	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Gash et al. (2008)
	Rat (female)	Inhalation	300 ppm	24 hrs/day for 24 days	LOAEL = 300 ppm	Decreased regeneration of sciatic nerve	274	127	93	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Kjellstrand et al. (1987)
	Mouse (male)	Inhalation	150 to 300 ppm	24 hrs/day for 24 days	LOAEL = 150 ppm		378	163	120	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-4 Immunotoxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Immune system	Mouse (female)	Oral (drinking water)	1.4 to 14 ppm (0.35 to 3.5 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100* [4]	Keil et al. (2009)
	Mouse (female)	Oral (drinking water)	1.4 to 14 ppm (0.35 to 3.5 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=3; *Total UF=30* [4]	Keil et al. (2009)
	Mouse (female)	Oral (drinking water)	18 to 660 mg/kg-bw/day	16 or 24 weeks (4 or 6 months)	LOAEL = 18 mg/kg-bw/day	Immuno-suppression	4.8	2.4	1.7	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*	Sanders et al. (1982)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hrs/day, 5 days/week for 4 weeks	$BMDL_{1SD}$= 24.9 ppm	Immuno-suppression	29	15	11	UF_S=10; UF_A= 3; UF_H=3; UF_L=1; *Total UF=100*	Woolhiser et al. (2006)
	Mouse (males; auto-immune prone strain)	Inhalation	500 to 2,000 ppm	4 hrs/day, 6 days/week for 8 weeks	LOAEL = 70 ppm	Autoimmunity (changes in immunoreactive organs)	97	48	37	UF_S=10; UF_A= 3; UF_H=1; UF_L=10; *Total UF=300*	Kaneko et al. (2000)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

[4] Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UF (EPA, 2011e).

L-5 Reproductive Toxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs)[3]	Reference
Reproductive system	Human (male)	Inhalation	29.6 ppm (mean exposure)	Measured values after an 8-hr work shift; mean 5.1 years on the job	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	1.4	0.7	0.5	UF_S=10; UF_A= 1; UF_H=3; UF_L=1; *Total UF=30*	Chia et al. (1996)
	Rat (male)	Oral (drinking water)	143 to 270 mg/kg-bw/day	14 days	LOAEL = 141 mg/kg-bw/day	Decreased *in vitro* fertilization	16	11	9.3	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	DuTeaux et al. (2004)
	Rat (male)	Inhalation	376 ppm	4 hrs/day, 5 days/week, 2-10 weeks exposed, 2-8 weeks unexposed	LOAEL = 45 ppm	Sperm effects and male reproductive tract effects	32	16	13	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Kumar et al., 2000 Kumar et al. (2000)
				4 hrs/day, 5 days/week for 12 or 24 weeks							Kumar et al. (2001)
	Rat (female damns)	Oral (gavage)	10.1 to 1,125 mg/kg-bw/day	9 days (during gestational days 6 to 15)	LOAEL = 475 mg/kg-bw/day	Delayed parturition	98	48	37	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*	Narotsky et al. (1995)
	Mouse (male)	Inhalation	1,000 ppm	6 hrs/day, 5 days/week for 19 days over 4 weeks	LOAEL = 180 ppm	Effects on epididymis epithelium	190	91	67	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Forkert et al. (2002)
				6 hrs/day, 5 days/week for 1-4 weeks							Kan et al. (2007)
	Mouse (male)	Inhalation	1,000 ppm	6 hrs/day, 5 days/week for 6 weeks	LOAEL = 180 ppm	Sperm effects (decreased in vitro sperm-oocyte binding and *in vivo* fertilization)	190	91	67	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Xu et al. (2004)

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Reproductive system	Rat (male)	Oral (drinking water)	72 to 389 mg/kg-bw/day	Breeders exposed 1 week premating and then for 13 weeks/ Pregnant females exposed throughout gestation (i.e., 18 weeks total)	LOAEL = 389 mg/kg-bw/day	Decreased mating (both sexes exposed)	204	97	71	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; UF_D=1 *Total UF=100*	NTP (1986)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-6 Developmental Toxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Developmental effects	**PRE- AND POSTNATAL MORTALITY**										
	Rat (female)	Inhalation	**1.** ppm	4 hrs/day, gestational days 8 to 21	LOAEL =17 ppm	Increased resorptions	16	8	6.2	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Healy et al. (1982)
	Rat (female)	Oral (gavage)	10.1 to 1,125 mg/kg-bw/day	Gestational days 6 to 15	$BMDL_{01}$= 32.2 mg/kg-bw/day	Increased resorptions	57	29	23	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Narotsky et al. (1995)
	PRE- AND POSTNATAL GROWTH										
	Rat (female)	Inhalation	100 ppm	4 hrs/day, gestational days 8 to 21	LOAEL = 17 ppm	Decreased fetal weight and skeletal effects	16	8	6.2	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Healy et al. (1982)
	CONGENITAL DEFECTS										
	Rat (female)	Oral (drinking water)	2.5 to 1,100 ppm (2.5 to 1,100 mg/kg-bw/day)	22 days throughout gestation (gestational days 0 to 22)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.012	0.0051	0.0037	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Johnson et al. (2003)
	DEVELOPMENTAL NEUROTOXICITY										
	Rat (male pups)	Oral (gavage)	50 to 290 mg/kg-bw/day	Postnatal days 10 to 16	LOAEL = 50 mg/kg-bw/day	Decreased rearing activity	8	4	3	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; Total UF=300	Fredriksson et al. (1993)
	Rat (female)	Oral (drinking water)	45 to 140 mg/kg-bw/day	Dams and pups exposed from 14 days prior to mating until end of lactation	LOAEL = 45 mg/kg-bw/day	Increased exploratory behavior in male pups (offspring)	22	11	8.4	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Taylor et al. (1985)

Notes: [1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.
[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.
[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

2.7 HUMAN HEALTH RISK CHARACTERIZATION

TCE and its metabolites are associated with adverse effects on cardiac development based on a weight-of-evidence analysis of developmental studies from rats, humans and chickens. These adverse cardiac effects are deemed important for acute and chronic risk estimation for the scenarios and populations addressed in this risk assessment. The rationale for using TCE associated fetal cardiovascular lesions for acute scenarios is based on the relatively short critical window of vulnerability in humans, rodent and avian cardiac development. The rationale for using fetal cardiac effects for chronic risks estimation is also based on the fact that relatively low dose short term/acute exposures can result on long-term adverse consequences on cardiac development persisting into adulthood.

Table 2-26. Summary of Hazard Information Used in the Risk Evaluation of Acute and Chronic Scenarios

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	POD Type	Effect	HEC_{99} (ppm)	Total Uncertainty Factor (UF) for Benchmark MOE	Reference
CHRONIC	Liver	Mouse (male)	Inhalation	$BMDL_{10}$ = 21.6 ppm	Increased liver/body weight ratio	9.1	*Total UF=10*	Kjellstrand et al. (1983)
	Kidney	Rat (female)	Oral (gavage)	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.0056	*Total UF=10*	NTP (1988)
	Nervous System	Rat (male)	Inhalation	LOAEL = 12 ppm	Significant decreases in wakefulness	4.8	*Total UF=300*	Arito et al. (1994)
	Immune System	Mouse (female)	Oral (drinking water)	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.033	*Total UF=100*	Keil et al. (2009)
		Mouse (female)	Oral (drinking water)	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.033	*Total UF=30*	Keil, D. E. et al. (2009)
	Reproductive System	Human (male)	Inhalation	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	0.5	*Total UF=30*	Chia et al. (1996)
ACUTE OR CHRONIC	Developmental effects	Rat (female)	Oral (drinking water)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.0037	Total UF=10	Johnson et al. (2003)

Notes:

[1] 1 ppm = 5.374 mg/m^3

[2] Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UFs for effects repoted by the same study (EPA, 2011e).

Other adverse non-cancer effects are deemed relevant for risk estimations for other populations for the chronic scenarios, but may not occur at the lowest exposures found with cardiac defects and they include kidney toxicity, immunotoxicity, male reproductive toxicity,

neurotoxicity, liver toxicity and cancer of kidney, liver and immune system (NHL).

TCE is carcinogenic to humans. The cancer risk assessment uses the IUR derived in the 2011 TCE IRIS assessment based on human kidney cancer. The weight-of-evidence analysis for the cancer endpoint was sufficient to conclude that TCE operates through a mutagenic mode of action for kidney tumors (EPA, 2011e).

2.7.1 Risk Estimation Approach for Acute and Repeated Exposures

Tables 2-27 and 2-28 show the use scenarios, populations of interest and toxicological endpoints used in the acute and chronic risk assessment, respectively.

Table 2-27. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Acute Risks to TCE-containing Degreasers, Spotting Agents and Arts/Crafts Products

Use Scenarios / Populations And Toxicological Approach	(1) Solvent degreasing at small commercial facilities	(2) Spot cleaning at dry cleaning facilities	(3) Residential use of degreaser product	(4) Residential use of arts/crafts clear protective coating spray
Population of Interest and Exposure Scenario: *Users*	Adult pregnant[1] worker (>16 years old) exposed to TCE for a single 2-hr exposure during an 8-hr workday [2,3,4].	Adult pregnant[1] worker (>16 years old) exposed to TCE for a single 8-hr exposure [2,3].	Adult pregnant [1] consumers (>16 yrs old) exposed to TCE for a single 1-hr exposure when using product 2X per month [2,3,4]. Residential exposure model provided the 24-hr acute exposure estimate.	Adult pregnant [1] consumers (>16 yrs old) exposed to TCE for a single 0.5-hr exposure when using product once per week [2,3,4]. Residential exposure model provided the 24-hr acute exposure estimate.
Population of Interest and Exposure Scenario: *Bystander*	Adult pregnant women [1] (>16 years old) exposed to TCE indirectly by being in the same building.		Adult pregnant bystander[1] and individuals of several age groups that are exposed to indirect TCE exposures by being in the rest of the house.	
Health Effects of Concern, Concentration and Time Duration	Non-Cancer Health Effects: Fetal cardiac defects (Johnson et al., 2005; Johnson, 2014; Johnson et al., 2003)[5] 1. *PBPK-derived Non-Cancer Hazard values or Point of Departures (PODs)* (EPA, 2011e): 24-hr HEC_{50}: 0.012 ppm 24-hr HEC_{95}: 0.0051 ppm 24-hr HEC_{99}: 0.0037 ppm Cancer Health Effects: Acute cancer risks were not estimated. Relationship is not known between a single short-term exposure to TCE and the induction of cancer in humans.			
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	(UF_S=1) x (UF_A= 3) x (UF_H=3) x (UF_L=1) [6] = 10 (EPA, 2011e). Total UF=Benchmark MOE=10			

Notes:

[1] The acute risk assessment focused on the most sensitive life stage in humans, which is women of childbearing age and fetus (i.e., pregnant worker) due to concerns for developmental effects.

[2] Exposure estimate was adjusted to a 24-hr exposure estimate in order to combine it with the 24-hr HECs.

[3] It is assumed no substantial buildup of TCE in the body between exposure events due to TCE's short biological half-life (~51 hrs).

[4] EPA/OPPT believes that the users of these products are generally adults, but teenagers and even children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.

[5] The acute risk assessment focused on developmental toxicity effects as the most sensitive health effect when compared to other potential acute effects (i.e., neurotoxicity).

[6] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF

Table 2-28. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Chronic Risks to TCE-containing Degreasers and Spotting Agents

Use Scenarios → / Populations And Toxicological Approach ↓	(1) Solvent degreasing at small commercial facilities	(2) Spot cleaning at dry cleaning facilities
Population of Interest and Exposure Scenario: *Users*	Adult worker (>16 years old) [1] exposed to TCE for 2-hr exposure during an 8-hr workday for 260 days per year for 40 working years. Lifetime average daily concentration was calculated. Note that the 8-hr exposure estimate was adjusted to a 24-hr exposure estimate.	Adult worker (>16 years old) [1] exposed to TCE for an 8-hr workday for 260 days per year for 40 working years. Lifetime average daily concentration was calculated. Note that the 8-hr exposure estimate was adjusted to a 24-hr exposure estimate.
Population of Interest and Exposure Scenario: *Bystander*	Adult worker (>16 years old) [1] repeatedly exposed to indirect TCE exposures by being in the same building.	
Health Effects of Concern, Concentration and Time Duration	Non-Cancer **2.** *Non-cancer health effects*: A range of possible chronic non-cancer effects in liver, kidney, nervous system, immune system, reproductive system and developmental effects[2] **3.** *PBPK-derived Non-Cancer Hazard values or Point of Departures (PODs):* The lowest POD (i.e., 24-hr HEC_{50}, HEC_{95} or HEC_{99} expressed in ppm) within each health endpoint domain (EPA, 2011e). See Table 2-18. Cancer **1.** *Cancer health effects:* Possible cancer effects in kidney, liver or non-Hodgkins lymphoma from chronic exposure. **2.** *PBPK-derived Cancer Inhalation Unit Risk (IUR)*: 2×10^{-2} per ppm (EPA, 2011e).	
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	Study- and endpoint-specific UFs from the TCE IRIS assessment. See Table 2-18.	

Notes:
[1] Adult workers (>16 years old) include both healthy female and male workers.
[2] The chronic risk assessment for developmental effects focused on the most sensitive life stage in humans, which are women of child-bearing age and fetus (i.e., pregnant worker). For other health effects (e.g., liver, kidney, etc.), healthy female or male workers were assumed to be the population of interest.

Acute or chronic MOEs (MOE_{acute} or $MOE_{chronic}$) were used in this assessment to estimate non-cancer risks (Table 2-29).

Table 2-29. Equation to Calculate Non-Cancer Acute or Chronic Risks Using Margin of Exposures

$$MOE_{acute\ or\ chronic} = \frac{\text{Non-cancer Hazard value (POD)}}{\text{Human Exposure}}$$

MOE =	Margin of exposure (unitless)
Hazard value (POD) =	HEC_{50}, HEC_{95}, or HEC_{99} (ppm) derived from TCE IRIS assessment (EPA, 2011e)
Human Exposure =	Exposure estimate (in ppm) from occupational or consumer exposure assessment. ADCs were used for non-cancer chronic risks and acute concentrations were used for acute risks (see sections 2.3.3 and 2.4.2).

As discussed previously, each non-hazard PBPK-derived POD was adjusted by endpoint/study-specific UFs as described in the TCE IRIS assessment (EPA, 2011e). These UFs accounted for (1) the variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4)the uncertainty in extrapolating from a LOAEL rather than from a NOAEL (EPA, 2011e).

The total UF for each non-cancer PBPK-derived POD was the benchmark MOE used to interpret the MOE risk estimates for each use scenario. The MOE estimate was interpreted as human health risk if the MOE estimate was less than the benchmark MOE (=total UF). On the other hand, the MOE estimate indicated negligible concerns for adverse human health effects if the MOE estimate exceeded the benchmark MOE. Typically, the larger the MOE, the more unlikely it is that a non-cancer adverse effect would occur.

Cancer risks for repeated exposures to TCE were estimated using the equation in Table 2-30. Estimates of cancer risks should be interpreted as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to the potential carcinogen (i.e., incremental or excess individual lifetime cancer risk).

Table 2-30. Equation to Calculate Cancer Risks

$$\text{Risk} = \text{Human Exposure} \times \text{IUR}$$

Risk =	Cancer risk (unitless)
Human exposure =	Exposure estimate (LADC in ppm) from occupational exposure assessment
IUR =	Inhalation unit risk (2×10^{-2} per ppm) (EPA, 2011e)

2.7.2 Acute Non-Cancer Risk Estimates for Inhalation Exposures to TCE

The acute inhalation risk assessment used developmental toxicity data to evaluate the acute risks for the TSCA TCE use scenarios. As indicated previously, EPA's policy supports the use of developmental studies to evaluate the risks of acute exposures. This policy is based on the presumption that a single exposure of a chemical at a critical window of fetal development, as in the case of cardiac development, may produce adverse developmental effects (EPA, 1991).

After evaluating the developmental toxicity literature of TCE, the TCE IRIS assessment concluded that the fetal heart malformations are the most sensitive developmental toxicity endpoint associated with TCE exposure (EPA, 2011e). Thus, EPA/OPPT based its acute risk assessment on the most health protective endpoint (i.e., fetal cardiac malformations; Johnson et al., 2003) representing the most sensitive human population (i.e., adult women of child-bearing age and fetus > 16 yrs).

The acute risk assessment used the PBPK-derived hazard values (HEC_{50}, HEC_{95}, or HEC_{99}) from Johnson et al. (2003) developmental study for each degreaser and spot cleaner use scenario. Note that the variability among these hazard values is small and no greater than 3-fold (i.e., 2-fold for HEC_{50}/HEC_{95} ratios; 3-fold for HEC_{50}/HEC_{99} ratios; 1.4-fold for HEC_{95}/HEC_{99} ratios).

Acute inhalation risks were reported for most occupational and residential exposure scenarios based on concerns for developmental effects, irrespective of who is using the product (user vs. bystander), the type of exposure (typical vs. worst case scenario) and the room ventilation system (LEV vs no LEV). For instance, most of the degreaser and spot cleaner exposure scenarios and all of the residential use scenarios reported MOE values below the benchmark MOE of 10 irrespective of the percentile HEC value used to estimate the MOEs. Only one use scenario reported MOEs above 10, which was the spot cleaner use scenario representing bystander exposures under typical occupational exposure levels with LEV (i.e., "Bystander + LEV—Typical Exposure") (Tables 2-31, 2-32 and 2-33).

Table 2-31. Acute Non-Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	WORKER NON-CANCER MOEs				BYSTANDER NON-CANCER MOEs				Total UF or Benchmark MOE
	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	
HEC_{50}= 0.012	**0.12**	**0.0018**	**0.012**	**0.00018**	**0.9**	**0.002**	**0.09**	**0.00021**	10
HEC_{95}= 0.0051	**0.051**	**0.0008**	**0.0051**	**0.00008**	**0.38**	**0.0009**	**0.038**	**0.000089**	
HEC_{99}= 0.0037	**0.037**	**0.0006**	**0.0037**	**0.00006**	**0.28**	**0.0007**	**0.028**	**0.000065**	

Notes:

– MOEs below benchmark MOE indicating risk are denoted in **bold** text. They indicate potential health risks.
– Exposure estimates with/without LEV are found in Table 2-10.

Table 2-32. Acute Non-Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	WORKER NON-CANCER MOEs				BYSTANDER NON-CANCER MOEs				Total UF or Benchmark MOE
	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	
HEC_{50}= 0.012	**4.5**	**0.018**	**0.45**	**0.0019**	51.4	**0.018**	**5.1**	**0.002**	10
HEC_{95}= 0.0051	**1.9**	**0.0077**	**0.19**	**0.00081**	21.9	**0.0077**	**2.2**	**0.00085**	
HEC_{99}= 0.0037	**1.4**	**0.0056**	**0.14**	**0.00058**	15.9	**0.0056**	**1.6**	**0.00062**	

Notes:

– MOEs below benchmark MOE indicating risk are denoted in **bold** text. They indicate potential health risks.
– Exposure estimates with/without LEV are found in Table 2-13.

Table 2-33. Acute Non-Cancer Risk Estimates for Residential Uses of TCE-containing degreasers and art/crafts products (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	RESIDENTIAL USE OF DEGREASER PRODUCT MOEs [1]		RESIDENTIAL USE OF ARTS/CRAFTS CLEAR PROTECTIVE COATING SPRAY MOEs [1]		Total UF or Benchmark MOE
	USER [2]	BYSTANDER [3]	USER [2]	BYSTANDER [3]	
HEC_{50}= 0.012	**0.0060**	**0.015**	**0.03**	**0.12**	10
HEC_{95}= 0.0051	**0.0026**	**0.0064**	**0.013**	**0.051**	
HEC_{99}= 0.0037	**0.0019**	**0.0046**	**0.0093**	**0.037**	

Notes:
1 MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks.
2 MOEs for the user categories could be extended to different age groups. EPA/OPPT believes that the users of these products are generally adults, but teenagers and even children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.
3 All age categories (<1 yrs; 1-2 yrs; 3-5 yrs; 6-10 yrs; 11-15 yrs; 16-20 yrs ; and >21 yrs)

2.7.3 Chronic Non-Cancer and Cancer Risk Estimates for Inhalation Exposures to TCE

Chronic non-cancer and cancer risk estimates for inhalation exposures to TCE were only derived for occupational scenarios since the exposures for consumer uses were not considered chronic in nature.

2.7.3.1 Cancer Risks for Occupational Scenarios

Figures 2-6 and 2-7 present the incremental individual lifetime cancer risks for continuous exposures to TCE occurring during the commercial use of degreaser and spot cleaner products. The cancer risk estimates were calculated by multiplying the EPA's inhalation unit risk for TCE (EPA, 2011e) by the exposure estimate (i.e., LADC) for both direct users and bystanders. Cancer risks were expressed as number of cancer cases per million. Calculations of cancer risks are provided in the supplemental Excel spreadsheet, *TCE OPPT Risk Estimates_061814.xlsx*.

It was assumed that the exposure frequency (i.e., the amount of days per year workers or bystanders are exposed to TCE) was 260 days per year and the occupational exposure duration was 40 years over a 70-year lifespan. It is recognized that these exposure assumptions are likely yielding conservative cancer risk estimates, but EPA/OPPT does not have additional information for further refinement.

EPA typically uses a target cancer risk level between $1x10^{-4}$ and $1x10^{-6}$ for determining the acceptability of the cancer risk in a population. Since the target cancer risk level will be determined during risk management, the occupational cancer risk estimates were compared to three target levels within EPA's acceptability range. The target levels were:

1. $1x10^{-6}$: the probability of 1 chance in 1 million of an individual developing cancer
2. $1x10^{-5}$: the probability of 1 chance in 100,000 of an individual developing cancer, which is equivalent to 10 cancer cases in 1 million
3. $1x10^{-4}$: the probability of 1 chance in 10,000 of an individual developing cancer, which is equivalent to 100 cancer cases in 1 million

All of the degreaser exposure scenarios exceeded the three target cancer levels, with the exception of one of the bystander exposure scenarios (i.e., "*Bystander + LEV—Typical Exposure*"). This particular bystander exposure scenario exceeded the target levels at $1x10^{-5}$ and $1x10^{-6}$ (Figure 2-6).

Likewise, all of the worst case exposures for the spot cleaner scenarios (i.e., both user and bystander scenarios) and one of the typical exposure scenarios with no LEV (i.e., "*Spot Cleaner No LEV—Typical Exposure*") exceeded the three target levels. The remaining spot cleaner scenarios exceeded the target level of $1x10^{-4}$ (i.e., "Spot cleaner + LEV—Typical Exposure"; "Bystander + LEV—Typical Exposure"; and "Bystander No LEV—Typical Exposure") (Figure 2-7).

Figure 2-6. Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops

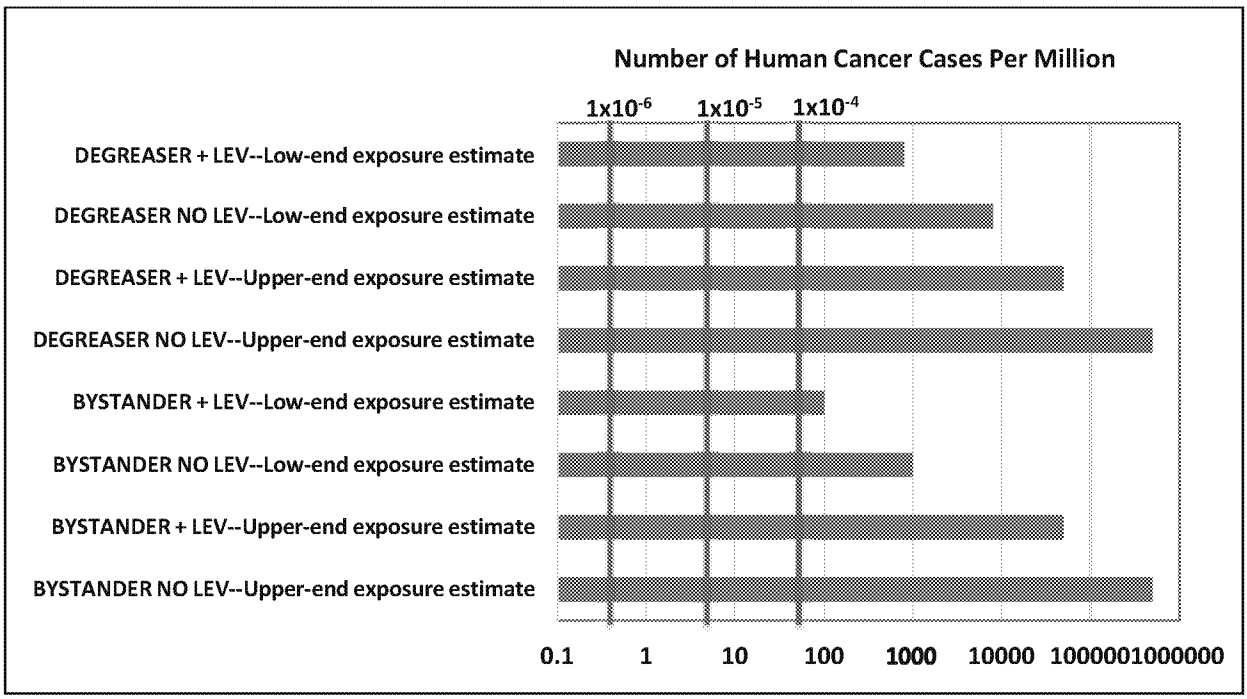
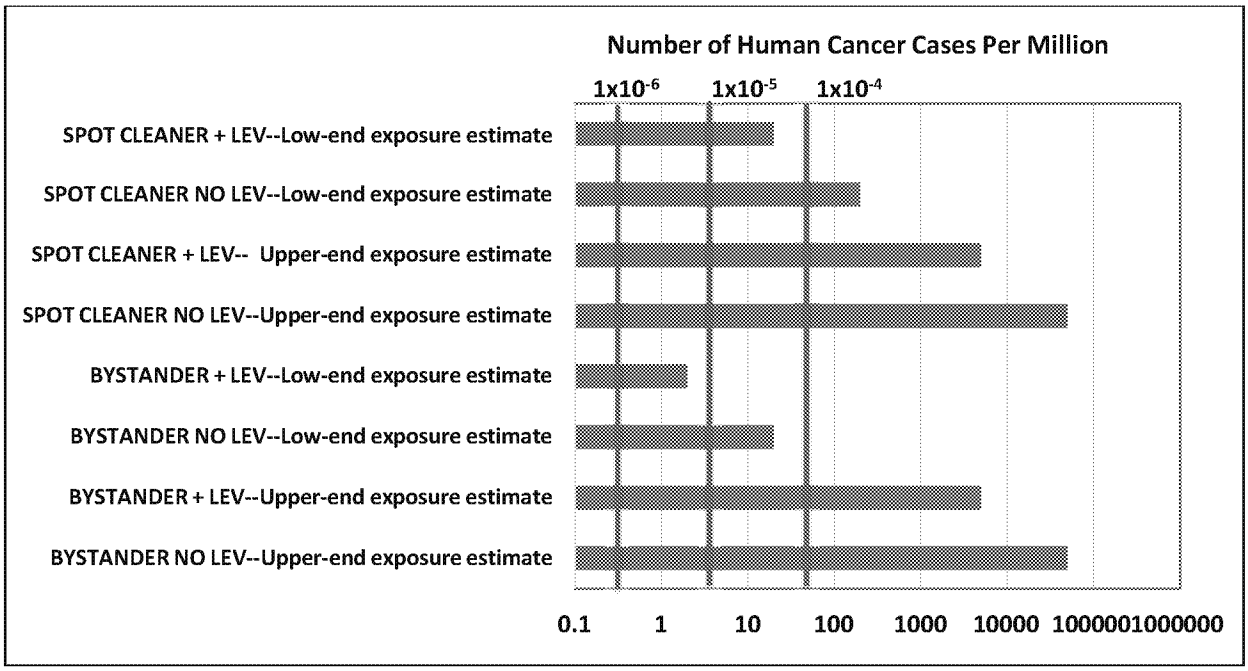


Figure 2-7. Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities



For both degreaser and spot cleaner scenarios, the results indicated that the cancer risk was 10 times greater in scenarios with no local exhaust ventilation that those with room ventilation (+LEV). Moreover, an 8-fold increase in cancer risk was observed in those workers directly using the TCE-containing product when compared to their corresponding bystanders (Figures 2-6 and 2-7). Similarly, a 10-fold increase in cancer risk was reported in those workers using spotting agents containing TCE when compared to their corresponding bystanders indirectly exposed in the dry cleaning facilities (Figure 2-7).

2.7.3.2 Chronic Non-Cancer Risks for Occupational Scenarios

EPA/OPPT estimated chronic non-cancer risks for the occupational use of TCE-containing degreasers and spot cleaners. Since TCE exposure has been associated with a variety of health effects, this assessment estimated human health inhalation chronic risks for developmental toxicity, kidney toxicity, immunotoxicity, reproductive toxicity, neurotoxicity and liver toxicity. As previously discussed, the TCE IRIS assessment developed PODs (i.e., HEC_{50}, HEC_{95} or HEC_{99}) for multiple studies that were suitable for dose-response analysis (Appendix L). EPA/OPPT used the lowest POD (or HEC) in each health effects domain for the non-cancer chronic MOE calculations. The risk estimates for the commercial degreaser and spot cleaner uses are presented in Tables 2-34 and 2-35, respectively[30].

Workers in direct contact with the degreaser products and occupational bystanders reported risks (i.e., MOEs<benchmark MOE) for the following chronic non-cancer effects: developmental toxicity, kidney and immunotoxicity. Also, all of the worker scenarios showed risks for reproductive effects and neurotoxicity. These risks were observed in the worker/bystander scenarios regardless of the type of TCE exposure (typical vs. worst case) and the availability of local exhaust ventilation (with LEV vs. no LEV). Moreover, risks for reproductive effects and neurotoxicity were also found in the degreaser bystander scenarios, but only for worst case exposure conditions and typical exposure circumstances with no local exhaust ventilation. Furthermore, risks were also found for liver effects, but only for those degreaser worker/bystander scenarios representing worst case exposure conditions irrespective of the presence of room ventilation (Table 2-34).

The non-cancer chronic risk profile was slightly different for the TCE use in spot cleaners because the TCE exposure concentrations in dry cleaning facilities were 10 to 60-fold lower than those estimated in degreaser small shops. Risks for developmental effects, kidney toxicity and immunotoxic effects were generally observed for all of the spot cleaning worker/bystander exposure scenarios (i.e., typical vs worst case; typical exposure vs worst case) with two exceptions. Non-risk findings were reported for few spot cleaning worker/bystander scenarios under LEV and typical exposure conditions that used the HEC^{50th} percentile for the MOE calculations. Also, the spot cleaning bystander exposure scenario did not report potential non-

[30] Risk estimates were calculated for all of the studies per health effects domain that the EPA's IRIS program identified as suitable for dose-response analysis. These risk estimates are found in the supplemental Excel file "TCE OPPT Risk Estimates_061814".

cancer chronic risks for the aforementioned health effects domains under LEV and typical exposure conditions (Table 2-35).

Risks for reproductive effects and neurotoxicity were less consistently seen across the board with the exception of the spot cleaning worker/bystander exposure scenarios characterizing typical or worst-case exposure condition under no ventilation system. As for risks for liver effects, most of the spot cleaning scenarios showed no risk concern with the exception of the worker/bystander worst case exposure scenarios with no LEV (Table 2-35).

2.7.4 Human Health Risk Characterization Summary

This risk assessment focused on the occupational and consumer uses of TCE-containing degreasers, spot cleaners and clear protective coating spray in arts/crafts. Specifically, the following exposure scenarios were evaluated: small commercial degreasing operations; spot cleaning in dry cleaning facilities; consumer use of an aerosol degreaser; and the consumer use of a clear protective coating spray in an arts/crafts home setting. The population of interest consisted of workers and consumers with direct (users) or indirect (bystander) exposure to TCE. Only the inhalation route of exposure was considered in this risk assessment.

The occupational and consumer exposure assessments generated the TCE exposure levels required to derive non-cancer and cancer risks. Cancer risks were presented as lifetime risks, meaning the risk of developing cancer as a result of the occupational exposure over a normal lifetime of 70 yrs. Lifetime cancer risks from TCE exposure were compared to target risks ranging from 10^{-6} to 10^{-4}.

Many of the degreaser and spot cleaning exposure scenarios exceeded the target cancer risks of 10^{-6}, 10^{-5} and 10^{-4}. This analysis resulted in higher modeled incidences of cancer in the small commercial degreaser than the users of spot cleaners. Thus, the greatest potential for cancer risk came from the occupational exposures to commercial degreasers. Furthermore, higher cancer risks resulted from direct use of the degreaser or lack of local exhaust ventilation at the workplace.

To characterize the risks of adverse health effects other than cancer, MOEs were used to evaluate non-cancer risks for both acute and chronic exposures using the hazard values published in the TCE IRIS assessment (EPA, 2011e). Hazard values based on developmental toxicity (i.e., fetal cardiac defects; Johnson et al., 2003) were used to estimate acute non-cancer risks for occupational and consumer exposures. On the other hand, the chronic non-cancer risks for the worker scenarios were evaluated with the hazard values associated with health effects following long-term exposure to TCE (i.e., developmental toxicity, kidney toxicity, immunotoxicity, reproductive toxicity, neurotoxicity and liver effects). Note that minimal variability (i.e., ≤ 3-fold) exist among the acute and chronic non-cancer hazard values (i.e., HEC_{50}, HEC_{95} or HEC_{99}) used in this assessment.

Most occupational and residential exposure scenarios reported acute risks based on concerns for developmental effects (i.e., cardiac defects) that may occur following a single exposure to TCE during a critical window of susceptibility. Particularly, the degreaser exposure scenarios showed greater acute risks than those reported for the spot cleaning exposure scenarios.

There is a concern for a range of human health effects other than cancer that may appear after chronic exposures to TCE during the occupational use of TCE-containing degreasers and spot cleaning agents. The greatest concern is for developmental effects (i.e., fetal cardiac defects), followed by kidney effects and then immunotoxicity, with an overall higher chronic risk for the degreaser exposure scenarios. In general, the concerns for these three health effects domains occur regardless of the type of exposure (typical vs worst case) and the availability of room ventilation (LEV vs no LEV), although there are some exceptions, particularly in the spot cleaning bystander exposure scenarios.

Potential chronic risks for reproductive effects and neurotoxicity were also observed for degreaser worker exposure scenarios and most of the degreaser bystander exposure scenarios. However, the risks concerns for these effects were reported for fewer spot cleaning worker/bystander scenarios and generally attributed to exposure conditions without room ventilation.

Concerns for liver effects following chronic exposure to TCE are less prominent than the concerns for other health effects domains as chronic risks for liver toxicity were not reported for the majority of the degreaser and spot cleaning worker/bystander scenarios. The exception was the degreaser worker/bystander exposure worst case scenarios and the spot cleaning worker/bystander worst case scenarios with no LEV.

Table 2-34. Chronic Non-Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops

Health Effect Domain and Study	Lowest HEC (ppm) of each health effects domain	WORKER NON-CANCER MOEs [1]				BYSTANDER NON-CANCER MOEs [1]				Total UF or Benchmark MOE
		With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	
DEVELOPMENTAL TOXICITY (Johnson et al., 2003)	HEC50= 0.012	**0.17**	**0.017**	**0.0025**	**0.0003**	**1.3**	**0.13**	**0.0030**	**0.0003**	10
	HEC95= 0.0051	**0.072**	**0.0072**	**0.0011**	**0.0001**	**0.54**	**0.05**	**0.0013**	**0.0001**	
	HEC99= 0.0037	**0.052**	**0.0052**	**0.0008**	**0.0001**	**0.40**	**0.04**	**0.0009**	**0.0001**	
KIDNEY (NTP, 1998)	HEC50= 0.042	**0.59**	**0.059**	**0.0088**	**0.0009**	**4.4**	**0.4**	**0.01**	**0.001**	10
	HEC95= 0.0085	**0.11**	**0.012**	**0.0018**	**0.0002**	**0.9**	**0.09**	**0.0021**	**0.0002**	
	HEC99= 0.0056	**0.079**	**0.0079**	**0.0012**	**0.0001**	**0.6**	**0.06**	**0.0014**	**0.0001**	
IMMUNOTOXICITY Keil et al., 2009 (Decrease in thymus weight and thymus cellularity)	HEC50= 0.092	**1.3**	**0.1**	**0.019**	**0.0020**	**9.7**	**0.97**	**0.023**	**0.0023**	100
	HEC95= 0.045	**0.6**	**0.06**	**0.0095**	**0.0010**	**4.7**	**0.47**	**0.011**	**0.0011**	
	HEC99= 0.033	**0.5**	**0.05**	**0.0069**	**0.0007**	**3.5**	**0.35**	**0.0082**	**0.0008**	
IMMUNOTOXICITY Keil et al., 2009 (Autoimmunity)	HEC50= 0.092	**1.3**	**0.13**	**0.019**	**0.0020**	**9.7**	**0.97**	**0.022**	**0.0023**	30
	HEC95= 0.045	**0.6**	**0.063**	**0.0095**	**0.0010**	**4.7**	**0.47**	**0.011**	**0.0011**	
	HEC99= 0.033	**0.5**	**0.046**	**0.0069**	**0.0007**	**3.5**	**0.35**	**0.0082**	**0.0008**	
REPRODUCTIVE TOXICITY (Chia et al. 1996)	HEC50= 1.4	**19.7**	**2.0**	**0.3**	**0.03**	147	**15**	**0.35**	**0.034**	30
	HEC95= 0.7	**9.8**	**1.0**	**0.15**	**0.015**	74	**7**	**0.17**	**0.017**	
	HEC99= 0.5	**7.0**	**0.7**	**0.11**	**0.011**	53	**5**	**0.12**	**0.012**	
NEUROTOXICITY (Arito et al., 1994)	HEC50= 13	**183**	**18**	**2.7**	**0.28**	1369	**137**	**3.2**	**0.32**	300
	HEC95= 6.4	**90**	**9**	**1.3**	**0.14**	674	**67**	**1.6**	**0.16**	
	HEC99= 4.8	**67**	**7**	**1.0**	**0.10**	505	**51**	**1.2**	**0.12**	
LIVER (Kjellstrand et al. 1983)	HEC50= 25	351	35	**5.3**	**0.53**	2632	263	**6**	**0.61**	10
	HEC95= 12	168	17	**2.5**	**0.26**	1263	126	**3**	**0.29**	
	HEC99= 9.1	128	13	**1.9**	**0.19**	958	96	**2**	**0.22**	

Notes: (1) MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks. (2) Exposure estimates with/without LEV are found in Table 2-10.

Table 2-35. Chronic Non-Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities

Health Effect Domain and Study	Lowest HEC (ppm) of each health effects domain	WORKER NON-CANCER MOEs [1]				BYSTANDER NON-CANCER MOEs [1]				Total UF or Benchmark MOE
		With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	
DEVELOPMENTAL TOXICITY (Johnson et al., 2003)	HEC50= 0.012	**6.3**	**0.0253**	**0.63**	**0.0027**	72	**0.0253**	**7.2**	**0.0028**	10
	HEC95= 0.0051	**2.7**	**0.0107**	**0.27**	**0.0011**	31	**0.0107**	**3.1**	**0.0012**	
	HEC99= 0.0037	**1.9**	**0.0078**	**0.19**	**0.0008**	22	**0.0078**	**2.2**	**0.0009**	
KIDNEY (NTP, 1998)	HEC50= 0.042	22	**0.088**	**2.2**	**0.0093**	253	**0.0884**	25	**0.0098**	10
	HEC95= 0.0085	**4.5**	**0.018**	**0.45**	**0.0019**	51	**0.0179**	**5.1**	**0.0020**	
	HEC99= 0.0056	**2.9**	**0.012**	**0.29**	**0.0012**	34	**0.0118**	**3.4**	**0.0013**	
IMMUNOTOXICITY Keil et al., 2009 (Decrease in thymus weight and thymus cellularity)	HEC50= 0.092	**48**	**0.194**	**4.8**	**0.020**	554	**0.194**	**55**	**0.022**	100
	HEC95= 0.045	**24**	**0.095**	**2.4**	**0.010**	271	**0.095**	**27**	**0.011**	
	HEC99= 0.033	**17**	**0.069**	**1.7**	**0.007**	199	**0.069**	**20**	**0.008**	
IMMUNOTOXICITY Keil et al., 2009 (Autoimmunity)	HEC50= 0.092	48	**0.194**	**4.8**	**0.020**	554	**0.194**	55	**0.022**	30
	HEC95= 0.045	**24**	**0.095**	**2.4**	**0.010**	271	**0.095**	**27**	**0.011**	
	HEC99= 0.033	**17**	**0.069**	**1.7**	**0.007**	199	**0.069**	**20**	**0.008**	
REPRODUCTIVE TOXICITY (Chia et al. 1996)	HEC50= 1.4	737	**2.9**	74	**0.31**	8423	**2.9**	842	**0.33**	30
	HEC95= 0.7	369	**1.5**	37	**0.16**	4212	**1.5**	421	**0.16**	
	HEC99= 0.5	263	**1.1**	**26**	**0.11**	3008	**1.1**	301	**0.12**	
NEUROTOXICITY (Arito et al., 1994)	HEC50= 13	6844	**27**	684	**2.9**	78214	**27**	7821	**3.0**	300
	HEC95= 6.4	3369	**13**	337	**1.4**	38505	**13**	3851	**1.5**	
	HEC99= 4.8	2527	**10**	**253**	**1.1**	28879	**10**	2888	**1.1**	
LIVER (Kjellstrand et al. 1983)	HEC50= 25	13161	53	1316	**5.5**	150412	53	15041	**5.8**	10
	HEC95= 12	6317	25	632	**2.7**	72198	25	7220	**2.8**	
	HEC99= 9.1	4791	19	479	**2.0**	54750	19	5475	**2.1**	

Notes: (1) MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks. (2) Exposure estimates with/without LEV are found in Table 2-13.

Extracted from the TSCA Work Plan Chemical Risk Assessment for Trichloroethylene: Degreasing, Spot Cleaning and Arts and Craft Uses, CASRN: 70-01-6, [HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-chemical-risk-assessment"]

2.6 HAZARD/DOSE-RESPONSE ASSESSMENT

2.6.1 Approach and Methodology

2.6.1.1 Selection of TCE IRIS Assessment as the Source Document for the TCE TSCA Assessment

EPA/OPPT's work plan risk assessment for TCE is based on the hazard and dose-response information published in the toxicological review that the U.S. EPA's Integrated Risk Information System (IRIS) published in 2011. EPA/OPPT used the TCE IRIS assessment as the preferred data source for toxicity information, rather than developing a new toxicological assessment. The TCE IRIS assessment used a weight-of-evidence approach, the latest scientific information and physiologically-based pharmacokinetic (PBPK) modeling to develop hazard and dose-response assessments for TCE's carcinogenic and non-carcinogenic health effects resulting from lifetime oral or inhalation exposure.

Development of TCE's hazard and dose-response assessments considered the principles set forth by the various risk assessment guidelines issued by the National Research Council and the U.S. EPA. Primary, peer-reviewed literature identified through December 2010 was included where that literature was determined to be critical to the assessment (EPA, 2011e). Appendix K provides the guidelines that were considered when developing the TCE IRIS assessment. Some of these guidelines discussed the type of considerations that should be made when evaluating the quality of toxicity data and study reliability. Also Appendix K describes the study selection and data quality criteria that the U.S. EPA's IRIS program and OPPT used to evaluate the hazard data.

The TCE IRIS assessment underwent several levels of peer review including agency review, science consultation on the draft assessment with other federal agencies and the Executive Office of the President, public comment, external peer review by the EPA's Science Advisory Board (SAB) in 2002, scientific consultation by the U.S. National Academy of Sciences (NAS) in 2006 (NRC, 2006)[15], external peer review of the revised draft assessment by the EPA's Science Advisory Board (SAB) in January 2011 (EPA, 2011c)[16], followed by final internal agency review and EPA-led science discussion on the final draft.

Furthermore, EPA/OPPT consulted the EPA's Guidelines for Developmental Toxicity Risk Assessment when making the decision to use developmental toxicity studies in the acute risk assessment of commercial and consumer uses of degreasers and arts/crafts spray fixatives containing TCE (EPA, 1991). The basis for this decision relies on the presumption and EPA's

[15] NAS report, "Assessing the human health risks of trichloroethylene: Key scientific issues (2006)": [HYPERLINK "http://www.nap.edu/catalog.php?record_id=11707" \h]

[16] EPA's SAB peer review report for the 2009 EPA's Draft Assessment entitled "Toxicological Review of Trichloroethylene": [HYPERLINK "http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f648525742400690127/B73D5D39A8F184BD8525" \h] 7817004A1988/$File/EPA-SAB-11-002-unsigned.pdf

policy that a single exposure at a critical window of fetal development may produce adverse developmental effects (EPA, 1991). In other words, a single dose in a developmental toxicity study may be enough to cause developmental effects.

2.6.1.2 Aspects of the TCE IRIS Assessment that Were Adopted in the OPPT Risk Assessment

2.6.1.2.1 Carcinogenic Hazard and Dose-Response Assessment

TCE is carcinogenic to humans by all routes of exposures as documented in the TCE IRIS assessment. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer (EPA, 2011e). The human epidemiological evidence is strong for kidney and more limited for non-Hodgkin lymphoma (NHL) and liver cancer, and less convincing for biliary tract cancer. Less human evidence is found for an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia (EPA, 2011e). Further support for TCE's carcinogenic characterization comes from positive results in multiple rodent cancer bioassays in rats and mice of both sexes, similar toxicokinetics between rodents and humans, mechanistic data supporting a mutagenic mode of action for kidney tumors, and the lack of mechanistic data supporting the conclusion that any of the mode(s) of action for TCE-induced rodent tumors are irrelevant to humans (EPA, 2011e).

The cancer dose-response analysis used linear-dose extrapolation to derive an inhalation unit risk (IUR) of 2×10^{-2} per ppm (4.1×10^{-6} per $\mu g/m^3$) for various cancers[17]. The IUR for TCE was based on human kidney cancer risks that were reported by Charbotel et al. (2006) and adjusted for potential risk for NHL and liver cancer based on human epidemiological data (EPA, 2011e). The IUR is defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air (EPA, 2011b). The IUR was used in the EPA/OPPT risk assessment to estimate excess cancer risks for the inhalation occupational exposures scenarios. There is high confidence in the IUR because it was based on good quality human data, and was similar to unit risk estimates derived from multiple rodent bioassays (EPA, 2011e). Moreover, there was sufficient weight of evidence to conclude that TCE operates through a mutagenic mode of action for kidney tumors (EPA, 2011e).

EPA/OPPT decided not to use the IUR to calculate the theoretical cancer risk associated with a single (acute) exposure to solvent degreasers, arts/crafts fixative and spotting agent products containing TCE. NRC (2001) published methodology for extrapolating cancer risks from chronic to short-term exposures to mutagenic carcinogens. These methods were published with the caveat that extrapolation of lifetime theoretical excess cancer risks to single exposures has great uncertainties.

[17] The dose-response analysis for cancer endpoints can be found in Chapter 5 of the TCE IRIS assessment EPA (2011e).

As NRC (2001) explains, "*There are no adopted state or federal regulatory methodologies for deriving short-term exposure standards for workplace or ambient air based on carcinogenic risk, because nearly all carcinogenicity studies in animals and retrospective epidemiologic studies have entailed high-dose, long-term exposures. As a result, there is uncertainty regarding the extrapolation from continuous lifetime studies in animals to the case of once-in-a-lifetime human exposures. This is particularly problematical, because the specific biologic mechanisms at the molecular, cellular, and tissue levels leading to cancer are often exceedingly diverse, complex, or not known. It is also possible that the mechanisms of injury of brief, high-dose exposures will often differ from those following long-term exposures. To date, U.S. federal regulatory agencies have not established regulatory standards based on, or applicable to, less than lifetime exposures to carcinogenic substances* (NRC, 2001)." Thus, the final EPA/OPPT work plan risk assessment for TCE does not estimate excess cancer risks for acute exposures because the relationship between a single short-term exposure to TCE and the induction of cancer in humans has not been established in the current scientific literature.

2.6.1.2.2 Non-Cancer Hazard and Dose-Response Assessment

EPA/OPPT used margin of exposures (MOEs)[18] to estimate non-cancer risks based on the following:

1. the lowest PBPK-derived human equivalent concentrations (HECs) within each health effects domain reported in the TCE IRIS assessment;
2. the same endpoint/study-specific uncertainty factors (UFs) that the IRIS program applied to the PBPK-derived HECs; and
3. the exposure estimates calculated for the TCE uses examined in this risk assessment (see *Environmental Releases and Exposure Summary*).

MOEs allow for the presentation of a range of risk estimates rather than a single risk estimate based on the inhalation reference concentration (RfC). Given the different exposure scenarios considered (both acute and chronic for small commercial degreasers, and just acute for the two consumer exposure scenarios), different endpoints were used based on the expected exposure durations. For non-cancer effects, risks to developmental effects were evaluated for acute (short-term) exposures, whereas risks to other adverse effects (toxicity to the liver, kidney, nervous system, immune system, and the reproductive system) were evaluated for repeated (chronic) exposures to TCE.

Table 2-18 lists the studies and corresponding HECs and UFs that EPA/OPPT used in the work plan risk assessment for TCE. Key studies in Table 2-18 are briefly described in the *Human Health Hazard Summary* along with other toxicity and epidemiological studies, with detailed descriptions provided in the TCE IRIS assessment (EPA, 2011e). Appendix L contains the complete list of oral and inhalation non-cancer studies within each health effects domain that the TCE IRIS assessment considered suitable for dose-response analysis.

[18] Margin of Exposure (MOE) = (Non-cancer hazard value, POD) ÷ (Human Exposure). See equation in Table 2-29. The benchmark MOE is used to interpret the MOEs and consists of the total UF set by the IRIS program for each study in Table 2-18. See section 2.7.1 for an explanation of the benchmark MOE.

The TCE IRIS assessment used a series of steps to generate the PBPK-derived HECs that OPPT used in its risk assessment (Table 2-19). EPA/OPPT did not rely on those steps that were associated with the derivation of candidate RfCs (cRfC) or final RfC value (Table 2-19). Below is a brief discussion of those steps that EPA/OPPT adopted in this risk assessment.

The non-cancer dose-response analysis in the TCE IRIS assessment commenced with the review and selection of high quality epidemiological and toxicity studies that reported both adverse non-cancer health effects and quantitative dose-response data[19] (Table 2-19). Subsequently, *point of departures (PODs)*[20] were identified for those studies that had suitable data for dose- response analysis. PODs can be a NOAEL[21] or LOAEL[22] for an observed incidence, or change in level of response, or the lower confidence limit on the dose at the benchmark dose (BMD)[23].

The dose-response assessment was organized in five health effects domains: (1) neurotoxicity; (2) systemic (body weight) and organ toxicity (liver and kidney effects); (3) immunotoxicity; (4) reproductive; and (5) developmental effects. PBPK modeling was used to estimate internal dose PODs (idPOD) and subsequently HECs based on the oral and inhalation PODs identified in earlier steps. The PBPK modeling integrated internal dose-metrics based on TCE's mode of action and the role of different TCE metabolites in toxicity (EPA, 2011e). Note that the effects within the same health effect domain were generally assumed to have the same relevant internal dose- metrics (EPA, 2011e).

Furthermore, the PBPK model was used to estimate the interspecies and within-human pharmacokinetic variability (or just within-human variability for the human-based PODs) corresponding to each idPOD for each candidate critical effect. The results of this calculation were 50th, 95th and 99th percentile HEC estimates for POD analyzed within each health effects domain. Also, the PBPK model integrated a Bayesian population analysis to characterize pharmacokinetic uncertainties and variability (EPA, 2011e). More information on the PBPK modeling is provided in the next section below, including how the HECs were calculated.

EPA/OPPT used the endpoint/study-specific UFs from the TCE IRIS assessment as the benchmark MOEs for the risk calculations. These UFs were applied to the PBPK-derived PODs to account for (1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL (EPA, 2011b).

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[19] Non-cancer toxicological and epidemiological studies are described in Chapter 4 of the TCE IRIS assessment. [20] A point of departure (POD) is a dose or concentration that can be considered to be in the range of observed responses, without significant extrapolation. A POD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures EPA (2011b).

[21] NOAEL=No-observed-adverse-effect level

[22] LOAEL= Lowest-observed-adverse-effect level

[23] The benchmark dose (BMD) is a dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background EPA (2011b).

Table 2-18. Lowest PBPK-derived HECs for different effects domains based on analysis in TCE IRIS assessment

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm)[3]	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) for Benchmark MOE[4]	Reference
CHRONIC	Liver	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures, variable time periods for 30-120 days	$BMDL_{10}$ = 21.6 ppm	Increased liver/body weight ratio	25	12	9.1	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Kidney	Rat (female)	Oral (gavage)	500 to 1,000 mg/kg-bw/day	5 days/week for 104 weeks	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.042	0.0085	0.0056	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	NTP (1988)
	Nervous System	Rat (male)	Inhalation	50 to 300 ppm	8 hrs/day, 5 days/weeks for 6 weeks	LOAEL = 12 ppm	Significant decreases in wakefulness	13	6.4	4.8	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; *Total UF=300*	Arito et al. (1994)
	Immune System	Mouse (female)	Oral (drinking water)	0.001 to 14 ppm (0.001 to 14 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*[5]	Keil et al. (2009)
		Mouse (female)	Oral (drinking water)	0.001 to 14 ppm (0.001 to 14 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=3; *Total UF=30*[5]	Keil, D. E. et al. (2009)
	Reproductive System	Human (male)	Inhalation	29.6 ppm (mean exposure)	Measured values after an 8-hour work shift; mean 5.1 years on job	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	1.4	0.7	0.5	UF_S=10; UF_A= 1; UF_H=3; UF_L=1; *Total UF=30*	Chia et al. (1996)

Table 2-18. Lowest PBPK-derived HECs for different effects domains based on analysis in TCE IRIS assessment

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm)[3]	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) for Benchmark MOE[4]	Reference
ACUTE OR CHRONIC	Developmental effects	Rat (female)	Oral (drinking water)	2.5 to 1,100 ppm (2.5 to 1,100 mg/kg-bw/day)	22 days throughout gestation (gestational days 0 to 22)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.012	0.0051	0.0037	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Johnson et al. (2003)

Notes:
1 Control concentrations were not included in the table, but discussed in the study summaries in section 2.6.2.
2 POD type can be NOAEL, LOAEL, or BMDL; the IRIS program adjusted all values to continuous exposure.
3 1 ppm = 5.374 mg/m^3
4 UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF. UF values were those used in the TCE IRIS assessment (EPA, 2011e).
5 Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UF (EPA, 2011e).

Table 2-19. Steps of the Non-Cancer TCE IRIS Process that Were Considered in OPPT's Non-Cancer Hazard/Dose-Response Approach [1]

Step#	NON-CANCER IRIS APPROACH	NON-CANCER OPPT APPROACH *Considered (+) / Not Considered (—)*
1	Evaluation of all studies (inhalation and oral) that provided (1) non-cancer adverse health effects and (2) quantitative dose-response data	+
2	Identification of the Points of Departure (POD) based on applied dose	+
3	Adjustment of each POD by endpoint/study-specific uncertainty factors (UFs)	—
4	Derivation of candidate reference concentrations (cRfCs) and selection of the lowest values within each health endpoint domain taking into account the confidence of the estimate	—
5	Application of PBPK modeling to estimate internal dose PODs (i.e., HECs) for those candidate critical effects selected from inhalation and oral studies based on applied dose	+
6	Estimation of interspecies and within-human pharmacokinetic variability for the internal dose PODs by PBPK modeling	+
7	Adjustment of each internal dose POD by endpoint/study-specific UFs [2]	—
8	Derivation of PBPK model-based candidate RfCs (p-cRfC) for each candidate critical effect	—
9	Characterization of the uncertainties of the cRfCs derived by applied dose and PBPK modeling (p-cRfC) by using quantitative uncertainty analyses of pharmacokinetic uncertainty and variability from the Bayesian population analysis [3]	—
10	Evaluation of the most sensitive cRfCs and set final RfC value.	—

Notes:

1 Table 2-19 is an adaptation of Figure 5-1 (Chapter 5) in the TCE IRIS assessment (EPA, 2011e).

2 Endpoint/study-specific UFs were used as benchmark MOEs in the OPPT's TCE risk assessment.

3 EPA/OPPT consulted the characterization of the uncertainties in the TCE IRIS assessment and those aspects related to the uncertainties of the individual studies and the generation of PBPK-derived HECs were discussed in the OPPT's TCE risk assessment.

APPENDIX L. LIST OF ORAL AND INHALATION STUDIES SUITABLE FOR NON-CANCER DOSE-RESPONSE ANALYSIS IN THE TCE IRIS ASSESSMENT

L-1 Liver Effects

Target Organ	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Liver	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures, variable time periods for 30-120 days	$BMDL_{10}$= 21.6 ppm	Increased liver/body weight ratio	25	12	9.1	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Mouse (male)	Oral (gavage)	100 to 3,200 mg/kg-bw/day	6 weeks	$BMDL_{10}$= 82 mg/kg-bw/day		32	15	11	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Buben and O'Flaherty (1985)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hr/day, 5 days/week for 4 weeks	$BMDL_{10}$= 25 ppm		53	24	19	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Woolhiser et al. (2006)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-2 Kidney Effects

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Kidney	Rat (female)	Oral (gavage)	500 to 1,000 mg/kg-bw/day	5 days/week for 104 weeks	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.042	0.0085	0.0056	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	NTP (1988)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hr/day, 5 days/week for 4 weeks	$BMDL_{10}$= 15.7 ppm	Increased kidney weight/body weight ratio	0.099	0.020	0.013	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Woolhiser et al. (2006)
	Rat (male)	Oral (gavage)	50 to 250 mg/kg-bw/day	4-5 days/week for 52 weeks	$BMDL_{10}$ = 34 mg/kg-bw/day	Pathology changes in renal tubule	0.19	0.038	0.025	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Maltoni and Cotti (1986)
	Rat (male)	Inhalation	100 to 600 ppm	7 hrs/day, 5 days/week for 2 years	$BMDL_{10}$= 40.2 ppm	Pathology changes in renal tubule	0.28	0.057	0.038	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Maltoni and Cotti (1986)
	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures for 30-120 days	$BMDL_{10}$ = 34.7 ppm	Increased kidney weight/body weight ratio	0.88	0.18	0.12	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Mouse (female)	Oral (gavage)	869 to 1,739 mg/kg-bw/day	5 days/week, TWA during exposure period (78 weeks), animals observed for 90 weeks	LOAEL = 620 mg/kg-bw/day	Pathology changes in renal tubule (toxic nephrosis)	3.9	0.77	0.5	UF_S=1; UF_A= 3; UF_H=3; UF_L=30; *Total UF=300*	NCI (1976)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-3 Neurotoxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Nervous system	Rat (male)	Inhalation	50 to 300 ppm	8 hrs/day, 5 days/weeks for 6 weeks	LOAEL = 12 ppm	Significant decreases in wakefulness	13	6.4	4.8	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; *Total UF=300*	Arito et al. (1994)
	Human (both sexes)	Inhalation	704 ppm × years of exposure (mean cumulative exposure)	Mean of 16 years	LOAEL = 14 ppm	Trigeminal nerve effects (increased latency in masseter reflex)	14	7.0	5.3	UF_S=1; UF_A= 1; UF_H=3; UF_L=3; *Total UF=10*	Ruijten et al. (1991)
	Rat (male)	Oral (drinking water)	24 to 47 mg/kg-bw/day	8 weeks	LOAEL = 47 mg/kg-bw/day	Cognitive effects (demyelination of hippocampus)	18	9.2	7.1	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Isaacson et al. (1990)
	Rat (male)	Oral (gavage)	1,000 mg/kg-bw/day	5 days/week for 6 weeks	LOAEL = 710 mg/kg-bw/day	Degeneration of dopamine-containing neurons in substantia nigra	126	62	47	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Gash et al. (2008)
	Rat (female)	Inhalation	300 ppm	24 hrs/day for 24 days	LOAEL = 300 ppm	Decreased regeneration of sciatic nerve	274	127	93	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Kjellstrand et al. (1987)
	Mouse (male)	Inhalation	150 to 300 ppm	24 hrs/day for 24 days	LOAEL = 150 ppm		378	163	120	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-4 Immunotoxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Immune system	Mouse (female)	Oral (drinking water)	1.4 to 14 ppm (0.35 to 3.5 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100* [4]	Keil et al. (2009)
	Mouse (female)	Oral (drinking water)	1.4 to 14 ppm (0.35 to 3.5 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=3; *Total UF=30* [4]	Keil et al. (2009)
	Mouse (female)	Oral (drinking water)	18 to 660 mg/kg-bw/day	16 or 24 weeks (4 or 6 months)	LOAEL = 18 mg/kg-bw/day	Immuno-suppression	4.8	2.4	1.7	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*	Sanders et al. (1982)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hrs/day, 5 days/week for 4 weeks	$BMDL_{1SD}$= 24.9 ppm	Immuno-suppression	29	15	11	UF_S=10; UF_A= 3; UF_H=3; UF_L=1; *Total UF=100*	Woolhiser et al. (2006)
	Mouse (males; auto-immune prone strain)	Inhalation	500 to 2,000 ppm	4 hrs/day, 6 days/week for 8 weeks	LOAEL = 70 ppm	Autoimmunity (changes in immunoreactive organs)	97	48	37	UF_S=10; UF_A= 3; UF_H=1; UF_L=10; *Total UF=300*	Kaneko et al. (2000)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

[4] Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UF (EPA, 2011e).

L-5 Reproductive Toxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs)[3]	Reference
Reproductive system	Human (male)	Inhalation	29.6 ppm (mean exposure)	Measured values after an 8-hr work shift; mean 5.1 years on the job	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	1.4	0.7	0.5	UF_S=10; UF_A= 1; UF_H=3; UF_L=1; *Total UF=30*	Chia et al. (1996)
	Rat (male)	Oral (drinking water)	143 to 270 mg/kg-bw/day	14 days	LOAEL = 141 mg/kg-bw/day	Decreased *in vitro* fertilization	16	11	9.3	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	DuTeaux et al. (2004)
	Rat (male)	Inhalation	376 ppm	4 hrs/day, 5 days/week, 2-10 weeks exposed, 2-8 weeks unexposed	LOAEL = 45 ppm	Sperm effects and male reproductive tract effects	32	16	13	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Kumar et al., 2000 Kumar et al. (2000)
				4 hrs/day, 5 days/week for 12 or 24 weeks							Kumar et al. (2001)
	Rat (female damns)	Oral (gavage)	10.1 to 1,125 mg/kg-bw/day	9 days (during gestational days 6 to 15)	LOAEL = 475 mg/kg-bw/day	Delayed parturition	98	48	37	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*	Narotsky et al. (1995)
	Mouse (male)	Inhalation	1,000 ppm	6 hrs/day, 5 days/week for 19 days over 4 weeks	LOAEL = 180 ppm	Effects on epididymis epithelium	190	91	67	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Forkert et al. (2002)
				6 hrs/day, 5 days/week for 1-4 weeks							Kan et al. (2007)
	Mouse (male)	Inhalation	1,000 ppm	6 hrs/day, 5 days/week for 6 weeks	LOAEL = 180 ppm	Sperm effects (decreased in vitro sperm-oocyte binding and *in vivo* fertilization)	190	91	67	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Xu et al. (2004)

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Reproductive system	Rat (male)	Oral (drinking water)	72 to 389 mg/kg-bw/day	Breeders exposed 1 week premating and then for 13 weeks/ Pregnant females exposed throughout gestation (i.e., 18 weeks total)	LOAEL = 389 mg/kg-bw/day	Decreased mating (both sexes exposed)	204	97	71	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; UF_D=1 *Total UF=100*	NTP (1986)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-6 Developmental Toxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Developmental effects	**PRE- AND POSTNATAL MORTALITY**										
	Rat (female)	Inhalation	**1.** ppm	4 hrs/day, gestational days 8 to 21	LOAEL =17 ppm	Increased resorptions	16	8	6.2	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Healy et al. (1982)
	Rat (female)	Oral (gavage)	10.1 to 1,125 mg/kg-bw/day	Gestational days 6 to 15	$BMDL_{01}$= 32.2 mg/kg-bw/day	Increased resorptions	57	29	23	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Narotsky et al. (1995)
	PRE- AND POSTNATAL GROWTH										
	Rat (female)	Inhalation	100 ppm	4 hrs/day, gestational days 8 to 21	LOAEL = 17 ppm	Decreased fetal weight and skeletal effects	16	8	6.2	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Healy et al. (1982)
	CONGENITAL DEFECTS										
	Rat (female)	Oral (drinking water)	2.5 to 1,100 ppm (2.5 to 1,100 mg/kg-bw/day)	22 days throughout gestation (gestational days 0 to 22)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.012	0.0051	0.0037	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Johnson et al. (2003)
	DEVELOPMENTAL NEUROTOXICITY										
	Rat (male pups)	Oral (gavage)	50 to 290 mg/kg-bw/day	Postnatal days 10 to 16	LOAEL = 50 mg/kg-bw/day	Decreased rearing activity	8	4	3	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; Total UF=300	Fredriksson et al. (1993)
	Rat (female)	Oral (drinking water)	45 to 140 mg/kg-bw/day	Dams and pups exposed from 14 days prior to mating until end of lactation	LOAEL = 45 mg/kg-bw/day	Increased exploratory behavior in male pups (offspring)	22	11	8.4	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Taylor et al. (1985)

Notes: [1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.
[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.
[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

2.7 HUMAN HEALTH RISK CHARACTERIZATION

TCE and its metabolites are associated with adverse effects on cardiac development based on a weight-of-evidence analysis of developmental studies from rats, humans and chickens. These adverse cardiac effects are deemed important for acute and chronic risk estimation for the scenarios and populations addressed in this risk assessment. The rationale for using TCE associated fetal cardiovascular lesions for acute scenarios is based on the relatively short critical window of vulnerability in humans, rodent and avian cardiac development. The rationale for using fetal cardiac effects for chronic risks estimation is also based on the fact that relatively low dose short term/acute exposures can result on long-term adverse consequences on cardiac development persisting into adulthood.

Table 2-26. Summary of Hazard Information Used in the Risk Evaluation of Acute and Chronic Scenarios

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	POD Type	Effect	HEC_{99} (ppm)	Total Uncertainty Factor (UF) for Benchmark MOE	Reference
CHRONIC	Liver	Mouse (male)	Inhalation	$BMDL_{10}$ = 21.6 ppm	Increased liver/body weight ratio	9.1	*Total UF=10*	Kjellstrand et al. (1983)
	Kidney	Rat (female)	Oral (gavage)	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.0056	*Total UF=10*	NTP (1988)
	Nervous System	Rat (male)	Inhalation	LOAEL = 12 ppm	Significant decreases in wakefulness	4.8	*Total UF=300*	Arito et al. (1994)
	Immune System	Mouse (female)	Oral (drinking water)	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.033	*Total UF=100*	Keil et al. (2009)
		Mouse (female)	Oral (drinking water)	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.033	*Total UF=30*	Keil, D. E. et al. (2009)
	Reproductive System	Human (male)	Inhalation	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	0.5	*Total UF=30*	Chia et al. (1996)
ACUTE OR CHRONIC	Developmental effects	Rat (female)	Oral (drinking water)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.0037	Total UF=10	Johnson et al. (2003)

Notes:

[1] 1 ppm = 5.374 mg/m^3

[2] Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UFs for effects repoted by the same study (EPA, 2011e).

Other adverse non-cancer effects are deemed relevant for risk estimations for other populations for the chronic scenarios, but may not occur at the lowest exposures found with cardiac defects and they include kidney toxicity, immunotoxicity, male reproductive toxicity,

neurotoxicity, liver toxicity and cancer of kidney, liver and immune system (NHL).

TCE is carcinogenic to humans. The cancer risk assessment uses the IUR derived in the 2011 TCE IRIS assessment based on human kidney cancer. The weight-of-evidence analysis for the cancer endpoint was sufficient to conclude that TCE operates through a mutagenic mode of action for kidney tumors (EPA, 2011e).

2.7.1 Risk Estimation Approach for Acute and Repeated Exposures

Tables 2-27 and 2-28 show the use scenarios, populations of interest and toxicological endpoints used in the acute and chronic risk assessment, respectively.

Table 2-27. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Acute Risks to TCE-containing Degreasers, Spotting Agents and Arts/Crafts Products

Use Scenarios / Populations And Toxicological Approach	(1) Solvent degreasing at small commercial facilities	(2) Spot cleaning at dry cleaning facilities	(3) Residential use of degreaser product	(4) Residential use of arts/crafts clear protective coating spray
Population of Interest and Exposure Scenario: *Users*	Adult pregnant[1] worker (>16 years old) exposed to TCE for a single 2-hr exposure during an 8-hr workday [2,3,4].	Adult pregnant[1] worker (>16 years old) exposed to TCE for a single 8-hr exposure [2,3].	Adult pregnant [1] consumers (>16 yrs old) exposed to TCE for a single 1-hr exposure when using product 2X per month [2,3,4]. Residential exposure model provided the 24-hr acute exposure estimate.	Adult pregnant [1] consumers (>16 yrs old) exposed to TCE for a single 0.5-hr exposure when using product once per week [2,3,4]. Residential exposure model provided the 24-hr acute exposure estimate.
Population of Interest and Exposure Scenario: *Bystander*	Adult pregnant women [1] (>16 years old) exposed to TCE indirectly by being in the same building.		Adult pregnant bystander[1] and individuals of several age groups that are exposed to indirect TCE exposures by being in the rest of the house.	
Health Effects of Concern, Concentration and Time Duration	Non-Cancer Health Effects: Fetal cardiac defects (Johnson et al., 2005; Johnson, 2014; Johnson et al., 2003)[5] 1. *PBPK-derived Non-Cancer Hazard values or Point of Departures (PODs)* (EPA, 2011e): 24-hr HEC_{50}: 0.012 ppm 24-hr HEC_{95}: 0.0051 ppm 24-hr HEC_{99}: 0.0037 ppm Cancer Health Effects: Acute cancer risks were not estimated. Relationship is not known between a single short-term exposure to TCE and the induction of cancer in humans.			
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	$(UF_S=1) \times (UF_A=3) \times (UF_H=3) \times (UF_L=1)$ [6] = 10 (EPA, 2011e). Total UF=Benchmark MOE=10			

Notes:

[1] The acute risk assessment focused on the most sensitive life stage in humans, which is women of childbearing age and fetus (i.e., pregnant worker) due to concerns for developmental effects.

[2] Exposure estimate was adjusted to a 24-hr exposure estimate in order to combine it with the 24-hr HECs.

[3] It is assumed no substantial buildup of TCE in the body between exposure events due to TCE's short biological half-life (~51 hrs).

[4] EPA/OPPT believes that the users of these products are generally adults, but teenagers and even children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.

[5] The acute risk assessment focused on developmental toxicity effects as the most sensitive health effect when compared to other potential acute effects (i.e., neurotoxicity).

[6] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF

Table 2-28. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Chronic Risks to TCE-containing Degreasers and Spotting Agents

Use Scenarios → / Populations And Toxicological Approach ↓	(1) Solvent degreasing at small commercial facilities	(2) Spot cleaning at dry cleaning facilities
Population of Interest and Exposure Scenario: *Users*	Adult worker (>16 years old) [1] exposed to TCE for 2-hr exposure during an 8-hr workday for 260 days per year for 40 working years. Lifetime average daily concentration was calculated. Note that the 8-hr exposure estimate was adjusted to a 24-hr exposure estimate.	Adult worker (>16 years old) [1] exposed to TCE for an 8-hr workday for 260 days per year for 40 working years. Lifetime average daily concentration was calculated. Note that the 8-hr exposure estimate was adjusted to a 24-hr exposure estimate.
Population of Interest and Exposure Scenario: *Bystander*	Adult worker (>16 years old) [1] repeatedly exposed to indirect TCE exposures by being in the same building.	
Health Effects of Concern, Concentration and Time Duration	Non-Cancer **2.** *Non-cancer health effects*: A range of possible chronic non-cancer effects in liver, kidney, nervous system, immune system, reproductive system and developmental effects[2] **3.** *PBPK-derived Non-Cancer Hazard values or Point of Departures (PODs):* The lowest POD (i.e., 24-hr HEC_{50}, HEC_{95} or HEC_{99} expressed in ppm) within each health endpoint domain (EPA, 2011e). See Table 2-18. Cancer **1.** *Cancer health effects:* Possible cancer effects in kidney, liver or non-Hodgkins lymphoma from chronic exposure. **2.** *PBPK-derived Cancer Inhalation Unit Risk (IUR)*: 2×10^{-2} per ppm (EPA, 2011e).	
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	Study- and endpoint-specific UFs from the TCE IRIS assessment. See Table 2-18.	

Notes:
[1] Adult workers (>16 years old) include both healthy female and male workers.
[2] The chronic risk assessment for developmental effects focused on the most sensitive life stage in humans, which are women of child-bearing age and fetus (i.e., pregnant worker). For other health effects (e.g., liver, kidney, etc.), healthy female or male workers were assumed to be the population of interest.

Acute or chronic MOEs (MOE_{acute} or $MOE_{chronic}$) were used in this assessment to estimate non-cancer risks (Table 2-29).

Table 2-29. Equation to Calculate Non-Cancer Acute or Chronic Risks Using Margin of Exposures

$$MOE_{acute\ or\ chronic} = \frac{\text{Non-cancer Hazard value (POD)}}{\text{Human Exposure}}$$

MOE =	Margin of exposure (unitless)
Hazard value (POD) =	HEC_{50}, HEC_{95}, or HEC_{99} (ppm) derived from TCE IRIS assessment (EPA, 2011e)
Human Exposure =	Exposure estimate (in ppm) from occupational or consumer exposure assessment. ADCs were used for non-cancer chronic risks and acute concentrations were used for acute risks (see sections 2.3.3 and 2.4.2).

As discussed previously, each non-hazard PBPK-derived POD was adjusted by endpoint/study-specific UFs as described in the TCE IRIS assessment (EPA, 2011e). These UFs accounted for (1) the variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4)the uncertainty in extrapolating from a LOAEL rather than from a NOAEL (EPA, 2011e).

The total UF for each non-cancer PBPK-derived POD was the benchmark MOE used to interpret the MOE risk estimates for each use scenario. The MOE estimate was interpreted as human health risk if the MOE estimate was less than the benchmark MOE (=total UF). On the other hand, the MOE estimate indicated negligible concerns for adverse human health effects if the MOE estimate exceeded the benchmark MOE. Typically, the larger the MOE, the more unlikely it is that a non-cancer adverse effect would occur.

Cancer risks for repeated exposures to TCE were estimated using the equation in Table 2-30. Estimates of cancer risks should be interpreted as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to the potential carcinogen (i.e., incremental or excess individual lifetime cancer risk).

Table 2-30. Equation to Calculate Cancer Risks

$$\text{Risk} = \text{Human Exposure} \times \text{IUR}$$

Risk =	Cancer risk (unitless)
Human exposure =	Exposure estimate (LADC in ppm) from occupational exposure assessment
IUR =	Inhalation unit risk (2×10^{-2} per ppm) (EPA, 2011e)

2.7.2 Acute Non-Cancer Risk Estimates for Inhalation Exposures to TCE

The acute inhalation risk assessment used developmental toxicity data to evaluate the acute risks for the TSCA TCE use scenarios. As indicated previously, EPA's policy supports the use of developmental studies to evaluate the risks of acute exposures. This policy is based on the presumption that a single exposure of a chemical at a critical window of fetal development, as in the case of cardiac development, may produce adverse developmental effects (EPA, 1991).

After evaluating the developmental toxicity literature of TCE, the TCE IRIS assessment concluded that the fetal heart malformations are the most sensitive developmental toxicity endpoint associated with TCE exposure (EPA, 2011e). Thus, EPA/OPPT based its acute risk assessment on the most health protective endpoint (i.e., fetal cardiac malformations; Johnson et al., 2003) representing the most sensitive human population (i.e., adult women of child-bearing age and fetus > 16 yrs).

The acute risk assessment used the PBPK-derived hazard values (HEC_{50}, HEC_{95}, or HEC_{99}) from Johnson et al. (2003) developmental study for each degreaser and spot cleaner use scenario. Note that the variability among these hazard values is small and no greater than 3-fold (i.e., 2-fold for HEC_{50}/HEC_{95} ratios; 3-fold for HEC_{50}/HEC_{99} ratios; 1.4-fold for HEC_{95}/HEC_{99} ratios).

Acute inhalation risks were reported for most occupational and residential exposure scenarios based on concerns for developmental effects, irrespective of who is using the product (user vs. bystander), the type of exposure (typical vs. worst case scenario) and the room ventilation system (LEV vs no LEV). For instance, most of the degreaser and spot cleaner exposure scenarios and all of the residential use scenarios reported MOE values below the benchmark MOE of 10 irrespective of the percentile HEC value used to estimate the MOEs. Only one use scenario reported MOEs above 10, which was the spot cleaner use scenario representing bystander exposures under typical occupational exposure levels with LEV (i.e., "Bystander + LEV—Typical Exposure") (Tables 2-31, 2-32 and 2-33).

Table 2-31. Acute Non-Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	WORKER NON-CANCER MOEs				BYSTANDER NON-CANCER MOEs				Total UF or Benchmark MOE
	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	
HEC_{50}= 0.012	**0.12**	**0.0018**	**0.012**	**0.00018**	**0.9**	**0.002**	**0.09**	**0.00021**	10
HEC_{95}= 0.0051	**0.051**	**0.0008**	**0.0051**	**0.00008**	**0.38**	**0.0009**	**0.038**	**0.000089**	
HEC_{99}= 0.0037	**0.037**	**0.0006**	**0.0037**	**0.00006**	**0.28**	**0.0007**	**0.028**	**0.000065**	

Notes:

– MOEs below benchmark MOE indicating risk are denoted in **bold** text. They indicate potential health risks.
– Exposure estimates with/without LEV are found in Table 2-10.

Table 2-32. Acute Non-Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	WORKER NON-CANCER MOEs				BYSTANDER NON-CANCER MOEs				Total UF or Benchmark MOE
	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	
HEC_{50}= 0.012	**4.5**	**0.018**	**0.45**	**0.0019**	51.4	**0.018**	**5.1**	**0.002**	10
HEC_{95}= 0.0051	**1.9**	**0.0077**	**0.19**	**0.00081**	21.9	**0.0077**	**2.2**	**0.00085**	
HEC_{99}= 0.0037	**1.4**	**0.0056**	**0.14**	**0.00058**	15.9	**0.0056**	**1.6**	**0.00062**	

Notes:

– MOEs below benchmark MOE indicating risk are denoted in **bold** text. They indicate potential health risks.
– Exposure estimates with/without LEV are found in Table 2-13.

Table 2-33. Acute Non-Cancer Risk Estimates for Residential Uses of TCE-containing degreasers and art/crafts products (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	RESIDENTIAL USE OF DEGREASER PRODUCT MOEs [1]		RESIDENTIAL USE OF ARTS/CRAFTS CLEAR PROTECTIVE COATING SPRAY MOEs [1]		Total UF or Benchmark MOE
	USER [2]	BYSTANDER [3]	USER [2]	BYSTANDER [3]	
HEC_{50}= 0.012	**0.0060**	**0.015**	**0.03**	**0.12**	10
HEC_{95}= 0.0051	**0.0026**	**0.0064**	**0.013**	**0.051**	
HEC_{99}= 0.0037	**0.0019**	**0.0046**	**0.0093**	**0.037**	

Notes:
1 MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks.
2 MOEs for the user categories could be extended to different age groups. EPA/OPPT believes that the users of these products are generally adults, but teenagers and even children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.
3 All age categories (<1 yrs; 1-2 yrs; 3-5 yrs; 6-10 yrs; 11-15 yrs; 16-20 yrs ; and >21 yrs)

2.7.3 Chronic Non-Cancer and Cancer Risk Estimates for Inhalation Exposures to TCE

Chronic non-cancer and cancer risk estimates for inhalation exposures to TCE were only derived for occupational scenarios since the exposures for consumer uses were not considered chronic in nature.

2.7.3.1 Cancer Risks for Occupational Scenarios

Figures 2-6 and 2-7 present the incremental individual lifetime cancer risks for continuous exposures to TCE occurring during the commercial use of degreaser and spot cleaner products. The cancer risk estimates were calculated by multiplying the EPA's inhalation unit risk for TCE (EPA, 2011e) by the exposure estimate (i.e., LADC) for both direct users and bystanders. Cancer risks were expressed as number of cancer cases per million. Calculations of cancer risks are provided in the supplemental Excel spreadsheet, *TCE OPPT Risk Estimates_061814.xlsx*.

It was assumed that the exposure frequency (i.e., the amount of days per year workers or bystanders are exposed to TCE) was 260 days per year and the occupational exposure duration was 40 years over a 70-year lifespan. It is recognized that these exposure assumptions are likely yielding conservative cancer risk estimates, but EPA/OPPT does not have additional information for further refinement.

EPA typically uses a target cancer risk level between $1x10^{-4}$ and $1x10^{-6}$ for determining the acceptability of the cancer risk in a population. Since the target cancer risk level will be determined during risk management, the occupational cancer risk estimates were compared to three target levels within EPA's acceptability range. The target levels were:

1. $1x10^{-6}$: the probability of 1 chance in 1 million of an individual developing cancer
2. $1x10^{-5}$: the probability of 1 chance in 100,000 of an individual developing cancer, which is equivalent to 10 cancer cases in 1 million
3. $1x10^{-4}$: the probability of 1 chance in 10,000 of an individual developing cancer, which is equivalent to 100 cancer cases in 1 million

All of the degreaser exposure scenarios exceeded the three target cancer levels, with the exception of one of the bystander exposure scenarios (i.e., "*Bystander + LEV—Typical Exposure*"). This particular bystander exposure scenario exceeded the target levels at $1x10^{-5}$ and $1x10^{-6}$ (Figure 2-6).

Likewise, all of the worst case exposures for the spot cleaner scenarios (i.e., both user and bystander scenarios) and one of the typical exposure scenarios with no LEV (i.e., "*Spot Cleaner No LEV—Typical Exposure*") exceeded the three target levels. The remaining spot cleaner scenarios exceeded the target level of $1x10^{-4}$ (i.e., "Spot cleaner + LEV—Typical Exposure"; "Bystander + LEV—Typical Exposure"; and "Bystander No LEV—Typical Exposure") (Figure 2-7).

Figure 2-6. Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops

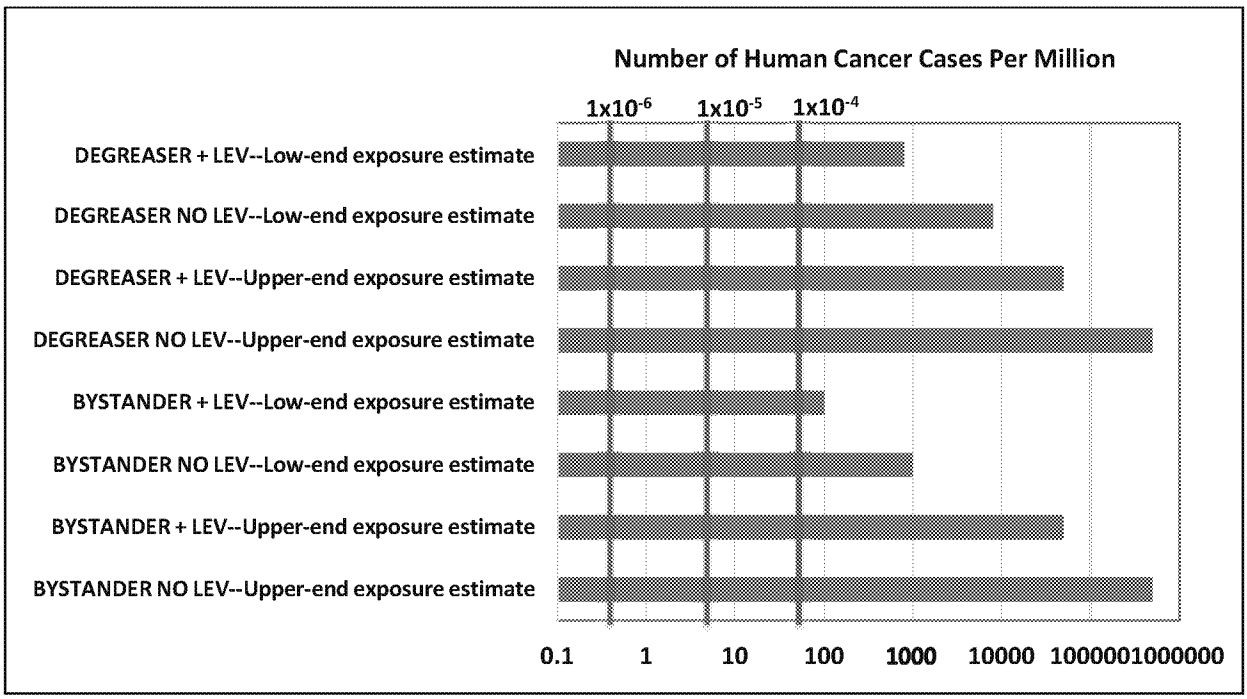
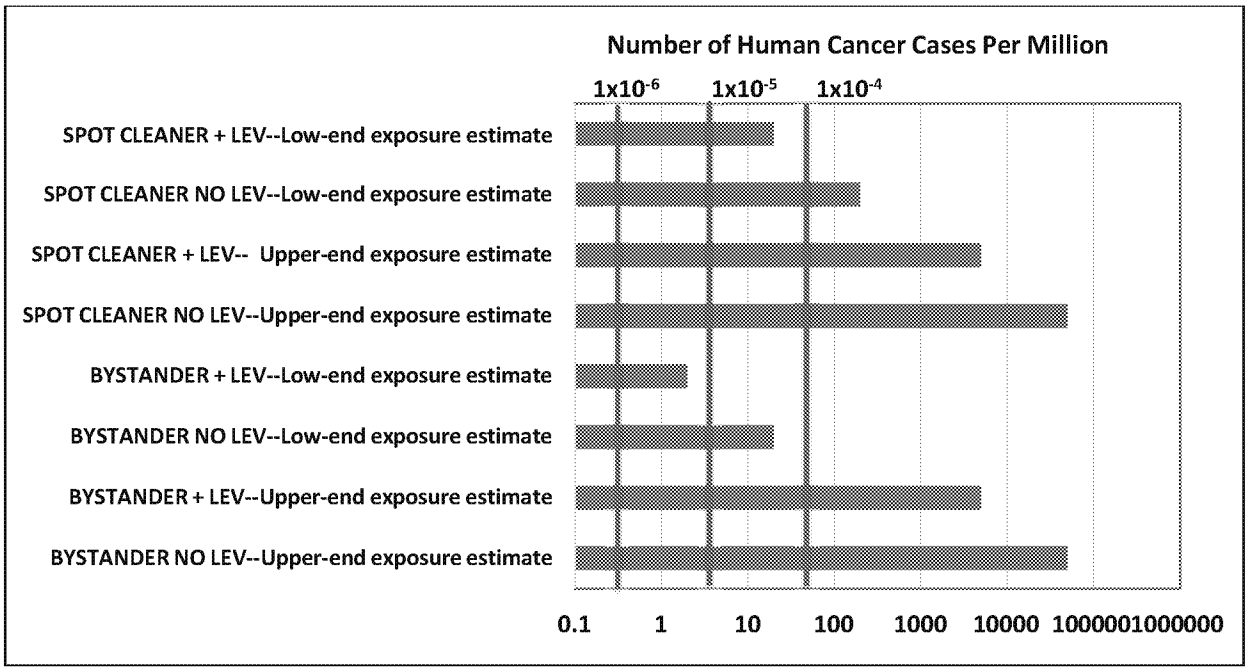


Figure 2-7. Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities



For both degreaser and spot cleaner scenarios, the results indicated that the cancer risk was 10 times greater in scenarios with no local exhaust ventilation that those with room ventilation (+LEV). Moreover, an 8-fold increase in cancer risk was observed in those workers directly using the TCE-containing product when compared to their corresponding bystanders (Figures 2-6 and 2-7). Similarly, a 10-fold increase in cancer risk was reported in those workers using spotting agents containing TCE when compared to their corresponding bystanders indirectly exposed in the dry cleaning facilities (Figure 2-7).

2.7.3.2 Chronic Non-Cancer Risks for Occupational Scenarios

EPA/OPPT estimated chronic non-cancer risks for the occupational use of TCE-containing degreasers and spot cleaners. Since TCE exposure has been associated with a variety of health effects, this assessment estimated human health inhalation chronic risks for developmental toxicity, kidney toxicity, immunotoxicity, reproductive toxicity, neurotoxicity and liver toxicity. As previously discussed, the TCE IRIS assessment developed PODs (i.e., HEC_{50}, HEC_{95} or HEC_{99}) for multiple studies that were suitable for dose-response analysis (Appendix L). EPA/OPPT used the lowest POD (or HEC) in each health effects domain for the non-cancer chronic MOE calculations. The risk estimates for the commercial degreaser and spot cleaner uses are presented in Tables 2-34 and 2-35, respectively[30].

Workers in direct contact with the degreaser products and occupational bystanders reported risks (i.e., MOEs<benchmark MOE) for the following chronic non-cancer effects: developmental toxicity, kidney and immunotoxicity. Also, all of the worker scenarios showed risks for reproductive effects and neurotoxicity. These risks were observed in the worker/bystander scenarios regardless of the type of TCE exposure (typical vs. worst case) and the availability of local exhaust ventilation (with LEV vs. no LEV). Moreover, risks for reproductive effects and neurotoxicity were also found in the degreaser bystander scenarios, but only for worst case exposure conditions and typical exposure circumstances with no local exhaust ventilation. Furthermore, risks were also found for liver effects, but only for those degreaser worker/bystander scenarios representing worst case exposure conditions irrespective of the presence of room ventilation (Table 2-34).

The non-cancer chronic risk profile was slightly different for the TCE use in spot cleaners because the TCE exposure concentrations in dry cleaning facilities were 10 to 60-fold lower than those estimated in degreaser small shops. Risks for developmental effects, kidney toxicity and immunotoxic effects were generally observed for all of the spot cleaning worker/bystander exposure scenarios (i.e., typical vs worst case; typical exposure vs worst case) with two exceptions. Non-risk findings were reported for few spot cleaning worker/bystander scenarios under LEV and typical exposure conditions that used the HEC^{50th} percentile for the MOE calculations. Also, the spot cleaning bystander exposure scenario did not report potential non-

[30] Risk estimates were calculated for all of the studies per health effects domain that the EPA's IRIS program identified as suitable for dose-response analysis. These risk estimates are found in the supplemental Excel file "TCE OPPT Risk Estimates_061814".

cancer chronic risks for the aforementioned health effects domains under LEV and typical exposure conditions (Table 2-35).

Risks for reproductive effects and neurotoxicity were less consistently seen across the board with the exception of the spot cleaning worker/bystander exposure scenarios characterizing typical or worst-case exposure condition under no ventilation system. As for risks for liver effects, most of the spot cleaning scenarios showed no risk concern with the exception of the worker/bystander worst case exposure scenarios with no LEV (Table 2-35).

2.7.4 Human Health Risk Characterization Summary

This risk assessment focused on the occupational and consumer uses of TCE-containing degreasers, spot cleaners and clear protective coating spray in arts/crafts. Specifically, the following exposure scenarios were evaluated: small commercial degreasing operations; spot cleaning in dry cleaning facilities; consumer use of an aerosol degreaser; and the consumer use of a clear protective coating spray in an arts/crafts home setting. The population of interest consisted of workers and consumers with direct (users) or indirect (bystander) exposure to TCE. Only the inhalation route of exposure was considered in this risk assessment.

The occupational and consumer exposure assessments generated the TCE exposure levels required to derive non-cancer and cancer risks. Cancer risks were presented as lifetime risks, meaning the risk of developing cancer as a result of the occupational exposure over a normal lifetime of 70 yrs. Lifetime cancer risks from TCE exposure were compared to target risks ranging from 10^{-6} to 10^{-4}.

Many of the degreaser and spot cleaning exposure scenarios exceeded the target cancer risks of 10^{-6}, 10^{-5} and 10^{-4}. This analysis resulted in higher modeled incidences of cancer in the small commercial degreaser than the users of spot cleaners. Thus, the greatest potential for cancer risk came from the occupational exposures to commercial degreasers. Furthermore, higher cancer risks resulted from direct use of the degreaser or lack of local exhaust ventilation at the workplace.

To characterize the risks of adverse health effects other than cancer, MOEs were used to evaluate non-cancer risks for both acute and chronic exposures using the hazard values published in the TCE IRIS assessment (EPA, 2011e). Hazard values based on developmental toxicity (i.e., fetal cardiac defects; Johnson et al., 2003) were used to estimate acute non-cancer risks for occupational and consumer exposures. On the other hand, the chronic non-cancer risks for the worker scenarios were evaluated with the hazard values associated with health effects following long-term exposure to TCE (i.e., developmental toxicity, kidney toxicity, immunotoxicity, reproductive toxicity, neurotoxicity and liver effects). Note that minimal variability (i.e., ≤ 3-fold) exist among the acute and chronic non-cancer hazard values (i.e., HEC_{50}, HEC_{95} or HEC_{99}) used in this assessment.

Most occupational and residential exposure scenarios reported acute risks based on concerns for developmental effects (i.e., cardiac defects) that may occur following a single exposure to TCE during a critical window of susceptibility. Particularly, the degreaser exposure scenarios showed greater acute risks than those reported for the spot cleaning exposure scenarios.

There is a concern for a range of human health effects other than cancer that may appear after chronic exposures to TCE during the occupational use of TCE-containing degreasers and spot cleaning agents. The greatest concern is for developmental effects (i.e., fetal cardiac defects), followed by kidney effects and then immunotoxicity, with an overall higher chronic risk for the degreaser exposure scenarios. In general, the concerns for these three health effects domains occur regardless of the type of exposure (typical vs worst case) and the availability of room ventilation (LEV vs no LEV), although there are some exceptions, particularly in the spot cleaning bystander exposure scenarios.

Potential chronic risks for reproductive effects and neurotoxicity were also observed for degreaser worker exposure scenarios and most of the degreaser bystander exposure scenarios. However, the risks concerns for these effects were reported for fewer spot cleaning worker/bystander scenarios and generally attributed to exposure conditions without room ventilation.

Concerns for liver effects following chronic exposure to TCE are less prominent than the concerns for other health effects domains as chronic risks for liver toxicity were not reported for the majority of the degreaser and spot cleaning worker/bystander scenarios. The exception was the degreaser worker/bystander exposure worst case scenarios and the spot cleaning worker/bystander worst case scenarios with no LEV.

Table 2-34. Chronic Non-Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops

Health Effect Domain and Study	Lowest HEC (ppm) of each health effects domain	WORKER NON-CANCER MOEs [1]				BYSTANDER NON-CANCER MOEs [1]				Total UF or Benchmark MOE
		With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	
DEVELOPMENTAL TOXICITY (Johnson et al., 2003)	HEC50= 0.012	**0.17**	**0.017**	**0.0025**	**0.0003**	**1.3**	**0.13**	**0.0030**	**0.0003**	10
	HEC95= 0.0051	**0.072**	**0.0072**	**0.0011**	**0.0001**	**0.54**	**0.05**	**0.0013**	**0.0001**	
	HEC99= 0.0037	**0.052**	**0.0052**	**0.0008**	**0.0001**	**0.40**	**0.04**	**0.0009**	**0.0001**	
KIDNEY (NTP, 1998)	HEC50= 0.042	**0.59**	**0.059**	**0.0088**	**0.0009**	**4.4**	**0.4**	**0.01**	**0.001**	10
	HEC95= 0.0085	**0.11**	**0.012**	**0.0018**	**0.0002**	**0.9**	**0.09**	**0.0021**	**0.0002**	
	HEC99= 0.0056	**0.079**	**0.0079**	**0.0012**	**0.0001**	**0.6**	**0.06**	**0.0014**	**0.0001**	
IMMUNOTOXICITY Keil et al., 2009 (Decrease in thymus weight and thymus cellularity)	HEC50= 0.092	**1.3**	**0.1**	**0.019**	**0.0020**	**9.7**	**0.97**	**0.023**	**0.0023**	100
	HEC95= 0.045	**0.6**	**0.06**	**0.0095**	**0.0010**	**4.7**	**0.47**	**0.011**	**0.0011**	
	HEC99= 0.033	**0.5**	**0.05**	**0.0069**	**0.0007**	**3.5**	**0.35**	**0.0082**	**0.0008**	
IMMUNOTOXICITY Keil et al., 2009 (Autoimmunity)	HEC50= 0.092	**1.3**	**0.13**	**0.019**	**0.0020**	**9.7**	**0.97**	**0.022**	**0.0023**	30
	HEC95= 0.045	**0.6**	**0.063**	**0.0095**	**0.0010**	**4.7**	**0.47**	**0.011**	**0.0011**	
	HEC99= 0.033	**0.5**	**0.046**	**0.0069**	**0.0007**	**3.5**	**0.35**	**0.0082**	**0.0008**	
REPRODUCTIVE TOXICITY (Chia et al. 1996)	HEC50= 1.4	**19.7**	**2.0**	**0.3**	**0.03**	147	**15**	**0.35**	**0.034**	30
	HEC95= 0.7	**9.8**	**1.0**	**0.15**	**0.015**	74	**7**	**0.17**	**0.017**	
	HEC99= 0.5	**7.0**	**0.7**	**0.11**	**0.011**	53	**5**	**0.12**	**0.012**	
NEUROTOXICITY (Arito et al., 1994)	HEC50= 13	**183**	**18**	**2.7**	**0.28**	1369	**137**	**3.2**	**0.32**	300
	HEC95= 6.4	**90**	**9**	**1.3**	**0.14**	674	**67**	**1.6**	**0.16**	
	HEC99= 4.8	**67**	**7**	**1.0**	**0.10**	505	**51**	**1.2**	**0.12**	
LIVER (Kjellstrand et al. 1983)	HEC50= 25	351	35	**5.3**	**0.53**	2632	263	**6**	**0.61**	10
	HEC95= 12	168	17	**2.5**	**0.26**	1263	126	**3**	**0.29**	
	HEC99= 9.1	128	13	**1.9**	**0.19**	958	96	**2**	**0.22**	

Notes: (1) MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks. (2) Exposure estimates with/without LEV are found in Table 2-10.

Table 2-35. Chronic Non-Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities

Health Effect Domain and Study	Lowest HEC (ppm) of each health effects domain	WORKER NON-CANCER MOEs [1]				BYSTANDER NON-CANCER MOEs [1]				Total UF or Benchmark MOE
		With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	
DEVELOPMENTAL TOXICITY (Johnson et al., 2003)	HEC50= 0.012	**6.3**	**0.0253**	**0.63**	**0.0027**	72	**0.0253**	**7.2**	**0.0028**	10
	HEC95= 0.0051	**2.7**	**0.0107**	**0.27**	**0.0011**	31	**0.0107**	**3.1**	**0.0012**	
	HEC99= 0.0037	**1.9**	**0.0078**	**0.19**	**0.0008**	22	**0.0078**	**2.2**	**0.0009**	
KIDNEY (NTP, 1998)	HEC50= 0.042	22	**0.088**	**2.2**	**0.0093**	253	**0.0884**	25	**0.0098**	10
	HEC95= 0.0085	**4.5**	**0.018**	**0.45**	**0.0019**	51	**0.0179**	**5.1**	**0.0020**	
	HEC99= 0.0056	**2.9**	**0.012**	**0.29**	**0.0012**	34	**0.0118**	**3.4**	**0.0013**	
IMMUNOTOXICITY Keil et al., 2009 (Decrease in thymus weight and thymus cellularity)	HEC50= 0.092	**48**	**0.194**	**4.8**	**0.020**	554	**0.194**	**55**	**0.022**	100
	HEC95= 0.045	**24**	**0.095**	**2.4**	**0.010**	271	**0.095**	**27**	**0.011**	
	HEC99= 0.033	**17**	**0.069**	**1.7**	**0.007**	199	**0.069**	**20**	**0.008**	
IMMUNOTOXICITY Keil et al., 2009 (Autoimmunity)	HEC50= 0.092	48	**0.194**	**4.8**	**0.020**	554	**0.194**	55	**0.022**	30
	HEC95= 0.045	**24**	**0.095**	**2.4**	**0.010**	271	**0.095**	**27**	**0.011**	
	HEC99= 0.033	**17**	**0.069**	**1.7**	**0.007**	199	**0.069**	**20**	**0.008**	
REPRODUCTIVE TOXICITY (Chia et al. 1996)	HEC50= 1.4	737	**2.9**	74	**0.31**	8423	**2.9**	842	**0.33**	30
	HEC95= 0.7	369	**1.5**	37	**0.16**	4212	**1.5**	421	**0.16**	
	HEC99= 0.5	263	**1.1**	**26**	**0.11**	3008	**1.1**	301	**0.12**	
NEUROTOXICITY (Arito et al., 1994)	HEC50= 13	6844	**27**	684	**2.9**	78214	**27**	7821	**3.0**	300
	HEC95= 6.4	3369	**13**	337	**1.4**	38505	**13**	3851	**1.5**	
	HEC99= 4.8	2527	**10**	**253**	**1.1**	28879	**10**	2888	**1.1**	
LIVER (Kjellstrand et al. 1983)	HEC50= 25	13161	53	1316	**5.5**	150412	53	15041	**5.8**	10
	HEC95= 12	6317	25	632	**2.7**	72198	25	7220	**2.8**	
	HEC99= 9.1	4791	19	479	**2.0**	54750	19	5475	**2.1**	

Notes: (1) MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks. (2) Exposure estimates with/without LEV are found in Table 2-13.

Extracted from the TSCA Work Plan Chemical Risk Assessment for Trichloroethylene: Degreasing, Spot Cleaning and Arts and Craft Uses, CASRN: 70-01-6, [HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-chemical-risk-assessment"]

2.6 HAZARD/DOSE-RESPONSE ASSESSMENT

2.6.1 Approach and Methodology

2.6.1.1 Selection of TCE IRIS Assessment as the Source Document for the TCE TSCA Assessment

EPA/OPPT's work plan risk assessment for TCE is based on the hazard and dose-response information published in the toxicological review that the U.S. EPA's Integrated Risk Information System (IRIS) published in 2011. EPA/OPPT used the TCE IRIS assessment as the preferred data source for toxicity information, rather than developing a new toxicological assessment. The TCE IRIS assessment used a weight-of-evidence approach, the latest scientific information and physiologically-based pharmacokinetic (PBPK) modeling to develop hazard and dose-response assessments for TCE's carcinogenic and non-carcinogenic health effects resulting from lifetime oral or inhalation exposure.

Development of TCE's hazard and dose-response assessments considered the principles set forth by the various risk assessment guidelines issued by the National Research Council and the U.S. EPA. Primary, peer-reviewed literature identified through December 2010 was included where that literature was determined to be critical to the assessment (EPA, 2011e). Appendix K provides the guidelines that were considered when developing the TCE IRIS assessment. Some of these guidelines discussed the type of considerations that should be made when evaluating the quality of toxicity data and study reliability. Also Appendix K describes the study selection and data quality criteria that the U.S. EPA's IRIS program and OPPT used to evaluate the hazard data.

The TCE IRIS assessment underwent several levels of peer review including agency review, science consultation on the draft assessment with other federal agencies and the Executive Office of the President, public comment, external peer review by the EPA's Science Advisory Board (SAB) in 2002, scientific consultation by the U.S. National Academy of Sciences (NAS) in 2006 (NRC, 2006)[15], external peer review of the revised draft assessment by the EPA's Science Advisory Board (SAB) in January 2011 (EPA, 2011c)[16], followed by final internal agency review and EPA-led science discussion on the final draft.

Furthermore, EPA/OPPT consulted the EPA's Guidelines for Developmental Toxicity Risk Assessment when making the decision to use developmental toxicity studies in the acute risk assessment of commercial and consumer uses of degreasers and arts/crafts spray fixatives containing TCE (EPA, 1991). The basis for this decision relies on the presumption and EPA's

[15] NAS report, "Assessing the human health risks of trichloroethylene: Key scientific issues (2006)": [HYPERLINK "http://www.nap.edu/catalog.php?record_id=11707" \h]

[16] EPA's SAB peer review report for the 2009 EPA's Draft Assessment entitled "Toxicological Review of Trichloroethylene": [HYPERLINK "http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f648525742400690127/B73D5D39A8F184BD8525" \h] 7817004A1988/$File/EPA-SAB-11-002-unsigned.pdf

policy that a single exposure at a critical window of fetal development may produce adverse developmental effects (EPA, 1991). In other words, a single dose in a developmental toxicity study may be enough to cause developmental effects.

2.6.1.2 Aspects of the TCE IRIS Assessment that Were Adopted in the OPPT Risk Assessment

2.6.1.2.1 Carcinogenic Hazard and Dose-Response Assessment

TCE is carcinogenic to humans by all routes of exposures as documented in the TCE IRIS assessment. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer (EPA, 2011e). The human epidemiological evidence is strong for kidney and more limited for non-Hodgkin lymphoma (NHL) and liver cancer, and less convincing for biliary tract cancer. Less human evidence is found for an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia (EPA, 2011e). Further support for TCE's carcinogenic characterization comes from positive results in multiple rodent cancer bioassays in rats and mice of both sexes, similar toxicokinetics between rodents and humans, mechanistic data supporting a mutagenic mode of action for kidney tumors, and the lack of mechanistic data supporting the conclusion that any of the mode(s) of action for TCE-induced rodent tumors are irrelevant to humans (EPA, 2011e).

The cancer dose-response analysis used linear-dose extrapolation to derive an inhalation unit risk (IUR) of 2×10^{-2} per ppm (4.1×10^{-6} per $\mu g/m^3$) for various cancers[17]. The IUR for TCE was based on human kidney cancer risks that were reported by Charbotel et al. (2006) and adjusted for potential risk for NHL and liver cancer based on human epidemiological data (EPA, 2011e). The IUR is defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air (EPA, 2011b). The IUR was used in the EPA/OPPT risk assessment to estimate excess cancer risks for the inhalation occupational exposures scenarios. There is high confidence in the IUR because it was based on good quality human data, and was similar to unit risk estimates derived from multiple rodent bioassays (EPA, 2011e). Moreover, there was sufficient weight of evidence to conclude that TCE operates through a mutagenic mode of action for kidney tumors (EPA, 2011e).

EPA/OPPT decided not to use the IUR to calculate the theoretical cancer risk associated with a single (acute) exposure to solvent degreasers, arts/crafts fixative and spotting agent products containing TCE. NRC (2001) published methodology for extrapolating cancer risks from chronic to short-term exposures to mutagenic carcinogens. These methods were published with the caveat that extrapolation of lifetime theoretical excess cancer risks to single exposures has great uncertainties.

[17] The dose-response analysis for cancer endpoints can be found in Chapter 5 of the TCE IRIS assessment EPA (2011e).

As NRC (2001) explains, "*There are no adopted state or federal regulatory methodologies for deriving short-term exposure standards for workplace or ambient air based on carcinogenic risk, because nearly all carcinogenicity studies in animals and retrospective epidemiologic studies have entailed high-dose, long-term exposures. As a result, there is uncertainty regarding the extrapolation from continuous lifetime studies in animals to the case of once-in-a-lifetime human exposures. This is particularly problematical, because the specific biologic mechanisms at the molecular, cellular, and tissue levels leading to cancer are often exceedingly diverse, complex, or not known. It is also possible that the mechanisms of injury of brief, high-dose exposures will often differ from those following long-term exposures. To date, U.S. federal regulatory agencies have not established regulatory standards based on, or applicable to, less than lifetime exposures to carcinogenic substances* (NRC, 2001)." Thus, the final EPA/OPPT work plan risk assessment for TCE does not estimate excess cancer risks for acute exposures because the relationship between a single short-term exposure to TCE and the induction of cancer in humans has not been established in the current scientific literature.

2.6.1.2.2 Non-Cancer Hazard and Dose-Response Assessment

EPA/OPPT used margin of exposures (MOEs)[18] to estimate non-cancer risks based on the following:

1. the lowest PBPK-derived human equivalent concentrations (HECs) within each health effects domain reported in the TCE IRIS assessment;
2. the same endpoint/study-specific uncertainty factors (UFs) that the IRIS program applied to the PBPK-derived HECs; and
3. the exposure estimates calculated for the TCE uses examined in this risk assessment (see *Environmental Releases and Exposure Summary*).

MOEs allow for the presentation of a range of risk estimates rather than a single risk estimate based on the inhalation reference concentration (RfC). Given the different exposure scenarios considered (both acute and chronic for small commercial degreasers, and just acute for the two consumer exposure scenarios), different endpoints were used based on the expected exposure durations. For non-cancer effects, risks to developmental effects were evaluated for acute (short-term) exposures, whereas risks to other adverse effects (toxicity to the liver, kidney, nervous system, immune system, and the reproductive system) were evaluated for repeated (chronic) exposures to TCE.

Table 2-18 lists the studies and corresponding HECs and UFs that EPA/OPPT used in the work plan risk assessment for TCE. Key studies in Table 2-18 are briefly described in the *Human Health Hazard Summary* along with other toxicity and epidemiological studies, with detailed descriptions provided in the TCE IRIS assessment (EPA, 2011e). Appendix L contains the complete list of oral and inhalation non-cancer studies within each health effects domain that the TCE IRIS assessment considered suitable for dose-response analysis.

[18] Margin of Exposure (MOE) = (Non-cancer hazard value, POD) ÷ (Human Exposure). See equation in Table 2-29. The benchmark MOE is used to interpret the MOEs and consists of the total UF set by the IRIS program for each study in Table 2-18. See section 2.7.1 for an explanation of the benchmark MOE.

The TCE IRIS assessment used a series of steps to generate the PBPK-derived HECs that OPPT used in its risk assessment (Table 2-19). EPA/OPPT did not rely on those steps that were associated with the derivation of candidate RfCs (cRfC) or final RfC value (Table 2-19). Below is a brief discussion of those steps that EPA/OPPT adopted in this risk assessment.

The non-cancer dose-response analysis in the TCE IRIS assessment commenced with the review and selection of high quality epidemiological and toxicity studies that reported both adverse non-cancer health effects and quantitative dose-response data[19] (Table 2-19). Subsequently, *point of departures (PODs)*[20] were identified for those studies that had suitable data for dose- response analysis. PODs can be a NOAEL[21] or LOAEL[22] for an observed incidence, or change in level of response, or the lower confidence limit on the dose at the benchmark dose (BMD)[23].

The dose-response assessment was organized in five health effects domains: (1) neurotoxicity; (2) systemic (body weight) and organ toxicity (liver and kidney effects); (3) immunotoxicity; (4) reproductive; and (5) developmental effects. PBPK modeling was used to estimate internal dose PODs (idPOD) and subsequently HECs based on the oral and inhalation PODs identified in earlier steps. The PBPK modeling integrated internal dose-metrics based on TCE's mode of action and the role of different TCE metabolites in toxicity (EPA, 2011e). Note that the effects within the same health effect domain were generally assumed to have the same relevant internal dose- metrics (EPA, 2011e).

Furthermore, the PBPK model was used to estimate the interspecies and within-human pharmacokinetic variability (or just within-human variability for the human-based PODs) corresponding to each idPOD for each candidate critical effect. The results of this calculation were 50th, 95th and 99th percentile HEC estimates for POD analyzed within each health effects domain. Also, the PBPK model integrated a Bayesian population analysis to characterize pharmacokinetic uncertainties and variability (EPA, 2011e). More information on the PBPK modeling is provided in the next section below, including how the HECs were calculated.

EPA/OPPT used the endpoint/study-specific UFs from the TCE IRIS assessment as the benchmark MOEs for the risk calculations. These UFs were applied to the PBPK-derived PODs to account for (1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL (EPA, 2011b).

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[19] Non-cancer toxicological and epidemiological studies are described in Chapter 4 of the TCE IRIS assessment. [20] A point of departure (POD) is a dose or concentration that can be considered to be in the range of observed responses, without significant extrapolation. A POD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures EPA (2011b).

[21] NOAEL=No-observed-adverse-effect level

[22] LOAEL= Lowest-observed-adverse-effect level

[23] The benchmark dose (BMD) is a dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background EPA (2011b).

Table 2-18. Lowest PBPK-derived HECs for different effects domains based on analysis in TCE IRIS assessment

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm)[3]	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) for Benchmark MOE[4]	Reference
CHRONIC	Liver	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures, variable time periods for 30-120 days	$BMDL_{10}$ = 21.6 ppm	Increased liver/body weight ratio	25	12	9.1	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Kidney	Rat (female)	Oral (gavage)	500 to 1,000 mg/kg-bw/day	5 days/week for 104 weeks	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.042	0.0085	0.0056	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	NTP (1988)
	Nervous System	Rat (male)	Inhalation	50 to 300 ppm	8 hrs/day, 5 days/weeks for 6 weeks	LOAEL = 12 ppm	Significant decreases in wakefulness	13	6.4	4.8	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; *Total UF=300*	Arito et al. (1994)
	Immune System	Mouse (female)	Oral (drinking water)	0.001 to 14 ppm (0.001 to 14 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*[5]	Keil et al. (2009)
		Mouse (female)	Oral (drinking water)	0.001 to 14 ppm (0.001 to 14 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=3; *Total UF=30*[5]	Keil, D. E. et al. (2009)
	Reproductive System	Human (male)	Inhalation	29.6 ppm (mean exposure)	Measured values after an 8-hour work shift; mean 5.1 years on job	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	1.4	0.7	0.5	UF_S=10; UF_A= 1; UF_H=3; UF_L=1; *Total UF=30*	Chia et al. (1996)

Table 2-18. Lowest PBPK-derived HECs for different effects domains based on analysis in TCE IRIS assessment

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm)[3]	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) for Benchmark MOE[4]	Reference
ACUTE OR CHRONIC	Developmental effects	Rat (female)	Oral (drinking water)	2.5 to 1,100 ppm (2.5 to 1,100 mg/kg-bw/day)	22 days throughout gestation (gestational days 0 to 22)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.012	0.0051	0.0037	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Johnson et al. (2003)

Notes:
1 Control concentrations were not included in the table, but discussed in the study summaries in section 2.6.2.
2 POD type can be NOAEL, LOAEL, or BMDL; the IRIS program adjusted all values to continuous exposure.
3 1 ppm = 5.374 mg/m^3
4 UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF. UF values were those used in the TCE IRIS assessment (EPA, 2011e).
5 Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UF (EPA, 2011e).

Table 2-19. Steps of the Non-Cancer TCE IRIS Process that Were Considered in OPPT's Non-Cancer Hazard/Dose-Response Approach [1]

Step#	NON-CANCER IRIS APPROACH	NON-CANCER OPPT APPROACH *Considered (+) / Not Considered (—)*
1	Evaluation of all studies (inhalation and oral) that provided (1) non-cancer adverse health effects and (2) quantitative dose-response data	+
2	Identification of the Points of Departure (POD) based on applied dose	+
3	Adjustment of each POD by endpoint/study-specific uncertainty factors (UFs)	—
4	Derivation of candidate reference concentrations (cRfCs) and selection of the lowest values within each health endpoint domain taking into account the confidence of the estimate	—
5	Application of PBPK modeling to estimate internal dose PODs (i.e., HECs) for those candidate critical effects selected from inhalation and oral studies based on applied dose	+
6	Estimation of interspecies and within-human pharmacokinetic variability for the internal dose PODs by PBPK modeling	+
7	Adjustment of each internal dose POD by endpoint/study-specific UFs [2]	—
8	Derivation of PBPK model-based candidate RfCs (p-cRfC) for each candidate critical effect	—
9	Characterization of the uncertainties of the cRfCs derived by applied dose and PBPK modeling (p-cRfC) by using quantitative uncertainty analyses of pharmacokinetic uncertainty and variability from the Bayesian population analysis [3]	—
10	Evaluation of the most sensitive cRfCs and set final RfC value.	—

Notes:

1 Table 2-19 is an adaptation of Figure 5-1 (Chapter 5) in the TCE IRIS assessment (EPA, 2011e).

2 Endpoint/study-specific UFs were used as benchmark MOEs in the OPPT's TCE risk assessment.

3 EPA/OPPT consulted the characterization of the uncertainties in the TCE IRIS assessment and those aspects related to the uncertainties of the individual studies and the generation of PBPK-derived HECs were discussed in the OPPT's TCE risk assessment.

APPENDIX L. LIST OF ORAL AND INHALATION STUDIES SUITABLE FOR NON-CANCER DOSE-RESPONSE ANALYSIS IN THE TCE IRIS ASSESSMENT

L-1 Liver Effects

Target Organ	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Liver	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures, variable time periods for 30-120 days	$BMDL_{10}$= 21.6 ppm	Increased liver/body weight ratio	25	12	9.1	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Mouse (male)	Oral (gavage)	100 to 3,200 mg/kg-bw/day	6 weeks	$BMDL_{10}$= 82 mg/kg-bw/day		32	15	11	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Buben and O'Flaherty (1985)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hr/day, 5 days/week for 4 weeks	$BMDL_{10}$= 25 ppm		53	24	19	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Woolhiser et al. (2006)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-2 Kidney Effects

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Kidney	Rat (female)	Oral (gavage)	500 to 1,000 mg/kg-bw/day	5 days/week for 104 weeks	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.042	0.0085	0.0056	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	NTP (1988)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hr/day, 5 days/week for 4 weeks	$BMDL_{10}$= 15.7 ppm	Increased kidney weight/body weight ratio	0.099	0.020	0.013	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Woolhiser et al. (2006)
	Rat (male)	Oral (gavage)	50 to 250 mg/kg-bw/day	4-5 days/week for 52 weeks	$BMDL_{10}$ = 34 mg/kg-bw/day	Pathology changes in renal tubule	0.19	0.038	0.025	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Maltoni and Cotti (1986)
	Rat (male)	Inhalation	100 to 600 ppm	7 hrs/day, 5 days/week for 2 years	$BMDL_{10}$= 40.2 ppm	Pathology changes in renal tubule	0.28	0.057	0.038	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Maltoni and Cotti (1986)
	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures for 30-120 days	$BMDL_{10}$ = 34.7 ppm	Increased kidney weight/body weight ratio	0.88	0.18	0.12	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Mouse (female)	Oral (gavage)	869 to 1,739 mg/kg-bw/day	5 days/week, TWA during exposure period (78 weeks), animals observed for 90 weeks	LOAEL = 620 mg/kg-bw/day	Pathology changes in renal tubule (toxic nephrosis)	3.9	0.77	0.5	UF_S=1; UF_A= 3; UF_H=3; UF_L=30; *Total UF=300*	NCI (1976)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-3 Neurotoxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Nervous system	Rat (male)	Inhalation	50 to 300 ppm	8 hrs/day, 5 days/weeks for 6 weeks	LOAEL = 12 ppm	Significant decreases in wakefulness	13	6.4	4.8	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; *Total UF=300*	Arito et al. (1994)
	Human (both sexes)	Inhalation	704 ppm × years of exposure (mean cumulative exposure)	Mean of 16 years	LOAEL = 14 ppm	Trigeminal nerve effects (increased latency in masseter reflex)	14	7.0	5.3	UF_S=1; UF_A= 1; UF_H=3; UF_L=3; *Total UF=10*	Ruijten et al. (1991)
	Rat (male)	Oral (drinking water)	24 to 47 mg/kg-bw/day	8 weeks	LOAEL = 47 mg/kg-bw/day	Cognitive effects (demyelination of hippocampus)	18	9.2	7.1	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Isaacson et al. (1990)
	Rat (male)	Oral (gavage)	1,000 mg/kg-bw/day	5 days/week for 6 weeks	LOAEL = 710 mg/kg-bw/day	Degeneration of dopamine-containing neurons in substantia nigra	126	62	47	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Gash et al. (2008)
	Rat (female)	Inhalation	300 ppm	24 hrs/day for 24 days	LOAEL = 300 ppm	Decreased regeneration of sciatic nerve	274	127	93	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Kjellstrand et al. (1987)
	Mouse (male)	Inhalation	150 to 300 ppm	24 hrs/day for 24 days	LOAEL = 150 ppm		378	163	120	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-4 Immunotoxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Immune system	Mouse (female)	Oral (drinking water)	1.4 to 14 ppm (0.35 to 3.5 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100* [4]	Keil et al. (2009)
	Mouse (female)	Oral (drinking water)	1.4 to 14 ppm (0.35 to 3.5 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=3; *Total UF=30* [4]	Keil et al. (2009)
	Mouse (female)	Oral (drinking water)	18 to 660 mg/kg-bw/day	16 or 24 weeks (4 or 6 months)	LOAEL = 18 mg/kg-bw/day	Immuno-suppression	4.8	2.4	1.7	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*	Sanders et al. (1982)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hrs/day, 5 days/week for 4 weeks	$BMDL_{1SD}$= 24.9 ppm	Immuno-suppression	29	15	11	UF_S=10; UF_A= 3; UF_H=3; UF_L=1; *Total UF=100*	Woolhiser et al. (2006)
	Mouse (males; auto-immune prone strain)	Inhalation	500 to 2,000 ppm	4 hrs/day, 6 days/week for 8 weeks	LOAEL = 70 ppm	Autoimmunity (changes in immunoreactive organs)	97	48	37	UF_S=10; UF_A= 3; UF_H=1; UF_L=10; *Total UF=300*	Kaneko et al. (2000)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

[4] Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UF (EPA, 2011e).

L-5 Reproductive Toxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs)[3]	Reference
Reproductive system	Human (male)	Inhalation	29.6 ppm (mean exposure)	Measured values after an 8-hr work shift; mean 5.1 years on the job	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	1.4	0.7	0.5	UF_S=10; UF_A= 1; UF_H=3; UF_L=1; *Total UF=30*	Chia et al. (1996)
	Rat (male)	Oral (drinking water)	143 to 270 mg/kg-bw/day	14 days	LOAEL = 141 mg/kg-bw/day	Decreased *in vitro* fertilization	16	11	9.3	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	DuTeaux et al. (2004)
	Rat (male)	Inhalation	376 ppm	4 hrs/day, 5 days/week, 2-10 weeks exposed, 2-8 weeks unexposed	LOAEL = 45 ppm	Sperm effects and male reproductive tract effects	32	16	13	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Kumar et al., 2000 Kumar et al. (2000)
				4 hrs/day, 5 days/week for 12 or 24 weeks							Kumar et al. (2001)
	Rat (female damns)	Oral (gavage)	10.1 to 1,125 mg/kg-bw/day	9 days (during gestational days 6 to 15)	LOAEL = 475 mg/kg-bw/day	Delayed parturition	98	48	37	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*	Narotsky et al. (1995)
	Mouse (male)	Inhalation	1,000 ppm	6 hrs/day, 5 days/week for 19 days over 4 weeks	LOAEL = 180 ppm	Effects on epididymis epithelium	190	91	67	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Forkert et al. (2002)
				6 hrs/day, 5 days/week for 1-4 weeks							Kan et al. (2007)
	Mouse (male)	Inhalation	1,000 ppm	6 hrs/day, 5 days/week for 6 weeks	LOAEL = 180 ppm	Sperm effects (decreased in vitro sperm-oocyte binding and *in vivo* fertilization)	190	91	67	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Xu et al. (2004)

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Reproductive system	Rat (male)	Oral (drinking water)	72 to 389 mg/kg-bw/day	Breeders exposed 1 week premating and then for 13 weeks/ Pregnant females exposed throughout gestation (i.e., 18 weeks total)	LOAEL = 389 mg/kg-bw/day	Decreased mating (both sexes exposed)	204	97	71	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; UF_D=1 *Total UF=100*	NTP (1986)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-6 Developmental Toxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Developmental effects	**PRE- AND POSTNATAL MORTALITY**										
	Rat (female)	Inhalation	**1.** ppm	4 hrs/day, gestational days 8 to 21	LOAEL =17 ppm	Increased resorptions	16	8	6.2	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Healy et al. (1982)
	Rat (female)	Oral (gavage)	10.1 to 1,125 mg/kg-bw/day	Gestational days 6 to 15	$BMDL_{01}$= 32.2 mg/kg-bw/day	Increased resorptions	57	29	23	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Narotsky et al. (1995)
	PRE- AND POSTNATAL GROWTH										
	Rat (female)	Inhalation	100 ppm	4 hrs/day, gestational days 8 to 21	LOAEL = 17 ppm	Decreased fetal weight and skeletal effects	16	8	6.2	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Healy et al. (1982)
	CONGENITAL DEFECTS										
	Rat (female)	Oral (drinking water)	2.5 to 1,100 ppm (2.5 to 1,100 mg/kg-bw/day)	22 days throughout gestation (gestational days 0 to 22)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.012	0.0051	0.0037	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Johnson et al. (2003)
	DEVELOPMENTAL NEUROTOXICITY										
	Rat (male pups)	Oral (gavage)	50 to 290 mg/kg-bw/day	Postnatal days 10 to 16	LOAEL = 50 mg/kg-bw/day	Decreased rearing activity	8	4	3	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; Total UF=300	Fredriksson et al. (1993)
	Rat (female)	Oral (drinking water)	45 to 140 mg/kg-bw/day	Dams and pups exposed from 14 days prior to mating until end of lactation	LOAEL = 45 mg/kg-bw/day	Increased exploratory behavior in male pups (offspring)	22	11	8.4	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Taylor et al. (1985)

Notes: [1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.
[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.
[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

2.7 HUMAN HEALTH RISK CHARACTERIZATION

TCE and its metabolites are associated with adverse effects on cardiac development based on a weight-of-evidence analysis of developmental studies from rats, humans and chickens. These adverse cardiac effects are deemed important for acute and chronic risk estimation for the scenarios and populations addressed in this risk assessment. The rationale for using TCE associated fetal cardiovascular lesions for acute scenarios is based on the relatively short critical window of vulnerability in humans, rodent and avian cardiac development. The rationale for using fetal cardiac effects for chronic risks estimation is also based on the fact that relatively low dose short term/acute exposures can result on long-term adverse consequences on cardiac development persisting into adulthood.

Table 2-26. Summary of Hazard Information Used in the Risk Evaluation of Acute and Chronic Scenarios

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	POD Type	Effect	HEC_{99} (ppm)	Total Uncertainty Factor (UF) for Benchmark MOE	Reference
CHRONIC	Liver	Mouse (male)	Inhalation	$BMDL_{10}$ = 21.6 ppm	Increased liver/body weight ratio	9.1	*Total UF=10*	Kjellstrand et al. (1983)
	Kidney	Rat (female)	Oral (gavage)	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.0056	*Total UF=10*	NTP (1988)
	Nervous System	Rat (male)	Inhalation	LOAEL = 12 ppm	Significant decreases in wakefulness	4.8	*Total UF=300*	Arito et al. (1994)
	Immune System	Mouse (female)	Oral (drinking water)	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.033	*Total UF=100*	Keil et al. (2009)
		Mouse (female)	Oral (drinking water)	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.033	*Total UF=30*	Keil, D. E. et al. (2009)
	Reproductive System	Human (male)	Inhalation	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	0.5	*Total UF=30*	Chia et al. (1996)
ACUTE OR CHRONIC	Developmental effects	Rat (female)	Oral (drinking water)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.0037	Total UF=10	Johnson et al. (2003)

Notes:

[1] 1 ppm = 5.374 mg/m^3

[2] Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UFs for effects repoted by the same study (EPA, 2011e).

Other adverse non-cancer effects are deemed relevant for risk estimations for other populations for the chronic scenarios, but may not occur at the lowest exposures found with cardiac defects and they include kidney toxicity, immunotoxicity, male reproductive toxicity,

neurotoxicity, liver toxicity and cancer of kidney, liver and immune system (NHL).

TCE is carcinogenic to humans. The cancer risk assessment uses the IUR derived in the 2011 TCE IRIS assessment based on human kidney cancer. The weight-of-evidence analysis for the cancer endpoint was sufficient to conclude that TCE operates through a mutagenic mode of action for kidney tumors (EPA, 2011e).

2.7.1 Risk Estimation Approach for Acute and Repeated Exposures

Tables 2-27 and 2-28 show the use scenarios, populations of interest and toxicological endpoints used in the acute and chronic risk assessment, respectively.

Table 2-27. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Acute Risks to TCE-containing Degreasers, Spotting Agents and Arts/Crafts Products

Use Scenarios / Populations And Toxicological Approach	(1) Solvent degreasing at small commercial facilities	(2) Spot cleaning at dry cleaning facilities	(3) Residential use of degreaser product	(4) Residential use of arts/crafts clear protective coating spray
Population of Interest and Exposure Scenario: *Users*	Adult pregnant[1] worker (>16 years old) exposed to TCE for a single 2-hr exposure during an 8-hr workday [2,3,4].	Adult pregnant[1] worker (>16 years old) exposed to TCE for a single 8-hr exposure [2,3].	Adult pregnant [1] consumers (>16 yrs old) exposed to TCE for a single 1-hr exposure when using product 2X per month [2,3,4]. Residential exposure model provided the 24-hr acute exposure estimate.	Adult pregnant [1] consumers (>16 yrs old) exposed to TCE for a single 0.5-hr exposure when using product once per week [2,3,4]. Residential exposure model provided the 24-hr acute exposure estimate.
Population of Interest and Exposure Scenario: *Bystander*	Adult pregnant women [1] (>16 years old) exposed to TCE indirectly by being in the same building.		Adult pregnant bystander[1] and individuals of several age groups that are exposed to indirect TCE exposures by being in the rest of the house.	
Health Effects of Concern, Concentration and Time Duration	Non-Cancer Health Effects: Fetal cardiac defects (Johnson et al., 2005; Johnson, 2014; Johnson et al., 2003)[5] 1. *PBPK-derived Non-Cancer Hazard values or Point of Departures (PODs)* (EPA, 2011e): 24-hr HEC_{50}: 0.012 ppm 24-hr HEC_{95}: 0.0051 ppm 24-hr HEC_{99}: 0.0037 ppm Cancer Health Effects: Acute cancer risks were not estimated. Relationship is not known between a single short-term exposure to TCE and the induction of cancer in humans.			
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	$(UF_S=1) \times (UF_A=3) \times (UF_H=3) \times (UF_L=1)$ [6] = 10 (EPA, 2011e). Total UF=Benchmark MOE=10			

Notes:

[1] The acute risk assessment focused on the most sensitive life stage in humans, which is women of childbearing age and fetus (i.e., pregnant worker) due to concerns for developmental effects.

[2] Exposure estimate was adjusted to a 24-hr exposure estimate in order to combine it with the 24-hr HECs.

[3] It is assumed no substantial buildup of TCE in the body between exposure events due to TCE's short biological half-life (~51 hrs).

[4] EPA/OPPT believes that the users of these products are generally adults, but teenagers and even children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.

[5] The acute risk assessment focused on developmental toxicity effects as the most sensitive health effect when compared to other potential acute effects (i.e., neurotoxicity).

[6] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF

Table 2-28. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Chronic Risks to TCE-containing Degreasers and Spotting Agents

Use Scenarios → / Populations And Toxicological Approach ↓	(1) Solvent degreasing at small commercial facilities	(2) Spot cleaning at dry cleaning facilities
Population of Interest and Exposure Scenario: *Users*	Adult worker (>16 years old) [1] exposed to TCE for 2-hr exposure during an 8-hr workday for 260 days per year for 40 working years. Lifetime average daily concentration was calculated. Note that the 8-hr exposure estimate was adjusted to a 24-hr exposure estimate.	Adult worker (>16 years old) [1] exposed to TCE for an 8-hr workday for 260 days per year for 40 working years. Lifetime average daily concentration was calculated. Note that the 8-hr exposure estimate was adjusted to a 24-hr exposure estimate.
Population of Interest and Exposure Scenario: *Bystander*	Adult worker (>16 years old) [1] repeatedly exposed to indirect TCE exposures by being in the same building.	
Health Effects of Concern, Concentration and Time Duration	Non-Cancer **2.** *Non-cancer health effects*: A range of possible chronic non-cancer effects in liver, kidney, nervous system, immune system, reproductive system and developmental effects[2] **3.** *PBPK-derived Non-Cancer Hazard values or Point of Departures (PODs):* The lowest POD (i.e., 24-hr HEC_{50}, HEC_{95} or HEC_{99} expressed in ppm) within each health endpoint domain (EPA, 2011e). See Table 2-18. Cancer **1.** *Cancer health effects:* Possible cancer effects in kidney, liver or non-Hodgkins lymphoma from chronic exposure. **2.** *PBPK-derived Cancer Inhalation Unit Risk (IUR)*: 2×10^{-2} per ppm (EPA, 2011e).	
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	Study- and endpoint-specific UFs from the TCE IRIS assessment. See Table 2-18.	

Notes:
[1] Adult workers (>16 years old) include both healthy female and male workers.
[2] The chronic risk assessment for developmental effects focused on the most sensitive life stage in humans, which are women of child-bearing age and fetus (i.e., pregnant worker). For other health effects (e.g., liver, kidney, etc.), healthy female or male workers were assumed to be the population of interest.

Acute or chronic MOEs (MOE_{acute} or $MOE_{chronic}$) were used in this assessment to estimate non-cancer risks (Table 2-29).

Table 2-29. Equation to Calculate Non-Cancer Acute or Chronic Risks Using Margin of Exposures

$$MOE_{acute\ or\ chronic} = \frac{\text{Non-cancer Hazard value (POD)}}{\text{Human Exposure}}$$

MOE =	Margin of exposure (unitless)
Hazard value (POD) =	HEC_{50}, HEC_{95}, or HEC_{99} (ppm) derived from TCE IRIS assessment (EPA, 2011e)
Human Exposure =	Exposure estimate (in ppm) from occupational or consumer exposure assessment. ADCs were used for non-cancer chronic risks and acute concentrations were used for acute risks (see sections 2.3.3 and 2.4.2).

As discussed previously, each non-hazard PBPK-derived POD was adjusted by endpoint/study-specific UFs as described in the TCE IRIS assessment (EPA, 2011e). These UFs accounted for (1) the variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4)the uncertainty in extrapolating from a LOAEL rather than from a NOAEL (EPA, 2011e).

The total UF for each non-cancer PBPK-derived POD was the benchmark MOE used to interpret the MOE risk estimates for each use scenario. The MOE estimate was interpreted as human health risk if the MOE estimate was less than the benchmark MOE (=total UF). On the other hand, the MOE estimate indicated negligible concerns for adverse human health effects if the MOE estimate exceeded the benchmark MOE. Typically, the larger the MOE, the more unlikely it is that a non-cancer adverse effect would occur.

Cancer risks for repeated exposures to TCE were estimated using the equation in Table 2-30. Estimates of cancer risks should be interpreted as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to the potential carcinogen (i.e., incremental or excess individual lifetime cancer risk).

Table 2-30. Equation to Calculate Cancer Risks

$$\text{Risk} = \text{Human Exposure} \times \text{IUR}$$

Risk =	Cancer risk (unitless)
Human exposure =	Exposure estimate (LADC in ppm) from occupational exposure assessment
IUR =	Inhalation unit risk (2×10^{-2} per ppm) (EPA, 2011e)

2.7.2 Acute Non-Cancer Risk Estimates for Inhalation Exposures to TCE

The acute inhalation risk assessment used developmental toxicity data to evaluate the acute risks for the TSCA TCE use scenarios. As indicated previously, EPA's policy supports the use of developmental studies to evaluate the risks of acute exposures. This policy is based on the presumption that a single exposure of a chemical at a critical window of fetal development, as in the case of cardiac development, may produce adverse developmental effects (EPA, 1991).

After evaluating the developmental toxicity literature of TCE, the TCE IRIS assessment concluded that the fetal heart malformations are the most sensitive developmental toxicity endpoint associated with TCE exposure (EPA, 2011e). Thus, EPA/OPPT based its acute risk assessment on the most health protective endpoint (i.e., fetal cardiac malformations; Johnson et al., 2003) representing the most sensitive human population (i.e., adult women of child-bearing age and fetus > 16 yrs).

The acute risk assessment used the PBPK-derived hazard values (HEC_{50}, HEC_{95}, or HEC_{99}) from Johnson et al. (2003) developmental study for each degreaser and spot cleaner use scenario. Note that the variability among these hazard values is small and no greater than 3-fold (i.e., 2-fold for HEC_{50}/HEC_{95} ratios; 3-fold for HEC_{50}/HEC_{99} ratios; 1.4-fold for HEC_{95}/HEC_{99} ratios).

Acute inhalation risks were reported for most occupational and residential exposure scenarios based on concerns for developmental effects, irrespective of who is using the product (user vs. bystander), the type of exposure (typical vs. worst case scenario) and the room ventilation system (LEV vs no LEV). For instance, most of the degreaser and spot cleaner exposure scenarios and all of the residential use scenarios reported MOE values below the benchmark MOE of 10 irrespective of the percentile HEC value used to estimate the MOEs. Only one use scenario reported MOEs above 10, which was the spot cleaner use scenario representing bystander exposures under typical occupational exposure levels with LEV (i.e., "Bystander + LEV—Typical Exposure") (Tables 2-31, 2-32 and 2-33).

Table 2-31. Acute Non-Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	WORKER NON-CANCER MOEs				BYSTANDER NON-CANCER MOEs				Total UF or Benchmark MOE
	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	
HEC_{50}= 0.012	**0.12**	**0.0018**	**0.012**	**0.00018**	**0.9**	**0.002**	**0.09**	**0.00021**	10
HEC_{95}= 0.0051	**0.051**	**0.0008**	**0.0051**	**0.00008**	**0.38**	**0.0009**	**0.038**	**0.000089**	
HEC_{99}= 0.0037	**0.037**	**0.0006**	**0.0037**	**0.00006**	**0.28**	**0.0007**	**0.028**	**0.000065**	

Notes:

– MOEs below benchmark MOE indicating risk are denoted in **bold** text. They indicate potential health risks.
– Exposure estimates with/without LEV are found in Table 2-10.

Table 2-32. Acute Non-Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	WORKER NON-CANCER MOEs				BYSTANDER NON-CANCER MOEs				Total UF or Benchmark MOE
	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	
HEC_{50}= 0.012	**4.5**	**0.018**	**0.45**	**0.0019**	51.4	**0.018**	**5.1**	**0.002**	10
HEC_{95}= 0.0051	**1.9**	**0.0077**	**0.19**	**0.00081**	21.9	**0.0077**	**2.2**	**0.00085**	
HEC_{99}= 0.0037	**1.4**	**0.0056**	**0.14**	**0.00058**	15.9	**0.0056**	**1.6**	**0.00062**	

Notes:

– MOEs below benchmark MOE indicating risk are denoted in **bold** text. They indicate potential health risks.
– Exposure estimates with/without LEV are found in Table 2-13.

Table 2-33. Acute Non-Cancer Risk Estimates for Residential Uses of TCE-containing degreasers and art/crafts products (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	RESIDENTIAL USE OF DEGREASER PRODUCT MOEs [1]		RESIDENTIAL USE OF ARTS/CRAFTS CLEAR PROTECTIVE COATING SPRAY MOEs [1]		Total UF or Benchmark MOE
	USER [2]	BYSTANDER [3]	USER [2]	BYSTANDER [3]	
HEC_{50}= 0.012	**0.0060**	**0.015**	**0.03**	**0.12**	10
HEC_{95}= 0.0051	**0.0026**	**0.0064**	**0.013**	**0.051**	
HEC_{99}= 0.0037	**0.0019**	**0.0046**	**0.0093**	**0.037**	

Notes:
1 MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks.
2 MOEs for the user categories could be extended to different age groups. EPA/OPPT believes that the users of these products are generally adults, but teenagers and even children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.
3 All age categories (<1 yrs; 1-2 yrs; 3-5 yrs; 6-10 yrs; 11-15 yrs; 16-20 yrs ; and >21 yrs)

2.7.3 Chronic Non-Cancer and Cancer Risk Estimates for Inhalation Exposures to TCE

Chronic non-cancer and cancer risk estimates for inhalation exposures to TCE were only derived for occupational scenarios since the exposures for consumer uses were not considered chronic in nature.

2.7.3.1 Cancer Risks for Occupational Scenarios

Figures 2-6 and 2-7 present the incremental individual lifetime cancer risks for continuous exposures to TCE occurring during the commercial use of degreaser and spot cleaner products. The cancer risk estimates were calculated by multiplying the EPA's inhalation unit risk for TCE (EPA, 2011e) by the exposure estimate (i.e., LADC) for both direct users and bystanders. Cancer risks were expressed as number of cancer cases per million. Calculations of cancer risks are provided in the supplemental Excel spreadsheet, *TCE OPPT Risk Estimates_061814.xlsx*.

It was assumed that the exposure frequency (i.e., the amount of days per year workers or bystanders are exposed to TCE) was 260 days per year and the occupational exposure duration was 40 years over a 70-year lifespan. It is recognized that these exposure assumptions are likely yielding conservative cancer risk estimates, but EPA/OPPT does not have additional information for further refinement.

EPA typically uses a target cancer risk level between $1x10^{-4}$ and $1x10^{-6}$ for determining the acceptability of the cancer risk in a population. Since the target cancer risk level will be determined during risk management, the occupational cancer risk estimates were compared to three target levels within EPA's acceptability range. The target levels were:

1. $1x10^{-6}$: the probability of 1 chance in 1 million of an individual developing cancer
2. $1x10^{-5}$: the probability of 1 chance in 100,000 of an individual developing cancer, which is equivalent to 10 cancer cases in 1 million
3. $1x10^{-4}$: the probability of 1 chance in 10,000 of an individual developing cancer, which is equivalent to 100 cancer cases in 1 million

All of the degreaser exposure scenarios exceeded the three target cancer levels, with the exception of one of the bystander exposure scenarios (i.e., "*Bystander + LEV—Typical Exposure*"). This particular bystander exposure scenario exceeded the target levels at $1x10^{-5}$ and $1x10^{-6}$ (Figure 2-6).

Likewise, all of the worst case exposures for the spot cleaner scenarios (i.e., both user and bystander scenarios) and one of the typical exposure scenarios with no LEV (i.e., "*Spot Cleaner No LEV—Typical Exposure*") exceeded the three target levels. The remaining spot cleaner scenarios exceeded the target level of $1x10^{-4}$ (i.e., "Spot cleaner + LEV—Typical Exposure"; "Bystander + LEV—Typical Exposure"; and "Bystander No LEV—Typical Exposure") (Figure 2-7).

Figure 2-6. Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops

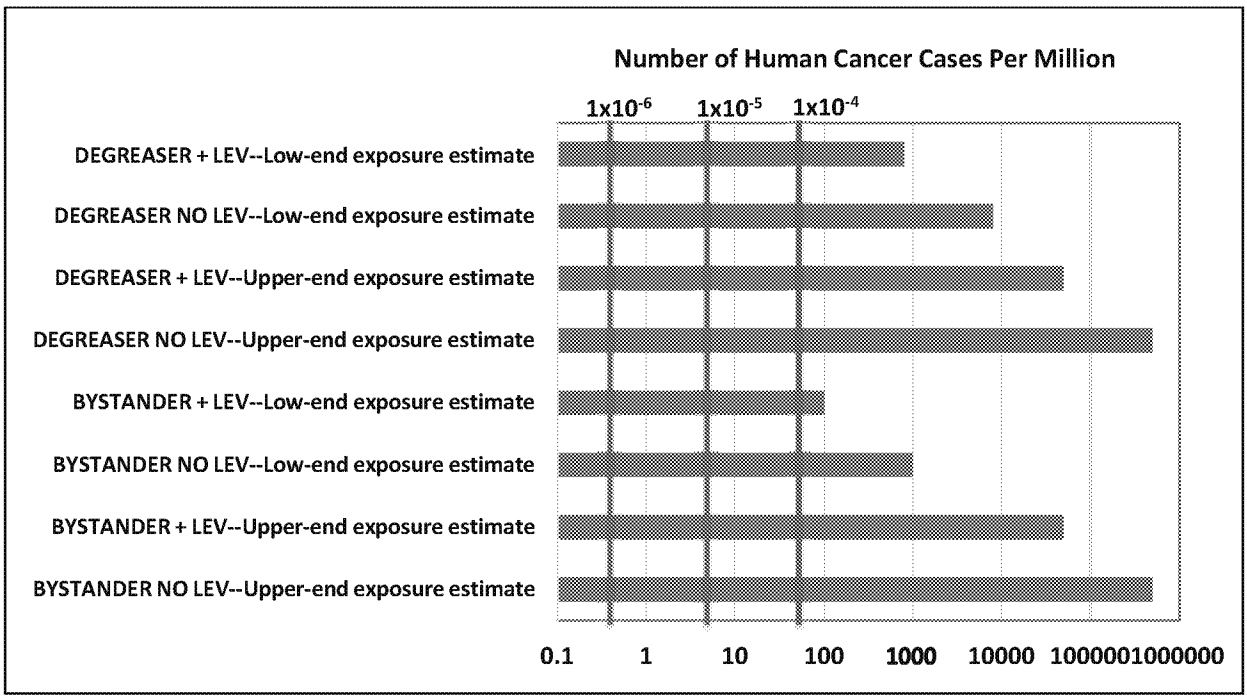
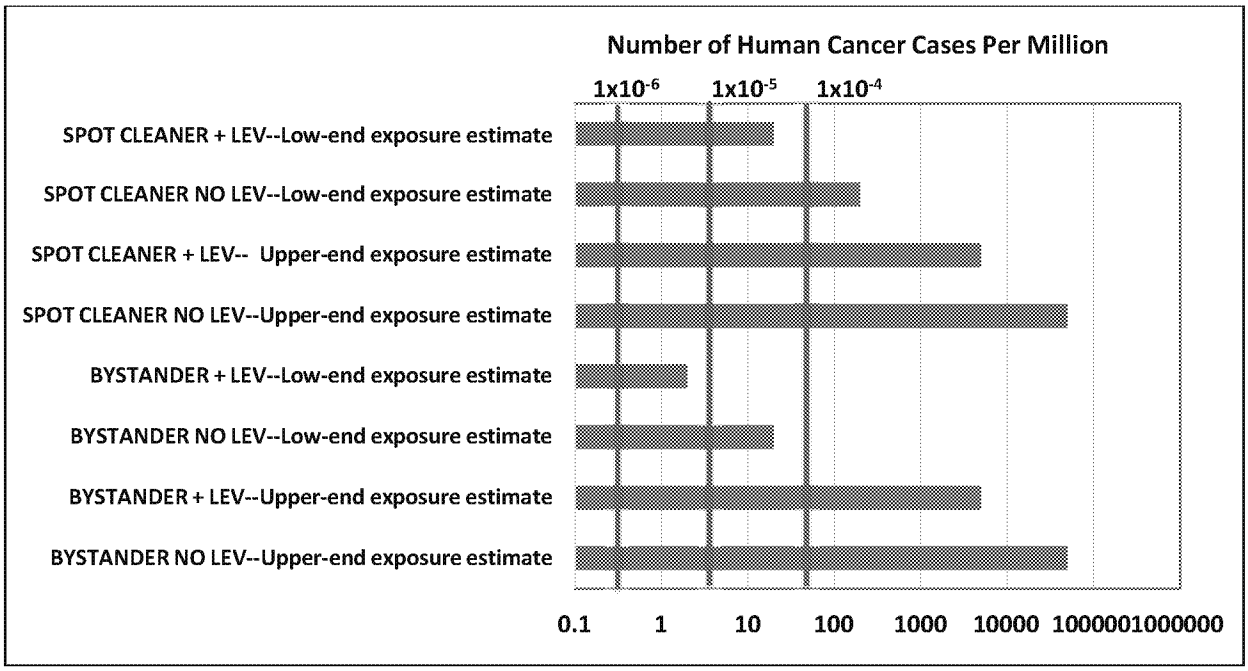


Figure 2-7. Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities



For both degreaser and spot cleaner scenarios, the results indicated that the cancer risk was 10 times greater in scenarios with no local exhaust ventilation that those with room ventilation (+LEV). Moreover, an 8-fold increase in cancer risk was observed in those workers directly using the TCE-containing product when compared to their corresponding bystanders (Figures 2-6 and 2-7). Similarly, a 10-fold increase in cancer risk was reported in those workers using spotting agents containing TCE when compared to their corresponding bystanders indirectly exposed in the dry cleaning facilities (Figure 2-7).

2.7.3.2 Chronic Non-Cancer Risks for Occupational Scenarios

EPA/OPPT estimated chronic non-cancer risks for the occupational use of TCE-containing degreasers and spot cleaners. Since TCE exposure has been associated with a variety of health effects, this assessment estimated human health inhalation chronic risks for developmental toxicity, kidney toxicity, immunotoxicity, reproductive toxicity, neurotoxicity and liver toxicity. As previously discussed, the TCE IRIS assessment developed PODs (i.e., HEC_{50}, HEC_{95} or HEC_{99}) for multiple studies that were suitable for dose-response analysis (Appendix L). EPA/OPPT used the lowest POD (or HEC) in each health effects domain for the non-cancer chronic MOE calculations. The risk estimates for the commercial degreaser and spot cleaner uses are presented in Tables 2-34 and 2-35, respectively[30].

Workers in direct contact with the degreaser products and occupational bystanders reported risks (i.e., MOEs<benchmark MOE) for the following chronic non-cancer effects: developmental toxicity, kidney and immunotoxicity. Also, all of the worker scenarios showed risks for reproductive effects and neurotoxicity. These risks were observed in the worker/bystander scenarios regardless of the type of TCE exposure (typical vs. worst case) and the availability of local exhaust ventilation (with LEV vs. no LEV). Moreover, risks for reproductive effects and neurotoxicity were also found in the degreaser bystander scenarios, but only for worst case exposure conditions and typical exposure circumstances with no local exhaust ventilation. Furthermore, risks were also found for liver effects, but only for those degreaser worker/bystander scenarios representing worst case exposure conditions irrespective of the presence of room ventilation (Table 2-34).

The non-cancer chronic risk profile was slightly different for the TCE use in spot cleaners because the TCE exposure concentrations in dry cleaning facilities were 10 to 60-fold lower than those estimated in degreaser small shops. Risks for developmental effects, kidney toxicity and immunotoxic effects were generally observed for all of the spot cleaning worker/bystander exposure scenarios (i.e., typical vs worst case; typical exposure vs worst case) with two exceptions. Non-risk findings were reported for few spot cleaning worker/bystander scenarios under LEV and typical exposure conditions that used the HEC^{50th} percentile for the MOE calculations. Also, the spot cleaning bystander exposure scenario did not report potential non-

[30] Risk estimates were calculated for all of the studies per health effects domain that the EPA's IRIS program identified as suitable for dose-response analysis. These risk estimates are found in the supplemental Excel file "TCE OPPT Risk Estimates_061814".

cancer chronic risks for the aforementioned health effects domains under LEV and typical exposure conditions (Table 2-35).

Risks for reproductive effects and neurotoxicity were less consistently seen across the board with the exception of the spot cleaning worker/bystander exposure scenarios characterizing typical or worst-case exposure condition under no ventilation system. As for risks for liver effects, most of the spot cleaning scenarios showed no risk concern with the exception of the worker/bystander worst case exposure scenarios with no LEV (Table 2-35).

2.7.4 Human Health Risk Characterization Summary

This risk assessment focused on the occupational and consumer uses of TCE-containing degreasers, spot cleaners and clear protective coating spray in arts/crafts. Specifically, the following exposure scenarios were evaluated: small commercial degreasing operations; spot cleaning in dry cleaning facilities; consumer use of an aerosol degreaser; and the consumer use of a clear protective coating spray in an arts/crafts home setting. The population of interest consisted of workers and consumers with direct (users) or indirect (bystander) exposure to TCE. Only the inhalation route of exposure was considered in this risk assessment.

The occupational and consumer exposure assessments generated the TCE exposure levels required to derive non-cancer and cancer risks. Cancer risks were presented as lifetime risks, meaning the risk of developing cancer as a result of the occupational exposure over a normal lifetime of 70 yrs. Lifetime cancer risks from TCE exposure were compared to target risks ranging from 10^{-6} to 10^{-4}.

Many of the degreaser and spot cleaning exposure scenarios exceeded the target cancer risks of 10^{-6}, 10^{-5} and 10^{-4}. This analysis resulted in higher modeled incidences of cancer in the small commercial degreaser than the users of spot cleaners. Thus, the greatest potential for cancer risk came from the occupational exposures to commercial degreasers. Furthermore, higher cancer risks resulted from direct use of the degreaser or lack of local exhaust ventilation at the workplace.

To characterize the risks of adverse health effects other than cancer, MOEs were used to evaluate non-cancer risks for both acute and chronic exposures using the hazard values published in the TCE IRIS assessment (EPA, 2011e). Hazard values based on developmental toxicity (i.e., fetal cardiac defects; Johnson et al., 2003) were used to estimate acute non-cancer risks for occupational and consumer exposures. On the other hand, the chronic non-cancer risks for the worker scenarios were evaluated with the hazard values associated with health effects following long-term exposure to TCE (i.e., developmental toxicity, kidney toxicity, immunotoxicity, reproductive toxicity, neurotoxicity and liver effects). Note that minimal variability (i.e., ≤ 3-fold) exist among the acute and chronic non-cancer hazard values (i.e., HEC_{50}, HEC_{95} or HEC_{99}) used in this assessment.

Most occupational and residential exposure scenarios reported acute risks based on concerns for developmental effects (i.e., cardiac defects) that may occur following a single exposure to TCE during a critical window of susceptibility. Particularly, the degreaser exposure scenarios showed greater acute risks than those reported for the spot cleaning exposure scenarios.

There is a concern for a range of human health effects other than cancer that may appear after chronic exposures to TCE during the occupational use of TCE-containing degreasers and spot cleaning agents. The greatest concern is for developmental effects (i.e., fetal cardiac defects), followed by kidney effects and then immunotoxicity, with an overall higher chronic risk for the degreaser exposure scenarios. In general, the concerns for these three health effects domains occur regardless of the type of exposure (typical vs worst case) and the availability of room ventilation (LEV vs no LEV), although there are some exceptions, particularly in the spot cleaning bystander exposure scenarios.

Potential chronic risks for reproductive effects and neurotoxicity were also observed for degreaser worker exposure scenarios and most of the degreaser bystander exposure scenarios. However, the risks concerns for these effects were reported for fewer spot cleaning worker/bystander scenarios and generally attributed to exposure conditions without room ventilation.

Concerns for liver effects following chronic exposure to TCE are less prominent than the concerns for other health effects domains as chronic risks for liver toxicity were not reported for the majority of the degreaser and spot cleaning worker/bystander scenarios. The exception was the degreaser worker/bystander exposure worst case scenarios and the spot cleaning worker/bystander worst case scenarios with no LEV.

Table 2-34. Chronic Non-Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops

Health Effect Domain and Study	Lowest HEC (ppm) of each health effects domain	WORKER NON-CANCER MOEs [1]				BYSTANDER NON-CANCER MOEs [1]				Total UF or Benchmark MOE
		With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	
DEVELOPMENTAL TOXICITY (Johnson et al., 2003)	HEC50= 0.012	**0.17**	**0.017**	**0.0025**	**0.0003**	**1.3**	**0.13**	**0.0030**	**0.0003**	10
	HEC95= 0.0051	**0.072**	**0.0072**	**0.0011**	**0.0001**	**0.54**	**0.05**	**0.0013**	**0.0001**	
	HEC99= 0.0037	**0.052**	**0.0052**	**0.0008**	**0.0001**	**0.40**	**0.04**	**0.0009**	**0.0001**	
KIDNEY (NTP, 1998)	HEC50= 0.042	**0.59**	**0.059**	**0.0088**	**0.0009**	**4.4**	**0.4**	**0.01**	**0.001**	10
	HEC95= 0.0085	**0.11**	**0.012**	**0.0018**	**0.0002**	**0.9**	**0.09**	**0.0021**	**0.0002**	
	HEC99= 0.0056	**0.079**	**0.0079**	**0.0012**	**0.0001**	**0.6**	**0.06**	**0.0014**	**0.0001**	
IMMUNOTOXICITY Keil et al., 2009 (Decrease in thymus weight and thymus cellularity)	HEC50= 0.092	**1.3**	**0.1**	**0.019**	**0.0020**	**9.7**	**0.97**	**0.023**	**0.0023**	100
	HEC95= 0.045	**0.6**	**0.06**	**0.0095**	**0.0010**	**4.7**	**0.47**	**0.011**	**0.0011**	
	HEC99= 0.033	**0.5**	**0.05**	**0.0069**	**0.0007**	**3.5**	**0.35**	**0.0082**	**0.0008**	
IMMUNOTOXICITY Keil et al., 2009 (Autoimmunity)	HEC50= 0.092	**1.3**	**0.13**	**0.019**	**0.0020**	**9.7**	**0.97**	**0.022**	**0.0023**	30
	HEC95= 0.045	**0.6**	**0.063**	**0.0095**	**0.0010**	**4.7**	**0.47**	**0.011**	**0.0011**	
	HEC99= 0.033	**0.5**	**0.046**	**0.0069**	**0.0007**	**3.5**	**0.35**	**0.0082**	**0.0008**	
REPRODUCTIVE TOXICITY (Chia et al. 1996)	HEC50= 1.4	**19.7**	**2.0**	**0.3**	**0.03**	147	**15**	**0.35**	**0.034**	30
	HEC95= 0.7	**9.8**	**1.0**	**0.15**	**0.015**	74	**7**	**0.17**	**0.017**	
	HEC99= 0.5	**7.0**	**0.7**	**0.11**	**0.011**	53	**5**	**0.12**	**0.012**	
NEUROTOXICITY (Arito et al., 1994)	HEC50= 13	**183**	**18**	**2.7**	**0.28**	1369	**137**	**3.2**	**0.32**	300
	HEC95= 6.4	**90**	**9**	**1.3**	**0.14**	674	**67**	**1.6**	**0.16**	
	HEC99= 4.8	**67**	**7**	**1.0**	**0.10**	505	**51**	**1.2**	**0.12**	
LIVER (Kjellstrand et al. 1983)	HEC50= 25	351	35	**5.3**	**0.53**	2632	263	**6**	**0.61**	10
	HEC95= 12	168	17	**2.5**	**0.26**	1263	126	**3**	**0.29**	
	HEC99= 9.1	128	13	**1.9**	**0.19**	958	96	**2**	**0.22**	

Notes: (1) MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks. (2) Exposure estimates with/without LEV are found in Table 2-10.

Table 2-35. Chronic Non-Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities

Health Effect Domain and Study	Lowest HEC (ppm) of each health effects domain	WORKER NON-CANCER MOEs [1]				BYSTANDER NON-CANCER MOEs [1]				Total UF or Benchmark MOE
		With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	
DEVELOPMENTAL TOXICITY (Johnson et al., 2003)	HEC50= 0.012	**6.3**	**0.0253**	**0.63**	**0.0027**	72	**0.0253**	**7.2**	**0.0028**	10
	HEC95= 0.0051	**2.7**	**0.0107**	**0.27**	**0.0011**	31	**0.0107**	**3.1**	**0.0012**	
	HEC99= 0.0037	**1.9**	**0.0078**	**0.19**	**0.0008**	22	**0.0078**	**2.2**	**0.0009**	
KIDNEY (NTP, 1998)	HEC50= 0.042	22	**0.088**	**2.2**	**0.0093**	253	**0.0884**	25	**0.0098**	10
	HEC95= 0.0085	**4.5**	**0.018**	**0.45**	**0.0019**	51	**0.0179**	**5.1**	**0.0020**	
	HEC99= 0.0056	**2.9**	**0.012**	**0.29**	**0.0012**	34	**0.0118**	**3.4**	**0.0013**	
IMMUNOTOXICITY Keil et al., 2009 (Decrease in thymus weight and thymus cellularity)	HEC50= 0.092	**48**	**0.194**	**4.8**	**0.020**	554	**0.194**	**55**	**0.022**	100
	HEC95= 0.045	**24**	**0.095**	**2.4**	**0.010**	271	**0.095**	**27**	**0.011**	
	HEC99= 0.033	**17**	**0.069**	**1.7**	**0.007**	199	**0.069**	**20**	**0.008**	
IMMUNOTOXICITY Keil et al., 2009 (Autoimmunity)	HEC50= 0.092	48	**0.194**	**4.8**	**0.020**	554	**0.194**	55	**0.022**	30
	HEC95= 0.045	**24**	**0.095**	**2.4**	**0.010**	271	**0.095**	**27**	**0.011**	
	HEC99= 0.033	**17**	**0.069**	**1.7**	**0.007**	199	**0.069**	**20**	**0.008**	
REPRODUCTIVE TOXICITY (Chia et al. 1996)	HEC50= 1.4	737	**2.9**	74	**0.31**	8423	**2.9**	842	**0.33**	30
	HEC95= 0.7	369	**1.5**	37	**0.16**	4212	**1.5**	421	**0.16**	
	HEC99= 0.5	263	**1.1**	**26**	**0.11**	3008	**1.1**	301	**0.12**	
NEUROTOXICITY (Arito et al., 1994)	HEC50= 13	6844	**27**	684	**2.9**	78214	**27**	7821	**3.0**	300
	HEC95= 6.4	3369	**13**	337	**1.4**	38505	**13**	3851	**1.5**	
	HEC99= 4.8	2527	**10**	**253**	**1.1**	28879	**10**	2888	**1.1**	
LIVER (Kjellstrand et al. 1983)	HEC50= 25	13161	53	1316	**5.5**	150412	53	15041	**5.8**	10
	HEC95= 12	6317	25	632	**2.7**	72198	25	7220	**2.8**	
	HEC99= 9.1	4791	19	479	**2.0**	54750	19	5475	**2.1**	

Notes: (1) MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks. (2) Exposure estimates with/without LEV are found in Table 2-13.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Comments on Scope of the Risk Evaluations for the
First Ten Chemicals under the Toxic Substances Control Act

Submitted via Regulations.gov

Docket Nos.: EPA-HQ-OPPT-2016-0723 (1,4-Dioxane): EPA-HQ-OPPT-2016-0741 (1-Bromopropane); EPA-HQ-OPPT-2016-0736 (Asbestos); No.: EPA-HQ-OPPT-2016-0733 (Carbon Tetrachloride); EPA-HQ-OPPT-2016-0735 (Cyclic Aliphatic Bromide Cluster (Hexabromocyclododecane or HBCD); EPA-HQ-OPPT-2016-0742 (Methylene Chloride); EPA-HQ-OPPT-2016-0743 (N-Methylpyrrolidone (NMP)); EPA-HQ-OPPT-2016-0725 (Pigment Violet 29 (Anthra[2,1,9- def:6,5,10-d'e'f]diisoquinoline- 1,3,8,10(2H,9H)-tetrone)); EPA-HQ-OPPT-2016-0737 (Trichloroethylene (TCE)); EPA-HQ-OPPT-2016-0732 (Tetrachloroethylene (also known as Perchloroethylene)); EPA-HQ-OPPT-2017-0002-0001 ("Meetings: Risk Evaluation Scoping Efforts Under Toxic Substances Control Act for Ten Chemical Substances")

March 15, 2017

Alaska Community Action on Toxics * Alliance of Nurses for Healthy Environments * American Public Health Association - Occupational Health and Safety Section * Azul * BlueGreen Alliance * Brazilian Worker Center * Breast Cancer Prevention Partners * Campaign for Healthier Solutions * CATA – The Farmworkers Support Committee * Center for Biological Diversity * Center for Environmental Health * Citizens' Environmental Coalition * Clean and Healthy New York * Coming Clean * Connecticut Coalition for Environmental Justice * Delaware Concerned Residents for Environmental Justice * Ecology Center * Empire State Consumer Project * Environmental Community Action * Environmental Health Strategy Center * Environmental Justice Leadership Forum on Climate Change * Environmental Justice Health Alliance for Chemical Policy Reform * Environmental Working Group * Farmworker Association of Florida * Glynn Environmental Coalition * Greater Syracuse Council on Occupational Safety and Health * GreenLatinos * Green Science Policy Institute * Headwater LLC * Healthy Building Network * Healthy Schools Network * The Imani Group * International Center for Technology Assessment * Just Transitions Alliance *Labor Council for Latin American Advancement * League of Conservation Voters * League of United Latin American Citizens * Little Village Environmental Justice Organization * Made Safe * National Council for Occupational Safety and Health * National Medical Association * Natural Resources Defense Council * New Jersey State Industrial Union Council * New Mexico Environmental Law Center *New York Lawyers for the Public Interest * Occupational Health Clinical Center * Ocean

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Futures Society * People Concerned about Chemical Safety * Physicians for Social Responsibility * Science and Environmental Health Network * Sheet Metal Occupational Health Institute Trust * Sierra Club * Sugar Law Center for Economic & Social Services * Union of Concerned Scientists * United Support and Memorial for Workplace Fatalities * Voces Verdes * WE ACT for Environmental Justice * West End Revitalization Association * WisCOSH * Women's Voices for the Earth * Worksafe

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The undersigned organizations submit these comments to assist the United States Environmental Protection Agency ("EPA") in identifying the appropriate scope of the risk evaluations to be conducted for 1, 4 dioxane, 1-bromopropane, asbestos, carbon tetrachloride, cyclic aliphatic bromide cluster (hexabromocyclododecane or HBCD), methylene chloride, N-methylpyrrolidone (NMP), pigment Violet 29, trichloroethylene (TCE), and tetrachloroethylene (also known as perchloroethylene. Together, these chemical substances are referred to as the "first 10 TSCA substances."

Our organizations advocate for environmental and human health on behalf of local and environmental justice communities, industrial workers, farmworkers, children, scientists, health care professionals and others.

INTRODUCTION

The amendment of TSCA offers EPA an unprecedented opportunity to protect vulnerable and chemically over-burdened populations around the country – children, workers, the elderly, people living in fenceline communities near industrial sources, and others who may be at greater risk than the general population – from toxic chemicals. But this promise will only be fulfilled if the scope of EPA's risk evaluations takes into account the full range of intended, known, or *reasonably foreseen* ways that people across the country are or will be exposed to the chemical substances under review during the full life-cycle of those chemicals.

These comments are intended to assist EPA by identifying the "reasonably available information" EPA should seek and develop, and from what sources, in order to comply with its legal obligation to broadly construe the terms "conditions of use," "reasonably foreseen" and "potentially exposed and susceptible subpopulations" to ensure that all intended, known or reasonably foreseeable pathways of exposure to the first 10 TSCA substances, throughout the life-cycle of the chemical (including manufacture, processing, distribution, use, storage and disposal) are taken into account in each risk evaluation.[1] In addition, these comments are

[1] While Section 6 of TSCA does not explicitly mention storage of chemicals, other sections of TSCA clarify that EPA is charged with ensuring that the storage of TSCA substances does not pose an unreasonable risk. *See, e.g.*, 15 U.S.C. § 2610 (to administer Title I of TSCA, EPA may inspect any establishment where chemical substances are stored).

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intended to lay out EPA's obligations deriving from its own guidance documents, longstanding Executive Orders, and the statutory language of TSCA, to conduct outreach to targeted communities in the vicinity of where the first 10 TSCA substances are known to be manufactured, processed, stored, disposed or recycled, as well as from workers who are employed in facilities that manufacture, process, store, and dispose or recycle these substances, or their unions or representatives. This outreach is critical to EPA's ability to identify conditions of use and potentially exposed or susceptible subpopulations via reasonably available information (including obtaining information directly from impacted communities and populations) in accordance with the best available science.

A. Pursuant to EPA Policy, the Agency Must Take Potential Environmental Justice Concerns into Account in Determining the Scope of the Risk Evaluations for the First 10 TSCA Substances

The scoping phase for the first 10 TSCA substances presents a critical opportunity for EPA to implement a systematic approach to identifying and reducing environmental and health disparities for minority, low-income, and tribal populations. EPA's EJ 2020 Action Agenda ("EJ 2020"),[2] a copy of which is attached as Exhibit 1, lays out a roadmap for the Agency's work to promote environmental justice. Key promises include a commitment to "expand [the Agency's] work with diverse stakeholders in communities,"[3] including by "routinely analyz[ing], consider[ing] and address[ing] environmental justice issues in all appropriate EPA rulemaking[s] . . . ."[4] Conveniently, the Office of Chemical Safety and Pollution Prevention ("OCSPP") is identified as the program lead in meeting the objective of "ensur[ing] environmental justice is appropriately analyzed, considered and addressed in EPA rules with potential environmental justice concerns, to the extent practicable and supported by relevant information and law."[5]

EJ 2020 commits EPA to meaningful engagement with communities:

> Vibrant stakeholder engagement and partnerships are the backbone of EJ 2020 and essential to achieving meaningful outcomes for overburdened communities. Through early, ongoing and meaningful stakeholder engagement, EPA will catalyze a new level of stakeholder dialogue and collaboration in the course of implementing EJ 2020 and environmental justice practice within our programs and regions. Examples of community engagement in EJ 2020 include community involvement in EPA rulemaking and

[2] EPA, EJ 2020 Action Agenda, Doc. No. EPA-300-B-1-6004 (Oct. 2016), https://www.epa.gov/sites/production/files/2016-05/documents/052216_ej_2020_strategic_plan_final_0.pdf.

[3] *Id.* at ii.

[4] *Id.* at 8.

[5] *Id.* at 13.

permitting processes, community-based participatory research and citizen science, and the development of outcome measures that are meaningful to communities.[6]

In addition, EJ 2020 builds on EPA's "Guidance on Considering Environmental Justice During the Development of Regulatory Actions" and "Technical Guidance for Assessing Environmental Justice in Regulatory Analysis," which provide specific ways that environmental justice principles should be applied to EPA actions. These Guidance documents are attached as Exhibits 2 and 3 hereto. Relevant to risk evaluations, "the Agency has expanded the concept of fair treatment to consider not only the distribution of burdens across all populations, but also the distribution of reductions in risk from EPA actions."[7] The Technical Guidance includes a lengthy section specifically on how to apply EJ principles to human health and risk assessments.[8]

Furthermore, EJ 2020 states that "each EPA program office responsible for writing rules will consider opportunities and develop strategies for achieving involvement of potentially impacted minority populations, low-income populations, and tribes and indigenous peoples as part of the process of developing the rule."[9] While it is not certain that EPA will ever promulgate rules addressing risks from any of the first 10 TSCA chemicals, the risk evaluations that are now underway would form the basis of future risk management rulemaking if any of these chemicals are found to pose an "unreasonable risk." Likewise, Executive Order 12,898, *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations* (Feb. 11, 1994), requires EPA "to the greatest extent practicable and permitted by law . . . [to] make achieving environmental justice part of its mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of its programs, policies, and activities on minority populations and low-income populations."[10] For these reasons, the risk evaluations now underway must take environmental justice concerns into account.

B. TSCA Requires EPA to Consider All of "The Conditions of Use" in Determining the

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[6] *Id.* at 10.

[7] EPA, Technical Guidance for Assessing Environmental Justice in Regulatory Analysis 1 (June 2016), https://www.epa.gov/sites/production/files/2016-06/documents/ejtg_5_6_16_v5.1.pdf

[8] *See id.* at 20.

[9] EJ 2020 at 15.

[10] In the Proposed Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, 82 Fed. Reg. 7562 (Jan. 19, 2017), EPA takes the view that Executive Order 12,898 does not apply to the proposed risk evaluation process rule because the rule "will not affect the level of protection provided to human health or the environment." *Id.* at 7575. We do not agree with this reasoning, but in any event, since the scope of the risk evaluations of the first 10 TSCA substances will plainly affect the level of protection EPA eventually adopts to safeguard health and the environment from these chemicals, if any, Executive Order 12,898 is applicable to the scoping process.

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Proper Scope of Risk Evaluations

Under TSCA, the scope of a risk evaluation must include "the hazards, exposures, *conditions of use*, and the potentially exposed or susceptible subpopulations the Administrator expects to consider."[11] As defined by Congress, the term "conditions of use" means "the circumstances, as determined by the Administrator, under which a chemical substance is *intended, known, or reasonably foreseen* to be manufactured, processed, distributed in commerce, used, or disposed of."[12] These terms, along with other TSCA requirements for conducting a risk evaluation, require that the scope of the risk evaluations for the first 10 TSCA substances include:

- consideration of risk from aggregate exposures;
- consideration of risk arising from "actual" – meaning "known" and "reasonably foreseen" – not only"intended" uses;
- ongoing exposures to chemicals from both current and legacy uses;
- consideration of exposures from substances not regulated under TSCA;
- consideration of uses for which hazard and/or exposure data are limited; and
- consideration of risk from cumulative exposures.
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EPA Is Correct to Reject a Tiered Approach that Considers the Conditions of Use in Isolation

In scoping the first 10 TSCA substances, EPA should consider all intended, known or reasonably foreseen conditions of use in each risk evaluation. The American Chemistry Council ("ACC"), in comments submitted to EPA in August 2016, recommended that the agency take a "tiered approach to risk evaluation." This approach would begin with "a quantitative screening level analysis" of various conditions of use, followed by "robust refined risk evaluations for only those conditions of use where unreasonable risks cannot be ruled out."[13] A central premise of this approach is that EPA should evaluate risk for separate conditions of use, rather than evaluate risk for a chemical substance across all conditions of use. EPA rightfully has proposed to reject a tiered approach in both the prioritization and risk evaluation procedures rules published in January 2017, and it should apply that approach to the risk evaluations for the first 10 TSCA substances.

As EPA lays out in section II(C)(2) of the Preamble to the Proposed Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act ("Proposed Risk Evaluation Process Rule"), TSCA section 6(b)(4)(A) requires EPA to conduct risk evaluations to determine

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[11] 15 U.S.C. § 2605(b)(4)(D) (emphasis added).

[12] *Id.* § 2602(4) (emphasis added).

[13] Am. Chemistry Council, ACC Comments to Inform EPA's Rulemaking on the Conduct of Risk Evaluations under the Lautenberg Chemical Safety Act, EPA-HQ-OPPT-2016-0400-0028 at 6 (Aug.24, 2016), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0400-0028.

ED_004056A_00227265-00005

whether "under *the* conditions of use" a chemical substance presents an unreasonable risk. The term "*the* conditions of use" signifies the full array of conditions of use, not a selection of conditions.[14] In addition, TSCA section 6 requires EPA to evaluate the risks of a chemical substance by evaluating whether "the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, *or . . . any combination of such activities*, presents an unreasonable risk of injury to health or the environment."[15] EPA cannot assess whether the "combination of such activities" poses an unreasonable risk if it excludes some conditions of use from its evaluation. Indeed, conditions of use that do not lead to significant exposure during use may do so during manufacturing, processing, storage, recycling, and disposal. It would undermine the cradle-to-grave TSCA regulatory scheme if EPA could determine that a select "use" of a substance did not present an unreasonable risk divorced from consideration of whether the manufacturing, processing, distribution in commerce, use in other contexts, storage, recycling, and disposal of that substance, in the aggregate, pose an unreasonable risk.

Rejecting the "tiered approach" is critical to protecting communities and workers from the real-world ways in which they are exposed to risk from toxic chemicals. There may be select conditions of use for the first 10 TSCA substances that, in isolation, would not result in an unreasonable risk of injury to health or the environment. However, in the real world, people are exposed to some of these substances from multiple sources and during different phases of the life of the substance. For example, a worker may use a substance on the job, and the same substance may be present in consumer products she uses at home; it may also be present in her family's drinking water. For populations that are exposed to the same substance via multiple pathways, the actual risk posed by the substance would be obscured if EPA's risk evaluation did not cover all conditions of use throughout the life cycle of the substance *in the aggregate*. EPA's scoping documents for the first 10 TSCA substances must explain when and how the Agency intends to assess risks from aggregate exposure.

The Term "The Conditions of Use" Includes Actual – Meaning "Known" and "Reasonably Foreseen" – *Not Only "Intended" Uses*

While manufacturers of chemical products might have preconceived notions of a product's "intended use," in actual practice the use of chemicals and chemical products—and their associated exposures—varies widely in manufacturing, processing, consumer and commercial applications, and disposal. To effectively characterize risks, EPA must account for the variability

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[14] Similarly, in the Preamble to the Proposed Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act, "EPA will make priority designations pursuant to these procedures for a chemical substance, not for a specific condition or conditions of use of a chemical substance." 82 Fed. Reg. 4834 (Jan. 17, 2017). The conditions of use will be "all circumstances under which the Agency determines that the chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." 82 Fed. Reg. at 7578.

[15] 15 U.S.C. § 2605(a)

ED_004056A_00227265-00006

in exposure that results from "actual" (meaning "known" and "reasonably foreseen") as compared to "intended" conditions of use. This follows from EPA's statutory requirement to "take into account, where relevant, the likely duration, intensity, frequency and number of exposures under the conditions of use of the chemical substance."[16]

Actual conditions of use can vary widely for several reasons. These include, but are not limited to the following:

- Highly exposed subgroups: In workplaces where chemicals and chemical products are used, exposures typically occur most intensely among a highly exposed subgroup, rather than uniformly across the population of workers. In a vehicle repair shop, for example, chemical-intensive tasks on brakes, engines, and drive-train components are performed by a subset of workers who experience high levels of exposure to aerosolized degreasing solvents, whereas other workers in the same shop who perform diagnostic or electrical work, for example, experience little or no exposure to these solvents. To effectively characterize the "conditions of use" among workers, EPA must account for the concentration of exposure—and therefore risk—that occurs within highly exposed subgroups as a consequence of actual workplace conditions, rather than relying on an "average" estimated exposure across a population of workers, based on an assumption of "intended" use.

- Safety culture: When workers are under pressure to perform tasks within a specific period of time, they may take short-cuts to maximize productivity. Safety is often an early casualty of short-cuts, including in handling chemicals and chemical products. Safe handling is further undermined when workers are unaware of the risks associated with exposure to chemical hazards; they are untrained in taking normal precautions; they assume chemicals in the workplace are safe to use; they use chemicals in confined and poorly ventilated spaces; and when co-workers, managers and the general workplace culture all actively discount the health risks associated with chemical exposures. To effectively characterize the conditions of actual use among workers, EPA must identify and account for these realities of the work environment and adjust risk estimates accordingly.

- Personal protective equipment ("PPE"): OSHA requires that employers reduce exposures to hazardous chemicals by controlling chemical hazards as close to the source as possible through the use of substitution, ventilation, containment, and worker procedures, before turning to personal protection equipment, such as air purifying respirators (APRs).[17] The

[16] 15 U.S.C. § 2605(b)(4)(F)(iv).

[17] 29 C.F.R. § 1910.134(a)(1).

ED_004056A_00227265-00007

use of APRs can be a useful adjunct to protect workers from occasional, intermittent exposures to hazardous chemicals; as a primary defense, however, the use of APRs is highly problematic. They impose an increased resistance to breathing, they dampen auditory, olfactory and visual sensations, they are cumbersome and uncomfortable to wear, and they isolate the worker from co-workers and the work environment. As a result, respiratory programs can be difficult to implement and enforce among employees. Moreover, they require technical competency: APR filters must be properly selected to ensure that they protect the worker from inhaling the chemical(s) of concern; they must be properly "fit tested" to individual workers to ensure that contaminated air does not "leak" into the respirator around the face seal; and they must be conscientiously worn, properly maintained and regularly replaced. If any one of these elements is missing, the efficacy of an APR program drops substantially. EPA must account for these weaknesses in characterizing exposures in workplaces where employers rely on respiratory protection as a means of preventing workers from hazardous chemicals and chemical products. For the reasons noted above, EPA must substantially discount the efficacy of APRs to appropriately characterize risks in these settings.

- Labeling: While warning labels on products might appeal to some manufacturers as a reasonable means of preventing chemical exposures, in actual practice these warnings can be difficult for workers to interpret and implement. The phrase "Use in a well-ventilated room," for example, has little meaning and will not reduce chemical risks among workers. Likewise, it is very difficult for workers to take protective action based on information presented in a Safety Data Sheet ("SDS"). While the Globally Harmonized System ("GHS") labels for specific chemicals are more illustrative, and they might motivate workers to demand protection from certain chemical exposures, the simple presence of GHS warning labels does not, in actual practice, translate to a reduction in exposures among workers. To effectively characterize the conditions of actual use among workers, EPA must substantially discount the efficacy of warning labels, SDS information, and GHS labeling.

- Enclosures: As a recognized approach under the hierarchy of controls, enclosed industrial processes (sometimes referred to as "closed systems") would be expected to reduce worker chemical exposures, particularly when compared to respiratory protection programs. Enclosed processes, however, do not eliminate the potential for exposure. Enclosures may need to be regularly accessed by workers as part of the manufacturing process; they can emit chemical vapors through cracks and openings; and they need to be periodically maintained. To effectively characterize the conditions of actual use among workers, EPA must take into account these limitations of enclosed industrial processes.

The Term "The Conditions of Use" Includes Both Current and Legacy Uses

By the terms of TSCA, the "intended, known or reasonably foreseen"[18] conditions of use include ongoing exposures to chemicals both from current use, and from legacy uses. The need to consider legacy uses is evident from the fact that "conditions of use" is defined to include circumstances under which a chemical substance is "disposed of."[19] The need to consider legacy uses in risk evaluations also follows from the statutory requirement that EPA "take into account, where relevant, the likely duration, intensity, frequency and number of exposures under the conditions of use of the chemical substance."[20] By requiring EPA to consider the "frequency" and "number" of exposures without limitation, Congress signaled the intent that risk evaluations must consider all ongoing exposures in the aggregate, irrespective of whether the substance is present in the environment due to a continuing use or a legacy use. Asbestos provides a good illustration of this principle. EPA's risk evaluation of asbestos must consider exposures from current uses of asbestos. In addition, it must "take into account" the "frequency" and "number" of exposures, some of which will arise, *inter alia*, when asbestos previously installed in buildings as insulation is disturbed.[21] When previously installed asbestos is removed from buildings, improper handling may result in exposure too.[22] In addition, asbestos is found at 78 National Priority List ("NPL") sites, largely as a result of historic use,[23] and EPA has developed guidance for assessing exposure to asbestos present at Superfund sites.[24] In communities near active NPL and Superfund sites, some exposure may occur due to legacy uses of chemical substances. A risk evaluation must consider these previous uses to capture the "likely duration, intensity, frequency and number of exposures."

"The Conditions of Use" Includes Uses Not Regulated Under TSCA

The requirement to consider all "conditions of use" and the "likely duration, intensity, frequency and number of exposures" requires EPA to take into account uses that are not regulated under

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[18] 15 U.S.C. § 2602(4).

[19] *Id.*.

[20] 15 U.S.C. § 2605(b)(4)(F)(iv).

[21] U.S. Dep't of Health & Human Servs., Agency for Toxic Substances and Disease Registry ("ATSDR"), Toxicological Profile for Asbestos 2-3 (Sept. 2001), https://www.atsdr.cdc.gov/toxprofiles/tp61.pdf.

[22] U.S. Dep't of Health & Human Servs., Nat'l Cancer Inst., *Asbestos Exposure and Cancer Risk* (last updated May 1, 2009), https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/asbestos/asbestos-fact-sheet.

[23] ATSDR has reported asbestos at 78 sites, chrysotile asbestos at 13 sites, and amosite asbestos at 9 sites. It was not clear to what extent these sites overlapped. *See* ATSDR, Summary Data for 2015 Priority List of Hazardous Substances (Feb. 2016), https://www.atsdr.cdc.gov/spl/resources/atsdr_2015_spl_detailed_data_table.pdf.

[24] EPA, Framework for Investigating Asbestos-Contaminated Superfund Sites (Sept. 2008), https://semspub.epa.gov/work/HQ/175329.pdf.

ED_004056A_00227265-00009

TSCA but which contribute to aggregate exposures from the manufacture, processing, distribution, storage, use, or disposal of the substance and which are intended, known or reasonably foreseen. This includes exposures from the presence of the first 10 TSCA chemicals in food, drinking water, personal care products, and other media and articles that cannot be directly regulated under TSCA. For example, while methylene chloride is used as a paint stripper and remover,[25] it is also approved by FDA as a food additive for uses including use as a solvent in the extraction of caffeine from green coffee beans.[26] It is entirely plausible that an individual who uses a methylene chloride-based paint stripper also drinks decaffeinated coffee, and while EPA would only regulate the former use under TSCA, both uses may contribute to exposure and thus contribute to an unreasonable risk of injury to health. A risk evaluation that does not account for all known uses of methylene chloride throughout the full life cycle of the substance will not adequately assess exposure or characterize risk.

EPA Must Include Consideration of All the Conditions of Use Even If Hazard and/or Exposure Data Are Limited

EPA must consider all "intended, known, or reasonably foreseen" conditions of use when conducting a risk evaluation for a chemical substance, but it is likely that the available data on hazard or exposure will vary among the conditions of use. EPA cannot exclude a known condition of use because of data gaps in characterizing the risk posed by that use. In other words, EPA cannot interpret the absence of data as an absence of risk and exclude it from consideration in its risk evaluation. Rather, when EPA identifies a data gap with respect to a condition of use, the agency should move immediately to fill the data gap using the authorities available to it. If EPA believes the data gap cannot be filled within statutory timeframes, EPA must either use science-based defaults, as recommended by the National Research Council ("NRC"),[27] or, at a minimum, indicate that the risks posed by the uses in question are currently unknown.

EPA Must Conduct a Cumulative Risk Assessment When Consistent with Best Available Science Principles

When the best available science indicates that the risk of injury to health or the environment posed by exposure to a chemical substance may vary with exposure to multiple agents or stressors, EPA must evaluate cumulative risk by conducting a *cumulative risk assessment*, defined by the agency as "an analysis, characterization, and possible quantification of the

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[25] ATSDR, Toxicological Profile for Methylene Chloride 1-2 (Sept. 2000), https://www.atsdr.cdc.gov/toxprofiles/tp14.pdf.

[26] 21 C.F.R. § 173.255(c).

[27] The use of science-based defaults is discussed in chapter 6 of *Science and Decisions*. See NRC, *Science and Decisions: Advancing Risk Assessment* (2009).

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combined risks to health and the environment from multiple agents or stressors."[28] A risk evaluation that fails to assess cumulative risk in spite of such evidence would be inconsistent with the best available science, in violation of TSCA section 26(h), and may underestimate risk. A risk determination based on an underestimation of risk in turn may result in risk management decisions that fail to provide adequate protection for public health or the environment.

EPA itself has recognized that risk may depend on multiple agents or stressors, and it has used cumulative risk assessment to evaluate such risk. In *Framework for Cumulative Risk Assessment* (2003), EPA states, "Assessing cumulative risk through complex exposures is one of the Agency's high priorities…and it is germane and of great interest to all program and regional offices."[29] EPA already has conducted cumulative risk assessments for five classes of pesticides grouped by common mechanism: organophosphates, N-methyl carbamates, triazines, chloroacetanilides, and pyrethrins/pyrethroids.[30]

The National Academies likewise have recognized the importance of cumulative risk assessments and have encouraged EPA to broaden the scopes of its risk assessments. *Pesticides in the Diets of Infants and Children* (1993) paved the way for enactment of the Food Quality Protection Act and its requirement that EPA assess cumulative risks posed by pesticides that share a common mechanism.[31] In *Phthalates and Cumulative Risk Assessment* (2008), the National Academies urged the agency to assess risks posed not just by exposure to a class of chemicals that share a common *mechanism* (*e.g.*, organophosphates) but by exposure to all chemicals that share a common *effect*—in that case, not just phthalates but all anti-androgenic chemicals.[32] *Science and Decisions* (2009) urges an even broader scope that accounts for "simultaneous exposure to multiple chemical and nonchemical stressors and other factors that could influence vulnerability," such as psychosocial stress.[33] It is thus clear that, in some instances, the best available science will requirethat EPA conduct a cumulative risk assessment that includes not just a single chemical substance but multiple chemical substances and other agents.

C. "Reasonably Foreseen" Conditions of Use Encompasses a Broad Range of Exposure

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[28] EPA, Framework for Cumulative Risk Assessment, Doc. No. EPA/630/P-02/001F at 6 (May 2003), https://www.epa.gov/sites/production/files/2014-11/documents/frmwrk_cum_risk_assmnt.pdf.

[29] *Id.* at xi.

[30] EPA, Cumulative Assessment of Risk from Pesticides (last updated May 19, 2016), https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides.

[31] NRC, *Pesticides in the Diets of Infants and Children* (1993).

[32] NRC, *Phthalates and Cumulative Risk Assessment: The Task Ahead* 9 (2008).

[33] NRC, *Science and Decisions: Advancing Risk Assessment* 213-14 (2009).

ED_004056A_00227265-00011

Pathways

The conditions of use that EPA must evaluate include "intended, known, or reasonably foreseen" uses. This expansive language requires EPA to evaluate a broad range of uses, including those that may not be intended, but that are nonetheless either known or reasonably foreseen. Congress's use of the alternative "or reasonably foreseen" makes it clear that "the conditions of use" go beyond intended or known uses.

"Reasonable foreseeability" is a core legal concept with a widely understood meaning across many fields of law.[34] In a range of contexts, courts have recognized that "reasonably foreseeable" uses include reasonably foreseeable misuses, accidents, or even criminal uses.[35] *See, e.g.*, *Suzik v. Sea-Land Corp.*, 89 F.3d 345, 350 (7th Cir. 1996) ("The law provides that it is reasonable for defendants to foresee some, but not all, accidents arising from their conduct.") In the context of toxic substances and pollution, leaks, spills, unintentional consumption and exposure through equipment failure, poorly designed workplace exposure protections, or worker error have been found in some circumstances to be reasonably foreseeable. For example:

- EPA and regulated industries recognize that inadvertent releases of hazardous air pollutants occur and are inevitable.[36]
- The Clean Water Act[37] requires preparation of a Spill Prevention Control and Countermeasures Plan by facilities that "could reasonably be expected to" discharge oil into navigable waters, implicitly acknowledging that such discharges are common

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[34] In general, an effect is reasonably foreseeable if it is so "likely to occur that a person of ordinary prudence would take it into account in reaching a decision." *Mid States Coal. for Progress v. Surface Transp. Bd.*, 345 F.3d 520, 549 (8th Cir. 2003) (internal quotation and citation omitted).

[35] The U.S. Supreme Court has held that criminal acts may be "reasonably foreseen." "While 'reasonable foreseeability of harm is an essential ingredient of Federal Employers' Liability Act negligence,' we have held that the fact that 'the foreseeable danger was from intentional or criminal misconduct is irrelevant; respondent nonetheless had a duty to make reasonable provision against it.'" *Harrison v. Mo. Pac. R. Co.*, 372 U.S. 248, 249 (1963) (internal citations omitted).

[36] *See, e.g. United States Sugar Corp. v. Envtl. Prot. Agency*, 830 F.3d 579, 606 (D.C. Cir. 2016), *on reh'g en banc in part*, No. 11-1108, 2016 WL 7427434 (D.C. Cir. Dec. 23, 2016), and *on reh'g en banc*, No. 11-1108, 2016 WL 7427453 (D.C. Cir. Dec. 23, 2016) ("Both [EPA and industry petitioners] agree that malfunctions are inevitable in the operation of area and major boilers. According to the EPA, "even equipment that is properly designed and maintained can sometimes fail and . . . such failure can sometimes cause an exceedance of the relevant emission standard.""). Indeed, the regulated industries have challenged EPA for failing to incorporate consideration of *anticipated malfunctions* resulting in releases of toxics into regulations. *Id.*

[37] 33 U.S.C. § 1321(j)(1); 40 C.F.R. § 112.3(a)(1) ("If [an onshore or offshore facility] becomes operational after November 10, 2011, and *could reasonably be expected to have a discharge* as described in § 112.1(b), you must prepare and implement a Plan before you begin operations.").

ED_004056A_00227265-00012

enough to necessitate this requirement.[38]

- A court found that it was "reasonably foreseeable" that farmers would tank-mix insecticide with fungicide, although this practice harms crops, because "the economics and utility of tank mixing make it almost inevitable that such mixing will occur"; and tank mixing is "common practice as it allows the farmer to address several problems with one spray application."[39]

The interpretation and implementation of the National Environmental Policy Act ("NEPA") shows that, in the realm of environmental law, "reasonable foreseeability" includes accidental releases. NEPA requires federal agencies to prepare an environmental impact statement ("EIS") for any proposed major federal action "significantly affecting the quality of the human environment."[40] An EIS must include an evaluation of the proposed action's "[i]ndirect effects, which are caused by the action and are later in time or farther removed in distance, but are still *reasonably foreseeable*."[41] Failure to include leaks, accidents and other unintended consequences of the proposed action -- when they are reasonably foreseeable -- is a basis for invalidating an EIS.[42] For this reason, EISs routinely include analysis of "reasonably foreseeable accidents."[43] Indeed, several federal agencies have issued guidance for preparation of EISs. For example, "[a]n important theme of the [Department of Energy's] guidance [for the preparation of EISs] is that the EIS's consideration of human health effects should involve 'realistic scenarios,' 'realistic exposure conditions,' and 'reasonably foreseeable accidents.'"[44] An EIS must comprehensively

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[38] *See, e.g., Pepperell Associates v. Envtl. Prot. Agency,* 246 F.3d 15 (1st Cir. 2001) (affirming EAB determination that "it was reasonably foreseeable" that textile mill would discharge oil into navigable waters).

[39] *Indian Brand Farms, Inc. v. Novartis Crop Prot., Inc.*, 617 F.3d, 207, 225-26 (3rd Cir. 2010).

[40] 42 U.S.C. § 4332(1)(C)(i).

[41] 40 C.F.R. § 1508.8(b) (emphasis added); *see Brady Campaign to Prevent Gun Violence v. Salazar*, 612 F. Supp. 2d 1, 21–22 (D.D.C. 2009) (finding that NEPA required the agency to analyze the foreseeable consequences that would occur as a result of the agency action).

[42] *See N.Y. v. Nuclear Regulatory Comm'n*, 681 F.3d 471, 479 (D.C. Cir. 2012) (finding that the Nuclear Regulatory Commission's NEPA analysis was "not supported by substantial evidence on the record because the Commission failed to properly examine the risk of leaks in a forward-looking fashion and failed to examine the potential consequences of pool fires.").

[43] *See, e.g., Lee v. U.S. Air Force*, 354 F.3d 1229, 1245 (10th Cir. 2004) (U.S. Air Force's EIS acknowledged that "fire and environmental contamination" may result from a crash of a plane near its base, described its methodology for calculating this risk, and described the results of these calculations.); *Spiller v. Walker*, No. A-98-CA-255-SS, 2002 WL 1609722, at *14 (W.D. Tex. July 19, 2002), *aff'd sub nom. Spiller v. White*, 352 F.3d 235 (5th Cir. 2003)(EPA's EIS for a sewage residuals landfill analyzed the impact of potential leaks on drinking water).

[44] NRC, *Evaluation of the Health and Safety Risks of the New USAMRIID High Containment Facilities at Fort Detrick, Maryland* (2010),

ED_004056A_00227265-00013

evaluate impacts to the human environment so that decisionmakers have access to all of the information that they need in order to make a decision about how to proceed with a potential project.[45] Similarly, TSCA risk evaluations must provide comprehensive information to support EPA's risk determination. Both require in-depth analysis of reasonably foreseeable future conditions in order to provide meaningful information to support agency decisionmaking.

The reading of "reasonably foreseen" to include inadvertent uses is further confirmed by other language in the amended TSCA. The statute requires that the process for prioritizing risk evaluations "shall include a consideration of the hazard and exposure potential of a chemical substance or a category of chemical substances (including consideration of persistence and bioaccumulation, potentially exposed or susceptible subpopulations ***and storage near significant sources of drinking water***)."[46] The mandate that EPA consider whether a substance is stored near drinking water reflects congressional intent that the potential for inadvertent leaks or spills leading to drinking water contamination is relevant to EPA's section 6 analyses. This provides additional confirmation that the conditions of use that Congress intended the Agency to include in risk evaluations encompass accidents and misuses.

Past experience and known industry practices are often the key to foreseeability. *See, e.g., G & K Dairy v. Princeton Elec. Plant Bd.*, 781 F. Supp. 485, 491 (W.D. Ky. 1991) ("When deciding whether the defendant could have reasonably foreseen or anticipated that stray voltage would injure the plaintiffs' dairy herd, the Court must consider the defendant's past experience and the practice of others in similar circumstances."). Releases of substances that are acknowledged or anticipated by industry or EPA are "known" or "reasonably foreseen" conditions of use, even if they are not "intended." For example, it is well known that several of the first 10 TSCA substances– TCE,[47] tetrachloroethylene,[48] 1,4-dioxane[49] – are present in many drinking water

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https://www.ncbi.nlm.nih.gov/books/NBK220309/pdf/Bookshelf_NBK220309.pdf, referencing U.S. Dep't of Energy, *NEPA: Recommendations for the Preparation of Environmental Assessments and Environmental Impact Statements* (2d ed. Dec. 2004), https://energy.gov/sites/prod/files/nepapub/nepa_documents/RedDont/G-DOE-greenbook.pdf.

[45] "[NEPA] first...places upon an agency the obligation to consider every significant aspect of the environmental impact of a proposed action. Second, it ensures that the agency will inform the public that it has indeed considered environmental concerns in its decisionmaking process." *Forest Guardians v. U.S. Fish & Wildlife Serv.*, 611 F.3d 692, 711 (10th Cir. 2010) (quoting *Balt. Gas & Elec. Co. v. Natural Res. Def. Council, Inc.*, 462 U.S. 87, 97 (1983)) (internal quotation marks omitted); *see also New Mexico ex rel. Richardson v. Bureau of Land Mgmt.*, 565 F.3d 683, 703 (10th Cir. 2009) ("By focusing both agency and public attention on the environmental effects of proposed actions, NEPA facilitates informed decisionmaking by agencies and allows the political process to check those decisions.").

[46] 15 U.S.C. § 2605(b)(1)(A)(emphasis added).

[47] *See, e.g., 20 Year Legal Battle in Tucson, Arizona,* Baron & Budd (last visited Mar. 15, 2017), https://baronandbudd.com/environment/water-contamination/tce-tucson-arizona/; World Health Org., Trichloroethene in Drinking-water, Doc. No. WHO/SDE/WSH/05.08/22 at 4 (2005), http://www.who.int/water_sanitation_health/dwq/chemicals/trichloroethenemay05.pdf; Linda Collins,

ED_004056A_00227265-00014

systems. While we presume this contamination was not intended, given the extent to which it has happened, EPA must consider it to be "reasonably foreseen" that these chemicals, either by their nature or by their manner of use, or both, have a propensity to leach into groundwater.

Because certain misuses are reasonably foreseeable, EPA must define conditions of use for its scoping of the first ten TSCA substances that include all known or anticipated exposure pathways. These include, without limitation: known or reasonably foreseeable leaks or spills in the vicinity of manufacturing, processing, and disposal sites; use of the chemical without effective use of safeguards such as ventilation or personal protective equipment; the presence of a chemical in a product or waste stream as an impurity or byproduct; state or federally permitted releases into air or water; releases from Superfund sites; drinking water groundwater contamination; and exposure through fish consumption by subsistence fishers for chemicals that are bio-accumulative.

D. EPA Must Actively Seek "Reasonably Available Information" from Stakeholders in Accordance with Best Available Science Principles

TSCA section 26(k) requires that "[i]n carrying out sections 4, 5, and 6, the Administrator shall take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is *reasonably available to the*

Enon water committee reveals test results, Fairborn Daily Herald, Feb. 28, 2017, http://fairborndailyherald.com/news/15290/enon-water-committee-reveals-test-results; Emily C. Dooley, *State to launch study of Bethpage groundwater plumes*, Newsday, Feb. 17, 2017, http://www.newsday.com/long-island/nassau/state-to-launch-new-study-of-bethpage-groundwater-plume-1.13140648.

[48] *See, e.g.*, World Health Org., Tetrachloroethene in Drinking-water, Doc. No. WHO/SDE/WSH/03.04/23 (2003), http://www.who.int/water_sanitation_health/dwq/chemicals/tetrachloroethene.pdf; *State officials testify for safe drinking water*, Register Citizen, Feb. 27, 2017, http://www.registercitizen.com/article/RC/20170227/news/170229778.

[49] *See, e.g.*, Minn. Dep't of Health, *1, 4-Dioxane in Drinking Water* (Jan. 2015), http://www.health.state.mn.us/divs/eh/risk/guidance/dwec/dioxaneinfo.pdf; N.C. Dep't of Envtl. Quality, 1,4-Dioxane in the Cape Fear River Basin of North Carolina: An Initial Screening and Source Identification Study (2016), https://ncdenr.s3.amazonaws.com/s3fs-public/Water%20Quality/Environmental%20Sciences/ECO/DioxaneReport_Yr1Final-20160127.pdf; *Possible carcinogen 1,4-dioxane found in LI water spurs push for stronger standards*, News 12/Newsday, Jan 9, 2017, http://longisland.news12.com/news/news-12-newsday-report-probable-carcinogen-1-4-dioxane-found-in-li-water-spurs-push-for-stronger-st-1.12903291; Elizabeth Shogren, *Toxic Chemical Dioxane Detected In More Water Supplies*, Nat'l Pub. Radio, Mar. 16, 2014, http://www.npr.org/2014/03/26/294639904/toxic-chemical-1-4-dioxane-detected-in-more-drinking-water-supplies; Water Research Found., 1,4-Dioxane White Paper (2014), http://www.waterrf.org/resources/StateOfTheScienceReports/1,4-dioxane.pdf.

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Administrator."[50] In addition, section 6(b)(4)(F)(i) requires EPA to "integrate and assess *available information* on hazards and exposures for the conditions of use" of the chemicals it is evaluating.[51] To comply with these mandates to use "available information," EPA is obligated to *seek out* information rather than simply open a docket on Regulations.gov and hope that the public will submit relevant information.[52] EPA must gather the reasonably available information for each of the first 10 TSCA substances that will enable it to conduct a scoping analysis that identifies specific exposures and risks to workers, occupational bystanders, fenceline community residents, consumers and any others who are exposed to these substances.

The Proposed Risk Evaluation Process Rule defines "reasonably available information" as "existing information that EPA possesses *or can reasonably obtain and synthesize* for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation."[53] This language confirms EPA's obligation to affirmatively obtain information. It also accords with the way that courts have interpreted what kinds of information are "reasonably available" in other contexts.[54]

From a practical standpoint, affirmatively seeking information about conditions of use and susceptible subpopulations during the scoping process of the first 10 TSCA substances is critical to conducting meaningful risk assessments. This is especially true because EPA did not have the benefit of developing information about these first 10 TSCA substances during a lengthy prioritization process. TSCA requires that the scoping process take no more than six months and that the scope must "include the hazards, exposures, conditions of use, and the potentially

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[50] 15 U.S.C. § 2625(k).

[51] *Id.* § 2605(b)(4)(F)(i).

[52] It is also important to bear in mind that "[i]nformation does not have to be perfect or infallible for the agency to be required to use it . . . ." *See Natural Res. Def. Council v. Kempthorne*, 506 F.Supp.2d 322, 373 (E.D.Cal. 2007); *see also Conner v. Burford*, 848 F.2d 1441, 1454 (9th Cir. 1988) (fact that information is "inexact" is not an excuse for failure to conduct comprehensive biological opinion).

[53] Proposed 40 C.F.R. § 702.33 (emphasis added).

[54] For example, under the Endangered Species Act ("ESA"), federal agencies must use the "best scientific and commercial data available" to insure that any action authorized, funded, or carried out by that agency is "not likely to jeopardize the continued existence of any endangered species or threatened species or result in the destruction or adverse modification of habitat of such species." 16 U.S.C. § 1536(a)(2). EPA's obligation to use "reasonably available information" coupled with the duty to use "best available science" is comparable to the statutory requirement under the ESA. Under the ESA provision, agencies cannot passively rely on readily available information. Rather, they may have to take affirmative steps to gather the information, such as by developing projections and conducting real time simulations. *See. e.g.*, *Conner v. Burford*, 848 F.2d 1441, 1454 (9th Cir. 1988) (ESA may require making projections, based on *potential* locations and levels oil and gas activity, of the impact of production on protected species), citing *Roosevelt Campobello Int'l Park Comm'n v. EPA*, 684 F.2d 1041, 1052-55 (1st Cir. 1982).

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exposed or susceptible subpopulations the Administer expects to consider[.]"[55] If EPA fails to conduct outreach to impacted communities and workers, and declines to review additional subpopulations and conditions of use after scoping has been completed, [56] then the Agency will not have availed itself of reasonably available information as required by the statute. TSCA requires EPA to find out how these chemicals are manufactured, processed, distributed, used, and disposed of *in the real world* if that information is "reasonably available."

In particular, EPA must affirmatively seek "reasonably available information" from: other governmental entities; manufacturers, processors, distributors, storage and disposal facilities and recyclers; and directly affected communities and workers. We amplify on each of these below.

> 1) EPA must obtain information from manufacturers, processors, storage facilities, recyclers, and other handlers of the first 10 TSCA substances.

Industries that work with, manufacture, process, distribute, store, transport, dispose, and recycle the first 10 TSCA substances undoubtedly have extensive information about the conditions of use of these substances. Information that EPA can obtain for the asking is information that is "reasonably available." At a minimum, EPA must affirmatively ask all industry stakeholders of which it is aware (via databases such as the CDR and the TRI, submissions during the public comment period, and all other sources) to produce all information in their possession about about environmental releases (including leaks, spills, discharges, and emissions), misuses, and accidents involving these substances, including an estimate of the amount and the frequency of releases, misuses, and accidents.[57]

In addition, to comport with the requirement that risk evaluations be based on "reasonably available information," EPA should also ask these industry stakeholders for additional information that would shed light on the real ways in which these chemicals are used. Specifically, to determine the "conditions of use," EPA should ask industry stakeholders: how the chemical is stored and in what volumes; how the chemical is transported to and from manufacturing and processing sites; how transport containers are cleaned and stored; the frequency of cleaning; and how much of the chemical is released with each cleaning. Operators

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[55] 15 U.S.C. § 2605(b)(4)(D).

[56] While the scoping process for the first 10 TSCA substances is not governed by the proposed risk evaluation rule, if EPA intends to take the approach articulated in that rule that conditions of use must be "locked down" during the scoping process, then outreach during scoping to identify all conditions of use becomes all the more critical. Proposed 40 C.F.R. § 702.39.

[57] Some of this information may be available through the Toxic Release Inventory, but not all of the first 10 TSCA substances are on the TRI, and 1-bromopropane and HBCD were only added within the last year. Therefore, release data will not be available in time for scoping and should be requested directly from industry handlers.

ED_004056A_00227265-00017

of manufacturing and waste facility sites handling the first 10 TSCA substances should be asked for their NPDES permit numbers so EPA can identify permitted discharges, review discharge reports, and ascertain if there have been NPDES permit violations. Similarly, EPA should ask these same industry actors to provide their Clean Air Act permit numbers, information about their control technologies, and the details of their Leak Detection & Repair programs.

If the information EPA requests from industry actors is not provided promptly, the Agency should use its TSCA section 11(c) subpoena authority to obtain it.[58] Information that can be obtained by subpoena is "reasonably available information."

2) EPA must seek information about the first 10 TSCA substances from federal, state and local government agencies.

Government agencies often have critical information on how substances impact particular subpopulations or their particular conditions of use. EPA must therefore affirmatively request that federal, state and local governmental bodies provide information about the first 10 TSCA substances during the scoping phase. Requests should include, but are not limited to:

- relevant data[59] from the Centers for Disease Control ("CDC") pertaining to toxicity of and exposures to these chemicals and disease trends among people with high exposures;

- information from state and local health departments about releases and exposures to these chemicals, and disease trends in communities near manufacturing, processing, storage, recycling and disposal;

- information from state and local labor departments about releases and exposures to these chemicals, accidents at sites where the chemicals are manufactured, processed, recycled and disposed of; and disease trends among workers at such sites;

- information from State Emergency Response Commissions ("SERCs") and Local

[58] *See* 15 U.S.C. § 2610(c) ("In carrying out this chapter, the Administrator may by subpoena require . . . the production of reports, papers, documents, answers to questions, and other information that the Administrator deems necessary."); *U.S. E.P.A. v. Alyeska Pipeline Serv. Co.*, 836 F.2d 443, 448 (9th Cir. 1988) (acknowledging EPA's broad discretion to issue subpoenas under TSCA).

[59] As the proposed definition of "reasonably available information" suggests, EPA can and must not only request information, but synthesize and analyze it where necessary to determine conditions of use and susceptible subpopulations. This should include, where appropriate, EPA analyses of raw data gathered by outside sources.

ED_004056A_00227265-00018

Emergency Planning Committees ("LEPCs") established pursuant to the Emergency Planning and Community Right to Know Act[60] about reported accidents and releases involving these chemicals.

- information from state and local environmental agencies about permit violations and releases of these chemicals into the environment including into drinking water.

- site-specific enforcement information from OSHA and NIOSH and medical surveillance data for asbestos and methylene chloride.

- information from the Agency for Toxic Substances and Disease Registry ("ATSDR"), particularly the Petition Assessment Branch and the Division of Health Assessment and Consultation.

3) EPA must seek information directly from communities.

EPA must actively seek input from exposed communities regarding the first 10 TSCA substances because this information is "reasonably available" and directly relevant to understanding the conditions of use of these substances. In addition, outreach to affected communities is consistent with the "best available science" and TSCA section 26 requires that EPA use "best available science" in conducting its risk evaluations.[61]

a. Seeking Community Input Is Consistent with Recommendations by Scientific Authorities

Seeking community input on the scope of EPA's risk evaluations for the first 10 TSCA substances is consistent with the recommendations of NRC. In *Science and Decisions*, NRC's Committee on Improving Risk Analysis Approaches Used by the U.S. EPA stressed the importance of involvement by stakeholders, including community groups: "Without [stakeholder] involvement, the committee sees no way to ensure that the decision process will be

[60] 42 U.S.C. § 11001 *et seq.*

[61] TSCA section 26(h) requires that, "to the extent that the Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science…." A risk determination, *i.e.*, a determination that a chemical substance does, or does not, pose an unreasonable risk of injury to health or the environment, is a decision based in part on a risk evaluation. A risk evaluation, in turn, is based largely on science, *e.g.*, toxicological and/or epidemiological studies of hazard, or studies of exposure. EPA must ensure that risk evaluations are consistent with the "best available science."

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satisfactory; indeed, without such involvement, it is inevitably deficient."[62] NRC emphasized that stakeholder involvement required more than public comment periods, calling these "obviously important, but…insufficient."[63] Rather, "stakeholder involvement…should include substantive involvement in the assessment process," including "explicit attempts to build capacity to ensure that all stakeholders have an equal opportunity to participate substantively in collaborative problem-solving."[64] To comport with "best available science" standards, EPA must reach out to communities to seek their input, rather than simply hope that communities will submit comments to the agency.

b. Seeking Community Input Is Essential When Conducting Cumulative Risk Assessments

As discussed above, when the risk of injury from exposure to a chemical substance may vary with exposure to multiple agents or stressors, EPA must evaluate cumulative risk by conducting a *cumulative risk assessment*. Conducting a cumulative risk assessment for one of the first 10 TSCA chemicals would require EPA to identify exposures to agents or stressors that may modify the risk posed by the chemical. These exposures may depend upon factors that only affected communities may know. For example, communities near facilities that emit the chemical may know what consumer products that also contain the chemical are used by members of the community, and how the products are used. The actual use of consumer products may vary from the directions for use on the product label. Separately, communities near facilities that emit the chemical can help EPA determine activity patterns relevant to exposure, *e.g.*, children may play near facilities due to the presence of a playground by the facility. EPA cannot conduct a cumulative risk assessment, as the best available science standard would require, without seeking community input. If the best available science suggests that the risk of injury posed by exposure may vary with exposure to other agents or stressors for one or more of the first 10 TSCA substances, community input will be critical to identifying other agents or stressors that should be included in a cumulative risk assessment.

E. EPA Should Use Reasonably Available Information to Identify the Disproportionately Impacted Subpopulations

As noted above, TSCA requires that the scope of a risk evaluation include "the potentially exposed or susceptible subpopulations the Administrator expects to consider." ACC, in its August 2016 comments, recommended that EPA "describe the process it will use to identify subpopulations and how it will make a determination that the subpopulation is relevant to the

[62] NRC, *Science and Decisions* 250 (2009).

[63] *Id.* at 250-51.

[64] *Id.* at 234-35.

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risk evaluation."[65] While it is important that EPA follow a rigorous process to identify relevant subpopulations, this argument misses the point. It would be inappropriate to define in advance which subpopulations will be considered during risk evaluations. Congress purposely left this definition broad and inclusive by specifying that the term "potentially exposed or susceptible subpopulation" means "a group of individuals . . . who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, *such as* infants, children, pregnant people, workers, or the elderly."[66] Congress could have limited the term, but rather left it up to EPA to decide on a substance by substance basis which populations have "greater susceptibility or greater exposure" and thus must be considered specially in the risk evaluation.

The explicit reference to pregnant people, infants and children in TSCA emphasizes EPA's obligation to consider these groups in the scoping of the first 10 TSCA substances. The need to consider the special vulnerability of fetuses and children to chemicals is underscored by Executive Order 13,045, *Protection of Children From Environmental Health Risks and Safety Risks* (April 21, 1997). Executive Order 13,045 recognizes that "children may suffer disproportionately from environmental health risks and safety risks,"[67] and therefore requires all federal agencies to "make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children; and...ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks."[68] With respect to the first 10 TSCA substances in particular, EPA must consider exposure pathways at day care facilities and schools, many of which are housed in older buildings.[69] Children have little control over their environment, and may be exposed to

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[65] American Chemistry Council, ACC Comments to Inform EPA's Rulemaking on the Conduct of Risk Evaluations under the Lautenberg Chemical Safety Act, EPA-HQ-OPPT-2016-0400-0028 at 10 (Aug.24, 2016), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0400-0028.

[66] 15 U.S.C. § 2602(12) (emphasis added).

[67] Exec. Order No. 13,045, 62 Fed. Reg. 19,885, 19,885 (Apr. 21, 1997).

[68] *Id.*

[69] Incidents of asbestos exposure in schools abound: *see, e.g.,* David Abel, *Schools fail to keep track of asbestos*, Boston Globe, Dec. 6, 2015, https://www.bostonglobe.com/metro/2015/12/05/schools-massachusetts-failing-monitor-asbestos-state-and-federal-officials-say/zyehlz8G01pI9lf7sI3meK/story.html; Tyler Silvy, *Greeley-Evans School District 6 in the Midst of Huge Asbestos Removal Project*, Greeley Tribune, Aug. 1, 2015 http://www.greeleytribune.com/news/17052947-113/greeleyevans-school-district-6-in-the-midst-of#; Michael Dinan, *Consultants Detail Asbestos, Lead Paint, PCB Levels at Saxe Middle School*, New Canaanite, Feb. 8, 2015, http://newcanaanite.com/consultants-detail-asbestos-leadpaint-pcb-levels-at-saxe-middle-school-22167; Andrew Davis, *Asbestos Found Inside Port Wentworth Elementary*, WSAV, June 5, 2015, http://wsav.com/2015/06/05/asbestos-found-inside-port-wentworth-elementary/; *School Board Cancels Classes Again After Mold, Asbestos Found in Elementary School*, Cent. Ill. Proud, http://www.centralillinoisproud.com/news/local-news/school-board-cancels-classes-again-after-mold-

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some of the ten chemicals during renovations or specialized courses such as shop class.[70] Pregnant individuals may also find themselves subject to workplace or drinking water exposures that they have little power to mitigate, and that have distinct effects on fetal development.[71]

TSCA requires EPA to identify which "potentially exposed or susceptible subpopulations" should be included in each of the risk evaluations for the first 10 TSCA substances by using reasonably available information to assess which subpopulations may have greater susceptibility or greater exposure to each substance. This will require actively seeking information from workers and unions, from communities near known or potential sources of each substance, as well as from other federal, state, and local agencies that may possess reasonably available information on those communities.

For example, according to the NRC, factors that influence susceptibility include age, gender, genetics, pre-existing disease, and exposures to other agents. The U.S. Census Bureau, the Bureau of Labor Statistics, and/or state and county demographers will have information on the age and gender of affected communities. In addition, CDC, ATSDR, and/or state and local health departments will have surveillance data that could inform analyses of pre-existing disease incidence and factors that explain such incidence.

For each of the first 10 TSCA substances, EPA's scoping analysis should determine whether any communities of color or people of lower socioeconomic status are disproportionately exposed and thus constitute a "potentially exposed or susceptible subpopulation." The Census Bureau has data on race, ethnicity and indicators of socio-economic status (such as income and level of education) that are essential for an environmental justice impact analysis. In addition, EPA should rely on geocoded locations of industrial facilities and disposal sites, and modeled or measured exposures.

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asbestos-found-in-elementary-school/352414397. *See also* Liza Lucas, *Group finds asbestos in children's crayons, toy crime lab kits*, CNN, July 8, 2015, http://www.cnn.com/2015/07/08/health/crayons-toys-asbestos-report//

[70] Methylene chloride is used in most paint strippers, and may be used in schools. *See Center For Public Integrity Details Dangers Of Paint Stripper Solvent*, Nat'l Pub. Radio, Sept. 21, 2015, http://www.npr.org/2015/09/21/442308286/center-for-public-integrity-details-dangers-of-paint-stripper-solvent. It is also present in adhesives that may be used in class projects. *Safe and Healthy School Environments* 197 (Howard Frumkin et al. eds., 2006).

[71] *See, e.g.*, Rose Goldman et al., Pediatric Envtl. Health Specialty Unit, *Trichloroethylene (TCE) Exposures in Pregnant Women and Children: Guidance for the General Public* (2016), http://www.pehsu.net/_Library/facts/TCE_PEHSU_National_Factsheet_FINAL.pdf; Gail Sullivan, *In Massachusetts, contaminated drinking water linked to stillbirths*, Washington Post, Oct. 6, 2014, https://www.washingtonpost.com/news/morning-mix/wp/2014/10/06/in-massachusetts-contaminated-drinking-water-linked-to-stillbirths/

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Finally, community groups are a critical source of information about many of these factors. Communities also are the best source of information about a range of factors relevant to exposure such as activity patterns near the sources (*e.g.*, the presence of playgrounds, nursing homes, or other infrastructure that draw potentially vulnerable populations) and the use of consumer products that contain the substance in question.

The diverse set of factors that can influence susceptibility and exposure make it impossible to prejudge what specific process will be necessary to identify potentially exposed or susceptible subpopulations. EPA is obligated to utilize all reasonably available information to determine which subpopulations are especially vulnerable to harm from the first 10 TSCA substances. This requires active outreach to stakeholders, including those closest to the problem -- workers, communities, health care providers, and state and local governments.

CONCLUSION

We appreciate the opportunity to participate in the scoping process for the first 10 TSCA substances. It is our intent to aid EPA in identifying the reasonably available information about the conditions of use of the first 10 TSCA substances so that EPA's risk evaluation takes into account the full range of ways in which vulnerable and chemically over-burdened populations around the country are placed at risk by these chemicals. We look forward to continuing to participate in EPA's risk evaluation and risk management efforts under TSCA. To schedule a meeting or telephone call, please contact Eve Gartner, Staff Attorney, Earthjustice, egartner@earthjustice.org, or 212-845-7381.

Submitted by:

Earthjustice *on behalf of*

Alaska Community Action on Toxics
Alliance of Nurses for Healthy Environments
American Public Health Association - Occupational Health and Safety Section
Azul
BlueGreen Alliance
Brazilian Worker Center
Breast Cancer Prevention Partners
Campaign for Healthier Solutions
CATA – The Farmworkers Support Committee
Center for Biological Diversity
Center for Environmental Health
Citizens' Environmental Coalition
Clean and Healthy New York
Coming Clean
Connecticut Coalition for Environmental Justice

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Delaware Concerned Residents for Environmental Justice
Ecology Center
Empire State Consumer Project
Environmental Community Action
Environmental Health Strategy Center
Environmental Justice Health Alliance for Chemical Policy Reform
Environmental Justice Leadership Forum on Climate Change
Environmental Working Group
Farmworker Association of Florida
Glynn Environmental Coalition
Greater Syracuse Council on Occupational Safety and Health
GreenLatinos
Green Science Policy Institute
Headwater LLC
Healthy Building Network
Healthy Schools Network
The Imani Group
International Center for Technology Assessment
Just Transition Alliance
Labor Council for Latin American Advancement
League of Conservation Voters
League of United Latin American Citizens
Little Village Environmental Justice Organization
Made Safe
National Council for Occupational Safety and Health
National Medical Association
Natural Resources Defense Council
New Jersey State Industrial Union Council
New Mexico Environmental Law Center
New York Lawyers for the Public Interest
Ocean Futures Society
Occupational Health Clinical Center
People Concerned about Chemical Safety
Physicians for Social Responsibility
Science and Environmental Health Network
Sheet Metal Occupational Health Institute Trust
Sierra Club
Sugar Law Center for Economic & Social Services
Union of Concerned Scientists
United Support and Memorial for Workplace Fatalities
Voces Verdes
WE ACT for Environmental Justice
West End Revitalization Association
WisCOSH
Women's Voices for the Earth
Worksafe

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Comments on Scope of the Risk Evaluations for the
First Ten Chemicals under the Toxic Substances Control Act

Submitted via Regulations.gov

Docket Nos.: EPA-HQ-OPPT-2016-0723 (1,4-Dioxane): EPA-HQ-OPPT-2016-0741 (1-Bromopropane); EPA-HQ-OPPT-2016-0736 (Asbestos); No.: EPA-HQ-OPPT-2016-0733 (Carbon Tetrachloride); EPA-HQ-OPPT-2016-0735 (Cyclic Aliphatic Bromide Cluster (Hexabromocyclododecane or HBCD); EPA-HQ-OPPT-2016-0742 (Methylene Chloride); EPA-HQ-OPPT-2016-0743 (N-Methylpyrrolidone (NMP)); EPA-HQ-OPPT-2016-0725 (Pigment Violet 29 (Anthra[2,1,9- def:6,5,10-d'e'f]diisoquinoline- 1,3,8,10(2H,9H)-tetrone)); EPA-HQ-OPPT-2016-0737 (Trichloroethylene (TCE)); EPA-HQ-OPPT-2016-0732 (Tetrachloroethylene (also known as Perchloroethylene)); EPA-HQ-OPPT-2017-0002-0001 ("Meetings: Risk Evaluation Scoping Efforts Under Toxic Substances Control Act for Ten Chemical Substances")

March 15, 2017

Alaska Community Action on Toxics * Alliance of Nurses for Healthy Environments * American Public Health Association - Occupational Health and Safety Section * Azul * BlueGreen Alliance * Brazilian Worker Center * Breast Cancer Prevention Partners * Campaign for Healthier Solutions * CATA – The Farmworkers Support Committee * Center for Biological Diversity * Center for Environmental Health * Citizens' Environmental Coalition * Clean and Healthy New York * Coming Clean * Connecticut Coalition for Environmental Justice * Delaware Concerned Residents for Environmental Justice * Ecology Center * Empire State Consumer Project * Environmental Community Action * Environmental Health Strategy Center * Environmental Justice Leadership Forum on Climate Change * Environmental Justice Health Alliance for Chemical Policy Reform * Environmental Working Group * Farmworker Association of Florida * Glynn Environmental Coalition * Greater Syracuse Council on Occupational Safety and Health * GreenLatinos * Green Science Policy Institute * Headwater LLC * Healthy Building Network * Healthy Schools Network * The Imani Group * International Center for Technology Assessment * Just Transitions Alliance *Labor Council for Latin American Advancement * League of Conservation Voters * League of United Latin American Citizens * Little Village Environmental Justice Organization * Made Safe * National Council for Occupational Safety and Health * Natural Resources Defense Council * New Jersey State Industrial Union Council * New Mexico Environmental Law Center *New York Lawyers for the Public Interest * Occupational Health Clinical Center * Ocean Futures Society * People

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Concerned about Chemical Safety * Physicians for Social Responsibility * Science and Environmental Health Network * Sheet Metal Occupational Health Institute Trust * Sierra Club * Sugar Law Center for Economic & Social Services * Union of Concerned Scientists * United Support and Memorial for Workplace Fatalities * Voces Verdes * WE ACT for Environmental Justice * West End Revitalization Association * WisCOSH * Women's Voices for the Earth * Worksafe

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The undersigned organizations submit these comments to assist the United States Environmental Protection Agency ("EPA") in identifying the appropriate scope of the risk evaluations to be conducted for 1, 4 dioxane, 1-bromopropane, asbestos, carbon tetrachloride, cyclic aliphatic bromide cluster (hexabromocyclododecane or HBCD), methylene chloride, N-methylpyrrolidone (NMP), pigment Violet 29, trichloroethylene (TCE), and tetrachloroethylene (also known as perchloroethylene. Together, these chemical substances are referred to as the "first 10 TSCA substances."

Our organizations advocate for environmental and human health on behalf of local and environmental justice communities, industrial workers, farmworkers, children, scientists, health care professionals and others.

INTRODUCTION

The amendment of TSCA offers EPA an unprecedented opportunity to protect vulnerable and chemically over-burdened populations around the country – children, workers, the elderly, people living in fenceline communities near industrial sources, and others who may be at greater risk than the general population – from toxic chemicals. But this promise will only be fulfilled if the scope of EPA's risk evaluations takes into account the full range of intended, known, or *reasonably foreseen* ways that people across the country are or will be exposed to the chemical substances under review during the full life-cycle of those chemicals.

These comments are intended to assist EPA by identifying the "reasonably available information" EPA should seek and develop, and from what sources, in order to comply with its legal obligation to broadly construe the terms "conditions of use," "reasonably foreseen" and "potentially exposed and susceptible subpopulations" to ensure that all intended, known or reasonably foreseeable pathways of exposure to the first 10 TSCA substances, throughout the life-cycle of the chemical (including manufacture, processing, distribution, use, storage and disposal) are taken into account in each risk evaluation.[1] In addition, these comments are

[1] While Section 6 of TSCA does not explicitly mention storage of chemicals, other sections of TSCA clarify that EPA is charged with ensuring that the storage of TSCA substances does not pose an unreasonable risk. *See, e.g.*, 15 U.S.C. § 2610 (to administer Title I of TSCA, EPA may inspect any establishment where chemical substances are stored).

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intended to lay out EPA's obligations deriving from its own guidance documents, longstanding Executive Orders, and the statutory language of TSCA, to conduct outreach to targeted communities in the vicinity of where the first 10 TSCA substances are known to be manufactured, processed, stored, disposed or recycled, as well as from workers who are employed in facilities that manufacture, process, store, and dispose or recycle these substances, or their unions or representatives. This outreach is critical to EPA's ability to identify conditions of use and potentially exposed or susceptible subpopulations via reasonably available information (including obtaining information directly from impacted communities and populations) in accordance with the best available science.

A. Pursuant to EPA Policy, the Agency Must Take Potential Environmental Justice Concerns into Account in Determining the Scope of the Risk Evaluations for the First 10 TSCA Substances

The scoping phase for the first 10 TSCA substances presents a critical opportunity for EPA to implement a systematic approach to identifying and reducing environmental and health disparities for minority, low-income, and tribal populations. EPA's EJ 2020 Action Agenda ("EJ 2020"),[2] a copy of which is attached as Exhibit 1, lays out a roadmap for the Agency's work to promote environmental justice. Key promises include a commitment to "expand [the Agency's] work with diverse stakeholders in communities,"[3] including by "routinely analyz[ing], consider[ing] and address[ing] environmental justice issues in all appropriate EPA rulemaking[s] . . . ."[4] Conveniently, the Office of Chemical Safety and Pollution Prevention ("OCSPP") is identified as the program lead in meeting the objective of "ensur[ing] environmental justice is appropriately analyzed, considered and addressed in EPA rules with potential environmental justice concerns, to the extent practicable and supported by relevant information and law."[5]

EJ 2020 commits EPA to meaningful engagement with communities:

> Vibrant stakeholder engagement and partnerships are the backbone of EJ 2020 and essential to achieving meaningful outcomes for overburdened communities. Through early, ongoing and meaningful stakeholder engagement, EPA will catalyze a new level of stakeholder dialogue and collaboration in the course of implementing EJ 2020 and environmental justice practice within our programs and regions. Examples of community engagement in EJ 2020 include community involvement in EPA rulemaking and

[2] EPA, EJ 2020 Action Agenda, Doc. No. EPA-300-B-1-6004 (Oct. 2016), https://www.epa.gov/sites/production/files/2016-05/documents/052216_ej_2020_strategic_plan_final_0.pdf.

[3] *Id.* at ii.

[4] *Id.* at 8.

[5] *Id.* at 13.

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permitting processes, community-based participatory research and citizen science, and the development of outcome measures that are meaningful to communities.[6]

In addition, EJ 2020 builds on EPA's "Guidance on Considering Environmental Justice During the Development of Regulatory Actions" and "Technical Guidance for Assessing Environmental Justice in Regulatory Analysis," which provide specific ways that environmental justice principles should be applied to EPA actions. These Guidance documents are attached as Exhibits 2 and 3 hereto. Relevant to risk evaluations, "the Agency has expanded the concept of fair treatment to consider not only the distribution of burdens across all populations, but also the distribution of reductions in risk from EPA actions."[7] The Technical Guidance includes a lengthy section specifically on how to apply EJ principles to human health and risk assessments.[8]

Furthermore, EJ 2020 states that "each EPA program office responsible for writing rules will consider opportunities and develop strategies for achieving involvement of potentially impacted minority populations, low-income populations, and tribes and indigenous peoples as part of the process of developing the rule."[9] While it is not certain that EPA will ever promulgate rules addressing risks from any of the first 10 TSCA chemicals, the risk evaluations that are now underway would form the basis of future risk management rulemaking if any of these chemicals are found to pose an "unreasonable risk." Likewise, Executive Order 12,898, *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations* (Feb. 11, 1994), requires EPA "to the greatest extent practicable and permitted by law . . . [to] make achieving environmental justice part of its mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of its programs, policies, and activities on minority populations and low-income populations."[10] For these reasons, the risk evaluations now underway must take environmental justice concerns into account.

B. TSCA Requires EPA to Consider All of "The Conditions of Use" in Determining the

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[6] *Id.* at 10.

[7] EPA, Technical Guidance for Assessing Environmental Justice in Regulatory Analysis 1 (June 2016), https://www.epa.gov/sites/production/files/2016-06/documents/ejtg_5_6_16_v5.1.pdf

[8] *See id.* at 20.

[9] EJ 2020 at 15.

[10] In the Proposed Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, 82 Fed. Reg. 7562 (Jan. 19, 2017), EPA takes the view that Executive Order 12,898 does not apply to the proposed risk evaluation process rule because the rule "will not affect the level of protection provided to human health or the environment." *Id.* at 7575. We do not agree with this reasoning, but in any event, since the scope of the risk evaluations of the first 10 TSCA substances will plainly affect the level of protection EPA eventually adopts to safeguard health and the environment from these chemicals, if any, Executive Order 12,898 is applicable to the scoping process.

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Proper Scope of Risk Evaluations

Under TSCA, the scope of a risk evaluation must include "the hazards, exposures, *conditions of use*, and the potentially exposed or susceptible subpopulations the Administrator expects to consider."[11] As defined by Congress, the term "conditions of use" means "the circumstances, as determined by the Administrator, under which a chemical substance is *intended, known, or reasonably foreseen* to be manufactured, processed, distributed in commerce, used, or disposed of."[12] These terms, along with other TSCA requirements for conducting a risk evaluation, require that the scope of the risk evaluations for the first 10 TSCA substances include:

- consideration of risk from aggregate exposures;
- consideration of risk arising from "actual" – meaning "known" and "reasonably foreseen" – not only"intended" uses;
- ongoing exposures to chemicals from both current and legacy uses;
- consideration of exposures from substances not regulated under TSCA;
- consideration of uses for which hazard and/or exposure data are limited; and
- consideration of risk from cumulative exposures.
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EPA Is Correct to Reject a Tiered Approach that Considers the Conditions of Use in Isolation

In scoping the first 10 TSCA substances, EPA should consider all intended, known or reasonably foreseen conditions of use in each risk evaluation. The American Chemistry Council ("ACC"), in comments submitted to EPA in August 2016, recommended that the agency take a "tiered approach to risk evaluation." This approach would begin with "a quantitative screening level analysis" of various conditions of use, followed by "robust refined risk evaluations for only those conditions of use where unreasonable risks cannot be ruled out."[13] A central premise of this approach is that EPA should evaluate risk for separate conditions of use, rather than evaluate risk for a chemical substance across all conditions of use. EPA rightfully has proposed to reject a tiered approach in both the prioritization and risk evaluation procedures rules published in January 2017, and it should apply that approach to the risk evaluations for the first 10 TSCA substances.

As EPA lays out in section II(C)(2) of the Preamble to the Proposed Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act ("Proposed Risk Evaluation Process Rule"), TSCA section 6(b)(4)(A) requires EPA to conduct risk evaluations to determine

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[11] 15 U.S.C. § 2605(b)(4)(D) (emphasis added).

[12] *Id.* § 2602(4) (emphasis added).

[13] Am. Chemistry Council, ACC Comments to Inform EPA's Rulemaking on the Conduct of Risk Evaluations under the Lautenberg Chemical Safety Act, EPA-HQ-OPPT-2016-0400-0028 at 6 (Aug.24, 2016), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0400-0028.

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whether "under *the* conditions of use" a chemical substance presents an unreasonable risk. The term "*the* conditions of use" signifies the full array of conditions of use, not a selection of conditions.[14] In addition, TSCA section 6 requires EPA to evaluate the risks of a chemical substance by evaluating whether "the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, *or . . . any combination of such activities*, presents an unreasonable risk of injury to health or the environment."[15] EPA cannot assess whether the "combination of such activities" poses an unreasonable risk if it excludes some conditions of use from its evaluation. Indeed, conditions of use that do not lead to significant exposure during use may do so during manufacturing, processing, storage, recycling, and disposal. It would undermine the cradle-to-grave TSCA regulatory scheme if EPA could determine that a select "use" of a substance did not present an unreasonable risk divorced from consideration of whether the manufacturing, processing, distribution in commerce, use in other contexts, storage, recycling, and disposal of that substance, in the aggregate, pose an unreasonable risk.

Rejecting the "tiered approach" is critical to protecting communities and workers from the real-world ways in which they are exposed to risk from toxic chemicals. There may be select conditions of use for the first 10 TSCA substances that, in isolation, would not result in an unreasonable risk of injury to health or the environment. However, in the real world, people are exposed to some of these substances from multiple sources and during different phases of the life of the substance. For example, a worker may use a substance on the job, and the same substance may be present in consumer products she uses at home; it may also be present in her family's drinking water. For populations that are exposed to the same substance via multiple pathways, the actual risk posed by the substance would be obscured if EPA's risk evaluation did not cover all conditions of use throughout the life cycle of the substance *in the aggregate*. EPA's scoping documents for the first 10 TSCA substances must explain when and how the Agency intends to assess risks from aggregate exposure.

The Term "The Conditions of Use" Includes Actual – Meaning "Known" and "Reasonably Foreseen" – *Not Only "Intended" Uses*

While manufacturers of chemical products might have preconceived notions of a product's "intended use," in actual practice the use of chemicals and chemical products—and their associated exposures—varies widely in manufacturing, processing, consumer and commercial applications, and disposal. To effectively characterize risks, EPA must account for the variability

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[14] Similarly, in the Preamble to the Proposed Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act, "EPA will make priority designations pursuant to these procedures for a chemical substance, not for a specific condition or conditions of use of a chemical substance." 82 Fed. Reg. 4834 (Jan. 17, 2017). The conditions of use will be "all circumstances under which the Agency determines that the chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." 82 Fed. Reg. at 7578.

[15] 15 U.S.C. § 2605(a)

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in exposure that results from "actual" (meaning "known" and "reasonably foreseen") as compared to "intended" conditions of use. This follows from EPA's statutory requirement to "take into account, where relevant, the likely duration, intensity, frequency and number of exposures under the conditions of use of the chemical substance."[16]

Actual conditions of use can vary widely for several reasons. These include, but are not limited to the following:

- Highly exposed subgroups: In workplaces where chemicals and chemical products are used, exposures typically occur most intensely among a highly exposed subgroup, rather than uniformly across the population of workers. In a vehicle repair shop, for example, chemical-intensive tasks on brakes, engines, and drive-train components are performed by a subset of workers who experience high levels of exposure to aerosolized degreasing solvents, whereas other workers in the same shop who perform diagnostic or electrical work, for example, experience little or no exposure to these solvents. To effectively characterize the "conditions of use" among workers, EPA must account for the concentration of exposure—and therefore risk—that occurs within highly exposed subgroups as a consequence of actual workplace conditions, rather than relying on an "average" estimated exposure across a population of workers, based on an assumption of "intended" use.

- Safety culture: When workers are under pressure to perform tasks within a specific period of time, they may take short-cuts to maximize productivity. Safety is often an early casualty of short-cuts, including in handling chemicals and chemical products. Safe handling is further undermined when workers are unaware of the risks associated with exposure to chemical hazards; they are untrained in taking normal precautions; they assume chemicals in the workplace are safe to use; they use chemicals in confined and poorly ventilated spaces; and when co-workers, managers and the general workplace culture all actively discount the health risks associated with chemical exposures. To effectively characterize the conditions of actual use among workers, EPA must identify and account for these realities of the work environment and adjust risk estimates accordingly.

- Personal protective equipment ("PPE"): OSHA requires that employers reduce exposures to hazardous chemicals by controlling chemical hazards as close to the source as possible through the use of substitution, ventilation, containment, and worker procedures, before turning to personal protection equipment, such as air purifying respirators (APRs).[17] The

[16] 15 U.S.C. § 2605(b)(4)(F)(iv).

[17] 29 C.F.R. § 1910.134(a)(1).

use of APRs can be a useful adjunct to protect workers from occasional, intermittent exposures to hazardous chemicals; as a primary defense, however, the use of APRs is highly problematic. They impose an increased resistance to breathing, they dampen auditory, olfactory and visual sensations, they are cumbersome and uncomfortable to wear, and they isolate the worker from co-workers and the work environment. As a result, respiratory programs can be difficult to implement and enforce among employees. Moreover, they require technical competency: APR filters must be properly selected to ensure that they protect the worker from inhaling the chemical(s) of concern; they must be properly "fit tested" to individual workers to ensure that contaminated air does not "leak" into the respirator around the face seal; and they must be conscientiously worn, properly maintained and regularly replaced. If any one of these elements is missing, the efficacy of an APR program drops substantially. EPA must account for these weaknesses in characterizing exposures in workplaces where employers rely on respiratory protection as a means of preventing workers from hazardous chemicals and chemical products. For the reasons noted above, EPA must substantially discount the efficacy of APRs to appropriately characterize risks in these settings.

- Labeling: While warning labels on products might appeal to some manufacturers as a reasonable means of preventing chemical exposures, in actual practice these warnings can be difficult for workers to interpret and implement. The phrase "Use in a well-ventilated room," for example, has little meaning and will not reduce chemical risks among workers. Likewise, it is very difficult for workers to take protective action based on information presented in a Safety Data Sheet ("SDS"). While the Globally Harmonized System ("GHS") labels for specific chemicals are more illustrative, and they might motivate workers to demand protection from certain chemical exposures, the simple presence of GHS warning labels does not, in actual practice, translate to a reduction in exposures among workers. To effectively characterize the conditions of actual use among workers, EPA must substantially discount the efficacy of warning labels, SDS information, and GHS labeling.

- Enclosures: As a recognized approach under the hierarchy of controls, enclosed industrial processes (sometimes referred to as "closed systems") would be expected to reduce worker chemical exposures, particularly when compared to respiratory protection programs. Enclosed processes, however, do not eliminate the potential for exposure. Enclosures may need to be regularly accessed by workers as part of the manufacturing process; they can emit chemical vapors through cracks and openings; and they need to be periodically maintained. To effectively characterize the conditions of actual use among workers, EPA must take into account these limitations of enclosed industrial processes.

The Term "The Conditions of Use" Includes Both Current and Legacy Uses

By the terms of TSCA, the "intended, known or reasonably foreseen"[18] conditions of use include ongoing exposures to chemicals both from current use, and from legacy uses. The need to consider legacy uses is evident from the fact that "conditions of use" is defined to include circumstances under which a chemical substance is "disposed of."[19] The need to consider legacy uses in risk evaluations also follows from the statutory requirement that EPA "take into account, where relevant, the likely duration, intensity, frequency and number of exposures under the conditions of use of the chemical substance."[20] By requiring EPA to consider the "frequency" and "number" of exposures without limitation, Congress signaled the intent that risk evaluations must consider all ongoing exposures in the aggregate, irrespective of whether the substance is present in the environment due to a continuing use or a legacy use. Asbestos provides a good illustration of this principle. EPA's risk evaluation of asbestos must consider exposures from current uses of asbestos. In addition, it must "take into account" the "frequency" and "number" of exposures, some of which will arise, *inter alia*, when asbestos previously installed in buildings as insulation is disturbed.[21] When previously installed asbestos is removed from buildings, improper handling may result in exposure too.[22] In addition, asbestos is found at 78 National Priority List ("NPL") sites, largely as a result of historic use,[23] and EPA has developed guidance for assessing exposure to asbestos present at Superfund sites.[24] In communities near active NPL and Superfund sites, some exposure may occur due to legacy uses of chemical substances. A risk evaluation must consider these previous uses to capture the "likely duration, intensity, frequency and number of exposures."

"The Conditions of Use" Includes Uses Not Regulated Under TSCA

The requirement to consider all "conditions of use" and the "likely duration, intensity, frequency and number of exposures" requires EPA to take into account uses that are not regulated under

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[18] 15 U.S.C. § 2602(4).

[19] *Id.*.

[20] 15 U.S.C. § 2605(b)(4)(F)(iv).

[21] U.S. Dep't of Health & Human Servs., Agency for Toxic Substances and Disease Registry ("ATSDR"), Toxicological Profile for Asbestos 2-3 (Sept. 2001), https://www.atsdr.cdc.gov/toxprofiles/tp61.pdf.

[22] U.S. Dep't of Health & Human Servs., Nat'l Cancer Inst., *Asbestos Exposure and Cancer Risk* (last updated May 1, 2009), https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/asbestos/asbestos-fact-sheet.

[23] ATSDR has reported asbestos at 78 sites, chrysotile asbestos at 13 sites, and amosite asbestos at 9 sites. It was not clear to what extent these sites overlapped. *See* ATSDR, Summary Data for 2015 Priority List of Hazardous Substances (Feb. 2016), https://www.atsdr.cdc.gov/spl/resources/atsdr_2015_spl_detailed_data_table.pdf.

[24] EPA, Framework for Investigating Asbestos-Contaminated Superfund Sites (Sept. 2008), https://semspub.epa.gov/work/HQ/175329.pdf.

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TSCA but which contribute to aggregate exposures from the manufacture, processing, distribution, storage, use, or disposal of the substance and which are intended, known or reasonably foreseen. This includes exposures from the presence of the first 10 TSCA chemicals in food, drinking water, personal care products, and other media and articles that cannot be directly regulated under TSCA. For example, while methylene chloride is used as a paint stripper and remover,[25] it is also approved by FDA as a food additive for uses including use as a solvent in the extraction of caffeine from green coffee beans.[26] It is entirely plausible that an individual who uses a methylene chloride-based paint stripper also drinks decaffeinated coffee, and while EPA would only regulate the former use under TSCA, both uses may contribute to exposure and thus contribute to an unreasonable risk of injury to health. A risk evaluation that does not account for all known uses of methylene chloride throughout the full life cycle of the substance will not adequately assess exposure or characterize risk.

EPA Must Include Consideration of All the Conditions of Use Even If Hazard and/or Exposure Data Are Limited

EPA must consider all "intended, known, or reasonably foreseen" conditions of use when conducting a risk evaluation for a chemical substance, but it is likely that the available data on hazard or exposure will vary among the conditions of use. EPA cannot exclude a known condition of use because of data gaps in characterizing the risk posed by that use. In other words, EPA cannot interpret the absence of data as an absence of risk and exclude it from consideration in its risk evaluation. Rather, when EPA identifies a data gap with respect to a condition of use, the agency should move immediately to fill the data gap using the authorities available to it. If EPA believes the data gap cannot be filled within statutory timeframes, EPA must either use science-based defaults, as recommended by the National Research Council ("NRC"),[27] or, at a minimum, indicate that the risks posed by the uses in question are currently unknown.

EPA Must Conduct a Cumulative Risk Assessment When Consistent with Best Available Science Principles

When the best available science indicates that the risk of injury to health or the environment posed by exposure to a chemical substance may vary with exposure to multiple agents or stressors, EPA must evaluate cumulative risk by conducting a *cumulative risk assessment*, defined by the agency as "an analysis, characterization, and possible quantification of the

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[25] ATSDR, Toxicological Profile for Methylene Chloride 1-2 (Sept. 2000), https://www.atsdr.cdc.gov/toxprofiles/tp14.pdf.

[26] 21 C.F.R. § 173.255(c).

[27] The use of science-based defaults is discussed in chapter 6 of *Science and Decisions*. See NRC, *Science and Decisions: Advancing Risk Assessment* (2009).

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combined risks to health and the environment from multiple agents or stressors."[28] A risk evaluation that fails to assess cumulative risk in spite of such evidence would be inconsistent with the best available science, in violation of TSCA section 26(h), and may underestimate risk. A risk determination based on an underestimation of risk in turn may result in risk management decisions that fail to provide adequate protection for public health or the environment.

EPA itself has recognized that risk may depend on multiple agents or stressors, and it has used cumulative risk assessment to evaluate such risk. In *Framework for Cumulative Risk Assessment* (2003), EPA states, "Assessing cumulative risk through complex exposures is one of the Agency's high priorities…and it is germane and of great interest to all program and regional offices."[29] EPA already has conducted cumulative risk assessments for five classes of pesticides grouped by common mechanism: organophosphates, N-methyl carbamates, triazines, chloroacetanilides, and pyrethrins/pyrethroids.[30]

The National Academies likewise have recognized the importance of cumulative risk assessments and have encouraged EPA to broaden the scopes of its risk assessments. *Pesticides in the Diets of Infants and Children* (1993) paved the way for enactment of the Food Quality Protection Act and its requirement that EPA assess cumulative risks posed by pesticides that share a common mechanism.[31] In *Phthalates and Cumulative Risk Assessment* (2008), the National Academies urged the agency to assess risks posed not just by exposure to a class of chemicals that share a common *mechanism* (*e.g.*, organophosphates) but by exposure to all chemicals that share a common *effect*—in that case, not just phthalates but all anti-androgenic chemicals.[32] *Science and Decisions* (2009) urges an even broader scope that accounts for "simultaneous exposure to multiple chemical and nonchemical stressors and other factors that could influence vulnerability," such as psychosocial stress.[33] It is thus clear that, in some instances, the best available science will requirethat EPA conduct a cumulative risk assessment that includes not just a single chemical substance but multiple chemical substances and other agents.

C. "Reasonably Foreseen" Conditions of Use Encompasses a Broad Range of Exposure

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[28] EPA, Framework for Cumulative Risk Assessment, Doc. No. EPA/630/P-02/001F at 6 (May 2003), https://www.epa.gov/sites/production/files/2014-11/documents/frmwrk_cum_risk_assmnt.pdf.

[29] *Id.* at xi.

[30] EPA, Cumulative Assessment of Risk from Pesticides (last updated May 19, 2016), https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides.

[31] NRC, *Pesticides in the Diets of Infants and Children* (1993).

[32] NRC, *Phthalates and Cumulative Risk Assessment: The Task Ahead* 9 (2008).

[33] NRC, *Science and Decisions: Advancing Risk Assessment* 213-14 (2009).

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Pathways

The conditions of use that EPA must evaluate include "intended, known, or reasonably foreseen" uses. This expansive language requires EPA to evaluate a broad range of uses, including those that may not be intended, but that are nonetheless either known or reasonably foreseen. Congress's use of the alternative "or reasonably foreseen" makes it clear that "the conditions of use" go beyond intended or known uses.

"Reasonable foreseeability" is a core legal concept with a widely understood meaning across many fields of law.[34] In a range of contexts, courts have recognized that "reasonably foreseeable" uses include reasonably foreseeable misuses, accidents, or even criminal uses.[35] *See, e.g.*, *Suzik v. Sea-Land Corp.*, 89 F.3d 345, 350 (7th Cir. 1996) ("The law provides that it is reasonable for defendants to foresee some, but not all, accidents arising from their conduct.") In the context of toxic substances and pollution, leaks, spills, unintentional consumption and exposure through equipment failure, poorly designed workplace exposure protections, or worker error have been found in some circumstances to be reasonably foreseeable. For example:

- EPA and regulated industries recognize that inadvertent releases of hazardous air pollutants occur and are inevitable.[36]
- The Clean Water Act[37] requires preparation of a Spill Prevention Control and Countermeasures Plan by facilities that "could reasonably be expected to" discharge oil into navigable waters, implicitly acknowledging that such discharges are common

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[34] In general, an effect is reasonably foreseeable if it is so "likely to occur that a person of ordinary prudence would take it into account in reaching a decision." *Mid States Coal. for Progress v. Surface Transp. Bd.*, 345 F.3d 520, 549 (8th Cir. 2003) (internal quotation and citation omitted).

[35] The U.S. Supreme Court has held that criminal acts may be "reasonably foreseen." "While 'reasonable foreseeability of harm is an essential ingredient of Federal Employers' Liability Act negligence,' we have held that the fact that 'the foreseeable danger was from intentional or criminal misconduct is irrelevant; respondent nonetheless had a duty to make reasonable provision against it.'" *Harrison v. Mo. Pac. R. Co.*, 372 U.S. 248, 249 (1963) (internal citations omitted).

[36] *See, e.g. United States Sugar Corp. v. Envtl. Prot. Agency*, 830 F.3d 579, 606 (D.C. Cir. 2016), *on reh'g en banc in part*, No. 11-1108, 2016 WL 7427434 (D.C. Cir. Dec. 23, 2016), and *on reh'g en banc*, No. 11-1108, 2016 WL 7427453 (D.C. Cir. Dec. 23, 2016) ("Both [EPA and industry petitioners] agree that malfunctions are inevitable in the operation of area and major boilers. According to the EPA, "even equipment that is properly designed and maintained can sometimes fail and . . . such failure can sometimes cause an exceedance of the relevant emission standard.""). Indeed, the regulated industries have challenged EPA for failing to incorporate consideration of *anticipated malfunctions* resulting in releases of toxics into regulations. *Id.*

[37] 33 U.S.C. § 1321(j)(1); 40 C.F.R. § 112.3(a)(1) ("If [an onshore or offshore facility] becomes operational after November 10, 2011, and *could reasonably be expected to have a discharge* as described in § 112.1(b), you must prepare and implement a Plan before you begin operations.").

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enough to necessitate this requirement.[38]

- A court found that it was "reasonably foreseeable" that farmers would tank-mix insecticide with fungicide, although this practice harms crops, because "the economics and utility of tank mixing make it almost inevitable that such mixing will occur"; and tank mixing is "common practice as it allows the farmer to address several problems with one spray application."[39]

The interpretation and implementation of the National Environmental Policy Act ("NEPA") shows that, in the realm of environmental law, "reasonable foreseeability" includes accidental releases. NEPA requires federal agencies to prepare an environmental impact statement ("EIS") for any proposed major federal action "significantly affecting the quality of the human environment."[40] An EIS must include an evaluation of the proposed action's "[i]ndirect effects, which are caused by the action and are later in time or farther removed in distance, but are still *reasonably foreseeable*."[41] Failure to include leaks, accidents and other unintended consequences of the proposed action -- when they are reasonably foreseeable -- is a basis for invalidating an EIS.[42] For this reason, EISs routinely include analysis of "reasonably foreseeable accidents."[43] Indeed, several federal agencies have issued guidance for preparation of EISs. For example, "[a]n important theme of the [Department of Energy's] guidance [for the preparation of EISs] is that the EIS's consideration of human health effects should involve 'realistic scenarios,' 'realistic exposure conditions,' and 'reasonably foreseeable accidents.'"[44] An EIS must comprehensively

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[38] *See, e.g., Pepperell Associates v. Envtl. Prot. Agency,* 246 F.3d 15 (1st Cir. 2001) (affirming EAB determination that "it was reasonably foreseeable" that textile mill would discharge oil into navigable waters).

[39] *Indian Brand Farms, Inc. v. Novartis Crop Prot., Inc.*, 617 F.3d, 207, 225-26 (3rd Cir. 2010).

[40] 42 U.S.C. § 4332(1)(C)(i).

[41] 40 C.F.R. § 1508.8(b) (emphasis added); *see Brady Campaign to Prevent Gun Violence v. Salazar*, 612 F. Supp. 2d 1, 21–22 (D.D.C. 2009) (finding that NEPA required the agency to analyze the foreseeable consequences that would occur as a result of the agency action).

[42] *See N.Y. v. Nuclear Regulatory Comm'n*, 681 F.3d 471, 479 (D.C. Cir. 2012) (finding that the Nuclear Regulatory Commission's NEPA analysis was "not supported by substantial evidence on the record because the Commission failed to properly examine the risk of leaks in a forward-looking fashion and failed to examine the potential consequences of pool fires.").

[43] *See, e.g., Lee v. U.S. Air Force*, 354 F.3d 1229, 1245 (10th Cir. 2004) (U.S. Air Force's EIS acknowledged that "fire and environmental contamination" may result from a crash of a plane near its base, described its methodology for calculating this risk, and described the results of these calculations.); *Spiller v. Walker*, No. A-98-CA-255-SS, 2002 WL 1609722, at *14 (W.D. Tex. July 19, 2002), *aff'd sub nom. Spiller v. White*, 352 F.3d 235 (5th Cir. 2003)(EPA's EIS for a sewage residuals landfill analyzed the impact of potential leaks on drinking water).

[44] NRC, *Evaluation of the Health and Safety Risks of the New USAMRIID High Containment Facilities at Fort Detrick, Maryland* (2010),

ED_004056A_00227267-00013

evaluate impacts to the human environment so that decisionmakers have access to all of the information that they need in order to make a decision about how to proceed with a potential project.[45] Similarly, TSCA risk evaluations must provide comprehensive information to support EPA's risk determination. Both require in-depth analysis of reasonably foreseeable future conditions in order to provide meaningful information to support agency decisionmaking.

The reading of "reasonably foreseen" to include inadvertent uses is further confirmed by other language in the amended TSCA. The statute requires that the process for prioritizing risk evaluations "shall include a consideration of the hazard and exposure potential of a chemical substance or a category of chemical substances (including consideration of persistence and bioaccumulation, potentially exposed or susceptible subpopulations ***and storage near significant sources of drinking water***)."[46] The mandate that EPA consider whether a substance is stored near drinking water reflects congressional intent that the potential for inadvertent leaks or spills leading to drinking water contamination is relevant to EPA's section 6 analyses. This provides additional confirmation that the conditions of use that Congress intended the Agency to include in risk evaluations encompass accidents and misuses.

Past experience and known industry practices are often the key to foreseeability. *See, e.g., G & K Dairy v. Princeton Elec. Plant Bd.*, 781 F. Supp. 485, 491 (W.D. Ky. 1991) ("When deciding whether the defendant could have reasonably foreseen or anticipated that stray voltage would injure the plaintiffs' dairy herd, the Court must consider the defendant's past experience and the practice of others in similar circumstances."). Releases of substances that are acknowledged or anticipated by industry or EPA are "known" or "reasonably foreseen" conditions of use, even if they are not "intended." For example, it is well known that several of the first 10 TSCA substances– TCE,[47] tetrachloroethylene,[48] 1,4-dioxane[49] – are present in many drinking water

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https://www.ncbi.nlm.nih.gov/books/NBK220309/pdf/Bookshelf_NBK220309.pdf, referencing U.S. Dep't of Energy, *NEPA: Recommendations for the Preparation of Environmental Assessments and Environmental Impact Statements* (2d ed. Dec. 2004), https://energy.gov/sites/prod/files/nepapub/nepa_documents/RedDont/G-DOE-greenbook.pdf.

[45] "[NEPA] first...places upon an agency the obligation to consider every significant aspect of the environmental impact of a proposed action. Second, it ensures that the agency will inform the public that it has indeed considered environmental concerns in its decisionmaking process." *Forest Guardians v. U.S. Fish & Wildlife Serv.*, 611 F.3d 692, 711 (10th Cir. 2010) (quoting *Balt. Gas & Elec. Co. v. Natural Res. Def. Council, Inc.*, 462 U.S. 87, 97 (1983)) (internal quotation marks omitted); *see also New Mexico ex rel. Richardson v. Bureau of Land Mgmt.*, 565 F.3d 683, 703 (10th Cir. 2009) ("By focusing both agency and public attention on the environmental effects of proposed actions, NEPA facilitates informed decisionmaking by agencies and allows the political process to check those decisions.").

[46] 15 U.S.C. § 2605(b)(1)(A)(emphasis added).

[47] *See, e.g., 20 Year Legal Battle in Tucson, Arizona,* Baron & Budd (last visited Mar. 15, 2017), https://baronandbudd.com/environment/water-contamination/tce-tucson-arizona/; World Health Org., Trichloroethene in Drinking-water, Doc. No. WHO/SDE/WSH/05.08/22 at 4 (2005), http://www.who.int/water_sanitation_health/dwq/chemicals/trichloroethenemay05.pdf; Linda Collins,

systems. While we presume this contamination was not intended, given the extent to which it has happened, EPA must consider it to be "reasonably foreseen" that these chemicals, either by their nature or by their manner of use, or both, have a propensity to leach into groundwater.

Because certain misuses are reasonably foreseeable, EPA must define conditions of use for its scoping of the first ten TSCA substances that include all known or anticipated exposure pathways. These include, without limitation: known or reasonably foreseeable leaks or spills in the vicinity of manufacturing, processing, and disposal sites; use of the chemical without effective use of safeguards such as ventilation or personal protective equipment; the presence of a chemical in a product or waste stream as an impurity or byproduct; state or federally permitted releases into air or water; releases from Superfund sites; drinking water groundwater contamination; and exposure through fish consumption by subsistence fishers for chemicals that are bio-accumulative.

D. EPA Must Actively Seek "Reasonably Available Information" from Stakeholders in Accordance with Best Available Science Principles

TSCA section 26(k) requires that "[i]n carrying out sections 4, 5, and 6, the Administrator shall take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is *reasonably available to the*

Enon water committee reveals test results, Fairborn Daily Herald, Feb. 28, 2017, http://fairborndailyherald.com/news/15290/enon-water-committee-reveals-test-results; Emily C. Dooley, *State to launch study of Bethpage groundwater plumes*, Newsday, Feb. 17, 2017, http://www.newsday.com/long-island/nassau/state-to-launch-new-study-of-bethpage-groundwater-plume-1.13140648.

[48] *See, e.g.,* World Health Org., Tetrachloroethene in Drinking-water, Doc. No. WHO/SDE/WSH/03.04/23 (2003), http://www.who.int/water_sanitation_health/dwq/chemicals/tetrachloroethene.pdf; *State officials testify for safe drinking water*, Register Citizen, Feb. 27, 2017, http://www.registercitizen.com/article/RC/20170227/news/170229778.

[49] *See, e.g.,* Minn. Dep't of Health, *1, 4-Dioxane in Drinking Water* (Jan. 2015), http://www.health.state.mn.us/divs/eh/risk/guidance/dwec/dioxaneinfo.pdf; N.C. Dep't of Envtl. Quality, 1,4-Dioxane in the Cape Fear River Basin of North Carolina: An Initial Screening and Source Identification Study (2016), https://ncdenr.s3.amazonaws.com/s3fs-public/Water%20Quality/Environmental%20Sciences/ECO/DioxaneReport_Yr1Final-20160127.pdf; *Possible carcinogen 1,4-dioxane found in LI water spurs push for stronger standards*, News 12/Newsday, Jan 9, 2017, http://longisland.news12.com/news/news-12-newsday-report-probable-carcinogen-1-4-dioxane-found-in-li-water-spurs-push-for-stronger-st-1.12903291; Elizabeth Shogren, *Toxic Chemical Dioxane Detected In More Water Supplies*, Nat'l Pub. Radio, Mar. 16, 2014, http://www.npr.org/2014/03/26/294639904/toxic-chemical-1-4-dioxane-detected-in-more-drinking-water-supplies; Water Research Found., 1,4-Dioxane White Paper (2014), http://www.waterrf.org/resources/StateOfTheScienceReports/1,4-dioxane.pdf.

ED_004056A_00227267-00015

Administrator."[50] In addition, section 6(b)(4)(F)(i) requires EPA to "integrate and assess *available information* on hazards and exposures for the conditions of use" of the chemicals it is evaluating.[51] To comply with these mandates to use "available information," EPA is obligated to *seek out* information rather than simply open a docket on Regulations.gov and hope that the public will submit relevant information.[52] EPA must gather the reasonably available information for each of the first 10 TSCA substances that will enable it to conduct a scoping analysis that identifies specific exposures and risks to workers, occupational bystanders, fenceline community residents, consumers and any others who are exposed to these substances.

The Proposed Risk Evaluation Process Rule defines "reasonably available information" as "existing information that EPA possesses *or can reasonably obtain and synthesize* for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation."[53] This language confirms EPA's obligation to affirmatively obtain information. It also accords with the way that courts have interpreted what kinds of information are "reasonably available" in other contexts.[54]

From a practical standpoint, affirmatively seeking information about conditions of use and susceptible subpopulations during the scoping process of the first 10 TSCA substances is critical to conducting meaningful risk assessments. This is especially true because EPA did not have the benefit of developing information about these first 10 TSCA substances during a lengthy prioritization process. TSCA requires that the scoping process take no more than six months and that the scope must "include the hazards, exposures, conditions of use, and the potentially

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[50] 15 U.S.C. § 2625(k).

[51] *Id.* § 2605(b)(4)(F)(i).

[52] It is also important to bear in mind that "[i]nformation does not have to be perfect or infallible for the agency to be required to use it . . . ." *See Natural Res. Def. Council v. Kempthorne*, 506 F.Supp.2d 322, 373 (E.D.Cal. 2007); *see also Conner v. Burford*, 848 F.2d 1441, 1454 (9th Cir. 1988) (fact that information is "inexact" is not an excuse for failure to conduct comprehensive biological opinion).

[53] Proposed 40 C.F.R. § 702.33 (emphasis added).

[54] For example, under the Endangered Species Act ("ESA"), federal agencies must use the "best scientific and commercial data available" to insure that any action authorized, funded, or carried out by that agency is "not likely to jeopardize the continued existence of any endangered species or threatened species or result in the destruction or adverse modification of habitat of such species." 16 U.S.C. § 1536(a)(2). EPA's obligation to use "reasonably available information" coupled with the duty to use "best available science" is comparable to the statutory requirement under the ESA. Under the ESA provision, agencies cannot passively rely on readily available information. Rather, they may have to take affirmative steps to gather the information, such as by developing projections and conducting real time simulations. *See, e.g.*, *Conner v. Burford*, 848 F.2d 1441, 1454 (9th Cir. 1988) (ESA may require making projections, based on *potential* locations and levels oil and gas activity, of the impact of production on protected species), citing *Roosevelt Campobello Int'l Park Comm'n v. EPA*, 684 F.2d 1041, 1052-55 (1st Cir. 1982).

ED_004056A_00227267-00016

exposed or susceptible subpopulations the Administer expects to consider[.]"[55] If EPA fails to conduct outreach to impacted communities and workers, and declines to review additional subpopulations and conditions of use after scoping has been completed, [56] then the Agency will not have availed itself of reasonably available information as required by the statute. TSCA requires EPA to find out how these chemicals are manufactured, processed, distributed, used, and disposed of *in the real world* if that information is "reasonably available."

In particular, EPA must affirmatively seek "reasonably available information" from: other governmental entities; manufacturers, processors, distributors, storage and disposal facilities and recyclers; and directly affected communities and workers. We amplify on each of these below.

> 1) EPA must obtain information from manufacturers, processors, storage facilities, recyclers, and other handlers of the first 10 TSCA substances.

Industries that work with, manufacture, process, distribute, store, transport, dispose, and recycle the first 10 TSCA substances undoubtedly have extensive information about the conditions of use of these substances. Information that EPA can obtain for the asking is information that is "reasonably available." At a minimum, EPA must affirmatively ask all industry stakeholders of which it is aware (via databases such as the CDR and the TRI, submissions during the public comment period, and all other sources) to produce all information in their possession about about environmental releases (including leaks, spills, discharges, and emissions), misuses, and accidents involving these substances, including an estimate of the amount and the frequency of releases, misuses, and accidents.[57]

In addition, to comport with the requirement that risk evaluations be based on "reasonably available information," EPA should also ask these industry stakeholders for additional information that would shed light on the real ways in which these chemicals are used. Specifically, to determine the "conditions of use," EPA should ask industry stakeholders: how the chemical is stored and in what volumes; how the chemical is transported to and from manufacturing and processing sites; how transport containers are cleaned and stored; the frequency of cleaning; and how much of the chemical is released with each cleaning. Operators

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[55] 15 U.S.C. § 2605(b)(4)(D).

[56] While the scoping process for the first 10 TSCA substances is not governed by the proposed risk evaluation rule, if EPA intends to take the approach articulated in that rule that conditions of use must be "locked down" during the scoping process, then outreach during scoping to identify all conditions of use becomes all the more critical. Proposed 40 C.F.R. § 702.39.

[57] Some of this information may be available through the Toxic Release Inventory, but not all of the first 10 TSCA substances are on the TRI, and 1-bromopropane and HBCD were only added within the last year. Therefore, release data will not be available in time for scoping and should be requested directly from industry handlers.

ED_004056A_00227267-00017

of manufacturing and waste facility sites handling the first 10 TSCA substances should be asked for their NPDES permit numbers so EPA can identify permitted discharges, review discharge reports, and ascertain if there have been NPDES permit violations. Similarly, EPA should ask these same industry actors to provide their Clean Air Act permit numbers, information about their control technologies, and the details of their Leak Detection & Repair programs.

If the information EPA requests from industry actors is not provided promptly, the Agency should use its TSCA section 11(c) subpoena authority to obtain it.[58] Information that can be obtained by subpoena is "reasonably available information."

2) EPA must seek information about the first 10 TSCA substances from federal, state and local government agencies.

Government agencies often have critical information on how substances impact particular subpopulations or their particular conditions of use. EPA must therefore affirmatively request that federal, state and local governmental bodies provide information about the first 10 TSCA substances during the scoping phase. Requests should include, but are not limited to:

- relevant data[59] from the Centers for Disease Control ("CDC") pertaining to toxicity of and exposures to these chemicals and disease trends among people with high exposures;

- information from state and local health departments about releases and exposures to these chemicals, and disease trends in communities near manufacturing, processing, storage, recycling and disposal;

- information from state and local labor departments about releases and exposures to these chemicals, accidents at sites where the chemicals are manufactured, processed, recycled and disposed of; and disease trends among workers at such sites;

- information from State Emergency Response Commissions ("SERCs") and Local

[58] *See* 15 U.S.C. § 2610(c) ("In carrying out this chapter, the Administrator may by subpoena require . . . the production of reports, papers, documents, answers to questions, and other information that the Administrator deems necessary."); *U.S. E.P.A. v. Alyeska Pipeline Serv. Co.*, 836 F.2d 443, 448 (9th Cir. 1988) (acknowledging EPA's broad discretion to issue subpoenas under TSCA).

[59] As the proposed definition of "reasonably available information" suggests, EPA can and must not only request information, but synthesize and analyze it where necessary to determine conditions of use and susceptible subpopulations. This should include, where appropriate, EPA analyses of raw data gathered by outside sources.

ED_004056A_00227267-00018

Emergency Planning Committees ("LEPCs") established pursuant to the Emergency Planning and Community Right to Know Act[60] about reported accidents and releases involving these chemicals.

- information from state and local environmental agencies about permit violations and releases of these chemicals into the environment including into drinking water.

- site-specific enforcement information from OSHA and NIOSH and medical surveillance data for asbestos and methylene chloride.

- information from the Agency for Toxic Substances and Disease Registry ("ATSDR"), particularly the Petition Assessment Branch and the Division of Health Assessment and Consultation.

3) EPA must seek information directly from communities.

EPA must actively seek input from exposed communities regarding the first 10 TSCA substances because this information is "reasonably available" and directly relevant to understanding the conditions of use of these substances. In addition, outreach to affected communities is consistent with the "best available science" and TSCA section 26 requires that EPA use "best available science" in conducting its risk evaluations.[61]

a. Seeking Community Input Is Consistent with Recommendations by Scientific Authorities

Seeking community input on the scope of EPA's risk evaluations for the first 10 TSCA substances is consistent with the recommendations of NRC. In *Science and Decisions*, NRC's Committee on Improving Risk Analysis Approaches Used by the U.S. EPA stressed the importance of involvement by stakeholders, including community groups: "Without [stakeholder] involvement, the committee sees no way to ensure that the decision process will be

[60] 42 U.S.C. § 11001 *et seq.*

[61] TSCA section 26(h) requires that, "to the extent that the Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science…." A risk determination, *i.e.*, a determination that a chemical substance does, or does not, pose an unreasonable risk of injury to health or the environment, is a decision based in part on a risk evaluation. A risk evaluation, in turn, is based largely on science, *e.g.*, toxicological and/or epidemiological studies of hazard, or studies of exposure. EPA must ensure that risk evaluations are consistent with the "best available science."

ED_004056A_00227267-00019

satisfactory; indeed, without such involvement, it is inevitably deficient."[62] NRC emphasized that stakeholder involvement required more than public comment periods, calling these "obviously important, but…insufficient."[63] Rather, "stakeholder involvement…should include substantive involvement in the assessment process," including "explicit attempts to build capacity to ensure that all stakeholders have an equal opportunity to participate substantively in collaborative problem-solving."[64] To comport with "best available science" standards, EPA must reach out to communities to seek their input, rather than simply hope that communities will submit comments to the agency.

b. Seeking Community Input Is Essential When Conducting Cumulative Risk Assessments

As discussed above, when the risk of injury from exposure to a chemical substance may vary with exposure to multiple agents or stressors, EPA must evaluate cumulative risk by conducting a *cumulative risk assessment*. Conducting a cumulative risk assessment for one of the first 10 TSCA chemicals would require EPA to identify exposures to agents or stressors that may modify the risk posed by the chemical. These exposures may depend upon factors that only affected communities may know. For example, communities near facilities that emit the chemical may know what consumer products that also contain the chemical are used by members of the community, and how the products are used. The actual use of consumer products may vary from the directions for use on the product label. Separately, communities near facilities that emit the chemical can help EPA determine activity patterns relevant to exposure, *e.g.*, children may play near facilities due to the presence of a playground by the facility. EPA cannot conduct a cumulative risk assessment, as the best available science standard would require, without seeking community input. If the best available science suggests that the risk of injury posed by exposure may vary with exposure to other agents or stressors for one or more of the first 10 TSCA substances, community input will be critical to identifying other agents or stressors that should be included in a cumulative risk assessment.

E. EPA Should Use Reasonably Available Information to Identify the Disproportionately Impacted Subpopulations

As noted above, TSCA requires that the scope of a risk evaluation include "the potentially exposed or susceptible subpopulations the Administrator expects to consider." ACC, in its August 2016 comments, recommended that EPA "describe the process it will use to identify subpopulations and how it will make a determination that the subpopulation is relevant to the

[62] NRC, *Science and Decisions* 250 (2009).

[63] *Id.* at 250-51.

[64] *Id.* at 234-35.

ED_004056A_00227267-00020

risk evaluation."[65] While it is important that EPA follow a rigorous process to identify relevant subpopulations, this argument misses the point. It would be inappropriate to define in advance which subpopulations will be considered during risk evaluations. Congress purposely left this definition broad and inclusive by specifying that the term "potentially exposed or susceptible subpopulation" means "a group of individuals . . . who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, *such as* infants, children, pregnant people, workers, or the elderly."[66] Congress could have limited the term, but rather left it up to EPA to decide on a substance by substance basis which populations have "greater susceptibility or greater exposure" and thus must be considered specially in the risk evaluation.

The explicit reference to pregnant people, infants and children in TSCA emphasizes EPA's obligation to consider these groups in the scoping of the first 10 TSCA substances. The need to consider the special vulnerability of fetuses and children to chemicals is underscored by Executive Order 13,045, *Protection of Children From Environmental Health Risks and Safety Risks* (April 21, 1997). Executive Order 13,045 recognizes that "children may suffer disproportionately from environmental health risks and safety risks,"[67] and therefore requires all federal agencies to "make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children; and...ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks."[68] With respect to the first 10 TSCA substances in particular, EPA must consider exposure pathways at day care facilities and schools, many of which are housed in older buildings.[69] Children have little control over their environment, and may be exposed to

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[65] American Chemistry Council, ACC Comments to Inform EPA's Rulemaking on the Conduct of Risk Evaluations under the Lautenberg Chemical Safety Act, EPA-HQ-OPPT-2016-0400-0028 at 10 (Aug.24, 2016), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0400-0028.

[66] 15 U.S.C. § 2602(12) (emphasis added).

[67] Exec. Order No. 13,045, 62 Fed. Reg. 19,885, 19,885 (Apr. 21, 1997).

[68] *Id.*

[69] Incidents of asbestos exposure in schools abound: *see, e.g.,* David Abel, *Schools fail to keep track of asbestos*, Boston Globe, Dec. 6, 2015, https://www.bostonglobe.com/metro/2015/12/05/schools-massachusetts-failing-monitor-asbestos-state-and-federal-officials-say/zyehlz8G01pI9lf7sI3meK/story.html; Tyler Silvy, *Greeley-Evans School District 6 in the Midst of Huge Asbestos Removal Project*, Greeley Tribune, Aug. 1, 2015 http://www.greeleytribune.com/news/17052947-113/greeleyevans-school-district-6-in-the-midst-of#; Michael Dinan, *Consultants Detail Asbestos, Lead Paint, PCB Levels at Saxe Middle School*, New Canaanite, Feb. 8, 2015, http://newcanaanite.com/consultants-detail-asbestos-leadpaint-pcb-levels-at-saxe-middle-school-22167; Andrew Davis, *Asbestos Found Inside Port Wentworth Elementary*, WSAV, June 5, 2015, http://wsav.com/2015/06/05/asbestos-found-inside-port-wentworth-elementary/; *School Board Cancels Classes Again After Mold, Asbestos Found in Elementary School*, Cent. Ill. Proud, http://www.centralillinoisproud.com/news/local-news/school-board-cancels-classes-again-after-mold-

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some of the ten chemicals during renovations or specialized courses such as shop class.[70] Pregnant individuals may also find themselves subject to workplace or drinking water exposures that they have little power to mitigate, and that have distinct effects on fetal development.[71]

TSCA requires EPA to identify which "potentially exposed or susceptible subpopulations" should be included in each of the risk evaluations for the first 10 TSCA substances by using reasonably available information to assess which subpopulations may have greater susceptibility or greater exposure to each substance. This will require actively seeking information from workers and unions, from communities near known or potential sources of each substance, as well as from other federal, state, and local agencies that may possess reasonably available information on those communities.

For example, according to the NRC, factors that influence susceptibility include age, gender, genetics, pre-existing disease, and exposures to other agents. The U.S. Census Bureau, the Bureau of Labor Statistics, and/or state and county demographers will have information on the age and gender of affected communities. In addition, CDC, ATSDR, and/or state and local health departments will have surveillance data that could inform analyses of pre-existing disease incidence and factors that explain such incidence.

For each of the first 10 TSCA substances, EPA's scoping analysis should determine whether any communities of color or people of lower socioeconomic status are disproportionately exposed and thus constitute a "potentially exposed or susceptible subpopulation." The Census Bureau has data on race, ethnicity and indicators of socio-economic status (such as income and level of education) that are essential for an environmental justice impact analysis. In addition, EPA should rely on geocoded locations of industrial facilities and disposal sites, and modeled or measured exposures.

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asbestos-found-in-elementary-school/352414397. *See also* Liza Lucas, *Group finds asbestos in children's crayons, toy crime lab kits*, CNN, July 8, 2015, http://www.cnn.com/2015/07/08/health/crayons-toys-asbestos-report//

[70] Methylene chloride is used in most paint strippers, and may be used in schools. *See Center For Public Integrity Details Dangers Of Paint Stripper Solvent*, Nat'l Pub. Radio, Sept. 21, 2015, http://www.npr.org/2015/09/21/442308286/center-for-public-integrity-details-dangers-of-paint-stripper-solvent. It is also present in adhesives that may be used in class projects. *Safe and Healthy School Environments* 197 (Howard Frumkin et al. eds., 2006).

[71] *See, e.g.*, Rose Goldman et al., Pediatric Envtl. Health Specialty Unit, *Trichloroethylene (TCE) Exposures in Pregnant Women and Children: Guidance for the General Public* (2016), http://www.pehsu.net/_Library/facts/TCE_PEHSU_National_Factsheet_FINAL.pdf; Gail Sullivan, *In Massachusetts, contaminated drinking water linked to stillbirths*, Washington Post, Oct. 6, 2014, https://www.washingtonpost.com/news/morning-mix/wp/2014/10/06/in-massachusetts-contaminated-drinking-water-linked-to-stillbirths/

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Finally, community groups are a critical source of information about many of these factors. Communities also are the best source of information about a range of factors relevant to exposure such as activity patterns near the sources (*e.g.*, the presence of playgrounds, nursing homes, or other infrastructure that draw potentially vulnerable populations) and the use of consumer products that contain the substance in question.

The diverse set of factors that can influence susceptibility and exposure make it impossible to prejudge what specific process will be necessary to identify potentially exposed or susceptible subpopulations. EPA is obligated to utilize all reasonably available information to determine which subpopulations are especially vulnerable to harm from the first 10 TSCA substances. This requires active outreach to stakeholders, including those closest to the problem -- workers, communities, health care providers, and state and local governments.

CONCLUSION

We appreciate the opportunity to participate in the scoping process for the first 10 TSCA substances. It is our intent to aid EPA in identifying the reasonably available information about the conditions of use of the first 10 TSCA substances so that EPA's risk evaluation takes into account the full range of ways in which vulnerable and chemically over-burdened populations around the country are placed at risk by these chemicals. We look forward to continuing to participate in EPA's risk evaluation and risk management efforts under TSCA. To schedule a meeting or telephone call, please contact Eve Gartner, Staff Attorney, Earthjustice, egartner@earthjustice.org, or 212-845-7381.

Submitted by:

Earthjustice *on behalf of*

Alaska Community Action on Toxics
Alliance of Nurses for Healthy Environments
American Public Health Association - Occupational Health and Safety Section
Azul
BlueGreen Alliance
Brazilian Worker Center
Breast Cancer Prevention Partners
Campaign for Healthier Solutions
CATA – The Farmworkers Support Committee
Center for Biological Diversity
Center for Environmental Health
Citizens' Environmental Coalition
Clean and Healthy New York
Coming Clean
Connecticut Coalition for Environmental Justice

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Delaware Concerned Residents for Environmental Justice
Ecology Center
Empire State Consumer Project
Environmental Community Action
Environmental Health Strategy Center
Environmental Justice Health Alliance for Chemical Policy Reform
Environmental Justice Leadership Forum on Climate Change
Environmental Working Group
Farmworker Association of Florida
Glynn Environmental Coalition
Greater Syracuse Council on Occupational Safety and Health
GreenLatinos
Green Science Policy Institute
Headwater LLC
Healthy Building Network
Healthy Schools Network
The Imani Group
International Center for Technology Assessment
Just Transition Alliance
Labor Council for Latin American Advancement
League of Conservation Voters
League of United Latin American Citizens
Little Village Environmental Justice Organization
Made Safe
National Council for Occupational Safety and Health
Natural Resources Defense Council
New Jersey State Industrial Union Council
New Mexico Environmental Law Center
New York Lawyers for the Public Interest
Ocean Futures Society
Occupational Health Clinical Center
People Concerned about Chemical Safety
Physicians for Social Responsibility
Science and Environmental Health Network
Sheet Metal Occupational Health Institute Trust
Sierra Club
Sugar Law Center for Economic & Social Services
Union of Concerned Scientists
United Support and Memorial for Workplace Fatalities
Voces Verdes
WE ACT for Environmental Justice
West End Revitalization Association
WisCOSH
Women's Voices for the Earth
Worksafe

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