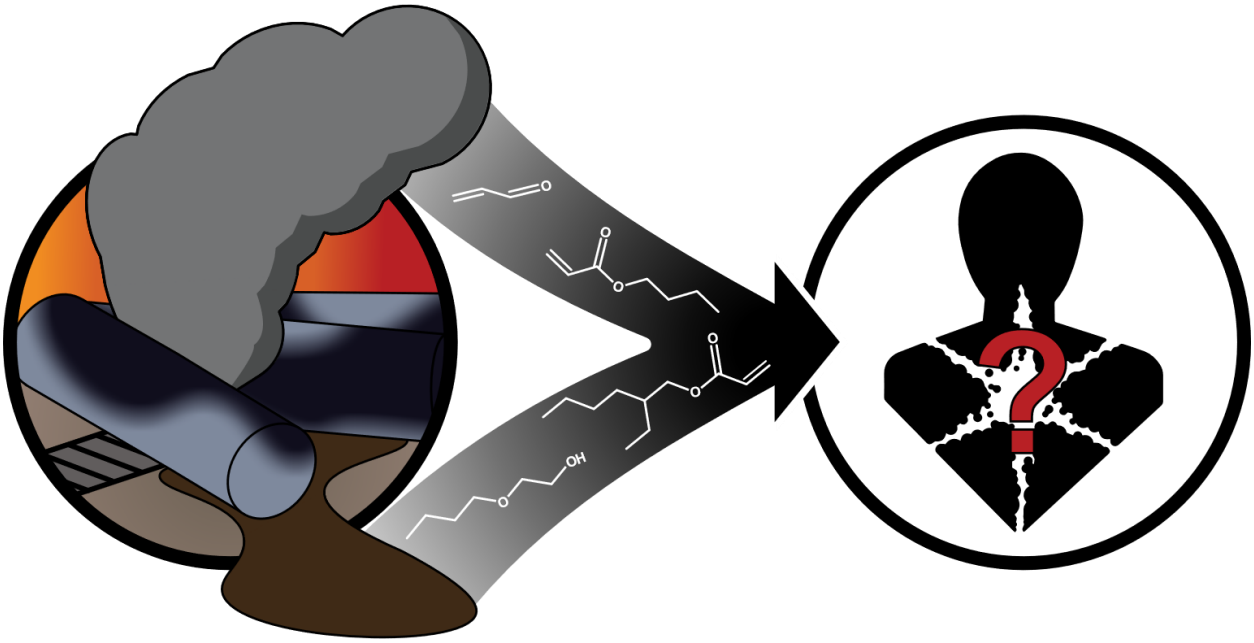
Rapid Scoping Review of East Palestine, Ohio Chemicals of Interest

October 2023



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Acronyms and Abbreviations

ACE	Assessment of Chemical Exposures
AEGL	Acute Exposure Guideline Levels for Airborne Chemicals
AR-AFFF	Alcohol Resistant Aqueous Film Forming Foam
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
BMDL	Lower 95% Confidence Limit of the Benchmark Dose
CalEPA	California Environmental Protection Agency
CASRN	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control and Prevention
CNS	Central Nervous System
CompTox	CompTox Chemicals Dashboard
CSF	Cancer Slope Factors
DNEL	Do Not Exceed Limits
DR2	Disaster Research Response Network
ECB	European Chemicals Bureau
ECHA	European Chemicals Agency
EECO	Evidence Stream, Exposure, Comparator, and Outcome
EPA	Environmental Protection Agency
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
LD50/LC50	Lethal Dose or Concentration at which 50% of the population does not survive
MeSH	Medical Subject Headings
MRL	Minimal Risk Levels
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OEHHA	CalEPA Office of Environmental Health Hazard Assessment
OR	Odds Ratio
PECO	Population, Exposure, Comparator, and Outcome
PFAS	Per- and polyfluoroalkyl substances
POD	Points of Departure
RA	Risk Estimate Available
REL	Recommended Exposure Limits
RfC	Reference Concentration
RfD	Reference Dose
SR	Systematic Review
TAMU	Texas A&M University
TCDD	Tetrachlorodibenzo-p-dioxin

Rapid Scoping Review of East Palestine, Ohio Chemicals of Interest

Introduction

Questions on the potential health effects from exposures associated with emergencies (e.g., disasters), emerging environmental contaminants, and novel human health concerns with unknown origins occur unexpectedly, yet regularly, and decision makers depend on timely access to high-quality, actionable information to protect public health. To respond effectively to disasters involving large-scale chemical releases and emerging contaminant issues and to provide information to communities, scoping reviews and systematic reviews (SRs) are critical resources to identify what we know about potential health effects, what we do not know, and thereby judge what we need to know. This information can also help in risk communication to affected communities, who have the right to know the potential short- and long-term health effects associated with exposure to chemicals they may not have heard of previously.

On February 3, 2023, a Norfolk Southern Railway general merchandise freight train derailed, releasing vinyl chloride and other hazardous chemicals into the environment in East Palestine, Ohio. Three days later, first responders conducted a controlled burn to prevent an explosion, releasing volatile organic compounds (e.g., acrolein, benzene) into the air and potentially leaving other residual chemicals in the soil. Unified Command, led by the Environmental Protection Agency (EPA), local/state government, and academic researchers (e.g., the Disaster Research Response [DR2] Network) have monitored—and continue to monitor—the air, soil, and water for chemicals of interest and untargeted analyses (not all of which has been shared publicly yet). Updates on available monitoring data are published for public access on EPA's East Palestine, Ohio Train Derailment webpage. Preliminary results from the Assessment of Chemical Exposures (ACE) Survey, administered by the Agency for Toxic Substances and Disease Registry (ATSDR) in conjunction with the Ohio and Pennsylvania Departments of Health, found that residents, Centers for Disease Control and Prevention (CDC) survey workers, and first responders reported short-term adverse symptoms (e.g., headaches, respiratory effects) consistent with acute chemical irritant exposure, mental health symptoms, and concerns about long-term health effects. Health agencies, the community, and others are concerned about potential long-term effects.

Objective: To inform potential future research on health effects and facilitate communication with affected communities, we conducted a phased scoping and rapid SR of health hazard information for the East Palestine chemicals of interest.

Methods

Overall Methods

This project included the following phases, which were iterative:

1. Scoping and visualization: Identification of chemicals of interest (Phase 1a)
2. Scoping and visualization: Summary of authoritative review conclusions on selected health outcomes for chemicals of interest (Phase 1b)
3. Targeted literature searching and screening: Summary of literature reviews and primary studies regarding key research gaps contributing to uncertainty on potential health effects for higher-priority (i.e., highest- and high-priority) chemicals (Phase 2)

A rapid SR may be conducted if Phase 2 scoping identifies any chemicals and health outcomes with an adequate database.

Identification of Chemicals of Interest

For this first phase, all the chemicals released during the train derailment and response with possible human exposures were chemicals of initial interest. We identified 15 chemicals of initial interest to review for available health effects data. These chemicals were released during the train derailment (N = 12) and from the controlled fire (N = 3), and the list of chemicals came from publicly available media sources (consistent with the Texas A&M University (TAMU) DR2 unit list), and internal communications (see Appendix B, Table B-1.). Subsequently, isobutylene was removed from the list based on correspondence with EPA clarifying that the train car carrying this chemical did not spill or burn.

Next, we conducted an initial prioritization (i.e., high vs. low) of the 15 chemicals to identify those with a higher likelihood of potential human exposure following release during the train derailment and/or subsequent fire. Available monitoring data and informal discussions were considered in this prioritization. The priority chemicals from this list included acrolein, benzene, butyl acrylate, ethylene glycol monobutyl ether ("2-butoxyethanol"), 2-ethylhexyl acrylate, hydrogen chloride, phosgene gas, and vinyl chloride. All chemicals were reviewed for available health-related evidence.

To extinguish the controlled burn, the fire was smothered in approximately 20 gal. of T-STORM F-787A alcohol resistant aqueous film forming foam (AR-AFFF) diluted in water. The product is manufactured by Williams Fire/Ansul and believed to contain per- and polyfluoroalkyl substances (PFAS) typical of other Ansul products (e.g., 6:2 FTNO [CASRN 80475-32-7], 6:2 FTSHA [CASRN 88992-45-4], 6:2 FTSAS [CASRN 88992-47-6], 6:2 FTSA [27619-97-2], 6:2 FTSA-PrB [CASRN 34455-29-3]) (Houtz et al. 2013; Place and Field 2012; Ruyle et al. 2021). According to the Safety Data Sheet, it also contained 4%–7% v/v diethylene glycol monobutyl ether. Common smaller chain breakdown products of these PFAS have been reported (Harding-Marjanovic et al. 2015; Ruyle et al. 2021; Yi et al. 2018), and some terminal PFAS (those that will not further breakdown) are estimated to stay in the environment for up to a century without remediation (Ruyle et al. 2023). There is a high probability that other products such as 2-(2-butoxyethoxy)ethanol [CASRN 112-34-5] and laurylamidopropyl betaine [CASRN 4292-10-8] were in this product (identified in other Ansul products) and may be a fairly large proportion of the remaining volume (Ruyle et al. 2021). Ultimately, the five PFAS (6:2 FTNO, 6:2 FTSHA, 6:2 FTSAS, 6:2 FTSA, and 6:2 FTSA-PrB) suspected to be in the AR-AFFF that was used to extinguish the burn were also included in this review.

Box 1. Authoritative Sources Reviewed for Hazard Conclusions

- CalEPA OEHHA Chemical Summaries
- CDC's ATSDR Toxicological Profiles
- ECHA Risk Assessment Reports and Toxicological Summaries
- EPA's CompTox Dashboard
- EPA's IRIS Assessments
- Health Canada's Priority Substances List Assessment Reports
- IARC Monographs
- National Academies' AEGL Reports (select chemicals)
- NIOSH Chemical Pocket Guides
- NTP carcinogenicity, genotoxicity, and teratology results

Although EPA and others have detected numerous other chemicals in the environment (air, soil, and water) as part of East Palestine-related monitoring activities, it is unclear whether those additional elevated chemicals are related to the East Palestine spill or may have been there prior to the train derailment. We are actively engaging with relevant government agencies (and respective websites) and academic communities to identify additional chemicals related to the East Palestine train derailment and may conduct additional scoping for other relevant chemicals.

Phase 1: Summary of Authoritative Review Conclusions

To inform our understanding of potential health effects and key data gaps for the chemicals of interest, including the five PFAS, we searched for and extracted data on human health hazards available from selected authoritative sources (see Box 1). The National Academies' Acute Exposure Guideline Level (AEGL) Reports were extracted for select chemicals (phosgene gas and hydrogen chloride) after identifying data gaps.

Data from the authoritative sources were extracted for the health outcome categories listed in Box 2. Human health hazard conclusions were prioritized for extraction, along with human-relevant risk estimates (e.g., cancer slope factors [CSF], minimal risk levels [MRL], reference doses [RfD], reference concentrations [RfC], recommended exposure limits [REL], do not exceed limits [DNEL]). If human health hazard conclusions or risk estimate values were not available, we made note of available toxicity values (e.g., points of departure [POD], lethal dose or concentration at which 50% of the study population does not survive [LD50 or LC50]) and critical effects. If none of the above information was available, we noted if human and/or animal data were available for the category.

Box 2. Health Outcome Categories for Data Extraction

Cancer[a]	Immune[a]
Cardiovascular[b]	Nervous[a]
Developmental[a]	Ocular[a]
Endocrine	Renal[b]
Gastrointestinal[b]	Reproductive[a]
Genotoxicity	Respiratory irritation[a]
Hematological[b]	Skin irritation/sensitivity[a]
Hepatic[b]	Systemic[b]

[a]Major health outcomes
[b]Less reported health outcomes

We completed data extraction in Microsoft Excel. In addition to publication information (e.g., source name, access link, date of publication), we extracted the following information for each health effect category (when applicable): hazard conclusion or risk estimate and critical effect, evidence type (e.g., human or animal), duration and route of exposure, and additional relevant information (as necessary). A primary extractor reviewed and extracted the health effects data from all sources for each chemical, and the extraction was checked for completeness and accuracy by a secondary extractor.

Following initial extraction, we compiled results into a summary file to better understand data gaps across the chemicals and health outcome categories. For each chemical, we compiled major health hazard conclusions and relevant risk estimates in summary lists and included information on available data for the major health outcome categories presented in Box 2. We also included a list of authoritative sources (with links to web pages) with available data for each chemical.

We conducted additional targeted searches in the Causaly platform (accessible at: https://www.causaly.com/) for all chemicals using the term “diseases affected” by chemical name. Causaly leverages artificial intelligence to rapidly search the body of available biomedical literature for a given chemical and, therefore, provides timely output. The output provides a list of health outcome categories identified in the published literature for the chemical, the projected relationship between the chemical and the health outcome (e.g., upregulated, downregulated, bidirectional), and the citation for the published literature. These outputs from Causaly should be considered with caution, as we were unable to determine whether studies or data on specific health evidence were missing from the results. However, our use of a phased approach, starting with an assessment of authoritative reviews for each chemical, increases confidence that major health effects data were captured. When Causaly identified relationships between a priority chemical and a health outcome, we compared those results with the gaps identified from authoritative source reviews. If the Causaly results indicated an identified gap may have available literature, we reviewed the citations to better understand the available evidence. Based on this information, we prioritized additional health outcome categories as suggestive data gaps.

Identification of Key Research Gaps

We used the integrated extraction results in the summary file to identify health effect data gaps for each chemical (see Results and Discussion below). Specific chemical and health outcome (“chemical × health outcome”) research gaps were considered for additional targeted searches in PubMed®.[3]
Chemical × health outcome research gaps were further prioritized and selected according to the following

[3]Note that given the rapid nature of the review, a single bibliographic database was searched; PubMed was selected due to its broad coverage of health effects research.

criteria:

1. Initial priority of the chemical based on potential for human exposure following release (see Identification of Chemicals of Interest). Higher-priority chemicals were considered for additional review.
2. Hazard conclusion data available. Chemical × health outcome pairings with gaps (i.e., those that lacked definitive conclusions or had no or few studies) were candidates for additional literature searches.
3. Recency of available hazard conclusion. Chemicals with recent (i.e., published 2022–2023) reviews from authoritative sources that reported hazard conclusions were not prioritized. In contrast, chemicals with few studies from older reviews were prioritized.

Phase 2: Targeted Literature Searches and Screenings

Literature Searches

In Phase 2, literature searches were conducted to identify primary and review articles relevant to the chemical × health outcome pairings identified in Phase 1 reviews. Given the goals of this rapid review, a comprehensive literature search (e.g., using chemical names, synonyms, and CASRNs for all health effect-related studies across multiple bibliographic databases) and screening approach to identify relevant literature was not undertaken. Instead, two approaches were employed in Phase 2: first, targeted searches were conducted in PubMed to identify review articles on a given topic; then, additional searches were conducted in PubMed to identify primary articles published on the topic. If the search for reviews returned ≤20 results, the search for primary articles was immediately conducted. If the search for reviews returned >20 results, the need for a subsequent search to identify primary literature was assessed by the review team.

Terms to identify the appropriate chemical, health outcome, evidence type (e.g., human or animal), and study type were used to search for relevant primary and review articles.

1. Separate chemical search strings were developed for each chemical of interest. Chemical search terms were identified through EPA's CompTox Dashboard chemical synonym lists, which classifies the quality of listed synonyms as "Valid," "Good," and "Other." Each chemical was searched, and synonyms listed as "Valid" and "Good" were captured for the search string. The chemical was also searched in PubMed's Medical Subject Headings (MeSH) thesaurus to identify and retrieve indexing terms.
2. Search terms for each health outcome, evidence type, and epidemiological study design were identified using SWIFT-Review's publicly available Search Strategies Word documents (Sciome 2023) and the National Toxicology Program's (NTP's) Report on Carcinogens literature search approach (NTP 2015). Terms were then translated into the appropriate syntax for use in PubMed.

Strings were compiled according to chemical × health outcome pairings that were based on Phase 1 results (see Figure 1 and Figure 2; Appendix A, Table A-1). Additionally, when selecting chemical and health outcome pairings, we identified whether searches should target review or primary articles and designated which searches should return human vs. animal evidence. Search strings were adapted accordingly and are available in Appendix A.

Searches for designated chemical × health outcome pairings were conducted in PubMed in June and July 2023. For a given chemical × health outcome pairing, if the Phase 1 results included a recent authoritative review (i.e., published in 2019 through June/July 2023), a date restriction was added to the search to identify studies published after the authoritative review publication date and up to June or July 2023 when searches were conducted. Table 1 provides a list of conducted searches, and the Population, Exposure, Comparator, and Outcome (PECO) criteria used to guide the Phase 2 screening are available in Table A-1.

Following Phase 1 extractions, we anticipated that limited published literature would be available on the

five PFAS of interest for Phase 2 and sought information from EPA about ongoing reviews of the available literature for a variety of PFAS. Recent EPA literature reviews returned no literature for 6:2 FTSHA, 6:2 FTSAS, or 6:2 FTSA-PrB. As a result, we did not pursue these chemicals further. 6:2 FTNO was not represented in any of the existing EPA literature reviews, and 6:2 FTSA was included in a PFAS systematic evidence map published by EPA in 2022 (Carlson et al. 2022). To identify additional information about these chemicals, we conducted a nonrestricted literature search for 6:2 FTNO and a literature search to identify publications post-dating EPA's most recent search for 6:2 FTSA. Searches were conducted in PubMed in August 2023. Chemical search strings were developed using the approach outlined above, but searches were not otherwise restricted by health outcome category, evidence type, or study type in order to identify as much available literature as possible. Literature search details and results for relevant PFAS are included in Table 1.

Title-Abstract Screening

For title-abstract screening, results from literature searches were uploaded to DistillerSR, a platform for literature screening and management. Results from each chemical × health outcome search were screened completely before moving to the next pairing. For each reference, one screener reviewed the title and abstract and indicated PECO relevance. References were tagged as supplemental if a comparator population was not included (e.g., case reports/series, worker surveillance studies). References without an abstract were screened based on the title only. Ten percent of all excluded references were reviewed by a senior-level screener as a quality control and assurance measure. Full-text documents for relevant or supplemental references identified during title-abstract screening were retrieved by expert librarians.

Full-text Review and Extraction

References deemed PECO relevant or supplemental at the title-abstract level were reviewed at the full-text level in DistillerSR, which included an additional screening using the PECO criteria. Relevant and supplemental references also underwent tagging and data extraction. For relevant review articles and primary studies, information was extracted on the publication type, study design, evidence type, population characteristics (human), exposure conditions (animal), health outcomes, and findings.

Screeners were instructed to capture the most informative data on observed effects/conclusions to best capture the overall findings of each publication. For example, if a study reported a significant effect as a main finding alongside other null or nonsignificant results, the significant effect was extracted along with a summary of the other findings.

Data extraction was conducted by a primary screener and then reviewed by a senior-level screener for quality control and assurance purposes.

Supplementary Searches

During the scoping and review phases, additional monitoring data revealed elevated levels of dioxins in soil samples obtained from East Palestine. While not included in our initial scoping efforts, we conducted supplementary searches to identify available information on each chemical.

First, we conducted high-level searches to understand how authoritative sources from Phase 1 presented information on the health effects of dioxins. The web pages of select authoritative sources (ATSDR, California Environmental Protection Agency [CalEPA] Office of Environmental Health Hazard Assessment [OEHHA], European Chemicals Agency [ECHA], EPA CompTox and Integrated Risk Information System [IRIS], Health Canada, International Agency for Research on Cancer [IARC], and National Institute for Occupational Safety and Health [NIOSH]) were searched using the term "dioxins," and resources with relevant health information were identified. As dioxins are frequently discussed as a class rather than individual chemicals, we also noted how these resources referred to dioxins (e.g., whether information was provided only at the class level or whether information was provided for individual chemicals).

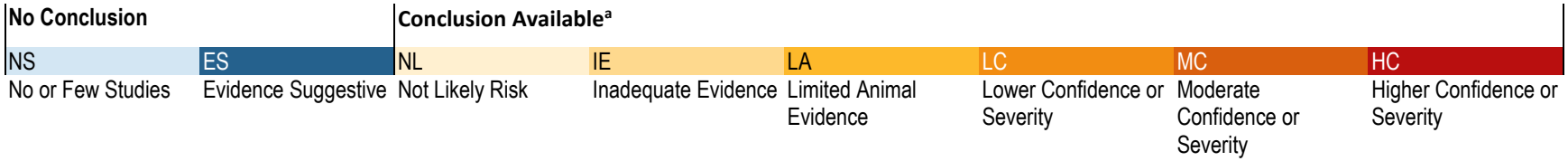
Next, to identify available information in recent peer-reviewed literature, we conducted a targeted search in PubMed. Search terms for dioxins were used to identify SRs and meta-analyses published from August 2018 through August 2023. Searches were conducted in August 2023 and were not restricted by evidence type or health outcome terms to identify as many results as possible. Titles of search results were screened to identify references discussing dioxins and health effects.

Results and Discussion

Phase 1

We integrated the extracted health outcome data for the initial 15 chemicals from each authoritative source (see Appendix B) to create an overview/map of the evidence (see Figure 1 and Table B-1.). The map provides information on whether, for each chemical, there is a health hazard conclusion and, if so, the confidence of the evidence or severity of the outcome (e.g., higher, moderate, lower) stratified by chemical priority (see Methods). If authoritative conclusions were not available, the map indicates whether the studies in the reviewed sources suggested an association with the health outcome or whether no/few studies were available. Determinations from the targeted Causaly searches were also incorporated for select chemicals (acrolein; 2-butoxyethanol; diethylene glycol; dipropylene glycol; hydrogen chloride; and 1,2 propylene glycol). See Figure 2 and Table B-2 for the overview/map of integrated health outcome data from authoritative sources for the five PFAS. Access information for the full data extraction Excel files is available in Appendix B.

Figure 1. Summary of Findings from Phase 1 Authoritative Source Reviews for 15 East Palestine Chemicals of Interest



Chemical (CASRN)	Cancer	Noncancer					Irritants/Sensitizers			
		Nervous	Immune	Developmental	Reproductive	Other Organs	Skin Sensitization	Skin Irritation	Eye Irritation	Respiratory Irritation
Highest-priority Chemicals										
Acrolein (107-02-8)	MC	ES	ES	NL	NL	MC / ES	ES	HC	HC	HC
Butyl Acrylate (141-32-2)	IE	NS	NS	NL	NL	ES	HC	HC	HC	MC
2-Butoxyethanol (EGBE) (111-76-2)	LA	ES	ES	NL	NL	HC / LC	NL	HC	HC	HC
2-Ethylhexyl Acrylate (103-11-7)	LC	NS	NS	NL	NL	NS	HC	HC	HC	HC
High-priority Chemicals										
Benzene (71-43-2)	HC	MC	HC	MC	LC	HC	NL	HC	HC	ES
Hydrogen Chloride (7647-01-0)	IE	NS	NS	NS	NS	ES	NL	HC	HC	HC
Phosgene Gas (75-44-5)	NS	NS	ES	NS	NS	HC	NS	HC	HC	HC

Chemical (CASRN)	Cancer	Noncancer					Irritants/Sensitizers			
		Nervous	Immune	Developmental	Reproductive	Other Organs	Skin Sensitization	Skin Irritation	Eye Irritation	Respiratory Irritation
Vinyl Chloride (75-01-4)	HC	MC	LC	LC	NS	MC	HC	HC	HC	HC
Moderate-priority Chemicals										
Diethylene Glycol (111-46-6)	NL	ES	NS	NL	NL	ES	NL	NL	NL	NS
Dipropylene Glycol (25265-71-8)	NL	NS	NS	NL	NL	NS	NL	LC	LC	NS
Polypropylene Glycol (25322-69-4)	NS	ES	NS	NS	NS	ES	NL	ES	HC	NL
1,2 Propylene Glycol (57-55-6)	NL	NS	NS	NL	NL	LC	NL	NL	NL	ES
Low-priority Chemicals										
Petroleum Lube Oil (64742-58-1)	NS	NS	NS	NS	NS	NS	NS	HC	HC	NS
Polyethylene (9002-88-4)	IE	NS	NS	NS	NS	NS	NS	NS	NS	NS
Polyvinyl Alcohol (9002-89-5)	IE	NS	NS	NS	NS	NS	NS	NS	NS	NS

See Table B-1. for more details.

[a]"Conclusions available" relate to language used by authoritative sources as follows: inadequate evidence = nonclassifiable (cancer); limited animal evidence = nonclassifiable (cancer); lower confidence or severity = possibly (cancer), suspected (noncancer), irritant category with other conflicting data, conflicting sensitizing data; moderate confidence or severity = probably (cancer), presumed (noncancer), animal data-derived risk estimate value, category 3 (irritant), category 1B (sensitizer); higher confidence or severity = known (cancer, noncancer), human data-derived risk estimate value, category 1 and 2 (irritant), category 1A (sensitizer).

Figure 2. Summary of Findings from Phase 1 Authoritative Source[a] Reviews for Five PFAS Chemicals

No Conclusion		Conclusion Available[b]					
NS	ES	NL	IE	LA	LC	MC	HC
No or Few Studies	Evidence Suggestive	Not Likely Risk	Inadequate Evidence	Limited Animal Evidence	Lower Confidence or Severity	Moderate Confidence or Severity	Higher Confidence or Severity

Chemical (CASRN)	Cancer	Noncancer					Irritants/Sensitizers			
		Nervous	Immune	Developmental	Reproductive	Other Organs	Skin Sensitization	Skin Irritation	Eye Irritation	Respiratory Irritation
6:2 FTSHA (88992-45-4)	NS	NS	NS	MC	MC	NS	LC	NL	HC	NS
6:2 FTSAS (88992-47-6)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
6:2 FTSA (27619-97-2)	NS	NS	NS	NL	NL	NS	NL	HC	HC	NS
6:2 FTSA-PrB (34455-29-3)	NS	NS	NS	NS	NS	NS	NL	NL	ES	NS
6:2 FTNO (80475-32-7)	NS	NL	NS	NL	NL	NS	NL	NL	NL	NS

See Table B-2 for more details.
PFAS = per- and polyfluoroalkyl substances.
[a]A list of authoritative sources is available in Box 1.
[b]"Conclusions available" relate to language used by authoritative sources as follows: inadequate evidence = nonclassifiable (cancer); limited animal evidence = nonclassifiable (cancer); lower confidence or severity = possibly (cancer), suspected (noncancer), irritant category with other conflicting data, conflicting sensitizing data; moderate confidence or severity = probably (cancer), presumed (noncancer), animal data-derived risk estimate value, category 3 (irritant), category 1B (sensitizer); higher confidence or severity = known (cancer, noncancer), human data-derived risk estimate value, category 1 and 2 (irritant), category 1A (sensitizer).

Irritation

Testing or health characterization of chemicals was the most complete for acute effects such as irritation or sensitization (see Figure 3). Most chemicals were classified as causing skin (10 of 15 chemicals) or eye (11 of 15 chemicals) irritation, including all the higher-priority chemicals, two moderate-priority chemicals (dipropylene glycol for both outcomes and polypropylene glycol for eye), and one low-priority chemical. The reviews concluded that diethylene glycol was not a skin or eye irritant, and 1,2 propylene glycol was not an eye irritant. No other conclusions were identified for the other moderate- and low-priority chemicals. Approximately half (7 of 15 chemicals) cause respiratory irritation, including seven higher-priority chemicals. Polypropylene glycol was not considered a respiratory irritant. No authorative conclusions were found for benzene, three of the four moderate-priority chemicals, and all three low-priority chemicals. However, the reviews reported individual study findings for benzene, diethylene glycol, and 1, 2 propylene glycol. Adverse respiratory effects or irritation from multiple chemicals are consistent with reported symptoms (e.g., running nose; congestion; coughing; burning nose, throat, or eyes; irritation) from the affected community and first responders in CDC's ACE survey.

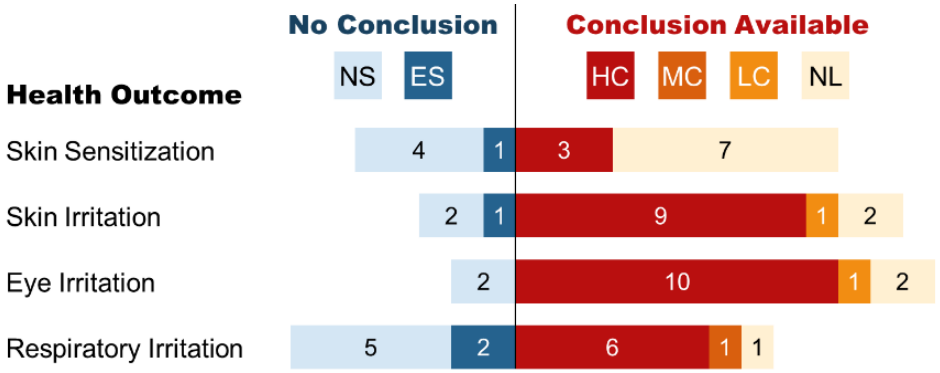
For PFAS, one chemical (6:2 FTSA) was classified for corrosive effects to the skin, whereas three chemicals (6:2 FTSHA, 6:2 FTSA-PrB, and 6:2 FTNO) did not have irritating effects to the skin in studies reported in Phase 1 sources. Conclusions for eye irritation were available for two chemicals (6:2 FTSHA and 6:2 FTSA); some irritation was reported following exposure to 6:2 FTSA-PrB in rabbits, and no eye irritation was predicted for 6:2 FTNO based on in vitro assay results. Data were not available for categorizing irritating effects to the respiratory system following PFAS exposures.

Skin Sensitization

While some authoritative sources discussed skin sensitization in the context of immune effects, skin sensitization was characterized as a separate outcome category in this review. Three higher-priority chemicals were categorized for skin sensitizing effects (butyl acrylate, 2-ethylhexyl acrylate, and vinyl chloride). ECHA reported sensitizing properties for acrolein, another higher-priority chemical, but did not categorize it for sensitization. Little or no indication of skin sensitization was reported for seven chemicals (2-butoxyethanol, benzene, hydrogen chloride, diethylene glycol, dipropylene glycol, polypropylene glycol, and 1,2 propylene glycol). No or unclear conclusions were available for the remaining chemicals.

Among the five PFAS, authoritative sources reported little or no concern for skin sensitization following exposure to three chemicals (6:2 FTSA, 6:2 FTSA-PrB, and 6:2 FTNO). Mixed results were reported from animal and in vitro studies for one chemical (6:2 FTSHA). Skin sensitization data were not available for the remaining PFAS (6:2 FTSAS).

Figure 3. Phase 1 Irritant and Sensitizer Findings for 15 East Palestine Chemicals of Interest



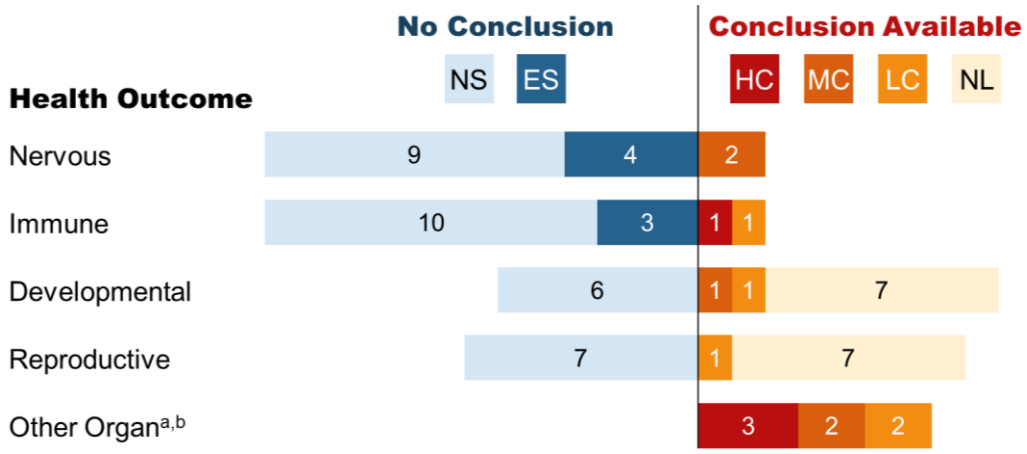
NS = no or few studies; ES = evidence suggestive; NL = not likely to be irritating or sensitizing; LC = lower confidence: irritant category with other conflicting data; MC = moderate confidence or severity: animal data-derived risk estimate value, category 3 (irritant), category 1B (sensitizer); HC = higher confidence or severity: human data-derived risk estimate value, category 1 and 2 (irritant), category 1A (sensitizer).

Other Noncancer Outcomes

Authoritative conclusions for reproductive and developmental toxicities were available for approximately half of all chemicals (see Figure 4 for noncancer outcome findings). Of the eight higher-priority chemicals, two (benzene and vinyl chloride) may be linked to developmental effects. CalEPA Proposition 65 lists benzene as a chemical that can cause developmental and reproductive effects; other reviews agreed with the developmental effects conclusions (particularly for developmental hematotoxicity) but stated that the evidence for reproductive effects was limited. Although positive associations have been observed for 2-butoxyethanol exposure and adverse reproductive (e.g., effects to reproductive organs or in pregant animals) and developmental outcomes, these effects occurred at high doses or at doses causing maternal toxicity. As a result, several authoritative sources concluded that the chemical is not significantly toxic to reproduction or the developing fetus. ECHA concluded there was little concern for the reproductive and developmental effects from exposure to three other higher-priority chemicals (acrolein, butyl acrylate, and 2-ethylhexyl acrylate) and three moderate-priority chemicals (diethylene glycol, dipropylene glycol, and 1,2 propylene glycol). No or unclear conclusions for both reproductive and developmental effects are available for the remaining high-priority chemicals: hydrogen chloride and phosgene gas. ECHA classified one of the five PFAS (6:2 FTSHA) as a presumed toxicant to fertility and development. Three of the remaining PFAS did not display either reproductive (6:2 FTSA and 6:2 FTNO) or developmental (6:2 FTSA, 6:2 FTSA-PrB, and 6:2 FTNO) toxicity. No conclusions were available for the remaining PFAS (6:2 FTSAS).

Health outcome conclusions were sparse for neurotoxicity (2 of 15 chemicals) and immunotoxicity (2 of 15 chemicals). Vinyl chloride was deemed a presumed neurotoxicant and a suspected immunotoxicant, and benzene was associated with both neurotoxicity in workers exposed to high doses and adverse immune effects. Some authoritative sources noted that some immunotoxicity outcomes associated with benzene exposure may result from hematotoxicity or may occur at levels like those inducing hematotoxicity.

Figure 4. Phase 1 Noncancer Findings for 15 East Palestine Chemicals of Interest



NS = no or few studies; ES = evidence suggestive; NL = not likely risk; LC = lower confidence: suspected; MC = moderate confidence: presumed, animal data-derived risk estimate value; HC = higher confidence: known, human data-derived risk estimate value.
[a]The "Other Organ" category includes double counts for one chemical (2-butoxyethanol), wherein different conclusions (e.g., lower confidence and higher confidence) were available for different organ systems.
[b]Information on "Other Organ" systems was not reported consistently across authoritative reviews. "No conclusion" determinations for the Other Organ category are not included in this figure due to the heterogeneous reporting.

Based on identifed research gaps for the higher-priority chemicals, we selected the following chemical-outcome pairs for Phase 2 activities (see Methods).

Neurotoxicity: Acrolein, 2-ethylhexyl acrylate, butyl acrylate, 2-butoxyethanol

Immunotoxicity: Butyl acrylate, 2-butoxyethanol

Hepatotoxicity: Butyl acrylate

Cancer Outcomes

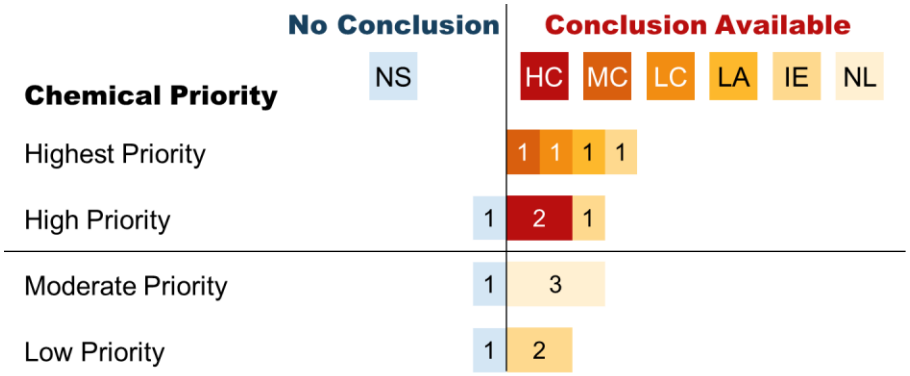
Cancer conclusions were available for approximately two-thirds (12 of 15) of the chemicals (see Figure 5). Of the eight higher-priority chemicals, five can cause cancer in humans or experimental animals: benzene and vinyl chloride are “known human carcinogens” (IARC, NTP Report on Carcinogens), acrolein is “probably carcinogenic to humans” based on mechanistic and animal cancer data (IARC 2A), 2-ethylhexyl acrylate is “possibly carcinogenic to humans” (IARC 2B) based on sufficient evidence from studies in experimental animals, and 2-butoxyethanol induces tumors (hemangiosarcoma of the liver in male mice). IARC considered the evidence limited in experimental animals for 2-butoxyethanol and, thus, not classifiable as to its carcinogenicity (Group 3). Butyl acrylate and hydrogen chloride are also classified as Group 3 by IARC based on inadequate evidence from experimental animal and human studies. No conclusions were available for phosgene gas. The other moderate- and low-priority chemicals were either not likely to cause cancer or had no identifiable conclusions. Cancer types were available for the known human carcinogens: benzene causes acute myeloid leukemia and other acute nonlymphocytic leukemia and may cause other lymphohematopoietic cancers (chronic myeloid leukemia, chronic lymphocytic leukemia, childhood leukemia, non-Hodgkin lymphoma, and multiple myeloma) and lung cancer; vinyl chloride causes angiosarcomas in the liver.

Data on cancer effects were not available from authoritative sources for the five PFAS. Based on these research gaps, we identified the following chemicals for Phase 2 searches for cancer outcomes:

Human cancer studies: Acrolein, 2-ethylhexyl acrylate, 2-butoxyethnanol

Human and animal cancer studies: Butyl acrylate

Figure 5. Phase 1 Cancer Findings for 15 East Palestine Chemicals of Interest



NS = no or few studies; NL = not likely risk; IE = inadequate evidence: nonclassifiable; LA = limited animal evidence: nonclassifiable; LC = lower confidence: possibly carcinogenic to humans; MC = moderate confidence: probably carcinogenic to humans, animal data-derived risk estimate value; HC = higher confidence: known human carcinogen, human data-derived risk estimate value.

Phase 2

Overview

Results from the 13 targeted searches and screenings conducted during Phase 2 are available in Table 1. For six of the 13 searches (acrolein-cancer, 2-ethylhexyl acrylate-cancer, 2-ethylhexyl acrylate-nervous, butyl acrylate-hepatic, butyl acrylate-nervous, 6:2 FTNO-any health outcome), no relevant results were identified during title-abstract and/or full-text screening.

At least one PECO-relevant reference was identified for each of the remaining seven searches (acrolein-nervous [n = 8], 2-butoxyethanol-cancer [n = 1], 2-butoxyethanol-immune [n = 10], 2-butoxyethanol-

nervous [PECO relevant n = 1; PECO supplemental n = 3], butyl acrylate-cancer [n = 1], butyl acrylate-immune [PECO relevant n = 2; PECO supplemental n = 3], and 6:2 FTSA-any health outcome [n = 2]). Although five PECO-relevant studies were identified for butyl-acrylate-immune, all five reported on skin sensitization findings only. As skin sensitization data were considered separately from immune data during Phase 1, the five studies were not considered for further analysis during Phase 2.

For the remaining six chemical × health outcome pairings, PECO-relevant studies were compared with the list of studies included in authoritative source reports identified during Phase 1. New studies were identified for each chemical × health outcome pair. For chemical × health outcome pairings with at least one new study (acrolein-nervous, 2-butoxyethanol-cancer, 2-butoxyethanol-immune, 2-butoxyethanol-nervous, and 6:2 FTSA-any health outcome), we examined and summarized all studies identified during Phase 2, alongside some findings from authoritative source reports in Phase 1. Findings for each chemical × health outcome pair are summarized by endpoint in the text (acrolein-nervous; 2-butoxyethanol cancer; and 6:2 FTSA-any health outcome) and Table 2 (2-butoxyethanol-immune) and Table 3 (2-butoxyethanol-nervous) below.

Table 1. Overview of Phase 2 Results

Chemical-Outcome Category	Phase 1 Authoritative Source Conclusions	Search Limits, Date Completed	Results (N)	PECO-relevant Studies (N)	Phase 2 New Studies (N)	Evidence Gap
Acrolein-Cancer	Probably carcinogenic to humans (Group 2A); Inadequate human evidence	Studies published 2020–present, June 22, 2023	183	0	0	Research gap remains (human cancer studies)
Acrolein-Nervous	No conclusions: Suggestive evidence from Causaly	No date limit, June 20, 2023	226	8 reviews	7 reviews	Systematic review may be warranted
2-butoxyethanol-Cancer	Not classifiable (Group 3); Limited evidence in experimental animals	No date limit, July 6, 2023	35	1 human	1 human	Research gap remains
2-butoxyethanol-Immune	No conclusions: Suggestive evidence	No date limit, July 5, 2023	151	1 human 9 animal	1 human 1 animal	Additional studies with focus on functional immunotoxicity are needed
2-butoxyethanol-Nervous	No conclusions: Suggestive evidence	No date limit, July 5, 2023	112	1 animal 3 supplemental	1 animal	Additional studies designed to assess neurological effects are needed
Butyl acrylate-Cancer	Not classifiable (Group 3); Inadequate human and animal evidence	No date limit, July 6, 2023	65	1 animal	0	Research gap remains
Butyl acrylate-Hepatic	No conclusion: Suggestive evidence	No date limit, July 7, 2023	19	0	0	Research gap remains
Butyl acrylate-Immune	No conclusions: Few studies; Skin sensitization: Category 1	No date limit, July 5, 2023	92	2 animal[a] 3 supplemental[a]	0	Research gap remains (immune endpoints other than skin sensitization)
Butyl acrylate-Nervous	No conclusions: Few studies	No date limit, July 5, 2023	97	0	0	Research gap remains
2-ethylhexyl acrylate-Cancer	Possibly carcinogenic (Group 2B); Inadequate human evidence	Studies published 2019–present, June 20, 2023	6	0	0	Research gap remains (human cancer studies)
2-ethylhexyl acrylate-Nervous	No conclusions: Few studies	No date limit, June 23, 2023	9	0	0	Research gap remains

Chemical-Outcome Category	Phase 1 Authoritative Source Conclusions	Search Limits, Date Completed	Results (N)	PECO-relevant Studies (N)	Phase 2 New Studies (N)	Evidence Gap
6:2 FTSA-Any	Skin irritation: Category 1B; Eye irritation: Category 1; No effects for developmental, reproductive outcomes or skin sensitization in animal studies. No other conclusions based on limited evidence in experimental animals.	Studies published 2020–present, August 10, 2023	45	1 human 1 animal	1 human 1 animal	Research gaps remain
6:2 FTNO-Any	No effects observed on nervous, reproductive, developmental, hematologic, dermal, or ocular outcomes in animal studies.	No date limit, August 10, 2023	0	0	0	Research gaps remain

Bold chemical x outcome pairings are discussed in more detail in the following sections.
PECO = Population, Exposure, Comparator, and Outcome.
[a]All studies on skin sensitization.

Selected Chemical-Outcome: Acrolein-Nervous System

Four authoritative reviews—(ATSDR 2007a) (12 studies), (ECB 2001) (1 study), (USEPA 2003b) (1 study), and (OEHHA 2014) (4 studies)—discussed findings from studies examining acrolein exposures and neurological effects, although none made hazard conclusions. Additionally, outputs from Causaly identified reviews and primary articles that discussed potential associations between acrolein levels and various neurological outcomes, including Alzheimer's disease, Parkinson's disease, and strokes.

Our scoping search to find published reviews on neurological outcomes identified eight reviews discussing effects associated with acrolein exposure in humans and animals (Alarie 1973; Chang et al. 2022; Igarashi et al. 2018; 2020; Moghe et al. 2015; Muguruma et al. 2020; Park and Igarashi 2013; Singh et al. 2010). One review was discussed in ATSDR, 2007 (Alarie 1973), but the remaining four were not included in any authoritative sources. The four authoritative reports also included 14 primary studies in experimental animals—reporting effects related to neurotransmitter (neuropeptide) depletion, increased brain weight, inflammatory responses, loss of nerve tissue, and nonspecific histopathological effects (in inhalation studies)—and one primary study in humans—reporting increased acrolein levels in the brains of Alzheimer's patients compared to control subjects at autopsy. Most studies discussed in the ATSDR Toxicological Profile examined general toxicity in experimental animals and were not designed to measure neurotoxicity. A crosswalk of studies discussed in authoritative reviews and identified during Phase 2 is available in Table B-3.

Detailed results from the eight reviews identified in our scoping search are provided in the text below. As our search identified reviews only, a summary table is not provided. Importantly, exposure to acrolein can occur both exogenously and endogenously, as the chemical is a byproduct of lipid peroxidation initiated by oxidative stress. In the eight identified reviews, acrolein is often used as a biomarker for oxidative stress and lipid peroxidation. Therefore, it was often unclear whether neurological effects are related specifically to acrolein or to oxidative stress. The review findings should be considered in this context.

Three other reviews identified during Phase 2 reported on the mechanistic effects of acrolein in nervous tissues, although mechanistic evidence was not the primary focus of our scoping activities (Arlt et al. 2002; Iqubal et al. 2020; LoPachin et al. 2008). Acrolein was discussed as a highly toxic product of lipid peroxidation that can cross the blood-brain barrier (Iqubal et al. 2020). In vitro and in vivo studies of neuroinflammation and neurodegeneration and acrolein's role in the development of Alzheimer's Disease, Parkinson's Disease, and spinal cord injury were cited as evidence of its neurotoxic potential. Other reported mechanistic evidence suggests that acrolein induces demyelination of nerves—which impacts nerve conduction—neuronal apoptosis, neurotransmitter alterations, and protein adduct formation. Other reviews reported inhibition of glutamate and glucose uptake in acrolein-exposed neuronal cell cultures (Arlt et al. 2002) and disruption of nerve terminals and subsequent potential for synaptic damage in in vitro studies (LoPachin et al. 2008). These reviews suggest that acrolein, whether endogenous or exogenous, has the potential for neurotoxic effects.

Reviews of human and animal studies discussed the association between acrolein and strokes of varying severity (Chang et al. 2022; Igarashi et al. 2020; Moghe et al. 2015; Muguruma et al. 2020); however, the discussion of acrolein's role differed across reviews. Some reviews assessed acrolein's role in development of stroke or brain infarction, whereas others examined acrolein as a byproduct of the oxidative stress induced by stroke or brain infarction and its potential to cause additional neurological damage. Acrolein may be produced endogenously via lipid peroxidation during ischemic stroke (Chang et al. 2022), and increased endogenous acrolein production has been reported in connection with both severe strokes and silent brain infarctions (Muguruma et al. 2020). A mechanistic study summarized in Muguruma et al. (2020) suggested that acrolein elicited a cycling of oxidative stress, resulting in stroke-related neuronal damage, and is a suspected driver of neuronal damage in stroke patients. Plasma levels of protein-conjugated acrolein (along with acrolein-producing enzymes) were shown to be appropriate biomarkers for human stroke (Igarashi et al. 2018; 2020; Moghe et al. 2015; Park and Igarashi 2013) and silent brain infarctions (Igarashi et al. 2020). Multiple human studies have found dysregulated acrolein

metabolism in stroke patients (Chang et al. 2022).

Findings from reviews of animal studies further support an association between acrolein and stroke, although it was unclear whether animals were dosed in studies cited in the reviews or whether effects were associated with endogenous acrolein. A review of animal studies reported an association between decreasing levels of acrolein and decreased infarction size (Chang et al. 2022). A study in mice indicated that, during brain infarction, acrolein is "more strongly involved" in cell damage than reactive oxygen species (Igarashi et al. 2020). Other reviews reported increased levels of acrolein at the site of brain infarction in mouse models (Igarashi et al. 2018; Park and Igarashi 2013). Neuronal damage was also reported in a review of animal studies, including acrolein-induced neuronal damage in pigs and rats, although some studies reported effects of endogenous acrolein only and should be considered accordingly (Moghe et al. 2015). In an in vitro study, acrolein induced mitochondrial dysfunction leading to neuronal death in HT22 mouse hippocampal cells (Moghe et al. 2015).

Other neurological outcomes have also been considered for their association with acrolein exposure. In humans, significantly increased levels of acrolein were reported in the brains of patients with mild cognitive impairment (Igarashi et al. 2020; Muguruma et al. 2020; Singh et al. 2010) and cognitive impairment that had progressed to Alzheimer's disease compared to control subjects (Chang et al. 2022; Igarashi et al. 2020; Muguruma et al. 2020; Singh et al. 2010). For cases of Parkinson's disease, both human and animal studies reported that acrolein exposure leads to damage of the substantia nigra (Chang et al. 2022). In a mouse model of multiple sclerosis, acrolein was found to be a critical pathological factor in development of autoimmune encephalomyelitis (Chang et al. 2022). Finally, in a review of animals exposed to acrolein via inhalation, alterations in reflex reactions and sensory irritation were reported in guinea pigs. Alterations were a result of pulmonary nerve ending stimulation from the chemical. Decreased respiratory rates were also reported in guinea pigs and in rabbits (Alarie 1973).

Evidence Gap Summary: *A systematic review* critically assessing the body of evidence may be warranted of human, animal, and mechanistic studies, with a particular focus on effects from exogenous acrolein exposures.

Selected Chemical-Outcome: 2-Butoxyethanol-Cancer

IARC (2006) concluded that 2-butyoxyethanol was not classifiable based on its carcinogenicity to humans due to limited evidence from studies in experimental animals and inadequate evidence from studies in humans. One human study with limited information on 2-butoxyethanol exposure was identified. The limited evidence of carcinogenicity in experimental animals was from a study of 2-butoxyethanol inhalation in rats and mice published in NTP Technical Report 484 (NTP TR-484) (2000). Additional studies published after the IARC Monograph were not identified for the other two authoritative reviews (EPA IRIS (2010) and OEHHA (2018)). In mice, NTP (2000) concluded there was some evidence of carcinogenicity in males based on liver hemangiosarcomas and in females based on forestomach squamous cell papilloma or carcinoma (mainly papilloma). For rats, there was equivocal evidence of carcinogenicity in females based on benign and malignant pheochromocytoma (mostly benign) of the adrenal medulla and no evidence of carcinogenicity in males.

Our scoping activities to find cancer studies in the literature identified one primary article published after the authoritative reviews that described cancer effects associated with 2-butoxyethanol exposure in humans (Rodrigues et al. 2020). Rodrigues et al. (2020), an occupational nested case-control study of workers at three semiconductor and storage device manufacturing facilities, evaluated the association between exposure to 31 known or possible carcinogens, including 2-butoxyethanol, and central nervous system (CNS) cancers. The study reported significant exposure-response associations ($p_{trend} < 0.01$) with increased odds ratios (ORs) for CNS cancer incidence in all quartiles (vs. Quartile 1) at two of the three module manufacturing work sites assessed; ORs were <1 at the third site. Statistically significant positive trends were reported for several chemicals that were present in the module manufacturing work sites in addition to 2-butoxyethanol.

Evidence Gap Summary: A *research gap remains* for additional primary studies of the carcinogenicity of

2-butoxyethanol, particularly for studies of effects in human populations.

Selected Chemical-Outcome: 2-Butoxyethanol-Immune

Three authoritative reviews – (ATSDR 1998) (24 studies), (USEPA 2010) (5 studies), and (OEHHA 2018) (5 studies) – discussed findings from studies examining 2-butoxyethanol exposures and immune effects, although none made hazard conclusions. Despite the lack of hazard conclusions, each review provided summaries of immunological findings from several studies in animals and humans. Our scoping activities to find immunological studies in the published literature identified 10 discussing immune-related outcomes associated with 2-butoxyethanol exposure, including one primary article in a human population (Song et al. 2017) and nine primary articles in experimental rodents (rats and mice) (Chereshnev et al. 2014; Dodd et al. 1983; Exon et al. 1991; Ghanayem et al. 1987a; Grant et al. 1985; Krasavage 1986; Singh et al. 2001; Smialowicz et al. 1992; Starek et al. 2008). Two of these studies were not included in the collective authoritative source reports (Song et al. 2017; Starek et al. 2008). Additional animal toxicology studies summarized in ATSDR (1998) identified immunological effects in studies designed to assess general toxicity (and thus, not all were identified by our immune-targeted literature searches). These studies largely reported effects in lymphoreticular organs (e.g., thymus weight changes, thymus histopathology), whereas reviews from EPA IRIS (2010) and OEHHA (2023d) were primarily of studies designed to evaluate immunotoxicity and found evidence of immunomodulatory effects (see study summaries in Table 2). A crosswalk of studies discussed in authoritative reviews and identified during Phase 2 is available in Table B-4.

We reviewed studies identified in our scoping activities and the summaries of studies from authoritative reviews (that were not identified in our literature searches). In their discussion of immunotoxic effects, ATSDR (1998) discussed immune and lymphoreticular effects separately and noted that some impacts to lymphoreticular organs can be attributed to hematotoxicity rather than immunotoxicity (noting that there is overlap between the two, as leukocytes can be classified as part of both systems). These studies were not considered in this report's summary of immune effects. Additionally, we did not include four studies from the reports that examined skin sensitization in humans (CMA 1993; Greenspan et al. 1995), guinea pigs (Zissu 1995), and mice (Singh et al. 2002) because our review of authoritative sources discussed skin sensitization as a separate health outcome category (see Figure 1). Detailed summaries from 16 studies reporting immunotoxicity effects (functional and observational findings) are available in Table 2.

Evidence Gap Summary: *Additional studies focusing on functional immunotoxicity* are needed to provide more specific information on the direct effects of 2-butoxyethanol on the immune system. Available studies may not be adequate for an SR.

Table 2. Detailed Summary of 2-Butoxyethanol Immune Studies Identified during Phase 2

Endpoint, Identified Studies	Summary of Findings	Endpoint Summary
	Functional Immune Findings	
Antibody Response (Functional Assay) 3 *primary* articles in animals (Exon et al. 1991; Singh et al. 2001; Smialowicz et al. 1992)	• No significant findings in male and female rats exposed via drinking water for 21 days at doses ranging from 1,600 to 6,000 ppm (Exon et al. 1991) or in male rats dosed by oral gavage for 2 days after immunization at doses ranging from 50 to 100 mg/kg/day (Smialowicz et al. 1992). The authors attributed signficant findings at 200 mg/kg/day to hematotoxicity and mortality (Smialowicz et al. 1992). • No significant effects to IgM plaque-forming cell response to sheep red blood cells in female mice exposed topically for 4 days at doses ranging from 100 to 1,500 mg/kg/day (Singh et al. 2001).	No significant findings in two studies of rats at nontoxic doses and in one study of female mice.
Autoimmune Response	• A study of male rats following a single intraperitoneal injection of 20 mg/kg-bw reported significantly increased in vitro agglutination to the rat's own red blood cells collected prior to	Increased autoimmune response in one study of male rats that also

Endpoint, Identified Studies	Summary of Findings	Endpoint Summary
1 *primary* article in animals (Chereshnev et al. 2014)	study initiation, suggestive of autoimmune response (Chereshnev et al. 2014). The study also reported histopathological changes in the thymus, indicative of organ stress response (see Observational Findings below).	reported histopathological thymus effects.
Natural Killer (NK) Cell Activity 2 *primary* articles in animals (Exon et al. 1991; Singh et al. 2001)	• Significant increase in NK cytotoxic responses in male and female rats exposed via drinking water for 21 days at doses ranging from 1,600 to 6,000 ppm (Exon et al. 1991). • No effect on NK cytotoxic activity in female mice exposed topically for 4 days at doses ranging from 100 to 1,500 mg/kg/day (Singh et al. 2001).	Increased responses reported in one rat study; no change in one mouse study exposed to lower doses.
Delayed-type Hypersensitivity (DTH) Response 1 *primary* article in animals (Exon et al. 1991)	• No significant effects on the DTH response in male and female rats exposed via drinking water for 21 days at doses ranging from 1,600 to 6,000 ppm (Exon et al. 1991).	No significant findings in one study in rats.
Cytotoxic T Lymphocyte (CTL) Activity 1 *primary* article in animals (Singh et al. 2001)	• No signficant response to cytotoxic T-cell response (primarily CD8+ cells) (Singh et al. 2001).	No significant response in one study in mice.
Mixed Lymphocyte Response (MLR) 1 *primary* article in animals (Singh et al. 2001)	• Signficant reduction of the MLR to allogenic antigen in female mice exposed topically for 4 days at doses ranging from 100 to 1,500 mg/kg/day (Singh et al. 2001).	Reduced MLR in one study in mice.
Nonspecific Mitogenic Response (Lymphoproliferative Assays) 1 *primary* article in animals (Singh et al. 2001)	• B-cell mitogens: No significant effects to splenic B-cell lymphoproliferate response to LPS in female mice exposed topically for 4 days at doses ranging from 100 to 1,500 mg/kg/day (Singh et al. 2001). • T-cell mitogens: Significant reduction of lymphoproliferative response to splenic T-cell lymphoproliferate response to Con a in female mice exposed topically for 4 days at doses ranging from 100 to 1,500 mg/kg/day (Singh et al. 2001).	Reduced lymphoproliferative response results in T-cell assays in one study in mice. No effects in B-cell assays.
Observational Immune Findings		
Cytokines 1 *primary* article in animals (Exon et al. 1991)	• No significant findings in interleukin-2 (IL-2) or interferon (IFN) production in male and female rats exposed via drinking water for 21 days at doses ranging from 1,600 to 6,000 ppm (Exon et al. 1991).	Histopathology of the thymus was reported in one study that also found increased autoimmune response in rats. Other observational findings were largely mixed and lacked consistency, as studies reporting effects varied in design, route of exposure, and
Immune Organ Histopathology 9 *primary* articles in animals (CMA 1983; Chereshnev et al. 2014; Duprat and Gradiski 1979; Exon et al. 1991; Grant et al. 1985; Krasavage 1986;	• One study reporting autoimmune response following exposure also observed involution of the thymus (Chereshnev et al. 2014). Another study observed changes in thymic cellularity, including transient lymphocyte depletion in the cortex and increased lymphocytes in the medulla (Grant et al. 1985). • Two studies reported histopathological changes in the spleen, including a significant decrease in relative volume of white pulp (Chereshnev et al. 2014) and white atrophic pulp after death (Duprat and Gradiski 1979).	

Endpoint, Identified Studies	Summary of Findings	Endpoint Summary
Nachreiner 1994; NTP 1993; Shepard 1994)	• No histopathological changes were reported in the thymus or lymph nodes in other studies of rats, guinea pigs, mice, and rabbits of various designs. Most studies provided observational data only and did not include functional measures.	species. The study heterogeneity limits the ability to draw conclusions about observational immune findings.
Immune Organ Weight 6 *primary* articles in animals (CMA 1983; Exon et al. 1991; Grant et al. 1985; NTP 1993; NTP 2000; Singh et al. 2001)	• Mixed results were reported for relative and absolute thymus weights across studies of various designs, exposure routes, and measurement timings.	
White Blood Cell Counts and Differentials 1 *primary* article in humans (Song et al. 2017) 7 *primary* articles in animals (Dodd et al. 1983; Ghanayem et al. 1987a; Grant et al. 1985; Krasavage 1986; NTP 1993; NTP 2000; Starek et al. 2008)	• Mixed results were reported for white blood cell changes, including for total leukocyte counts and differentials, with studies reporting significant increases, significant decreases, and no significant changes across a variety of study designs, exposure routes, and measurement timings. • Lymphocyte counts were mixed across one study in humans and six studies in animals. Some studies of longer duration reported significant findings (increases and decreases) at earlier timepoints that were not reported at later timepoints. • Of studies reporting neutrophil counts, several reported significantly increased counts at various time points that were not observed at later time points. Other studies reported decreases or no change in counts.	

Selected Chemical-Outcome: 2-Butoxyethanol-Nervous System

Three authoritative reviews—(ATSDR 1998) (24 studies), (USEPA 2010) (9 studies), and (OEHHA 2018) (5 studies)—discussed studies of neurological effects following exposure to 2-butoxyethanol. ATSDR's review of the association between exposure to 2-butyoxyethanol and neurological effects included many general toxicology studies of animals exposed by oral, dermal, and inhalation routes and several case reports. Reviews from EPA and OEHHA were limited to case-reports. Our scoping activities to find neurological studies in the published literature identified one primary article in rats that was not included in any authoritative reviews (Nyska et al. 1999) and three human case reports included in the reviews (Burkhart and Donovan 1998; Dean and Krenzelok 1992; Osterhoudt 2002).

Below, we review the combined body of relevant literature (human and animal studies), which consists of animal evidence reported by ATSDR, an additional animal study identified in our scoping review, and the collective case reports/series identified in our scoping review and discussed in authoritative reviews.

ATSDR (1998) concluded that exposure to high doses in experimental animals can cause nervous system effects (e.g., physical weakness, unsteadiness, drowsiness, prostration, abnormal eye movement, convulsions). Studies also reported clinical observations prior to death (e.g., convulsions, nystagmus, moderate to marked inactivity, ataxia). While ATSDR classifies many of these as clinical signs of neurotoxicity, these could also be attributed to other causes. Thus, we did not include 14 animal studies reporting on these symptoms and clinical observations. Brain weight findings were also not included in this review, as ATSDR reported results from only two studies, and it was unclear whether this endpoint was measured in other general toxicity studies. Other observed effects in case reports and animal studies that may be more reflective of impacts to neurological function are included, such as cases of coma following exposure, severe CNS depression, and effects related to the motor and vestibular systems (e.g., impacts to coordination, loss of equilibrium), sensory systems (e.g., disturbed taste), and neurological histopathology (e.g., histopathological changes to the brain and nerves). A crosswalk of

studies discussed in our report from authoritative reviews and identified during Phase 2 is available in Table B-5.

Detailed summaries of neurotoxicity findings from 17 studies (8 case reports/series, 9 primary studies) are available in Table 3.

Evidence Gap Summary: *Additional studies are needed* including human epidemiological and additional animal studies specifically designed to assess neurological effects following exposure. Inadequate database for an SR.

Table 3. Detailed Summary of 2-Butoxyethanol Nervous Studies Identified during Phase 2

Endpoint, Identified Studies	Summary of Findings	Endpoint Summary
	Animal Studies	
Brain and Nerve Histopathology 5 *primary* articles in animals (CMA 1983; Dodd et al. 1983; Eastman Kodak 1983; Krasavage 1986; NTP 1993)	• No lesions or histopathological changes were noted in the brains or nervous tissue of rats, mice, or rabbits exposed via oral, inhalation, and dermal routes (CMA 1983; Dodd et al. 1983; Eastman Kodak 1983; Krasavage 1986; NTP 1993).	No histopathological changes identified.
Motor and Vestibular Deficits 3 *primary* articles in animals (Dodd et al. 1983; Dow 1986; Wier et al. 1987)	• Loss of coordination was observed in male and female rats after inhalation exposure to 523 and 867 ppm, respectively, for 4 hours (Dodd et al. 1983). • Male albino rabbits showed loss of equilibrium and poor coordination from inhalation exposure for 7 hours/day for 1–2 days at ~400 ppm (Dow 1986). • Pregnant mice exposed via gavage at ≥1,500 mg/kg/day experienced lethargy and failure to right (Wier et al. 1987).	Signs of coordination and equilibrium loss in three animal studies.
Sensory Impacts 1 *primary* article in animals (Nyska et al. 1999)	• Photoreceptor degeneration observed in 5/8 female rats following daily gavage exposure to 250 mg/kg-bw for 3 days (Nyska et al. 1999).	Photoreceptor effects in one animal study.
	Human Studies	
Severe Nervous System Depression (Including Coma) 5 *case reports* in humans (Bauer et al. 1992; Burkhart and Donovan 1998; Dean and Krenzelok 1992; Gijsenbergh et al. 1989; Litovitz et al. 1991; Rambourg-Schepens et al. 1988).	• Comas were observed in males and females ranging from 19 to 87 years old after ingestion of 2-butoxyethanol, largely from household cleaners, ranging in estimated dose from 391 mg/kg to 650 mg/kg (Bauer et al. 1992; Burkhart and Donovan 1998; Gijsenbergh et al. 1989; Litovitz et al. 1991; Rambourg-Schepens et al. 1988). • After ingesting a household cleaner containing 22% 2-butoxyethanol, an 18-year-old male experienced severe central nervous system depression, although this was not reported after a second ingestion event of the same cleaner (Gualtieri et al. 2003). • Two children (14 months and 2 years old) had no evidence of nervous system depression after ingestion event at estimated doses of 290 and 1,862 mg/kg, respectively (Dean and Krenzelok 1992).	Comas and severe nervous system depression observed in case reports only.
Dysautonomia 2 *case reports* in humans (Burkhart and Donovan 1998; Osterhoudt 2002)	• A 19-year-old male with preexisting neurological conditions showed inhibited reflexes immediately following ingestion (Burkhart and Donovan 1998).	Impacts to reflexes observed in case reports only.

Endpoint, Identified Studies	Summary of Findings	Endpoint Summary
	• A 16-month-old female was unable to open her eyes to voice immediately following ingestion; her gag and withdrawal reflexes were unaffected (Osterhoudt 2002).	
Sensory Impacts 1 *experimental study* in humans (Carpenter et al. 1956)	• Male and female volunteers reported disturbed taste sensation after inhalation at 113 and 195 ppm, respectively, for 4–8 hours in an experimental study (Carpenter et al. 1956).	Taste sensation effects in one human study.
Verbal Function 1 *case report* in humans (Burkhart and Donovan 1998)	• A 19-year-old male with preexisting neurological conditions was unable to speak beyond sounds 2 months after an ingestion event (Burkhart and Donovan 1998).	Verbal function effects in one case report.

Selected Chemical-Outcome: 6:2 FTSA-Any Health Outcome

No reports from authoritative sources that discussed health effects associated with 6:2 FTSA exposure were identified during Phase 1. Our scoping review identified two *primary* studies (one *human* study and one *animal* study) that examined the health effects associated with 6:2 FTSA. Studies assessed reproductive and developmental effects and immune effects.

Reproductive and Developmental Effects

Both studies assessed reproductive and developmental effects associated with 6:2 FTSA exposure (Bohannon et al. 2023; Tian et al. 2023). In humans, a case-control study in Hangzhou, China of 82 preeclamptic pregnant women and 169 healthy control subjects measured 6:2 FTSA in maternal serum prior to delivery (Tian et al. 2023). The study observed no significant associations between maternal serum 6:2 FTSA levels and odds of preeclampsia or odds of low birth weight in infants. A study of male and female white-footed field mice exposed to 6:2 FTSA by oral gavage for 112 days (from 4 weeks premating to ≥4 weeks postmating) observed no associations between 6:2 FTSA exposure and reproductive and fertility endpoints in the exposed mice or developmental endpoints in their offspring. Reproductive and developmental measures included number of mating pairs, number of pregnant animals, total litter loss, proportion of stillbirths, live litter size, total litter size, male sperm parameters, male and female sex hormone levels, and pup weights (Bohannon et al. 2023).

Immune Effects

One primary study in an ecological model assessed the association between 6:2 FTSA exposure and immune endpoints (Bohannon et al. 2023). Male and female white-footed field mice were exposed to 6:2 FTSA by oral gavage for 112 days (from 4 weeks premating to ≥4 weeks postmating). Researchers observed significantly decreased plaque forming cell counts in both males and females, significantly increased spleen weights in males only, and no changes in thymus organ weight or histopathology of the thymus or spleen in either sex (Bohannon et al. 2023). A benchmark dose (BMD) was derived using data for decreased plaque forming cell counts (BMD for males = 4.06 mg/kg/day; for females = 3.72 mg/kg/day). The lower 95% confidence limits (BMDLs) were 2.63 mg/kg/day (males) and 2.26 mg/kg/day (females).

Evidence Gap Summary: A *research gap remains* for primary studies of health hazards associated with 6:2 FTSA exposure in humans and animals. Few studies were identified.

Supplementary Searches

Resources identified from authoritative sources largely discussed effects from dioxins as a class or discussed the health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a dioxin with well-established human health toxicity that is often referenced as a proxy for the class. Only OEHHA

presented data for the individual dioxin chemicals that were measured in East Palestine. As most resources discussed solely TCDD or dioxins as a class, further exploration of health information from a specific source was not pursued.

The peer-reviewed literature search identified 61 SRs and meta-analyses on dioxins published in the past five years. Based on title-level screening of these 61 references, 17 appeared to report on dioxins and health effects in animals or humans. These reviews were not screened at the title-abstract or full-text levels and were not evaluated for inclusion in our report. No additional searching or screening for literature on dioxins was pursued.

Review Limitations

While we aimed to conduct a robust assessment of the available literature on health effects following exposure to the chemicals of interest, this scoping review has some limitations. First, the heterogeneity of reviews from authoritative sources should be acknowledged. Reports from authoritative sources did not always provide clear interpretations of the available data, and, in some cases, different reports provided conflicting interpretations of largely similar databases, making it difficult to synthesize across some authoritative conclusions. Additionally, some reports (e.g., reports from ECHA) presented hazard data but drew risk-based conclusions, whereas others made hazard conclusions only. Some reviews emphasized animal studies designed to assess toxicities to a specific organ system, such as neurotoxicity or immunotoxicity studies, whereas other authoritative reviews also integrated relevant endpoints from animal studies of general toxicity. Finally, language used to describe hazard and risk is not harmonized across sources. While some provide clear hazard conclusions with specific codified language, others summarize health effects data without obvious conclusive statements. This variable language across sources made it difficult to discern hazard conclusions in some cases.

Second, industrial chemicals, including those in this review, often have substantial publicly available toxicological data that are not accessible in research journal articles or databases, such as PubMed. While ECHA reports and classification and labelling documents were reviewed in an effort to identify as much data as possible, some information in the gray literature may not have been identified. Our search and synthesis of the information in the gray literature relied upon interpretations by authoritative sources (i.e., conclusions available in their reviews and reports).

Third, in reviewing the published literature, formal SRs were not conducted for chemical × health outcome pairings; thus, there may have been some literature that was not identified during our searches. For example, some measures that are common in most animal studies (e.g., brain weight) may not be reported in study titles and abstracts. If relevant endpoints were not discussed in the title and abstract, these studies were not identified in our review process. Additionally, our search for studies examining neurological effects associated with acrolein exposure focused on review articles only. As such, the available primary literature is not summarized in this report but may provide useful information on the effects to the nervous system. Finally, our assessment of the available literature did not include an evaluation of study quality and risk of bias, per SR protocols. While efforts were made to consider the available data in a standardized way, our results should be interpreted with appropriate caution.

Summary

In this scoping review, eight chemicals were considered in high-priority categories (i.e., highest or high) for identification of key health effect data gaps (acrolein, butyl acrylate, 2-butoxyethanol, 2-ethylhexyl acrylate, benzene, hydrogen chloride, phosgene gas, and vinyl chloride) based on available environmental monitoring data, available hazard data, and recency of authoritative reviews. Our review found that irritant was the most established health outcome for the chemicals. Authoritative sources identified all eight chemicals as skin and eye irritants and seven as respiratory irritants. These findings are consistent with symptoms reported by those affected following the train derailment in East Palestine, Ohio.

Most of the chemicals had been evaluated for cancer in experimental animals; however, studies in humans remain a research gap. Five of the eight chemicals were human or animal carcinogens, whereas the remaining three were not classifiable due to inadequate studies, few available studies, or older studies or reviews. Benzene and vinyl chloride are known human carcinogens. Searches and screens conducted to identify human cancer studies in the published literature for acrolein, butyl acrylate, 2-butoxyethanol, and 2-ethylhexyl acrylate did not return any new studies in human populations that would alter cancer conclusions.

Reproductive and developmental outcomes were the most studied noncancer outcomes, and a paucity of conclusions were available from authoritative sources for other noncancer outcomes, including neurological and immunological effects. Two of the eight high-priority chemicals were deemed harmful to reproductive and/or developmental systems, and four were of low or no concern. Two chemicals were associated with both neurological and immunological effects. Suggestive evidence was available for two chemicals for neurological effects and for three chemicals for immunological effects. Relevant data from subsequent searches for neurological and immunological studies in the published literature did not alter these findings.

Results from our review identify and summarize the main health effects data and reveal key health hazard evidence gaps for the chemicals spilled in the East Palestine train derailment. First, additional studies examining neurological effects following exposures to acrolein, butyl acrylate, 2-butoxyethanol, and 2-ethylhexyl acrylate would be useful to better understand potential impacts to the human nervous system following exposure. Our search for studies examining neurological effects associated with acrolein exposure focused on available review articles; thus, primary studies were not reviewed. A systematic review may be warranted to identify and critically assess available primary literature. Next, additional studies of carcinogenic effects in human populations are needed for acrolein and 2-ethylhexyl acrylate based on positive findings in experimental animals. Finally, studies assessing immunotoxicity following 2-butoxyethanol and butyl acrylate exposure should be pursued, as many identified studies reported observational immune findings from studies of general toxicity. Additional research may be needed before pursuit of a systematic review.

This rapid review summarizes the available health hazard data for 20 chemicals released in the East Palestine, Ohio train derailment and subsequent controlled burn. While we aimed to provide information that would be useful context for the health concerns expressed by the affected community and, thus, focused on this specific incident, these chemicals remain in use in a variety of contexts and enter the environment regularly. As such, our evaluation serves to inform the affected individuals and organizations in the East Palestine community, foster further efforts to better characterize health hazards following environmental exposures, and protect the general population from such hazardous health effects in the future.

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U.S. Environmental Protection Agency (USEPA). 2023m. CompTox Chemicals Dashboard: Lubricating oils, petroleum, hydrotreated spent, 64742-58-1 | DTXSID7028223: Executive summary. Washington, DC: U.S. Environmental Protection Agency. https://comptox.epa.gov/dashboard/chemical/executive-summary/DTXSID7028223

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U.S. Environmental Protection Agency (USEPA). 2023p. CompTox Chemicals Dashboard: Polyethylene AS low Mol.Wt., 9002-88-4 | DTXSID8031946: Executive summary. Washington, DC: U.S. Environmental Protection Agency. https://comptox.epa.gov/dashboard/chemical/executive-summary/DTXSID8031946

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U.S. Environmental Protection Agency (USEPA). 2023s. CompTox Chemicals Dashboard: Vinyl chloride, 75-01-4 | DTXSID8021434: Executive summary. Washington, DC: U.S. Environmental Protection Agency. https://comptox.epa.gov/dashboard/chemical/executive-summary/DTXSID8021434

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Appendix A Phase 2 Supplemental Methods

Table A-1. Population, Exposure, Comparator, and Outcome/Evidence Stream, Exposure, Comparator, and Outcome Statements

Publication Type/Evidence Stream	Population or Evidence Type (Primary Studies)	Exposure[a]	Comparison Group[b]	Outcome[c]
Human epidemiological reviews:[d] Post recent IARC publication (2021) Primary epidemiological studies: Post recent IARC publication (2021); not restricted to design • Studies reporting risk estimate or correlation (ecological studies) • Case reports, case series	Humans: Workers, community, not restricted	Acrolein	Low or no exposure to acrolein	Cancer
Human epidemiological, animal, mechanistic reviews	NA	Acrolein	Low or no exposure to acrolein	Neurotoxicity
Human epidemiological reviews[d] Primary epidemiological studies • Studies reporting risk estimate or correlation (ecological studies) • Case reports, case series	Humans: Workers, community, not restricted	2-Butoxyethanol	Low or no exposure to 2-butoxyethanol	Cancer
Human epidemiological, animal, mechanistic reviews Primary epidemiological and toxicology studies • Studies reporting risk estimate or correlation (ecological studies) • Case reports, case series	Humans: Workers, community, not restricted Animals: Nonhuman mammalian	2-Butoxyethanol	Low or no exposure to 2-butoxyethanol	Immunotoxicity
Human epidemiological, animal, mechanistic reviews Primary epidemiological and toxicology studies • Studies reporting risk estimate or correlation (ecological studies) • Case reports, case series	Humans: Workers, community, not restricted Animals: Nonhuman mammalian	2-Butoxyethanol	Low or no exposure to 2-butoxyethanol	Neurotoxicity
Human epidemiological, animal, mechanistic reviews Primary epidemiological and toxicology studies • Studies reporting risk estimate or correlation (ecological studies) • Case reports, case series	Humans: Workers, community, not restricted Animals: Nonhuman mammalian	Butyl acrylate	Low or no exposure to butyl acrylate	Cancer
Human epidemiological, animal, mechanistic reviews Primary epidemiological and toxicology studies • Studies reporting risk estimate or correlation (ecological studies)	Humans: Workers, community, not restricted Animals: Nonhuman mammalian	Butyl acrylate	Low or no exposure to butyl acrylate	Hepatotoxicity

Publication Type/Evidence Stream	Population or Evidence Type (Primary Studies)	Exposure[a]	Comparison Group[b]	Outcome[c]
• Case reports, case series				
Human epidemiological, animal, mechanistic reviews Primary epidemiological and toxicology studies • Studies reporting risk estimate or correlation (ecological studies) • Case reports, case series	Humans: Workers, community, not restricted Animals: Nonhuman mammalian	Butyl acrylate	Low or no exposure to butyl acrylate	Immunotoxicity
Human epidemiological, animal, mechanistic reviews Primary epidemiological and toxicology studies • Studies reporting risk estimate or correlation (ecological studies) • Case reports, case series	Humans: Workers, community, not restricted Animals: Nonhuman mammalian	Butyl acrylate	Low or no exposure to butyl acrylate	Neurotoxicity
Human epidemiological reviews:[d] Post recent IARC publication (2019) Primary epidemiological studies: Post recent IARC publication (2019); not restricted to design • Studies reporting risk estimate or correlation (ecological studies) • Case reports, case series	Humans: Workers, community, not restricted	2-Ethylhexyl acrylate	Low or no exposure to 2-ethylhexyl acrylate	Cancer
Human epidemiological, animal, mechanistic reviews Primary epidemiological and toxicology studies • Studies reporting risk estimate or correlation (ecological studies) • Case reports, case series	Humans: Workers, community, not restricted Animals: Nonhuman mammalian	2-Ethylhexyl acrylate	Low or no exposure to 2-ethylhexyl acrylate	Neurotoxicity

IARC = International Agency for Research on Cancer; NA = not applicable.
[a]Includes all routes, all life stages, and exposure proxies (e.g., biomarkers); does not include endogenous formation.
[b]Case reports/case series do not include a nonexposed control group but are considered supplemental.
[c]Outcomes are defined in Table A-2.
[d]Reviews reporting on individual epidemiological studies.

Table A-2. Health Outcome Concepts

Outcomes	Example Concepts
Cancer	Cancers of any type in the following systems: • Digestive/gastrointestinal • Endocrine • Female reproductive • Head and neck • Hematologic/lymphatic/immune • Hepatic • Male reproductive • Musculoskeletal • Nervous • Respiratory • Skin • Special senses • Systemic • Urinary • Other

Neurotoxicity	Effects to the nervous system in any of the following categories:
	• Human effect categories
	  ○ Academic achievement
	  ○ Attention
	  ○ Autonomic function
	  ○ Clinical conditions (e.g., depression, Alzheimer's disease, Parkinson's disease, autism, intellectual disabilities)
	  ○ Executive function
	  ○ General intelligence (i.e., IQ)
	  ○ Hearing impairment
	  ○ Learning and memory
	  ○ Motor function
	  ○ Neurodevelopment
	  ○ Peripheral nervous system
	  ○ Social-emotional behavioral regulation
	  ○ Verbal-language
	  ○ Visuospatial function
	  ○ Other
	• Animal effect categories
	  ○ Structural (e.g., organ weights; nerve tissue effects; lesions to nerves; impacts to neurons, axons, terminals)
	  ○ Neurophysiological (e.g., seizures; impacts to electrical activity, including never conduction and action or evoked potentials; tests of electrical activity)
	  ○ Neurochemical (e.g., impacts to sodium or calcium levels/transmission, impacts to neurotransmitters and receptors, impacts to transport of important neurochemicals)
	  ○ Behavioral (e.g., sensory, motor, or learning and memory changes; may be measured by functional observation batteries)

Immunotoxicity	• Allergy • Autoimmune diseases (e.g., multiple sclerosis, lupus, rheumatoid arthritis) • General immune assays (e.g., white blood cell counts) • Hypersensitivity • Immunoglobulins (e.g., IgE, IgG, IgM)

Outcomes	Example Concepts
	• Infectious diseases • Serum globulin levels • Vaccine response • White blood cell activity assays • Other
Hepatotoxicity	• Albumin • Albumin/globulin ratio • Bile acids/salts • Bilirubin • Hepatic steatosis/fatty liver • Liver disease • Liver enzymes (e.g., alanine transaminase, aspartate transferase, alkaline phosphatase) • Liver-specific serum biochemistry markers (e.g., gamma-glutamyl transferase, sorbitol dehydrogenase) • Other

Search Strings

Chemical Strings

Acrolein

("107-02-8"[rn] OR "2-Propenal"[tiab] OR "Acrolein"[tiab] OR "Prop-2-enal"[tiab] OR "2-Propen-1-al"[tiab] OR "2-Propen-1-one"[tiab] OR "Acroleina"[tiab] OR "Acrylaldehyd"[tiab] OR "Acrylaldehyde"[tiab] OR "Acrylic aldehyde"[tiab] OR "Allyl aldehyde"[tiab] OR "Aqualin"[tiab] OR "Magnacide B"[tiab] OR "Magnacide H"[tiab] OR "NSC 8819"[tiab] OR "Prop-2-en-1-al"[tiab] OR "Propenal"[tiab] OR "UN 1092"[tiab] OR "DTXSID5020023"[tiab] OR "Acrolein"[mh])

2-Ethylhexyl Acrylate

("103-11-7"[rn] OR "2-Ethylhexyl acrylate"[tiab] OR "2-Ethylhexyl prop-2-enoate"[tiab] OR "2-Propenoic acid, 2-ethylhexyl ester"[tiab] OR "EC No.: 203-080-7"[tiab] OR "2-Ethylhexyl 2-propenoate"[tiab] OR "2-Ethylhexylacrylat"[tiab] OR "2-Propenoic acid 2-ethylhexyl ester"[tiab] OR "2-Propenoic acid, 2-ethylhexyl ester"[tiab] OR "acrilato de 2-etilhexilo"[tiab] OR "ACRYLATE, 2-ETHYLHEXYL"[tiab] OR "Acrylic acid, 2-ethylhexyl ester"[tiab] OR "ACRYLSAEURE-(2-AETHYLHEXYL)-ESTER"[tiab] OR "NSC 4803"[tiab] OR "Octyl acrylate"[tiab] OR "PROP-2-ENOATE, 2-ETHYLHEXYL"[tiab] OR "DTXSID9025297"[tiab])

Butyl Acrylate

("Butyl acrylate"[tiab] OR "141-32-2"[rn] OR "DTXSID6024676"[tiab] OR "141-32-2"[tiab] OR "2-Propenoic acid, butyl ester"[tiab] OR "ACRYLATE, BUTYL"[tiab] OR "ACRYLIC ACID, BUTYL ESTER"[tiab] OR "Butan-1-yl acrylate"[tiab] OR "Butyl acrylate"[tiab] OR "Butyl prop-2-enoate"[tiab] OR "Butyl propenoate"[tiab] OR "n-Butyl acrylate"[tiab] OR "PROP-2-ENOATE, BUTYL"[tiab] OR "UN 2348 (DOT)"[tiab] OR "2-Propenoic acid butyl ester"[tiab] OR "2-Propenoic acid, n-butyl ester"[tiab] OR "ACRYLATE, BUTYL"[tiab] OR "Acrylic acid butyl ester"[tiab] OR "ACRYLIC ACID, BUTYL ESTER"[tiab] OR "Acrylic acid n-butyl ester"[tiab] OR "ACRYLSAEURE-BUTYLESTER"[tiab] OR "Butyl 2-propenoate"[tiab] OR "Butylacrylat"[tiab] OR "NSC 5163"[tiab] OR "PROP-2-ENOATE, BUTYL"[tiab] OR "UN 2348"[tiab] OR "n-butyl acrylate"[Supplementary Concept])

2-Butoxyethanol

("111-76-2"[rn] OR "2-butoxietanol"[tiab] OR "2-Butoxyethan-1-ol"[tiab] OR "2-Butoxyethanol"[tiab] OR "EGBE"[tiab] OR "Ethanol, 2-butoxy-"[tiab] OR "Ethylene glycol monobutyl ether"[tiab] OR "2-butoxietanol"[tiab] OR "2-Butoxy-1-ethanol"[tiab] OR "2-BUTOXY ETHANOL"[tiab] OR "2-butoxyethanol m"[tiab] OR "2-n-Butoxyethanol"[tiab] OR "3-Oxa-1-heptanol"[tiab] OR "AETHYLENGLYKOL-MONOBUTYLAETHER"[tiab] OR "Bikanol B 1"[tiab] OR "Buchiseru"[tiab] OR "Butoxyethanol"[tiab] OR "Butyl Cellosolve"[tiab] OR "Butyl Cellu-Sol"[tiab] OR "BUTYL GLYCOL"[tiab] OR "Butyl Glysolv"[tiab] OR "Butyl icinol"[tiab] OR "Butyl monoether glycol"[tiab] OR "Butyl Oxitol"[tiab] OR "Chimec NR"[tiab] OR "DB solvent"[tiab] OR "Dowanol EB"[tiab] OR "Eastman EB"[tiab] OR "Ektasolve EB"[tiab] OR "Ethanol, 2-butoxy-"[tiab] OR "ETHYLENE GLYCOL BUTYL ETHER"[tiab] OR "Ethylene glycol mono-n-butyl ether"[tiab] OR "Ethylene glycol n-butyl ether"[tiab] OR "Gafcol EB"[tiab] OR "Glycol butyl ether"[tiab] OR "Glycol EB"[tiab] OR "Glycol monobutyl ether"[tiab] OR "Hydroxyethyl butyl ether"[tiab] OR "K Foam Lo"[tiab] OR "Mearcell 3532"[tiab] OR "Minex BDH"[tiab] OR "Monobutyl glycol ether"[tiab] OR "n-Butoxyethanol"[tiab] OR "n-Butyl cellosolve"[tiab] OR "NSC 60759"[tiab] OR "O-Butyl ethylene glycol"[tiab] OR "Poly-Solv EB"[tiab] OR "UN 2369"[tiab] OR "β-Butoxyethanol"[tiab])

6:2 FTNO

("1-Octanesulfonamide, N-[3-(dimethylamino)propyl]-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-, N-oxide"[tiab] OR "1-Octanesulfonamide, N-[3-(dimethylnitroryl)propyl]-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-"[tiab] OR "1-Octanesulfonamide, N-[3-(dimethyloxidoamino)propyl]-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-"[tiab] OR "80475-32-7"[rn] OR "N-[3-(dimethylamino)propyl]-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonamide N-oxide"[tiab] OR "N-[3-(Dimethyloxidoamino)propyl]-

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octanesulfonamide"[tiab] OR "N,N-Dimethyl-3-[(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctane-1-sulfonyl)amino]propan-1-amine N-oxide"[tiab] OR "N,N-Dimethyl-3-{[(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)sulfonyl]amino}-1-propanamine N-oxide"[tiab] OR "N,N-Dimethyl-3-((perfluorohexyl)ethylsulfonyl)aminopropanamine N-oxide"[tiab] OR "6:2 FTNO"[tiab] OR "6:2 fluorotelomer sulfonamide amine oxide"[tiab])

6:2 FTSA

("1H,1H,2H,2H-perfluorooctanesulfonic acid"[tiab] OR "1H,1H,2H,2H-Perfluorooctanesulfonic acid"[tiab] OR "1-Octanesulfonic acid, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-"[tiab] OR "27619-97-2"[rn] OR "2-(Perfluorohexyl)ethane-1-sulfonic acid"[tiab] OR "2-(Perfluorohexyl)ethanesulfonic acid"[tiab] OR "3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-octanesulfonic acid"[tiab] OR "3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoroctansulfonsaure"[tiab] OR "3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctane-1-sulfonic acid"[tiab] OR "3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctanesulfonic acid"[tiab] OR "3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid"[tiab] OR "6:2 Fluorotelomer sulfonic acid"[tiab] OR "Acide 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulfonique"[tiab] OR "Fluorotelomer sulfonic acid 6:2"[tiab] OR "6:2 FtS"[tiab] OR "6:2 FTS"[tiab] OR "6:2 FTSA"[tiab] OR ("fluorotelomer sulfonic acids" [Supplementary Concept] AND 6:2[tiab]))

Health Outcome Strings

Note that health outcome strings are based on SWIFT-Review search filters (Sciome 2023).

Cancer

(acanthoma*[tiab] OR acrochord*[tiab] OR acrospiroma*[tiab] OR adamantinoma*[tiab] OR adenoacanthoma*[tiab] OR adenoameloblast*[tiab] OR adenocarcin*[tiab] OR adenofibrom*[tiab] OR adenol*[tiab] OR adenom*[tiab] OR "adenosquamous"[tiab] OR ameloblast*[tiab] OR androblast*[tiab] OR angiofib*[tiab] OR angiog*[tiab] OR angiok*[tiab] OR angiol*[tiab] OR angiom*[tiab] OR "angiomatosis"[tiab] OR "angiomatosis"[mh] OR "angiosarc*"[tiab] OR "antibodies, neoplasm"[tiab] OR "antibodies, neoplasm"[mh] OR "antigens, neoplasm"[tiab] OR "antigens, neoplasm"[mh] OR apudom*[tiab] OR argentaffin*[tiab] OR arrhenoblast*[tiab] OR astroblast*[tiab] OR astrocytom*[tiab] OR astrogliom*[tiab] OR "atypia"[tiab] OR "baltoma"[tiab] OR "barrett esophagus"[tiab] OR "barrett esophagus"[mh] OR blastom*[tiab] OR "cancer"[tiab] OR cancero*[tiab] OR "cancers"[tiab] OR carcinog*[tiab] OR "carcinogenicity tests"[tiab] OR "carcinogenicity tests"[mh] OR "carcinogens"[tiab] OR "carcinogens"[mh] OR carcinoid*[tiab] OR carcinom*[tiab] OR carcinos*[tiab] OR cavernom*[tiab] OR "cell line, tumor"[tiab] OR "cell line, tumor"[mh] OR cementom*[tiab] OR cerumin*[tiab] OR chloroma*[tiab] OR cholangio*[tiab] OR chondrob*[tiab] OR chondrom*[tiab] OR chondros*[tiab] OR chord*[tiab] OR chorioa*[tiab] OR choriocarc*[tiab] OR chorioep*[tiab] OR chorionep*[tiab] OR chromaffinom*[tiab] OR collagenom*[tiab] OR comedocarcinom*[tiab] OR condylom*[tiab] OR "condylomata acuminata"[tiab] OR "condylomata acuminata"[mh] OR corticotrop*[tiab] OR craniopharyng*[tiab] OR cylindrom*[tiab] OR cystadeno*[tiab] OR cystoma*[tiab] OR cystosa*[tiab] OR dentinom*[tiab] OR dermatofibro*[tiab] OR "dermoid"[tiab] OR "desmoid"[tiab] OR desmoplastic*[tiab] OR "dictyota"[tiab] OR dysgerm*[tiab] OR dyskerat*[tiab] OR "dysmyelopoiesis"[tiab] OR dysplas*[tiab] OR ectomesenchym*[tiab] OR elastofibr*[tiab] OR enchondrom*[tiab] OR endotheliom*[tiab] OR ependymo*[tiab] OR epidermoid*[tiab] OR epitheliom*[tiab] OR erythrol*[tiab] OR erythropl*[tiab] OR esthesioneuro*[tiab] OR etiolog*[tiab] OR fibroaden*[tiab] OR fibrochond*[tiab] OR fibroe*[tiab] OR fibrofol*[tiab] OR fibroid*[tiab] OR fibrolip*[tiab] OR fibrom*[tiab] OR fibroodontom*[tiab] OR fibrosarcom*[tiab] OR fibrothecom*[tiab] OR fibroxantho*[tiab] OR ganglioblast*[tiab] OR gangliocytom*[tiab] OR ganglioglom*[tiab] OR ganglioneuro*[tiab] OR gastrinom*[tiab] OR "genes, neoplasm"[tiab] OR "genes, neoplasm"[mh] OR germinom*[tiab] OR glioblast*[tiab] OR gliom*[tiab] OR glomangio*[tiab] OR glucagonom*[tiab] OR gonadoblastom*[tiab] OR gonocytom*[tiab] OR gynandroblastom*[tiab] OR haemangio*[tiab] OR hamartom*[tiab] OR hemangio*[tiab] OR hepatoblastom*[tiab] OR hepatom*[tiab] OR hibernom*[tiab] OR hidradenom*[tiab] OR hidrocy*[tiab] OR hodgkin*[tiab] OR hydatidiform*[tiab] OR hydradenom*[tiab] OR hypernephrom*[tiab] OR "IARC"[tiab] OR immunocytom*[tiab] OR insulinom*[tiab] OR leiomyo*[tiab] OR lesion*[tiab] OR leukaemia*[tiab] OR leukemia*[tiab] OR leukoplak*[tiab] OR leukostas*[tiab] OR

"leukostasis"[tiab] OR "leukostasis"[mh] OR lipoadenom*[tiab] OR lipoblastom*[tiab] OR lipom*[tiab] OR liposarcom*[tiab] OR luteinom*[tiab] OR luteom*[tiab] OR lymphangio*[tiab] OR lymphoepitheliom*[tiab] OR lymphom*[tiab] OR lymphoscintigraph*[tiab] OR macroglobulinem*[tiab] OR macroprolactinom*[tiab] OR malignan*[tiab] OR maltom*[tiab] OR masculinovoblastom*[tiab] OR mastocyto*[tiab] OR "mcf-7"[tiab] OR "medullo*"[tiab] OR "meigs syndrome"[tiab] OR melanoa*[tiab] OR melanocytom*[tiab] OR melanom*[tiab] OR meningio*[tiab] OR mesenchymom*[tiab] OR mesonephrom*[tiab] OR mesotheliom*[tiab] OR metaplas*[tiab] OR "metaplasia"[tiab] OR "metaplasia"[mh] OR metasta*[tiab] OR microgliom*[tiab] OR micrometastas*[tiab] OR "mucositis"[tiab] OR "mucositis"[mh] OR mycosis fungoides*[tiab] OR myelodysplas*[tiab] OR "myelodysplastic syndromes"[tiab] OR "myelodysplastic syndromes"[mh] OR "myelodysplastic-myeloproliferative diseases"[tiab] OR "myelodysplastic-myeloproliferative diseases"[mh] OR "myelofibrosis"[tiab] OR myelol*[tiab] OR myeloma*[tiab] OR myeloproliferat*[tiab] OR "myeloproliferative disorders"[tiab] OR "myeloproliferative disorders"[mh] OR myelosuppression*[tiab] OR myoblastom*[tiab] OR myoepitheliom*[tiab] OR myofibro*[tiab] OR myolipom*[tiab] OR myoma*[tiab] OR myosarcom*[tiab] OR myxof*[tiab] OR myxom*[tiab] OR "naevus"[tiab] OR neoplas*[tiab] OR "neoplasm proteins"[tiab] OR "neoplasm proteins"[mh] OR "neoplasms"[tiab] OR "neoplasms"[mh] OR "neoplastic stem cells"[tiab] OR "neoplastic stem cells"[mh] OR nephroblastom*[tiab] OR neurilem*[tiab] OR neurinom*[tiab] OR neuroblastom*[tiab] OR neurocytom*[tiab] OR neuroepitheliom*[tiab] OR neurofibro*[tiab] OR neurolipocytom*[tiab] OR neuroma*[tiab] OR neuronevus[tiab] OR neurothekeom*[tiab] OR "nevus"[tiab] OR "non coding RNA"[tiab] OR nonseminom*[tiab] OR odontoam*[tiab] OR odontom*[tiab] OR oligoastrocytom*[tiab] OR oligodendrogliom*[tiab] OR oncocytom*[tiab] OR "oncogen*"[tiab] OR "oncogene fusion"[tiab] OR "oncogene fusion"[mh] OR "oncogene proteins"[tiab] OR "oncogene proteins"[mh] OR "oncogenic viruses"[tiab] OR "oncogenic viruses"[mh] OR oncolog*[tiab] OR "oncolytic viruses"[tiab] OR "oncolytic viruses"[mh] OR oncoprotein*[tiab] OR "opsoclonus-myoclonus"[tiab] OR orchioblastom*[tiab] OR osteoblastom*[tiab] OR osteoch*[tiab] OR osteofibrosarcom*[tiab] OR osteom*[tiab] OR osteosarcom*[tiab] OR pancreatoblastom*[tiab] OR papillom*[tiab] OR parachordom*[tiab] OR paragangliom*[tiab] OR paraneoplas*[tiab] OR perineuriom*[tiab] OR phaeochromocytom*[tiab] OR pheochromo*[tiab] OR pilomatri*[tiab] OR plasmacytom*[tiab] OR pneumoblast*[tiab] OR pneumocytom*[tiab] OR polyembryom*[tiab] OR polyhistiom*[tiab] OR polyp*[tiab] OR "polyps"[tiab] OR "polyps"[mh] OR porocarcinom*[tiab] OR porom*[tiab] OR pre-cancer*[tiab] OR precancer*[tiab] OR preleukaem*[tiab] OR preleukem*[tiab] OR prelymphom*[tiab] OR pre-lymphom*[tiab] OR pre-malign*[tiab] OR premalignan*[tiab] OR preneoplas*[tiab] OR pre-neoplas*[tiab] OR prolactinom*[tiab] OR protooncogen*[tiab] OR pseudotum*[tiab] OR reninom*[tiab] OR retinoblastom*[tiab] OR rhabdo*[tiab] OR "RNA, neoplasm"[tiab] OR "RNA, neoplasm"[mh] OR sarcoma*[tiab] OR schwannom*[tiab] OR "SEER program"[tiab] OR "SEER program"[mh] OR seminom*[tiab] OR "sentinel lymph node"[tiab] OR "sentinel lymph node biopsy"[tiab] OR "sentinel lymph node biopsy"[mh] OR "sertoli-leydig cell tumor"[tiab] OR "sezary syndrome"[tiab] OR somatostatinom*[tiab] OR somatotropinom*[tiab] OR spermatocytom*[tiab] OR spiradenom*[tiab] OR spongioblastom*[tiab] OR subependymom*[tiab] OR thecom*[tiab] OR thymom*[tiab] OR trichilemmom*[tiab] OR trichoadenom*[tiab] OR trichoblastom*[tiab] OR trichodiscom*[tiab] OR trichoepitheliom*[tiab] OR trichofolliculom*[tiab] OR tricholemm*[tiab] OR "tumor"[tiab] OR "tumor markers, biological"[tiab] OR "tumor markers, biological"[mh] OR tumorgen*[tiab] OR tumorig*[tiab] OR tumor-inhibit*[tiab] OR tumorog*[tiab] OR "tumors"[tiab] OR "tumors"[tiab] OR "tumour"[tiab] OR up-regulat*[tiab] OR vipom*[tiab] OR waldenstrom*[tiab] OR xantho*[tiab])

Neurological

(acetylcholine*[tiab] OR "ADHD"[tiab] OR adrenergic*[tiab] OR "adrenoleukodystrophy"[tiab] OR afferent*[tiab] OR "agoraphobia"[tiab] OR alzheimer*[tiab] OR amacrine*[tiab] OR "amnesia"[tiab] OR "amygdala"[tiab] OR "angelman-syndrome"[tiab] OR "anorexia"[tiab] OR antisocial*[tiab] OR anxiet*[tiab] OR anxious*[tiab] OR aphasi*[tiab] OR "aphonia"[tiab] OR apraxia*[tiab] OR "arachnoid"[tiab] OR "arousal"[tiab] OR astrocyte*[tiab] OR ataxia*[tiab] OR attention-deficit*[tiab] OR autis*[tiab] OR autonomic*[tiab] OR axon*[tiab] OR "baroreflex"[tiab] OR binge-eat*[tiab] OR "bipolar"[tiab] OR bovine-spongiform*[tiab] OR "brain"[tiab] OR "bulimia"[tiab] OR canavan*[tiab] OR cannabinoid*[tiab] OR "capgras"[tiab] OR cerebellar*[tiab] OR cerebral*[tiab] OR cerebro*[tiab] OR "cervical-cord"[tiab] OR charcot-marie-tooth*[tiab] OR "child behavior"[tiab] OR chronic-fatigue*[tiab] OR "circumventricular"[tiab]

OR "cockayne-syndrome"[tiab] OR "cognition"[tiab] OR "cognitiv*"[tiab] OR "corpus callosum"[tiab] OR "cortical"[tiab] OR cranial*[tiab] OR "craniocerebral"[tiab] OR creutzfeldt-jakob*[tiab] OR "cyclothymi*"[tiab] OR "delirium"[tiab] OR "dementia"[tiab] OR demyelinat*[tiab] OR dendrit*[tiab] OR "dentate-gyrus"[tiab] OR "depressed"[tiab] OR "depression"[tiab] OR developmental-disabilit*[tiab] OR "dissociative"[tiab] OR dopamine*[tiab] OR "down-syndrome"[tiab] OR "drug-abuse"[tiab] OR "dura-matter"[tiab] OR dysautonomia*[tiab] OR dyscalcul*[tiab] OR dyskines*[tiab] OR dyslexi*[tiab] OR "dysphonia"[tiab] OR dyssomnia*[tiab] OR dyston*[tiab] OR eating-disorder*[tiab] OR efferent*[tiab] OR "encephalitis"[tiab] OR encephalo*[tiab] OR "entorhinal cortex"[tiab] OR ependy*[tiab] OR "epilep*"[tiab] OR "epithalamus"[tiab] OR "essential-tremor"[tiab] OR excitatory amino acid*[tiab] OR "extra-pyramidal"[tiab] OR extrapyramidal*[tiab] OR "fibromyalgia"[tiab] OR "friedreich ataxia"[tiab] OR "fronto-temporal"[tiab] OR frontotemporal*[tiab] OR ganglia*[tiab] OR ganglion*[tiab] OR "glia"[tiab] OR "glial"[tiab] OR "gliogenesis"[tiab] OR glossopharyngeal*[tiab] OR "gray-matter"[tiab] OR guillain-barre*[tiab] OR "hemiplegia"[tiab] OR hippocamp*[tiab] OR huntington*[tiab] OR "hydranencephaly"[tiab] OR hydrocephal*[tiab] OR "hyperkinesis"[tiab] OR hypochondr*[tiab] OR "hypokinesia"[tiab] OR hypomani*[tiab] OR "hypotha*"[tiab] OR insomnia*[tiab] OR "intell*"[tiab] OR "interneuron"[tiab] OR "inter-neuron"[tiab] OR intracranial*[tiab] OR "IQ"[tiab] OR "ischemi*"[tiab] OR "learning"[tiab] OR leukodystrophy*[tiab] OR leukoencephal*[tiab] OR lewy-bod*[tiab] OR limbic*[tiab] OR "memory"[tiab] OR meningeal*[tiab] OR "meninges"[tiab] OR meningitis*[tiab] OR "meningoencephalitis"[tiab] OR "mesencephalon"[tiab] OR microglia*[tiab] OR mononeuropath*[tiab] OR "mood"[tiab] OR motor-skill*[tiab] OR movement-disorder*[tiab] OR multiple-personalit*[tiab] OR "Munchausen"[tiab] OR muscarinic*[tiab] OR muscular-dystroph*[tiab] OR "myalgia*"[tiab] OR myasthen*[tiab] OR "myeli*"[tiab] OR "myoclonus"[tiab] OR "myokymia"[tiab] OR myopath*[tiab] OR "myositis"[tiab] OR myotoni*[tiab] OR nerve*[tiab] OR "nervous system"[tiab] OR "nervous system"[mh] OR "nervous system diseases"[tiab] OR "nervous system diseases"[mh] OR "nervous system physiological phenomema"[tiab] OR "nervous system physiological phenomema"[mh] OR nervous*[tiab] OR neural*[tiab] OR "neurit*"[tiab] OR "neuroaspergillosis"[tiab] OR neuroaxon*[tiab] OR neuro-axon*[tiab] OR neurobehav*[tiab] OR neurodegenerat*[tiab] OR "neuroeffector"[tiab] OR neuroendocrine*[tiab] OR neurofib*[tiab] OR neurofun*[tiab] OR neurogen*[tiab] OR "neuroglia*"[tiab] OR "neuroim*"[tiab] OR neurokinin*[tiab] OR neurologic*[tiab] OR neuromuscular*[tiab] OR neuromyelitis*[tiab] OR neuron*[tiab] OR neuropath*[tiab] OR "neuropil"[tiab] OR neurosecret*[tiab] OR neurotox*[tiab] OR neurotrans*[tiab] OR "neurotransmitter agents"[tiab] OR "neurotransmitter agents"[mh] OR nicotinic*[tiab] OR nissl-bod*[tiab] OR obsessive-compulsive*[tiab] OR "OCD"[tiab] OR oculomotor*[tiab] OR "olfact*"[tiab] OR "oligodendroglia"[tiab] OR ophthalmoplegia*[tiab] OR palsy*[tiab] OR "panic"[tiab] OR parahippocamp*[tiab] OR "paraly*"[tiab] OR parano*[tiab] OR "paraparesis"[tiab] OR "paraplegia"[tiab] OR parasomnia*[tiab] OR "paresis"[tiab] OR parkinson*[tiab] OR perforant*[tiab] OR perimeningeal*[tiab] OR "personality"[tiab] OR phob*[tiab] OR "pica"[tiab] OR piloerect*[tiab] OR pineal*[tiab] OR pituitary*[tiab] OR plasticity*[tiab] OR "poliomyelitis"[tiab] OR polyneuropath*[tiab] OR polyradicul*[tiab] OR "potentia*"[tiab] OR prader-willi*[tiab] OR "premenstrual dysphoric disorder"[tiab] OR presynap*[tiab] OR "primary dysautonomias"[tiab] OR prion*[tiab] OR propriocept*[tiab] OR "prosencephalon"[tiab] OR "psychiatry and psychology category"[tiab] OR "psychiatry and psychology category"[mh] OR psychomotor*[tiab] OR purinergic*[tiab] OR "radicul*"[tiab] OR receptor*[tiab] OR "receptors, cell surface"[tiab] OR "receptors, cell surface"[mh] OR reflex*[tiab] OR "rett-syndrome"[tiab] OR "rhabdomyolysis"[tiab] OR "rhombencephalon"[tiab] OR rhythm*[tiab] OR schizophreni*[tiab] OR schwann-cell*[tiab] OR sclerosis*[tiab] OR scrapi*[tiab] OR "season* affective disorder"[tiab] OR seizure*[tiab] OR senil*[tiab] OR sensation*[tiab] OR "sensory gating"[tiab] OR seroton*[tiab] OR sleep*[tiab] OR somatosensory*[tiab] OR speech*[tiab] OR spinal-cord*[tiab] OR spinocerebellar*[tiab] OR "stress"[tiab] OR "stroke"[tiab] OR subarachnoid*[tiab] OR subdural*[tiab] OR "substance abuse"[tiab] OR "substantia-nigra"[tiab] OR synap*[tiab] OR "syncope"[tiab] OR tauopath*[tiab] OR "thalamic"[tiab] OR tic-disorder*[tiab] OR tourette*[tiab] OR "vagal"[tiab] OR vagus*[tiab] OR "vertigo"[tiab] OR "voice disorders"[tiab] OR "white-matter"[tiab] OR "williams-syndrome"[tiab] OR "wolfram-syndrome"[tiab])

Liver/Hepatic

((portal[tiab] AND hypertension[tiab]) OR ("alanine aminotransferase"[tiab] OR "alanine aminotransferase"[mh] OR "alkaline phosphatase"[tiab] OR "alkaline phosphatase"[mh] OR aspartate

aminotransferase*[tiab] OR "aspartate aminotransferases"[tiab] OR "aspartate aminotransferases"[mh] OR bilirubin*[tiab] OR bilirubin*[mh] OR cholestasis*[tiab] OR cirrhosis*[tiab] OR "erythropoietic protoporphyria"[tiab] OR "extrahepatic"[tiab] OR "fascioliasis"[tiab] OR "focal nodular hyperplasia"[tiab] OR hepatic*[tiab] OR hepatitis*[tiab] OR "hepato"[tiab] OR hepatobil*[tiab] OR "hepatoc*"[tiab] OR "hepatocytes"[tiab] OR "hepatocytes"[mh] OR hepatolent*[tiab] OR hepatomeg*[tiab] OR hepatopulm*[tiab] OR hepato-pulm*[tiab] OR hepatorenal*[tiab] OR hepato-renal*[tiab] OR hepatotox*[tiab] OR hepato-tox*[tiab] OR hyperbilirubin*[tiab] OR "hyperbilirubinemia"[tiab] OR "hyperbilirubinemia"[mh] OR intrahepatic*[tiab] OR intra-hepatic*[tiab] OR jaundice*[tiab] OR "liver"[tiab] OR "liver"[mh] OR "liver diseases"[tiab] OR "liver diseases"[mh] OR "liver function tests"[tiab] OR "liver function tests"[mh] OR liver*[tiab] OR porphyria*[tiab] OR "Reye syndrome"[tiab] OR "Reye syndrome"[mh]))

Immunological

(diabetes[tiab] AND type 1[tiab]) OR (hepatitis[tiab] AND autoimmune[tiab]) OR (addison*[tiab] OR adhesin*[tiab] OR agglutinat*[tiab] OR allergen*[tiab] OR allergi*[tiab] OR alpha-fetoprotein*[tiab] OR anaphylatoxin*[tiab] OR anemi*[tiab] OR angiotensin*[tiab] OR antibod*[tiab] OR anticoagulan*[tiab] OR "antifibrinolytic agents"[tiab] OR antigen*[tiab] OR "antigens"[tiab] OR "antigens"[mh] OR antisickling agent*[tiab] OR antithrombin*[tiab] OR "arrestin"[tiab] OR arthritis*[tiab] OR autoantigen*[tiab] OR autocoid*[tiab] OR autoimmun*[tiab] OR basophil*[tiab] OR b-cell*[tiab] OR bleed*[tiab] OR "blood physiological phenomena"[tiab] OR "blood physiological phenomena"[mh] OR "blood proteins"[tiab] OR "blood proteins"[mh] OR blood*[tiab] OR b-lymphocyt*[tiab] OR "bone-marrow"[tiab] OR "cd25"[tiab] OR "cd27"[tiab] OR "cd28"[tiab] OR "cd29"[tiab] OR "cd3"[tiab] OR "cd4"[tiab] OR "cd45"[tiab] OR "cd8"[tiab] OR chemokine*[tiab] OR "churg-strauss syndrome"[tiab] OR coagulat*[tiab] OR "coccidioidin"[tiab] OR "crp"[tiab] OR cytokine*[tiab] OR cytophagocytos*[tiab] OR dendrit*[tiab] OR dermatitis*[tiab] OR eicosanoid*[tiab] OR enterochromaffin*[tiab] OR eosinophil*[tiab] OR epitheloid-cell*[tiab] OR "epitope mapping"[tiab] OR erythrocyte*[tiab] OR fibrin-clot*[tiab] OR fibrinoly*[tiab] OR fluoroimmunoas*[tiab] OR foam-cell*[tiab] OR gamma-globulin*[tiab] OR giant cell*[tiab] OR glomerulonephritis*[tiab] OR granulocyte*[tiab] OR "graves disease"[tiab] OR guillain-barre*[tiab] OR "haematopoietic"[tiab] OR "haemic"[tiab] OR hemangioma*[tiab] OR hematinic*[tiab] OR hematocrit*[tiab] OR "hematologic agents"[tiab] OR "hematologic agents"[mh] OR "hematologic diseases"[tiab] OR "hematologic diseases"[mh] OR "hematologic tests"[tiab] OR "hematologic tests"[mh] OR hematologic*[tiab] OR hematop*[tiab] OR "hemic and immune systems"[tiab] OR "hemic and immune systems"[mh] OR hemocyte*[tiab] OR hemoglo*[tiab] OR "hemolytic"[tiab] OR hemophil*[tiab] OR hemorheolog*[tiab] OR hemorrhag*[tiab] OR hemostas*[tiab] OR hemostatic*[tiab] OR histamine*[tiab] OR histocompatib*[tiab] OR "histoplasmin"[tiab] OR "host-resistance"[tiab] OR hyperresponsiv*[tiab] OR hypersensitiv*[tiab] OR "il-6"[tiab] OR "il-8"[tiab] OR "immune system diseases"[tiab] OR "immune system diseases"[mh] OR "immune system phenomena"[tiab] OR "immune system phenomena"[mh] OR immune*[tiab] OR immunit*[tiab] OR immunoassay*[tiab] OR immunobl*[tiab] OR immunochroma*[tiab] OR immunoco*[tiab] OR immunog*[tiab] OR immunolog*[tiab] OR "immunologic techniques"[tiab] OR "immunologic techniques"[mh] OR "immunologic tests"[tiab] OR "immunologic tests"[mh] OR immunom*[tiab] OR immunophenotyp*[tiab] OR immunopr*[tiab] OR immunosuppress*[tiab] OR immunotherap*[tiab] OR immunotox*[tiab] OR inflamm*[tiab] OR "inflammation"[tiab] OR "inflammation"[mh] OR "inflammation mediators"[tiab] OR "inflammation mediators"[mh] OR "insulin-dependent"[tiab] OR interferon*[tiab] OR interleukin*[tiab] OR isoimmunizat*[tiab] OR killer cell*[tiab] OR kinin*[tiab] OR kupffer-cell*[tiab] OR langerhans*[tiab] OR "lepromin"[tiab] OR leukocyte*[tiab] OR leukopoies*[tiab] OR lupus*[tiab] OR lymphoc*[tiab] OR lymphokine*[tiab] OR lymphom*[tiab] OR lymphop*[tiab] OR macrophage*[tiab] OR mast-cell*[tiab] OR monocyte*[tiab] OR monokine*[tiab] OR "multiple sclerosis"[tiab] OR "myasthenia gravis"[tiab] OR myelop*[tiab] OR "neprilysin"[tiab] OR neutrophil*[tiab] OR nk-cell*[tiab] OR "osmotic fragility"[tiab] OR phagocyt*[tiab] OR "plasma"[tiab] OR platelet*[tiab] OR polyradiculoneuropath*[tiab] OR prostaglandin*[tiab] OR protein-c-deficienc*[tiab] OR prothrombin*[tiab] OR purpura*[tiab] OR radioim*[tiab] OR reticulocyt*[tiab] OR rheumatoid*[tiab] OR sensitiz*[tiab] OR serodiagnosis*[tiab] OR serotyp*[tiab] OR sperm agglutinat*[tiab] OR "spleen"[tiab] OR "splenic"[tiab] OR splenocyte*[tiab] OR staphylococc*[tiab] OR t-cell*[tiab] OR "t-helper"[tiab] OR thrombin*[tiab] OR thromboc*[tiab] OR thrombop*[tiab] OR "thymic"[tiab] OR thymocyte*[tiab] OR thymus*[tiab] OR t-lympho*[tiab] OR "tnf

alpha"[tiab] OR "transverse myelitis"[tiab] OR "trichophytin"[tiab] OR vaccinat*[tiab] OR vaccine*[tiab] OR von-willebrand*[tiab])

Population Strings

Note that population strings are based on SWIFT-Review search filters (Sciome 2023).

Human

(humans[mh] OR "human development"[mh]) OR (human[tiab] OR Humans[tiab] OR person[tiab] OR people[tiab]) OR ((“age groups”[mh]) OR (pediatric[tiab] OR pediatrician[tiab] OR paediatric[tiab] OR paediatrician[tiab] OR baby [tiab]OR babies[tiab] OR toddler[tiab] OR toddlers[tiab] OR child[tiab] OR children[tiab] OR youth[tiab] OR youngster[tiab] OR tween[tiab] OR tweens[tiab] OR teen[tiab] OR teens[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab]) OR (("in utero"[tiab] OR prenatal[tiab] OR perinatal[tiab] OR neonatal[tiab] OR postnatal[tiab]) NOT (mice[tiab] OR mouse[tiab] OR rat[tiab] OR rats[tiab]))) OR (preschool[tiab] OR preschooler[tiab] OR pre-school[tiab] OR kindergarten[tiab] OR kindergartener[tiab] OR schoolchild[tiab] OR schoolchildren[tiab] OR student[tiab] OR students[tiab]) OR ("middle age"[tiab] OR “middle-aged”[tiab] OR aged[tiab] OR elder[tiab] OR elderly[tiab] OR "senior citizen"[tiab] OR seniors[tiab] OR retiree[tiab] OR septuagenarian[tiab] OR octagenarian[tiab] OR sexagenarian[tiab] OR nonagenarian[tiab] OR centenarian[tiab]) OR ("nuclear family"[mh]) OR (family[tiab] OR families[tiab] OR parent[tiab] OR parents[tiab] OR father[tiab] OR fathers[tiab] OR mother[tiab] OR mothers[tiab] OR sibling[tiab] OR siblings[tiab] OR brother[tiab] OR brothers[tiab] OR sister[tiab] OR sisters[tiab] OR twin[tiab] OR twins[tiab] OR "stepfather"[tiab] OR "step father"[tiab] OR "stepmother"[tiab] OR "step mother"[tiab] OR "stepdaughter"[tiab] OR "step daughter"[tiab] OR "stepson"[tiab] OR "step son"[tiab] OR aunt[tiab] OR aunts[tiab] OR uncle[tiab] OR uncles[tiab] OR niece[tiab] OR nieces[tiab] OR nephew[tiab] OR nephews[tiab] OR grandparent[tiab] OR grandparents[tiab] OR grandfather[tiab] OR "grand father"[tiab] OR grandmother[tiab] OR "grand mother"[tiab] OR grandchild[tiab] OR granddaughter[tiab] OR grandson[tiab] OR spouse[tiab] OR spouses[tiab] OR spousal[tiab] OR partner[tiab] OR partners[tiab] OR husband[tiab] OR husbands[tiab] OR wife[tiab] OR wives[tiab] OR guardian[tiab] OR caregiver[tiab] OR caregivers[tiab] OR "care giver"[tiab]) OR (men[mh] OR women[mh]) OR (men[tiab] OR man[tiab] OR boy[tiab] OR boys[tiab] OR boyhood[tiab] OR women[tiab] OR woman[tiab] OR girl[tiab] OR girls[tiab] OR girlhood[tiab]) OR ("population groups"[mh] OR "vulnerable populations"[mh]) OR ("african american"[tiab] OR "asian american"[tiab] OR hispanic[tiab] OR latina[tiab] OR latino[tiab] OR "mexican american"[tiab] OR underserved[tiab] OR disadvantaged[tiab]) OR ("epidemiologic studies"[mh] OR "double-blind method"[mh] OR "single-blind method"[mh]) OR (epidemiology[mh]) OR ("case control"[tiab] OR cohort[tiab] OR "cross sectional"[tiab] OR "follow-up study"[tiab] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab]) OR ("case reports"[mh] OR "clinical trial"[mh] OR "observational study"[mh] OR "randomized control trial"[mh] OR "twin study"[mh]) OR ("clinical trial"[tiab] OR observational[tiab] OR "randomized control trial"[tiab]) OR ("research subjects"[mh] OR "human experimentation"[mh] OR patients[mh] OR "Patient Participation"[mh]) OR ("human subjects"[tiab] OR "research subjects"[tiab] OR clients[tiab] OR patient[tiab] OR inpatient[tiab] OR outpatient[tiab] OR participants[tiab] OR volunteers[tiab]) OR ("occupational groups"[mh] OR "occupational exposure"[mh]) OR (occupation[tiab] OR occupational[tiab] OR workplace[tiab] OR "work place"[tiab] OR "work-related"[tiab] OR administrators[tiab] OR aides[tiab] OR assistants[tiab] OR crew[tiab] OR crews[tiab] OR employees[tiab] OR personnel[tiab] OR professional[tiab] OR staff[tiab] OR technicians[tiab] OR workers[tiab] OR educators[tiab] OR instructors[tiab] OR teachers[tiab] OR clinicians[tiab] OR doctors[tiab] OR physicians[tiab] OR pharmacists[tiab] OR nurses[tiab] OR residents[tiab] OR veterinarians[tiab]) OR (epidemiologic[tiab])

Animal

"animal experimentation”[mh] OR "models, animal”[mh] OR "behavior, animal”[mh] OR "animal population groups”[mh] OR "invertebrates”[mh] OR "chordata, nonvertebrate”[mh] OR "amphibians”[mh] OR "birds”[mh] OR "fishes”[mh] OR "reptiles”[mh] OR "carnivora”[mh] OR "insectivora”[mh] OR "lagomorpha”[mh] OR "rodentia”[mh] OR "strepsirhini”[mh] OR "platyrrhini"[mh] OR "tarsii”[mh] OR

"cercopithecidae"[mh] OR "hylobatidae"[mh] OR "gorilla gorilla"[mh] OR "pan paniscus"[mh] OR "pan troglodytes"[mh] OR "pongo pygmaeus"[mh] OR "Animals"[mh] OR "chordata"[mh] OR "vertebrates"[mh] OR "mammals"[mh] OR "primates"[mh] OR "haplorhini"[mh] OR "catarrhini"[mh] OR "hominidae"[mh] OR animal[tiab] OR animals[tiab] OR mice[tiab] OR mus[tiab] OR mouse[tiab] OR murine[tiab] OR rats[tiab] OR rat[tiab] OR murinae[tiab] OR muridae[tiab] OR "cotton rat"[tiab] OR "cotton rats"[tiab] OR hamster[tiab] OR hamsters[tiab] OR rodent[tiab] OR rodents[tiab] OR pigs[tiab] OR pig[tiab] OR swine[tiab] OR piglet[tiab] OR piglets[tiab] OR "guinea pigs"[tiab] OR "guinea pig"[tiab] OR cavia[tiab] OR callithrix[tiab] OR marmoset[tiab] OR marmosets[tiab] OR cebuella[tiab] OR hapale[tiab] OR octodon[tiab] OR chinchilla[tiab] OR chincillas[tiab] OR gerbillinae[tiab] OR gerbil[tiab] OR gerbils[tiab] OR rabbit[tiab] OR rabbits[tiab] OR hares[tiab] OR hare[tiab] OR cats[tiab] OR cat[tiab] OR carus[tiab] OR felis[tiab] OR dogs[tiab] OR dog[tiab] OR canine[tiab] OR canines[tiab] OR canis[tiab] OR haplorhini[tiab] OR monkey[tiab] OR monkeys[tiab] OR anthropoid[tiab] OR saguinus[tiab] OR tamarin[tiab] OR leontopithecus[tiab] OR hominidae[tiab] OR ape[tiab] OR apes[tiab] OR "pan paniscus"[tiab] OR bonobo[tiab] OR "pan troglodytes"[tiab] OR gibbon[tiab] OR gibbons[tiab] OR nomascus[tiab] OR symphalangus[tiab] OR chimpanzee[tiab] OR chimpanzees[tiab] OR chimp[tiab] OR chimps[tiab] OR prosimian[tiab] OR pongidae[tiab] OR gorilla[tiab] OR gorillas[tiab] OR "pongo pygmaeus"[tiab] OR orangutan[tiab] OR orangutans[tiab] OR lemur[tiab] OR lemurs[tiab] OR lemuridae[tiab] OR chicken[tiab] OR chickens[tiab] OR gallus[tiab] OR quail[tiab] OR quails[tiab] OR bird[tiab] OR birds[tiab] OR poultry[tiab] OR fowl[tiab] OR fowls[tiab] OR reptile[tiab] OR reptiles[tiab] OR turtle[tiab] OR turtles[tiab] OR amphibian[tiab] OR frog[tiab] OR frogs[tiab] OR xenopus[tiab] OR bombina[tiab] OR salientia[tiab] OR toad[tiab] OR toads[tiab] OR "epidalea calamita"[tiab] OR salamander[tiab] OR fish[tiab] OR fishes[tiab] OR pisces[tiab] OR catfish[tiab] OR perch[tiab] OR percidae[tiab] OR perca[tiab] OR trout[tiab] OR char[tiab] OR salmon[tiab] OR salvelinus[tiab] OR minnow[tiab] OR cyprinidae[tiab] OR carp[tiab] OR zebrafish[tiab] OR "zebra fish"[tiab] OR nematode[tiab] OR elegans[tiab] OR diptera[tiab] OR flies[tiab] OR dipteral[tiab] OR drosophila[tiab]

Study Type

Reviews

("Meta-Analysis"[pt] OR "Review"[pt] OR "Systematic Review" [pt] OR review[ti] OR metaanalysis[tiab] OR case-report[tiab] OR metaanalyses[tiab] OR meta-analysis[tiab] OR meta-analyses[tiab])

Appendix B Supplementary Results for Phases 1 and 2

Detailed extractions of authoritative source reports and resources are available in the Excel file "East Palestine_Rapid Scoping_Phase 1 Extractions." The file is available as a separate document.

Table B-1. Detailed Findings from Phase 1 Authoritative Source Reviews for 15 East Palestine Chemicals of Interest

Chemicals (CASRN)	Cancer	Nervous	Immune	Developmental	Reproductive	Other Organs	Skin Sensitiza-tion	Skin Irritation	Eye Irritation	Respiratory Irritation
Highest-priority Chemicals										
Acrolein (107-02-8)	IARC Group 2A (Probably) Gap: Human	Gap: Suggestive, no conclusion	Gap: Suggestive, no conclusion	No risk or concern: Guideline study	Low risk or concern: Guideline study	*Cardio and metabolic*: Suggestive *GI*: Stomach irritant in animals; RA [animals]	Suggestive, no conclusion	Irritant: Category 1B	Irritant: Category 1; RA [humans]	Irritant: RA [humans]
Butyl Acrylate (141-32-2)	IARC Group 3: Inadequate evidence from animal studies (negative) (1999)	Gap: No or few studies	Gap: No or few studies	No risk or concern: Guideline study	No risk or concern: Guideline study	*Hepatic*: Suggestive, no conclusion	Sensitizing: Category 1	Irritant: Category 2	Irritant: Category 2	Irritant: RA [animals]
Ethylene Glycol Monobutyl Ether (EGBE or 2-Butoxyethanol) (111-76-2)	IARC Group 3: Hemangiosarcoma and forestomach in animals (2006) Gap: Human	Gap: Suggestive, no conclusion	Gap: Suggestive, no conclusion	Low risk or concern: Positive effects at doses causing maternal toxicity in animal studies	Low risk or concern: Positive effects at high doses	*Hemo*: Causes hematotoxicity; RA [humans] *Hepatic*: Causes liver toxicity; RA [animals]	No or low concern	Irritant: Category 2	Irritant: Category 2; RA [humans]	Irritant: RA [humans]
2-Ethylhexyl Acrylate (103-11-7)	IARC Group 2B (Possibly) Skin, animal studies (2019) Gap: Human	Gap: No or few studies	Gap: No or few studies	No or low concern	No or low concern	Gap: No or few studies	Sensitizing: Category 1	Irritant: Category 2	Irritant: Category 2	Irritant: RA [animals]
High-priority Chemicals										
Benzene (71-43-2)	IARC Group 1 (Known) for humans RA [humans]	Evidence indicates neurotoxicity from high exposure (e.g., workplace) in humans	Adverse effects in humans RA [humans]	Causes developmental effects [hematotoxicity] in animals; RA [animals] Gap: Human	May harm the reproductive system (limited evidence)	*Hemo*: Bone marrow depression; RA [humans] *GI*: Suggestive	No or low concern	Irritant: Category 2	Irritant: Category 2	Gap: Suggestive, no conclusion
Hydrogen Chloride (7647-01-0)	IARC Group 3: Inadequately designed animal studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	*Renal*: Suggestive, no conclusion	No or low concern	Irritant: Category 1	Irritant: Category 1 RA [humans]	Irritant: RA [humans]

Chemicals (CASRN)	Cancer	Nervous	Immune	Developmental	Reproductive	Other Organs	Skin Sensitization	Skin Irritation	Eye Irritation	Respiratory Irritation
Phosgene Gas (75-44-5)	Gap: No or few studies	Gap: No or few studies	Immune in lung Gap: Suggestive, no conclusion	Gap: No or few studies	Gap: No or few studies	*Respiratory (other than irritation)*: RA [humans]	Gap: No or few studies	Irritant: Category 1	Irritant: Category 1	Irritant: RA [humans]
Vinyl Chloride (75-01-4)	IARC Group 1 (Known) for humans RA [humans]	Presumed for humans	Suspected for humans	Suspected for humans	Gap: No or few studies	*Hepatic*: Presumed liver effects for humans RA [animals]	Sensitizing: Category 1	Irritant: Category 2	RA [humans]	Irritant: RA [humans]
Moderate-priority Chemicals										
Diethylene Glycol (111-46-6)	No carcinogenic potential	Gap: Suggestive, no conclusion	Gap: No or few studies	No or low concern	No or low concern	*Renal*: Suggestive, no conclusion	No or low concern	No or low concern	Negative studies	Gap: Suggestive, no conclusion
Dipropylene Glycol (25265-71-8)	No carcinogenic potential	Gap: No or few studies	Gap: No or few studies	No or low concern	No or low concern	Gap: No or few studies	No or low concern	Irritant: Category 3	Irritant: Category 2A	Gap: No or few studies
Polypropylene Glycol (25322-69-4)	Gap: No or few studies	Gap: Suggestive	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	*Cardiovascular*: Suggestive, no conclusion	No or low concern	Suggestive, no conclusion	Irritant: Category 2A	No or low concern
1,2 Propylene Glycol (57-55-6)	Not likely carcinogenic	Gap: No or few studies	Gap: No or few studies	No or low concern	No or low concern	*Hemo:* Effects (not severe) and hyperglycemia in animals RA [animals]	No or low concern	Suggestive, no conclusion	No or low concern	Suggestive: RA [animals] but overall evidence incon-clusive
Low-priority Chemicals										
Petroleum Lube Oil (64742-58-1)	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No conclusions	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Irritant: Category 2	Irritant: Category 2	Gap: No or few studies
Polyethylene (9002-88-4)	IARC Group 3: Inadequately designed animal studies (1979)	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies
Polyvinyl Alcohol (9002-89-5)	IARC Group 3: Conflicting animal evidence (1979)	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies

CASRN = Chemical Abstracts Service Registry Number; IARC = International Agency for Research on Cancer; GI = gastrointestinal; RA = Risk Estimate Available.

Table B-2. Detailed Findings from Phase 1 Authoritative Source Reviews for Five PFAS Chemicals

Chemical (CASRN)	Cancer	Nervous	Immune	Developmental	Reproductive	Other Organs	Skin Sensitization	Skin Irritation	Eye Irritation	Respiratory Irritation
6:2 FTSHA (88992-45-4)	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Presumed (Category 1B) in guideline animal study	Presumed (Category 1B) in guideline animal study	Gap: No or few studies	Not sensitizing (in vitro); sensitizing in guideline animal study	No or low concern	Irritant: Category 1	Gap: No or few studies
6:2 FTSAS (88992-47-6)	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies
6:2 FTSA (27619-97-2)	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	No or low concern	No or low concern	Gap: No or few studies	No or low concern	Irritant: Category 1B	Irritant: Category 1	Gap: No or few studies
6:2 FTSA-PrB (34455-29-3)	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	Gap: No or few studies	No or low concern	No or low concern	Suggestive: Some irritation in guideline study (reversed in 24 hours)	Gap: No or few studies
6:2 FTNO (80475-32-7)	Gap: No or few studies	No or low concern	Gap: No or few studies	No or low concern	No or low concern	*Cardiovascular*: Suggestive, some decreased serum lipids in guideline studies *Hemo:* No or low concern	No or low concern	No or low concern	No or low concern	Gap: No or few studies

PFAS = per- and polyfluoroalkyl substances; CASRN = Chemical Abstracts Service Registry Number.

Table B-3. Acrolein-Nervous Phase 2 Search Results and Studies from Phase 1 Reviews

Study Citation	Evidence Type	Reference Source[a]				
		Phase 2 Search	ATSDR (2007a)	ECHA[b] (2001)	EPA IRIS (2003b)	OEHHA (2014)
Alarie (1973)	Review, animal only	X	X			
Arlt et al. (2002)	Review, human, animal, mechanistic	X				
Chang et al. (2022)	Review, human and animal	X				
Dorman et al. (2008)	Primary animal					X
Feron et al. (1978)	Primary animal		X			
Igarashi et al. (2018)	Review, human, animal, mechanistic	X				
Igarashi et al. (2020)	Review, human and animal	X				
Iqubal et al. (2020)	Review, human, animal, mechanistic	X				
Kutzman et al. (1984)	Primary animal		X			
Kutzman et al. (1985)	Primary animal		X			
LoPachin et al. (2008)	Review, human, animal, mechanistic	X				
Lovell et al. (2001)	Primary human					X
Lyon et al. (1970)	Primary animal		X	X		X
Moghe et al. (2015)	Review, animal only (no human studies found)	X				
Morris et al. (1999)	Primary animal		X			
Morris et al. (2003)	Primary animal					X
Muguruma et al. (2020)	Review, human only	X				
Parent et al. (1991)	Primary animal		X			
Parent et al. (1992b)	Primary animal		X			
Parent et al. (1992a)	Primary animal		X			
Park and Igarashi (2013)	Review, human, animal, mechanistic	X				
Schroeter et al. (2008)	Primary animal					X

Study Citation	Evidence Type	Reference Source[a]				
		Phase 2 Search	ATSDR (2007a)	ECHA[b] (2001)	EPA IRIS (2003b)	OEHHA (2014)
Singh et al. (2010)	Review, human, animal, mechanistic	X				
Sprince et al. (1979)	Primary animal		X			
Springall et al. (1990)	Primary animal		X		X	

[a]Studies are identified for authoritative reviews if reports discussed neurological outcomes. Authoritative reviews may have discussed some studies but not reported effects for the health system of interest.
[b]Report published by the European Chemicals Bureau (ECB), a precursor to the European Chemicals Agency (ECHA).

Table B-4. 2-Butoxyethanol-Immune Phase 2 Search Results and Studies from Phase 1 Reviews

Study Citation	Evidence Type	Reference Source[a]			
		Phase 2 Search	ATSDR (1998)	EPA IRIS (2010)	OEHHA (2018)
Song et al. (2017)	Primary human	X			
Carpenter et al. (1956)	Primary animal		X		
Chereshnev et al. (2014)	Primary animal	X			X
CMA (1983)	Primary animal		X		
CMA (1993)	Primary animal		X		
Dodd et al. (1983)	Primary animal	X	X		X
Duprat and Gradiski (1979)	Primary animal		X		
Eastman Kodak (1983)	Primary animal		X		
Exon et al. (1991)	Primary animal	X	X	X	X
Ghanayem et al. (1987a)	Primary animal	X	X	X	
Ghanayem et al. (1987b)	Primary animal		X		
Ghanayem et al. (1992)	Primary animal		X		
Grant et al. (1985)	Primary animal	X	X	X	
Greenspan et al. (1995)	Primary human		X		
Krasavage (1986)	Primary animal	X	X		
Nachreiner (1994)	Primary animal		X		
NTP (1989)	Primary animal		X		
NTP (1993)	Primary animal		X		
Shepard (1994)	Primary animal		X		
Singh et al. (2001)	Primary animal	X		X	X
Smialowicz et al. (1992)	Primary animal	X	X	X	X
Starek et al. (2008)	Primary animal	X			
Tyl et al. (1984)	Primary animal		X		
Union Carbide (1989a)	Primary animal		X		
Union Carbide (1989b)	Primary animal		X		
Werner et al. (1943a)	Primary animal		X		
Werner et al. (1943b)	Primary animal		X		
Zissu (1995)	Primary animal		X		

[a]Studies are identified for authoritative reviews if reports discussed immune outcomes. Authoritative reviews may have discussed some studies but not reported effects for the health system of interest.

Table B-5. 2-Butoxyethanol-Nervous Phase 2 Search Results and Studies from Phase 1 Reviews

Study Citation	Evidence Type	Reference Source[a]			
		Phase 2 Search	ATSDR (1998)	EPA IRIS (2010)	OEHHA (2018)
Bauer et al. (1992)	Case report, human		X	X	X
Burkhart and Donovan (1998)	Case report, human	X		X	
Carpenter et al. (1956)	Primary animal and human		X	X	X
CMA (1983)	Primary animal		X		
Dean and Krenzelok (1992)	Case series, human	X	X	X	X
Dodd et al. (1983)	Primary animal		X		
Dow (1986)	Primary animal		X		
Eastman Kodak (1983)	Primary animal		X		
Gijsenbergh et al. (1989)	Case report, human		X	X	X
Gualtieri et al. (2003)	Case report, human			X	X
Krasavage (1986)	Primary animal		X		
Litovitz et al. (1991)	Case report, human		X		
NTP (1993)	Primary animal		X		
Nyska et al. (1999)	Primary animal	X			
Osterhoudt (2002)	Case report, human	X		X	
Rambourg-Schepens et al. (1988)	Case report, human		X	X	X
Wier et al. (1987)	Primary animal		X		

[a]Studies are identified for authoritative reviews if reports discussed neurological outcomes. Authoritative reviews may have discussed some studies but not reported effects for the health system of interest.