ORNL/TM-2024/3651

Identification and Reclassification of Mutagenic Chemicals for Improved Human Health Screening Levels

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October 2024

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Environmental Sciences Division
Environmental Risk and Energy Analysis Group

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Prepared by
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Oak Ridge, TN 37831
managed by
UT-BATTELLE LLC
for the
US DEPARTMENT OF ENERGY
under contract DE-AC05-00OR22725

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ABBREVIATIONS

ADAF	Age Dependent Adjustment Factor
ATSDR	Agency for Toxic Substance and Disease Registry
CMD	Carcinogens and Mutagens Directive
COPC	Chemical of Potential Concern
DOE	Department of Energy
ECHA	European Chemicals Agency
ELCR	Estimated Lifetime Cancer Risk
EPA	Environmental Protection Agency
HEAST	Health Effects Assessment Summary Tables
HHBP	Human Health Benchmarks for Pesticides
IRIS	Integrated Risk Information System
IUR	Inhalation Unit Risk
MOA	Mode of Action
MRL	Minimal Risk Level
NCI	National Cancer Institutes
OLEM	Office of Land and Emergency Management
OPP	Office of Pesticide Programs
ORNL	Oak Ridge National Laboratory
OSF	Oral Slope Factor
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
PPRTV	Provisional Peer Reviewed Toxicity Value
RSL	Regional Screening Level

ACKNOWLEDGEMENTS

This research was supported in part by an appointment to the Oak Ridge National Laboratory Graduate Research Student Internship, sponsored by the U.S. Department of Energy, and administered by the Oak Ridge Institute for Science and Education.

This research was also supported in part by the U.S. Department of Energy, Office of Science, Office of Workforce Development for Teachers and Scientists, under the Science Undergraduate Laboratory Internship Program.

ABSTRACT

The United States Environmental Protection Agency (EPA) Office of Land and Emergency Management (OLEM) produces the Regional Screening Levels (RSLs) for environmentally contaminated Superfund sites across all EPA regions. The RSLs are health-based screening levels for residential and commercial/industrial exposures to soil, air, and tap water that are deemed protective of human health for noncarcinogenic and carcinogenic chemicals by the EPA. The RSL website (as of May 2024) provides a calculator, default equations, and tables of screening levels for 858 chemicals, including noncarcinogenic and carcinogenic chemicals. Some chemical carcinogens cause damage by a mutagenic mode of action (MOA), which may result in irreversible changes to DNA and exhibit a greater adverse effect in early-life versus later-life exposure. For these chemicals, the RSLs include separate equations to provide an extra level of protection for the child age segments of 0-2, 2-6, and 6-16 years. In fact, this report shows that a chemical identified to act via a mutagenic mode of action will have a smaller and more protective RSL value (up to 78% decrease) than if it was not identified as a mutagen.

Previous work by the EPA identified some chemicals as mutagens and provided them on a former EPA website, "Chemicals with a Mutagenic Mode of Action (MOA) for Carcinogenesis" (Web Archive 2015). That site contained 19 known mutagens, and the associated technical guidance recommended updating the list of mutagens based on future EPA IRIS and PPRTV toxicity assessments. Chemicals not included in the list were generally not treated as mutagens in the RSL calculations. Since the website was deactivated in 2015, only 8 additional chemicals were identified by EPA as mutagens and included in the RSL calculations, bringing the total to 27 chemicals identified as mutagens in the May 2024 RSLs.

This report investigates mutagenicity in the toxicity profiles for the 251 non-mutagenic chemicals with an oral or inhalation cancer toxicity value in the May 2024 RSLs. Definitive evidence for a mutagenic mode of action was found in 5 chemicals that the RSL workgroup is including as mutagens in the November 2024 RSLs. Strong evidence for a mutagenic mode of action was found in 10 chemicals currently not identified in the May 2024 RSLs as mutagenic (classified as "yes" in this paper). Another 16 chemicals are classified as "likely" mutagenic, and 74 chemicals are classified as "cannot be determined (CBD)". This research strongly recommends the 10 chemicals identified as "yes" be reclassified as mutagens by the EPA for use in the RSLs. It is recommended that the 16 chemicals classified as "Likely" mutagenic by this research be verified by EPA toxicologists for potential mutagen classification. The chemicals classified herein as "CBD" need a more extensive review and evaluation for potential classification as a mutagen.

1. INTRODUCTION

The purpose of this report is: 1) to quantify the impact of applying mutagenic age-dependent adjustment factors (ADAFs) to RSL calculations, 2) to summarize the methodology and results of the literature review addressing mutagenicity of carcinogenic chemicals that are not labeled as mutagens in the RSLs, and 3) to make recommendations to EPA's Superfund program for restoration and update of the "Chemicals with a Mutagenic Mode of Action (MOA) for Carcinogenesis*"* website.

2. BACKGROUND

2.1 REGIONAL SCREENING LEVELS OVERVIEW

EPA Superfund sites (locations) are addressed under the authority of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) of 1980, which was amended by the 1986 Superfund Amendments and Reauthorization Act. EPA is responsible for enforcing cleanup of environmentally contaminated sites from previous activities that have led to residual pollution in environmental media. The purpose of the RSL website is to provide a health risk-based screening level calculation tool to assist risk assessors, remedial project managers, and others involved with risk assessment and decision-making at CERCLA sites based on Risk Assessment Guidance for Superfund: Volume I, Human Health Evaluation Manual (Parts A and B) (EPA 1989a and 1991a) and Guidelines for Carcinogen Risk Assessment (EPA 2005a).

Health risk-based screening levels (such as the RSLs) are used to determine whether levels of environmental contamination at a site are harmful and may warrant further investigation. Specifically, the RSLs are chemical-specific concentrations for individual contaminants in air, drinking water, and soil that are derived from calculations and models combining exposure assumptions with chemical-specific toxicity values.

2.2 TOXICITY VALUES

Oral slope factors and inhalation unit risk values are the toxicity data most commonly used to evaluate potential human carcinogenesis. The oral slope factor (OSF) estimates an upper-bound lifetime probability of an individual developing cancer as a result of exposure to a particular level of a potential carcinogen. The inhalation unit risk (IUR) is defined as the upper-bound lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 microgram per cubic meter (µg/m3) in air. Slope factors and unit risks are accompanied by a weight-of-evidence classification that addresses the chemical's human carcinogenic potential.

Toxicity values for the RSLs are compiled from multiple sources based on an EPA Superfund memo (EPA 2003a), which details a three-tier hierarchy (**Table 1**). Additional Tier 3 values have been included in the RSLs since the 2003 memo.

Table 1. EPA RSL Toxicity Value Sources by Tiers

Tier	Toxicity Source(s)
Tier 1	• EPA's Integrated Risk Information System (IRIS)
Tier 2	• EPA's Superfund Health Risk Technical Support Center (STSC) Provisional Peer Reviewed Toxicity Values (PPRTVs)
Tier 3	• EPA's Office of Pesticide Programs (OPP) Human Health Benchmarks for Pesticides (HHBPs) • The Agency for Toxic Substances and Disease Registry (ATSDR) minimal risk levels (MRLs). • The EPA Office of Water Human Health Toxicity Assessments • The California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database • PPRTV Appendix Screening Values • EPA's Office of Research and Development (ORD) Human Health Toxicity Values • The 11th Cycle of Groundwater Standards Proposals from the State of Wisconsin Department of Health Services • The EPA Superfund program's Health Effects Assessment Summary Table (HEAST)

2.3 MUTAGENICITY

When evaluating a chemical for toxicity, the mutagenicity potential is typically identified. A mutagen is a chemical that is carcinogenic by a mutagenic mode of action (MOA). Mutagenic agents cause permanent mutations or changes in a cell's DNA that can harm cells or cause diseases like cancer. A chemical is classified as a mutagen if tests show positive effects for genetic endpoint changes, such as gene mutations, structural chromosome aberrations, or other endpoints that indicate damage to DNA. Detections of chemical-specific DNA adducts can provide information on the ability of a chemical to interact with DNA (EPA 2005b). One characteristic of a mutagenic MOA is evidence that the carcinogen or metabolite is either DNA-reactive or has the ability to bind to DNA.

Identifying potential mutagens is the first step towards accurately understanding the potential risk that certain chemicals can pose to human receptors and taking steps to prevent harm from occurring. The EPA recommends specific risk assessment procedures for carcinogens acting through a mutagenic MOA, specifically the application of age-dependent adjustment factors (ADAFs) when calculating exposure (EPA 2005b). This is due to distinct differences in biological processes during early-life exposure as opposed to later-life exposure. For example, certain aspects of the developing immune system will be less functional during the early stages of life, and the hormonal system is known to operate at different levels depending on age. The standard methodologies for estimating cancer risk, which are based on estimations of lifetime exposure, do not take susceptibility differences across different life stages into account (EPA 2005b). Therefore, there are separate mutagenic equations used for chemicals classified as mutagens to calculate screening levels for the RSLs.

To illustrate the different approaches when assessing exposure to a carcinogenic chemical versus a mutagenic chemical, two versions of the RSL resident soil ingestion screening level equation are shown below: carcinogenic (**Equation 1**) and mutagenic (**Equation 2**). The associated variables are described in **Table 2**. Similar changes would be applied to both the air and tap water equations for standard carcinogenic versus mutagenic values.

Resident Soil Carcinogenic Ingestion Screening Level Equation

$$SL_{res-sol-ingc} = \frac{TR \times AT_{res}\left(\frac{365\ days}{year} \times LT(years)\right)}{CSF_O \times \left(\frac{10^{-6}\ kg}{mg}\right) \times RBA \times IFS_{res-adj}} \textbf{ [1]}$$

where:

$$IFS_{res-adj} = \left[\frac{EF_{res-c} \times ED_{res-c} \times IRS_{res-c}}{BW_{res-c}} + \frac{EF_{res-a} \times ED_{res-a} \times IRS_{res-a}}{BW_{res-a}}\right]$$

Resident Soil Mutagenic Ingestion Screening Level Equation

$$SL_{res-sol-ingmu} = \frac{TR \times AT_{res}\left(\frac{365\ days}{year} \times LT(years)\right)}{CSF_O \times \left(\frac{10^{-6}\ kg}{mg}\right) \times RBA \times IFSM_{res-adj}} \textbf{ [2]}$$

where:

$$IFSM_{res-adj} = \left[\frac{EF_{0-2} \times ED_{0-2} \times IRS_{0-2} \times 10}{BW_{0-2}} + \frac{EF_{2-6} \times ED_{2-6} \times IRS_{2-6} \times 3}{BW_{2-6}} + \frac{EF_{6-16} \times ED_{6-16} \times IRS_{6-16} \times 3}{BW_{6-16}} + \frac{EF_{16-26} \times ED_{16-26} \times IRS_{16-26} \times 1}{BW_{16-26}}\right]$$

Table 2. Parameters for Carcinogenic and Mutagenic Soil Ingestion Screening Levels

Parameter	Description	Value	Units
$SL_{res\text{-}sol\text{-}ingc}$	Resident Soil Carcinogenic Ingestion Screening Level	Contaminant-Specific	mg/kg
$SL_{res\text{-}sol\text{-}ingmu}$	Resident Soil Mutagenic Ingestion Screening Level	Contaminant-Specific	mg/kg
TR	Target Risk	10^{-6}	unitless
AT_{res}	Averaging Time – Resident Age-adjusted	25,550	days
LT	Lifetime	70	years
CSF_O	Oral Slope Factor	Contaminant-Specific	$(mg/kg\text{-}day)^{-1}$
RBA	Relative Bioavailability factor	6 (Arsenic) 1 (All Others)	unitless
$IFS_{res\text{-}adj}$	Resident Soil Ingestion Rate – Age-adjusted	36,750	mg/kg
$IFSM_{res\text{-}adj}$	Resident Mutagenic Soil Ingestion Rate – Age-adjusted	166,833.3	mg/kg
$EF_{res\text{-}c}$	Resident Exposure Frequency – Child	350	days/year
$ED_{res\text{-}c}$	Resident Exposure Duration – Child	6	years
$IRS_{res\text{-}c}$	Soil Ingestion Rate – Child	200	mg/day
$BW_{res\text{-}c}$	Resident Body Weight – Child	15	kg
$EF_{res\text{-}a}$	Resident Exposure Frequency – Adult	350	days/year
$ED_{res\text{-}a}$	Resident Exposure Duration – Adult	20	years
$IRS_{res\text{-}a}$	Soil Ingestion Rate – Adult	100	mg/day
$BW_{res\text{-}a}$	Resident Body Weight – Adult	80	kg
$EF_{0\text{-}2}$	Resident Exposure Frequency – Age Segment (0-2)	350	days/year
$ED_{0\text{-}2}$	Resident Exposure Duration – Age Segment (0-2)	2	years
$IRS_{0\text{-}2}$	Soil Ingestion Rate – Age Segment (0-2)	200	mg/day
$BW_{0\text{-}2}$	Resident Body Weight – Age Segment (0-2)	15	kg
$EF_{2\text{-}6}$	Resident Exposure Frequency – Age Segment (2-6)	350	days/year
$ED_{2\text{-}6}$	Resident Exposure Duration – Age Segment (2-6)	4	years
$IRS_{2\text{-}6}$	Soil Ingestion Rate – Age Segment (2-6)	200	mg/day
$BW_{2\text{-}6}$	Resident Body Weight – Age Segment (2-6)	15	kg
$EF_{6\text{-}16}$	Resident Exposure Frequency – Age Segment (6-16)	350	days/year
$ED_{6\text{-}16}$	Resident Exposure Duration – Age Segment (6-16)	10	years
$IRS_{6\text{-}16}$	Soil Ingestion Rate – Age Segment (6-16)	100	mg/day
$BW_{6\text{-}16}$	Resident Body Weight – Age Segment (6-16)	80	kg
$EF_{16\text{-}26}$	Resident Exposure Frequency – Age Segment (16-26)	350	days/year
$ED_{16\text{-}26}$	Resident Exposure Duration – Age Segment (16-26)	10	years
$IRS_{16\text{-}26}$	Soil Ingestion Rate – Age Segment (16-26)	100	mg/day
$BW_{16\text{-}26}$	Resident Body Weight – Age Segment (16-26)	80	kg

Risk-based screening levels are derived from equations that combine exposure assumptions (e.g., exposure frequency, duration, and time) with chemical-specific toxicity values (e.g., oral slope factors and inhalation unit risks) (EPA 2024a). While similarities can be seen in **Equations 1** and **2**, the derivation of the adjusted soil ingestion rates differs dramatically between the carcinogenic ($IFS_{res\text{-}adj}$) and mutagenic ($IFSM_{res\text{-}adj}$) equations (indicated with red text). The mutagenic equation derives the soil ingestion rate by considering four separate age segments or life stages: 0-2 years, 2-6 years, 6-16 years, and 16-26 years. In contrast, the carcinogenic equation derives the soil ingestion rate by only considering two separate age segments: child (0-6 years) and adult (6-26 years). The mutagenic equation acknowledges that there are susceptibility differences between various life stages by applying ADAFs of 10, 3, 3, and 1 for age segments 0-2, 2-6, 6-16, and 16-26, respectively.

2.4 MUTAGENIC STATUS FOR RSLS

As of May 2024, the EPA RSLs contain 27 chemicals as mutagens (EPA 2024a), which began with 19 chemicals found on EPA's former website "Chemicals with a Mutagenic Mode of Action (MOA) for Carcinogenesis" (Web Archive 2015). This former, archived website references EPA 2005b, which identifies these twelve chemicals as mutagens: benzidine, benzo[a]pyrene, dibenz[a,h]anthracene, diethylnitrosamine, dimethylbenz[a]anthracene, dimethylnitrosamine, ethylnitrosourea, 3-methylcholanthrene, methylnitrosurea, safrole, urethane, and vinyl chloride. Additionally, it presents mutagenic chemicals from three other sources: the Federal Register 19992 for coke oven emissions (EPA 2005c); EPA's provisional peer-reviewed toxicity values (PPRTVs) for 4,4'-methylenebis(2-chloroaniline) and 1,2-dibromo-3-chloropropane (EPA 2006a and 2006b, respectively); and EPA's Integration Risk Information System (IRIS) for 1,2,3-trichloropropane, acrylamide, dichloromethane, and trichloroethylene (EPA 2009a, 2010a, 2011a, and 2011b, respectively).

Between the removal of the former EPA website in 2015 and May 2024, eight additional chemicals were added to the RSL list of known mutagens. Five PAHs (Benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, and indeno[1,2,3-cd]pyrene) were added based on their toxicity equivalent factors to benzo[a]pyrene. Chromium VI and ethylene oxide were added due to their IRIS assessments (EPA 2024b and 2016a, respectively). Total Petroleum Hydrocarbons (Aromatic High) was given mutagen status, as the representative compound is currently benzo[a]pyrene.

Five additional chemicals will be added to the RSL list of known mutagens for the November 2024 RSLs. Chloroprene and formaldehyde will be added due to mutagenic mode of action determinations in their IRIS assessments (EPA 2010b and 2024c, respectively). 3,3'-dimethoxybenzidine, 3,3'-dimethylbenzidine, and o-phenylenediamine will be added due to mutagenic mode of action determinations in their PPRTV assessments (EPA 2013, 2008, and 2016b, respectively).

There are other IRIS or PPRTV papers, however, that address mutagenicity or possible mutagenicity that should be considered. Additionally, many chemicals were not evaluated for mutagenicity for the RSLs because they were from tier 3 sources. Since the EPA now recognizes many tier 3 sources (see Table 1) as providing robust toxicity information, they should assist in further identification of mutagenic chemicals.

Designating a chemical as a mutagen is outside the purview of the RSLs. The RSLs rely on consensus from other technical and nontechnical sources within the EPA to designate a chemical as a mutagen. Therefore, this paper urges the EPA to consider approving the mutagens identified in this research to be included as mutagens in the RSLs.

2.5 RSL COMPARISON WITH KNOWN MUTAGENIC CHEMICALS

The first step in this research effort was to determine the impact of using mutagenic RSL equations instead of standard carcinogenic RSL equations for the 27 mutagens in the May 2024 RSLs; note that the five additional mutagens being added to the November 2024 RSLs were not identified as mutagens when this research was conducted. The land uses evaluated were residential exposure to air, water, and soil. Water and soil RSLs include ingestion, dermal, and inhalation pathways, while the resident air only includes inhalation. Trichloroethylene and vinyl chloride were not included in this step, since they have unique mutagenic equations that cannot be manipulated in site-specific mode with the RSL calculator. Additionally, total petroleum hydrocarbons (aromatic high) does not have carcinogenic toxicity values, so it was not included. Therefore, 24 mutagens were evaluated.

For this comparison, RSLs were first generated using the RSL calculator site-specific mode to essentially "deactivate" the mutagenicity status and calculate RSL values using the standard carcinogenic equations.

Next, the RSLs were generated assuming a mutagenic mode of action and resident land use with the mutagenic equations. The two different values for each chemical were compared to calculate a percent change using **Equation 3**:

$$Percent\ Change = \frac{(Car - Mut)}{|\ Car\ |} * 100 \quad \textbf{[3]}$$

where: Car = RSL calculated using standard carcinogenic equation and
Mut = RSL calculated using mutagenicity equation.

Standard carcinogenic values, mutagenic values, and the percent changes are presented in **Appendix A**. This comparison demonstrated that for all 24 mutagens evaluated, using mutagen equations instead of the standard carcinogenic equations resulted in equal or decreased RSL values (64-78% decreased). The only RSL values with identical values were all 3 media for Methylene chloride and the air media for benzo(a)pyrene and 1,2,3-Trichloropropane; in all cases, the noncarcinogenic screening levels were the drivers for risk, so the changes to the carcinogenic equations did not affect the RSLs. For all other chemicals in **Appendix A**, the mutagenic equations yielded smaller values, which are more conservative and therefore more protective of human health.

2.6 LITERATURE REVIEW FOR ADDITIONAL MUTAGENS

A comparison of mutagenic versus carcinogenic RSL calculations is provided in **Appendix A** to demonstrate the importance of using mutagenic equations for mutagens. To advance the RSLs and consider additional potential mutagenic chemicals, a comprehensive literature review was performed for every carcinogenic chemical in the May 2024 RSLs that has an oral slope factor (OSF) or inhalation unit risk (IUR) to determine if they should be classified as mutagens.

Of the 879 chemicals in the May 2024 RSLs, 278 chemicals had either an OSF (249), an IUR (191), or both (162). The review excluded chemicals that were already classified as mutagens for the May 2024 RSLs; therefore, a total of 251 chemicals were the focus of the literature search.

Toxicity value derivation profiles and reference documents for the RSL chemicals were searched for mutagenicity information. For each chemical, the review started with the toxicity source associated with the RSL cancer toxicity value. If no supporting information was available in that source, other EPA information sources were consulted. **Table 1** displays the EPA RSL toxicity value sources by tiers.

If the mutagenicity status in the EPA source documentation from **Table 1** was missing or inconclusive, other external sources were reviewed. These include the European Chemicals Agency (ECHA) Carcinogens and Mutagens Directive (CMD) (ECHA, 2024) and National Institutes of Health (NIH) National Toxicology Program Chemical Effects in Biological Systems (CEBS) (NIH 2024a) and PubChem (NIH 2024b) databases.

2.7 CLASSIFICATION RESULTS

The results of the literature search and review were summarized by assigning each chemical to one of four classifications that described the possibility of mutagenicity: Yes, Likely, CBD (cannot be determined), and No. Classifications were chosen based on the language in the toxicity derivation profiles and reference documents.

If there was sufficient evidence for a mutagenic MOA in the RSL toxicity source plus verification by an additional source, the chemical was classified as “Yes”. Chemicals were classified as “Likely” if there

was evidence for a mutagenic MOA in the RSL toxicity source but negative or questionable results in an additional source; if there was limited evidence for mutagenesis in the RSL toxicity source but positive evidence in an additional source; or if a mutagenic mode of action was inconclusive or not addressed in the RSL toxicity source but positive in two additional sources. CBD was used if mutagenicity results were weak, limited, inconclusive, or not mentioned in the RSL source document and results were weak, limited, inconclusive, or not mentioned in an additional source; the term CBD was also used if the RSL source document had negative results for a mutagenic MOA but an additional source identified mutagenesis or if the RSL source document provided evidence for mutagenesis but an additional source was negative for mutagenesis. These CBD chemicals will need further research to determine their classification. Finally, chemicals were classified as "No" if mutagenicity was specifically denied in the RSL source document or if there was no information to support mutagenesis in the RSL source document or another source.

For the 251 chemicals evaluated, 15 showed definitive or strong evidence of mutagenicity ("Yes"), 16 were identified as likely to be mutagenic ("Likely"), and 74 have a classification of "CBD". Five of the "yes" chemicals (Chloroprene, 3,3'-Dimethoxybenzidine; 3,3'-Dimethylbenzidine, Formaldehyde; and o-Phenylenediamine) will be added as mutagens to the November 2024 RSLs and are therefore removed from the classifications in this paper. The remaining 10 "yes" chemicals that this paper urges to be formally classified as mutagens are: 2-Chloroacetaldehyde; 1,2-Dibromoethane; Diesel engine exhaust; Epichlorohydrin; 4,4'-Methylene-bis(N,N-dimethyl) aniline; 2-Nitropropane; Propylene oxide; Trimethyl phosphate; 2,4,6-Trinitrotoluene; and Vinyl bromide.

Figure 1 shows the distribution of the proposed classification. **Appendix B** provides the toxicity value sources for the carcinogenic values, the mutagenic status presented in those sources, and the recommended mutagenic classification with the same color coding as **Figure 1**. **Appendix C** provides the references and justification text from those references for the classification of the "Yes" and "Likely" categories (except for the five chemicals being added as mutagens to the November 2024 RSLs.

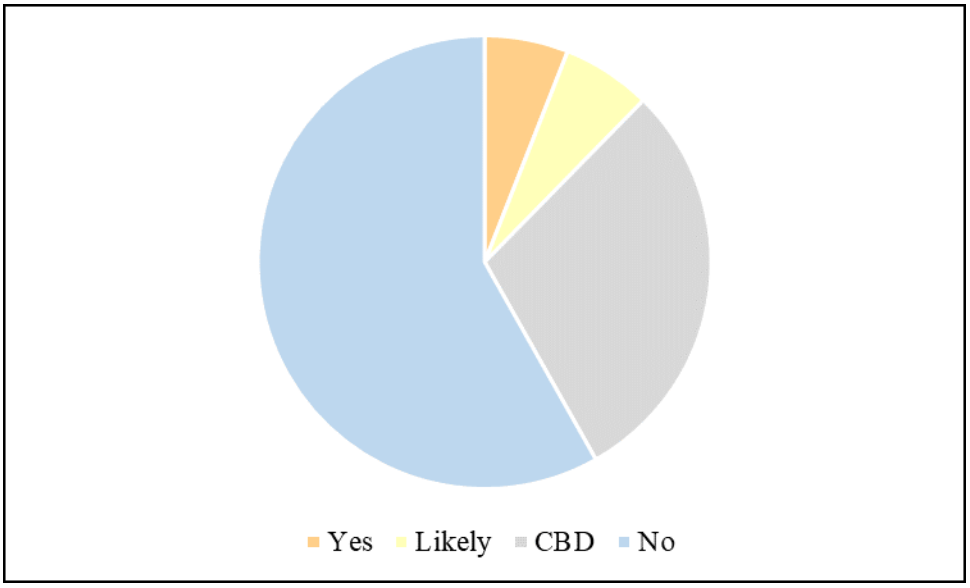

Figure 1. Proposed Mutagenicity Classification
(Number of chemicals for each proposed classification: Yes/Orange = 15; Likely/Yellow = 16; CBD/Gray = 74; No/Blue = 146)

3. CONCLUSION

Designating a chemical as a mutagen falls outside the scope of the RSLs, which depend on EPA consensus from various sources. Although some recent toxicity profiles provide positive evidence for mutagenesis, only five chemicals have been classified as mutagens for the RSLs since May 2012, with these scheduled for inclusion in the November 2024 update. This paper urges the EPA to reconvene its experts to address the remaining chemicals identified in this paper, ensuring the RSLs reflect protective screening levels for human health.

As demonstrated in this paper, using mutagenic calculations for known mutagens decreases RSL values by up to 78% compared to using standard carcinogenic equations. Consequently, applying standard carcinogenic equations to chemicals with a potential mutagenic MOA could result in RSL values that are underprotective of human health.

This research found definitive or strong evidence of a mutagenic mode of action ("Yes") in 15 chemicals currently not identified by the EPA as mutagens in the May 2024 RSLs. Five of these will be included in the November 2024 RSLs. This paper recommends the remaining 10 "Yes" chemicals, supported by strong evidence in their IRIS or PPRTV toxicity profiles, also be reclassified as mutagens by the EPA for the RSLs. Additionally, the 16 chemicals classified as "Likely" mutagenic by this research should be reviewed by EPA toxicologists for potential mutagen classification. The chemicals classified in this paper as "CBD" will need more extensive review and evaluation for mutagenicity.

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APPENDIX A. COMPARISON OF MUTAGENIC VERSUS CARCINOGENIC RSL CALCULATIONS FOR RESIDENTIAL LAND USE WITH CURRENT MUTAGENS

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Chemical	Standard Carcinogenic Values			Mutagenic Values			Percent Change (Decrease)		
	Soil SL (mg/kg)	Air SL (ug/m^3)	Tap Water SL (ug/L)	Soil SL (mg/kg)	Air SL (ug/m^3)	Tap Water SL (ug/L)	Soil	Air	Tap Water
Acrylamide	1.09E+00	2.81E-02	1.55E-01	2.44E-01	1.01E-02	5.00E-02	78%	64%	68%
Benz[a]anthracene	4.97E+00	4.68E-02	8.36E-02	1.13E+00	1.69E-02	2.98E-02	77%	64%	64%
Benzidine	2.36E-03	4.19E-05	3.32E-04	5.30E-04	1.51E-05	1.07E-04	78%	64%	68%
Benzo[a]pyrene	5.09E-01	2.09E-04	7.79E-02	1.15E-01	2.09E-04	2.51E-02	77%	0%	68%
Benzo[b]fluoranthene	5.09E+00	4.68E-02	7.79E-01	1.15E+00	1.69E-02	2.51E-01	77%	64%	68%
Benzo[k]fluoranthene	5.09E+01	4.68E-01	7.79E+00	1.15E+01	1.69E-01	2.51E+00	77%	64%	68%
Chromium (VI)	1.35E+00	3.34E-05	1.09E-01	3.01E-01	1.21E-05	3.50E-02	78%	64%	68%
Chrysene	5.09E+02	4.68E+00	7.79E+01	1.15E+02	1.69E+00	2.51E+01	77%	64%	68%
Coke Oven Emissions	--	4.53E-03	--	--	1.64E-03	--	--	64%	--
Dibenz[a,h]anthracene	5.09E-01	4.68E-03	7.79E-02	1.15E-01	1.69E-03	2.51E-02	77%	64%	68%
Dibromo-3-chloropropane, 1,2-	1.47E-02	4.68E-04	9.25E-04	5.26E-03	1.69E-04	3.34E-04	64%	64%	64%
Dimethylbenz(a)anthracene, 7,12-	2.04E-03	3.95E-05	3.12E-04	4.59E-04	1.43E-05	1.00E-04	78%	64%	68%
Ethylene Oxide	5.68E-03	9.36E-04	1.86E-03	2.05E-03	3.38E-04	6.70E-04	64%	64%	64%
Indeno[1,2,3-cd]pyrene	5.09E+00	4.68E-02	7.79E-01	1.15E+00	1.69E-02	2.51E-01	77%	64%	68%
Methylcholanthrene, 3-	2.47E-02	4.46E-04	3.54E-03	5.54E-03	1.61E-04	1.14E-03	78%	64%	68%
Methylene Chloride	3.50E+01	6.26E+01	1.07E+01	3.50E+01	6.26E+01	1.07E+01	0%	0%	0%
Methylene-bis(2-chloroaniline), 4,4'-	5.42E+00	6.53E-03	4.93E-01	1.22E+00	2.36E-03	1.58E-01	77%	64%	68%
Nitroso-N-ethylurea, N-	2.01E-02	3.65E-04	2.87E-03	4.51E-03	1.32E-04	9.22E-04	78%	64%	68%
Nitroso-N-methylurea, N-	4.52E-03	8.26E-05	6.46E-04	1.02E-03	2.98E-05	2.08E-04	77%	64%	68%
Nitrosodiethylamine, N-	3.62E-03	6.53E-05	5.14E-04	8.12E-04	2.36E-05	1.65E-04	78%	64%	68%
Nitrosodimethylamine, N-	7.47E-03	2.01E-04	3.18E-04	2.00E-03	7.24E-05	1.12E-04	73%	64%	65%
Safrole	2.47E+00	4.46E-02	2.98E-01	5.54E-01	1.61E-02	9.57E-02	78%	64%	68%
Trichloropropane, 1,2,3-	2.32E-02	3.13E-02	2.33E-03	5.10E-03	3.13E-02	7.49E-04	78%	0%	68%
Urethane	5.43E-01	9.68E-03	7.76E-02	1.22E-01	3.50E-03	2.49E-02	78%	64%	68%

APPENDIX B. MUTAGENICITY EVALUATION

APEENDIX B. MUTAGENICITY EVALUATION

This table is sorted alphabetically by chemical within the following color groupings: Orange = Yes (mutagenic); Yellow = Likely mutagenic; Gray = CBD (Cannot Be Determined); Blue = No (not mutagenic)

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Chloroacetaldehyde, 2-	107-20-0	PPRTV Screen	Mutagenic	Journal articles/ NRC/NTP	Mutagenic	Yes
Dibromoethane, 1,2-	106-93-4	IRIS	Mutagenic	ATSDR/ Journal article	Mutagenic	Yes
Diesel Engine Exhaust	E17136615	IRIS	Mutagenic	Multiple	Mutagenic	Yes
Epichlorohydrin	106-89-8	IRIS	Mutagenic	NTP/PubChem	Suspected Mutagen	Yes
Methylene-bis(N,N-dimethyl) Aniline, 4,4'-	101-61-1	IRIS	Mutagenic	FS MSDS/NTP	Mutagenic	Yes
Nitropropane, 2-	79-46-9	PPRTV Screen	Mutagenic	NTP/PubChem	Mutagenic	Yes
Propylene Oxide	75-56-9	IRIS	Mutagenic	ECHA	Mutagenic	Yes
Trimethyl Phosphate	512-56-1	PPRTV	Mutagenic	NTP	Mutagenic	Yes
Trinitrotoluene, 2,4,6-	118-96-7	IRIS	Mutagenic	ATSDR	Mutagenic	Yes
Vinyl Bromide	593-60-2	PPRTV	Mutagenic	NTP/PubChem	Mutagenic	Yes
Acetaldehyde	75-07-0	IRIS	Not mentioned	ECHA/NTP	Mutagenic	Likely
Acetylaminofluorene, 2-	53-96-3	CALEPA	Not mentioned	NTP/Journal article	Mutagenic	Likely
Butadiene, 1,3-	106-99-0	IRIS	Not mentioned	ECHA/NTP	Mutagenic	Likely
Cadmium (diet and water)	7440-43-9	IRIS	Inconclusive	Journal article/ PubChem	Mutagenic	Likely
Chloromethyl Methyl Ether	107-30-2	IRIS	Limited evidence	Journal article	Mutagenic	Likely
Crotonaldehyde, trans-	123-73-9	IRIS	Mutagenic	Journal article	May be a weak mutagen	Likely
Ethyleneimine	151-56-4	CALEPA	Not mentioned	NRC/NTP	Mutagenic	Likely
Methyl methanesulfonate	66-27-3	CALEPA	Not mentioned	PubChem/NTP	Mutagenic	Likely
Methylenebisbenzenamine, 4,4'-	101-77-9	CalEPA	Not mentioned	ECHA/NTP	Suspected Mutagen	Likely

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Methyl-N-nitro-N-nitrosoguanidine, N-	70-25-7	CALEPA	Not mentioned	Journal article/ PubChem	Mutagenic	Likely
Nitroaniline, 4-	100-01-6	PPRTV	Limited evidence	NTP/PubChem	Mutagenic/ Inconclusive	Likely
Nitrosomorpholine [N-]	59-89-2	CALEPA	Not mentioned	NTP/PubChem	Mutagenic	Likely
Nitrosopiperidine [N-]	100-75-4	CALEPA	Not mentioned	Journal Article/ PubChem/NTP	Mutagenic	Likely
Nitrosopyrrolidine, N-	930-55-2	IRIS	Limited evidence	Journal Article/ PubChem	Mutagenic	Likely
Quinoline	91-22-5	IRIS	Mutagenic	NTP	Inconclusive	Likely
Toxaphene	8001-35-2	IRIS	Inconclusive	ATSDR	Inconclusive	Likely
Acrylonitrile	107-13-1	IRIS	Metabolite is mutagenic	NTP	Inconclusive	CBD
Allyl Chloride	107-05-1	CALEPA	Maybe with metabolites	NTP	Inconclusive	CBD
Aminobiphenyl, 4-	92-67-1	CALEPA	Not mentioned	NTP	Inconclusive	CBD
Aniline	62-53-3	IRIS	Inconclusive	NTP	Inconclusive	CBD
Azobenzene	103-33-3	IRIS	Not mentioned	NTP/IARC	Inconclusive	CBD
Benzaldehyde	100-52-7	PPRTV	Inconclusive	Multiple	Inconclusive	CBD
Benzene	71-43-2	IRIS	Negative	ECHA	Mutagenic	CBD
Benzotrichloride	98-07-7	IRIS	Inconclusive	PubChem	Inconclusive	CBD
Benzyl Chloride	100-44-7	IRIS	Negative or weak	NTP	Weakly positive	CBD
Bis(2-chloroethyl)ether	111-44-4	IRIS	Limited evidence	NTP	Inconclusive	CBD
Bis(chloromethyl)ether	542-88-1	IRIS	Inconclusive	Journal article	Limited evidence	CBD
Bromate	15541-45-4	IRIS	Inconclusive, may be weak	Journal article	Limited evidence	CDB
Bromoform	75-25-2	IRIS	Not mentioned	ATSDR	Inconclusive	CBD
Chloroaniline, p-	106-47-8	PPRTV	Inconclusive	NTP	Inconclusive	CBD
Chloronitrobenzene, o-	88-73-3	PPRTV	Limited evidence	NTP	Inconclusive	CBD
Chloronitrobenzene, p-	100-00-5	PPRTV	Inconclusive	NTP	Inconclusive	CBD
Chlorothalonil	1897-45-6	CALEPA	Limited evidence	Multiple	Inconclusive	CBD

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Chlorozotocin	54749-90-5	CALEPA	Not mentioned	PubChem	Limited evidence	CBD
Cupferron	135-20-6	CALEPA	Not mentioned	Journal article	Limited evidence	CBD
Cyanazine	21725-46-2	HEAST	Not mentioned	Multiple	Inconclusive	CBD
DDE, p,p'-	72-55-9	IRIS	Limited evidence	NTP	Inconclusive/ Weakly positive	CBD
Diallate	2303-16-4	HEAST	Not mentioned	Multiple	Inconclusive	CBD
Dibromoacetic acid	631-64-1	CALEPA	Inconclusive	PubChem	Limited evidence	CBD
Dibromochloromethane	124-48-1	IRIS	Limited evidence	ATSDR	Inconclusive	CBD
Dichloro-2-butene, 1,4-	764-41-0	PPRTV	Inconclusive	Not available		CBD
Dichloro-2-butene, cis-1,4-	1476-11-5	PPRTV	Inconclusive	Not available		CBD
Dichloro-2-butene, trans-1,4-	110-57-6	PPRTV	Inconclusive	Not available		CBD
Dichlorobenzidine, 3,3'-	91-94-1	IRIS	Limited evidence	ATSDR	Very weak	CBD
Dichloroethane, 1,1-	75-34-3	PPRTV	Inconclusive	ATSDR	Inconclusive	CBD
Dichloroethane, 1,2-	107-06-2	IRIS	Limited evidence	ATSDR	Very weak	CBD
Dichloropropane, 1,2-	78-87-5	PPRTV	Very weak	NTP	Inconclusive	CBD
Dichloropropene, 1,3-	542-75-6	IRIS	Mutagenic	Journal article	Negative	CBD
Dichlorvos	62-73-7	IRIS	Limited evidence	NTP	Inconclusive	CBD
Dieldrin	60-57-1	IRIS	Inconclusive	NTP	Inconclusive	CBD
Dimethyl methylphosphonate	756-79-6	PPRTV	Inconclusive	NTP	Inconclusive	CBD
Dimethylaniline, 2,4-	95-68-1	PPRTV	Inconclusive	PubChem	Inconclusive	CBD
Dimethylvinylchloride	513-37-1	CALEPA	Not mentioned	NTP	Inconclusive	CBD
Dinitrotoluene Mixture, 2,4/2,6-	E1615210	IRIS	Inconclusive	NTP	Inconclusive	CBD
Dinitrotoluene, 2,4-	121-14-2	CALEPA	Not mentioned	PubChem	Inconclusive	CBD
Dinitrotoluene, 2,6-	606-20-2	PPRTV	Inconclusive	PubChem	Inconclusive	CBD
Dinitrotoluene, Technical grade	25321-14-6	PPRTV Screen	Inconclusive	PubChem	Inconclusive	CBD
Diphenylhydrazine, 1,2-	122-66-7	IRIS	Not mentioned	ATSDR	Inconclusive	CBD
Direct Black 38	1937-37-7	CALEPA	Not mentioned	NTP/PubChem	Inconclusive	CBD
Ethylene Thiourea	96-45-7	CALEPA	Not mentioned	NTP/PubChem	Inconclusive	CBD
Furazolidone	67-45-8	HEAST	Not mentioned	PubChem	Limited evidence	CBD

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Hydrazine	302-01-2	IRIS	Mutagenic	Journal Article	Negative	CBD
Hydrazine Sulfate	10034-93-2	IRIS	Mutagenic	Journal Article	Negative	CBD
Hydroquinone	123-31-9	PPRTV	Inconclusive	PubChem	Inconclusive	CBD
Lead Phosphate	7446-27-7	CALEPA	Not mentioned	PubChem	Inconclusive	CBD
Methoxy-5-nitroaniline, 2-	99-59-2	CALEPA	Not mentioned	NTP	Inconclusive	CBD
Methyl Hydrazine	60-34-4	PPRTV Screen	Inconclusive	PubChem	Inconclusive	CBD
Methyl-5-Nitroaniline, 2-	99-55-8	PPRTV	Inconclusive or weak	NTP	Inconclusive	CBD
Nickel Acetate	373-02-4	CALEPA	Not mentioned	PubChem	Inconclusive	CBD
Nickel Soluble Salts	7440-02-0	CALEPA	Not mentioned	PubChem	Inconclusive	CBD
Nitrofurazone	59-87-0	CALEPA	Not mentioned	NTP	Inconclusive	CBD
Nitropyrene, 4-	57835-92-4	CALEPA	Not mentioned	PubChem	Limited evidence	CBD
Nitrosodiethanolamine, N-	1116-54-7	IRIS	Limited evidence	PubChem	Maybe with metabolites	CBD
Nitroso-di-N-butylamine, N-	924-16-3	IRIS	Limited evidence	Not available		CBD
Nitroso-di-N-propylamine, N-	621-64-7	IRIS	Limited evidence	PubChem	Inconclusive	CBD
Nitrosodiphenylamine, N-	86-30-6	IRIS	Not mentioned	NTP/PubChem	Inconclusive	CBD
Nitrosomethylethylamine, N-	10595-95-6	IRIS	Limited evidence	Not available		CBD
Nitrotoluene, p-	99-99-0	PPRTV	Inconclusive	NTP	Inconclusive	CBD
Oxyfluorfen	42874-03-3	OPP	Inconclusive	Not available		CBD
Stirofos (Tetrachlorovinphos)	961-11-5	OPP	Inconclusive	NTP	Inconclusive	CBD
Tetrachloroethylene	127-18-4	IRIS	Inconclusive	NTP/PubChem	Inconclusive	CBD
Thiophanate, Methyl	23564-05-8	OPP	Inconclusive	NTP/PubChem	Inconclusive	CBD
Toluene-2,6-diisocyanate	91-08-7	CALEPA	Not mentioned	NTP/PubChem	Inconclusive	CBD
Toluidine, o- (Methylaniline, 2-)	95-53-4	PPRTV	Inconclusive	NTP/PubChem	Limited evidence	CBD
Toluidine, p-	106-49-0	PPRTV	Inconclusive	NTP/PubChem	Limited evidence	CBD
Triallate	2303-17-5	OPP	Inconclusive	PubChem	Mutagenic	CBD
Trichloroacetic Acid	76-03-9	IRIS	Inconclusive	Multiple	Inconclusive	CBD
Trichloroaniline, 2,4,6-	634-93-5	PPRTV Screen	Inconclusive	PubChem	Mutagenic	CBD

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Tris(2,3-dibromopropyl)phosphate	126-72-7	CALEPA	Not mentioned	PubChem	Inconclusive	CBD
Vanadium Pentoxide	1314-62-1	PPRTV	Inconclusive	NTP/PubChem	Inconclusive	CBD
Alachlor	15972-60-8	CALEPA	Negative	Not necessary		No
Aldrin	309-00-2	IRIS	Negative	Not necessary		No
Ammonium perfluorooctanoate	3825-26-1	OW	Negative	Not necessary		No
Anthraquinone, 9,10-	84-65-1	PPRTV	Negative	Not necessary		No
Aroclor 1016	12674-11-2	Surrogate, ATSDR	Negative or weak	Not necessary		No
Aroclor 1221	11104-28-2	Surrogate, ATSDR	Negative or weak	Not necessary		No
Aroclor 1232	11141-16-5	Surrogate, ATSDR	Negative or weak	Not necessary		No
Aroclor 1242	53469-21-9	Surrogate, ATSDR	Negative or weak	Not necessary		No
Aroclor 1248	12672-29-6	Surrogate, ATSDR	Negative or weak	Not necessary		No
Aroclor 1254	11097-69-1	Surrogate, ATSDR	Negative or weak	Not necessary		No
Aroclor 1260	11096-82-5	Surrogate, ATSDR	Negative or weak	Not necessary		No
Arsenic, Inorganic	7440-38-2	IRIS	Negative or weak	Not necessary		No
Atrazine	1912-24-9	CALEPA	Negative or weak	Not necessary		No
Auramine	492-80-8	CALEPA	Negative or weak	Not necessary		No
Benzenediamine-2-methyl sulfate, 1,4-	6369-59-1	PPRTV Screen	Negative	Not necessary		No
Benzo(j)fluoranthene	205-82-3	CALEPA	Negative	Not necessary		No
Beryllium and compounds	7440-41-7	IRIS	Negative	Not necessary		No
Biphenyl, 1,1'-	92-52-4	IRIS	Negative or weak	NTP	Negative	No
Bis(2-ethylhexyl)phthalate	117-81-7	IRIS	Negative	Not necessary		No
Bromodichloromethane	75-27-4	IRIS	Negative or weak	NTP	Negative	No
Bromopropane, 1-	106-94-5	CALEPA	Not mentioned	ATSDR/NTP	Negative	No
Bromoxynil	1689-84-5	OPP	Negative	Not necessary		No
Bromoxynil Octanoate	1689-99-2	OPP	Negative	Not necessary		No
Butyl Alcohol, t-	75-65-0	IRIS	Inconclusive	NTP	Negative	No
Butyl Benzyl Phthalate	85-68-7	PPRTV	Negative	Not necessary		No
Butylated hydroxyanisole	25013-16-5	CALEPA	Not mentioned	NTP	Negative	No
Butylated hydroxytoluene	128-37-0	PPRTV	Negative	Not necessary		No

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Captafol	2425-06-1	CALEPA	Not mentioned	PubChem	Negative	No
Captan	133-06-2	CALEPA	Not mentioned	PubChem	Negative	No
Carbon Tetrachloride	56-23-5	IRIS	Negative	Not necessary		No
Chloranil	118-75-2	HEAST	Not mentioned	Journal article	Negative	No
Chlordane (technical mixture)	12789-03-6	IRIS	Inconclusive	ATSDR/NTP	Negative	No
Chlordecone (Kepone)	143-50-0	IRIS	Negative	Not necessary		No
Chloro-2-methylaniline HCl, 4-	3165-93-3	HEAST, CALEPA	Not mentioned	Not available		No
Chloro-2-methylaniline, 4-	95-69-2	PPRTV	Negative	Not necessary		No
Chlorobenzilate	510-15-6	CALEPA	Not mentioned	NTP	Negative	No
Chlorobenzotrifluoride, 4-	98-56-6	CALEPA	Negative	NTP	Negative	No
Chloroform	67-66-3	IRIS	Negative	Not necessary		No
Cobalt	7440-48-4	PPRTV	Negative	Not necessary		No
Cyclohexane, 1,2,3,4,5-pentabromo-6-chloro-	87-84-3	PPRTV Screen	Not mentioned	NTP	Negative	No
Daminozide	1596-84-5	CALEPA	Not mentioned	NTP	Negative	No
DDD, p,p`- (DDD)	72-54-8	IRIS	Not mentioned	NTP	Negative	No
DDT	50-29-3	IRIS	Not mentioned	NTP	Negative	No
Decabromodiphenyl ether, 2,2',3,3',4,4',5,5',6,6'- (BDE-209)	1163-19-5	IRIS	Negative	Not necessary		No
Di(2-ethylhexyl)adipate	103-23-1	IRIS	Negative	Not necessary		No
Dibenzo(a,e)pyrene	192-65-4	CALEPA	Not mentioned	PubChem	Negative	No
Dichloroacetic Acid	79-43-6	IRIS	Unlikely	PubChem	Negative or weak	No
Dichlorobenzene, 1,4-	106-46-7	ATSDR	Negative	Not necessary		No
Diethylstilbestrol	56-53-1	CALEPA	Negative	Not necessary		No
Dihydrosafrole	94-58-6	CALEPA	Negative	Not necessary		No
Dimethylamino azobenzene [p-]	60-11-7	CALEPA	Not mentioned	PubChem	Weak mutagen	No
Dimethylaniline HCl, 2,4-	21436-96-4	HEAST	Negative	Not necessary		No
Dimethylaniline, N,N-	121-69-7	PPRTV	Inconclusive	PubChem	Negative	No
Dimethylhydrazine, 1,2-	540-73-8	CALEPA	Not mentioned	Journal article	Negative or weak	No

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Dioxane, 1,4-	123-91-1	IRIS	Negative	Not necessary		No
Direct Blue 6	2602-46-2	CALEPA	Not mentioned	NTP	Negative	No
Direct Brown 95	16071-86-6	CALEPA	Not mentioned	NTP	Negative	No
Ethyl Tertiary Butyl Ether (ETBE)	637-92-3	IRIS	Inconclusive	NTP/PubChem	Negative	No
Ethylbenzene	100-41-4	IRIS	Negative	Not necessary		No
Furium	531-82-8	CALEPA	Not mentioned	Not available		No
Furmecyclox	60568-05-0	IRIS	Not mentioned	PubChem	Negative	No
Heptachlor	76-44-8	IRIS	Negative	Not necessary		No
Heptachlor Epoxide	1024-57-3	IRIS	Negative	Not necessary		No
Heptachlorobiphenyl, 2,3,3',4,4',5,5'- (PCB 189)	39635-31-9	TEF, ATSDR	Negative or weak	Not necessary		No
Hexachlorobenzene	118-74-1	IRIS	Inconclusive	PubChem	Negative or weak	No
Hexachlorobiphenyl, 2,3,3',4,4',5- (PCB 156)	38380-08-4	TEF, ATSDR	Negative or weak	Not necessary		No
Hexachlorobiphenyl, 2,3,3',4,4',5'- (PCB 157)	69782-90-7	TEF, ATSDR	Negative or weak	Not necessary		No
Hexachlorobiphenyl, 2,3',4,4',5,5'- (PCB 167)	52663-72-6	TEF, ATSDR	Negative or weak	Not necessary		No
Hexachlorobiphenyl, 3,3',4,4',5,5'- (PCB 169)	32774-16-6	TEF, ATSDR	Negative or weak	Not necessary		No
Hexachlorobutadiene	87-68-3	IRIS	Negative	Not necessary		No
Hexachlorocyclohexane, Alpha-	319-84-6	IRIS	Not mentioned	ATSDR	Negative or weak	No
Hexachlorocyclohexane, Beta-	319-85-7	IRIS	Not mentioned	ATSDR	Negative or weak	No
Hexachlorocyclohexane, Gamma- (Lindane)	58-89-9	IRIS	Not mentioned	ATSDR	Negative or weak	No
Hexachlorocyclohexane, Technical	608-73-1	IRIS	Not mentioned	ATSDR	Negative or weak	No
Hexachlorodibenzo-p-dioxin, Mixture	34465-46-8	IRIS	Not mentioned	PubChem	Not mentioned	No
Hexachloroethane	67-72-1	IRIS	Negative	Not necessary		No
Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)	121-82-4	IRIS	Negative	Not necessary		No
Hexane, Commercial	E5241997	PPRTV Screen	Negative	Not necessary		No
Hexanol, 1-,2-ethyl- (2-Ethyl-1-hexanol)	104-76-7	PPRTV	Negative	Not necessary		No

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Imazalil	35554-44-0	OPP	Negative	Not necessary		No
Isophorone	78-59-1	IRIS	Negative	Not necessary		No
Lead acetate	301-04-2	CALEPA	Not mentioned	NTP/PubChem	Negative	No
Lead subacetate	1335-32-6	CALEPA	Not mentioned	NTP/PubChem	Negative	No
Mercaptobenzothiazole, 2-	149-30-4	PPRTV	Negative	Not necessary		No
Methyl tert-Butyl Ether (MTBE)	1634-04-4	CALEPA	Negative	ATSDR	Negative	No
Methylaniline Hydrochloride, 2-	636-21-5	CALEPA	Not mentioned	NTP	Negative	No
Methylbenzene-1,4-diamine sulfate, 2-	615-50-9	PPRTV Screen	Negative	Not necessary		No
Methylnaphthalene, 1-	90-12-0	PPRTV	Negative	Not necessary		No
Midrange Aliphatic Hydrocarbon Streams	E1790669	PPRTV Screen	Negative	Not necessary		No
Mirex	2385-85-5	CALEPA	Not mentioned	ATSDR	Negative	No
Naphthalene	91-20-3	CALEPA	Not mentioned	ATSDR	Negative	No
Naphthylamine, 2-	91-59-8	CALEPA	Not mentioned	PubChem	Negative	No
Nickel Carbonate	3333-67-3	CALEPA	Not mentioned	PubChem	Negative or weak	No
Nickel Carbonyl	13463-39-3	CALEPA	Not mentioned	PubChem	Negative or weak	No
Nickel Hydroxide	12054-48-7	CALEPA	Not mentioned	PubChem	Negative or weak	No
Nickel Oxide	1313-99-1	CALEPA	Not mentioned	PubChem	Negative or weak	No
Nickel Refinery Dust	E715532	IRIS	Not mentioned	PubChem	Negative or weak	No
Nickel Subsulfide	12035-72-2	IRIS	Not mentioned	PubChem	Negative or weak	No
Nickelocene	1271-28-9	CALEPA	Not mentioned	NTP	Negative	No
Nitrobenzene	98-95-3	IRIS	Negative or weak	NTP	Negative	No
Nitroglycerin	55-63-0	PPRTV	Inconclusive	FDA	Negative	No
Nitromethane	75-52-5	PPRTV	Negative	Not necessary		No
Nitrotoluene, o-	88-72-2	PPRTV	Inconclusive	NTP	Negative	No
Oryzalin	19044-88-3	OPP	Negative	Not necessary		No
Pentachlorobiphenyl, 2,3,3',4,4'- (PCB 105)	32598-14-4	TEF	Negative or weak	Not necessary		No
Pentachlorobiphenyl, 2,3,4,4',5- (PCB 114)	74472-37-0	TEF	Negative or weak	Not necessary		No
Pentachlorobiphenyl, 2,3',4,4',5- (PCB 118)	31508-00-6	TEF	Negative or weak	Not necessary		No
Pentachlorobiphenyl, 2',3,4,4',5- (PCB 123)	65510-44-3	TEF	Negative or weak	Not necessary		No

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Pentachlorobiphenyl, 3,3',4,4',5- (PCB 126)	57465-28-8	TEF	Negative or weak	Not necessary		No
Pentachloroethane	76-01-7	PPRTV	Inconclusive/ Negative	NTP/PubChem	Negative	No
Pentachloronitrobenzene	82-68-8	OPP	Negative	Not necessary		No
Pentachlorophenol	87-86-5	IRIS	Negative or weak	Not necessary		No
Pentaerythritol tetranitrate (PETN)	78-11-5	PPRTV Screen	Negative	Not necessary		No
Perfluorooctanesulfonate	45298-90-6	OW	Negative	Not necessary		No
Perfluorooctanesulfonic acid (PFOS)	1763-23-1	OW	Negative	Not necessary		No
Perfluorooctanoate	45285-51-6	OW	Negative	Not necessary		No
Perfluorooctanoic acid (PFOA)	335-67-1	OW	Negative	Not necessary		No
Phenacetin	62-44-2	CALEPA	Not mentioned	NTP	Negative	No
Phenylphenol, 2-	90-43-7	HEAST	Not mentioned	NTP	Negative or weak	No
Polybrominated Biphenyls	36355-01-8	CALEPA	Not mentioned	ATSDR	Negative	No
Polychlorinated Biphenyls (high risk)	1336-36-3	IRIS	Not mentioned	Journal Article	Negative	No
Polychlorinated Biphenyls (low risk)	1336-36-3	IRIS	Not mentioned	Journal Article	Negative	No
Polychlorinated Biphenyls (lowest risk)	1336-36-3	IRIS	Not mentioned	Journal Article	Negative	No
Potassium perfluorooctanesulfonate	2795-39-3	OW	Negative	Not necessary		No
Prochloraz	67747-09-5	IRIS	Negative	Not necessary		No
Propargite	2312-35-8	OPP	Negative	Not necessary		No
Simazine	122-34-9	CALEPA	Weakly Mutagenic	ATSDR	Negative	No
Sodium Diethyldithiocarbamate	148-18-5	HEAST	Not mentioned	NTP	Negative	No
Sulfurous acid, 2-chloroethyl 2-[4-(1,1-dimethylethyl)phenoxy]-1-methylethyl ester	140-57-8	IRIS	Negative	Not necessary		No
TCDD, 2,3,7,8-	1746-01-6	ATSDR	Negative	Not necessary		No
Tert-Butyl Acetate	540-88-5	CALEPA	Negative	Not necessary		No
Tetrachlorobiphenyl, 3,3',4,4'- (PCB 77)	32598-13-3	TEF, ATSDR	Negative	Not necessary		No
Tetrachlorobiphenyl, 3,4,4',5- (PCB 81)	70362-50-4	TEF, ATSDR	Negative	Not necessary		No
Tetrachloroethane, 1,1,1,2-	630-20-6	IRIS	Negative	Not necessary		No
Tetrachloroethane, 1,1,2,2-	79-34-5	IRIS	Negative	Not necessary		No

Chemical Name	CASRN	EPA Source(s)*	EPA Source Mutagen Status	External^ Source	External Source Mutagen Status	Mutagenic?
Tetrachlorotoluene, p- alpha, alpha, alpha-	5216-25-1	PPRTV Screen	No data	NTP/PubChem	No data	No
Toluene-2,4-diisocyanate	584-84-9	CALEPA	Not mentioned	PubChem	Negative	No
Toluene-2,5-diamine	95-70-5	PPRTV Screen	Negative	Not necessary		No
Tributyl Phosphate	126-73-8	PPRTV	Negative	Not necessary		No
Trichloroaniline HCl, 2,4,6-	33663-50-2	HEAST	Not mentioned	PubChem	Not mentioned	No
Trichlorobenzene, 1,2,4-	120-82-1	PPRTV	Negative	Not necessary		No
Trichloroethane, 1,1,2-	79-00-5	IRIS	Negative	Not necessary		No
Trichlorophenol, 2,4,6-	88-06-2	IRIS	Negative or weak	Not necessary		No
Trifluralin	1582-09-8	IRIS	Negative	Not necessary		No
Tris(2-chloroethyl)phosphate	115-96-8	PPRTV	Negative	Not necessary		No
Tris(2-ethylhexyl)phosphate	78-42-2	PPRTV	Negative	Not necessary		No

***EPA Sources (in alphabetical order): ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California EPA; HEAST = EPA Health Effects Assessment Summary Tables; IRIS = EPA Integrated Risk Information System; OPP = EPA Office of Pesticide Programs; OW = EPA Office of Water; PPRTV = EPA Provisional Peer-Reviewed Toxicity Values; PPRTV Screen = PPRTV Appendix/Screening Value; Surrogate = PCB surrogate; TEF = Toxicity Equivalence Factor**

^External Sources: ECHA = European Chemicals Agency; FDA = US Food and Drug Administration; FS MSDS = Fisher Scientific Material Safety Data Sheets; IARC = International Agency for Research on Cancer; NRC = National Research Council; NTP = National Institutes of Health (NIH) National Toxicology Program; PubChem = NIH PubChem database

APPENDIX C. JUSTIFICATION AND REFERENCES FOR YES AND LIKELY CATEGORIES

APPENDIX C. JUSTIFICATION AND REFERENCES FOR YES AND LIKELY CATEGORIES

The chemicals identified as "Yes" or "Likely" in this paper are presented here in alphabetical order within their respective groupings. Justification for the mutagenicity is provided with a web link and callout to the reference(s). Full references are provided in the main section of the report.

CHEMICALS IDENTIFIED AS "YES" (MUTAGENIC)

- **2-Chloroacetaldehyde (CASRN 107-20-0)**
    - "Genotoxicity data show that CAA is mutagenic in both bacteria and human cells. Under the 2005 Guidelines for Carcinogen Risk Assessment, there is 'Suggestive Evidence of Carcinogenic Potential for 2-chloroacetaldehyde,' based on a positive response in a limited animal bioassay and strong evidence of mutagenicity." (https://hhpprtv.ornl.gov/issue_papers/Chloroacetaldehyde2.pdf) (EPA 2009b).
    - "In view of the accumulating evidence of the correlation between mutagenicity and carcinogenicity, we believe that the mutagenic activity of chloroacetaldehyde indicates it has a high probability of being a carcinogen" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC432947/pdf/pnas00051-0360.pdf) (McCann et al. 1975).
    - "Chloroacetaldehyde was found to be mutagenic in several stains of *S. typhimurium, A. nidulans, S. coelicolor*, and Chinese hamster V79 cells" (https://www.ncbi.nlm.nih.gov/books/NBK201462/) (NRC 2010b).
    - Positive for mutagenesis in bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/107-20-0) (NIH 2024a).

- **1,2-Dibromoethane (CASRN 106-93-4)**
    - "The evidence for 1,2-dibromoethane's potential genotoxicity is strong. 1,2-Dibromoethane is a direct-acting mutagen in bacteria" and "The available evidence further supports a conclusion that 1,2-dibromoethane is a genotoxic carcinogen based on evidence from a variety of in vitro and in vivo test systems". (https://iris.epa.gov/static/pdfs/0361tr.pdf) (EPA 2004).
    - "Evidence from animal bioassays supports the hypothesis that the GST pathway is responsible for the mutagenicity and carcinogenicity of 1,2-dibromoethane" (https://www.atsdr.cdc.gov/ToxProfiles/tp37.pdf) (ATSDR 2018).
    - "The mutagenicity of EDB has been demonstrated in a number of genetic systems, including bacteria, yeast and other fungi, plants, insects, mammals and human cells" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988426/) (Foster et al. 1988).

- **Diesel Engine Exhaust (CASRN NA)**

  - "Using U.S. EPA's revised draft 1999 Guidelines for Carcinogen Risk Assessment, diesel exhaust (DE) is likely to be carcinogenic to humans by inhalation from environmental exposures. The basis for this conclusion includes the following lines of evidence:…extensive supporting data including the demonstrated mutagenic and/or chromosomal effects of DE and its organic constituents, and knowledge of the known mutagenic and/or carcinogenic activity of a number of individual organic compounds that adhere to the particles and are present in the DE gases" (https://iris.epa.gov/static/pdfs/0642_summary.pdf) (EPA 2003b).

  - "These results show that DEP are mutagenic in a mammalian cell line in vitro and that additional pathways besides ROS production, such as those involving the presence of polycyclic aromatic hydrocarbons, likely are involved in the mutagenesis" (https://pubmed.ncbi.nlm.nih.gov/18423769/) (Jacobsen et al. 2008).

- **Epichlorohydrin (CASRN 106-89-8)**

  - "Epichlorohydrin is a direct-acting mutagen by virtue of its activity as an alkylating agent. Positive results have been obtained in mutagenicity tests in several bacterial species, Neurospora, Saccharomyces, Drosophilia (including recessive lethal), and cultured mammalian cells (reviewed in Sram et al., 1981)" (https://iris.epa.gov/static/pdfs/0050_summary.pdf) (EPA 1992).

  - Positive for mutagenesis in mammalian cell cytogenetic and bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/106-89-8) (NIH 2024a).

- **4,4'-Methylene-bis(N,N-dimethyl)aniline (CASRN 101-61-1)**

  - "There is evidence of mutagenic activity… 4,4'-Methylenebis(N,N-dimethylaniline) was found to be mutagenic in Salmonella typhimurium strains TA98 and TA100 in the presence of hepatic microsomal preparations from mice and rats…Positive results were produced in host- mediated assays in the mouse using S. typhimurium TA1538…It also produced a slight increase in sister chromatid exchange in cultured rabbit lymphocytes…and induced transformation of a hamster embryo cell line. In addition, positive results were obtained in several mammalian cell systems for mutagenesis, DNA damage, and cell transformation…" (https://iris.epa.gov/static/pdfs/0386_summary.pdf) (EPA 1989b).

  - "Laboratory experiments have resulted in mutagenic effects" (https://fscimage.fishersci.com/msds/96253.htm) (Fisher Scientific 2004).

  - Positive for mutagenesis in mammalian cell mutagenicity and bacterial mutagenicity studies but negative in mammalian cell cytogenetic studies (https://cebs.niehs.nih.gov/cebs/test_article/101-61-1) (NIH 2024a).

- **2-Nitropropane (CASRN 79-46-9)**

  - "Available data indicate that 2-nitropropane is a genotoxic agent. It is an established mutagen, and there is consistent evidence for chromosomal effects and DNA damage in hepatic cells and tissues" and "The available evidence demonstrates that 2-nitropropane is a mutagen, and

produces chromosomal and DNA damage in the liver, which is the site of tumor development" and "Because mutagenicity is involved in a plausible mixed MOA, a linear approach is appropriate to extrapolate from the POD in deriving a screening provisional inhalation unit risk (p-IUR)". (https://hhpprtv.ornl.gov/issue_papers/Nitropropane2.pdf) (EPA 2019).

- Positive for mutagenesis in mammalian cell cytogenetic and bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/79-46-9) (NIH 2024a).

- **Propylene Oxide (CASRN 75-56-9)**

  - "Propylene oxide has been found to be mutagenic in a variety of test systems" (https://iris.epa.gov/static/pdfs/0403_summary.pdf) (EPA 1990).

  - Identified as mutagenic (https://echa.europa.eu/carcinogens-mutagens-oels) (ECHA 2024).

  - Positive for mutagenesis in rodent cytogenic, mammalian cell mutagenic and cytogenetic, and bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/75-56-9) (NIH 2024a).

- **Trimethyl phosphate (CASRN 512-56-1)**

  - "There is strong evidence that trimethyl phosphate induces micronuclei and chromosomal aberrations in laboratory animals tested in vivo; it is often used as a positive control substance in such assays. In vitro tests for mutagenicity have given mixed results" (https://hhpprtv.ornl.gov/issue_papers/TrimethylPhosphate.pdf) (EPA 2010d).

  - Positive for mutagenesis in mammalian cell cytogenetic studies and bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/512-56-1) (NIH 2024a).

- **2,4,6-Trinitrotoluene (CASRN 118-96-7)**

  - "Mutagenic activity for TNT was reported by the U.S. DOD (1978a). As little as 10 ug/plate dissolved in DMSO, with or without metabolic activation, was mutagenic in Salmonella typhimurium strains TA98, TA1538 and TA1537. At 30 ug/plate TNT was mutagenic in TA100 as well as the other three strains" (https://iris.epa.gov/static/pdfs/0269_summary.pdf) (EPA 1988b).

  - "Based on the existing information, there is sufficient valid in vitro data to conclude that 2,4,6-trinitrotoluene is a direct-acting mutagen in bacterial and mammalian cells. There is also suggestive evidence that 2,4,6-trinitrotoluene is a direct acting genotoxic agent in cultured human cells." (https://www.atsdr.cdc.gov/ToxProfiles/tp81.pdf) (ATSDR 1995).

- **Vinyl bromide (CASRN 593-60-2)**

  - "Studies consistently show that vinyl bromide and/or its metabolites are mutagenic in bacterial and invertebrate systems and have the potential to cause chromosomal damage" and "Carcinogenicity of vinyl bromide is likely mediated via a genotoxic MOA. As discussed above, vinyl bromide is a direct-acting mutagen" and " While direct evidence for the proposed MOA for

vinyl bromide is limited, the proposed MOA is supported by similarities in reactive metabolites, adduct formation, and primary tumor type (hepatic angiosarcoma) to the established human carcinogen, vinyl chloride. (https://hhpprtv.ornl.gov/issue_papers/VinylBromide.pdf) (EPA 2020).

- Positive for mutagenesis in bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/593-60-2) (NIH 2024a).

CHEMICALS IDENTIFIED AS "LIKELY" MUTAGENIC

- **Acetaldehyde (CASRN 75-07-0)**
  - "The RIVM proposal seeks to alter the classification of acetaldehyde as it pertains to carcinogenicity and germ cell mutagenicity. Acetaldehyde is currently classified for carcinogenicity in Category 2 (suspected human carcinogen) and is not classified for mutagenic activity. RIVM is proposing to upgrade the carcinogenicity classification to Cat. 1B and to establish a category 1B classification for germ cell mutagenicity" (https://echa.europa.eu/documents/10162/b9885f2c-b491-4ad4-8900-8cba349b15a0) (ECHA 2015).
  - Positive for mutagenesis in mammalian and germ cell studies but negative results in bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/75-07-0) (NIH 2024a).

- **2-Acetylaminofluorene (CASRN 53-96-3)**
  - Positive for mutagenesis in rodent chromosome aberration, mammalian cell mutagenicity, and mammalian cell cytogenetic studies (https://cebs.niehs.nih.gov/cebs/test_article/53-96-3) (NIH 2024a).
  - "2-Acetylaminofluorene and 2-aminofluorene are among the most intensively studied of all chemical mutagens and carcinogens. Fundamental research findings concerning the metabolism of 2-acetylaminofluorene to electrophilic derivatives, the interaction of these derivatives with DNA, and the carcinogenic and mutagenic responses that are associated with the resulting DNA damage have formed the foundation upon which much of genetic toxicity testing is based" (https://pubmed.ncbi.nlm.nih.gov/7521935/) (Heflich and Neft 1994).

- **1,3-Butadiene (CASRN 106-99-0)**
  - Identified as mutagenic (https://echa.europa.eu/carcinogens-mutagens-oels) (ECHA 2024).
  - Positive for mutagenesis in rodent chromosome aberration and bacterial mutagenicity studies but negative in mammalian cell and germ cell mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/106-99-0) (NIH 2024a).

- **Cadmium (CASRN 7440-43-9)**
  - "Based on the strong similarity between cadmium mutagenesis and the mutator effects of MMR-null alleles, we conclude that cadmium is a new kind of mutagen that acts by inhibiting the MMR system rather than through DNA damage" (https://pubmed.ncbi.nlm.nih.gov/12796780/) (Jin et al. 2003).
  - "suspected of causing genetic defects (warning germ cell mutagenicity)" (https://pubchem.ncbi.nlm.nih.gov/compound/Cadmium) (NIH 2024b)

- **Chloromethyl methyl ether (CASRN 107-30-2)**

  - "CMME is mutagenic to E. coli and S. typhimurium in the absence of exogenous metabolism" (https://iris.epa.gov/static/pdfs/0245_summary.pdf) (EPA 2010c).

  - "Both BCME and CMME are powerful alkylating agents that are mutagenic in bacteria" (https://www.ncbi.nlm.nih.gov/books/NBK304419/) (IARC 2012).

- **Crotonaldehyde, trans (CASRN 123-73-9)**

  - "The results of Salmonella mutagenicity assays are variable, possibly due to the use of different methods. Liquid suspension methods indicate that crotonaldehyde is mutagenic" (https://iris.epa.gov/static/pdfs/0464_summary.pdf) (EPA 1991b).

  - "Croton-aldehyde is a compound that may be easily classified as non-mutagenic under inappropriate testing conditions…sufficiently high bacterial cell densities are an important factor in demonstrating its mutagenic potential" (https://onlinelibrary.wiley.com/doi/epdf/10.1002/em.2850140303) (Neudecker et al. 1989).

- **Ethyleneimine (CASRN 151-56-4)**

  - "… ethylenimine had been tested for genetic toxicity in about 150 species and concluded that it is a very potent direct-acting mutagen, producing point mutations and chromosome aberrations. This chemical "is very mutagenic in all test systems investigated;" only a few negative results have been published and these were attributed to the use of low doses… (https://www.ncbi.nlm.nih.gov/books/NBK220002/) (NRC 2010a).

  - Positive for mutagenesis in bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/151-56-4) (NIH 2024a).

- **Methyl methanesulfonate (CASRN 66-27-3)**

  - "This substance is an alkylating agent and acts as a mutagen by altering and damaging DNA and is reasonably anticipated to be a human carcinogen" (https://pubchem.ncbi.nlm.nih.gov/compound/Methyl-methanesulfonate) (NIH 2024b).

  - Positive for mutagenesis in bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/66-27-3) (NIH 2024a).

- **4,4'-Methylelebisbenzeneamine (CASRN 101-77-9)**

  - Listed as suspected mutagen (https://echa.europa.eu/carcinogens-mutagens-oels) (ECHA 2024).

  - Positive for mutagenesis in micronucleus test and bacterial mutagenicity studies but mixed results in mammalian cell cytogenetic studies (https://cebs.niehs.nih.gov/cebs/test_article/101-77-9) (NIH 2024a).

- **N-Methyl-N-nitro-N-nitrosoguanidine (CASRN 70-25-7)**

  - "Extremely hazardous as a mutagen" (https://pubchem.ncbi.nlm.nih.gov/compound/1-Methyl-3-nitro-1-nitrosoguanidine) (NIH 2024b).

  - "The values found indicate that NG can be classified as a mutagen of a very high efficiency and can be put on the same level as EMS, although EMS must be applied in concentrations 50 times higher" (https://www.nature.com/articles/2011149b0)(Müller and Gichner 1964).

- **4-Nitroaniline (CASRN 100-01-6)**

  - "Limited evidence supports the mutagenic mode of action for 4-nitroaniline tumorigenicity" (https://hhpprtv.ornl.gov/issue_papers/Nitroaniline4.pdf) (EPA 2009c).

  - "p-Nitroaniline is mutagenic in vitro" (NIH 2024b).

  - Positive for mutagenesis in mammalian cell mutagenic and cytogenetic studies and bacterial mutagenicity studies but negative results in germ cell mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/100-01-6) (NIH 2024a).

- **N-Nitrosomorpholine (CASRN 59-89-2)**

  - "A carcinogen and mutagen, it is found in snuff tobacco. It has a role as a carcinogenic agent and a mutagen." (NIH 2024b).

  - Positive for mutagenesis in mammalian cell cytogenetic studies and bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/59-89-2) (NIH 2024a).

- **N-Nitrosopiperidine (CASRN 100-75-4)**

  - "N-Nitrosopyrrolidine (NPyrr) and N-nitrosopiperidine (NPip) are carcinogenic and mutagenic cyclic nitrosamines. Their biotransformation by rat liver post-mitochondrial fraction into 1,4-butanediol and 1,5-pentanediol, respectively, is evaluated by determining these ultimate metabolites with a sensitive and suitable method. Their mutagenic activity towards the Salmonella typhimurium strain TA 1530 was simultaneously observed. A relationship exists between their metabolism and their mutagenicity" (https://pubmed.ncbi.nlm.nih.gov/7342373/) (Gilbert et al. 1981).

  - "It has a role as a carcinogenic agent, an apoptosis inducer, a mutagen and an environmental contaminant" https://pubchem.ncbi.nlm.nih.gov/compound/N-Nitrosopiperidine (NIH 2024b).

  - N-Nitrosopiperidine is positive for mutagenesis in germ cell mutagenicity and bacterial mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/100-75-4) (NIH 2024a).

- **N-Nitrosopyrrolidine (CASRN 930-55-2)**

  - "N-nitrosopyrrolidine is mutagenic for Salmonella typhimurium upon addition of mammalian metabolic enzymes" (https://iris.epa.gov/static/pdfs/0081_summary.pdf) (EPA 1987)

  - "N-Nitrosopyrrolidine (NPyrr) and N-nitrosopiperidine (NPip) are carcinogenic and mutagenic cyclic nitrosamines. Their biotransformation by rat liver post-mitochondrial fraction into 1,4-butanediol and 1,5-pentanediol, respectively, is evaluated by determining these ultimate metabolites with a sensitive and suitable method. Their mutagenic activity towards the Salmonella typhimurium strain TA 1530 was simultaneously observed. A relationship exists between their metabolism and their mutagenicity" (https://pubmed.ncbi.nlm.nih.gov/7342373/) (Gilbert et al. 1981).

  - "An excellent correlation was found between the metabolism of nitrosopyrrolidine and nitrosohexamethylenimine (probably via oxidation at the alpha-C) in rat liver microsomes and mutagenic potency in 2 bacterial mutagenic systems (https://pubchem.ncbi.nlm.nih.gov/compound/1-Nitrosopyrrolidine) (NIH 2024b).

- **Quinoline (CASRN 91-22-5)**

  - "the genotoxicity of quinoline is supported by a large database of mutagenicity assays, particularly from in vitro studies… It is possible that the hepatocarcinogenicity of quinoline is promoted to some extent by a nongenotoxic mechanism that impacts the mitotic activity of rat and mouse liver cells, but more work needs to be done in this area before anything definitive can be concluded." (https://iris.epa.gov/static/pdfs/1004tr.pdf) (EPA 2001).

  - Positive for mutagenesis in mammalian cell mutagenicity and cytogenetic studies and bacterial mutagenicity studies but negative in germ cell mutagenicity studies (https://cebs.niehs.nih.gov/cebs/test_article/91-22-5) (NIH 2024a).

- **Toxaphene CASRN 8001-35-2)**

  - "Toxaphene is mutagenic to Salmonella…It was negative in a modified dominant lethal assay of male ICR/Ha Swiss mice (Epstein, 1972). No significant differences were found between rates of chromosomal aberrations in leukocytes of workers occupationally exposed to toxaphene and of unexposed workers" (https://iris.epa.gov/static/pdfs/0346_summary.pdf) (EPA 1988a).

  - "Toxaphene was mutagenic in reverse mutation assays using Salmonella typhimurium strains TA98 and/or TA100…However, mutagenic responses were diminished or abolished in some assays upon the addition of mammalian hepatic activation systems that play a role in xenobiotic metabolism... Negative or only weakly positive results were obtained in reverse mutation assays using S. typhimurium strains TA 1535 and TA1537 (non-plasmid containing strains) (https://www.atsdr.cdc.gov/ToxProfiles/tp94.pdf) (ATSDR 2014).