

OBJECTIVES

- New approach methods (NAMs) in chemical safety research rely an understanding of the mechanisms underpinning chemical toxicity.
- The biomedical literature is a rich source of information about mechanisms of toxicity, but because resources like PubMed are so large and complex, literature informatics methods are needed to help researchers use this resource more effectively.
- We have developed a freely available Excel-based literature tool called the Abstract Sifter to retrieve and triage articles and to visualize the literature landscape for a set of chemicals.
- The tool streamlines exploration of mechanisms behind chemical activity.

APPROACH

- Define mechanism through PubMed queries

Toxicity type queries	Genetox	(dna/drug effects OR DNA Damage OR chromosome aberrations OR genotoxicity OR micronucleus OR DNA Repair OR
	Cancer	neoplasms or cancer
	ReproTox	(reproduction AND (toxicity OR abnormal OR adverse effects))
	NeuroTox	(neurotoxicity OR (Nervous system diseases and chemically induced) OR ((neurons OR brain OR behavior) AND drug ef
	DevTox	(toxicity OR congenital abnormalities OR Prenatal Exposure Delayed Effects) AND (fetus OR embryo OR embryonic dev
	Skin sensitization	("allergic" AND "contact" And dermatitis) OR Dermatitis, Allergic Contact[mh]

Key characteristics of carcinogens queries	KCC1 Adducts	protein Adducts OR dna adducts OR epoxides OR quinones OR aldehydes
	KCC2 DNA	(dna/drug effects OR DNA Damage OR chromosome aberrations OR genotoxicity OR micronucleus OR mutagenicity te
	KCC3 DNA break/repair	(topoisomerase OR DNA Repair/drug effects OR double-strand break repair)
	KCC4 Epigenetics	(DNA methylation OR histone modification OR Histone Code OR Chromatin Assembly and Disassembly OR microRNAs
	KCC5 Oxidative stress	(oxidative stress OR reactive oxygen species OR mitochondria/drug effects)
	KCC6 Inflammation	(inflammation OR macrophages)

- Run queries with chemical compounds
- Visualize and explore article count results

MAIN RESULTS

- Landscape sheet visualizes results and is entry point to agile exploration of citations

Landscape View		Subject queries: Summary heading				
Preferred Name	Chemical / Entity query	Genetox	Cancer	ReproTox	NeuroTox	DevTox
Thalidomide	Thalidomide[majr]	328	2604	323	454	338
Hexachlorobenzene	118-74-1 OR Hexachlorobenzene	63	313	161	86	62
Trichloroethylene[majr]	Trichloroethylene[majr]	116	628	79	211	61
Bisphenol AF	1478-61-1 OR Bisphenol AF OR 4,4'-hexafluoropropylidene diphenol	12	28	19	11	10
Fadrozole OR 102676-47-1	Fadrozole OR 102676-47-1	10	153	18	131	23
1-Bromopropane	1-Bromopropane	17	18	11	60	1
Resorcinol	108-46-3 OR Resorcinol	128	227	12	42	8
Eugenol	Eugenol[majr]	201	258	5	119	5
2,4,6-Tribromophenol	118-79-6 OR 2,4,6-Tribromophenol	12	84	9	8	7
Methyl methacrylate	Methyl methacrylate	113	815	9	176	28
Citral	Citral	45	100	8	68	31
Vanadium pentoxide	1314-62-1 OR Vanadium pentoxide	31	43	5	14	7
2,2',4,4'-Tetrahydroxybenzophenone	131-55-5 OR 2,2',4,4'-Tetrahydroxybenzophenone	4	7	5	4	4
1,4-Dioxane OR 123-91-1	1,4-Dioxane OR 123-91-1	57	156	5	126	4

IMPACT

- The Abstract Sifter is a free, innovative tool that provides an effective way to retrieve, read, screen, tag, and export PubMed citations.
- The tool provides a literature landscape for chemical lists and visual entry point for mechanism exploration.
- The Abstract Sifter is downloadable here: <https://comptox.epa.gov/dashboard/downloads>
- Contact: Nancy Baker, Baker.Nancy@epa.gov

OBJECTIVES

- Despite the growth in data repositories, most of the knowledge of what chemicals do in biological systems resides in the biomedical literature.
- Finding evidence to support chemical mechanism of action are particularly complex because the evidence spans a wide variety of publications.
- We built the Abstract Sifter Landscape sheet to facilitate the exploration of mechanism literature for a set of chemicals of interest.

Abstract Sifter: A literature informatics tool for computational toxicology

APPROACH

- Explore the literature landscape for a chemical set using the Landscape sheet

First, compose queries that will retrieve relevant publications.

Genetox	(dna/drug effects OR DNA Damage OR chromosome aberrations OR genotoxicity OR micronucleus OR DNA Repair OR mutagenicity te
Cancer	neoplasms or cancer
ReproTox	(reproduction AND (toxicity OR abnormal OR adverse effects))
NeuroTox	(neurotoxicity OR (Nervous system diseases and chemically induced) OR ((neurons OR brain OR behavior) AND drug effects)
DevTox	(toxicity OR congenital abnormalities OR Prenatal Exposure Delayed Effects) AND (fetus OR embryo OR embryonic development)
Skin sensitization	("allergic" AND "contact" And dermatitis) OR Dermatitis, Allergic Contact[mh]

Then: 1. Populate the chemical list

2. Populate the subject matter queries

3. Select cells and click on Update Article Counts

Landscape View		Subject queries:				
Update Article Counts		View / hide queries	Heat Map by column	Heat Map by row		
Preferred Name	Chemical Entity query	Genetox	Cancer	ReproTox	NeuroTox	DevTox
Thalidomide	Thalidomide[majr]	328	2604	323	454	338
Hexachlorobenzene	118-74-1 OR Hexachlorobenzene	63	313	161	86	62
Trichloroethylene[majr]	Trichloroethylene[majr]	116	628	79	211	61
Bisphenol AF	1478-61-1 OR Bisphenol AF OR 4,4'-hexafluoropropylidene diphenol	12	28	19	11	10
Fadrozole OR 102676-47-1	Fadrozole OR 102676-47-1	10	153	18	131	23
1-Bromopropane	1-Bromopropane	17	19	12	60	1
Resorcinol	108-46-3 OR Resorcinol	128	227	11	42	8
Eugenol	Eugenol[majr]	201	258	5	119	5
2,4,6-Tribromophenol	118-79-6 OR 2,4,6-Tribromophenol	12	14	9	5	7
Methyl methacrylate	Methyl methacrylate	113	815	9	176	28
Citral	Citral	45	100	8	68	31
Vanadium pentoxide	1314-62-1 OR Vanadium pentoxide	31	43	5	14	7
2,2',4,4'-Tetrahydroxybenzophenone	131-55-5 OR 2,2',4,4'-Tetrahydroxybenzophenone	4	7	5	4	4
1,4-Dioxane OR 123-91-1	1,4-Dioxane OR 123-91-1	57	156	5	126	4
2-Mercaptobenzothiazole	149-30-4 OR 2-Mercaptobenzothiazole OR captax	20	29	4	1	4

This is what you get

4. Browse and sort article counts. Double-click to start exploration

Abstract Sifter: A literature informatics tool for computational toxicology

MAIN RESULTS

Double-clicking on an article count cell on the Landscape sheet runs the query and puts the results on the Main sheet for browsing and sifting.

Landscape View

Update Article Counts | View / hide queries | Heat Map by column | Heat Map by row

Subject queries: DNA Damage OR chromosome aberrations OR genotoxicity OR micronucleus OR DNA Repair OR neoplasms or cancer OR carcinogen* OR precancerous OR reproduction AND (toxicity OR abnormal OR adverse effects) OR (neurotoxicity OR brain OR behavior) AND drug effects OR (nervous system diseases and chemically induced) OR (neurons OR brain OR behavior) AND drug effects OR congenital abnormalities OR Prenatal Exposure Delayed Effects) AND (fetus OR embryo OR embryonic

Summary heading: Toxicity | Toxicity | Toxicity | Toxicity | Toxicity

Preferred Name | Chemical / Entity query | Genetox | Cancer | ReproTox | NeuroTox | DevTox

Thalidomide	Thalidomide[majr]	328	2904	323	454	338
Hexachlorobenzene	118-74-1 OR Hexachlorobenzene	63	313	161	86	62
Trichloroethylene[majr]	Trichloroethylene[majr]	116	628	79	211	61
Bisphenol AF	1478-61-1 OR Bisphenol AF OR 4,4'-hexafluoroisopropylene diphenol	12	28	19	11	10
Fadrozole OR 102676-47-1	Fadrozole OR 102676-47-1	38	352	18	121	23
1-Bromopropane	1-Bromopropane	17	13	12	60	1
Resorcinol	108-46-3 OR Resorcinol	128	227	11	42	8
Eugenol	Eugenol[majr]	201	258	5	119	5
2,4,6-Tribromophenol	118-79-6 OR 2,4,6-Tribromophenol	12	34	9	5	7
Methyl methacrylate	Methyl methacrylate	113	815	9	176	28
Citral	Citral	45	100	8	68	31
Vanadium pentoxide	Vanadium pentoxide	31	43	5	14	7
2,2',4,4'-Tetrahydro-1,4-Dioxane OR 123-91-1	(1,4-Dioxane OR 123-91-1) AND ((neurotoxicity OR (Nervous system diseases and chemically induced) OR (neurons OR brain OR behavior) AND drug effects))	4	7	5	4	4
2-Mercaptobenzoic acid	2-Mercaptobenzoic acid	57	15	5	126	4
2-Mercaptobenzoic acid	2-Mercaptobenzoic acid	20	4	4	1	4

Enter your PubMed query and click on Submit.

Delete then add Append

Abstract Sifter | Query PubMed

PubMed query run: (1,4-Dioxane OR 123-91-1) AND ((neurotoxicity OR (Nervous system diseases and chemically induced) OR (neurons OR brain OR behavior) AND drug effects))

Provided by the US EPA's Center for Computational Toxicology and Exposure

v5.5 | Your sifter terms and frequency counts

	dioxan	brain	mg/kg	Score	Pub Yr	Title	Review	PMC	Authors
PMID									
18544906	10	1	2	13	2008	Thirteen-week oral toxicity of 1,4-dioxane in rats and mice.	0	0	Kano H, Umeda Y, Saito M, Senoh H, (
27363050	7	3	3	13	2016	INHIBITORY ACTIVITY OF PROTECTED EDIBLE PLANTS ON OXIDATIVE STRESS INDUCED BY ORAL 1,4-DIOXANE.	0	0	Mnaa S, Shaker ES, Mahmoud HI
8667368	7	0	0	7	1996	Synthesis, absolute configuration, and biological profile of the enantiomers of trans-[2-(2,6-dimethoxyphenoxy)ethyl] [(3-p-to	0	0	Quaglia W, Pignini M, Tayebati SK, Pie
19042127	5	1	0	6	2009	Synthesis of novel twin drug consisting of 8-oxaendoethanotetrahydromorphides with a 1,4-dioxane spacer and its pharmacolog	0	0	Fujii H, Watanabe A, Nemoto T, Narit
11740571	5	4	0	9	2001	Effect of chronic inhalation of toluene and dioxane on activity of free radical processes in rat ovaries and brain.	0	0	Burmistrov SO, Arutyunyan AV, Stepa
29884692	4	0	0	4	2018	Identification of WB4101, an α 1-Adrenoceptor Antagonist, as a Sodium Channel Blocker.	0	0	Li M, Wu Y, Zou B, Wang X, Li M, Yu
23902232	4	0	0	4	2013	6-methoxy-7-benzofuranoxo and 6-methoxy-7-indolyloxy analogues of 2-[2-(2,6-Dimethoxyphenoxy)ethyl]aminomethyl-1,4-benz	0	0	Fumagalli L, Pallavicini M, Budriesi R
19068225	4	0	0	4	2009	Stimulation of alpha(1)-adrenoceptors reduces glutam			
17337632	4	0	0	4	2007	Alpha1A-adrenergic receptors are functionally expres			
12818701	4	0	9	13	2003	Functional characterization of alpha-adrenoceptors m			
9527505	4	0	0	4	1997	Characterization of alpha1-adrenoceptor subtypes in f			
9007530	4	0	0	4	1996	Functional characterisation of alpha 1-adrenoceptor s			
8813537	4	0	0	4	1996	Alpha 1B-adrenoceptor-mediated excitation of pirifro			
7988647	4	0	0	4	1994	The spinal analgesic role of alpha 2-adrenoceptor sub			
8369284	4	0	0	4	1993	Hypersensitivity of an enzyme reaction to solvent wat			
1358645	4	0	0	4	1992	The effect of intrathecally administered imiloxan and			
1681442	4	0	2	6	1991	Clozapine attenuates N-methyl-D-aspartate receptor c			

Take Group Notes | More things

Abstract with highlights | <- Main | Add Note | See Note -> | Like this?

PMID: [18544906](#)

Title: Thirteen-week oral toxicity of 1,4-dioxane in rats and mice.

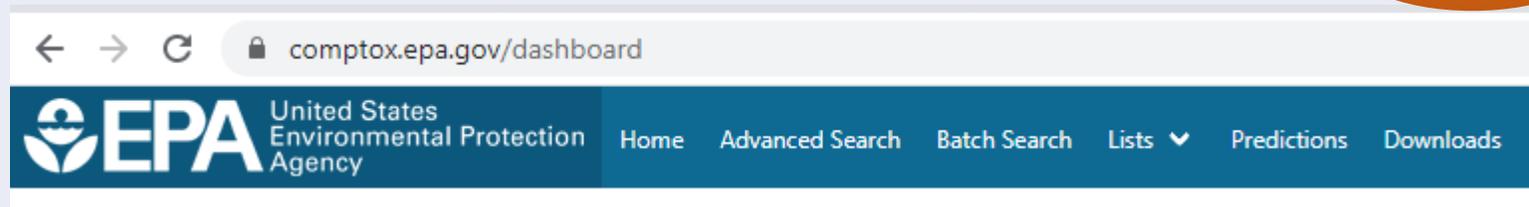
Title and Abstract: Thirteen-week oral toxicity of 1,4-dioxane in rats and mice. ABSTRACT: Subchronic oral toxicity of 1,4-dioxane was examined by administering 1,4-dioxane in drinking water at 6 different concentrations of 0 (control), 640, 1,600, 4,000, 10,000 or 25,000 ppm (wt/wt) to F344 rats and BDF(1)mice of both sexes for 13 weeks. Food and water consumption and terminal body weight were decreased dose-dependently in rats and mice. A dose-dependent increase in the relative weights of kidney and lung was noted in rats and mice, while the relative liver weight was increased only in rats. Increases in plasma levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and a decrease in plasma glucose were noted primarily in the rats and mice dosed 25,000 ppm. Histopathological examination revealed that 1,4-dioxane affected the upper and lower respiratory tracts, liver, kidneys and brain in rats, while only the former two organs were affected in mice. Nuclear enlargement occurred in the respiratory, olfactory, tracheal and bronchial epithelia of the 1,4-dioxane-dosed rats and mice. The 1,4-dioxane-induced hepatic lesions were characterized by centrilobular swelling and necrosis in rats and mice and by glutathione S-transferase placental form (GST-P)-positive altered hepatocellular foci in rats, which are known as preneoplastic lesions. A no-observed-adverse-effect-level (NOAEL) was determined at 640 ppm for both rats and mice, since the nuclear enlargement in the nasal respiratory epithelium and the centrilobular swelling of hepatocytes in rats and the nuclear enlargement in the bronchial epithelium in mice were observed at 1,600 ppm. The NOAEL value corresponded to the estimated 1,4-dioxane intake of 52 mg/kg/day in rats and 170 mg/kg/day in mice. KEYWORDS: Dioxanes, Solvents, 1,4-dioxane, Administration, Oral, Animals, Dioxanes/toxicity, Female, Liver/drug effects/growth & development/pathology, Male, Mice, No-Observed-Adverse-Effect Level, Organ Size, Rats, Rats, Inbred F344, Respiratory System/drug effects/growth & development/pathology, Solvents/toxicity

Double-clicking on a citation row lets the user read the abstract, then take notes, add tagging, curate and export.

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IMPACT/SIGNIFICANCE

- The Abstract Sifter makes literature tasks more effective and enjoyable.
- The PubMed Abstract Sifter with user guide with links to on-line training is available through the downloads button on the EPA Chemicals Dashboard at comptox.epa.gov/dashboard



- Also check out the Dashboard version of the Abstract Sifter.
- What's coming: Abstract Sifter Public Plus – this version includes retrieval from PubMed, EuroPMC, PubAg and other sources.
- Contact for questions, training, documentation: Nancy.baker@epa.gov