EPA
United States
Environmental Protection
Agency

Generation of Alternative Assessment Scores using TEST and online data sources

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Sources of alternative assessment scores

- US EPA
  - Chemistry Dashboard: http://comptox.ag.epa.gov/dashboard
    - ACToR/ToxRefDB
  - T.E.S.T. (Toxicity Estimation Software Tool)
- ECHA (European Chemicals Agency)
  - REACH dossiers / Hazard statement codes
- ChemHAT
  - Free compilation of data from EU (both R and H scores), New Zealand, Australia, Japan (NITE), Korea, Malaysia, and miscellaneous lists
- Wehage developed a system to assign scores from Japan's NITE data
- Future work
  - QSAR/read across models based on compiled experimental values

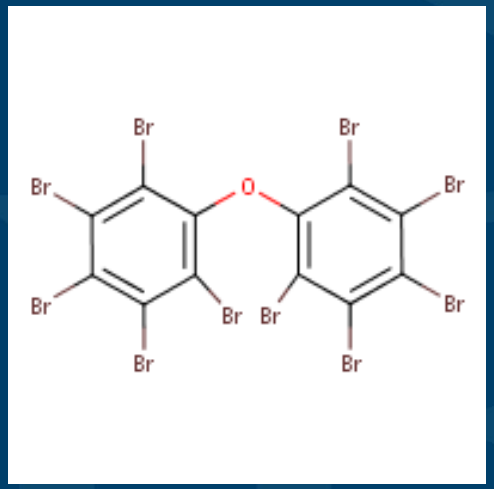
Converting between systems

Acute toxicity scoring

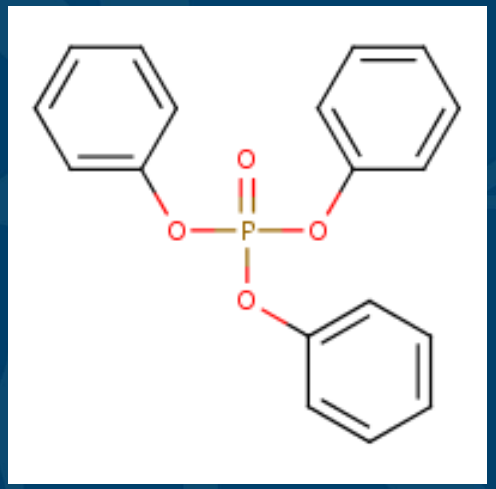
Risk phrase[a]	R28		R25		R22		
LD50, mg/kg	≤5	5-25	25-50	50-200	200-300	300-2000	2000-5000
GHS[b]	Cat 1	Category 2		Category 3		Category 4	Category 5
EU CLP[c]	H300			H301		H302	H303
DfE Score[d]	Very high			High		Moderate	Low

- Quantitative toxicity scores are preferable due to differing systems

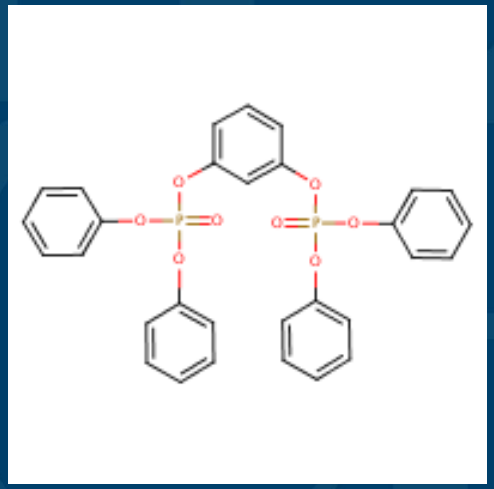
Case Study: flame retardant alternatives and their metabolities



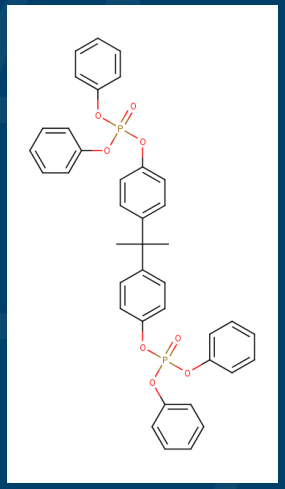
DecaBDE



TPP

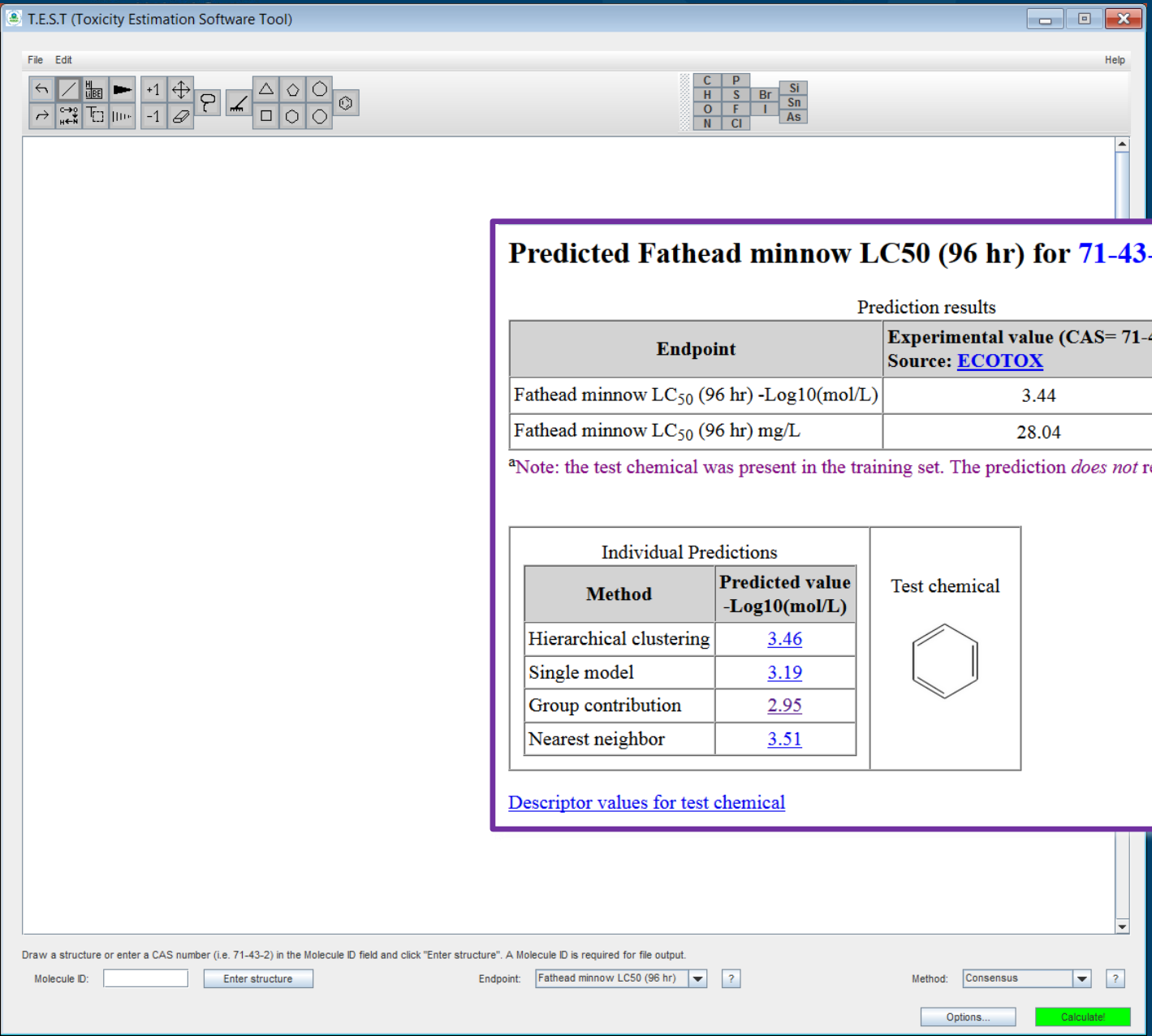


RDP



BPADP

T. E. S. T. Java Application



Predicted Fathead minnow LC50 (96 hr) for 71-43-2 from Consensus method

Prediction results

Endpoint	Experimental value (CAS= 71-43-2) Source: ECOTOX	Predicted value[a]
Fathead minnow LC_{50} (96 hr) -Log10(mol/L)	3.44	3.28
Fathead minnow LC_{50} (96 hr) mg/L	28.04	41.05

[a]Note: the test chemical was present in the training set. The prediction *does not* represent an external prediction.

Individual Predictions

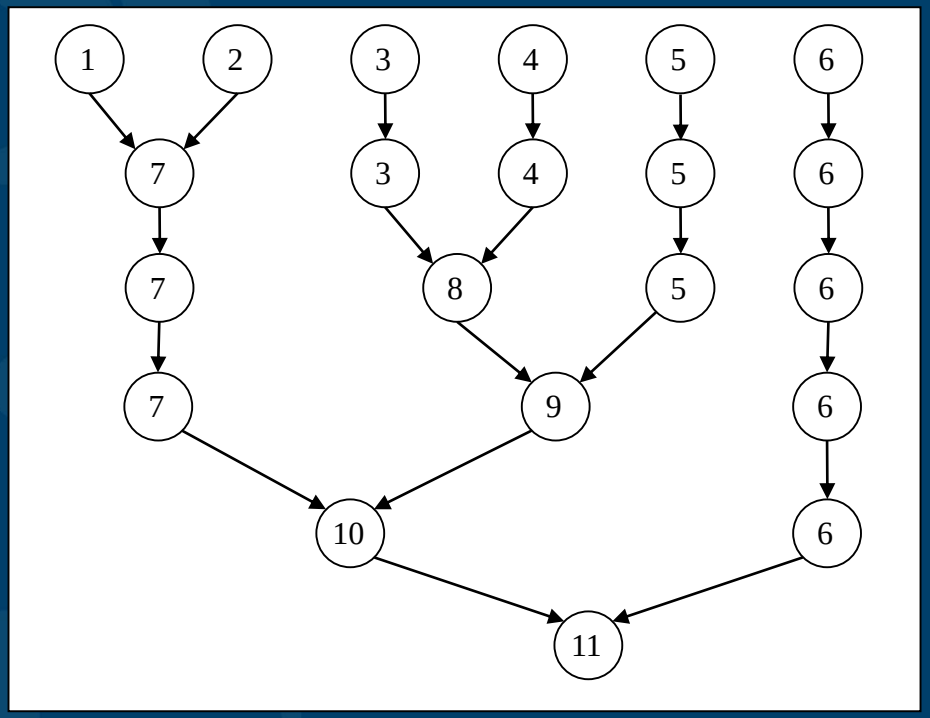
Method	Predicted value -Log10(mol/L)
Hierarchical clustering	3.46
Single model	3.19
Group contribution	2.95
Nearest neighbor	3.51

Test chemical

Descriptor values for test chemical

QSAR Methods

- Hierarchical clustering
- Single Model
- Group contribution
- Nearest neighbor
- Consensus



Physical properties from T.E.S.T.

Name	MP*, ° C	BP, ° C	FP, ° C	VP, mmHg
DecaBDE	295[e]	530[e]	241[e]	3.01E-12
TPP	51[e]	381	201[e]	6.28E-06[e]
RDP	87	446	307	4.76E-08
BPADP	114	435	378[e]	4.21E-10

[e] experimental value

- MP, BP: indicate state of matter
- VP: inhalation implications
- FP: flammability

Water based properties from T.E.S.T

Name	WS, mg/L	log Kow	log BCF	Bioacc. score
DecaBDE	1.00E-04[e]	12.11	1.20[e]	L
TPP	1.90E+00[e]	4.70	2.48[e]	M
RDP	2.90E-01	7.41	1.82	L
BPADP	9.19E-02	10.02	1.28	L

[e] experimental value

- WS: aquatic toxicity implications
- LogKow: can be used to estimate partitioning
- BCF: bioaccumulation in fish

Human health hazards and ecotoxicity values from T.E.S.T

Chemical	Oral rat LD50 mg/kg	Fathead minnow LC50 mg/L	Dev. Tox.	Mutagenicity	Acute Mammalian Tox Score	Acute Aquatic Tox Score	Dev. Tox. Score	Mutagenicity Score
DecaBDE	>5000[e]	6.44E-04	N/A	–[e]	L	VH*	N/A	L
TPP	3496[e]	9.30E-01[e]	+	–[e]	L	VH	H	L
RDP	2216	3.15E-02	N/A	–	L	VH	N/A	L
BPADP	2261	7.30E-01	N/A	–	L	VH*	N/A	L

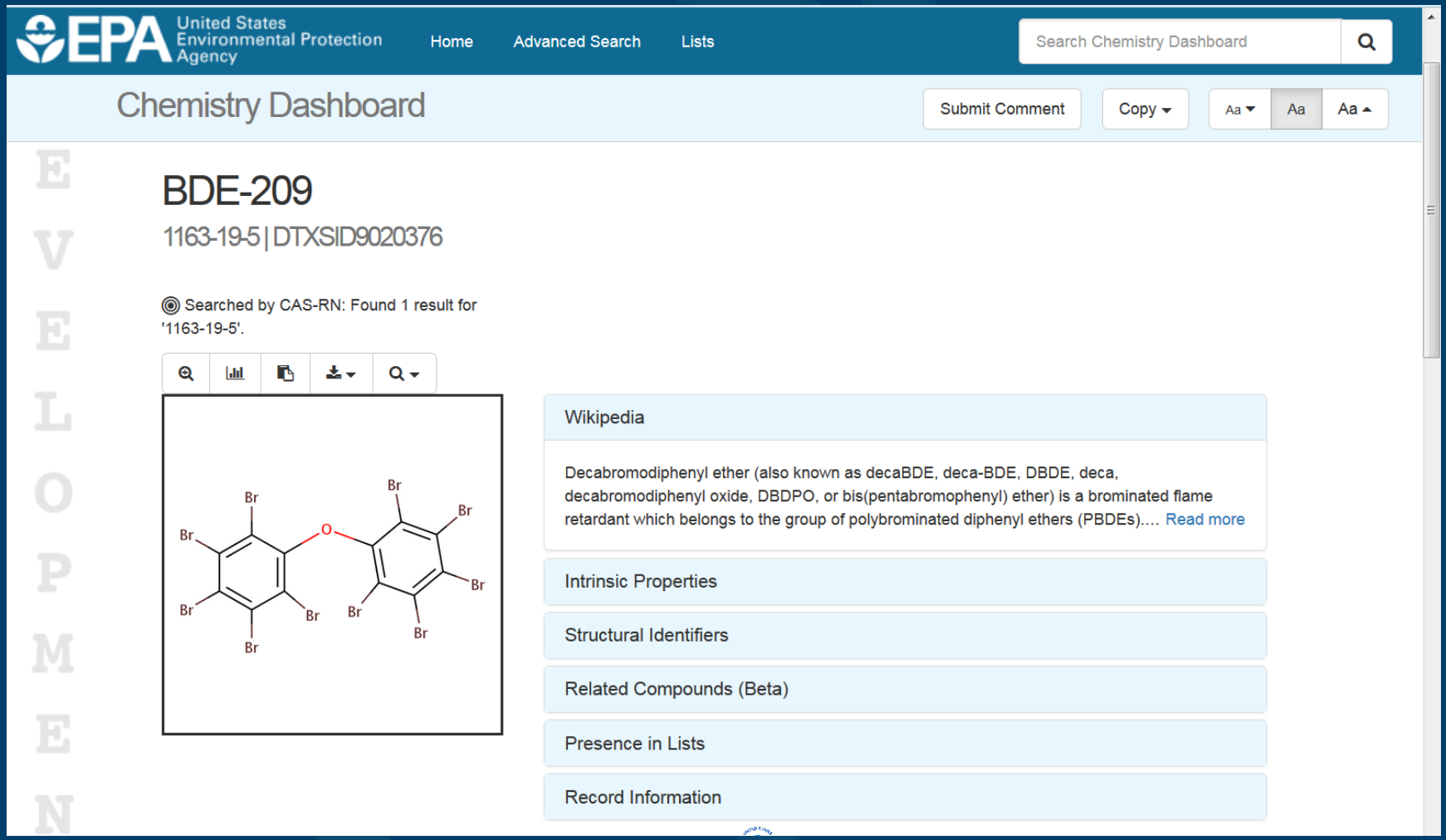
*Toxicity value exceeds water solubility so score is “L”

T.E.S.T. (Toxicity Estimation Software Tool)

- Currently T.E.S.T. is available as a downloadable standalone Java application
- In 2017, T.E.S.T. will be converted to a web-services based application which will allow predictions on the CompTox dashboard
  - **http://comptox.ag.epa.gov/dashboard/**
- Predictions using T.E.S.T. models for 743,000 chemicals are now being stored within the CompTox dashboard

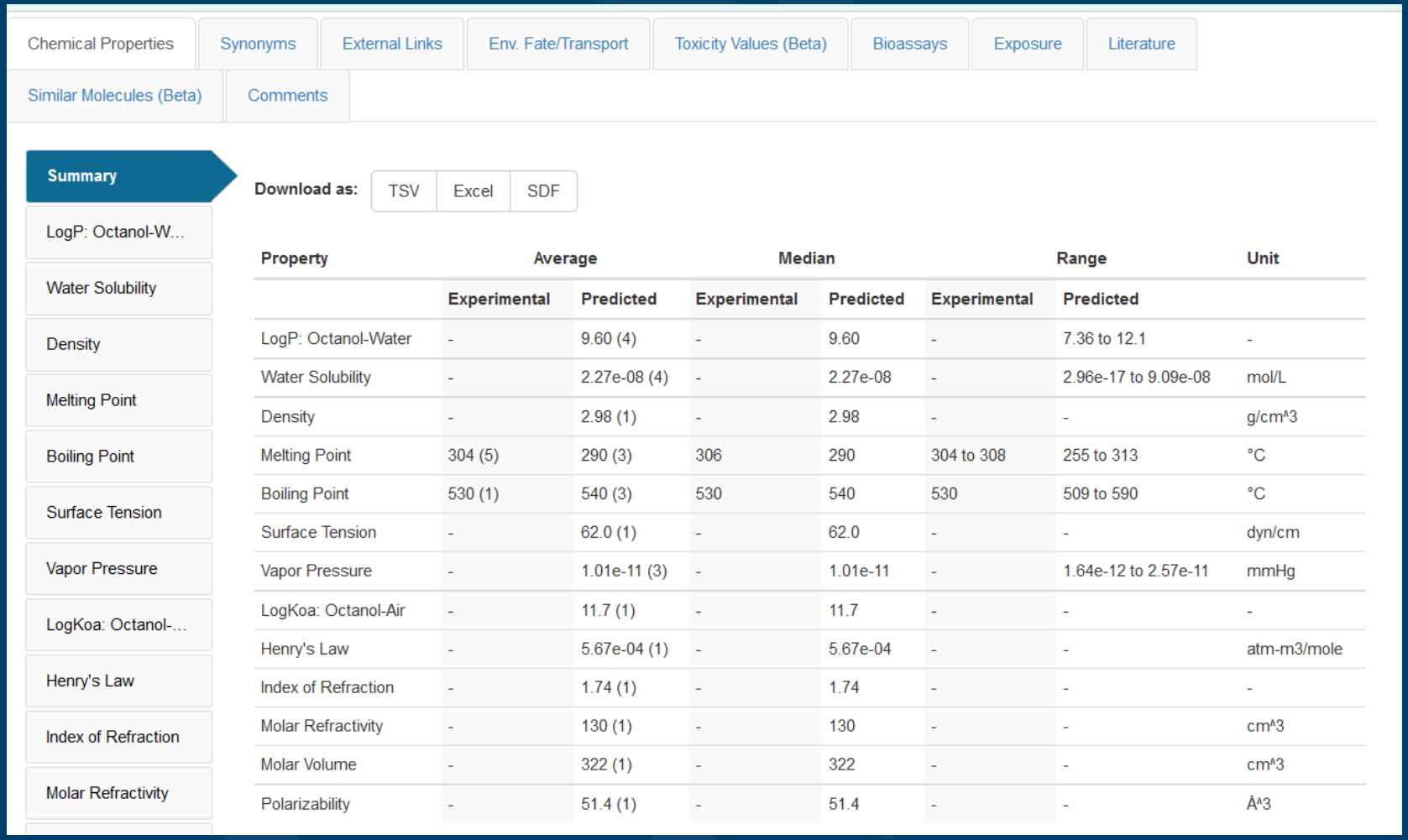
Chemistry Dashboard

http://comptox.ag.epa.gov/dashboard/



- Predictions for 743,000 chemicals are now available

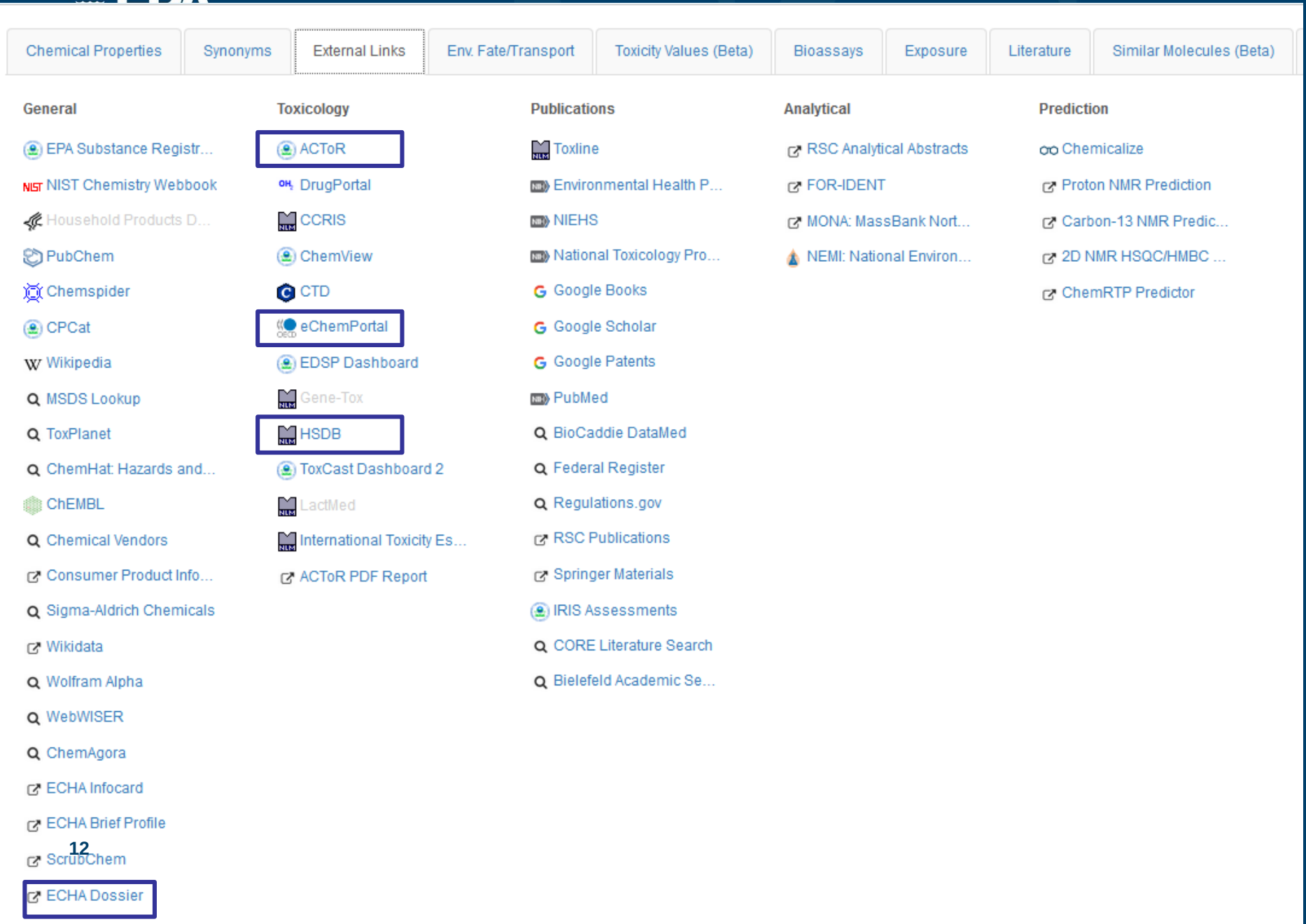
Chemistry Dashboard, cont.

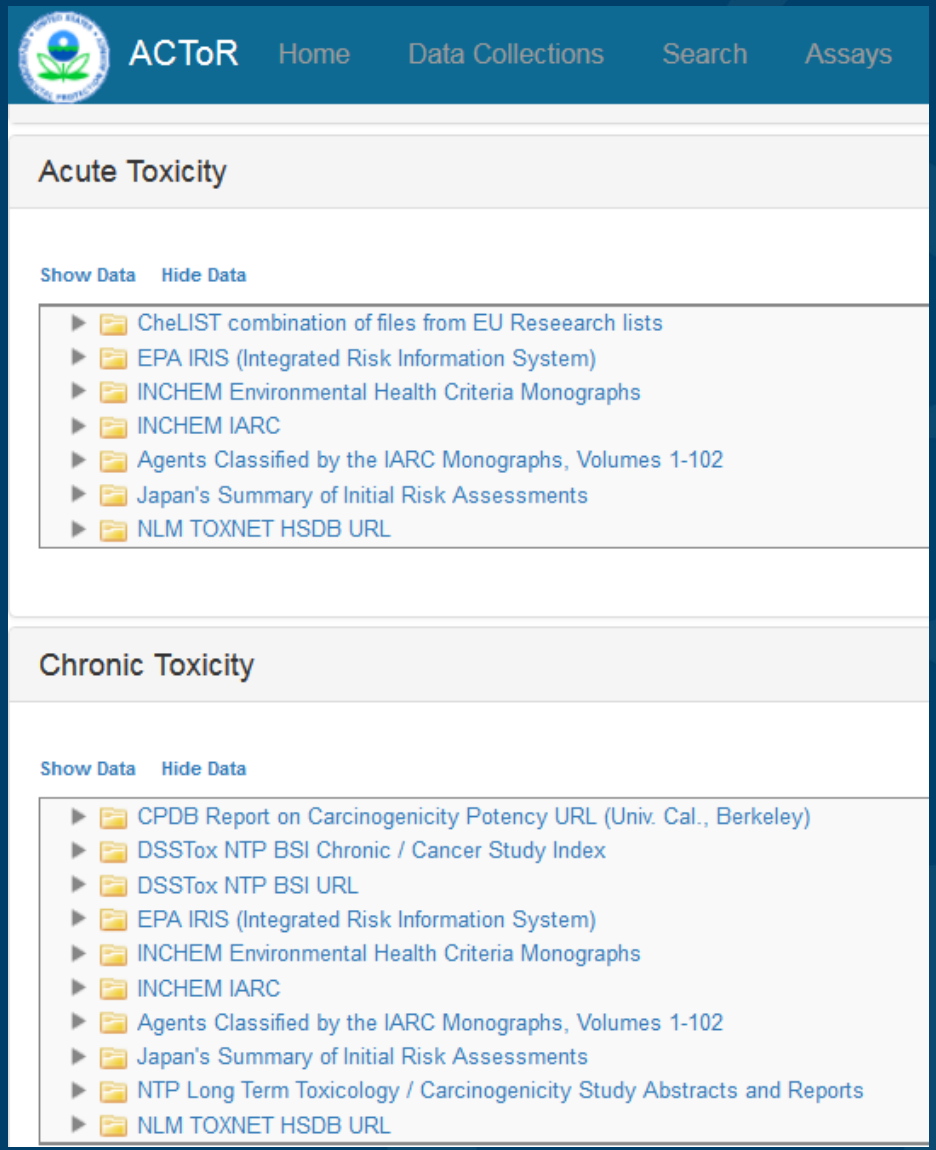


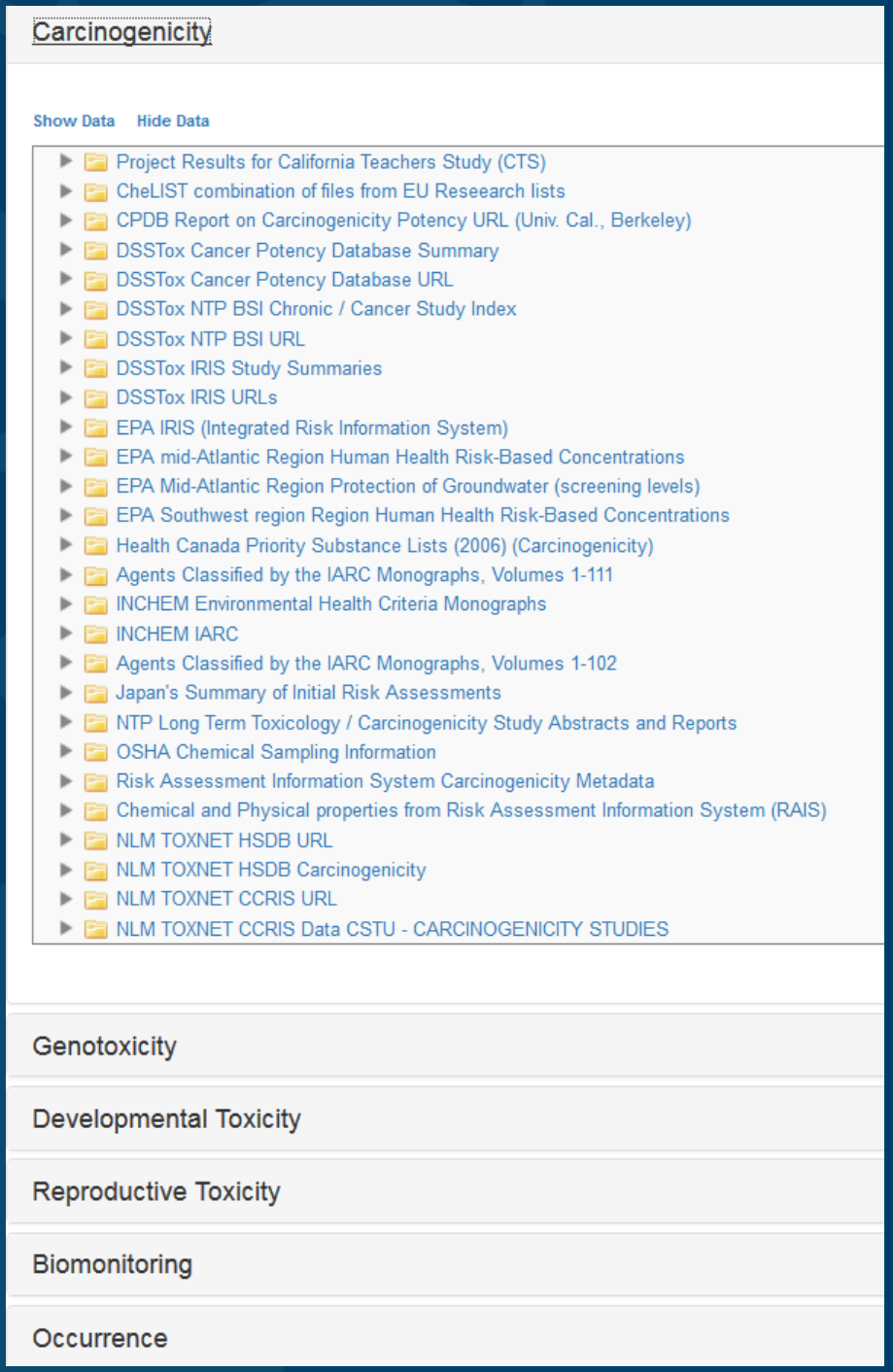
Property	Average		Median		Range		Unit
	Experimental	Predicted	Experimental	Predicted	Experimental	Predicted	
LogP: Octanol-Water	-	9.60 (4)	-	9.60	-	7.36 to 12.1	-
Water Solubility	-	2.27e-08 (4)	-	2.27e-08	-	2.96e-17 to 9.09e-08	mol/L
Density	-	2.98 (1)	-	2.98	-	-	g/cm^3
Melting Point	304 (5)	290 (3)	306	290	304 to 308	255 to 313	°C
Boiling Point	530 (1)	540 (3)	530	540	530	509 to 590	°C
Surface Tension	-	62.0 (1)	-	62.0	-	-	dyn/cm
Vapor Pressure	-	1.01e-11 (3)	-	1.01e-11	-	1.64e-12 to 2.57e-11	mmHg
LogKoa: Octanol-Air	-	11.7 (1)	-	11.7	-	-	-
Henry's Law	-	5.67e-04 (1)	-	5.67e-04	-	-	atm-m3/mole
Index of Refraction	-	1.74 (1)	-	1.74	-	-	-
Molar Refractivity	-	130 (1)	-	130	-	-	cm^3
Molar Volume	-	322 (1)	-	322	-	-	cm^3
Polarizability	-	51.4 (1)	-	51.4	-	-	Å^3

- Predictions for 743,000 chemicals are being made available

Chemistry Dashboard, cont..




ACToR
Home
Data Collections
Search
Assays
Acute Toxicity
Show Data
Hide Data
CheLIST combination of files from EU Reseearch lists
EPA IRIS (Integrated Risk Information System)
INCHEM Environmental Health Criteria Monographs
INCHEM IARC
Agents Classified by the IARC Monographs, Volumes 1-102
Japan's Summary of Initial Risk Assessments
NLM TOXNET HSDB URL
Chronic Toxicity
Show Data
Hide Data
CPDB Report on Carcinogenicity Potency URL (Univ. Cal., Berkeley)
DSSTox NTP BSI Chronic / Cancer Study Index
DSSTox NTP BSI URL
EPA IRIS (Integrated Risk Information System)
INCHEM Environmental Health Criteria Monographs
INCHEM IARC
Agents Classified by the IARC Monographs, Volumes 1-102
Japan's Summary of Initial Risk Assessments
NTP Long Term Toxicology / Carcinogenicity Study Abstracts and Reports
NLM TOXNET HSDB URL


Carcinogenicity
Show Data
Hide Data
Project Results for California Teachers Study (CTS)
CheLIST combination of files from EU Reseearch lists
CPDB Report on Carcinogenicity Potency URL (Univ. Cal., Berkeley)
DSSTox Cancer Potency Database Summary
DSSTox Cancer Potency Database URL
DSSTox NTP BSI Chronic / Cancer Study Index
DSSTox NTP BSI URL
DSSTox IRIS Study Summaries
DSSTox IRIS URLs
EPA IRIS (Integrated Risk Information System)
EPA mid-Atlantic Region Human Health Risk-Based Concentrations
EPA Mid-Atlantic Region Protection of Groundwater (screening levels)
EPA Southwest region Region Human Health Risk-Based Concentrations
Health Canada Priority Substance Lists (2006) (Carcinogenicity)
Agents Classified by the IARC Monographs, Volumes 1-111
INCHEM Environmental Health Criteria Monographs
INCHEM IARC
Agents Classified by the IARC Monographs, Volumes 1-102
Japan's Summary of Initial Risk Assessments
NTP Long Term Toxicology / Carcinogenicity Study Abstracts and Reports
OSHA Chemical Sampling Information
Risk Assessment Information System Carcinogenicity Metadata
Chemical and Physical properties from Risk Assessment Information System (RAIS)
NLM TOXNET HSDB URL
NLM TOXNET HSDB Carcinogenicity
NLM TOXNET CCRIS URL
NLM TOXNET CCRIS Data CSTU - CARCINOGENICITY STUDIES
Genotoxicity
Developmental Toxicity
Reproductive Toxicity
Biomonitoring
Occurrence

NITE Data

HEALTH HAZARDS

	Hazard class	Classification	Symbol	Signal word	Hazard statement	Rationale for the classification
1	Acute toxicity (Oral)	Category 5	-	Warning	May be harmful if swallowed	Rat LD50 value: 3500mg/kg (MOE Risk Assessment vol.4, 2005, EHC 111, 1991), 3800mg/kg (EHC 111, 1999, ACGIH 7th, 2001, DFGOT vol.2, 1991), 10800mg/kg (EHC 111, 1991, DFGOT vol.2, 1991), >5000mg/kg (EHC 111, 1991) and >6400mg/kg (PATTY 4th, 1994). Calculated based on the data above. Since the calculated values was 3723.1mg/kg, it was classified to category 5.
1	Acute toxicity (Dermal)	Not classified	-	-	-	Based on rabbit LD50 value: >7900mg/kg (MOE Risk Assessment the 4th volume, 2005, EHC 111, 1991, DFGOT vol.2, 1991), and >10000mg/kg (DFGOT vol.2, 1991), it was set as the outside of Category.
1	Acute toxicity (Inhalation: Gases)	Not applicable	-	-	-	Solid (GHS definition)
1	Acute toxicity (Inhalation: Vapours)	Classification not possible	-	-	-	No data available
1	Acute toxicity (Inhalation: Dusts and mists)	Classification not possible	-	-	-	No data available
2	Skin corrosion/irritation	Not classified	-	-	-	From description that irritation was not admitted in the test applied to the skin of the rat for 4 hours on DFGOT (2 vol. 1991) and ACGIH (7th, 2001), it was carried out the outside of Category.
3	Serious eye damage/eye irritation	Category 2B	-	Warning	Causes eye irritation	We classified it as Category 2B based on the description that a slight conjunctival reddening was acknowledged and it disappeared within 7 days in the test applied to the eyes of the rabbits (DFGOT(vol.2,1991)).
4	Respiratory sensitization	Classification not possible	-	-	-	No data
4	Skin sensitization	Classification not possible	-	-	-	ACGIH (7th, 2001) and HSDB (2006) had description of the case report of allergic contact dermatitis, however, both of which were considered to be the same description of one case and did not have the report of two or more cases which is a judging standard of skin sensitization, and we thought the data was insufficient, therefore we presupposed that we could not classify it.
5	Germ cell mutagenicity	Classification not possible	-	-	-	Classification not possible due to lack of data
6	Carcinogenicity	Not classified	-	-	-	Since it was classified into A4 in ACGIH (ACGIH 7th, 2001), it was considered as the outside of Category.
7	Reproductive toxicity	Not classified	-	-	-	It was considered as out of Category based on the description that clear reproductive toxicity was not observed at the dose as which general toxicity is observed in parent animals in the test administered orally before mating till the term pregnancy using rat (MOE Risk Assessment 4th volume (2005), ACGIH (7th, 2001), and EHC 111 (1991)).
8	Specific target organ toxicity – Single exposure	Classification not possible	-	-	-	Insufficient data available.
9	Specific target organ toxicity – Repeated exposure	Not classified	-	-	-	We classified it into Out Of Category based on the description that in the oral study using the rat, the serious toxic effect was not observed with the dose which exceeds the guidance value range of Category 2 (MOE Risk Assessment The 4th volume (2005), EHC 111 (1991), DFGOT (vol.2, 1991) and ACGIH (7th, 2001)).
10	Aspiration hazard	Classification not possible	-	-	-	No data available

ENVIRONMENTAL HAZARDS

	Hazard class	Classification	Symbol	Signal word	Hazard statement	Rationale for the classification
11	Hazardous to the aquatic environment (Acute)	Category 1	Environment	Warning	Very toxic to aquatic life	It was classified into Category 1 from 96-hour LC50=0.18-0.32mg/L of Crustacea (Mysid shrimp) (EHC111, 1991).
11	Hazardous to the aquatic environment (Long-term)	Category 1	Environment	Warning	Very toxic to aquatic life with long lasting effects	Classified into Category 1, since acute toxicity is Category 1, and supposedly bioaccumulative (log Kow=4.59(PHYSPROP Database, 2005)), though rapidly degrading (BOD: 90% (existing chemical substances safety inspections data)).

Greenscreen scores from NITE*

108-95-2.json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*Wehage, K., Chenhansa, P. and Schoenung, J. M. (2017), An open framework for automated chemical hazard assessment based on GreenScreen for Safer Chemicals: A proof of concept. Integr Environ Assess Manag, 13: 167–176


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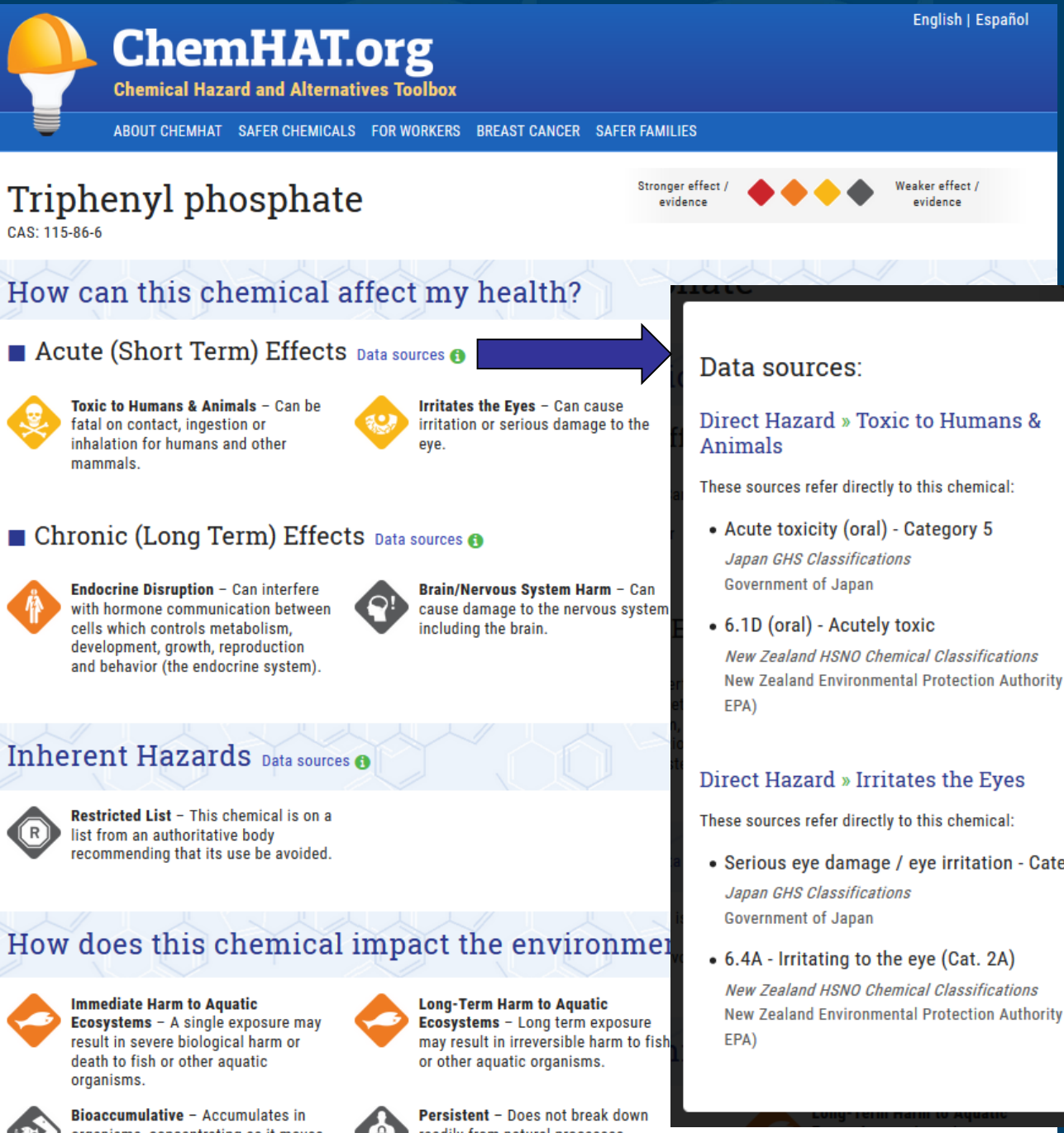
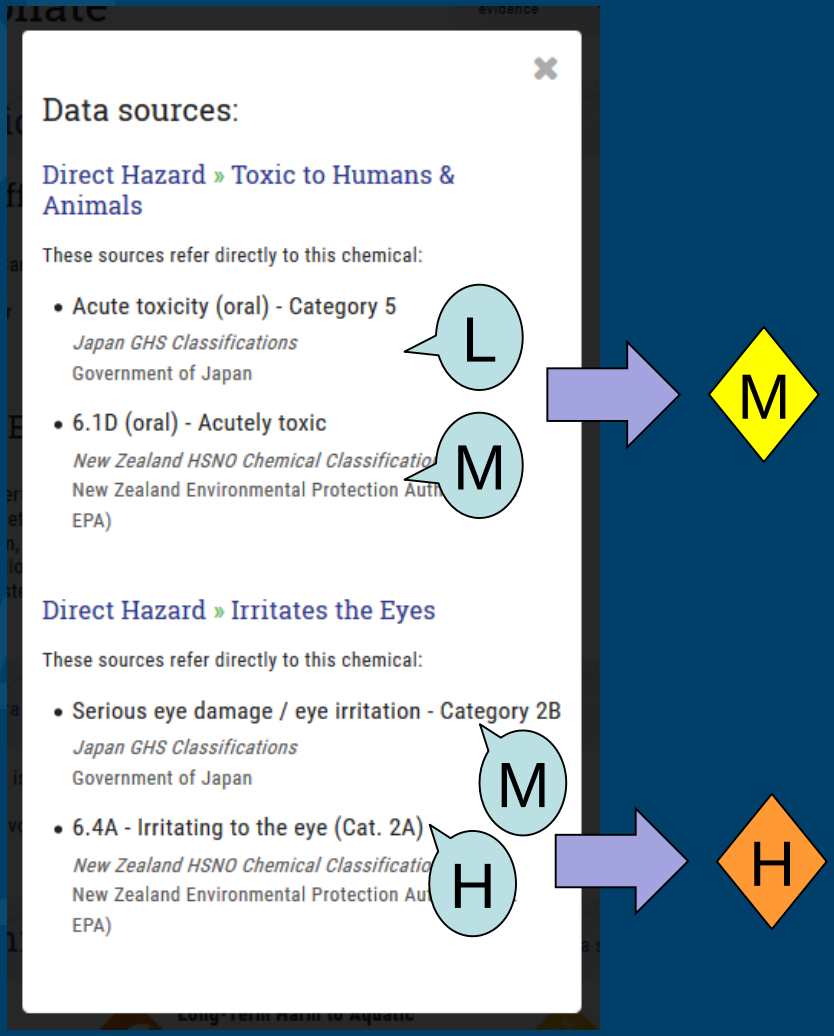

ChemHAT.org
Chemical Hazard and Alternatives Toolbox
English | Español
ABOUT CHEMHAT
SAFER CHEMICALS
FOR WORKERS
BREAST CANCER
SAFER FAMILIES
Triphenyl phosphate
CAS: 115-86-6
Stronger effect / evidence
Weaker effect / evidence
How can this chemical affect my health?
Acute (Short Term) Effects
Data sources
Toxic to Humans & Animals – Can be fatal on contact, ingestion or inhalation for humans and other mammals.
Irritates the Eyes – Can cause irritation or serious damage to the eye.
Chronic (Long Term) Effects
Data sources
Endocrine Disruption – Can interfere with hormone communication between cells which controls metabolism, development, growth, reproduction and behavior (the endocrine system).
Brain/Nervous System Harm – Can cause damage to the nervous system including the brain.
Inherent Hazards
Data sources
Restricted List – This chemical is on a list from an authoritative body recommending that its use be avoided.
How does this chemical impact the environme
Immediate Harm to Aquatic Ecosystems – A single exposure may result in severe biological harm or death to fish or other aquatic organisms.
Long-Term Harm to Aquatic Ecosystems – Long term exposure may result in irreversible harm to fish or other aquatic organisms.
Bioaccumulative – Accumulates in organisms, concentrating as it moves up the food chain.
Persistent – Does not break down readily from natural processes.
Data sources:
Direct Hazard » Toxic to Humans & Animals
These sources refer directly to this chemical:
Acute toxicity (oral) - Category 5
Japan GHS Classifications
Government of Japan
6.1D (oral) - Acutely toxic
New Zealand HSNO Chemical Classifications
New Zealand Environmental Protection Authority (NZ EPA)
Direct Hazard » Irritates the Eyes
These sources refer directly to this chemical:
Serious eye damage / eye irritation - Category 2B
Japan GHS Classifications
Government of Japan
6.4A - Irritating to the eye (Cat. 2A)
New Zealand HSNO Chemical Classifications
New Zealand Environmental Protection Authority (NZ EPA)

GHS Scores from ChemHAT

Priority	Source	Acute Tox Score VH	H	M	L
1	EU_H	H300	H301	H302	
2	EU_R	R28	R25	R22	
3	New Zealand	6.1A, 6.1B	6.1C	6.1D	6.1E
4	Japan (NITE)	Cat 1, Cat 2	Cat 3	Cat 4	Cat 5
5	Australia	H300	H301	H302	
6	Korea	H300	H301	H302	
7	Malaysia	H300	H301	H302	
8	WHMIS-SIMDUT	D1A	D1B		

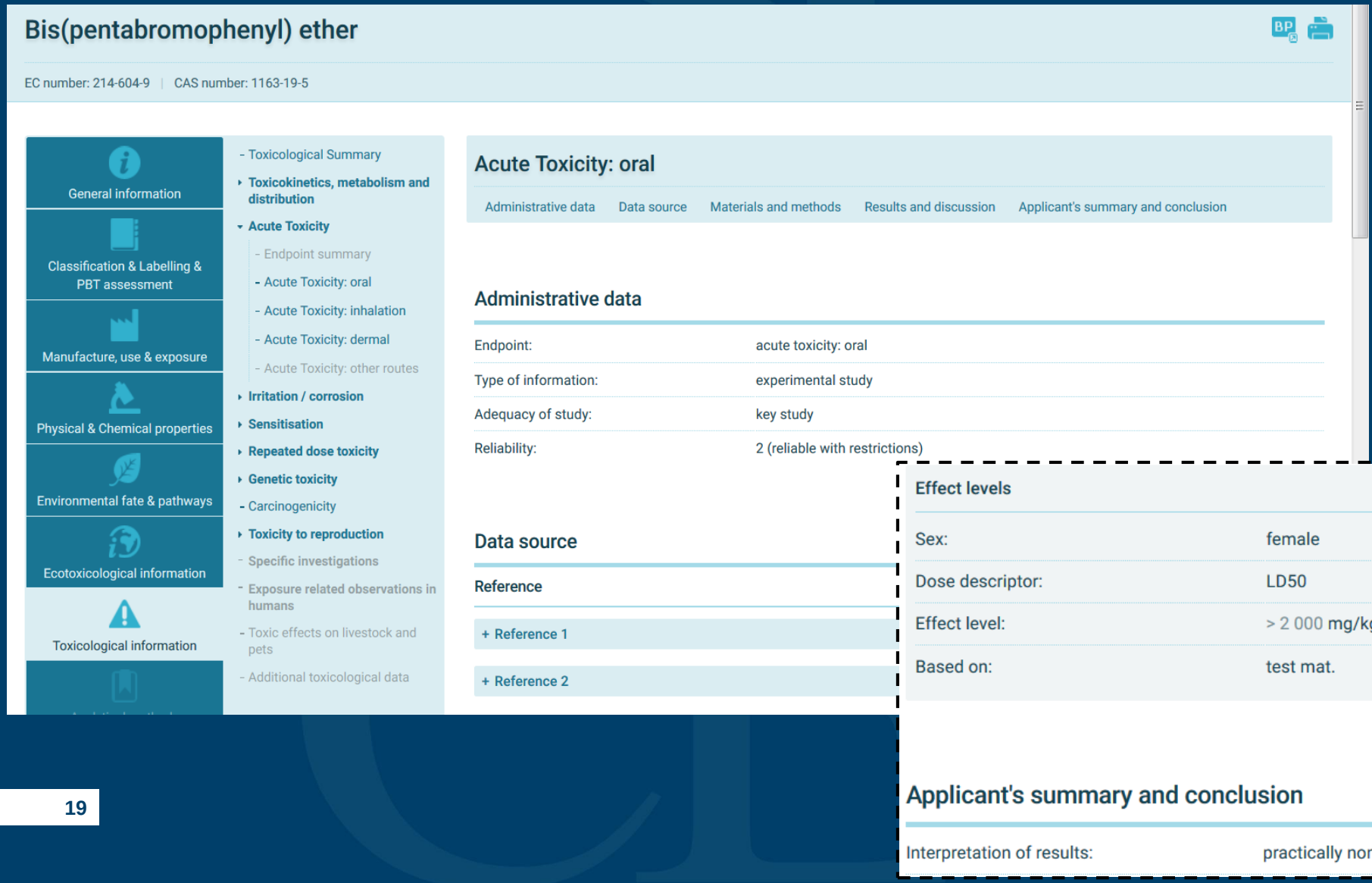
cha Priority	Source	Eye Irritation Score VH	H	M	L
1	EU_H	H318	H319	H320	
2	EU_R	R41	R36		
3	New Zealand	Cat 1	Cat 2A		
4	Japan (NITE)	Cat 1	Cat 2, Cat 2A	Cat 2B	
5	Australia	H318	H319	H320	
6	Korea	H318	H319	H320	
7	Malaysia	H318	H319	H320	



Sources of acute toxicity data in ChemHat

Source	# chemicals
EU H Score	1631
EU R Score	1498
New Zealand	1402
Japan	877
Australia	1626
Korea	567
Malaysia	138
WHMIS-SIMDUT	378
All sources	**2873**

ECHA (REACH dossiers)



Bis(pentabromophenyl) ether

EC number: 214-604-9 | CAS number: 1163-19-5

- General information
- Classification & Labelling & PBT assessment
- Manufacture, use & exposure
- Physical & Chemical properties
- Environmental fate & pathways
- Ecotoxicological information
- Toxicological information

- Toxicological Summary
- **Toxicokinetics, metabolism and distribution**
- **Acute Toxicity**
  - Endpoint summary
  - Acute Toxicity: oral
  - Acute Toxicity: inhalation
  - Acute Toxicity: dermal
  - Acute Toxicity: other routes
- **Irritation / corrosion**
- **Sensitisation**
- **Repeated dose toxicity**
- **Genetic toxicity**
- Carcinogenicity
- **Toxicity to reproduction**
- Specific investigations
- Exposure related observations in humans
- Toxic effects on livestock and pets
- Additional toxicological data

Acute Toxicity: oral

Administrative data | Data source | Materials and methods | Results and discussion | Applicant's summary and conclusion

Administrative data

Endpoint:	acute toxicity: oral
Type of information:	experimental study
Adequacy of study:	key study
Reliability:	2 (reliable with restrictions)

Data source

Reference

+ Reference 1

+ Reference 2

Effect levels

Sex:	female
Dose descriptor:	LD50
Effect level:	> 2 000 mg/kg bw
Based on:	test mat.

Applicant's summary and conclusion

Interpretation of results:	practically nontoxic

REACH Field Mapping

GHS Category	Link in REACH dossier
Acute Toxicity	Acute Toxicity: oral / inhalation / dermal
Carcinogenicity	Carcinogenicity
Genotoxicity / Mutagenicity	Genetic toxicity: in vitro / in vivo
Endocrine Disruption	N/A
Reproductive	Toxicity to reproduction
Developmental	Developmental toxicity / teratogenicity
Neurological	Neurotoxicity
Repeated Dose	Repeated dose toxicity: oral / inhalation / dermal
Skin Sensitization	Skin sensitisation
Eye Irritation	Eye irritation
Dermal Irritation	Skin irritation / corrosion
Acute aquatic	Short-term toxicity to fish
Chronic aquatic	Long-term toxicity to fish
Persistance	Biodegradation in water: screening tests
Bioaccumulation	Bioaccumulation: aquatic / sediment

EPA United States Environmental Protection Agency

Comparison of flame retardants

Tool / Study	CAS / Name	Human Health Effects										Ecotox.		Fate	
		Acute Toxicity	Carcinogenicity	Genotoxicity / Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistance	Bioaccumulation
T.E.S.T.	1163-19-5 DecaBDE	M		L	nd		nd						L		VH	L
ChemHAT			H	H	VH		VH	VH	H		M	L			VH	H
NITE		L	L	M		L	L		H	L	M	M	L			
ECHA		L	L	L		L	L		L	L	L	L	L	L	VH	L
DfE		L	M	L	nd	L	H	L	M	L	L	L	L	L	VH	H
Green Screen		L	M	L	M	L	M	M	L	L	L	L	L	L	VH	M
T.E.S.T.	115-86-6 TPP	L		L	nd		H						VH		H	M
ChemHAT		M			H						H		VH	VH	M	M
NITE		L	L			L	L				M	L	VH			
ECHA		L	L	L		L	L	L	L	L	M	L	VH	H	L	M
DfE		L	M	L	nd	L	L	L	H	L	L	VL	VH	VH	L	M
Green Screen		L	L	L	nd	L	L	L	M	L	M	L	H	H	L	M
T.E.S.T.	57583-54-7 RDP	L		L	nd		nd						VH		VH	L
ChemHAT																
NITE																
ECHA		L	L	L		L	L	L		L	L	L	L	L	L	M
DfE		L	M§	L	nd	L	M	M	M	L	L	VL	VH	VH	M	H
Green Screen		L	L	L	nd	L	L	L	M	L	M	L	L	H	M	H
T.E.S.T.	5945-33-5 BPADP	L		L	nd		nd						L		VH	L
ChemHAT														L		
NITE																
ECHA																
DfE		L	M	L	nd	L	L§	L§	L	L	L	L	L	L	H	H
Green Screen		L	L	L	nd	L	L	L	M	L	M	L	L	L	H	L

Not available

Not implemented

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Questions???

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