Madia et al.:

Making Better Use of Toxicity Studies for Human Health by Extrapolating across Endpoints

Supplementary Data

Tab. S1: Common target organ toxicities in chemicals with acute oral toxic and/or STOT RE/SE classification

Compound	[a]Annex VI (acute oral toxicity)	[a]Annex VI (STOT)	[b]CLP inventory (notifications)	[c]Specific mechanisms contributing to acute oral toxicity
(4-ammonio-m-tolyl) ethyl(2-hydroxyethyl) ammonium sulphate	Acute Tox. 3 H301	STOT RE 2	**Kidney**	**Kidney toxicity**: alterations in cell viability (necrosis of tubular epithelium)
1,2,3,4-tetrachlorobenzene	n.a.	n.a.	Oral Acute Tox. 4	n.a.
1,2,4-trichlorobenzene	Acute Tox. 4 H302	n.a.	n.a.	n.a.
1,2-dichlorobenzene	Acute Tox. 4 H302	STOT SE 3	Respiratory tract by inhalation	n.a.
17a-ethynylestradiol	n.a.	n.a.	STOT RE 1 (damage to organs)	Liver: disturbance of normal bile acid secretion
1-naphthylamine	Acute Tox. 4 H302	n.a.	n.a.	Toxicity of the blood: oxidation of the oxygen carrying iron molecule to Fe^{3+}
1-phenyl-2-thiourea	n.a.	n.a.	n.a.	Lung toxicity: pulmonary endothelium damage
1-phenyl-3-pyrazolidone	Acute Tox. 4 H302	n.a.	n.a.	n.a.
2,4,6 tris (dimethylaminomethyl) phenol	Acute Tox. 4 H302	n.a.	n.a.	n.a.
2,4-dichlorophenoxyacetic acid	Acute Tox. 4 H302	STOT SE 3	Lungs	n.a.
2,6-diethylaniline	Acute Tox. 4 H302	n.a.	n.a.	n.a.
2-chloro-4-nitroaniline	Acute Tox. 4 H302	n.a.	n.a.	n.a.
2-phenoxyethanol	Acute Tox. 4 H302		*STOT SE 3 (lung)* in some notifications	n.a.
5,5-diphenylhydantoin	n.a.	n.a.	STOT RE 1 (liver, **nervous system**, gums, lymph node); STOT RE 1 (liver); STOT SE 1 (**nervous system**)	**Cardiovascular toxicity**: interference with sodium and/or potassium channels; **nervous system**: interaction with membrane ion channels (Na^+, K^+, Cl^-, Ca^{2+})
5-fluorouracil	n.a.	n.a.	S*TOT SE 3 (respiratory tract)*	GI: inflammation of the mucosa
acetaldehyde	not classified	STOT SE 3	Reasons for not classifying for acute oral: data lacking, conclusive but not sufficient for classification. STOT SE 3 Inhalation (respiratory tract); STOT SE 3 (respiratory tract);	n.a.

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Compound	[a]Annex VI (acute oral toxicity)	[a]Annex VI (STOT)	[b]CLP inventory (notifications)	[c]Specific mechanisms contributing to acute oral toxicity
acetonitrile	Acute Tox. 4 H302	n.a.	Some notifications indicate *STOT SE 3 (CNS, respiratory system); STOT RE 2 (blood system, CNS and kidneys); STOT SE 3 Inhalation (respiratory tract irritation); STOT SE 2 (stomach, kidney, lung)*	n.a.
acetophenone	Acute Tox. 4 H302	n.a.	n.a.	n.a.
acetylsalicylic acid	n.a.	n.a.	*STOT SE 3 (lungs); STOT SE 2 (stomach, **kidney**, lung); STOT RE 2 (liver, blood (system), **CNS**, auditory system)*	**Kidney**: deficiency vasodilators (PG2), interstitial nephritis; **CNS**: uncouples mitochondrial oxidative phosphorylation and also inhibits Krebs cycle dehydrogenases at CNS level
aconitine	Acute Tox. 2 H300	n.a.	n.a.	Cardiovascular toxicity: interference with Ca^{2+} channels; neurotoxicity: interaction with membrane ion channels (Na^+, K^+, Cl^-, Ca^{2+}), interference with transporter enzymes (e.g. Na^+-K^+-ATPase)
acrylaldehyde	Acute Tox. 2 H300	n.a.	Some notifications indicate: *STOT RE 1 by oral (respiratory system, gastrointestinal tract); STOT RE 1 by inhalation (respiratory system, gastrointestinal tract); STOT SE 3 (respiratory tract)*	n.a.
acrylamide	Acute Tox. 2 H300	STOT RE 1	**(PNS)**	**Neurotoxicity: PNS,** peripheral neuropathy/ polyneuropathy - axonopathy: blocking neuro-filament transport via cross linking of neuro-filaments; Neuro-filament filled swelling of proximal axon
aminopterin	n.a.	n.a.	Oral: some notifications indicate Acute Tox. 2	n.a.
amitriptyline hydrochloride	n.a.	n.a.	Some notifications indicate STOT SE 1 (CNS), STOT SE 3 (lung, inhalation)	Cardiovascular toxicity: interference with sodium and/or potassium channels; prevention of the reuptake of heart noradrenaline
ammonium chloride	Acute Tox. 4 H302	n.a.	n.a.	Kidney toxicity: interference with ion balance
arsenic trioxide	Acute Tox. 2 H300	n.a.	n.a.	n.a.
atropine sulfate monohydrate	n.a.	n.a.	Oral: notifications indicate Acute Tox. 2 or Acute Tox. 4	Cardiovascular toxicity: mimic/block parasympathetic activity. Neurotoxicity: blockage of the action of acetylcholine at muscarinic receptors
barium Chloride	Acute Tox. 3 H301	n.a.	n.a.	Cardiovascular toxicity: interference with sodium and/or potassium channels. Gastrointestinal toxicity: interference with potassium channels. Liver toxicity: fat accumulation in hepatocytes
benzaldehyde	Acute Tox. 4 H302	n.a.	Some notifications indicate *STOT SE 3 (lungs, respiratory tract, inhalation)*	n.a.
benzyl benzoate	Acute Tox. 4 H302	n.a.	n.a.	n.a.
brucine	Acute Tox. 2 H300	n.a.	n.a.	Neurotoxicity: antagonist at the glycine receptor. Kidney toxicity: arteriolar vasoconstriction indirect effect by rhabdomyolysis; necrosis of tubular epithelium

Compound	[a]Annex VI (acute oral toxicity)	[a]Annex VI (STOT)	[b]CLP inventory (notifications)	[c]Specific mechanisms contributing to acute oral toxicity
busulfan	n.a.	n.a.	Oral: several notifications indicate Acute Tox. 3 and others Acute Tox. 2. STOT SE 3 (respiratory tract)	n.a.
cadmium chloride	Acute Tox. 3 H301	STOT RE 1	**Lungs** (oral)	**Lung toxicity:** destruction of Type I epithelial cells. Kidney toxicity: alterations in tubule cell structure (accumulation in cells of proximal tubular cells); alterations in cell viability (necrosis of tubular epithelium)
caffeine	Acute Tox. 4 H302	n.a.	n.a.	Cardiovascular toxicity: interference with adenosine receptors. Neurotoxicity: competitive antagonism of cellular adenosine receptors
carbon tetrachloride	Acute Tox. 3 H301	STOT RE 1	**Liver**, kidneys	**Liver toxicity**: lipid peroxidation
chloral hydrate	Acute Tox. 3 H301	n.a.	n.a.	Neurotoxicity: inhibition of the dopamine transporter; attenuation of glutamate release and reduction of activation of glutamate receptors
chloroform	Acute Tox. 4 H302	STOT RE 1	STOT SE 3 (**CNS** by inhalation) STOT RE 1 (liver, kidneys by inhalation)	Lung toxicity: inflammation **Neurotoxicity**: interference at the level of GABAA receptors
chloroquine bis(phosphate)	n.a.	n.a.	Oral: Acute Tox. 4 H373; STOT RE 2; STOT SE 3	Cardiovascular toxicity: stabilization of cell membrane leading to reduced excitation and conduction
chlorpromazine hydrochloride	n.a.	n.a.	Oral: Acute Tox. 3, Acute Tox. 2; STOT SE 3 (respiratory tract)	n.a.
cis-diammineplatinum(II) dichloride	n.a.	n.a.	Oral: Acute Tox. 3, Acute Tox. 2; STOT SE 3 (respiratory tract, inhalation); STOT SE 1 (**kidney**, bone marrow); STOT RE 1 (**kidney**, bone marrow)	**Kidney toxicity**: accumulation in cells of proximal tubular cells; impaired Na^+ and water reabsorption; generation of inflammatory and vasoactive mediators
codeine	n.a.	n.a.	Oral: Acute Tox. 3, Acute Tox. 4	Kidney toxicity: arteriolar vasoconstriction indirect effect by rhabdomyolysis. Neurotoxicity: blocking the release of inhibitory neurotransmitters such as GABA and acetylcholine
colchicine	Acute Tox. 2 H300	n.a.	One notification indicates STOT SE 2 (respiratory tract)	Gastrointestinal tract toxicity: epithelial cell damage. Neurotoxicity: axonopathy - inhibition of microtubule formation via binding to tubulin
copper sulphate	Acute Tox. 4 H302	n.a.	Notifications indicate: *STOT RE 2 (lungs by inhalation);* *STOT SE 1 (no data about organs);* *STOT SE 3 (respiratory tract)*	Blood toxicity: lysis of cells
cupric sulfate pentahydrate	Acute Tox. 4 H302	n.a.	Notifications indicate: *STOT RE 2 (lungs by inhalation);* *STOT SE 1 (no data about organs);* *STOT SE 3 (respiratory tract)*	n.a.
cycloheximide	Acute Tox. 2 H300	n.a.	n.a.	n.a.

Compound	[a]Annex VI (acute oral toxicity)	[a]Annex VI (STOT)	[b]CLP inventory (notifications)	[c]Specific mechanisms contributing to acute oral toxicity
cyclosporine A	n.a.	n.a.	Oral: Acute Tox. 4; STOT RE 1 (liver, **kidney**, immune system)	**Kidney toxicity**: endothelial damage with increase in vasoconstrictors
D-amphetamine sulphate	n.a.	n.a.	Oral: Acute Tox. 2 and Acute Tox. 3	Neurotoxicity: slowing down catecholamine metabolism by inhibiting monoamine oxidase; stimulation of the release of norepinephrine and dopamine from stores in adrenergic nerve terminals; direct stimulation of α- and β-adrenergic receptors
diallyl phthalate	Acute Tox. 4	n.a.	n.a.	n.a.
diazepam	n.a.	n.a.	*STOT SE 3 (respiratory tract, inhalation);* *STOT RE 2*	Nervous system: down-regulation of GABA receptors
dichlorvos	Acute Tox. 3 H301	n.a.	n.a.	Lung toxicity: increase capillary permeability. Neurotoxicity: inhibition of acetylcholinesterase and accumulation of acetylcholine.
diethylene glycol	Acute Tox. 4 H302		Notifications indicate: STOT RE 2 (**kidney**, oral)	**Kidney** toxicity: tubular obstruction - Distal cast formation
digoxin	n.a.	n.a.	*STOT RE 1;* *STOT RE 2 (oral and inhalation);* *STOT RE 2 (respiratory tract);* *STOT RE 2 (**heart**)*	**Cardiovascular system**: mimic substrate/block transporter enzymes such as Na^+-K^+-ATPase
diphenhydramine hydrochloride	n.a.	n.a.	Oral: Acute Tox. 4; STOT SE 3 (respiratory system)	Neurotoxicity: blockade of the H1-receptors
diquat dibromide	Acute Tox. 4 H302	STOT SE 3 STOT RE 1	STOT SE 3 (respiratory tract), STOT RE 1 (eyes, skin, kidneys, liver, central nervous system)	n.a.
disopyramide	n.a.	n.a.	Oral: Acute Tox. 4	Neurotoxicity: anticholinergic effects. Cardiovascular toxicity: interference with sodium and/or potassium channels
disulfoton	Acute Tox. 2 H300	n.a.	n.a.	Neurotoxicity: inhibition of acetylcholinesterase and accumulation of acetylcholine
endosulfan	Acute Tox. 2 H300	n.a.	n.a.	Neurotoxicity: antagonizing chloride ion transport in GABA receptors. Kidney toxicity: arteriolar vasoconstriction indirect effect by rhabdomyolysis
epinephrine bitartrate	n.a.	n.a.	STOT SE 3 (respiratory system); STOT RE 2 (**heart**, lungs)	**Cardiovascular system**: activation of β1-adrenergic receptors, β2-adrenergic
ethoxyquin	Acute Tox. 4 H302	n.a.	n.a.	n.a.
ethyl chloroacetate	Acute Tox. 3 H301	n.a.	n.a.	n.a.
ethylene glycol	Acute Tox. 4 H302	n.a.	Notifications indicate: STOT RE 2 (kidney, oral). In few others STOT SE 3 (CNS); STOT SE 1; STOT RE 1 (heart, CNS, **respiratory organs**)	**Lung** toxicity: deposits of calcium oxalate crystals in lung parenchyma
fenpropathrin	Acute Tox. 3 H301	n.a.	n.a.	Neurotoxicity: interaction with membrane ion channels (Na^+, K^+, Cl^-, Ca^{2+})
formaldehyde	Acute Tox. 3 H301	n.a.	In several notifications: STOT SE 3 (lungs)	Gastrointestinal toxicity: formation of metabolite (formic acid) at the place of contact

Compound	[a]Annex VI (acute oral toxicity)	[a]Annex VI (STOT)	[b]CLP inventory (notifications)	[c]Specific mechanisms contributing to acute oral toxicity
glufosinate ammonium	Acute Tox. 4 H302	STOT RE 2	Organs not specified	Neurotoxicity: interference with neurotransmitters/ neurotransmission (inhibition of glutamine synthetase and glutamate decarboxylase); interference at level of receptor (glutamate receptor activation)
glutethimide	n.a.	n.a.	Oral: Acute Tox. 4	n.a.
haloperidol	n.a.	n.a.	*STOT SE 3 (respiratory tract and inhalation, **nervous system**)*	Heart: QT interval prolongation; **nervous system**: competitive blockade of postsynaptic dopamine (D2) receptors
hexachlorophene	Acute Tox. 3 H301	n.a.	n.a.	n.a.
iron (II) sulfate	Acute Tox. 4 H302	n.a.	n.a.	Gastrointestinal toxicity: corrosion/irritation of the mucosa
isoniazid	n.a.	n.a.	Oral: Acute Tox. 4; STOT SE 3 (lungs, inhalation); STOT SE 2 (**nervous system**, kidney, **liver**); STOT RE 2 (**liver, CNS**)	**Neurotoxicity**: depletion of γ-aminobutyric acid (GABA). **Liver** toxicity: membrane disruption and/or interference with macromolecules
lindane	Acute Tox. 3 H301	STOT RE 2	Organs not specified	Neurotoxicity: interference at level of receptor - blockade of the GABA-receptor coupled sodium channel; Impaired propagation of electrical activity - interference with the normal flux of Na^+ and K^+ ions across the axon membrane as nerve impulses pass
lithium carbonate	n.a.	n.a.	Oral: Acute Tox. 4; STOT SE 3 (respiratory system); STOT RE 1 (CNS, **kidney**, heart, thyroid); STOT SE 2 (liver, **kidney**, CNS); STOT RE 2 (**kidney,** CNS)	**Kidney** toxicity: interaction with renal V2-vasopressin receptor; glumerulonephritis
lithium sulfate	n.a.	n.a.	Oral: Acute Tox. 4; STOT SE 3 (respiratory system); STOT RE 1 (CNS, **kidney**, heart, thyroid); STOT SE 2 (liver, **kidney**, CNS); STOT RE 2 (**kidney,** CNS)	**Kidney** toxicity: interaction with renal V2-vasopressin receptor; glomerulonephritis
malathion	Acute Tox. 4 H302	n.a.	n.a.	n.a.
maleic acid	Acute Tox. 4 H302	STOT SE 3	Lungs (inhalation)	n.a.
malononitrile	Acute Tox. 3 H301		One notification indicates *STOT SE 3 (respiratory tract, inhalation); STOT SE 1 (CNS, cardiovascular system)*	n.a.
maprotiline	n.a.	n.a.	Oral: Acute Tox. 4	Neurotoxicity: selective norepinephrine re-uptake blockade
meprobamate	n.a.	n.a.	Oral: Acute Tox. 4	Neurotoxicity: interaction with GABAA receptors in a barbiturate-like fashion; inhibition of NMDA receptors
mercury chloride	Acute Tox. 2 H300	STOT RE 1	Organs not specified	Kidney toxicity: alterations in tubule cell structure (accumulation in cells of proximal tubular cells); alterations in cell viability (necrosis of tubular epithelium)

Compound	[a]Annex VI (acute oral toxicity)	[a]Annex VI (STOT)	[b]CLP inventory (notifications)	[c]Specific mechanisms contributing to acute oral toxicity
methadone hydrochloride	n.a.	n.a.	*STOT SE 3* (**CNS**)	**CNS**: NMDA antagonism and inhibition of serotonin/norepinephrine reuptake
methanol	Acute Tox. 3 H301	STOT SE 1	Optic nerve (*nervous opticus*), central nervous system, kidneys, liver and heart, lungs, respiratory tract, skin	n.a.
nicotine	Acute Tox. 2 H300	n.a.	n.a.	Neurotoxicity: agonist at nicotinic cholinergic receptors
N-isopropyl-N'-phenyl-p-phenylenediamine	Acute Tox. 4 H302	n.a.	n.a.	Blood toxicity: interference with haemoglobin
ochratoxin A	n.a.	n.a.	Oral: Acute Tox. 2 *STOT RE 2 (liver, **kidney**)*	Immune system: degenerative changes in combination with slow replacement of affected immune cells due to inhibition of protein synthesis; **kidney**: loss of tubular epithelial barrier and/or tight junctions
octyl 3,4,5-trihydroxybenzoate	Acute Tox. 4 H302	n.a.	n.a.	n.a.
orphenadrine hydrochloride	n.a.	n.a.	Oral: Acute Tox. 3	Neurotoxicity: competitive antagonism of acetylcholine at the neuro-receptor site
paraldehyde	NC	n.a.	Oral: *conclusive but not sufficient for classification (joint entries). Acute Tox. 4, one notification*	Neurotoxicity: impairment of the propagation of electrical activity. Gastrointestinal tract toxicity: inflammation of the GI mucosa
paraquat dichloride	Acute Tox. 3 H301	STOT SE 3 STOT RE 1	STOT SE 3 (**lungs**) STOT RE 2 (**lungs**)	**Lung toxicity**: intra-alveolar haemorrhage
parathion	Acute Tox. 2 H300	STOT RE 1	Organs not specified	Neurotoxicity: neurotransmitter clearance from synaptic cleft - Inhibition of acetylcholinesterase and accumulation of acetylcholine
p-benzoquinone	Acute Tox. 3 H301	STOT SE 3	Lungs, respiratory tract by inhalation; eyes, skin	n.a.
pentachlorobenzene	Acute Tox. 4 H302	n.a.	n.a.	n.a.
pentachlorophenol	Acute Tox. 3 H301	STOT SE 3	Respiratory tract irritation, lungs	n.a.
phenanthrene	n.a.	n.a.	Oral Acute Tox. 4; STOT SE 3 (lungs)	n.a.
phenobarbital	n.a.	n.a.	*STOT SE 3*	CNS: interference at level of GABAA receptors
phenol	Acute Tox. 3 H301	STOT RE 2	Kidney, liver, skin, **CNS**, blood vessels, lungs, heart, muscle, eyes	**Neurotoxicity:** neurotransmitter clearance from synaptic cleft - Increased acetylcholine release at the neuromuscular junction
phthalic anhydride	Acute Tox. 4 H302	STOT SE 3	Eyes, kidneys, liver, respiratory system, skin, lungs	n.a.
physostigmine	Acute Tox. 2 H300	n.a.	n.a.	Neurotoxicity: inhibition of acetylcholinesterase and accumulation of acetylcholine
potassium cyanide	n.a.	n.a.	*STOT RE 1 (thyroid gland)*; *STOT SE 1 (**CNS**, heart, cardio-vascular system), STOT RE 1 (**CNS**, heart, cardio-vascular system); STOT SE 1 (**brain**, heart, testes), STOT RE 1 (thyroid gland)*	**CNS**: stimulation of glutamate release which can activate glutamate receptors to initiate excito-toxic processes
procainamide hydrochloride	n.a.	n.a.	*STOT SE 3 (lungs, respiratory tract, inhalation)*	Heart: interference with Na^+ and/or K^+ channels
propranolol hydrochloride	n.a.	n.a.	Oral: Acute Tox. 4	Cardiovascular toxicity: pronounced negative chronotropic and inotropic effect and a quinidine-like effect

Compound	[a]Annex VI (acute oral toxicity)	[a]Annex VI (STOT)	[b]CLP inventory (notifications)	[c]Specific mechanisms contributing to acute oral toxicity
quinidine sulfate dihydrate	n.a.	n.a.	Oral: Acute Tox. 4	Blood toxicity: quinidine sulfate dehydrate immune-mediated destruction. Cardiovascular toxicity: interference with Na^+ and/or K^+ channels. Neurotoxicity: anticholinergic effects
resorcinol	Acute Tox. 4 H302	n.a.	Notifications indicate *STOT SE 2 (respiratory effects, oral),* *STOT SE 1 (CNS and **blood effects**, Oral)*	**Toxicity of the blood**: oxidation of the oxygen carrying iron molecule to Fe^{3+}
rifampicin	n.a.	n.a.	*STOT SE 3 (lungs, respiratory system, inhalation)*	Blood toxicity: binding to cell (antigen) triggers immune-mediated destruction
sodium arsenite	n.a.	n.a.	*STOT RE 1 (CNS, respiratory system, skin)*	n.a.
sodium cyanate	Acute Tox. 4 H302	n.a.	n.a.	n.a.
sodium dichromate dihydrate	n.a.	n.a.	*STOT RE 1*	n.a.
sodium fluoride	Acute Tox. 3 H301	n.a.	Notifications indicate: *STOT RE 1 (bone, teeth, gastrointestinal tract, oral).* *STOT SE 1 (cardiac vascular system, muscular system, CNS, metabolic),* *STOT RE 1 (metabolic, skeleton and bones)*	n.a.
sodium lauryl sulfate	n.a.	n.a.	*STOT SE 3 respiratory tract, inhalation*	n.a.
sodium oxalate	n.a.	n.a.	S*TOT SE 3 (respiratory system, inhalation)*	Kidney: crystal deposition and tubular obstruction
sodium pentobarbital	n.a.	n.a.	Oral: Acute Tox. 3, Acute Tox. 4	Neurotoxicity: GABAA receptor agonist
sodium salt of chloroacetic acid	Acute Tox. 3 H301	n.a.	Few notifications: *STOT RE 2 (kidney, liver, oral)*	n.a.
sodium selenate	n.a.	n.a.	*STOT RE 2*	n.a.
sodium valproate	n.a.	n.a.	*STOT SE 3 (respiratory system).* *STOT SE 3 (lung)*. One notification *STOT SE 3 (respiratory system),* *STOT SE 2 (liver, oral)*	CNS: increase of GABA by indirect mechanisms involving inhibition of the enzyme succinate semi-aldehyde dehydrogenase in the GABA shunt
strychnine	Acute Tox. 2 H300	n.a.	n.a.	Neurotoxicity: antagonist at the glycine receptor
tert-butyl hydroperoxide	NC	n.a.	Joint entries indicate harmful if *swallowed: Acute Tox. 4*. Some notifications indicate toxic if *swallowed Acute Tox. 3*. Some notifications: *STOT SE 3 (respiratory tract)*	n.a.
tetramethylthiuram monosulphide	Acute Tox. 4 H302	n.a.	Some joint entries and notifications *STOT RE 2 (liver)*	n.a.
thallium sulphate	Acute Tox. 2 H300	STOT RE 1	Organs not specified	Cardiovascular toxicity: interference with ion balance/signalling/ membrane potential of cell - mimic substrate/block transporter enzymes such as Na^+-K^+-ATPase; Interference with Na^+ and/or K^+ channels. Neurotoxicity: impaired propagation of electrical activity - Interference with transporter enzymes (e.g. Na^+-K^+-ATPase) (mimic substrate/block)

Compound	[a]Annex VI (acute oral toxicity)	[a]Annex VI (STOT)	[b]CLP inventory (notifications)	[c]Specific mechanisms contributing to acute oral toxicity
theophylline	n.a.	n.a.	*STOT SE 3*	CNS: interference at level of receptor; GI: enzyme activation
thioridazine hydrochloride	n.a.	n.a.	*STOT SE 3 (lungs, respiratory tract)*	Heart: QT interval prolongation; CNS: blockage of dopamine D2 receptor
triethanolamine	n.a.	n.a.	*Joint entries not classified*. Some notifications: Acute *Tox. 4 and STOT RE 2; STOT SE 3 (respiratory irritation, inhalation); STOT SE 3 (eyes and skin) (respiratory system)*;	n.a.
triethylene glycol dimethacrylate	n.a.	n.a.	Joint entries report *conclusive but not sufficient for classification*. Some notifications indicate *STOT SE 3 (Lungs, respiratory tract)*	n.a.
triethylenemelamine	n.a.	n.a.	n.a.	Immune system: changes in bone marrow cell proliferation; decrease in whole blood cell counts or subpopulations
triphenyltin hydroxide	Acute Tox. 3 H301	STOT SE 3	Organs not specified	Immune system: decrease in whole blood cell counts or subpopulations
valproic acid	n.a.	n.a.	Oral: Acute Tox. 4; STOT SE 3 (may cause respiratory irritation)	Neurotoxicity: inhibition of the reuptake of GABA into the glia and nerve endings; interference at the level of GABAA receptors
verapamil hydrochloride	n.a.	n.a.	*STOT SE 3 (lung, respiratory tract)*	n.a.
warfarin	Acute Tox. 2 H300	STOT RE 1 (blood)	STOT RE 1 (**blood**, hematopoietic system)	**Toxicity of the blood**: clotting factor exhaustion - Interference with clotting factor production. Cardiovascular toxicity: increased capillary fragility

STOT RE 1: Substances that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to be harmful to human health following repeated exposure; STOT RE 2: Substances that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to be harmful to human health following repeated exposure; STOT RE 3: May cause respiratory irritation; STOT SE 1: Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure; STOT 2: Substances that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to be harmful to human health following single exposure; STOT 3: Transient target organ effects (respiratory tract irritation and narcotic effects); Hazard Statement Code(s) are H300: fatal if swallowed; H301: toxic if swallowed; H302: harmful if swallowed. [a]*Harmonised classification - Annex VI of CLP Regulation* (EC Regulation 1272, 2008)*;* [b]*Notified classification and labelling according to CLP criteria* (CLP Inventory)*;* [c](Prieto et al., 2019). CNS: Central nervous system; n.a.: not available; NC: not classified; PNS: peripheral nervous system;.

Tab. S2: Distribution of chemical properties of substances with mutagenicity and skin sensitization information, according to Ames and LLNA test results

Organic Functional Groups	Ames + LLNA 1A (n= 27)	Ames + LLNA 1B (n=11)	Ames + LLNA - (n=8)	Ames - LLNA 1A (n=14)	Ames - LLNA 1B (n=32)	Ames - LLNA - (n=35)
Acrylate	1 (17%)	0 (0%)	0 (0%)	1 (17%)	4 (67%)	0 (0%)
Alcohol	1 (9%)	0 (0%)	0 (0%)	2 (18%)	2 (18%)	6 (55%)
Aldehyde	1 (11%)	0 (0%)	3 (33%)	0 (0%)	0 (0%)	5 (56%)
Alkyl halide	3 (60%)	0 (0%)	1 (20%)	1 (20%)	0 (0%)	0 (0%)
Allyl	1 (8%)	0 (0%)	0 (0%)	1 (8%)	9 (75%)	1 (8%)
Aniline	0 (0%)	2 (25%)	0 (0%)	0 (0%)	1 (13%)	5 (63%)
Aryl	3 (15%)	1 (5%)	1 (5%)	2 (10%)	7 (35%)	6 (30%)
Aryl halide	3 (38%)	2 (25%)	0 (0%)	1 (13%)	0 (0%)	2 (25%)
Benzyl	3 (50%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	2 (33%)
Carboxylic acid	0 (0%)	0 (0%)	1 (11%)	0 (0%)	2 (22%)	6 (67%)
Carboxylic acid ester	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	7 (88%)
Dihydroxyl group	0 (0%)	0 (0%)	1 (20%)	0 (0%)	1 (20%)	3 (60%)
Ether	1 (7%)	1 (7%)	0 (0%)	1 (7%)	4 (29%)	7 (50%)
Nitrobenzene	6 (75%)	1 (13%)	1 (13%)	0 (0%)	0 (0%)	0 (0%)
Phenol	1 (7%)	1 (7%)	1 (7%)	2 (13%)	3 (20%)	7 (47%)
Precursors quinoid compounds	5 (71%)	1 (14%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)
Saturated heterocyclic fragment	2 (29%)	1 (14%)	1 (14%)	0 (0%)	0 (0%)	3 (43%)
Protein binding alerts	**Ames + LLNA 1A**	**Ames + LLNA 1B**	**Ames + LLNA -**	**Ames - LLNA 1A**	**Ames - LLNA 1B**	**Ames - LLNA -**
Acylation	2 (22%)	1 (11%)	0 (0%)	3 (33%)	2 (22%)	1 (11%)
Michael addition	1 (8%)	1 (8%)	0 (0%)	2 (17%)	8 (67%)	0 (0%)
Nucleophilic addition	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Schiff base formation	3 (30%)	1 (10%)	1 (14%)	0 (0%)	4 (40%)	1 (10%)
SN2	6 (40%)	4 (27%)	1 (14%)	2 (13%)	1 (7%)	1 (7%)
SNAr	2 (67%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)
SNVinyl	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DNA binding alerts	**Ames + LLNA 1A**	**Ames + LLNA 1B**	**Ames + LLNA -**	**Ames - LLNA 1A**	**Ames - LLNA 1B**	**Ames - LLNA -**
AN2	6 (46%)	1 (8%)	1 (8%)	1 (8%)	3 (23%)	1 (8%)
Non-covalent interaction	0 (0%)	0 (0%)	1 (33%)	0 (0%)	1 (33%)	1 (33%)
Radical	10 (63%)	2 (13%)	2 (13%)	2 (13%)	0 (0%)	0 (0%)
SN1	12 (75%)	2 (13%)	1 (6%)	0 (0%)	0 (0%)	1 (6%)
SN2	7 (44%)	4 (25%)	3 (19%)	1 (6%)	0 (0%)	1 (6%)

Distribution of the most prevalent organic functional groups generated from the Organic Functional Groups (nested) profiler of the OECD QSAR Toolbox; distribution of protein binding alerts generated from the Protein Binding by OASIS v. 1.2. profiler of the OECD QSAR Toolbox, and distribution of the DNA binding alerts generated from the DNA Binding by OASIS v. 1.2. profiler of the OECD QSAR Toolbox among the chemicals according to the Ames test and the LLNA results. The percentages are calculated on the basis of total number of alerts of the same category. Potency classes of skin sensitizers were considered as: LLNA 1A: strong skin sensitizer; LLNA 1B: moderate skin sensitizer; LLNA -: not classified. n = no chemicals. AN2: bimolecular nucleophilic addition; SN1: monomolecular nucleophilic substitution; SN2: bimolecular nucleophilic substitution; SNAr: nucleophilic aromatic substitution; SNVinyl; nucleophilic vinylic substitution.

Tab. S3: List of data-rich chemicals prioritised from ED dataset collected for ED impact assessment

Chemical Name	CAS number	CLP Harmonised classification (as of 30-12-2019)
Linuron	330-55-2	Acute Tox. 4 (oral); Carc. 2; STOT RE 2 (affected organs not specified); Aquatic Acute 1; Aquatic Chronic 1; Repr. 1B
Metribuzin	21087-64-9	Acute Tox. 4 (oral); Aquatic Acute 1; Aquatic Chronic 1
2,4-D (2,4-dichlorophenoxy a	94-75-7	Acute Tox. 4 (oral); Eye Dam. 1; Skin Sens. 1; STOT SE 3; Aquatic Chronic 3
Mepiquat	15302-91-7	Aquatic Acute 4; Aquatic Chronic 3 (notified only)
Tebuconazole	107534-96-3	Acute Tox. 4 (oral); Aquatic Acute 1; Aquatic Chronic 1; Repr. 2
Oxamyl	23135-22-0	Acute Tox. 2 (oral); Acute Tox. 4 (dermal); Acute Tox. 2 (inhalation); Aquatic Chronic 2
Esfenvalerate	66230-04-4	Acute Tox. 3 (oral); Skin Sens. 1; Acute Tox. 3 (inhalation); Aquatic Acute 1; Aquatic Chronic 1
Chlorpyrifos-methyl	5598-13-0	Skin Sens. 1; Aquatic Acute 1; Aquatic Chronic 1 Not approved by EFSA on renewal: considered Repr. 1B (as of 26-11-2019)
Boric acid	10043-35-3	Repr. 1B
Flubendiamide	272451-65-7	Aquatic Acute 1; Aquatic Chronic 1 (notified only by submitter)
Thiram	137-26-8	Acute Tox. 4 (oral); Skin Irrit. 2; Eye Irrit. 2; Skin Sens. 1; Acute Tox. 4 (inhalation); STOT RE 2 (liver, oral); Aquatic Acute 1; Aquatic Chronic 1
beta-Cyfluthrin	68359-37-5	Acute Tox. 2 (oral); Acute Tox. 2 (inhalation); Aquatic Acute 1; Aquatic Chronic 1
Dimethoate	60-51-5	Acute Tox. 4 (oral); Acute Tox. 4 (dermal)
Bentazone	25057-89-0	Acute Tox. 4 (oral); Eye Irrit. 2; Skin Sens. 1; Aquatic Chronic 3
Disodium Tetraborates	anhydrous 1330-43-4; pentahydrate 12267-73-1; decahydrate 1303-96-4	Repr. 1B
Dimoxystrobin	149961-52-4	Acute Tox. 4 (inhalation); Carc. 2; Aquatic Acute 1; Aquatic Chronic 1; Repr. 2
Boric oxide	1303-86-2	Repr. 1B
Terbuthylazine	5915-41-3	Acute Tox. 4; STOT RE 2; Aquatic Acute 1; Aquatic Chronic 1
Ziram	137-30-4	Acute Tox. 4 (oral); Eye Dam. 1; Skin Sens. 1; Acute Tox. 2 (inhalation); STOT SE 3; STOT RE 2; Aquatic Acute 1; Aquatic Chronic 1; under assessment as Endocrine Disruptor
Chloridazon (aka pyrazone)	1698-60-8	Skin Sens. 1; Aquatic Acute 1; Aquatic Chronic 1
Tembotrione	335104-84-2	Skin Sens. 1; STOT RE 2; Aquatic Acute 1; Aquatic Chronic 1; Repr. 2
Fenamidone	161326-34-7	Aquatic Acute 1; Aquatic Chronic 1