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Environmental hazard and risk assessment of thiochemicals. Application of integrated testing and intelligent assessment strategies (ITS) to fulfil the REACH requirements for aquatic toxicity

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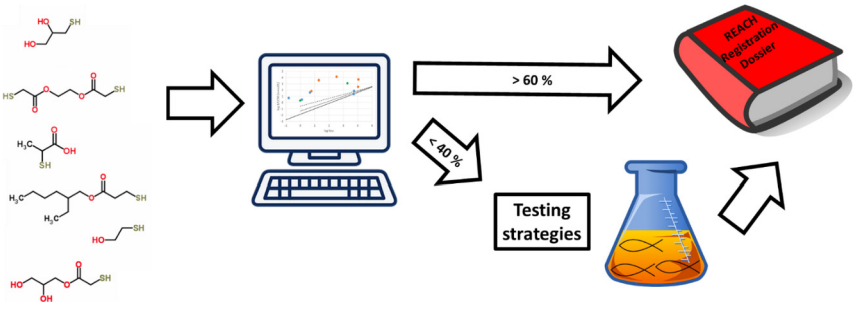
HIGHLIGHTS

- Case study on acute aquatic toxicity of 16 thiochemicals to be registered in 2018.
- Filling data gaps based on chemical similarity and common mode of action (MOA).
- Testing strategies with algae and daphnia, avoiding tests with fish if possible.
- >60% of required testing can be replaced by alternative information.

GRAPHICAL ABSTRACT



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ABSTRACT

REACH requires information on hazardous properties of substances to be generated avoiding animal testing where possible. It is the objective of the present case study with thiochemicals to extract as much information as possible from available experimental data with fish, daphnia and algae and to fill data gaps for analogues to be registered under REACH in 2018. Based on considerations of chemical similarity and common mode of action (MOA) the data gaps regarding the aquatic toxicity of the thiochemicals were largely closed by trend analysis ("category approach") and read-across within the same group, for example, thioglycolates or mercaptopropionates.

Among 16 thiochemicals to be registered by 2018 there are only 2 substances with sufficient data. 36 data gaps for 14 thiochemicals were identified. Most of the required data (>60%) could be estimated by in silico methods. Only 14 tests (6 algae, 6 daphnia, 1 limit fish test and 1 acute fish test) were proposed. When the results of these tests are available it has to be discussed whether 2 further fish (limit) tests are required. For two substances (exposure-based) waiving was suggested.

The relatively high toxicity of the thiochemicals is manifested in low predicted no-effect concentrations (PNECs). Only preliminary predicted environmental concentrations (PECs) could be derived for the thiochemicals for which a risk assessment has to be performed (production rate >10 t/y). The preliminary PEC/PNEC ratios indicate no risk for the aquatic compartment at the production site. PECs due to downstream use must not exceed the estimated PNECs.

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1. Introduction

The European Union established the regulation on registration, evaluation, authorization and restriction of chemicals (REACH) to protect human health and the environment from hazards of industrial chemicals. Industry has to register all substances produced in or imported into the EU at a rate ≥1 t/y. Physicochemical, (eco) toxicological and exposure-relevant information have to be supplied for registration depending on the production rate. For environmental assessment of chemicals to be registered by 2018 (1–100 t/y) at least the following information has to be presented:

- Acute toxicity to algae, daphnia and fish (the latter only for substances ≥10 t/y)
- Octanol/water partition coefficient (log K_{OW})
- Water solubility (S_W)
- Biodegradability

This information is used to decide whether a substance has to be classified as hazardous to the aquatic environment and labelled according to the CLP regulation (European Commission, 2009). For substances ≥10 t/y a chemical safety assessment (CSA) has to be performed, including the derivation of the predicted environmental concentration (PEC) as well as the predicted no effect concentration (PNEC) and the assessment of (very) persistent, (very) bioaccumulative and toxic (PBT/vPvB) properties. If the initial assessment indicates a risk for man and/or the environment additional information may be necessary.

The concept of integrated testing and intelligent assessment strategies (ITS) intends to increase the efficiency of hazard and risk assessment and at the same time reduce the use of animals by targeted testing of chemicals (Gabbert and Beninghaus, 2012; Jaworska et al., 2010). REACH demands that all available data are considered and missing core data may be substituted by alternative information on a case-by-case basis. Alternative information may be deviations from the standard test guidelines (for example limit tests), test results obtained with non-standard organisms, in vitro test data, intra- or extrapolation from possible analogues (read-across), predictions from (quantitative) structure-activity relationships (QSAR), extrapolations from acute to chronic data and vice versa. If new data need to be generated, vertebrate testing is the last resort. The possibilities and prerequisites for modifying the standard information requirements including exposure-based adaptation are specified in a comprehensive guidance on how to use alternatives to animal testing to fulfil the information requirements for REACH registrations (ECHA, 2016b). Guidance on the use of adverse outcome pathways in developing integrated approaches to testing and assessment (IATA) has been published by OECD (2016).

Essential for the substitution of standard tests is the availability of information that is equivalent to the results of standard testing and adequate to draw conclusions for classification and labelling, PBT/vPvB assessment and PNEC derivation. The equivalence and adequacy have to be substantiated by a Weight of Evidence (WoE) approach, making best use of all available data (Ahlers et al., 2008; Rovida et al., 2015; EFSA Scientific Committee, 2017). Lombardo et al. (2014) presented a comprehensive ITS approach for organizing and using existing aquatic toxicity data to fulfil the requirements of REACH. The difficulties in extrapolating from acute to chronic data or vice versa as well as its benefits for regulation of chemicals have been discussed by Ahlers et al. (2006), May et al. (2016) and Kienzler et al. (2016).

The equivalence and adequacy of alternative information has been demonstrated for only few registered substances as yet. The European Chemicals Agency (ECHA) flags that nine out of ten chemical registration dossiers have important data gaps regarding human health and environmental protection (ECHA, 2016a, 2017a). Mainly information on prenatal toxicity, aquatic toxicity, mutagenicity, genotoxicity and exposure is missing.

In this paper we present a case study on thiochemicals showing possibilities to fill data gaps with alternative information in accordance with the requirements of REACH. The thiochemicals discussed here are relatively homogeneous substances with a limited number of functional groups. These thiochemicals are produced in considerable amounts from <10 t/y up to >1000 t/y. They are further processed or end up directly in several downstream uses. The most important fields of application are to serve as reducing agents (antioxidants) in cosmetics, cleaners and polymers (here also used as chain transfer agents). In addition they are widely applied as (co)binders or hardeners in coatings, adhesives and sealants for the construction and electronics industry. Emerging fields are optical applications (films, lenses).

Experimental studies with fish, daphnia and algae are available for several case study chemicals. These data are the basis for read-across and trend analyses. It is the objective of the present study to extract as much information as possible from the available experimental data. In particular, we test the practicability of ITS/WoE for the case study chemicals and show possibilities and limitations of the approach. To fill remaining information gaps we propose testing strategies to comply with the information requirements of REACH. Preferably, tests with algae and daphnia are recommended. Tests with fish are avoided if possible.

2. Materials and methods

2.1. Testsubstances and available data

The present study is based on 36 thiochemicals representing 6 chemical classes (Table 1) with quality-controlled information on log K_{OW} (n = 36), S_W (n = 35), biodegradability (OECD 301) (n = 36), acute algae toxicity (OECD 201) (n = 17), acute daphnia toxicity (OECD 202) (n = 19), acute fish toxicity (OECD 203) (n = 22). Impurities due to by-products from chemical synthesis as well as degradation reactions are implicitly included in the available toxicity data and will not be further considered. The biodegradation data of the same thiochemicals are discussed in Rücker et al. (2018). In Table 2 the available physicochemical and ecotoxicological data as well as information on biodegradation are compiled. In addition calculated aquatic toxicities and the results of hazard assessments (PNEC, C&L) are provided.

2.2. Descriptors of the chemical structures

Two aspects are essential to describing the thiochemicals: (i) the reactivity of the substances related to the respective sulfur moiety (Table 1), and (ii) the hydrophobicity and size of the molecules expressed, for example, in terms of molecular weight (MW), chain length (#C) or log K_{OW} (Table 2).

MW were collected from Chemspider (Royal Society of Chemistry, 2017). #C were counted from SMILES. Multiple log K_{OW} were calculated for the undissociated thiochemicals with EpiSuite (US EPA, 2012a), ACD/Labs and ChemAxon from Chemspider (Royal Society of Chemistry, 2017), XLOGP and ALOGP from T.E.S.T. (US EPA, 2012b), Consensus, Read-across and LSER from ChemProp (UFZ Department of Ecolocical Chemistry, 2016). The mean of the results from the different independent algorithms (consolidated log K_{OW}) was calculated.

2.3. Data quality assessment

The data base of aquatic toxicities of thiochemicals has grown

Table 1
The chemical grouping of the thiochemicals.

Chem. group	SMILES	Substances
Thioglycolates (n = 10)	R1-OC(=O)CS	Free acid and salts Ester: R1 = linear and branched alkyl chains, some with OH Di(multi)meres: with 0–4 SH-groups
Mercaptopropionates (n = 11)	R1-OC(=O)CCS	Free acid Ester: R1 = linear and branched alkyl chains Di(multi)meres: with 0–6 SH-groups
Thiolactates (n = 2)	CC(S)C(O) = O	Free acid and salts
Thiodiglycolates (n = 2)	R1-OC(=O)CSCC(O) = O-R2	Free acid Ester: R1, R2 = linear and branched alkyl chains 1-2 Thioether no free SH-groups
Thiodipropionates (n = 5)	R1-OC(=O)CCSCCC(O) = O-R2	Free acid Ester: R1, R2 linear and branched alkyl chains 1-2 Thioether no free SH-groups
Mercaptanes (n = 6)	R1-CS	R1 = linear and branched alkyl chains, some with OH, SH

over several decades and reveals major variability due to different experimental protocols used in diverse laboratories. The test data have been evaluated according to Klimisch et al. (1997). Only experimental data with Klimisch code 1 (reliable without restrictions) or 2 (reliable with restrictions) have been selected to provide a sufficiently valid basis for the derivation of PNECs and for input (source) data for QSARs, category approaches and read-across. The only exception is the LC50 fish for EHTG with Klimisch code 4 (not assignable due to lack of documentation). In this case only the declaration that the test has been performed according to the test guidelines as well as the results but not the full test report are available. Experimental data with Klimisch code 3 (not reliable) have not been used.

The validated data on aquatic toxicity are included in Table 2 (columns EC50 algae (exp.), EC50 daphnia (exp.) and LC50 fish (exp.).

Classification Categories are presented according to CLP regulation (European Commission, 2009): A1 = Acute aquatic hazard, Category 1; C1 = Chronic aquatic hazard, Category 1; n = not to be classified as dangerous to the aquatic environment.

2.4. Data gaps

The registration status 2018 (Table 2) indicates either registered substances with acute aquatic toxicity data or chemicals to be registered in 2018 with some data gaps to be filled. The latter substances are 7 thiochemicals with production rates between 1 and 10 t/y, i.e. information on acute toxicity to algae and daphnia are required, and 9 thiochemicals with production rates between 10 and 100 t/y, i.e. information on acute toxicity to algae, daphnia and fish are necessary.

Columns EC50 algae (exp.), EC50 daphnia (exp.) and LC50 fish (exp.) (Table 2) indicate that valid experimental data on acute toxicity to algae, daphnia and fish are already available for 2 substances (ATL, TDPA), i.e. sufficient information to determine the regulatory endpoints. Information on acute fish toxicity exist for 4 substances (GDMA, EHMP, GDMP, DiPETMP), which have to be completed with estimates for daphnia and algae. No experimental data are available for 10 substances. The data gaps for acute toxicity to algae and daphnia (PETMA, BuMP, ODMP, DMDS) and additionally fish (TMPMP, TEMPIC, TLA, E1218, TG, HIDT) need to be filled.

2.5. Estimation of aquatic toxicity of thiochemicals applying in silico methods

QSARs, read-across, categories and trend analysis are alternative computational methods that can be used to obtain predictions for similar substances with the same mode of action (MOA) (see Section 4.1).

Read-across predicts endpoint information for one substance (target substance) by using data for the same endpoint from (an) other substance(s) (source substance(s)). Prerequisite for read-across is sufficient similarity of the target substance and the source substance(s) with regard to chemical structure, physicochemical properties, reactivity, (eco)toxicological MOA, toxicokinetics, metabolic fate and degradation pattern. Substances that are likely to be similar or follow a regular trend as a result of structural similarity may be considered as a group (category) of substances (ECHA, 2017b).

Trend analyses use the available experimental data for several chemicals within the same category, for example thioglycolates or mercaptopropionates (Table 1), to fill data gaps based on a trend related to MW, #C or log K_{OW}. Exploratory data analyses indicated #C to be the best descriptor within the categories, outperforming log K_{OW} and MW. The trends are based on acute aquatic toxicity data for 2 to 5 substances per species, with additional evidence for the trends provided by the data obtained with the other species due to the same reactive MOA within the groups of thiochemicals (see 4.1). Trends are presented graphically since it is not possible to specify the statistical uncertainties of the estimates. The uncertainty of the trend-based estimates for thioglycolates and mercaptopropionates can be limited to “within an order of magnitude” considering the variability of the input data.

The uncertainty of the estimates by read-across depends on the uncertainty of the experimental source values and the chemical and toxicological similarity between the source and target compounds. The geometric mean can be used if several estimates within a factor of 10 can be derived. If the deviations are larger, the possible causes of the variability have to be evaluated and experimental verification may be recommended.

3. Results

This case study was performed in four steps:

1. Experimental data on aquatic toxicity of thiochemicals were collected and validated (Section 2.3, Table 2).
2. Data gaps for thiochemicals to be registered in 2018 were partly closed by in silico methods like QSAR, trend analysis, read-across (Section 3.1, Table 2).
3. PNECs were derived and classifications as hazardous to the aquatic environment as well as PBT/vPvB assessments were performed (Section 3.2, Table 2).
4. Remaining data gaps were identified and testing strategies were proposed to obtain appropriate information and at the same time reduce the experimental costs and animal testing (Table 4).

Table 2
Experimental and estimated aquatic toxicities, PNECs and classification categories of thiochemicals.

CAS No.	Name	MW	log K_{OW}[a]	#C	S_W	Bio degradability[b]	EC50 algae (exp.)	EC50 algae (pred.)	EC50 daphnia (exp.)	EC50 daphnia (pred.)	LC50 fish (exp.)	LC50 fish (pred.)	PNEC	C & L	Registration status 2018
Thioglycolates															
68-11-1	thioglycolic acid (TGA)	92.12	0.10	2	>100 g/L	rb	P. subcapitata 72 h-EC50 27 mg/L	–	D. magna 48 h-EC50 38 mg/L	–	*P. promelas* 96 h-LC50 30 mg/L	–	27 μg/L	n	registered
5421-46-5	ammonium thioglycolate (ATG)	109.15	−2.66	2	>100 g/L	rb	no data	32 mg/L	no data	45 mg/L	*O. mykiss* 96 h-LC50 >100 mg/L	36 mg/L	32 μg/L	n	registered
126-97-6	monoethanolamine thioglycolate (MeaTG)	153.20	−3.09	2	>100 g/L	rb	D. subspicatus 72 h-EC50 **3.2 mg/L**	45 mg/L	D. magna 48 h-EC50 49 mg/L	63 mg/L	*O. mykiss* 96 h-LC50 >100 mg/L	50 mg/L	3.2 μg/L	n	registered
68223-93-8	diammonium dithiodiglycolate (DADTDG)	216.28	−0.31	4	>100 g/L	rb	D. subspicatus 72 h-EC50 > 100 mg/L	63 mg/L	D. magna 48 h-EC50 >100 mg/L	89 mg/L	no data	70 mg/L	–		registered
30618-84-9	glyceryl monothiol-glycolate (GMT)	166.19	−0.81	5	>100 g/L	rb	P. subcapitata 72 h-EC50 **8.7 mg/L**	8.7 mg/L	D. magna 48 h-EC50 **8.7 mg/L**	8.7 mg/L	*O. mykiss* 96 h-LC50 29 mg/L	13 mg/L	8.7 μg/L	n	registered
25103-09-7	isooctyl thioglycolate (iOTG)	204.33	3.74	10	11 mg/L	rb	no data	0.91 mg/L	D. magna 48 h-EC50 **0.39 mg/L**	0.45 mg/L	*L. idus* 48 h-LC50 2.65 mg/L	4.4 mg/L	0.39 μg/L	A1	registered
7659-86-1	2-ethylhexyl thioglycolate (EHTG)	204.33	3.72	10	5 mg/L	rb	P. subcapitata 72 h-EC50 0.91 mg/L	0.91 mg/L	D. magna 48 h-EC50 **0.53 mg/L**	0.45 mg/L	*L. idus* 48 h-LC50 9 mg/L	4.4 mg/L	0.53 μg/L	C1	registered
10047-28-6	butyl thioglycolate (BuTG)	148.22	1.87	6	no data	rb	no data	4.7 mg/L	no data	**4.1 mg/L**	no data	9.1 mg/L	4.1 μg/L	(n)	–
10193-99-4	pentaerythritol tetrakis (mercaptoacetate) (PETMA)	432.55	1.30	13	0.7 g/L	inh	no data	0.44 mg/L	no data	**(0,14 mg/L)**[c]	no data	4.3 mg/L	(0.14 μg/L)[c]	C1	1–10 t/y
123-81-9	glycol dimercapto-acetate (GDMA)	210.26	0.67	6	8 g/L	rb	no data	6.7 mg/L	no data	5.9 mg/L	*L. idus* 48 h-LC50 **4.85 mg/L**	13 mg/L	4.8 μg/L	n	10–100 t/y
Mercaptopropionates															
107-96-0	3-mercaptopropionic acid (3-MPA)	106.14	0.45	3	>100 g/L	rb	P. subcapitata 72 h-EC50 26 mg/L	–	D. magna 48 h-EC50 **4 mg/L**	–	*D. rerio* 96 h-LC50 98 mg/L	–	4 μg/L	n	registered
30374-01-7	isooctyl 3-mercapto-propionate (iOMP)	218.36	4.04	11	8 mg/L	inh.	D. subspicatus 72 h-EC50 0.046 mg/L	–	D. magna 48 h-EC50 0.31 mg/L	–	*O. mykiss* 96 h-LC50 **0.043 mg/L**	0.11 mg/L	0.043 μg/L	C1	registered
7575-23-7	pentaerythritol tetrakis (3-mercaptopropionate) (PETMP)	488.66	2.53	17	4 mg/L	inh	D. subspicatus 72 h-EC50 > 0.12 mg/L	–	D. magna 48 h-EC50 >0.35 mg/L	–	*O. mykiss* 96 h-LC50 **0.034 mg/L**	0.030 mg/L	0.034 μg/L	C1	registered
2935-90-2	methyl 3-mercapto-propionate (MMP)	120.17	0.77	4	21 g/L	rb	D. subspicatus 72 h-EC50 0.65 mg/L	–	D. magna 48 h-EC50 **0.55 mg/L**	–	*O. mykiss* 96 h-LC50 1.7 mg/L	0.72 mg/L	0.55 μg/L	A1	–
16215-21-7	butyl 3-mercapto-propionate (BuMP)	162.25	2.18	7	1 g/L (prel.)	rb	no data	**0.22 mg/L**	no data	0.45 mg/L	no data	0.34 mg/L	0.22 μg/L	A1	1–10 t/y
50448-95-8	2-ethylhexyl 3-mercaptopropionate (EHMP)	218.36	4.02	11	65 mg/L	rb	no data	(0.046 mg/L)[c]	no data	0.38 mg/L	*L. idus* 48 h-LC50 0.63 mg/L	0.07 mg/L	(0.046 μg/L)[c]	C1	1–10 t/y
31778-15-1	octadecyl-3-mercapto-propionate (ODMP)	358.62	9.12	21	10 mg/L	inh	no data	no reliable estimate	no data	no reliable estimate	no data	**(0.038 mg/L)**[c]	–	(C1)[c]	1–10 t/y
25359-71-1	DiPETMP	783.05	3.91	28	145 mg/L	(inh)[c]	no data	>0.12 mg/L	no data	>0.35 mg/L	G. rarus 96 h-LC50 >0.044 mg/L	**0.034 mg/L**	0.034 μg/L	C1	1–10 t/y
22504-50-3	glycol di(3-mercapto-propionate) (GDMP)	238.32	1.28	8	3 g/L	rb	no data	0.20 mg/L	no data	0.56 mg/L	*D. rerio* 96 h-LC50 **0.059 mg/L**	0.35 mg/L	0.059 μg/L	A1	10–100 t/y

(*continued on next page*)

Table 2 (*continued*)

CAS No.	Name	MW	log K_{OW}[a]	#C	S_W	Bio degradability[b]	EC50 algae (exp.)	EC50 algae (pred.)	EC50 daphnia (exp.)	EC50 daphnia (pred.)	LC50 fish (exp.)	LC50 fish (pred.)	PNEC	C & L	Registration status 2018
33007-83-9	trimethylolpropane tris (3-mercaptopropionate) (TMPMP)	412.59	3.26	16	0.3 g/L	inh	no data	>0.12 mg/L	no data	>0.35 mg/L	no data	**(0.036 mg/L)**[c]	(0.036 μg/L)[c]	C1	10–100 t/y
36196-44-8	TEMPIC	525.62	1.96	18	1.7 g/L	(inh)[c]	no data	no reliable estimate	no data	no reliable estimate	no data	no reliable estimate	–		10–100 t/y
Thiolactates															
13419-67-5	ammonium thiolactate (ATL)	123.17	0.57	3	>100 g/L	rb	D. subspicatus 72 h-EC50 > 140 mg/L a.i.	–	D. magna 48 h-EC50 >70 mg/L a.i.	–	*O. mykiss* 96 h-LC50 **>70 mg/L a.i.**	–	>70 μg/L (active ingredient)	n	10–100 t/y
79-42-5	thiolactic acid (TLA)	106.14	0.51	3	>100 g/L	rb	no data	>120 mg/L	no data	>60 mg/L	no data	**>60 mg/L**	>60 μg/L	n	10–100 t/y
Thiodiglycolates															
14338-82-0	methylene bis(butyl thioglycolate) (MBT)	308.46	3.92	13	14 mg/L	rb	D. subspicatus 72 h-EC50 **0.8 mg/L**	–	D. magna 48 h-EC50 15 mg/L	–	*D. rerio* 96 h-LC50 >10 mg/L	–	0.8 μg/L	C1	registered
24293-43-4	di(2-ethylhexyl) thiodiglycolate (Di-2-EHTDG)	374.58	6.92	20	≤0.083 mg/L	rb	D. subspicatus 72 h-NOEC >0.025 mg/L	–	D. magna 48 h-EC50 >0.14 mg/L	–	*O. mykiss* 96 h-LC50 **>0.056 mg/L**	–	>0.056 μg/L		registered
Thiodipropionates															
123-28-4	dilauryl thiodipropionate (E12)	514.84	11.78	30	<1 mg/L	rb	no effects in the range of S_w	–	no valid data	–	no valid data	–	–		registered
693-36-7	distearyl thiodipropionate (E18)	683.16	17.73	42	<4 μg/L	rb	no effects in the range of S_w	–	no effects in the range of S_w	–	no effects in the range of S_w	–	–		registered
10595-72-9	Ditridecyl thiodipropionate (E13)	542.90	12.77	32	<1 mg/L (calc.)	(rb)[c]	no data	–	D. magna 48 h-EC50 0.046 mg/L	–	no data	–	–		–
111-17-1	thiodipropionic acid (TDPA)	178.21	0.11	6	37 g/L	rb	S. capricornut. 72 h-EC50 **44 mg/L**	–	D. magna 48 h-EC50 73 mg/L	–	*O. latipes* 96 h-LC50 >99 mg/L	–	44 μg/L	n	1–10 t/y
13103-52-1	lauryl/stearyl thiodipropionate (E1218)	599.00	14.75	36	<1 mg/L	(rb)[c]	no data	no effects in the range of S_w	no valid data	no effects in the range of S_w	no data	no effects in the range of S_w	–		10 - 100 t/y
Mercaptanes															
60-24-2	2-mercaptoethanol	78.13	−0.01	2	>100 g/L	inh	D. subspicatus 72 h-EC50 19 mg/L	–	D. magna 48 h-EC50 0.4 mg/L	–	*L. idus* 96 h-EC50 37 mg/L	–	0.4 μg/L	C1	registered
131538-00-6	2,3-bis ((2-mercaptoethyl) thio)-1-propanethiol (DMPT)	260.53	3.28	7	12 mg/L	not rb	S. capricornut. 72 h-EC50 (1.5 mg/L)[d]	–	D. magna 48 h-EC50 (0.22 mg/L)[d]	–	*O. mykiss* 96 h-LC50 (0.21 mg/L)[d]	–	–		registered
25103-58-6	tert-dodecylmercaptan	202.40	5.37	12	3.9 μg/L	not rb	no valid data	–	D. magna 48 h-EC50 >0.56 mg/L	–	no effects in the range of S_w	–	–		registered
3570-55-6	dimercaptodiethyl sulfide (DMDS)	154.32	2.01	4	6.2 mg/L	(not rb)[c]	no data	(0.89 mg/L)[c]	no data	(0.13 mg/L)[c]	no data	**(0.12 mg/L)**[c]	(0.12 μg/L)	C1	1–10 t/y 100–1000 t/y (Intermediate)
96-27-5	thioglycerol (TG)	108.16	−0.57	3	>100 g/L	(rb)[c]	no data	(5.7 mg/L)[c]	no data	**(0.55 mg/L)**[c]	no data	(19 mg/L)[c]	(0.55 μg/L)[c]	(A1)	10–100 t/y
1095071-01-4	3,3-bis[[2-[(2-mercapto-ethyl)thio] ethyl]thio]-1-propanol (HIDT)	364.67	3.77	11	(1 g/L)	(inh)[c]	no data	(2.1 mg/L)[c]	no data	(0.31 mg/L)[c]	no data	**(0.29 mg/L)**[c]	(0.29 μg/L)[c]		10–100 t/y

ai.: active ingredient. PNEC = Predicted No Effect Concentration, input data for deriving PNECs are marked in **bold**; data in brackets are based on estimates of not sufficient reliability and tests are recommended.

[a] Consolidated log K_{OW} for the non-ionised form of the thiochemicals (mean of 8 calculated log K_{OW}, see section 2.2).

[b] Data from Rücker et al. (2018); rb = readily biodegradable, not rb = not readily biodegradable, inh. = inherently biodegradable.

[c] Uncertain/lowest estimates, which should be verified experimentally, are indicated in brackets.

[d] Unstable test substance, values based on nominal concentrations.

For substances with very low solubility (<1 mg/L) long-term tests may be necessary.

3.1. Filling of data gaps and estimation of aquatic toxicity

In the following sections we describe our attempts to fill data gaps on aquatic toxicity of thiochemicals by trend analysis and/or read-across. This is done separately for the structural groups presented in Table 1. To obtain some insight into the reliability of calculated toxicity data, we compared them with the measured ones. For daphnia we found good agreement (deviations less than a factor of two) as well as for algae (deviations less than a factor of three). In case of fish toxicities the discrepancies were somewhat higher.

Measured and calculated data are used for Classification and Labelling as well as for PNEC derivation and PBT/vPvB assessment.

3.1.1. Thioglycolates

Trend analyses are applicable for thioglycolates with two source data for algae, three for daphnia and four for fish to estimate acute aquatic toxicities for two target substances (Table 2). Assessments on the basis of two source data are not sufficient for adequate substitution of required standard test, but have to be supported by information on other substances of the same group and read-across or tests have to be proposed.

Fig. 1 illustrates the trends for thioglycolates based on #C. The source compounds cover #C from 5 to 10.

PETMA (#C = 13) has to be registered in 2018 in the range of 1–10 t/y. Trend-based estimates (algae: 0.44 mg/L, daphnia: 0.14 mg/L, fish: 4.3 mg/L) are obtained by extrapolation and considered not sufficiently reliable. As no experimental data for PETMA are available, the lowest estimate (0.14 mg/L for daphnia leading to a PNEC of 0.14 μg/L) should be verified experimentally.

If PETMA would have to be registered ≥10 t/y acute fish toxicity is required. According to the calculated data fish is more than one order of magnitude less sensitive than daphnia and a fish study can therefore be waived.

GDMA (#C = 6) has to be registered in 2018 in the range of 10–100 t/y. A PNEC of 4.8 μg/L was derived from the measured acute fish toxicity. Trend-based estimates (algae: 6.7 mg/L, daphnia: 5.9 mg/L, fish: 13 mg/L) are obtained by intrapolation and considered reliable. The calculated data are in good agreement (factor 3) with the experimental one. No further tests are required.

3.1.2. Mercaptopropionates

Trend analyses are applicable for mercaptopropionates with two source data for algae and daphnia and five for fish to estimate acute aquatic toxicities for seven target substances (Table 2). Fig. 2 illustrates the trends for mercaptopropionates based on #C. The source compounds cover #C from 4 to 11 (algae and daphnia) and from 4 to 17 (fish), respectively.

Four mercaptopropionates with production rates between 1 and 10 t/y have to be registered in 2018:

BuMP (#C = 7): Trend-based estimates (algae: 0.22 mg/L, daphnia: 0.45 mg/L, fish: 0.34 mg/L) are obtained by intrapolation and considered reliable. A PNEC of 0.22 μg/L was derived.

EHMP (#C = 11): Trend-based estimates (algae: 0.046 mg/L, daphnia: 0.38 mg/L, fish: 0.11 mg/L) are obtained by intrapolation and considered reliable. For fish, read-across (0.043 mg/L) from iOMP (different branching) is possible. The two estimates for fish are in agreement (within factor 3) and the geometric mean (0.07 mg/L) is recommended. This value agrees within factor 10 with the experimentally determined 48 h-LC50 (0.63 mg/L) for *Leuciscus idus*. Since the measured value is based on nominal concentrations the PNEC of 0.046 μg/L is based on calculated data. It is recommended to experimentally verify the lowest estimate (0.046 mg/L for algae).

ODMP (#C = 21): The aquatic toxicity for algae and daphnia was not calculated as the extrapolation from two possible source compounds would be far too large. For fish a preliminary EC50 of 0.038 mg/L is the mean of read-across from iOMP (0.071 mg/L) and the trend-based estimate (0.0054 mg/L) derived with a relatively small extrapolation range based on five source compounds. Due to the uncertainties and variability of the calculations tests on algae and daphnia should be performed.

DiPETMP (#C = 28): Read-across (algae: >0.12 mg/L, daphnia: >0.35 mg/L, fish: 0.034 mg/L) from PETMP is based on similarity of the source and the target compound due to 4 and 6 of the 3-mercaptopropionate substituents on one or two pentaerythritol units, respectively. The estimate (0.034 mg/L) for fish agrees with the measured fish toxicity (>0.044 mg/L). The estimate is preferred for PNEC derivation (0.034 μg/L) because it is not a censored (>) value. As fish is far more sensitive than algae and daphnia no further tests are recommended.

Three mercaptopropionates have to be registered in 2018 in the range of 10–100 t/y:

GDMP (#C = 8): Trend-based estimates (algae: 0.20 mg/L, daphnia: 0.56 mg/L, fish: 0.35 mg/L) are obtained by intrapolation and considered reliable. The estimates agree within factor 10 with the measured fish toxicity (0.059 mg/L), which presents the most sensitive result and is used for PNEC (0.059 μg/L) derivation.

TMPMP (#C = 16): Read-across (algae: >0.12 mg/L, daphnia: >0.35 mg/L) from PETMP is based on similarity due to 3 and 4 of the 3-mercaptopropionate substituents on trimethylolpropane and pentaerythritol, respectively. Trend-based estimates for algae and daphnia are not meaningful due to different numbers of thiol functions. The trend-based estimate (0.036 mg/L) for fish is in very good agreement with read-across (0.034 mg/L) from PETMP and was used for PNEC (0.036 μg/L) derivation. As for registration

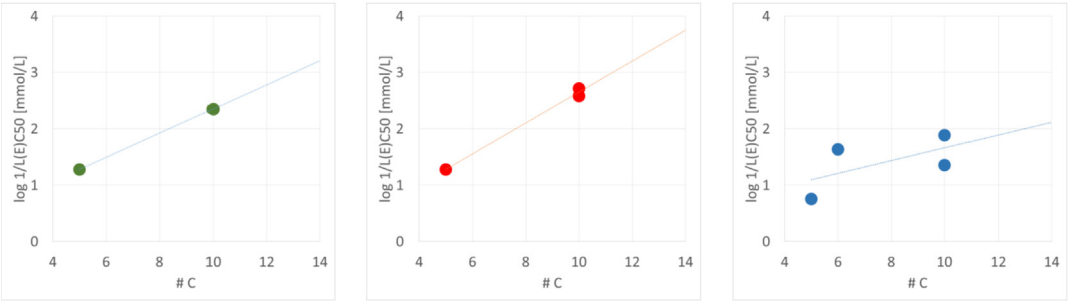

Fig. 1. Trend analyses for thioglycolates based on chain length (#C) for algae (left), daphnia (middle), and fish (right).

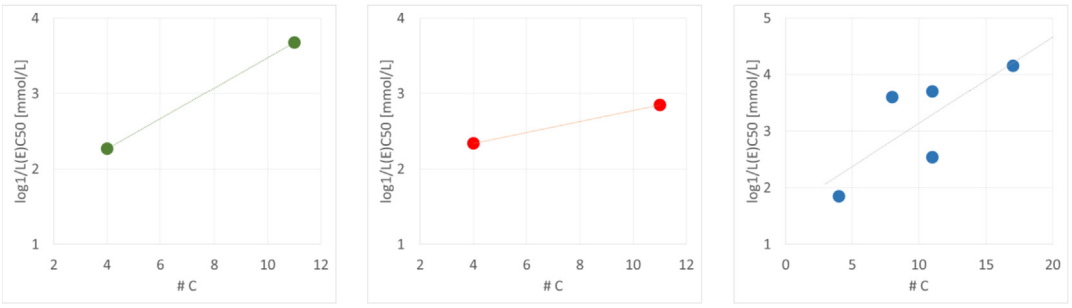

Fig. 2. Trend analyses for mercaptopropionates based on chain length (#C) for algae (left), daphnia (middle), and fish (right).

information on acute fish toxicity is needed, it is recommended to experimentally verify the calculations with an acute fish test (OECD 203). A limit test based on the estimates for fish is considered less useful as fish is much more sensitive than algae and daphnia.

TEMPIC (#C = 18): Trend-based estimates and read-across are not meaningful due to the different core structures with multiple nitrogen atoms as compared to the other mercaptopropionates. Therefore, it is recommended to perform an algae and a daphnia test for TEMPIC followed by a limit test on fish with the lowest EC50 of the above tests (step-down approach).

3.1.3. Thiolactates

Only the acid itself and its ammonium salt have to be registered in 2018, both in the range of 10–100 t/y. For ammonium thiolactate experimental data for fish, daphnia and algae are available. Up to a concentration of 100 mg/L test substance (70 mg/L active ingredient) no effects could be observed. A PNEC of >70 μg/L was derived.

Read-across from ammonium thiolactate to thiolactic acid (algae: >120 mg/L, daphnia: >60 mg/L, fish: >60 mg/L) is possible since in both cases the thiolactate ion is responsible for the toxic effect.

3.1.4. Thiodiglycolates and thiodipropionates

The esters of thiodiglycolic acid and thiodipropionic acid have similar chemical structures without free SH groups. The core structures are OC(=O)CSCC(=O)O and OC(=O)CCSCCC(=O)O, respectively, with the difference being two carbon atoms between the ester functions. Depending on the chain length of the alcohols, some esters have very low S_W and the available acute aquatic toxicity data have been determined well above water solubility.

TDPA has to be registered in 2018 in the range of 1–10 t/y. Based on measured acute toxicity for algae, daphnia and fish, a PNEC of 44 μg/L was derived from the algae test.

E1218 has to be registered in the range of 10–100 t/y in 2018. No valid data on acute aquatic toxicities are available. Given the low water solubility, long-term toxicity data should be used. The composition of E1218 (E12: 21-31%, E18: 18-28%, E1218: 35-57%) justifies read-across from E18 and E12. E18 long-term studies with algae, daphnia and fish conclude that no effects are observed in the range of S_W. In acute tests with E12 there were no effects up to the limit of S_W. Long-term testing was not considered necessary (data waiving). It can be assumed that E1218 behaves comparably due to similar structure and similar physicochemical properties, i.e. no effects in the range of S_W. Thus, a fish test required for the registration can be waived.

3.1.5. Mercaptanes

TG (#C = 3) has to be registered in 2018 in the range of 1–10 t/y. Read-across from GMT is based on sharing 2 hydroxy- and 1 thiol-group (algae: 5.7 mg/L, daphnia: 5.7 mg/L, fish: 19 mg/L) and from 2-mercaptoethanol being a substructure of TG (algae: 26 mg/L, daphnia: 0.55 mg/L, fish: 51 mg/L). A preliminary PNEC of 0.55 μg/L has been derived from the lowest estimate for daphnia (0.55 mg/L). Since the very limited data base does not allow to establish equivalent reactivity of the thiol functions of the source and target substances, it is recommended to verify the estimates with experimental data for algae and daphnia toxicity. The results of this comparison will show whether it is also necessary to conduct an experimental study with fish.

Two mercaptanes have to be registered in 2018 in the range of 10–100 t/y:

DMDS (#C = 4): Only calculated data of insufficient reliability have been obtained. Read-across from DMPT (algae: 0.89 mg/L, daphnia: 0.13 mg/L, fish: 0.12 mg/L) is limited by the instability and the different reactivities leading to different ring closures, i.e. different transformation products with different toxicities. Due to the uncertainties, it is suggested to perform acute algae and daphnia tests.

DMDS also has to be registered in the range of 100–1000 t/y as an internal intermediate (on-site or transported isolated intermediate under strictly controlled conditions). Due to exposure based waiving a (limit) fish test can be skipped.

HIDT (#C = 11): Read-across from DMPT is based on sharing SCCS substructures (algae: 2.1 mg/L, daphnia: 0.31 mg/L, fish: 0.29 mg/L) leading to a preliminary PNEC of 0.3 μg/L. Considering the instability of the source substance (DMPT) it is recommended to first carry out an algae and a daphnia test. On the basis of these results the necessity of a fish (limit) test has to be re-evaluated (step-down approach).

3.2. Derivation of the regulatory endpoints PNEC, C&L and PBT/vPvB

According to REACH guidance, PNECs were calculated by dividing the lowest valid E(L)C50 value of the acute aquatic tests by an assessment factor of 1000 (see Section 3.1). In case measured as well as calculated data are available, the experimental data are generally preferred for PNEC derivation and classification and labelling (columns PNEC and C&L in Table 2).

The relatively high aquatic toxicity of the thiochemicals (Table 2) resulted in most cases in a classification as C1 (6 substances) or A1 (3 substances). Only 4 substances do not have to be classified. For 3 substances the data are insufficient for classification. As no indication of persistence and high bioaccumulation exist, the thiochemicals do not have to be classified as PBT or vPvB.

3.3. PEC/PNEC ratios

A risk for the environment is defined as the quotient of PEC and PNEC. If PEC exceeds PNEC risk reduction measures are necessary.

The PECs for the compartment water from production and

Table 3
PEC/PNEC ratios for four thiochemicals.

Name	PEC_{local} (μg/L)	PNEC (μg/L)	PEC/PNEC
EHTG	0.033	0.5	0.066
ODMP	0.78×10^{-3}	(0.038)[a]	(0.02)[a]
PETMP	$<0.65 \times 10^{-3}$	0.034	<0.02
TEMPIC	$<0.65 \times 10^{-3}$		

[a] Preliminary estimates.

processing at the production site are obtained from analytical data of the following compounds:

- EHTG, registered, production rate >1000 t/y
- ODMP, production rate 1–10 t/y
- PETMP, registered, production rate >1000 t/y
- TEMPIC, production rate 10–100 t/y.

The measurements were performed in the sewage of the production site before release to the receiving river (Elbe). Applying a dilution factor of 1.5×10^5 (flow rate from waste water: 402 m^3/d; flow rate receiving river: 6×10^7 m^3/d (local authorities, 2016)) to the analytical data we were able to calculate PEC_{local} at the production site and derive PEC/PNEC ratios (Table 3).

4. Discussion

For several thiochemicals we present a case study of how "Good ITS Practices" (Rovida et al., 2015) can be realized with limited existing information based on available aquatic toxicity data (see Sections 2.5 and 3.1). Alternative data have been generated and feed into a testing strategy to fill information gaps with reasonable efforts.

4.1. Toxicological grouping and mode of action (MoA)

Prerequisite for deriving adequate alternative information by in silico methods is the characterisation of chemicals in terms of functional similarity[1] leading to either common or different MOA. The toxicological grouping of the thiochemicals follows the chemical grouping (Table 1).

Differences in toxicity between the groups of thiochemicals are thought to be due to differences in reactivity of the respective sulfur moiety, i.e. toxicodynamic differences. For example, mercaptopropionates are around 10 times more toxic than thioglycolates (Table 2). The toxic principle of the different sulfur moieties is further supported by a comparison of the same structures with and without thiol group. We observe a more than 10-fold decrease of the PNEC for thioglycolic acid (27 μg/L) as compared to acetic acid (>300 μg/L) and an even larger decrease for 3-mercaptopropionic acid (4 μg/L) as compared to propionic acid (>500 μg/L).[2]

Within each group the thiochemicals share the same reactivity due to the identical sulfur function, but are different with regard to partitioning between biophases related to increasing aliphatic chain length, i.e. toxicokinetic differences. Such trends are seen for thioglycolates with the PNECs decreasing from 27 μg/L for thioglycolic acid, via 4 μg/L for butylthioglycolate to 0.4 μg/L for isooctyl thioglycolate and, similarly, for mercaptopropionates with the PNECs being reduced from 4 μg/L for 3-mercaptopropionic acid, via 0.2 μg/L for butyl 3-mercaptopropionate to 0.04 μg/L for isooctyl 3-mercaptopropionate.

Thiochemicals are considered to be toxic due to reactivity of the sulfur functions causing so-called excess toxicity, i.e. the effects are much higher than estimated from baseline QSARs (Nendza et al., 2017). Comparison of the experimental acute toxicities of thiochemicals with log K_{OW}-based baseline QSARs for algae (Shigeoka et al., 1988), daphnia (Hermens et al., 1984; Deneer et al., 1989) and fish (Könemann, 1981; Nendza and Russom, 1991) reveals excess toxicities of more than one order of magnitude with distinct pattern for the different groups of thiochemicals (Fig. 3).

QSAR models that fulfil the criteria for scientific validity (OECD, 2007)[3] are not available for thiochemicals. Due to MOA considerations joint QSAR modelling of all thiochemicals is not appropriate and the present data base is too small to derive new statistically valid QSAR models for different groups of thiochemicals. Therefore, it was not possible to fill data gaps regarding the aquatic toxicity of thiochemicals with QSAR predictions. Instead, read-across and trend analyses have been used.

4.2. ITS and Weight of Evidence (WoE)

In the ITS framework, WoE is used to combine the evidence from multiple information sources that each alone may not be sufficient to fulfil a standard information requirement (Ahlers et al., 2008; Rovida et al., 2015; EFSA Scientific Committee, 2017). However, taken together the joint evidence of the individual studies may satisfy the needs. With regard to practical applications, WoE is neither scientifically well-defined nor an agreed formalized concept with defined tools and procedures (Weed, 2005). According to ECHA (2016b) factors such as the quality of the data, consistency of results, nature and severity of effects and relevance of the information will have an influence on the weight given to the available evidence.

We generally followed the REACH Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7b: Endpoint specific guidance (ECHA, 2017c: Fig. R.7.8–2, p.40ff) and Ahlers et al. (2008) to evaluate the hazard of a substance. This guidance proposes the following steps for a WoE approach:

Step 1 Characterisation of the substance (structure, physico-chemical properties, degradation, metabolites),
Step 2 Analysis of mode of action,
Step 3 Identification and evaluation of possible analogues,
Step 4 Evaluation of existing in vivo and in vitro testing data as well as QSAR results,
Step 5 Weight of evidence assessment including identification of data gaps,
Step 6 Evaluation of factors relevant for waiving.

For assessing thiochemicals step 1 was of importance as a number of them are "difficult substances" being rather unstable, showing low S_W and/or a high K_{OW} and therefore requiring much care analysing available test data or establishing a reliable design for the proposed tests (for example flow-through, semi-static, analytics). Step 2 revealed excess toxicity due to distinct reactivities of

[1] The concept of functional similarity can support the MOA classification of chemicals by combining toxicological knowledge (which toxicity pathways can happen in which species under which exposure conditions) with chemical expertise (which parts of the chemical structures and physicochemical properties are involved in which interactions) (Nendza et al., 2014).

[2] Data according to the ECHA registration dossiers (https://echa.europa.eu/registration-dossier/-/registered-dossier/15549/1, https://echa.europa.eu/registration-dossier/-/registered-dossier/14128/1).

[3] Criteria for the scientific validity of QSAR models (OECD, 2007): (i) a defined endpoint; (ii) an unambiguous algorithm; (iii) a defined domain of applicability; (iv) appropriate measures of goodness-of-fit, robustness and predictivity; and (v) a mechanistic interpretation, if possible.

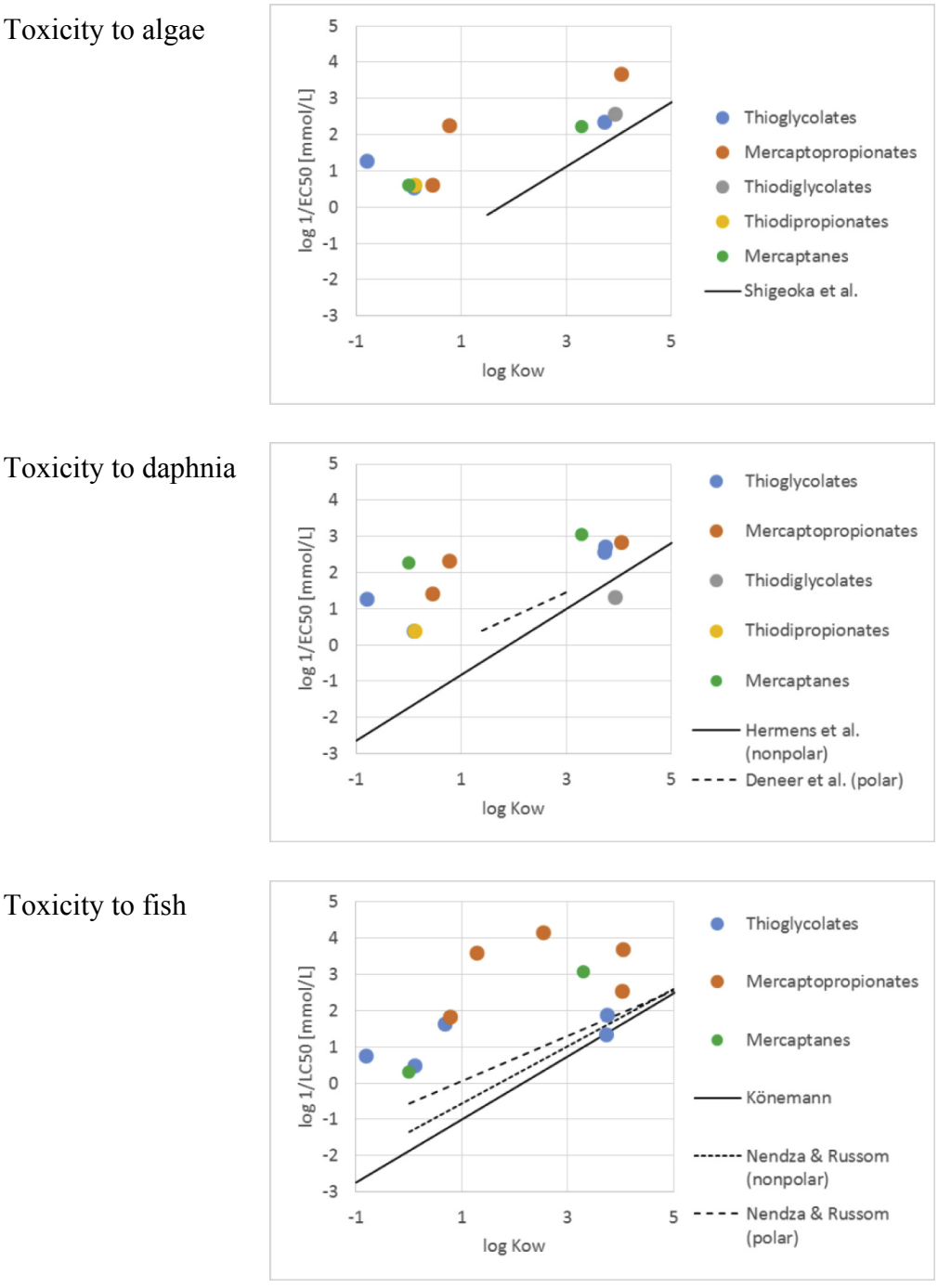

Fig. 3. MOA-related excess toxicity of thiochemicals.

the different groups of thiochemicals with the consequence that only trend-analysis and read-across, but no QSAR could be applied in this exercise. Step 3 as well as steps 4 and 5 were the main basis for filling data gaps (section 3.1). Step 6 could be applied for two substances (DMDS and E1218).

ECHA (2017a) stresses the necessity to examine structurally similar substances in order to identify substances that warrant further scrutiny and to speed up the processes of assessment and regulation. Beside an increase in efficiency the toxicological and chemical grouping ensures a consistent approach to similar substances and avoids unnecessary testing. The grouping of similar thiochemicals provides strong evidence of similar reactivities and common MOA within groups of thiochemicals and helps to evaluate differences in sensitivity for the individual trophic levels. Identification of common MOA is especially important for the integration of information across environmental endpoints (Pery et al., 2013).

4.3. Testing strategies

Most of the 36 data gaps for 16 thiochemicals to be registered by 2018 could be filled by in silico methods. Only 14 tests (6 algae, 6 daphnia, 1 limit fish test and 1 acute fish test) have been proposed (Table 4). When the results of these tests are available, it has to be discussed whether 2 further fish (limit) tests are required. The

Table 4
Required and recommended tests on aquatic toxicity of thiochemicals to fulfil the obligations of REACH.

Substance	Required Tests	ITS recommendations
PETMA	Acute Algae, Daphnia (OECD 201, 202)	Acute Daphnia
EHMP	Acute Algae, Daphnia (OECD 201, 202)	Acute Algae
ODMP	Acute Algae, Daphnia (OECD 201, 202)	Acute Algae, Daphnia
TMPMP	Acute Algae, Daphnia, Fish (OECD 201, 202, 203)	Acute Fish
Tempic	Acute Algae, Daphnia, Fish (OECD 201, 202, 203)	Acute Algae, Daphnia; instead of OECD 203: Limit Test
E1218	Long-Term Algae, Daphnia, Fish (OECD 201, 211, e.g. 210)	Waiving possible due to similarities with E12 and E18
TG	Acute Algae, Daphnia, Fish (OECD 201, 202, 203)	Acute Algae, Daphnia; the necessity for an acute fish (limit) test depends on the results from the acute algae and daphnia tests
DMDS	Acute Algae, Daphnia, Fish (OECD 201, 202, 203)	Acute Algae, Daphnia, (acute fish (limit) test: may be waived, when no exposure)
HIDT	Acute Algae, Daphnia, Fish (OECD 201, 202, 203)	Acute Algae, Daphnia; the necessity for an acute fish (limit) test depends on the results from the acute algae and daphnia tests

necessity of further tests for substances with PEC/PNEC >1 have to be discussed as consequence of the outcome of risk assessments (Section 4.4).

No additional information for three substances (GDMA, GDMP, DiPETMP) with empirical information on acute fish toxicity is needed. For EHMP the measured fish toxicity and the geometric mean of two estimates for fish are in reasonable agreement. However, a reliable estimate for algae is significantly lower. It is recommended to experimentally verify the estimate for algae.

Equivalent and adequate alternative information was obtained for the two thiochemicals BuMP based on a trend-based estimate and TLA based on read-across. No further tests are recommended for the two substances.

The WoE of the alternative information is not sufficient for four thiochemicals (PETMA, TMPMP, DMDS, ODMP) without empirical data. Only preliminary PNECs were derived based on trend-based estimates, read-across or a combination of both. Whereas for PETMA, DMDS and ODMP no PNECs are required (production rates 1–10 t/y), the preliminary PNEC for TMPMP should be verified experimentally.

Neither experimental data nor equivalent and adequate alternative information are available to derive PNECs for four thiochemicals to be registered in 2018 (TEMPIC, E1218, TG, HIDT). The recommended testing strategies for TEMPIC, TG and HIDT start with acute tests with algae and daphnia (OECD 201, 202). Depending on the results of these tests it has to be decided whether standard acute fish tests, alternative tests (fish embryo test (FET) or limit tests (step-down approach)) are recommended. For E1218 the required long-term tests can be waived due to analogy with substances already registered.

4.4. Risk assessment

For chemicals produced ≥10 t/y a Chemical Safety Report (CSR) has to be submitted including a chemical risk assessment. The risk for the environment is defined as the quotient of PEC and PNEC. If PEC exceeds PNEC risk reduction measures are necessary.

The PEC/PNEC ratios for EHTG, PETMP and ODMP (Section 3.3, Table 3) are below 1 and no risks from local releases to surface water at the production site are identified. However, the ratio for ODMP and TEMPIC should be (re)calculated when the PNECs have been revised based on experimental results. In terms of waste water release to the aquatic compartment, the high-volume compound EHTG can be considered as surrogate for those thiochemicals, which have to be registered under REACH in 2018. The EHTG PEC of 0.033 μg/L seems to be sufficiently conservative to calculate the PEC/PNEC ratios for the latter ones. All substances are produced in the same way as PETMP and EHTG but at lower rates, resulting in PEC_{local} <0.033 μg/L and PEC/PNEC ratios <1. This assumption is supported by the calculated PECs for ODMP and Tempic, which are about 50 fold lower compared to that of EHTG. Therefore no additional information is required for the thiochemicals of this study. However, we suggest to verify the estimations by additional analytical data.

For a risk assessment of the thiochemicals in connection with down-stream uses it has to be kept in mind that site-specific PECs must not exceed the PNECS given in Table 2.

5. Conclusion

The present case study based on available data for thiochemicals has shown that it is possible to derive sound predictions/alternative information for many but not for all substances and every endpoint.

- The collected evidence supports common MOA of thiochemicals within the same group (same sulfur function) to justify extrapolations to close data gaps.
- Scientifically valid QSARs for (groups of) thiochemicals are not available. Joint QSAR modelling of all the thiochemicals is not appropriate and the present data base is too small to derive new statistically valid QSAR models for different groups of thiochemicals. Therefore, it was not possible to fill data gaps regarding the aquatic toxicity of thiochemicals with QSAR predictions. Instead, read-across and trend analyses have been used.
- Among the 16 thiochemicals to be registered in 2018 there are only two substances without data gaps. For five substances the data gaps on aquatic toxicity could be filled by trend analyses (category approach) and read-across. For these extrapolations the requirements of REACH, annex XI, are fulfilled. For the remaining nine thiochemicals testing strategies were developed in order to obtain information that is sufficient to achieve a sound and reliable assessment.
- ITS allow to replace >60% of the required testing by alternative information. The derived testing strategies comply with the 3Rs principles (Replacement, Refinement and Reduction of vertebrate testing (Russel and Burch, 1959)) by recommending tests with algae and daphnia, avoiding tests with fish if possible.
- No risk for the aquatic environment from production and processing of thiochemicals at the production site has been identified.

Conflict of interest statement

J.A and M.N. are independent consultants and have no conflict of interest that could inappropriately influence or bias the content of the paper, D.S is an employee of Bruno Bock Thiochemicals.

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