Reporting format for the analogue approach for the read-across of aquatic and human toxicity of Sodium (bis)trifluoromethanesulfonimide (NaTFSI) from its structural analogue Lithium (bis)trifluoromethanesulfonimide (LiTFSI)

Introduction

This report addresses the analogue approach for the read-across of human toxicological and ecotoxicological properties of Sodium (bis)trifluoromethanesulfonimide (NaTFSI) from its structural analogue (source substance):

- Lithium (bis)trifluoromethanesulfonimide (LiTFSI) (CAS No: 90076-65-6; ELINCS No. 415-300-0)

The target and the source substance are used as electrolytes in the production of batteries.

1. Read-across hypothesis and justification

This Read-Across is based on the hypothesis that the target and the source substances have similar toxicological properties based on dissociation into common (identical) compounds as a consequence of their structural similarity. Non-common compounds are considered not to influence the read-across validity because they do not contribute to the toxicity. The toxicological properties of the source substance and those of the target substance are expected to be very similar since they have (bis)trifluoromethanesulfonimide as the common anion ("common compound" as defined by RAAF), with the cations being lithium or sodium. Their systemic toxicological effects in humans and the environment are expected to be mostly governed by the presence of the (bis)trifluoromethanesulfonimide anion.

The main difference between the target and the source substances lies in the fact that the source substance contains lithium as cation while the target substance contains sodium. Since the systemic toxicity of the target and the source substance is considered to be driven by the (bis)trifluoromethanesulfonimide anions, the amount of lithium originating from the source substance is considered not to contribute significantly to the toxicity effects observed in the studies. Moreover, no or little toxicity can be attributed sodium cations. Sodium is a macroelement and important electrolyte, required by living organisms in much higher amounts than those originated from the doses used in toxicological studies if studies would be conducted with the target substance.
Since sodium is considered not to contribute to the toxicity of the target substance, it is concluded that the present Read-across case represents a typical worst-case by which the strength of (systemic) toxicity effects produced by the source substance is equal or higher than that of the target substance if studies with the target substance were conducted. Thus, the Read-Across is considered to be justified.

In the following scheme the Read-Across hypothesis is presented:

	Parent substances	Dissociation products	Common compound	Non-common compound
Target substance; CAS RN: 91742-21-1	NaC	C→X	X	Na
Source material B; CAS RN: 90076-65-6	LiC	C→X	X	Li

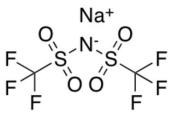
X (bis)trifluoromethanesulfonimide ion
Li – Lithium
Na – Sodium

2. Substance identity

a. Target substance

The target substance (Table 1) is the mono-constituent substance Sodium (bis)trifluoromethanesulfonimide (NaTFSI). The typical concentration and concentration range for each of the constituents and the identified impurities of the target substance are shown in Table 1.

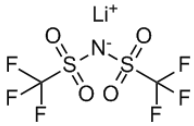
Table 1. Composition of the target substance

Target substance: Sodium (bis)trifluoromethanesulfonimide, EC No. 804-361-2, CAS No. 91742-21-1					
Main constituents					
Constituent No	IUPAC name	Structural formula	Min. Conc. (%w/w)	Max. Conc. (%w/w)	Typical Conc. (%w/w)
1 (EC no 804-361-2, CAS no 91742-21-1)	Sodium (bis)trifluoromethanesulfonimide		99.9	100	99.9
Identified impurities					
(EC no -, CAS no -)	-	-	-	-	-

b. Source substance

The Source substance is the monoconstituent substance Lithium (bis)trifluoromethanesulfonimide (LiTFSI), containing the (bis)trifluoromethanesulfonimide anion that is also present in the target substance. The typical concentrations and concentration ranges of the constituent and identified impurities of the source substance are shown in Table 2.

Table 2. Composition of the source substance

Source substance: Lithium (bis)trifluoromethanesulfonimide, EC No. 415-300-0, CAS No. 90076-65-6					
Main constituent					
Constituent No	IUPAC name	Structural formula	Min. Conc. (%w/w)	Max. Conc. (%w/w)	Typical Conc. (%w/w)
1 (EC no 415-300-0, CAS no 90076-65-6)	Lithium (bis)trifluoromethanesulfonimide		99.8	100	99.9
Identified impurities					
(EC no -, CAS no -)	-	-	-	-	-

c. Purity and impurities

The source and target substance are placed on the market as highly pure substances and therefore it is not expected that any impurities will significantly affect their physico-chemical parameters or their toxicological properties.

2.2 Structural similarity

a. Structural similarity and functional groups

The basic structure of the main constituents of the target substance – (bis)trifluoromethanesulfonimide anion – is identical to the main constituent of the source substance**.** The difference between the source and the target substance is in non-common products releasing by dissociation.

b. Common breakdown products

In contact with water, LiTFSI will dissociate immediately into ionic moieties as follows:

$LiTFSI \rightarrow TFSI^- + Li^+$

Also dissolution of NaTFSI will lead to the formation of the (bis)trifluoromethanesulfonimide anion:

$NaTFSI \rightarrow TFSI^- + Na^+$

3. Physicochemical properties

The physico-chemical properties of the source and target substances are presented in the Data Matrix in the Annex of this document.

The target and the source substance are solids with a high melting point (253°C for NaTFSI and ca. 233°C for LiTFSI) and negligible vapour pressure. Both target and source substance are very soluble in water.
In the aquatic environment, the substances will dissociate into the (bis)trifluoromethanesulfonimide anion and their respective cations (Li or Na).

4. Toxicity data of the target and source substances and conclusion on C&L and dose-descriptor

The toxicological properties of the source and target substance are presented in the Data Matrix in the Annex of this document.

Acute toxicity

Experimental data on acute toxicity are not available for the target substance, therefore the results of the source substance are used instead.

Two reliable studies studies with the source substance are available for acute oral toxicity. The study performed by Hazleton (Glaza, 1988) leads to an LD50 of 160 mg/kg bw (males) and 210 mg/kg bw (females). In the other study (Pelcot, 2002a), 2/6 animals were found dead after exposure to 200 mg/kg bw and it is considered unlikely that more than 50% of the animals will survive a dose of 2000 mg/kg bw. Based on the results of this study, it is expected that the oral LD50 in rat would be > 200 and < 2000 mg/kg bw.

The acute dermal toxicity of LiTFSI was evaluated in male and female rabbits when administered as a single topical application at levels of 200, 350, 500, and 2000 mg/kg of body weight. Based on the observed mortality, the estimated dermal LD50 was determined to be 371, 418 and 400 mg/kg for males, females, and the sexes combined, respectively.

Based on the experimental data of the source substance Lithium (bis)trifluoromethanesulfonimide, the target substance is to be classified as follows according to the GHS UN:
- "Toxic if swallowed" (Category 3, H301),

- "Toxic in contact with skin" (Category 3, H311).

Irritation potential

Skin and eye irritation are the endpoints for which Read-Across is intended. The source substance LiTFSI was found to be corrosive to skin in a dermal irritation/corrosion study according to OECD 404 and highly irritating to eyes in an eye irritation/corrosion study according to OECD 405

Based on the results of the studies conducted with the source substance, the target substance NaTFSI should be classified as "Corrosive to skin" (Category 1, H314) and "Highly irritating to eyes" (Category 1, H318) according to GHS UN.

Sensitization

Skin sensitisation is the endpoint for which Read-Across is intended. No experimental data on sensitization are available for NaTFSI. However, for the source substance LiTFSI no skin sensitising effects were observed in a Guinea Pig Maximisation test according to OECD 406.

Based on the structural similarities and common dissociation products, it can be concluded that the results of the sensitization studies conducted with the source substance are likely to predict the properties of the target substance. No C&L is warranted for the target substance.

Mutagenicity

This is the endpoint for which Read-Across is intended. Read-Across for mutagenicity endpoint for (bis)trifluoromethanesulfonimide ions is based on similar DNA binding behaviour of both target and source substance. Since the common dissociation compound – (bis)trifluoromethanesulfonimide ion – is very stable, it is unlikely that the ion will bind to DNA initiating molecular events and leading to mutations. The free dissociating sodium ions are not expected to produce genotoxicity.

The source substance Lithium bis(trifluoromethylsulfonyl)imide did not induce an increased mutation frequency in a GLP-compliant bacterial reverse mutation assay, performed according to OECD guideline 471. For this reason, the target substance is also expected to give a negative response in the *in vitro* Bacterial Reverse Mutation Assay (Ames test).

The available data show that classification for genotoxicity is not warrented for source and target substances according to EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008.

Repeated dose toxicity

For the target substance no subchronic toxicity data are available and therefore read-across is intended for this endpoint. This endpoint concerns systemic effects, which are expected to be primarily governed by the presence of (bis)trifluoromethanesulfonimide anions formed upon dissociation. Therefore it is considered acceptable to derive lacking data for NaTFSI by read-across from LiTFSI and an additional safety factor need not to be taken into account.

Two reliable 28-day studies via the oral route are available for the structural analogue ithium bis(trifluoromethylsulfonyl)imide.

The first sub-acute study with TFSILi was performed according to OECD guideline 407 and under GLP (Edwards, 1993). The test material formulated in distiled water was administered to groups of Sprague-Dawley rats at dosages of 1.67, 10 and 60 mg/kg/day for a minimum of 28 consecutive days. Control animals received the vehicle alone.All rats of Groups 2 and 3 (1.67 and 10 mg/kg/day) and five males and five females from each of Groups 1 and 4 (Controls and 60 mg/kg/day) were killed following the four-week treatment period (Day 32). The remaining animals (five males and five females from Groups 1 and 4) were retained for a minimum two-week recovery period, following which they were also killed (Day 46).

Based on the results of this study, the liver was identified as a principal target organ at 60 mg/kg/day, the high dosage. The effects of treatment at 10 mg/kg/day were considered minor in nature and for this reason this dose level is considered to be the No-Observed-Adverse Effect-Level (NOAEL).

In the second GLP compliant OECD guideline 407 study, sub-acute (28 days) oral toxicity of TFSILi was investigated in Sprague-Dawley rats (Mhedhbi, 2002). In this study, LiTFSI was administered once daily by gavage to Sprague-Dawley rats at dose-levels of 15, 45 and 90 mg/kg bw/day for 4 weeks, followed by a 2-week treatment-free period. The liver and central nervous system were identified as the target organs. A dose level of 15 mg/kg may be considered as a NOAEL for systemic effects. The Lowest Observable Adverse Effect Level (LOAEL) was established at 45 mg/kg bw/day.

Based on the experimental data and the observed LOAEL at 45 mg/kg bw/day, LiTFSI is classified "May cause damage to organs through prolonged or repeated exposure" for Specific Target Organ Toxicity - Repeated exposure (Category 2, H373, oral route, target organ: Central and peripheral nervous system). The same classification will be applied for NaTFSI.

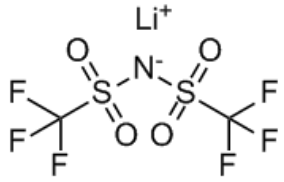
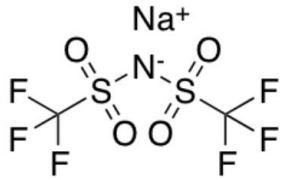
5. Environmental properties of the target and source substance and conclusion on classification

A summary of the available aquatic toxicity data for the source and target substances is presented in the Data Matrix in the Annex of this document.

For the target substance no data on environmental effects are available and therefore read-across is intended for these endpoints. The environmental fate properties and ecotoxicity of the target and source substances is expected to be mostly governed by the presence of the (bis)trifluoromethanesulfonimide anion formed upon dissociation. Therefore it is not expected that there is any significant difference in the environmental fate and aquatic toxicity of the two substances and a safety factor need not to be taken into account.

According to GHS UN Classification, sodium (bis)trifluoromethanesulfonimide is to be classified as harmful to the aquatic environment, Category Chronic 3; H412 (Harmful to aquatic life with long lasting effects). The source substance lithium (bis)trifluoromethanesulfonimide is classified the same for this endpoint.

Data Matrix – Toxicity data on the source and target substance:

Substance	Source Substance	Target Substance
Chemical Name	**Lithium (bis)trifluoromethanesulfonimide (LiTFSI)**	**Sodium (bis)trifluoromethanesulfonimide (NaTFSI)**
CAS RN	90076-65-6	91742-21-1
Molecular weight	287.09	303.14
Molecular formula	$C_2F6NO_4S_2.Li$	$C_2F_6NO_4S_2.Na$
Structural formula		
Information on the physicochemical properties		
Physical state	White powder	White powder
Melting point	232-233°C	253°C
Vapour pressure at 25°C (Pa)	Negligible (4.0E-6 Pa)	Negligible (6.01E-9 Pa)
Water solubility	> 1000 g/L at 20°C	≥ 428 g/L at 20°C
Log P_{ow}	-1.19 ± 0.11	Derived by read-across from Source substance. Low Log P supported by QSAR calculation.
Granulometry	MMAD: 51 µm Particles < 100 µm (96%)	D10, D50 and D90 values were determined at 3.0, 17.6 and 561 µm
Toxicological properties		
Acute oral toxicity	Test Guideline: OECD Guideline 423, GLP Species: Rat (Sprague-Dawley) Sex: Male/female Route: Oral, gavage LD50: > 200 - < 2000 mg/kg Reliability: Klimisch 1 Ref.: Pelcot, 2002 --- Test Guideline: OECD Guideline 401, non-GLP Species: Rat (Sprague-Dawley) Sex: Male/female Route: Oral, gavage LD50: 210 mg/kg (females); 160 mg/kg (males) Reliability: Klimisch 2 Ref.: Glaza, 1988	Derived by read-across from Source substance
Acute dermal toxicity	Test Guideline: OECD Guideline 402, non-GLP Species: Rabbit (New Zealand White) Sex: Male/female Route: Dermal, semi-occlusive LD50: 400 mg/kg Reliability: Klimisch 2 Ref.: Glaza, 1992	Derived by read-across from Source substance
Skin irritation	Test Guideline: OECD Guideline 404, non-GLP Species: Rabbit (New Zealand White) Coverage: semi-occlusive Result: Corrosive to skin Key study, 2 (reliable with restrictions) Ref.: Glaza, 1988	Derived by read-across from Source substance
Eye irritation	Test Guideline: OECD Guideline 405, GLP Species: Rabbit (New Zealand White) Result: Severe eye irritation Reliability: Klimisch 1 Ref.: Pelcot, 2002	Derived by read-across from Source substance

Substance	Source Substance	Target Substance
Skin sensitisation	Test Guideline: OECD Guideline 406 (Magnusson and Kligman test), GLP Species: Guinea pig (Dunkin-Hartley) Sex: male/female Result: Not sensitising Reliability: Klimisch 1 Ref.: Pelcot, 2002; Parcell 1993	Derived by read-across from Source substance
Genetic toxicity *in vitro* gene mutation study in bacteria	OECD Guideline 471 Strains: S. Typhimurium TA1535, 1537, 98, 100, 102; E. coli WP2 uvrA Result: Negative (with and without S9-mix) Reliability: Klimisch 1 Ref.: Haddouk, 2002	Derived by read-across from Source substance
Repeated dose toxicity – oral route 28 days	Test Guideline: OECD Guideline 407, GLP Species: Rat, (Sprague-Dawley) Sex: male/female Route: oral, gavage Duration: 28 days treatment followed by a 2-week treatment-free period Doses: 0, 15, 45, 90 mg/kg bw/day $NOAEL_{systemic}$: 15 mg/kg bw/day (based on increased liver weight, hepatocellular hypertrophy and changes in clinical biochemistry parameters at 45 mg/kg: lower cholesterol and triglycerides) Reliability: Klimisch 1 Ref.: Mhedhbi, 2002 ---------- Test Guideline: OECD Guideline 407, GLP Species: Rat, (Sprague-Dawley) Sex: male/female Route: oral, gavage Duration: 28 days treatment followed by a 2-week treatment-free period Doses: 0, 1.67, 10, 60 mg/kg bw/day $NOAEL_{systemic}$: 10 mg/kg bw/day (based on increased liver weight and hepatocyte enlargement in males and females and increased in kidney weights in males at 60 mg/kg) Reliability: Klimisch 1 Ref.: Edwards, 1993	Derived by read-across from Source substance
AQUATIC TOXICITY		
Short term toxicity to aquatic invertebrates	Test Guideline: OECD guideline 202, GLP Species: *Daphnia magna* Analytical monitoring: yes 48-EC50 (nom): >100 mg/L Reliability: Klimisch 1 Ref.: de Groot, 2004	Derived by read-across from Source substance
Green Algae	Test Guideline: OECD guideline 201, GLP Species: *Desmodesmus subspicatus* Analytical monitoring: yes 72-h EbC50: 36 mg/L 72-h ErC50: 178 mg/L 72-h NOEC (biomass, growth rate): 5 mg/L 72-h LOEC (biomass, growth rate): 10 mg/L 72-h ChV (biomass, growth rate): 7.1 mg/L Reliability: Klimisch 1 Ref.: L'Haridon, 2002	Derived by read-across from Source substance

ENVIRONMENTAL FATE AND BEHAVIOUR		
Biodegradation in water: screening test	Test Guideline: OECD guideline 302B, GLP Inoculum: Activated sludge, domestic Analytical monitoring: no Result: 9% degradation after 28 days Conclusion: not inherently biodegradable Reliability: Klimisch 1 Ref.: L'Haridon, 2002	Derived by read-across from Source substance