Manganese REACH Conference

Sept. 26-28, 2023

The Thon Hotel
Brussels, Belgium

DAY 1

REGISTRATION OF MN BASED SUBSTANCES

PUTTING IT INTO CONTEXT

Who We Are!

- The Manganese REACH Administration (MARA) is an EU based not-for-profit organization
- It was set up on 2008 to help the Mn industry comply with EU REACH
- Presently it has 33 members and is no taking any more members
- Its mandate is to support its members and the SIEF to comply with REACH (Registration, Evaluation, Authorization of chemicals) both within and outside the EU)

MN SUBSTANCES REGISTERED UNDER EU REACH

12 Substances within our portfolio

Substance name	EINECS	CAS	SIEF-nominated Lead Regis trants
Manganese	231-105-1	7439-96-5	Exponent OR for Assore
Manganese oxide	215-695-8	1344-43-0	Vibrantz
Manganese dioxide	215-202-6	1313-13-9	Tosoh Hellas A.I.C.
Trimanganese tetraoxide	215-266-5	1317-35-7	Vibrantz
Manganese carbonate	209-942-9	598-62-9	Vibrantz
Manganese sulphate	232-089-9	7785-87-7	Vibrantz
Manganese dinitrate	233-828-8	10377-66-9	Vibrantz
Slags, FeMn-manufacturing	273-728-1	69012-28-8	XEAL
Slags, SiMn-manufacturing	273-733-9	69012-33-5	XEAL
Manganese ores, reduced	273-748-0	69012-49-3	Ferroglobe Manganese France
Manganese dichloride	231-869-6	7773-01-5	Vibrantz
Manganese sulphide	242-599-3	18820-29-6	Höganäs AB

2010 Registrations

2013 Registrations

Lead Registrant logos

TOSOH HELLAS SINGLE MEMBER S.A.

xeal

VIBRANTZ TECHNOLOGIES™

Ferroglobe
Advancing Materials Innovation

ASSORE

Compliance checks stats- Draft Decision

In 2013 MARA received several draft decisions – In summary

1) Silicomanganese slags: 90 days, PND rats/Rabbits and Two Gen Repro
2) Mn3O4: PND rats/Rabbits, Two Gen Repro and Chronic Aquatic C&L concerns

In 2014 more draft decisions are issued– In summary

3) MnO2: PND rats/Rabbits, Two Gen Repro & DNEL derivation
4) MnCO3: 90 days, PND rats/Rabbits, Two Gen Repro & Chronic Aquatic C&L concerns
5) FeMn slags: 90 days, PND rats/Rabbits and Two Gen Repro

Compliance checks – Final outcome

In 2015 MARA received several Final decisions – In summary

1) Silicomanganese slags: 90 days, ~~PND rats/Rabbits and Two Gen Repro~~
2) *Mn3O4: PND rats~~/Rabbits, Two Gen Repro and Chronic Aquatic C&L concerns~~ * 2016

3) MnO2: ~~PND rats/Rabbits, Two Gen Repro & DNEL derivation~~
4) MnCO3: ~~90 days,~~ PND ~~rats~~/Rabbits, ~~Two Gen Repro & Chronic Aquatic C&L concerns~~
5) FeMn slags: ~~90 days,~~ PND rats~~/Rabbits~~ and ~~Two Gen Repro~~

UNHARMONISED REPORTING OF CLASSIFICATION & LABELLING

Registration outcomes: C&L

- Upon complying with all the Registration information requirements – we must use the available data to classify or not under CLP
- The classification & Labelling is considered the final outcome of the Phys-chem, Tox and ecotox investigations
- With the one substance one registration mantra, it was expected for industry to submit similar classification and labelling per substance
- On the ECHA information on chemicals Portal, it is clear that multiple C&L exist per substance

Examples of multiple C&L per substance

Manganese REACH Administration

- The Lead Registrants classification for Mn (Manganese metal) vs C&L Portal

a) Massives: Not Classified hence no labelling.
b) Classification is specific to particle size and quantity- particle size < 45 µm present at 2.5 to 25 % - Classified as follows

Classification	Particle size < 45 µm present at 2.5 to 25
Pictogram	
Signal word	
Hazard statement	
Precautionary statement Pr	
Precautionary statement Di	

Notified classification and labelling according to CLP criteria

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Classification affected by Impurities / Additives	Additional Notified Information	Number of Notifiers
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)					
Not Classified									1344
Aquatic Chronic 2	H411	H411		GHS09				State/Form	785
Aquatic Chronic	Water-react. 1	H260	H260	GHS02 Dgr				38	View details
Eye Irrit. 2	Repr. 1B	H360	H360	GHS08 Dgr			State/Form	16	View details
	STOT RE 2	H373 (other:Nervous S...)	H373						
Flam. Sol. 2	STOT RE 2	H373 (Nervous System,...)	H373						
STOT RE 2	Muta. 1B	H340	H340	GHS08 Dgr				11	View details
STOT RE 2	STOT SE 1	H370 (other:respirato...)	H370						
	STOT RE 1	H372 (nervous system,...)	H372						
	Water-react. 1	H260	H260	GHS02 GHS07 Dgr				9	View details
	Eye Irrit. 2	H319	H319						
	STOT RE 1	H372	H372	GHS08 Dgr			State/Form	6	View details
	Flam. Sol. 2	H228	H228	GHS08 GHS02 Wng			State/Form	4	View details
	STOT RE 2	H373 (not known)	H373						

c) Classification is spec
> 25 % percentage shou

Classification
Pictogram
Signal word
Hazard statement
Precautionary statement Prevention
Precautionary statement Response
Precautionary statement Disposal

Examples of multiple C&L per substance

Manganese REACH Administration

❖ Another Example with implications beyond REACH

Lead Registrant Dossier concludes Manganese Dioxide is classified as such

Classification	Acute Tox 4, Acute Tox 4, STOT RE2
Pictogram (GHS07, GHS08)	
Signal word	Warning
Hazard statement	H302: Harmful if swallowed. H332: Harmful if inhaled. H373: May cause damage to the brain through prolong or repeated exposure via inhalation
Precautionary statement Prevention	P260, P271, P270, P261, P264
Precautionary statement Response	P301+312, P304+340, P330, P314
CLP supplemental hazard	EUH031: Contact with acids liberates toxic gas. [European Union]

Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)
Acute Tox. 4	H302	H302
Acute Tox. 4	H332	H332
Acute Tox. 4	H302	H302
Acute Tox. 4	H332	H332
STOT RE 2	H373 (brain) (inhalation)	H373 (Target organ br...)
Acute Tox. 4	H302	H302
Acute Tox. 4	H332	H332
STOT RE 1	H372 (Central nervous...)	H372
Acute Tox. 4	H302	
		H302+H332
Acute Tox. 4	H332	
STOT RE 2	H373 (Central nervous...)	H373
STOT RE 2	H373 (other:Central n...)	H373
Acute Tox. 4	H332	
STOT RE 2	H373 (Heart) (inhalation)	
Acute Tox. 4	H302	
Acute Tox. 4	H332	
STOT RE 2	H373 (liver) (oral)	
Acute Tox. 4	H302	
Acute Tox. 4	H332	
STOT RE 1	H372 (Central nervous...)	
Muta. 2	H341	
STOT SE 1	H370 (other:respirato...)	
STOT RE 1	H372 (other:respirato...)	
Aquatic Chronic 4	H413	
Acute Tox. 4	H302	
Acute Tox. 4	H332	
STOT RE 2	H373 (blood) (inhalation)	

Last month's ECHA news:

- ECHA will support the European Commission in identifying substances of concern found in batteries or used in their manufacturing.
- It will also prepare proposals to restrict substances in batteries….

Implications of Multiple C&L

- ✓ Regulators see this as industry is unsure of the toxicity profile/potential hazard caused by the substances they place in the EU Market
- ✓ Non-EU Regulatory bodies that copy from the EU could simply copy/paste the worse C&L reported for precautionary reasons
- ✓ It has the potential to spill into other regulations applicable to uses/within the substance life cycle or waste
- ✓ Our workers will lose confidence in the industry in which they work in as the information provided portrays uncertainty
- ✓ Increases the possibility of substances being included into the candidate list (SVHC) or other Regulatory reviews/reports

Other regulatory reports

- The production of these reports is usually due to heighten regulatory concerns emanating wrong or over precautions classification & labelling or uses that highlight widespread dispersion.
- These report put a lot of pressure on industry and sometimes have financial implications
- The outcome of these reports do creep across national boundaries

A Few Examples:

- ✓ Japanese GHS
- ✓ ECHA Assessment of Regulatory Needs
- ✓ Restriction Roadmap
- ✓ ANSES ED Report

Regulatory Reports (1)

Manganese REACH Administration

ECHA
EUROPEAN CHEMICALS AGENCY

CONFIDENTIAL

Helsinki, 22 January 2018

Annex I - List of substances belonging to the Manganese compounds group as part of the 2018-shortlist of substances of potential concern

No.	EC/List no.	CAS no.	Regulatory notes	substance public name	Link to infocard
1	209-942-9*	598-62-9	registered	Manganese carbonate	https://echa.europa.eu/substance-information/-/substanceinfo/100.009.040
2	231-105-1*	7439-96-5	registered	Manganese	https://echa.europa.eu/substance-information/-/substanceinfo/100.028.277
3	233-828-8*	10377-66-9, 17141-63-8	registered	Manganese dinitrate	https://echa.europa.eu/substance-information/-/substanceinfo/100.030.741
4	215-202-6*	1313-13-9	registered	Manganese dioxide	https://echa.europa.eu/substance-information/-/substanceinfo/100.013.821

* *These substances have been identified as reproductive toxicants by GHS Japan*

Regulatory Reports (2)

ECHA Assessment of Regulatory Needs report was published 7 December 2021, version 1.0. The report covers “Simple Manganese Compounds”.

Six sub-groups are listed:

- Group I is a large group (14 substances) and includes soluble and poorly soluble manganese salts as well as manganese metal itself.
- Group II contains only sodium and potassium permanganate

Possible first outcome includes application of further harmonised classification and labelling (CLH) with respective to **aquatic toxicity, reproductive toxicity and STOT RE (neurotoxicity)**

We are working to a avoid blanket classifications being applied across substances within/outside the Groups

Regulatory Report (3)

Manganese REACH Administration

- ✓ Proposal for a Restriction Roadmap under the Chemical strategy For sustainability – June 2021
- ✓ The stated objectives of the Roadmap are to:
  - ensure 'transparent and timely' fulfilment of commitments
  - provide an overview of how authority resources are being used
  - provide transparency to stakeholders and enable companies to anticipate forthcoming restrictions (in their substitution efforts etc.)
- ✓ Pool 2: Potential restrictions where CLH or Candidate listing (to formally agree on the hazard at EU level) is part of the foreseen regulatory needs assessed by ECHA along with restriction– Includes Manganese
- ✓ 15 simple manganese compounds made up this group and are proposed for CLH.
- ✓ Proposal is based on 'R, STOT RE, Neurotox' concerns

EUROPEAN COMMISSION

Directorate-General for Environment
Circular Economy and Green Growth
Sustainable Chemicals

ECHA
EUROPEAN CHEMICALS AGENCY

Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs
Ecosystems I: Chemicals, food, retail
REACH
Bioeconomy, Chemicals & Cosmetics

Brussels,
Doc.CA/34/2021

40th Meeting of Competent Authorities for REACH and CLP (CARACAL)
Open session
29 June 2021
Online

Concerns: **Proposal for a Restrictions Roadmap under the Chemical Strategy for Sustainability**

Agenda Point: **AP - 8.1**

DRAFT

Regulatory report (4) - ED

Manganese REACH Administration

- Endocrine Disruptor Chemicals (EDCs) are substances that alter function(s) of the endocrine system and consequently cause adverse health effects
- The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) was mandated on 8 October 2019 to identify and prioritize“ chemicals that may present Endocrine Disruptor (ED) properties”
- To achieve this, a scientifically robust overview from an inventory of published lists at European and international levels as well as indepth literature review was carried out - regardless of their sectors of use and the sectorial regulations
- The review started with 96 substances, then reduced to 59 and now 20 substances which include MnCl2
- Criteria for selection uses, tonnage, harmonized classification for CMR and vPvB

anses

Élaboration d’une liste de substances chimiques d’intérêt en raison de leur activité endocrine potentielle

Méthode d’identification et stratégie de priorisation pour l’évaluation

Contribution à la Stratégie nationale sur les perturbateurs endocriniens 2019-2022

Summary of Concerns

- Reproductive Toxicity
- Specific Target Organ Toxicity (Neurotoxicity)
- Aquatic toxicity
- Endocrine Disruption

These are all concerns which if not addressed properly could :-

1) Lead to a Blanket classification
2) Lead to over classification for precautionary reasons (Cat 1's)
3) Lead several manganese-based substances into the candidate list (Substance of Very high concern) – Restriction and even substitution

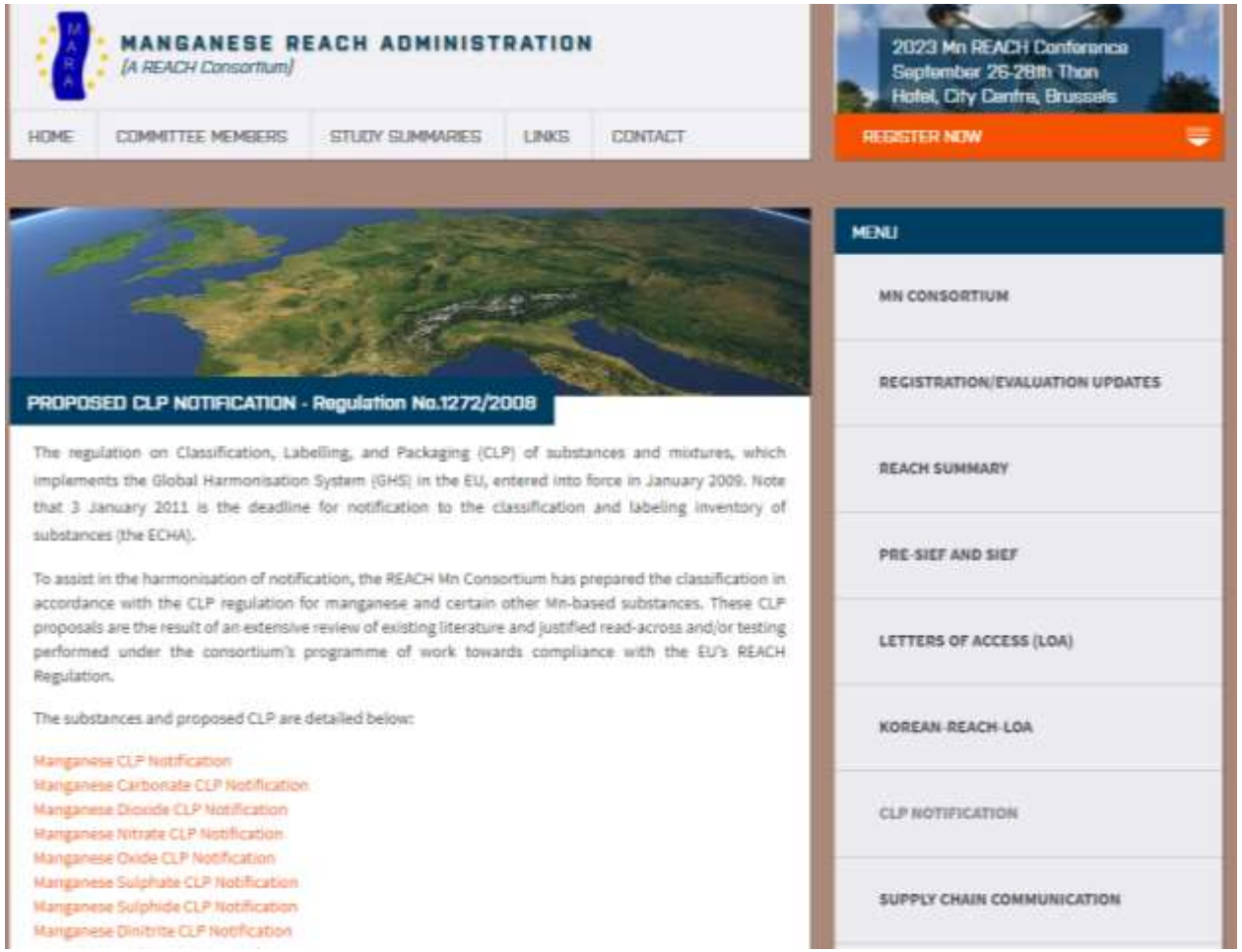
Therefore, we as Industry must work together to better understand and address these issues

Take home message

- Based on available data Mn-based substances is not carcinogenic nor mutagenic
- Industry does has notified different classifications for the same substances – this is a dangerous path.
- Regulatory concerns for several inorganic Mn-based substances are focused on reproductive toxicity, neurotoxicity, ED and Chronic aquatic toxicity – any one of which can lead to authorisation/restriction
- Industry must work together PROACTIVELY to address these concerns starting with adopting one substance, one registration, one classification
- Co-Registrants must work with lead registrants and MARA to update dossiers – strengthen waivers, eliminate inconsistencies, employ new good data, understand use patterns…because dossiers are the backbone of most regulatory reports

Thank you!
Any Questions?

Manganese REACH Administration



Go to the MARA's website and compare your classification (both that submitted to ECHA and that on your SDS) with that of the Lead Registrant. If different, amend or write to reach@manganese.org for supporting data justifying the LR/MARA's position

SVHC Status: manganese and manganese compounds

John Hislop

Relax Global Compliance

Content

- SVHC meaning under REACH
- Identification of SVHC
- Impact of SVHC designation
- ARN for Simple Manganese Compounds : scope and potential impact

What is SVHC under REACH? (1)

SVHC: Substance of Very High Concern

Defined in Article 57 of the REACH Regulation;

- (a)substances meeting the criteria for classification in the hazard class carcinogenicity category 1A or 1B in accordance with section 3.6 of Annex I to Regulation (EC) No 1272/2008;
- (b)substances meeting the criteria for classification in the hazard class germ cell mutagenicity category 1A or 1B in accordance with section 3.5 of Annex I to Regulation (EC) No 1272/2008;
- (c)substances meeting the criteria for classification in the hazard class reproductive toxicity category 1A or 1B, adverse effects on sexual function and fertility or on development in accordance with section 3.7 of Annex I to Regulation(EC) No 1272/2008;

What is SVHC under REACH? (2)

- (d)substances which are persistent, bioaccumulative and toxic in accordance with the criteria set out in Annex XIII of the REACH Regulation;
- (e)substances which are very persistent and very bioaccumulative in accordance with the criteria set out in Annex XIII
- (f)substances — such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties, which do not fulfil the criteria of points (d) or (e) — for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis

Identification of SVHC (1)

- Identification of Substances of Very High Concern (SVHC) comprises the core of ECHA's Strategic priority 1 and aims to accelerate data generation and regulatory action on substances of concern
- A MSCA submits an Annex XV dossier proposing identification of a substance or a group of substances as SVHC

Alternatively:

- The European Commission requests that ECHA prepares such an Annex XV SVHC dossier.
- Screening may also lead to assignment of a particular substance or group of substances in the category "high priority for risk management".

Identification of SVHC (2)

- The intention to propose a substance for identification as an SVHC is published in the registry of intentions before the proposal is submitted, to inform interested parties in advance of the submission of the report.
- The report is prepared according to Annex XV to REACH and includes two main parts; 1) data and justification for identifying the substance as an SVHC. 2) information on volumes on the EU market, the uses and possible alternatives to the substance.
- Once ECHA receives the final Annex XV SVHC dossier, it makes this available within 30 days of receipt to the other MSCAs and to interested parties for commenting during a 45-day consultation period.

Addition of SVHC to the Candidate List

- The Annex XV report is reviewed by the Member State Committee (MSC) to conclude on the identification of the substance as an SVHC.
- If the MSC reaches a unanimous agreement, the substance is added to the Candidate List for authorisation. If the committee does not reach a unanimous agreement, the matter is referred to the Commission.
- The procedure ends with either the identification of the substance as an SVHC and subsequent inclusion on the updated Candidate List or a decision that the substance has not been identified as an SVHC.

Route to Authorisation: The Candidate List

- ECHA's preference has been to ensure that substances identified as SVHC are progressively replaced by less dangerous substances via the authorisation process.
- The route to authorisation begins when a Member State or ECHA, at the request of the Commission, proposes a substance to be identified as SVHC.
- All substances concluded to be SVHC are included in ECHA's Candidate List, which is updated twice a year.
- The Candidate List now has more than 200 entries; some are for groups of chemicals so the overall number of impacted chemicals is higher.
- Candidate List substances may be placed on the Authorisation List in the future. If a substance is on that list, its use will be prohibited unless companies apply for authorisation and the European Commission authorises them to continue its use.

Mn & Mn compounds: Current C&L Assignment

Hazard	Hazard statement	Pictogram	Substances	Comments
STOT RE2 (neurotoxicity)	H373		Mn chloride Mn sulphate Mn nitrate Mn dioxide Sodium permanganate Potassium permanganate	Mn sulphate : harmonised C&L
Repro 2	H361		Trimanganese tetraoxide Slags, SiMn-manufacturing Slags, FeMn-manufacturing Manganese ores, reduced	Potassium permanganate : harmonised C&L (H361d)

Assessment of Regulatory Needs (ARN)

- ARN is a component of ECHA's Integrated Regulatory Strategy. The ARN is not a formal processes defined in the legislation but aims to support them.
- ARN aims to help authorities conclude on the most appropriate way to address the identified concerns for a group of substances or a single substance, i.e. to identify the regulatory risk management instruments to be used (if any) and any intermediate steps, such as data generation.
- It can be concluded that regulatory risk management at EU level is required (e.g. harmonised C&L, Candidate List inclusion, restriction, other EU legislation) or alternatively that no regulatory action is required at EU level.
- While the assessment is done for a group of substances, the need for regulatory action can be identified for the whole group, a subgroup, or for single substances.
- ARN does not necessarily initiate any regulatory processes but an authority can consequently do so and should indicate this by appropriate means, such as the Registry of Intentions.

ARN: Simple Manganese Compounds (1)

- ECHA Assessment of regulatory needs Authority: published 7 December 2021
- Status: Under development
- Group Name: Simple Manganese Compounds
- The group includes 29 manganese compounds. The substances are grouped to six sub-groups.
- I. Simple inorganic salts, oxides and manganese metal
- II. Permanganates
- III. Phosphates
- IV. Organometallic complexes
- V. Fatty acid salts
- VI. Simple organic salts

UVCB substances (SiMn flag, FeMn slag and Mn ores, reduced) are not included.

ARN: Simple Manganese Compounds (2)

- Subgrouping: ARN says that subgrouping is "based on chemical properties of the substances affecting their potential hazardous properties. Also, the use of read across among the substances and the clarity of substance identity was considered".
- First step: Confirmation of hazard(s) via harmonised classification (CLH)

Foreseen subsequent regulatory needs:

- Annex XIV (for reproductive toxicity and possibly neurotoxicity)
- Restriction (for reproductive toxicity, repeated dose toxicity and neurotoxicity hazards)

ARN: Simple Manganese Compounds (3)

- ARN states that a WoE analysis on all available information needs to be performed under CLH to conclude on reproductive toxicity and neurotoxicity (STOT RE) endpoints.
- Existing environmental classifications will also be assessed.
- CLH may trigger further RMM for workers and restrict the presence of manganese substances in consumer mixtures.

Impact of CLH on other regulations:

- Harmonised classification as CMR cat. 1 would trigger regulatory action under the Cosmetic products regulation (EC) No 1223/2009, since CMR cat. 1 are restricted by this regulation.
- Harmonised classification as CMR cat 1 would render the substances unacceptable co-formulants in plant protection products.

ARN: Simple Manganese Compounds (4)

- The need for regulatory risk management action is said to be strongest for the substances in sub-groups I and II, but it is expected to apply to other substances from sub-groups III to VI, following data generation steps to clarify the hazard
- Restriction of the substance as such or in mixtures (concentration limit in mixtures) used by professionals is suggested after CLH
- Restricting substances in articles used by professionals or consumers (reported for substances in sub-groups 1, 3, 4 and 6) is proposed since potential for exposure from articles cannot be excluded.
- For the remaining industrial uses where potential for exposure cannot be excluded it is suggested to use authorisation to control risks.

ARN: Simple Manganese Compounds (5)

Endocrine disruptor (ED) hazard:

- For all substances in the group ARN states that there is inconclusive evidence on human health ED hazard due to very limited relevant findings. The evidence is not considered sufficient to raise a concern or to suggest follow-up with further testing
- It is expected that the suggested classification for reproductive hazards will be adequate to lead to efficient RMMs).
- Note, however, that since ED is a new hazard class in CLP then increased scrutiny of this property is highly likely

Conclusions

- Assignment of SVHC has serious consequences
- The ECHA ARN is a likely precursor to regulatory action and SVHC listing
- Manganese compounds may face significant and wide-reaching actions, including harmonised classification and labelling, restriction and potentially authorisation
- There is a danger of all substances within the manganese ARN being tarred with the same brush
- It is important to consider now how these likely future regulatory requirements would affect business
- Ensure that the regulators are provided with the latest information to enable informed conclusions to be drawn

Questions

Any questions?

SEPTEMBER 2023

Reproductive toxicity – Rats and rabbits: Diversity in effects

Steve Renaut
Associate Director, DART
Labcorp

labcorp

Introduction

Diversity of effects

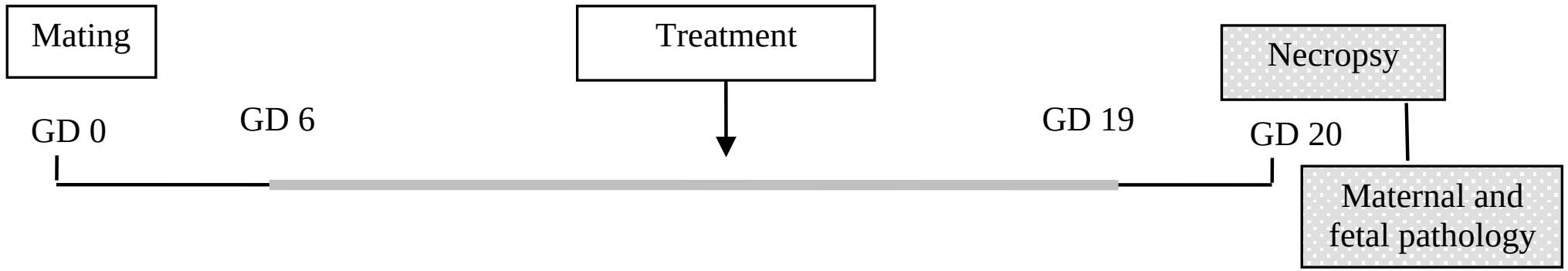
The purpose of this presentation is to provide an update on the outcome of OECD 414 studies in rats and rabbits, evaluating the diversity of effects observed following administration of manganese compounds across the two test species.

Ferromanganese slag

Ferromanganese slag: OECD 414 in rats

Study design

- Groups of 20 mated females dosed orally at 0, 100, 330 or 1,000 mg/kg/day from GD6 – GD 19, inclusive
- Maternal toxicity evaluated: Clinical signs, body weight gain, food consumption, macropathology
- Embryo-fetal survival, fetal growth and development evaluated on GD20



Ferromanganese slag: OECD 414 in rats

Results

- No unscheduled mortality/maternal toxicity
- All treated females pregnant
- Embryo-fetal survival unaffected
  - Live fetuses, levels of resorptions and pre/post-implantation loss
- Embryo-fetal development unaffected
  - No test item-related major fetal malformations or skeletal or visceral abnormalities observed at any dose level

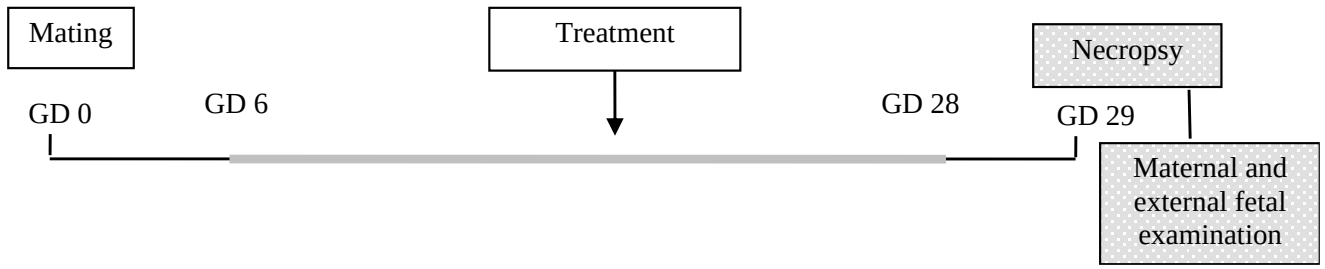
Conclusion: Rat maternal and embryo-fetal No Observed Adverse Effect Level (NOAEL) = 1,000 mg/kg/day

labcorp

Ferromanganese slag: OECD 414 study in rabbits

Study design

- Groups of 22 mated females dosed orally at 0, 100, 300 or 800 mg/kg/day from GD 6 to GD 28, inclusive
  - As no previous data was available in rabbits, study performed in two phases to guard against overt/adverse maternal toxicity; 6/group in Phase 1; 16/group in Phase 2
- Maternal toxicity evaluated: Clinical signs, body weight gain, food consumption, macropathology
- Embryo-fetal survival, fetal growth and development evaluated on GD 29



labcorp

Results

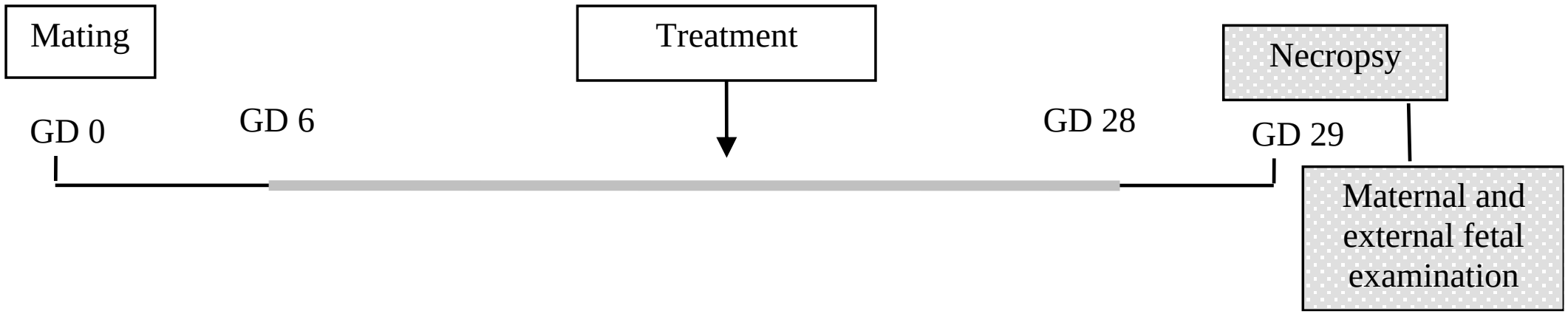
- No test item-related unscheduled mortality/maternal toxicity
- Consistent increase in post-implantation loss evident in both phases at 800 mg/kg/day
- No effect on fetal weights
- Unusual major fetal malformations in all treated groups:
  - Severe body edema, open eyelids, heart/blood vessel abnormalities, bent long bones
  - Majority not recorded in historical control data

Conclusion: maternal NOAEL = 800 mg/kg/day
Embryo-fetal survival NOAEL = 300 mg/kg/day
Embryo-fetal development NOAEL not established

Ferromanganese slag: investigative study in the rabbit

Objective

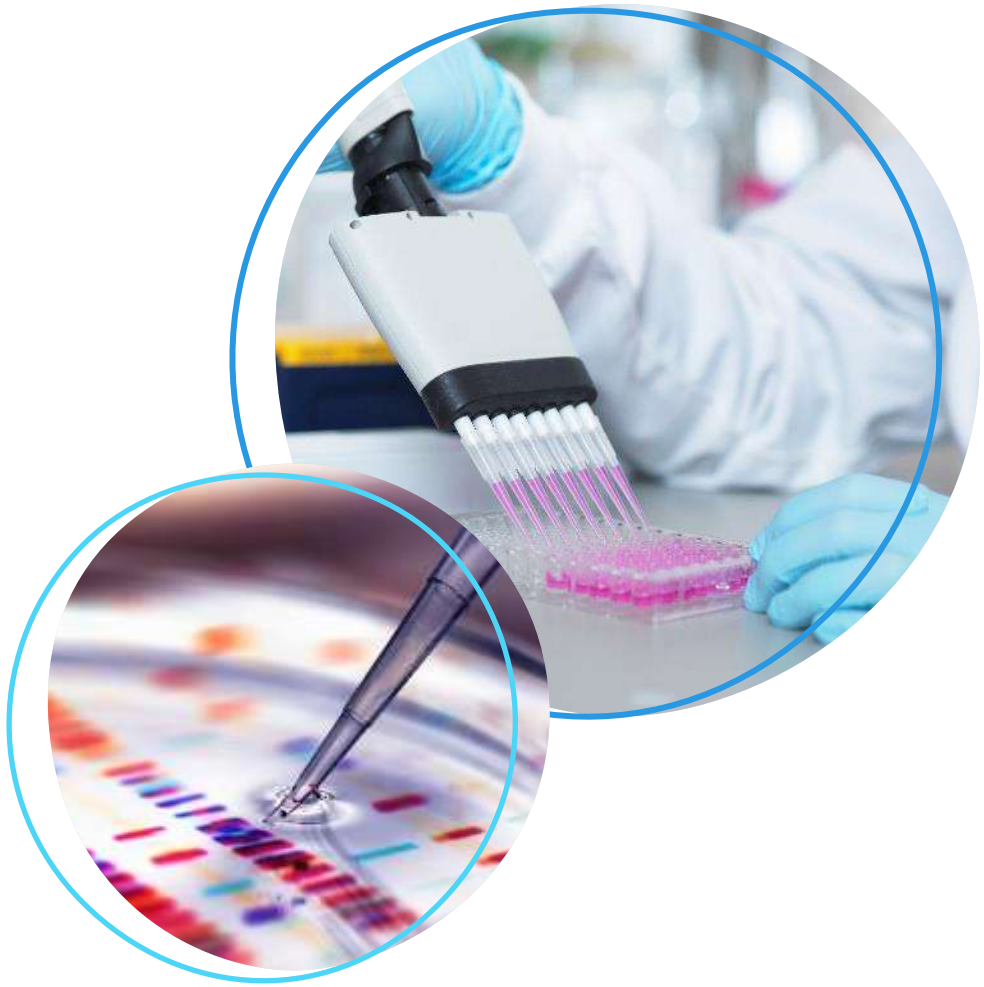
- Investigate potential cause of the increased post-implantation loss and major fetal malformations seen in the main rabbit OECD 414 study, which were not seen in the main rat OECD 414 study
- Single group of 5 mated females dosed orally at 400 mg/kg/day from GD 6 to GD 28, inclusive
- Additional endpoints:
  - Proof of exposure sampling, nutrient analysis (routine blood chemistry and Vitamins A, B6, B12 and folic acid) and gut flora analysis (various fecal microbial populations)



Ferromanganese slag: investigative study in the rabbit

Results

- Proof of absorption: No exposure detected
  - Manganese, silicon, aluminium, barium[1] all BLOQ
- No changes in nutrient levels
- No changes in gut flora
- All 5 females pregnant; no increase in post-implantation loss, fetuses macroscopically normal (fetal pathology not performed)



Conclusion: The cause of the increased post-implantation loss and fetal malformations observed in the OECD 414 rabbit study remains undetermined

1. Some of the primary components of the test item. These are known not to be absorbed by rats; it was possible that they may be absorbed by rabbits and a potential cause of the reprotoxic effects seen.

labcorp

Manganese dichloride

$MnCl_2$ (Mn2+)

Manganese dichloride: prenatal developmental toxicity study in the rat

Study design

- Groups of 22 mated females dosed by nose-only inhalation at 5, 15 or 25 µg/L air from GD 6 to GD 20 (day prior to caesarean section on GD 21)
- Once daily administration for 6 hours per day
- 6 non-mated Recovery animals included in the Control and 3 treated groups were observed for reversibility, persistence or delayed occurrence of systemic toxic effects in the lung. Treated from Day 1 to Day 15
- Maternal toxicity evaluated: Clinical signs, body weight gain, food consumption, reproduction (litter and fetal) data, macropathology, lung histopathology, fetal pathology

Manganese dichloride: prenatal developmental toxicity study in the rat

Results

- No unscheduled mortality. Breathing noises (8 females at 15 µg/L air, 18 females at 25 µg/L air). Dyspnea (breath shortness) in a single female at 15 µg/L air
- Histopathology (six selected pregnant females/group): Lung lesions with a dose-dependent frequency and severity at 15 or 25 µg/L air
- Dose-dependent reduction in food consumption at 15 or 25 µg/L air, considered adverse
- Dose-dependent effects upon body weight at 15 or 25 µg/L air, considered adverse
- Reproduction data (post-implantation loss and number of fetuses per dam, sex ratio) unaffected
- Fetal weight reduced at 25 µg/L air only: Not considered adverse
- Fetal thyroids enlarged at 25 µg/L air only: Histopathology revealed diffuse follicular hypertrophy/hyperplasia and an increase in mitotic figures in follicular epithelial cells
- Incomplete/lack of ossification of fetal skeletons at 25 µg/L air only: Linked to reduction in fetal weight and unlikely have any adverse impact on the post-natal growth and development

Manganese dichloride: prenatal developmental toxicity study in the rat

Results

- No Observed Adverse Effect Level (NOAEL) and No Observed Effect Level (NOEL) for the toxicity in pregnant females were considered to be 5 µg/L air
- NOEL as well as NOAEL for prenatal developmental toxicity was considered to be 15 µg/L air

Manganese carbonate

$MnCO_3$ (Mn2+)

Manganese carbonate: combined pilot/dose range finding study in rabbits

Study design

Pilot phase:

- Groups of 3 non-mated females dosed orally at 600 or 1,000 mg/kg/day (formulated in 1% methylcellulose) for up to 14 days
- Maternal toxicity evaluated: Clinical signs, body weight gain, food consumption, macropathology

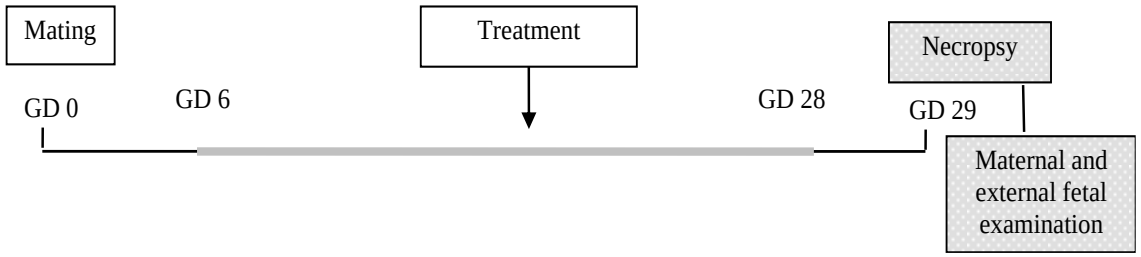
Results

- Treatment at 600 or 1,000 mg/kg/day was well tolerated
- At 1,000 mg/kg/day, possible effects of treatment were short periods of low food/water intake, pale faeces and reduced faecal pellet size

Manganese carbonate: combined pilot/dose range finding study in rabbits

Dose range finding embryo-fetal development phase (Part 1)

- Groups of 6 mated females dosed orally at 0, 300, 600 or 1,000 mg/kg/day from GD 6 to GD 28, inclusive
- Maternal toxicity evaluated: Clinical signs, body weight gain, food consumption, macropathology
- Embryo-fetal survival, growth and development evaluated GD29



Manganese carbonate: combined pilot/dose range finding study in rabbits

Phase 1 results

- No unscheduled mortality or maternal toxicity at 600 or 1,000 mg/kg/day but all females appeared not pregnant at uterine examination
- Overt maternal toxicity observed at 300 mg/kg/day:
  - Underactive behaviour, reduced body temperature, negligible food intake, body weight loss
  - 3/6 females euthanised for welfare reasons GD 16-18 (2 x total litter resorptions, one with 3 live fetuses)
  - Remaining three females survived to scheduled termination: One not pregnant, one total litter resorption, one with only one live fetus

labcorp

Manganese carbonate: combined pilot/dose range finding study in rabbits

Dose range finding embryo-fetal development phase (Part 2)

- Phase 2 added
- Groups of 6 mated females dosed orally at 30, 65 or 150 mg/kg/day from GD 6 to GD 28, inclusive
- Maternal toxicity evaluated: Clinical signs, body weight gain, food consumption, macropathology
- Embryo-fetal survival, growth and development evaluated GD29

labcorp

Manganese carbonate: combined pilot/dose range finding study in rabbits

Phase 2 results

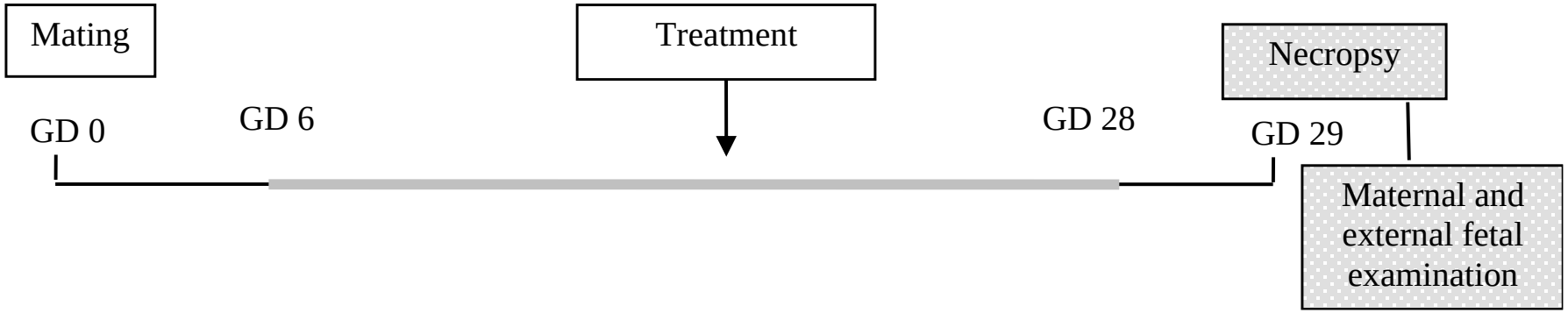
- No unscheduled mortality or maternal toxicity at 30 or 65 mg/kg/day
- Overt maternal toxicity observed at 150 mg/kg/day:
  - Underactive behaviour, reduced body temperature, negligible food intake, body weight loss
  - 3/6 females euthanised for welfare reasons GD 22-26 (one total litter resorption, two with live fetuses [6/5])
  - Remaining three females survived to scheduled termination: one not pregnant, one total litter resorption, two with eight live fetuses each

labcorp

Manganese carbonate: investigative study in the rabbit

Objective

- Investigate the potential cause of the implantation failure/pregnancy loss/premature deaths at doses above 65 mg/kg/day in the dose range finding embryo-fetal development study
- Single Group of 5 mated females dosed orally at 100 mg/kg/day from GD 6 to GD 28, inclusive
- Additional endpoints:
  - Proof of exposure sampling, nutrient analysis (routine blood chemistry and Vitamins A, B6, B12 and folic acid) and gut flora analysis (various fecal microbial populations)

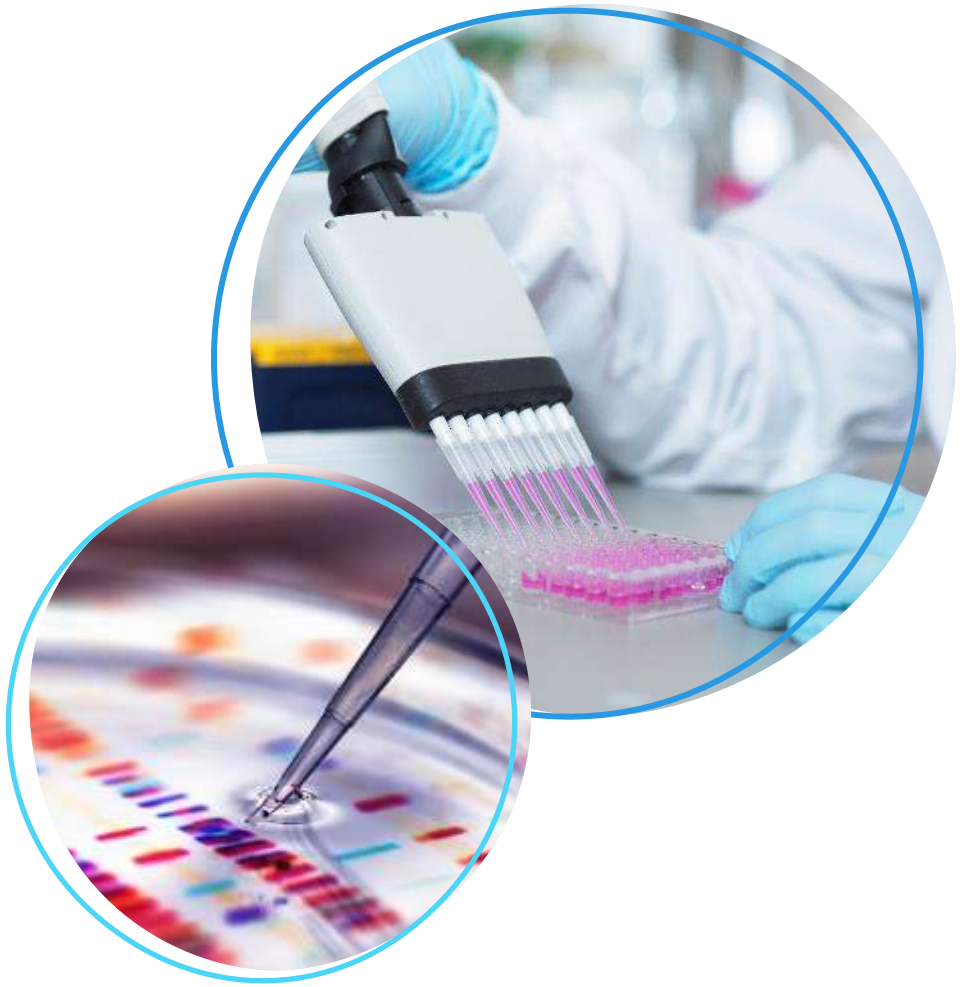


Manganese carbonate: investigative study in the rabbit

Results

- Proof of absorption: No exposure detected
  - Manganese, silicon, aluminium, barium all BLOQ
- No changes in nutrient levels
- No changes in gut flora
- 2 x Not pregnant; litter data for remaining 3 unaffected

Conclusion: The cause of the maternal toxicity, implantation failure and pregnancy loss observed in the dose range finding rabbit study remains undetermined.



Manganese carbonate: OECD 414 study in the rabbit

Currently ongoing at Labcorp, Eye, Suffolk, UK

- Groups of 24 mated females dosed orally at 0, 25 or 50 mg/kg/day and 28 mated females dosed orally at 100 mg/kg/day GD 6 to GD 28, inclusive
  - Increased group size to guard against potential non-pregnancy, to ensure sufficient litters are available for evaluation
- Maternal toxicity evaluated: Clinical signs, body weight gain, food consumption, macropathology
- Proof of exposure and clinical chemistry sampling GD 6 and GD 28
- Embryo-fetal survival, fetal growth and development evaluated GD 29
- In-life/fetal evaluation phase completed in mid-October 2023
- Audited draft report expected mid-December 2023

Reproductive toxicity – rats and rabbits: diversity in effects

Summary

- There are clear differences in the response of rats and rabbits to the administration of manganese compounds
- Ferromanganese slag: Tolerated by rats with no maternal toxicity or embryo-fetal malformations
- Manganese chloride (inhalation): Reproduction data unaffected, fetal findings restricted to enlarged thyroid
- Manganese compounds (ferromanganese slag and manganese carbonate) appear overtly toxic to pregnant rabbits either by increases in post-implantation loss or effects on embryo-fetal development (ferromanganese slag) or by implantation failure/pregnancy loss/adverse maternal toxicity (manganese carbonate)
- Mechanism for diversity in effects between the two test species has yet to be determined

Thank you

Manganese Neurotoxicity

David C. Dorman, DVM, PhD, DABVT, DABT, ERT
College of Veterinary Medicine
North Carolina State University
Raleigh, NC USA

Email: david_dorman@ncsu.edu

Manganese REACH Conference 2023

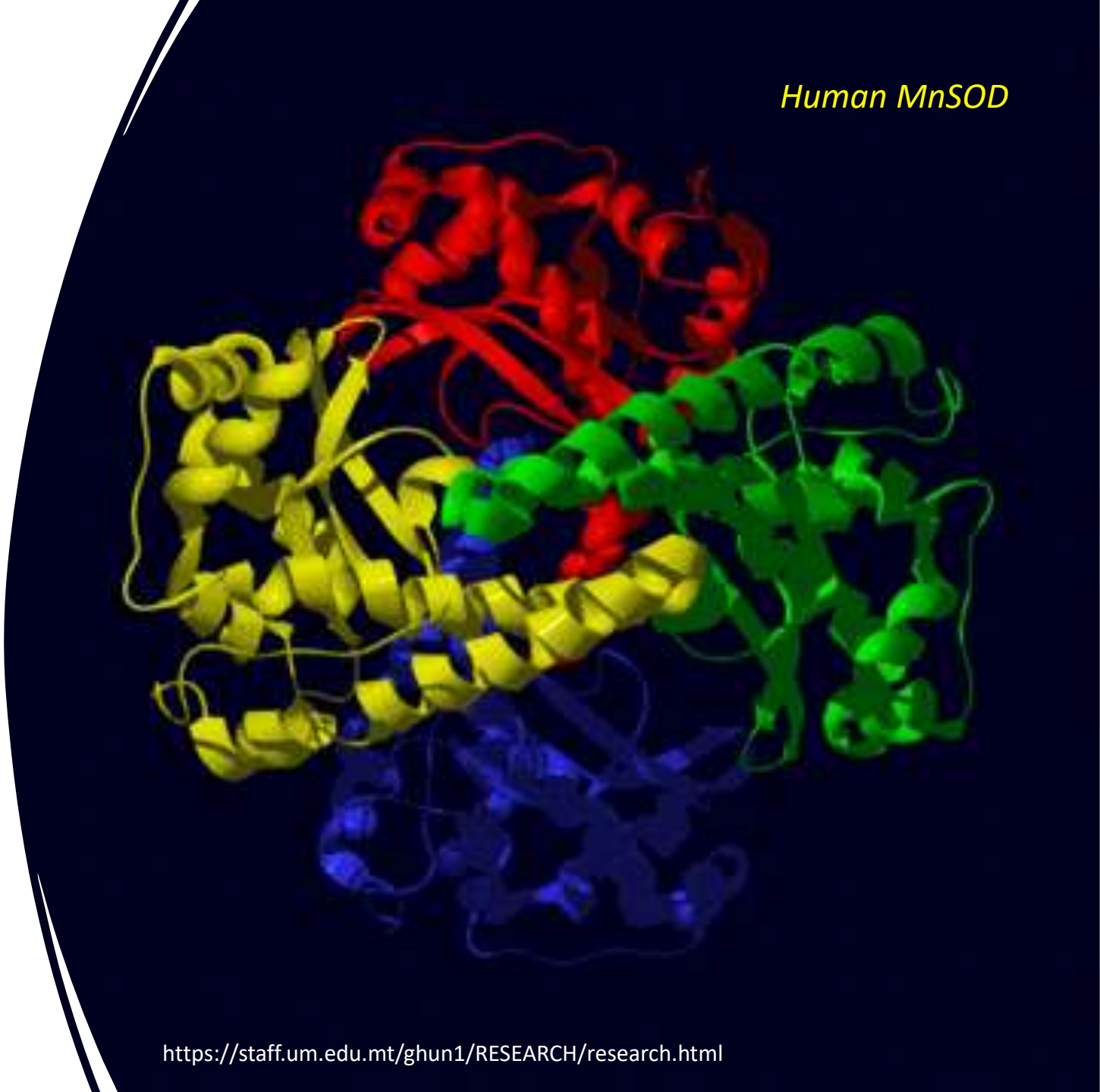
Travel supported by MARA

Overview

- Essentiality of manganese
- Manganese pharmacokinetics
- Manganese neurotoxicity
- Mechanisms of action
- Special considerations

Manganese Essentiality

- Essential element
- Involved in carbohydrate, cholesterol, and amino acid metabolism
- Cofactor for several enzymes
  - Manganese superoxide dismutase (MnSOD)
  - Glutamine synthetase
  - Others

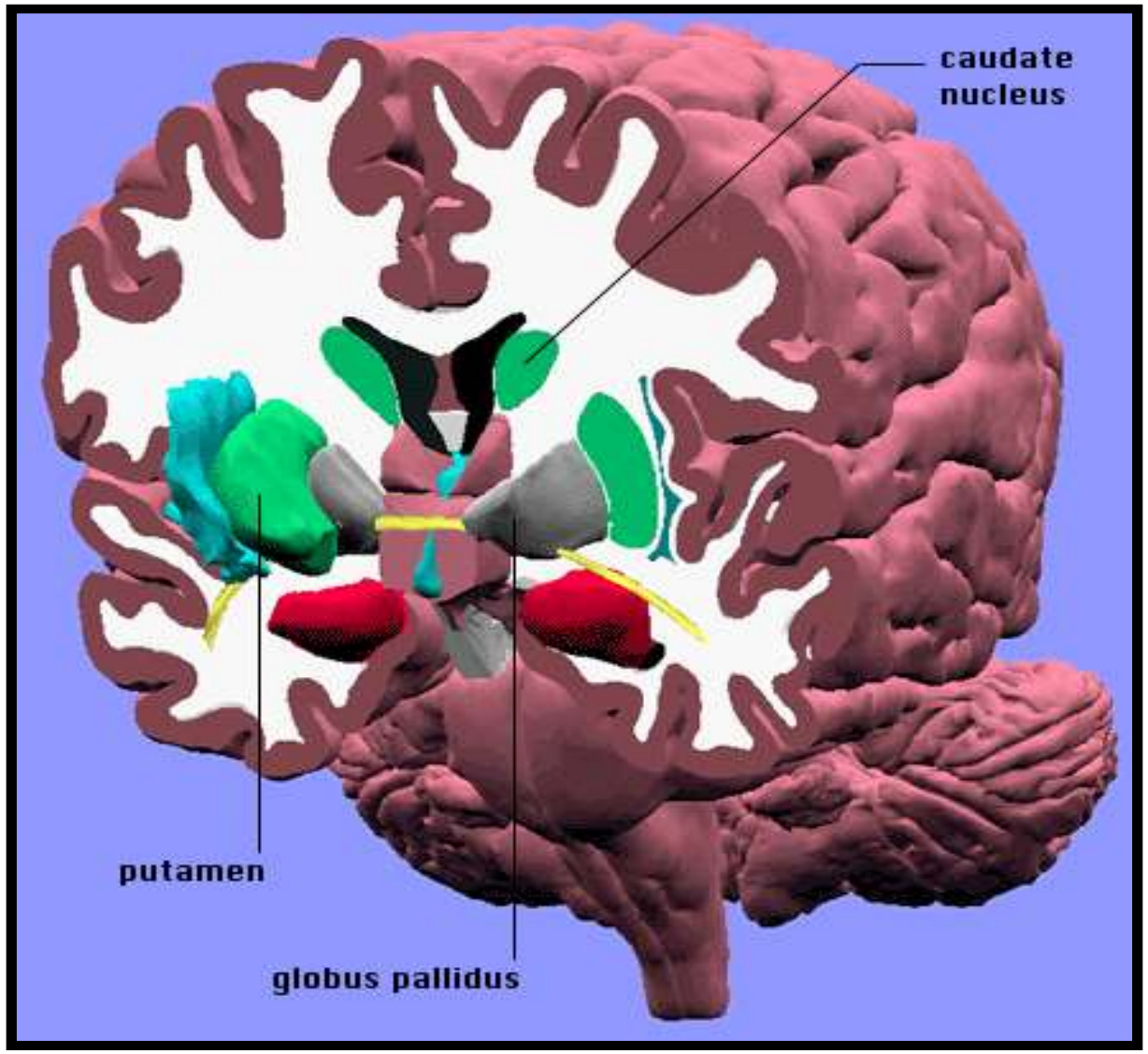


Manganese Essentiality

- Diet primary route of exposure
  - Estimated safe and adequate daily dietary intakes
    - 2 to 5 mg/day in adults
    - 1.5 to 2.0 mg/day for children 4 to 6 years of age

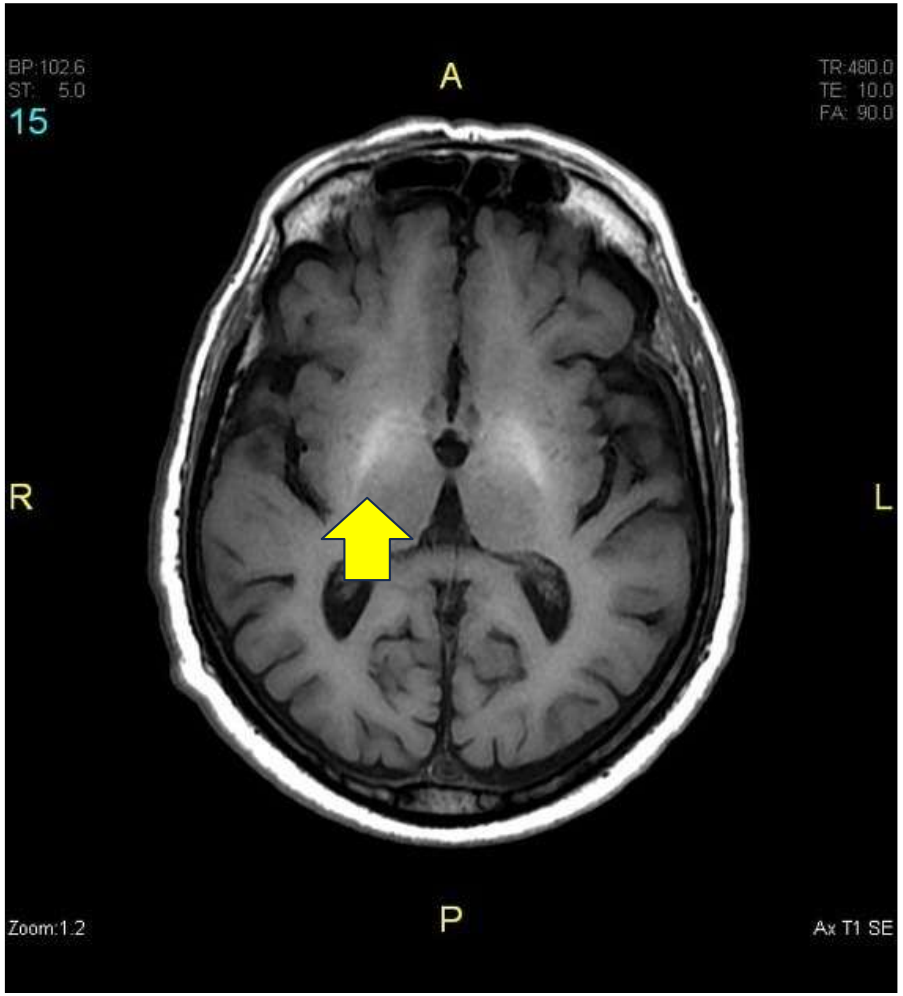
Manganese Neurotoxicity

- Manganese overload
  - Excess intake
  - Hepatobiliary disease
- Manganese initially accumulates in human brain structures associated with motor activity
  - Globus pallidus



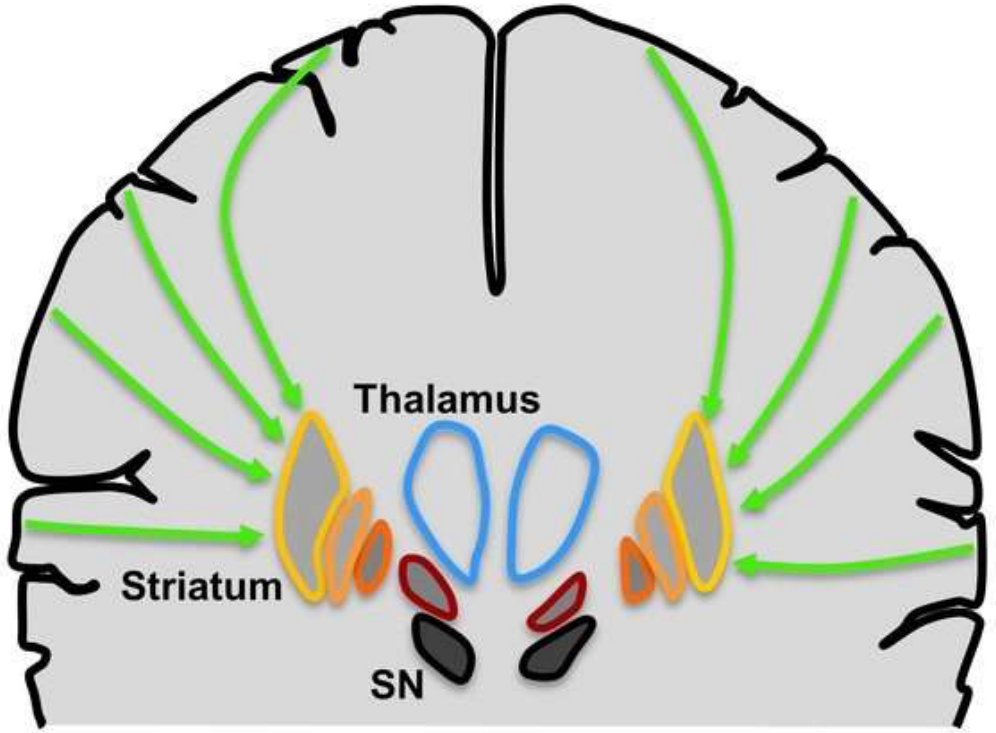
Manganese Neurotoxicity (Manganism)

- Form of parkinsonism in heavily exposed people
  - Primarily occurs following the chronic inhalation of Mn oxides
    - > 1 mg Mn/m^3
  - Motor impairments include bradykinesia, hypertonia with rigidity, stooped posture, cock-gait, rapid postural tremor, and postural instability



Manganese Neurotoxicity (Manganism)

- Damage to basal ganglial dopaminergic neurons
  - Other CNS sites are also affected

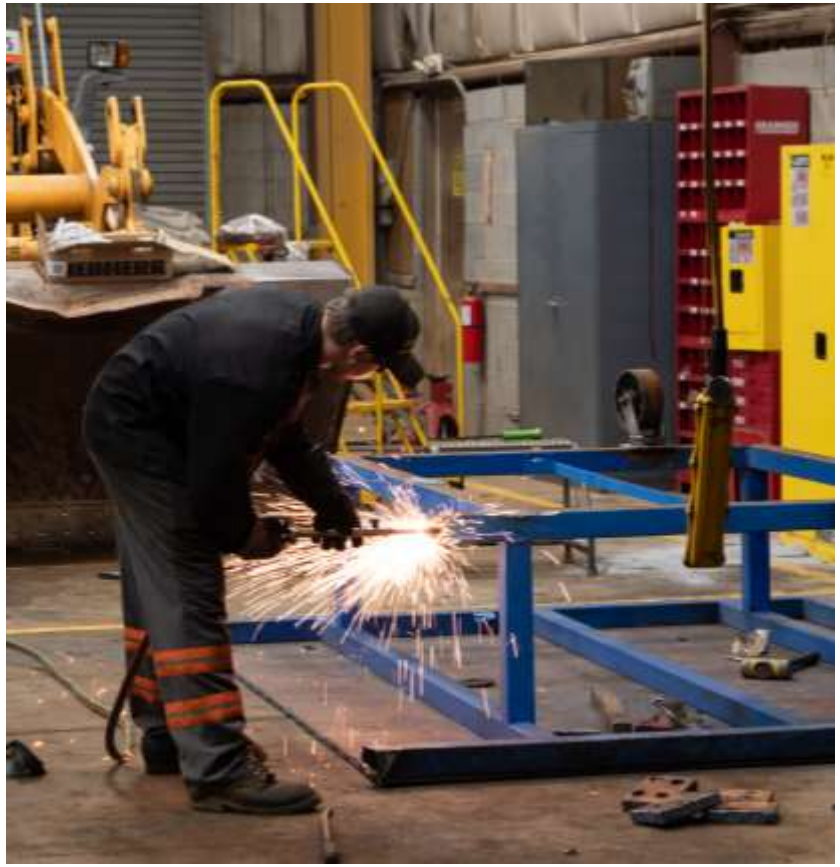


Tseng et al., 2017

GP: Globus pallidus
SN: Substantia nigra
ST: Subthalamic nucleus

Manganese Neurotoxicity (Occupational Exposure)

- Manganese workers include: welders, miners, and metal refinery workers (others)
- Occupational exposure is associated with:
  - Headache and fatigue
  - Altered libido
  - Cognitive dysfunction
  - Greater depression and anxiety
  - Motor deficits



Manganese Neurotoxicity (Environmental Exposure)

- Fewer reports arising from water or dietary intake
  - Relatively low Mn levels
    - Water Mn concentrations typically range from 1 to 100 µg/l, with most values below 10 µg/l
    - Associations reported between environmental manganese exposure and altered neurobehavioral performance
      - Chemical form of manganese is unknown

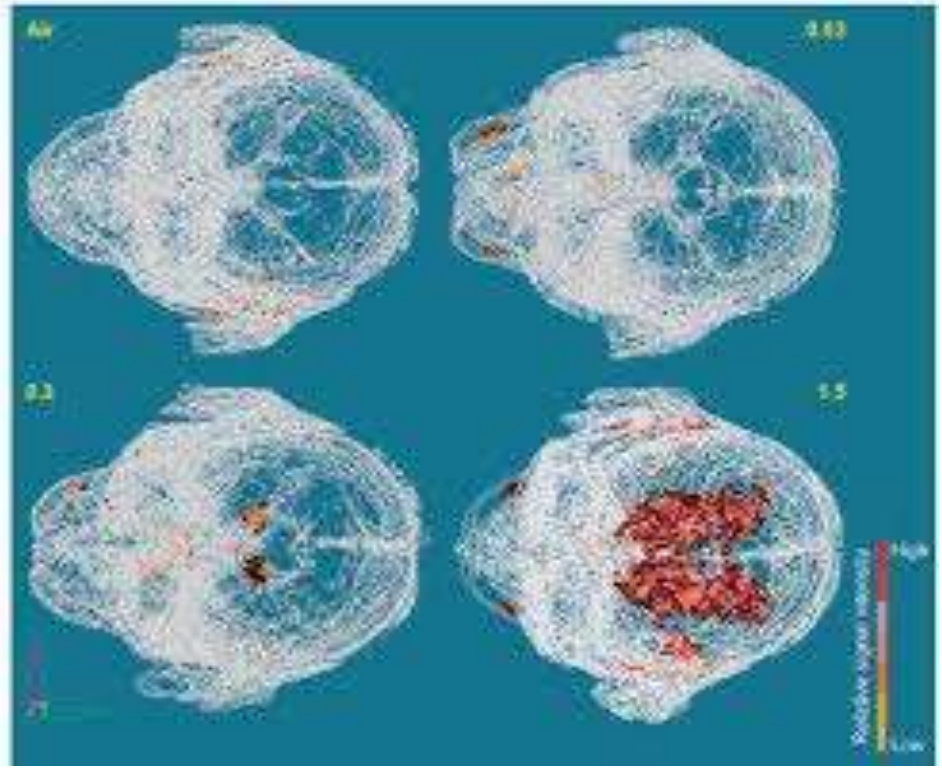
Manganese Neurotoxicity (Developmental Exposure)

- Concerns for potential vulnerability to Mn neurotoxicity during fetal and neonatal development have also been raised:
  - Childhood risk factors include higher intestinal absorption of ingested manganese
  - Lower basal hepatobiliary excretion rate
  - Enhanced delivery of manganese to the neonatal brain
  - Use of intravenous total parenteral nutrition (TPN) solutions that are supplemented with manganese

Manganese Neurotoxicity (Animal Studies)

- Species differences exist:
  - Nonhuman primates
    - Develop increased manganese levels in globus pallidus and motor deficits
  - Rodents
    - Don’t develop parkinsonism signs readily
    - Can develop behavioral, neurochemistry, and neuropathology changes

Rhesus monkey MRI following $MnSO_4$ inhalation (0, 0.6, 0.3, or 1.5 mg Mn/m^3) for 65 days



Dorman et al., 2006

Manganese Neurotoxicity (Animal Studies)

- Valuable for evaluating different chemical forms of manganese
- Available animal data for most forms of manganese supports Specific Target Organ Toxicity (STOT) Category 2 classification under REACH
  - Ongoing project

31.12.2008 EN Official Journal of the European Union L 353/1

I

(Acts adopted under the EC Treaty/Euratom Treaty whose publication is obligatory)

REGULATIONS

REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 December 2008

on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

(Text with EEA relevance)

Manganese Neurotoxicity – Some Substances are presently classified as STOT RE Cat 2

Based on available animal data

- Manganese Chloride
- Manganese Sulfate
- Manganese dioxide

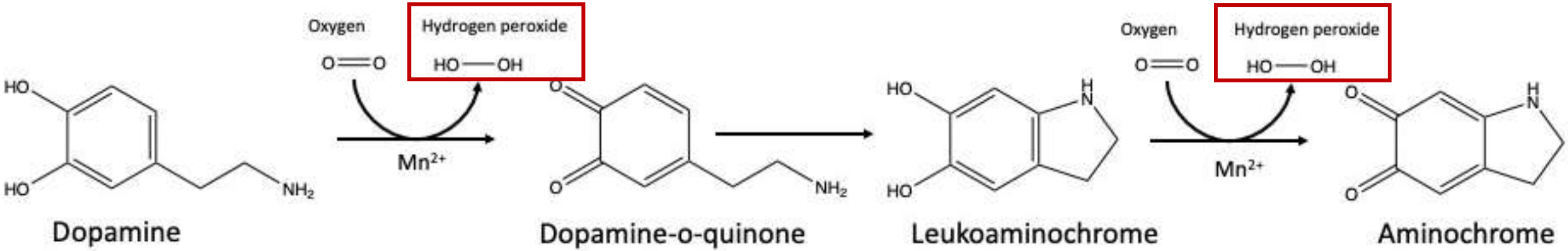
Corrosive substances hence classification is based on readacross

- Potassium permanganate
- Sodium permanganate
- Manganese dinitrate

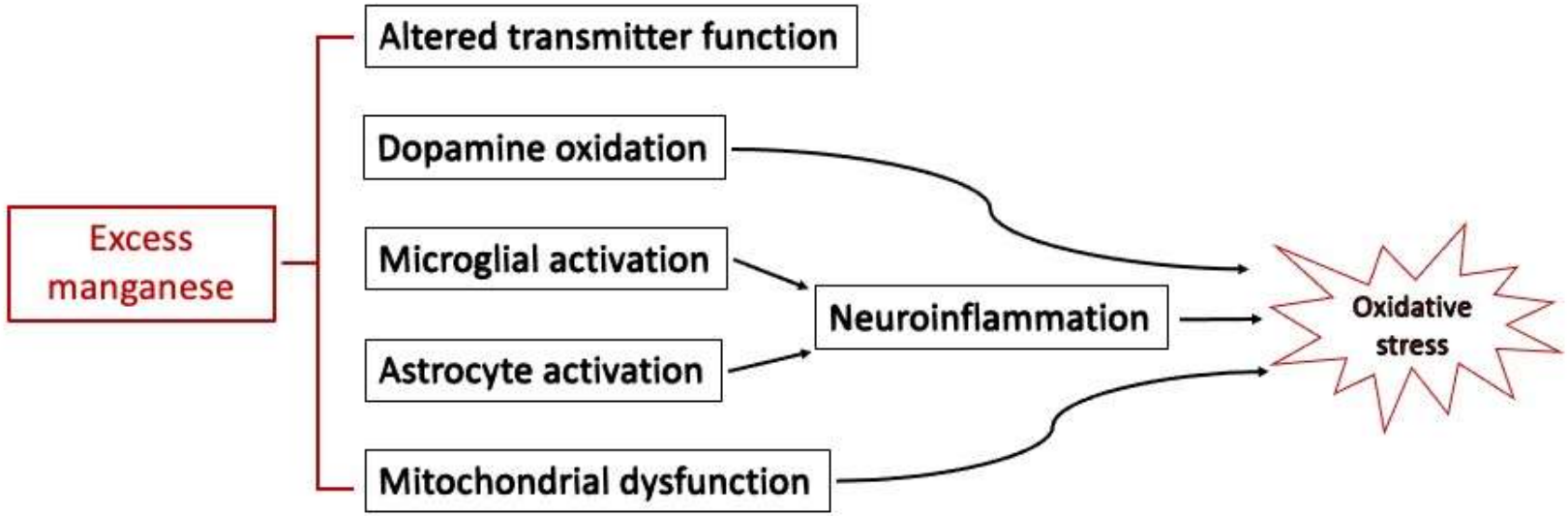
* Based on available data from Mn Mines, most ores under the CLP notification scheme will also be considered as STOT cat 1 or 2

Mechanisms of Manganese Neurotoxicity

- Precise mechanism of manganese neurotoxicity is incompletely understood
  - Mitochondria accumulate manganese
  - Generation of reactive oxygen species and oxidative stress may play a role



Mechanisms of Manganese Neurotoxicity

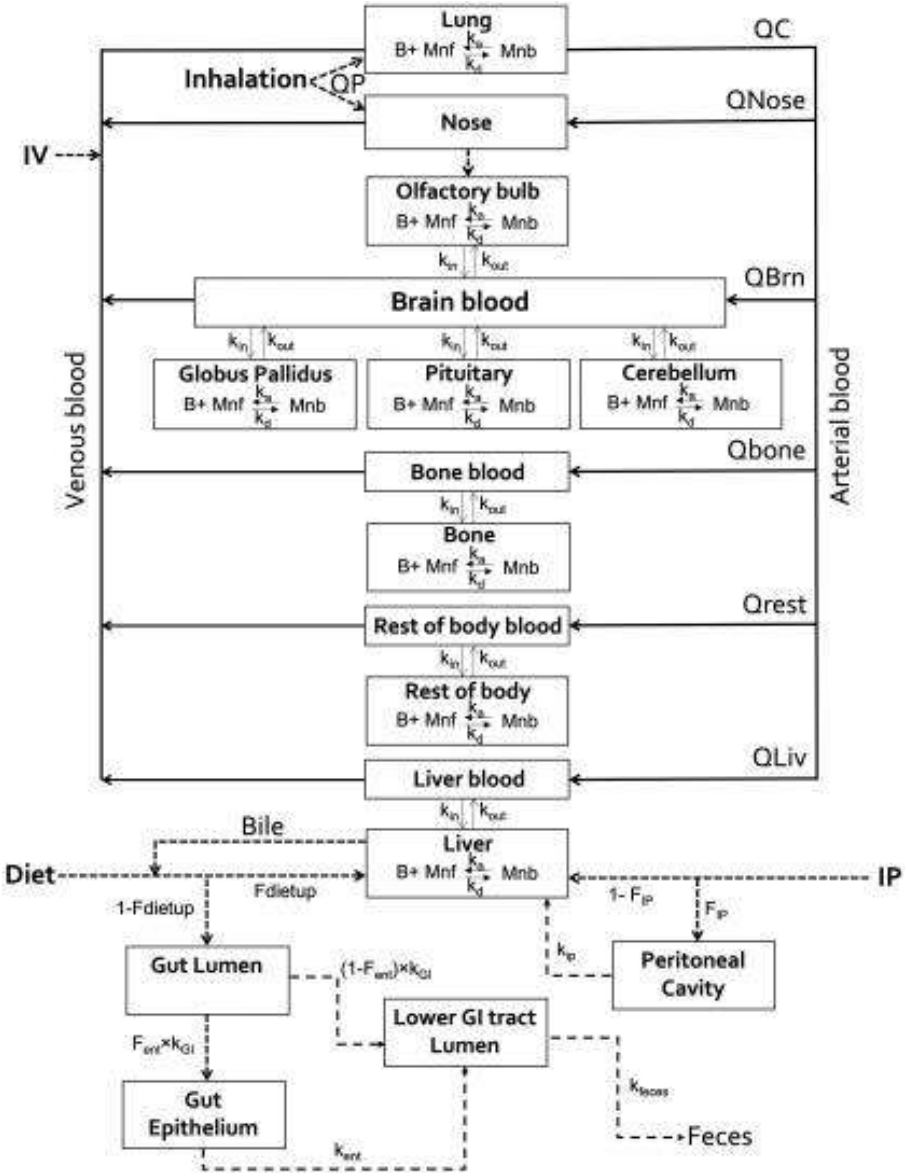


Dorman DC: Biomolecules 2023, 13, 1176

Manganese Neurotoxicity: Special Considerations

Physiologically-based pharmacokinetic (PBPK) models

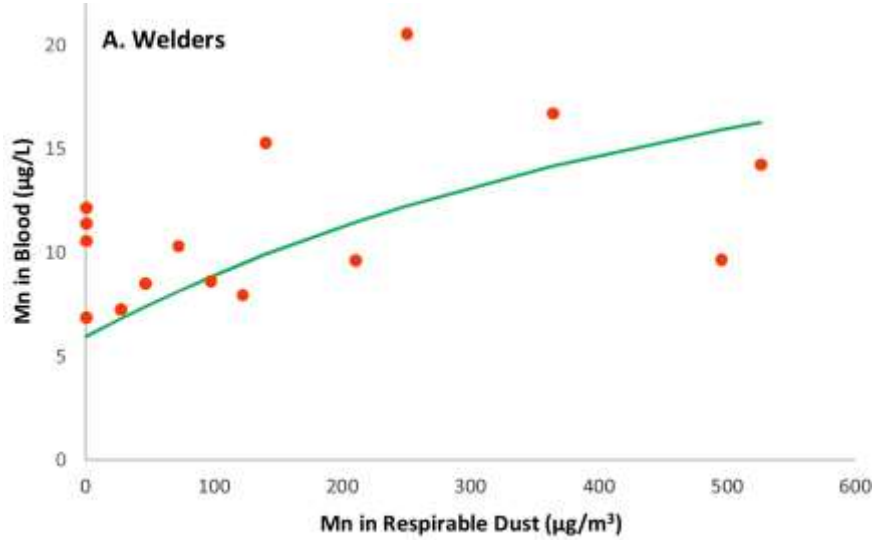
- Used to predict chemical concentrations in different organs
- Consider route of exposure:
  - GI tract: Ingestion
  - Respiratory tract: Inhalation
- Storage tissues
- Target tissues

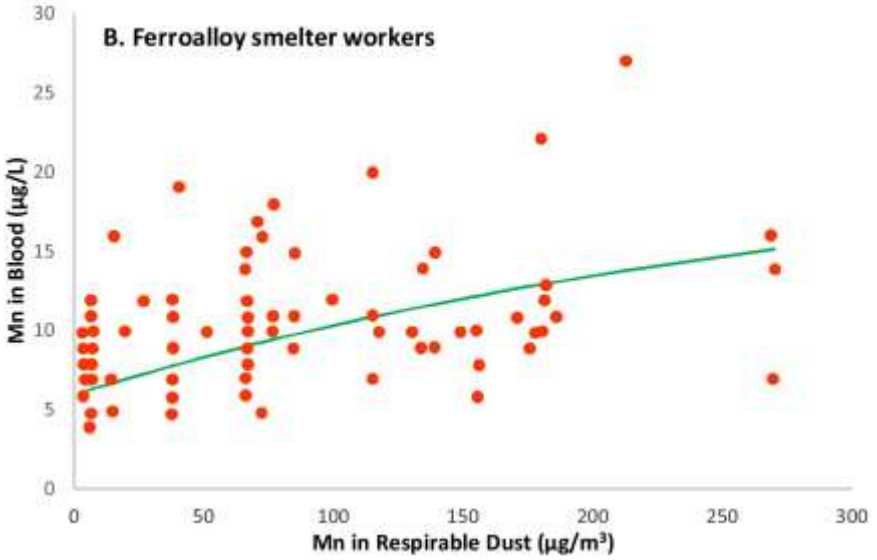


Campbell et al., 2023

Model Applications to Risk Assessment

Evaluation of manganese kinetics in manganese workers

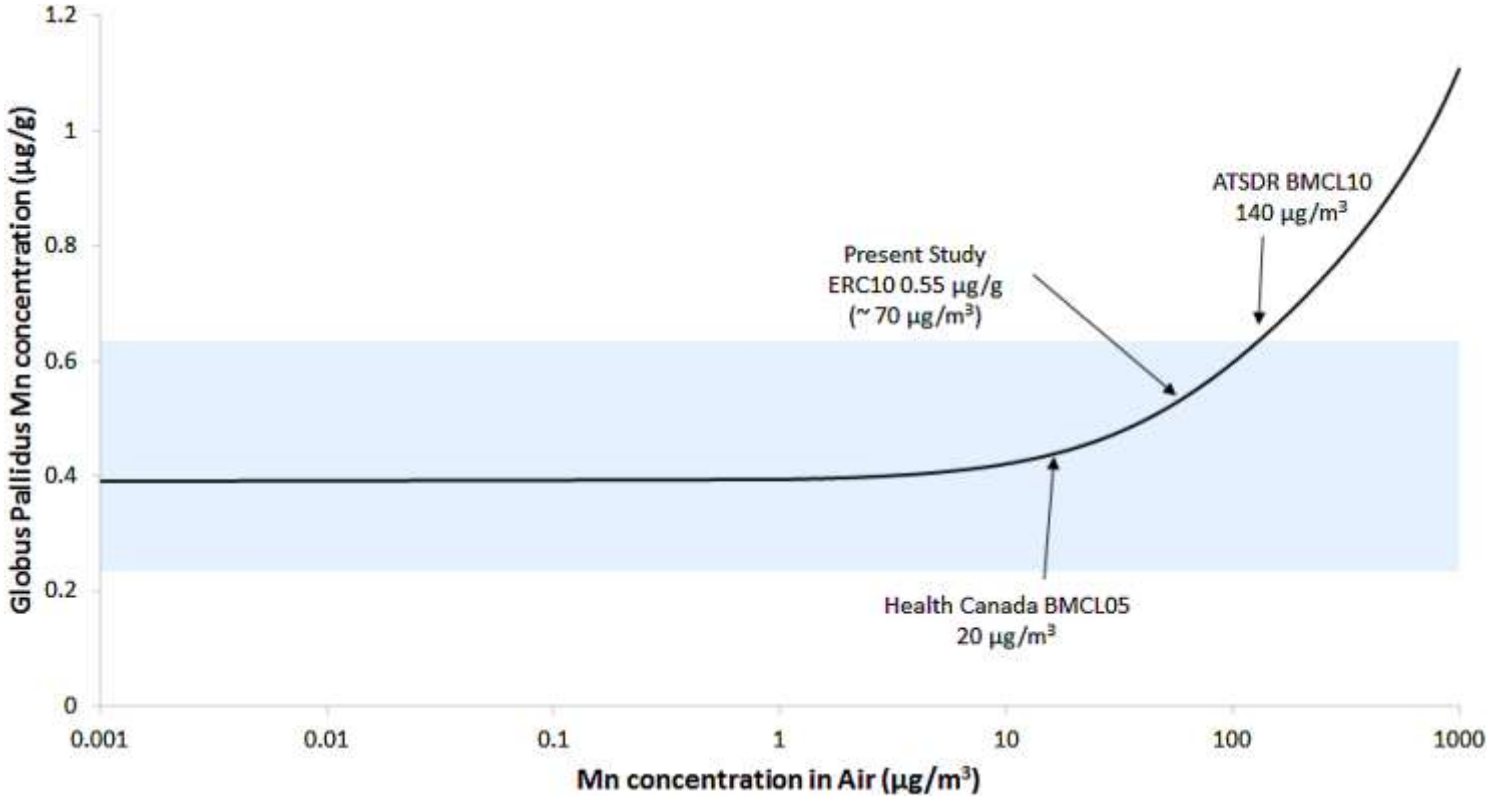




Ramoju SP, et al. The application of PBPK models in estimating human brain tissue manganese concentrations. Neurotoxicology. 2017;58:226-237.

Model Applications to Risk Assessment

- Developing toxicity values based on changes in brain Mn concentration following Mn inhalation



Ramoju SP, et al. The application of PBPK models in estimating human brain tissue manganese concentrations. Neurotoxicology. 2017;58:226-237.

Take Home Message: Manganese Neurotoxicity

Mn In

Mn Out

Fundamental biology is shared between humans and other mammals

Increased brain delivery and neurotoxicity occurs when control mechanisms fail

Questions?

Mn in the Restriction Roadmap: *where is it heading to?*

Hugo Waeterschoot en Violaine Verougstraete

27 September 2023

Why a Restriction Roadmap ?

Chemicals Strategy for Sustainability (CSS)

- **Main point of attention**: Improve efficiency and speed up risk management in the EU
- **By:**
  - Reviewing the REACH Authorisation and Restriction schemes
  - Expanding scope of existing risk management tools like GRA (restrictions Article 68(2))
  - Introducing new tools and concepts (Essential Use)
  - Using tools like grouping

Why a Restriction Roadmap ?

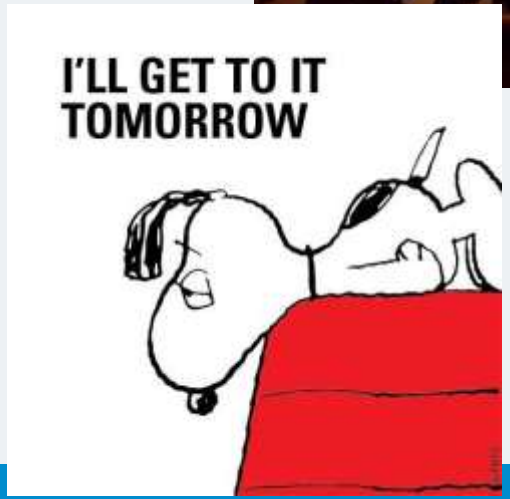
If REACH 2.0 is upcoming, why do we need a Restriction Roadmap?

EUROPEAN
COMMISSION

Brussels, 25.4.2022
SWD(2022) 128 final

COMMISSION STAFF WORKING DOCUMENT

Restrictions Roadmap under the Chemicals Strategy for Sustainability



Why a Restriction Roadmap ?

The Restriction Roadmap:

Formally:

- Increase the transparency on upcoming/planned restrictions
- Stimulate industry to pre-empt the restriction

Informally:

- Define what substances are the most important to work on
- Control Members States' hobby horses


EUROPEAN
COMMISSION

Brussels, 25.4.2022
SWD(2022) 128 final

COMMISSION STAFF WORKING DOCUMENT

Restrictions Roadmap under the Chemicals Strategy for Sustainability

is therefore a non-legally binding Commission staff working document

Objectives of the Restriction Roadmap according to the Commission Staff Working Document…

1. **Ensure transparent and timely fulfilment** of the strategy's commitments, specifically regarding restrictions on "the most harmful substances,"
   - i.e., CMR, PBT, vPvB, ED, immunotoxicants; neurotoxicants, respiratory sensitisers and STOT
2. **Provide stakeholders with transparency** into ongoing and upcoming work on chemical restrictions under the strategy

But not all restriction ideas are on an equal foot

3 levels of POOLS of restrictions

Already on the **Registry of Intentions**

Planned, preliminary work done but not on **Registry of Intentions**

A restriction would be a relevant risk management measure

	Subject of restriction proposal	Numbers of substances in group for regulatory action (if applicable)	Hazards in scope	Uses				Additional information	(Anticipated) year of submission of mandate to ECHA
			Confirmed or suspected hazards	Industrial	Professional	Consumer	Article service life		
Groups where CLH or candidate listing to be carried out with restriction as suggested risk management									
1.	Pyrazoles	Group (6)	R, ED HH, PM		x	x		The need for further regulatory risk management measures (e.g. restriction) is under discussion, focusing on their use as a fertiliser and potential reproductive, and ED HH properties as well as possible persistency and mobility.	TBD
2.	Simple manganese compounds	Group (15)	R, STOT RE, Neurotox.		x	x	x	The need for further regulatory risk management measures (e.g. combination of authorisation and restriction) is under discussion, focusing on subgroups 'Simple inorganic salts, oxides and manganese metal' and 'Permanganates'. Might apply to other substances in the group following steps taken to generate data in order to clarify the hazard.	TBD
3.	Simple vanadium compounds	Group (24)	CMR, STOT RE	x	x	x	x	Potential need for an exposure limit for workers under OSH (occupational health and safety) or restriction under discussion as well as potential group CLH proposal mainly for carcinogenicity.	TBD

What may (most probably) happen?

Preliminary investigation

- To define the relevancy and scope

RMOa

- To define preferred risk management measure (RMM)

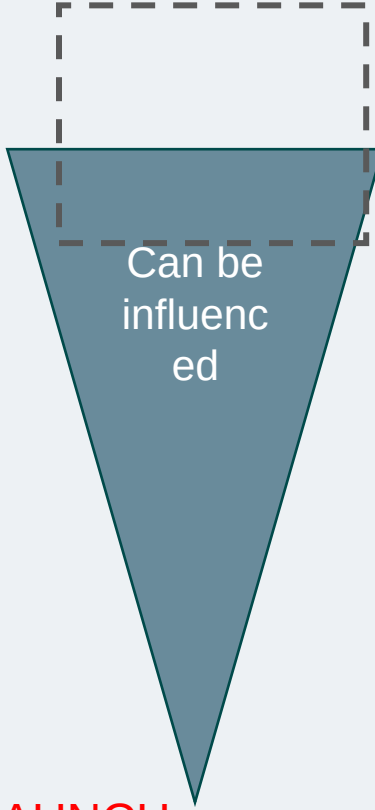
RIME mtg

- Member States' discussion to confirm RMMs

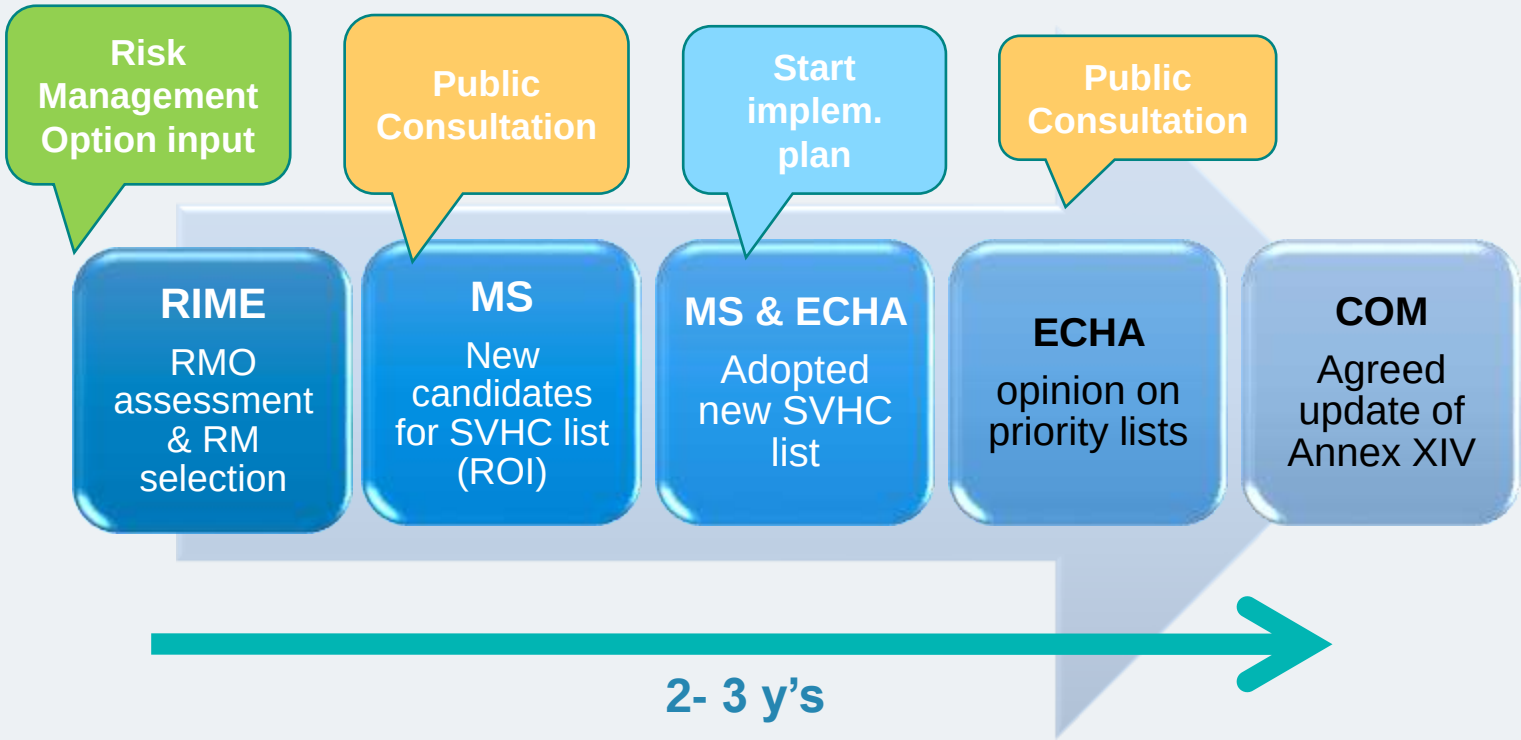
Regulatory RMM

- LAUNCH

- Launch of regulatory RMMs



Once launched



Steering the "timing" and "selection process" is feasible in many (not all) cases

What aspects will define the progress of risk management ?

- A voluntary Member State or a mandate for ECHA by Commission
  - No sign at this moment
  - Those that develop the RMOa, have high impact in the selection of the RMMs
  - Clarity on the hazard endpoints
  - Other regulatory processes

What is the most probably RMM selection ?
(if Member States and under REACH 1.0)

- Given its hazard properties:
  - Reprotox
  - Neurotox
  - STOT-RE

Authorisation on industrial use and complementary risk based restriction (art 68 (1))

EU wide harmonised OEL

- Given its status as Critical Raw Material
  - Promote substitution to restrict uses that are not (absolutely) essential

Risk Management need identification is …*moving…*

TOWARDS:

- From a substance/compound to a grouping approach?
  - ECHA and Commission prefer grouping for efficiency
  - And to avoid regrettable substitution (see CTP-HT case)

- After completing all data gaps or earlier?
  - ECHA decoupled the completion of registration file from risk management identification
  - Risk management measures on the basis of EXISTING info

What can be done to steer direction, scope & proposed RMM ?

POTENTIAL STRATEGIES:

=> Promote RMM under **REACH 2.0**:

- no experience so far….
- Commission may prefer Battery Regulations

=> **Prevent authorisation**:

- RMOa and Materials flow mapping

=> Impact proposed **Restriction measures**

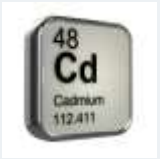
- RMOa, Materials flow mapping, exposure EU wide risk mapping

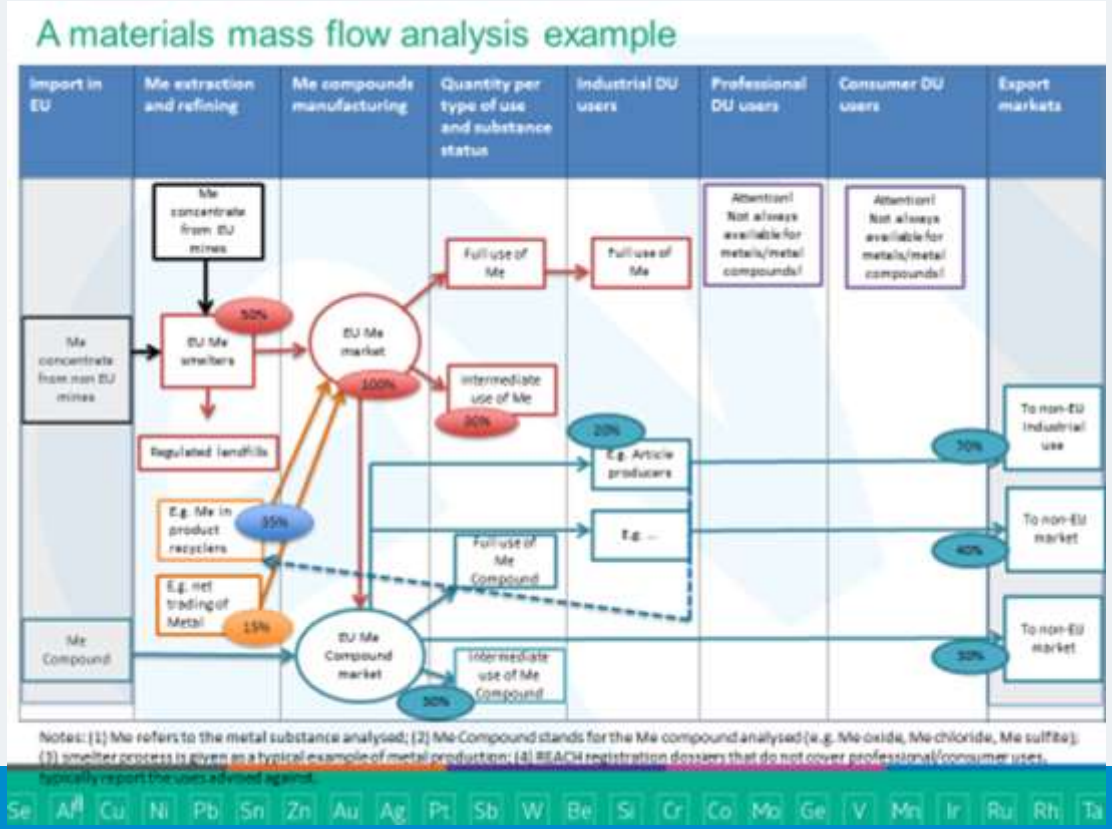
=> Steer to EU-wide OEL:

- RMOa, SEA and exposure mapping

Some explanation and experience

- Materials flow mapping
  - In Cd it reduced the volume in scope of prioritisation for authorisation
  - In Borates case it prevented Authorisation due to high volume under intermediate use





Some explanation and experience

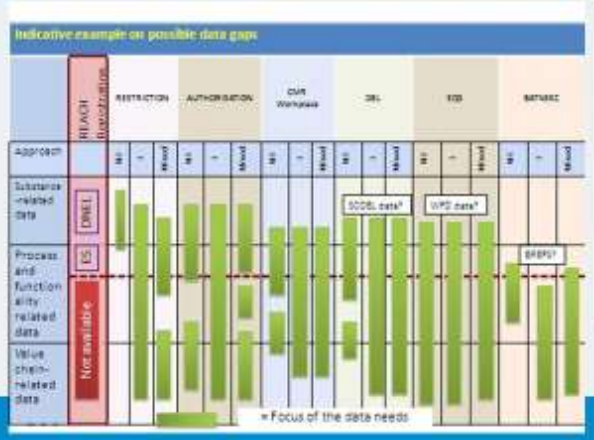
- RMOa
  - Helped Ni to stop RM process
  - Helped Co to define relevancy of OEL
  - Helped Ag to define additional info needs for regulatory RMOa

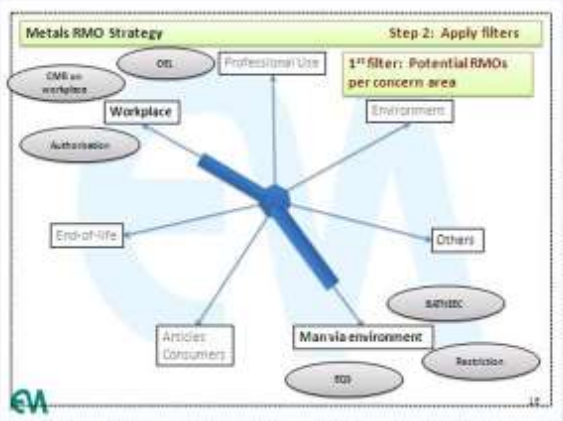
RMOa: the metals industry guidance…

AIMs:
- Help yourself to define alternatives and critical information
- Help regulators to ensure relevant information for proper decision making

What is made available:

- ***RMOa template**: to stimulate the thinking process and data gathering*
- ***RMOa guidance**: process description*





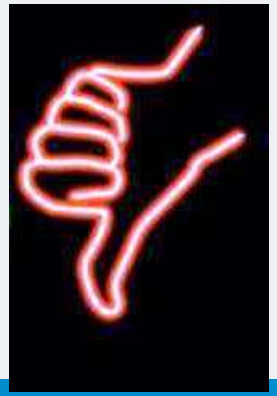
What can RMOA deliver
for a manufacturer or a downstream user ?

What may a RMOA do?

- Neutral overview on outstanding RISKS
- What is already appropriately covered under EU law?
- What is best tool under REACH?
- With other words: decrease appetite to trigger authorisation

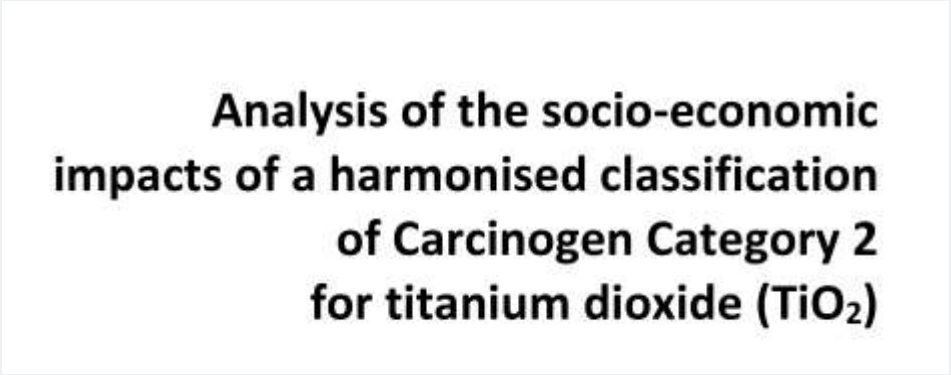
WHAT can a RMOA not do ?

- STOP Risk Management under REACH



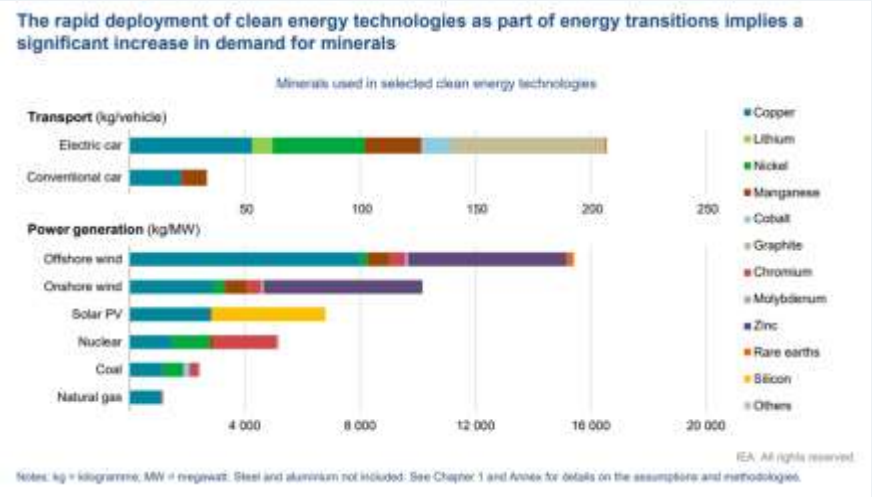
Some explanation and experience

- Socio-economic assessment
  - Helped Co to demonstrate cost efficiency of OEL above RAC DN/MEL based workplace exposure restriction
  - Helped TiO2 to understand the impact of an harmonised classification.



Some explanation and experience

- Risk mapping
  - **Volume by use data** to reduce priority scoring (Cd and compounds)
  - **MEED** for ENV and metals **Transition Pathway** for future impact



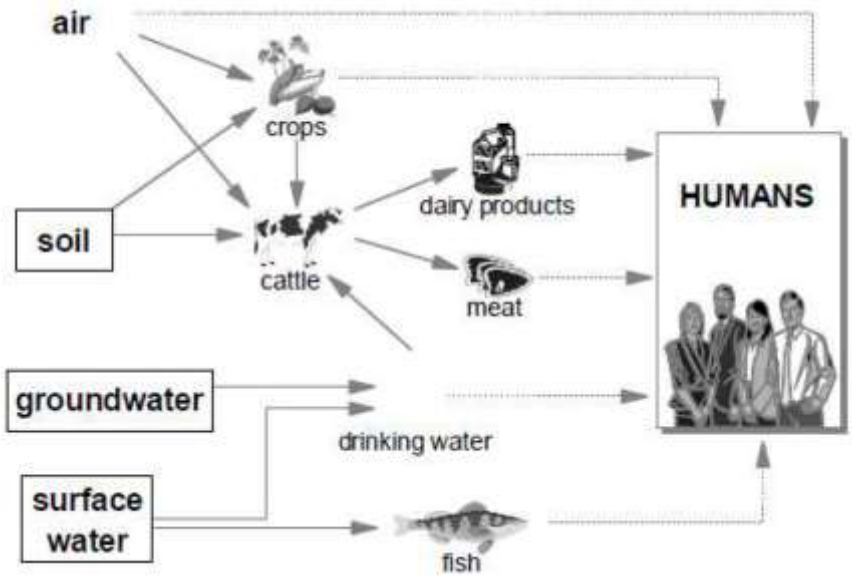
Some explanation and experience

- Risk mapping
  - **Man via the ENV(MvE)**, to reduce defaults for general population assessments
    - CrVI+ cases got attention by EP and MSs due to lack of investment in MvE !

Example of Man via the Environment assessment in a recent AfA case on Chromium trioxide use for Functional Chrome Plating

Estimated additional statistical fatal cancer cases, based on 40/70 years of exposures, RP applied

	Exposure duration per day (h)	Exposure 8h adjusted TWA (µg/m³)	Excess lung cancer risk	Number of exposed people	Estimated statistical fatal can exposure)	
					40 y	1
Workers – Combination of WCS	<1	0.25	0.001	4392	4.39	1
	1-3	0.75	0.003	2062	6.19	1
	4-6	1.5	0.006	2289	13.73	4
	6-8	2	0.008	7608	60.86	18
	Not regularly exposed	0.25	0.001	6577	6.58	1
Workers total				22928	91.75	27
	Exposure 24h (µg/m³)				70 y	1
Man via environment - Local	2.85 ×10⁻⁶		8.27 ×10⁻⁵	10,000 x 1,590 sites = 15,900,000	1314.93	
Man via environment - Regional	Not relevant					
Total					1406.68	



To conclude

- “Simple Mn compounds” may progress soon to the Risk Management phase as a group, IF a Member State or Commiss picks it up
- It is possible to steer…. but not without clear evidence…
- The RMOa phase is the most effective to change priority and direction
- RMOa can be anticipated
- Preparatory work usually takes up to 1-2 years

BUT... **REACH 2.0** is around the corner and unsure (yet) this being of help
Batteries Regulation may trigger restrictions (2027 onwards): high probability for Mn

And as a last note…

IT’s ALL ABOUT:

- CORRECT TIMING
- ANTICIPATION and ENGAGEMENT
- AND EFFICIENT PLANNING

It should be right from the first time
(no second chance)

Hugo Waeterschoot and Violaine Verougstraete

- waeterschoot@eurometaux.be
  verougstraete@eurometaux.be

For any further question on this presentation

fieldfisher

PFAS restriction and the grouping approach – a dangerous precedent for manganese compounds

Manganese REACH Conference

27 September 2023
Brussels

Contents

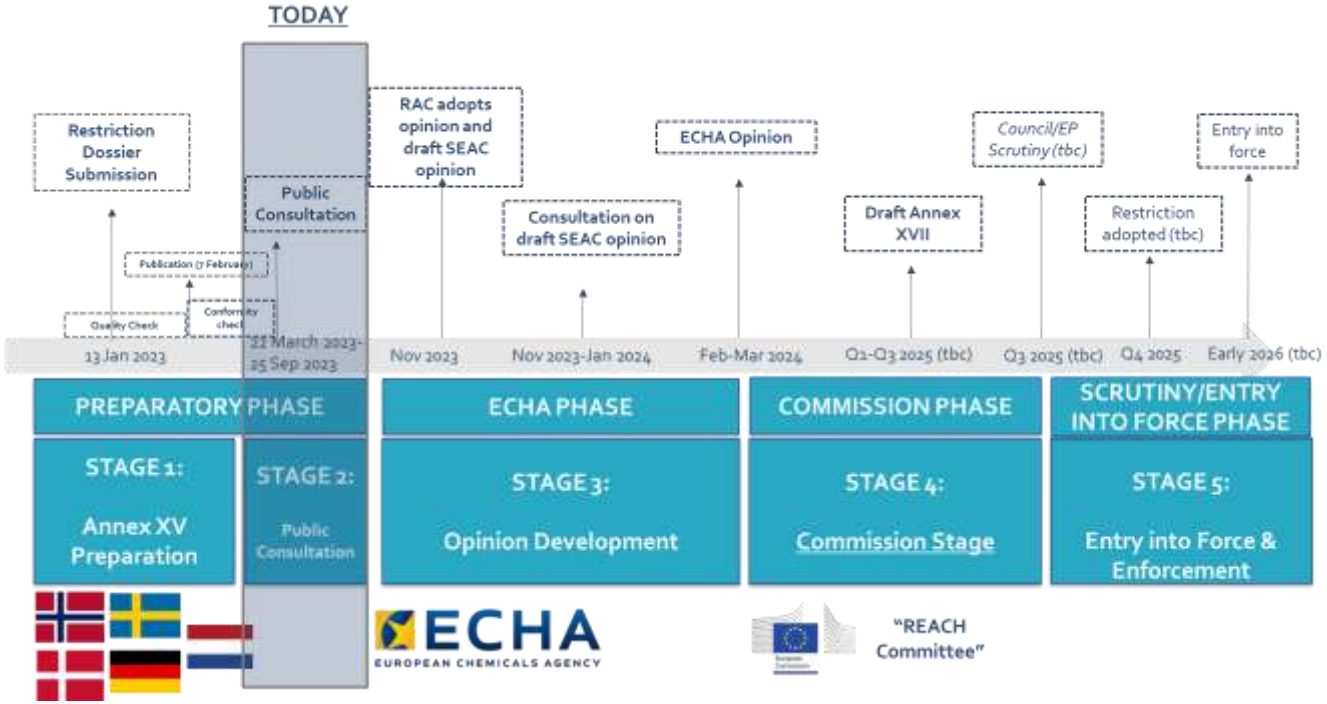
Grouping: the restrictions roadmap

- Main point in the CSS Action Plan (04/2022)
- Prioritises **groups** of substances identified as the most harmful to undergo the restriction process, applying and strengthening the **grouping approach**
- Rolling list of planned and prepared restrictions to be updated annually
- Includes potential restriction on a group of Mn-based substances ("Simple Manganese Compounds")

Grouping: precedents

- Groups of substances **based on hazard properties** – e.g. CMRs
- Groups of substances **belonging to the same chemistry** – e.g., lead and its compounds, tattoo inks, inorganic ammonium salts, microplastics and PFAS
- **Other** – substances in tattoo inks based on classification as skin corrosive category 1, 1A, 1B or 1C or skin irritant category 2, the listing in Annex II to the Cosmetics Regulation and other specific substances

Grouping: the example of PFAS



Grouping: the example of PFAS

- Unprecedented broad restriction dossier submitted in January 2023
- Choice of **2021 OECD PFAS definition**, which encompasses more than 10,000 PFASs (including those of negligible use)
- Grouping based on common hazard and risk – **very persistent** property of of the perfluorinated part(s) of PFAS molecules
- Broad grouping justified to **avoid regrettable substitution** of restricted-PFAS with non-restricted PFAS

Grouping: legal concerns (1)

- Restriction must be consistent with "**One Substance, One Registration**“ (OSOR) principle, as well as **general principles of EU law**
- No explicit legal basis in REACH for using the grouping approach for *risk management*
- Grouping for restriction purposes is **legally questionable** if it is based on hazards only (unacceptable risk?)

Grouping: legal concerns (2)

- Case-by-case assessment: restriction should take into account **exposure** as well as **socio economic risks/benefits**
- Clustering of specifying categories of substances into groups may be appropriate (administrative/procedural efficiency), but this must be **scientifically substantiated** and **not purely hazard-based**
- So far, legality of the grouping approach for risk management purposes only challenged in the context of **authorisation**

Grouping: legal concerns (PFAS)

- Insufficient justification on grouping
- Debatable P-sufficient approach
- Breach of Article 68 REACH
- Contradiction in relation to Annexes I and XV REACH

Restriction of manganese compounds

- Suggested RMM in ECHA's ARN (2021) to follow CLH proposal for Repr. 1B and STOT RE, in combination with SVHC/authorisation
- Group of 15 manganese compounds prioritised for potential restriction under CSS Restriction Roadmap, focusing on:
  - Simple inorganic salts, oxides and manganese metal
  - Permanganates

Restriction of manganese compounds: grouping

- ARN's **grouping** on structurally similar substances based on the presence of the manganese with different ionic charge;
- ARN's **subgrouping** based on chemical properties of the substances affecting their potential hazardous properties (read-accross data)

Restriction of manganese compounds: legal issues in relation to grouping

- Are read-accross adapation requirements met?
- Are risks scientifically substantiated for all the substances in the (sub-)group?
- Are risks unacceptable for all the substances?
- Are there other RMM than restriction to mitigate the risks for some substances?

What to do?

- Review legality of Mn proposal prepared by MS
- Assess ‘grouping approach’ followed for Mn compounds
- Provide comments on MS proposal to ECHA (fitness check)
- Provide comments to ECHA during public consultation.
- Engage with ECHA and MS authorities.
- Organise regular meetings and ensure overall legal compliance.
- Cooperate with MARA on scientific/legal/advocacy arguments
- Consider all options / legal actions as the process unfold

Conclusion

- Recent tendency of authorities to group the assessment of substances.
- However, this tendency does make grouped restrictions legitimate and this cannot crystalize into law.
- Grouping is legally questionable and runs counter some basic principles of EU law and REACH.
- Each substance should be assessed based on its own properties. A case-by-case assessment is key.
- Acting now is key to minimise adverse consequences and bad surprises!

Contacts

Claudio Mereu

Partner, EU Regulatory

+32 2 742 70 60

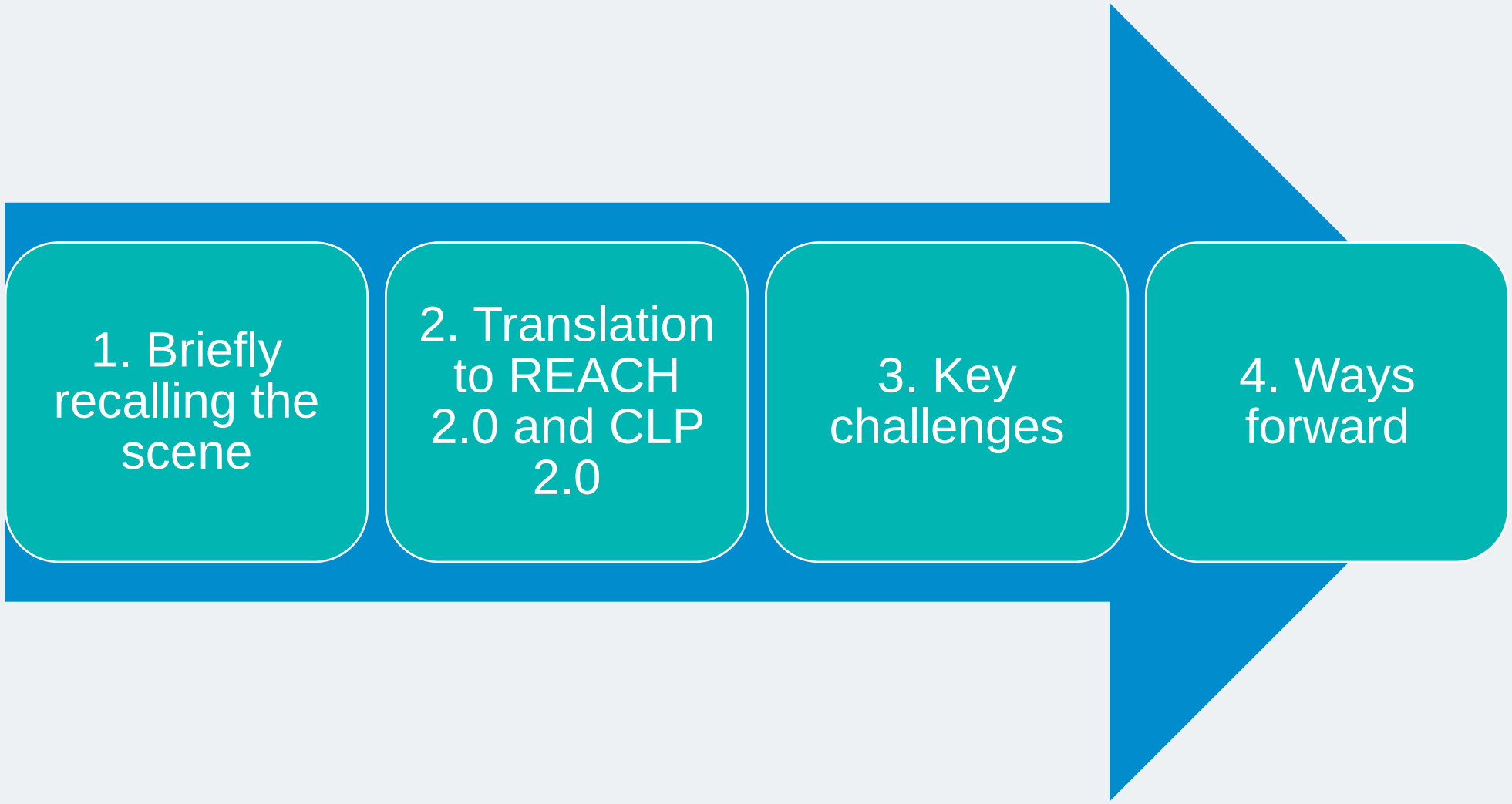
Claudio.Mereu@fieldfisher.com

REACH maintenance challenges and possible changes in REACH 2.0

Violaine Verougstraete and Hugo Waeterschoot

27 September 2023

Outline


1. Briefly recalling the scene
2. Translation to REACH 2.0 and CLP 2.0
3. Key challenges
4. Ways forward

1. The scene: the Green Deal is the starting point…

Zero Pollution Ambition for a toxic-free environment: 3 waves and more…

The Chemicals Strategy for Sustainability aims at re-vamping the chemicals management system

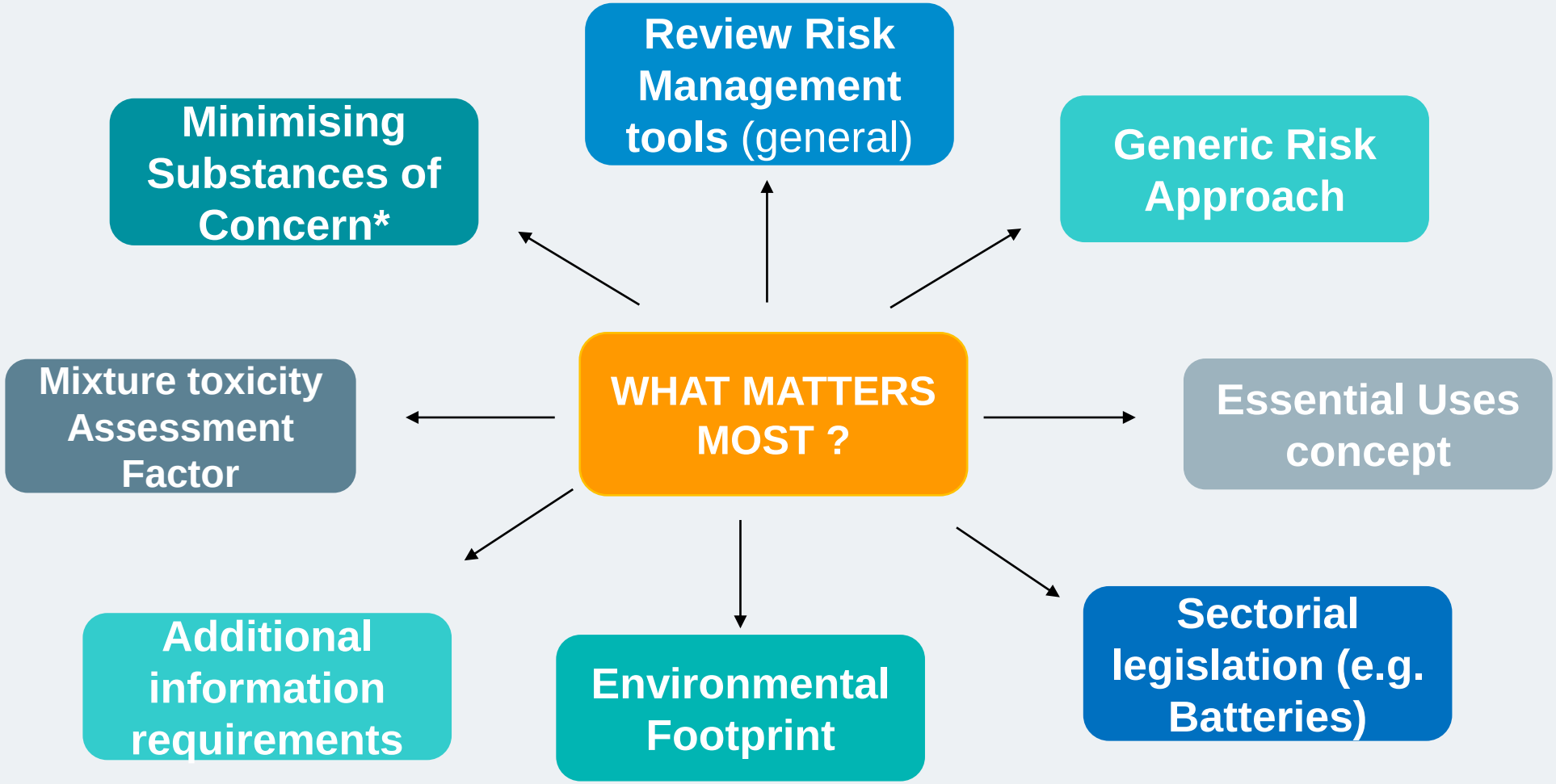
+50 actions to achieve a "Toxic free environment" along 5 pillars:

1. **Innovating** for safe and sustainable EU chemicals
2. **Stronger** EU **legal framework** to address pressing environmental and health concerns
3. **Simplifying** and consolidating the **legal framework**
4. A comprehensive **knowledge base** on chemicals
5. Setting "the example for" a **global** sound management of chemicals

Implementation started in 2020 and series of actions were expected to be **finalised by 2024 –** difficult given delays (e.g. on the REACH proposal, OSOA etc.)

The toxic-free hierarchy *– a new hierarchy in chemicals management*

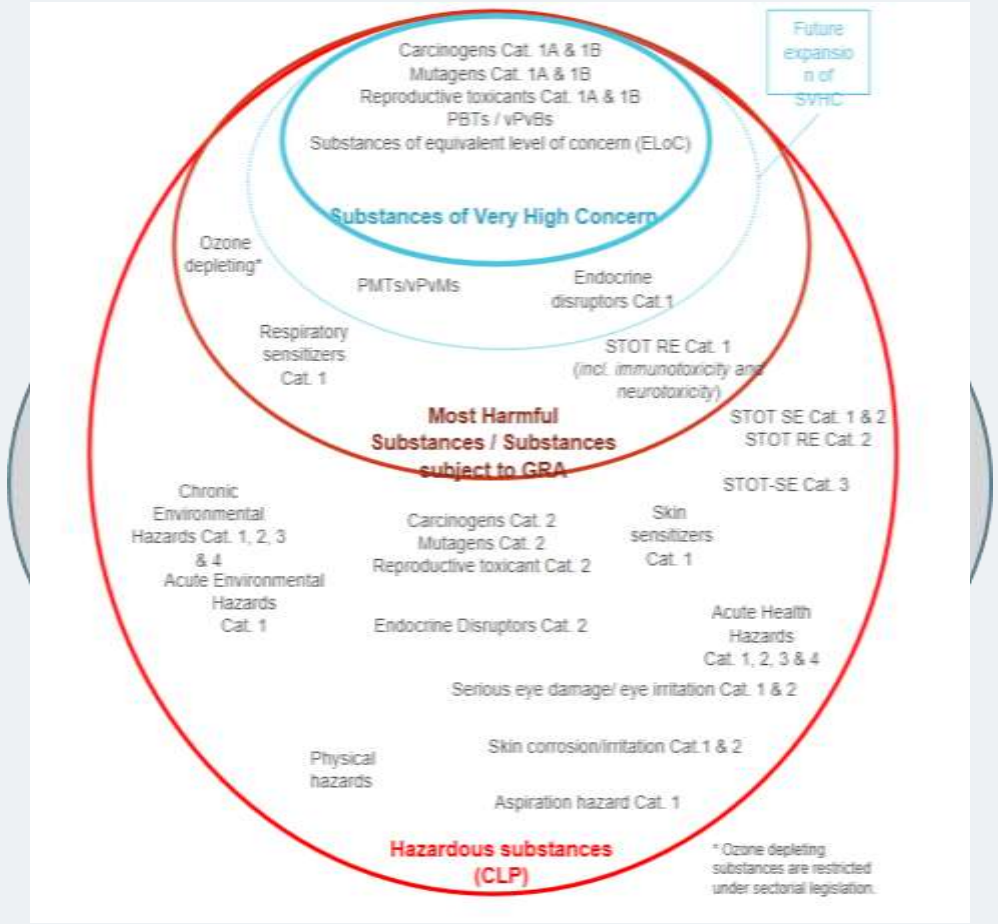
Which CSS concepts were expected to impact?



This was investigated for the Metals sector in a Business Impact study early 2021

Note: Hazardous substances in the CSS

- **Substances of Very High Concern (SVHCs)** :
  - **For substitution or banning**
  - to be extended to other endpoints (Persistent/ Mobile) and Endocrine Disruptors
- **Most Harmful Chemicals (MHCs):** focus on CMRs in **consumer uses (professional uses)**
  - **Horizontal restrictions** if not exempted (as an Essential Use)
  - For specific hazard endpoints: CMR + PBT/vPvB, PMT,…
  - Later, potentially extended to STOT and ED
- **Substances of Concern (SoCs):**
  - **Minimise concentration**



Source: European Commission

Chemicals are everywhere in our daily lives. They are fundamental for our well-being and high living standard and are important building blocks of key technologies to address future challenges. The REACH Regulation on Registration, Evaluation, Authorisation and Restriction of chemicals, together with the CLP Regulation on Classification, Labelling and Packaging of chemicals, are the key Union legislation for the assessment and management of chemicals. The REACH Regulation was last evaluated in 2018 (referred to as "latest REACH Review" below). It concluded that REACH is effective but that there are opportunities for further improvement, simplification and burden reduction. Following the evaluation, a number of non-legislative actions have been launched (some of them finalised, others still ongoing) to improve the implementation of REACH.

In addition, to deliver on the commitments made in the Chemicals Strategy for Sustainability, the CLP Regulation will also be subject to a targeted revision, along other sectoral chemical legislation.

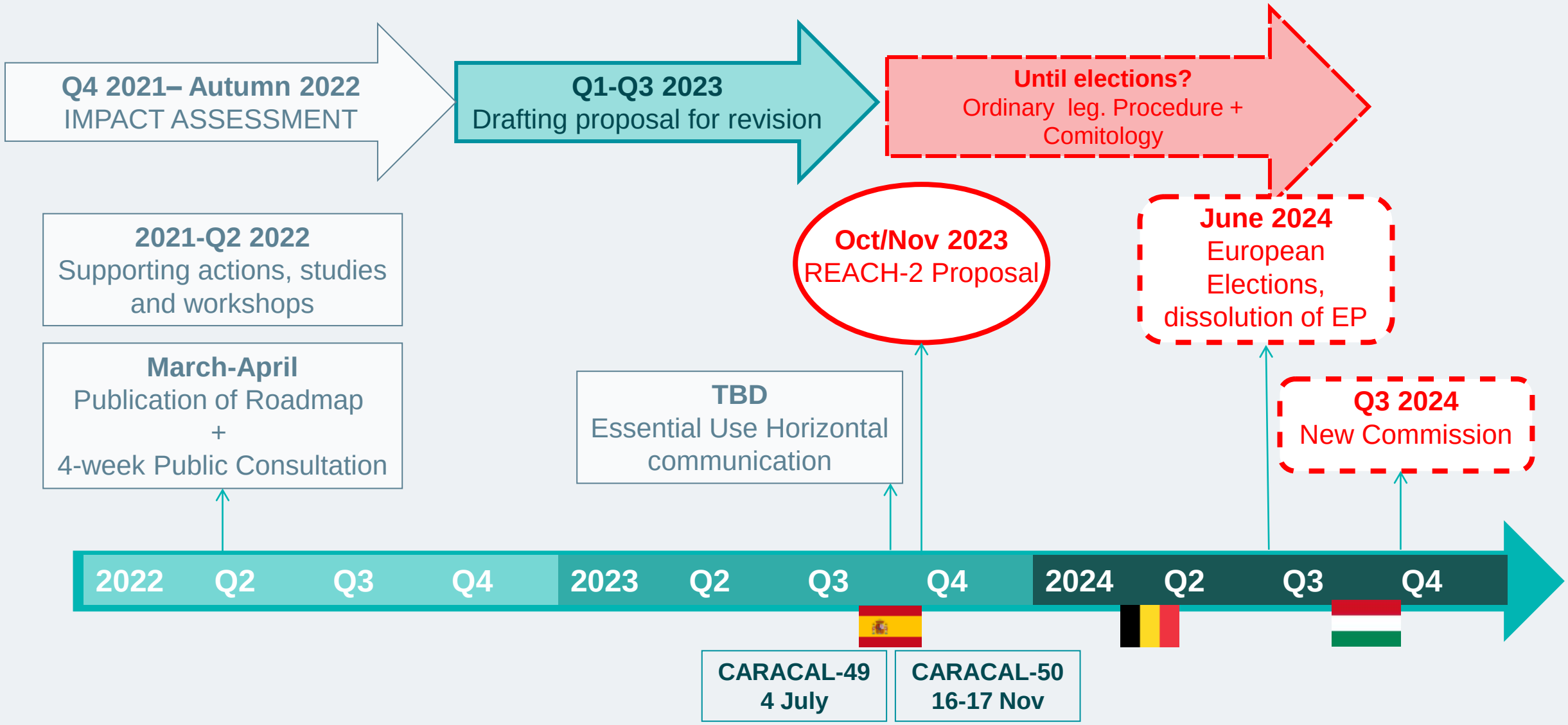
Problem the initiative aims to tackle

The Chemicals Strategy for Sustainability recognises the need for a targeted revision of REACH to achieve its objectives by addressing the following problems that have been identified:

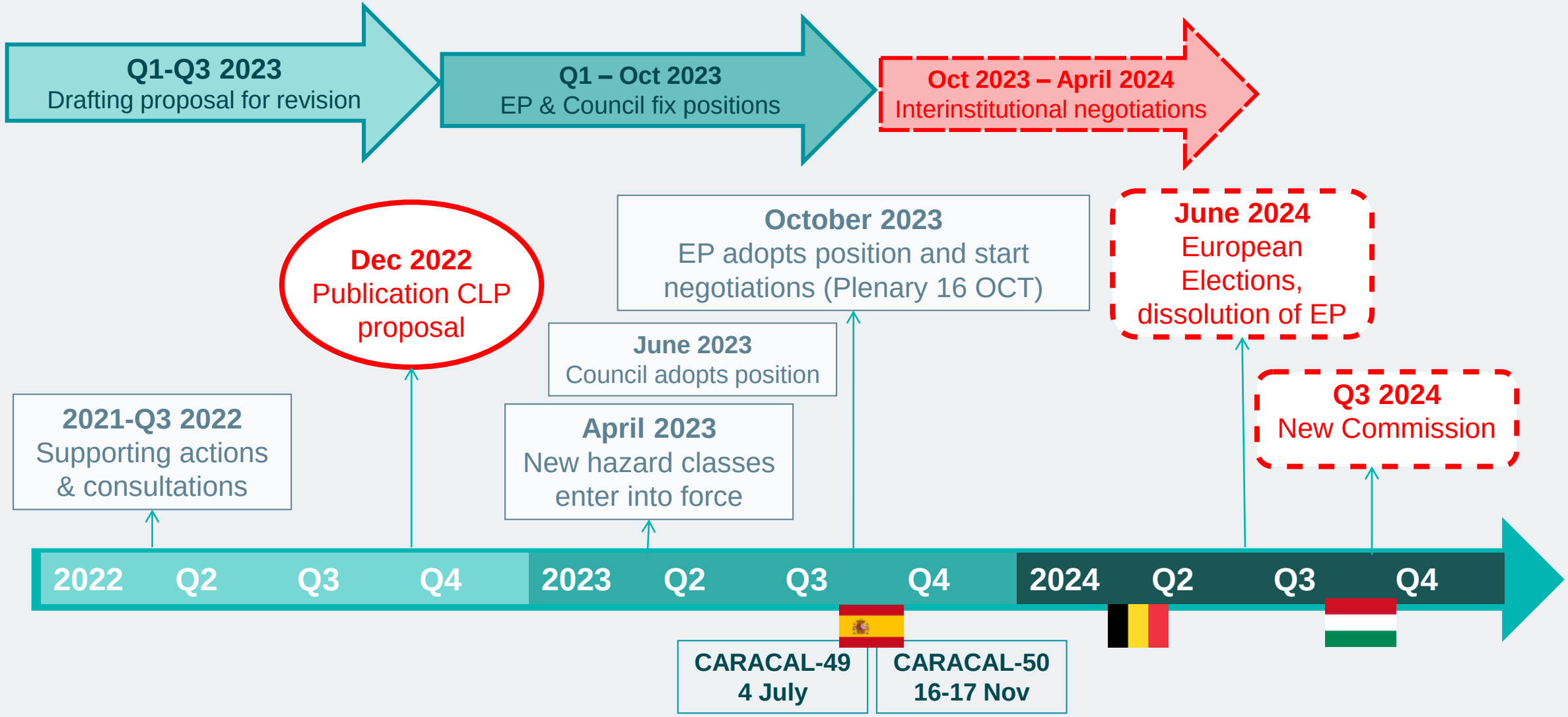
In order to achieve these objectives, the Strategy *inter alia* includes the revision of Regulation (EC) No 1272/2008 on hazard classification, labelling and packaging of chemicals (the CLP Regulation). The CLP Regulation is the core piece of Union legislation for the hazard assessment of chemicals, stemming from the United Nations' global standard (GHS)[3], and sets out the hazard classification of chemicals and how to communicate those hazards to consumers and workers. The CLP Regulation together with the REACH Regulation on Registration, Evaluation, Authorisation and Restriction of chemicals are the key EU legislation on chemicals. In order to deliver on the commitments in the Chemicals Strategy for Sustainability, the REACH Regulation will also be subject to a targeted revision, along a number of pieces of sectoral chemical legislation.

2. Translating CSS concepts in REACH and CLP

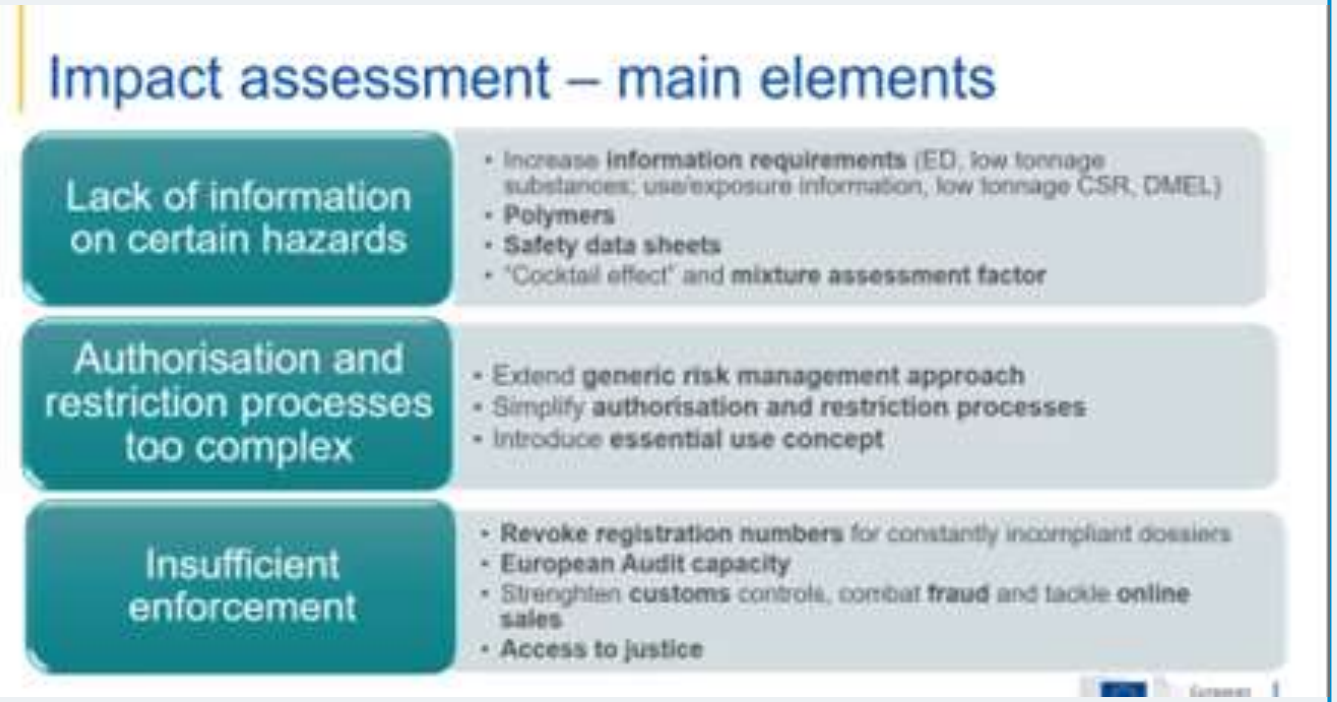
REACH REVISION TIMELINE



CLP REVISION TIMELINE



Changes to be expected

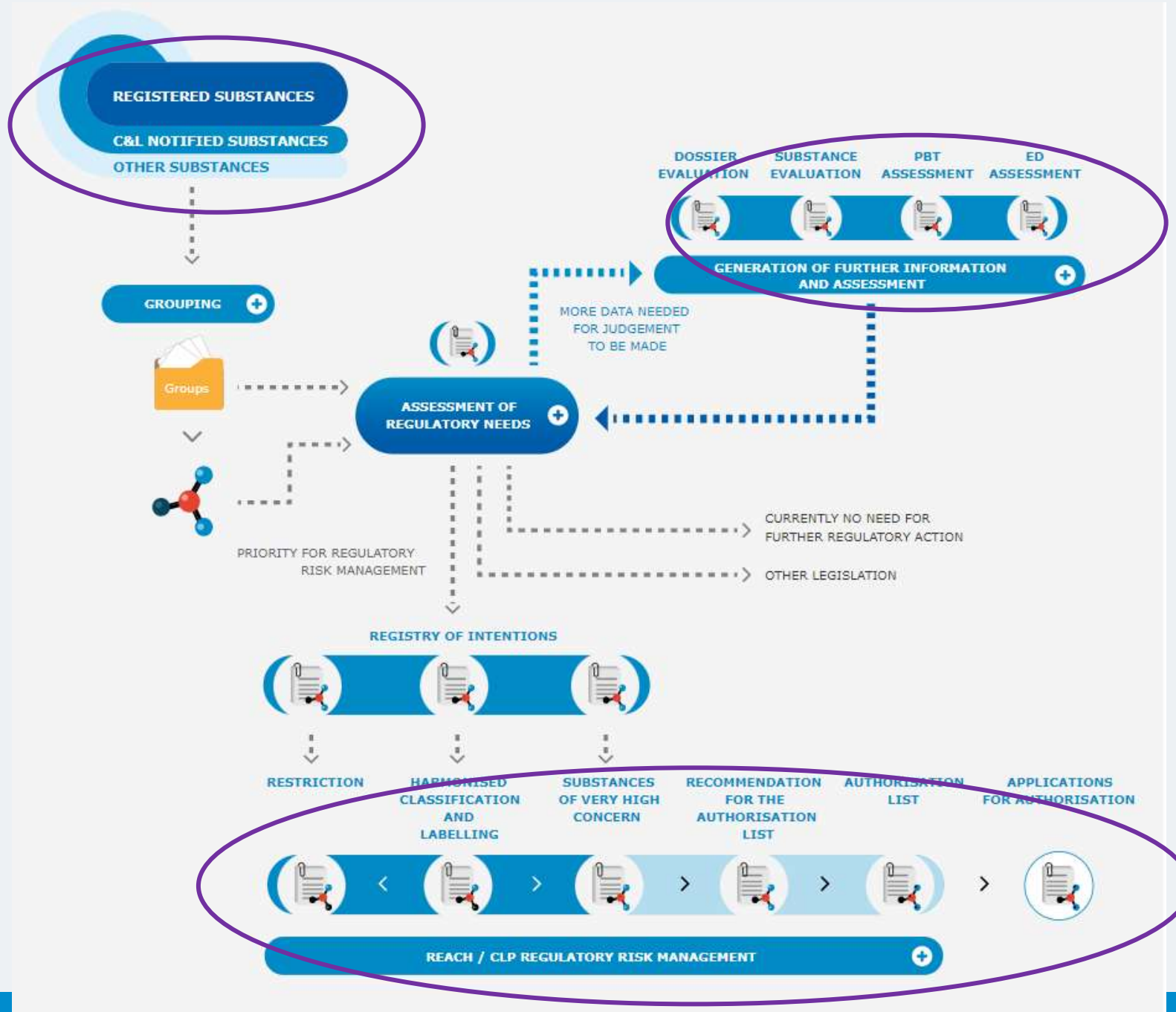


CLP: text still under discussion but new endpoints already into force!!

REACH

- Registration:
  - New information requirements (low tonnages, ED, environmental footprints, DMELs, NAMs etc.)
  - Supply chain activities
  - Mixture Allocation Factor to cover for unknown combined exposure
- Evaluation:
  - Streamlining processes (testing, waivers)
  - Extension T/C completeness check, etc
- Risk management!!
  - Generic Risk Management approach – Essential Uses
  - Reform autorisation?

3. Key challenges



- Completeness and compliance registration files and supply chain communication
- Changes in some REACH chapters
- GROUPING
- ECHA move from data completeness target to data for risk management

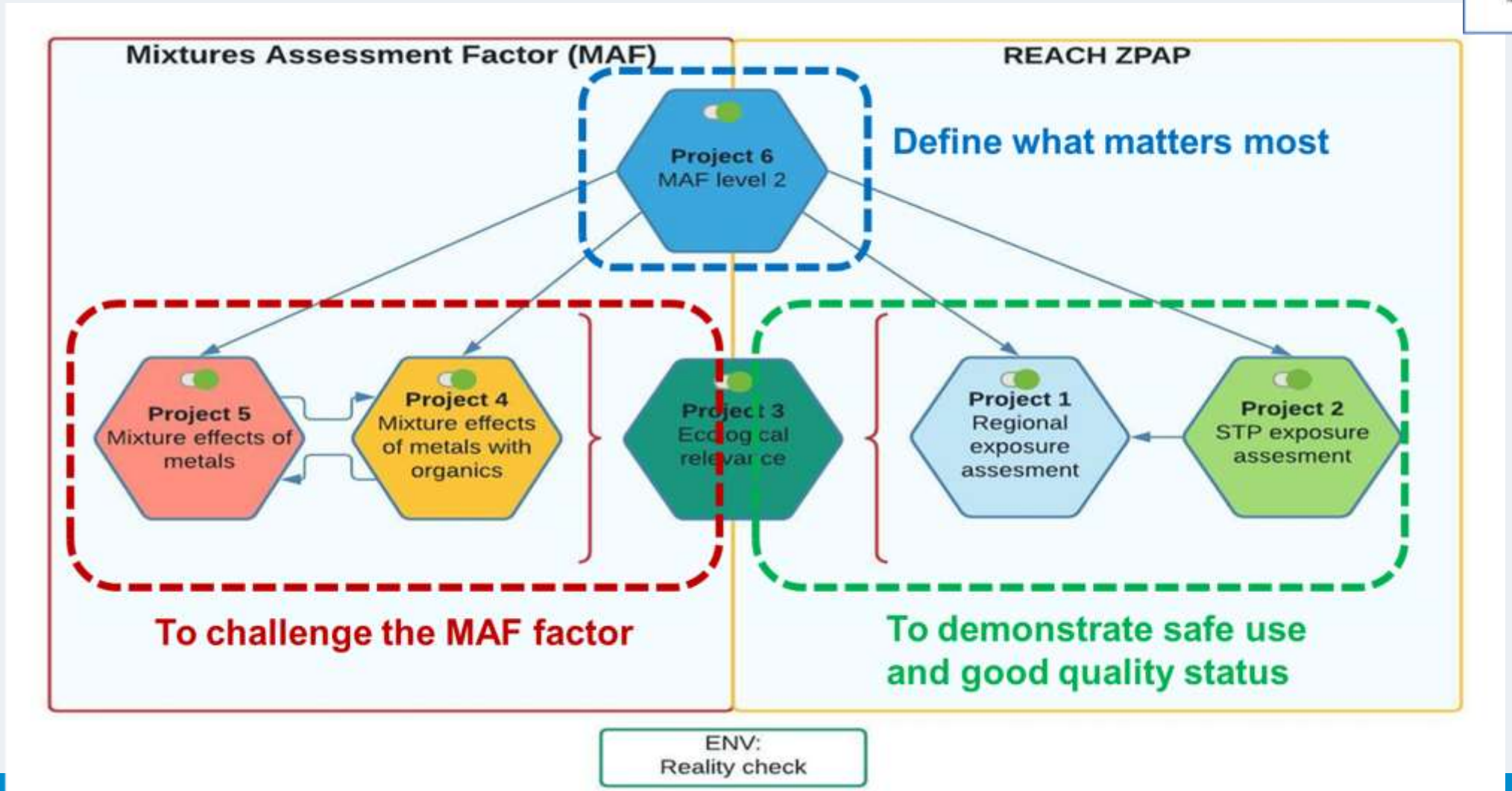
But also..risk management expands and makes links…

4. Ways forward

Preparatory work

- Technical work and advocacy: e.g.,
  - Mixture Allocation Factor: MEED project (metal specific approach)
  - Exposure/emissions data
  - New information requirements/endpoints: contribute to ECHA guidance
  - Regrettable substitution in Autorisation/Restriction
  - 4Cs concept (see later)
- Advocacy targeting REACH and CLP discussions but not only..

Work on emission data and MAF: Metals Environmental Exposure Program)



Advocacy

Eurometaux– Metal Sector priorities

Reach Revision advocacy Scoping

Eurometaux
European Association of Metals

1. REACH to focus on what matters

- …by ensuring a transparent identification, selection, and prioritisation of risks

2. More business certainty and predictability

- … through appropriate risk management for strategic/critical raw materials

3. Defend a risk-based approach,

- …considering exposure potential in addition to hazard

4. Avoid regrettable substitution and consider lifecycle approach

- … chemicals risks are controlled without hampering EU circularity, climate, CRM objectives towards safer and sustainable alternatives

5. Consider metal specificities

- …Refine/overrule default MAF

» Eurometaux calls *"for a more action-oriented legislation focussing on what matters and is of real concern, while ensuring that all types of chemicals are treated equally, from a risk-based perspective. This would ensure a more focussed and effective REACH, with a better allocation of resources for all actors including the value chains"*

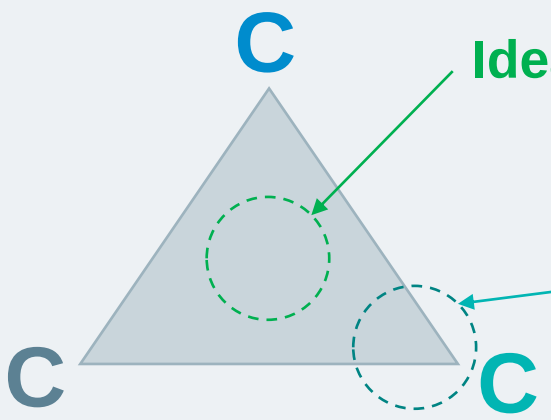
Advocacy priorities on CLP and REACH

- **Priorities**
- Ensure the identification of hazards under CLP remains science-driven
- Insist on the necessity to have a correct framework for grouping for classification
- Ensure the definitions on MOCs are improved (re-aligned) and clarity on how to use existing data to use mixture rules
- C&L inventory: Keep the current provisions that make the joint notification corresponding to the REACH registrations noticeable
- Formatting rules for labels
- Etc.

Priorities

- Ensure more business certainty and predictability through appropriate risk management for strategic/critical raw materials
- REACH to focus on “what matters” - by ensuring a transparent identification, selection, and prioritisation of risks
- Defend a risk-based approach, considering exposure potential in addition to hazard
- Avoid regrettable substitution and consider lifecycle approach
- Consider metal specificities (MAF, PBT/PMT)
- Proportional extension of information requirements
- REACH to take a holistic view – risks are controlled without hampering EU circularity, climate, CRM objectives (the 4 Cs)

More widely… management of metals requires a holistic approach



Ideally the CSS would be here

The CSS is here only

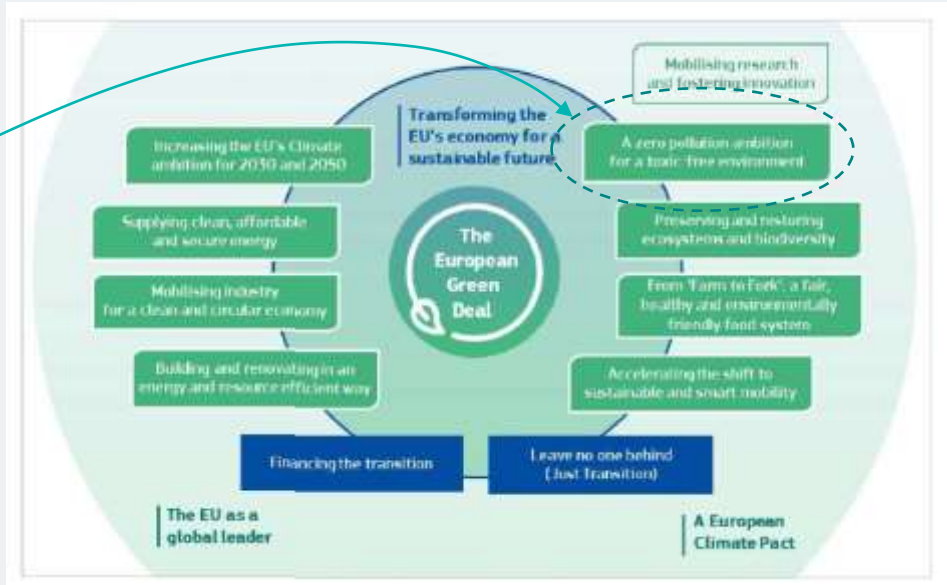
Chemicals + **Climate** + **Circularity** + **Criticality**

Control environment and health exposure across all lifecycle stages, keeping metals in safe use ⟵ **Zero pollution ambition**

Reduce GHG emissions, allowing metals to fully enable energy transition in their applications ⟵ **Decarbonisation**

Maintain lifetime of permanent resources, mitigating the need for additional extraction ⟵ **Circular economy**

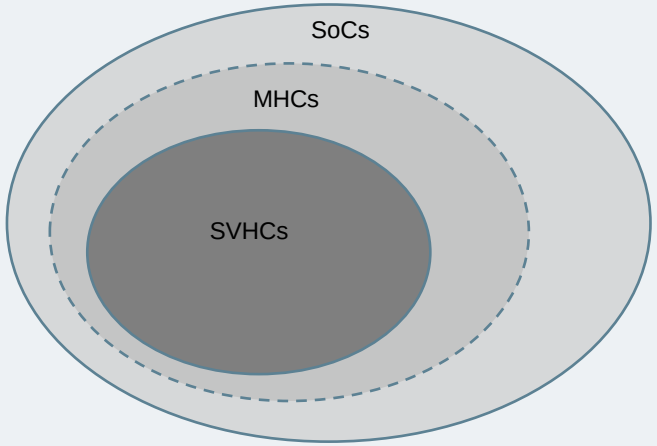
Ensure access to a sustainable supply of critical raw materials



Sustainable Metals Concept

Chemicals risk management should also take into account the climate, circularity and strategic autonomy objectives.

What does “safe” mean for uses of metals??



Is it - the absence of hazard

- No hazardous substances
  - No more SVHCs
  - No more MHCs
  - No more SoCs

Increasing impact on metals
More metals and metals compounds meet the definition

= no more metals, as even those that don’t fit the definition of SoCs (Fe, Al) are likely to be impacted due to hazardous alloying elements, coatings…

= **C**limate and **C**ircularity objective extremely difficult to achieve

Or is it – the absence of risk

- Ensuring that potential human health and environmental risks during the full life cycle of the substance are known and effectively controlled

A large volume of metals could be subject to duplicated risk management measures applicable to consumer and professional uses for adverse effects also associated to ED and STOT properties

We also work on the Critical Raw Materials Act and Net Zero Industry Act – legislative proposals

CRITICAL RAW MATERIALS ACT

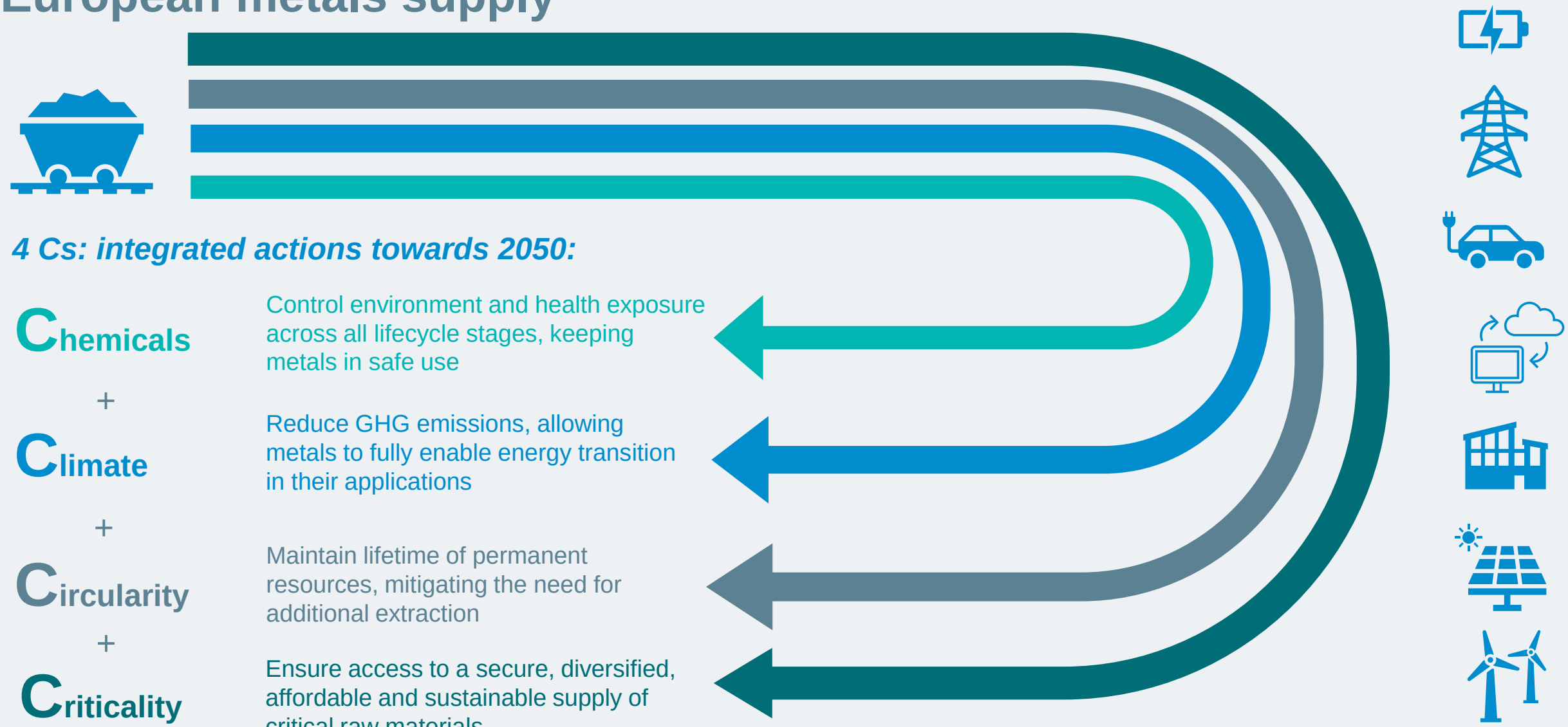
Mining, processing, recycling of target metals and minerals

NET ZERO INDUSTRY ACT

Manufacture of clean energy technologies & components

An attempt for a European framework to reduce the EU's reliance on imports & to reach 2050 Green Deal climate-neutrality goals

‘Four Cs’: Integrated priorities for achieving a Green Deal-ready European metals supply



4 Cs: integrated actions towards 2050:

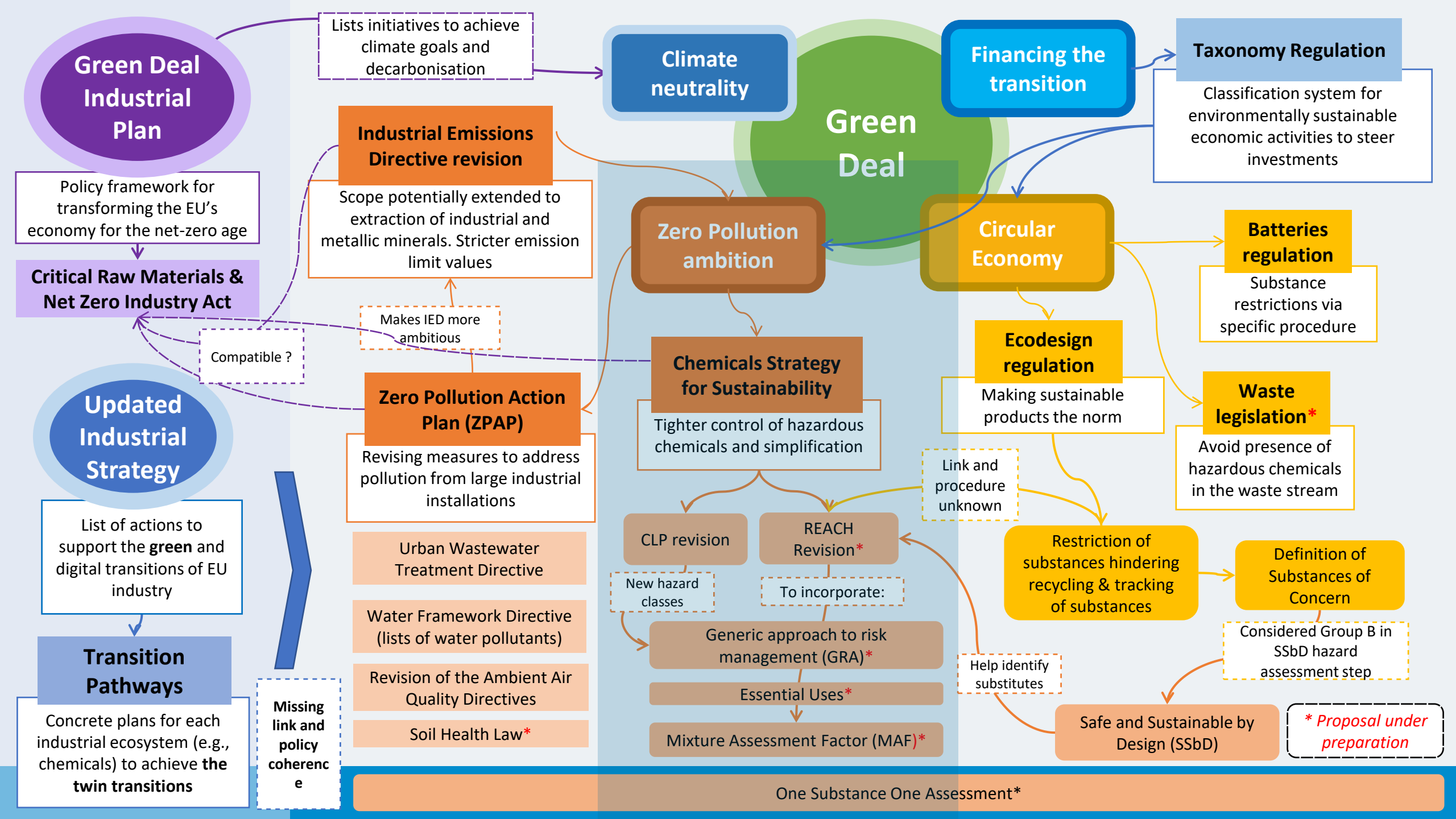
Chemicals + **Climate** + **Circularity** + **Criticality**

Control environment and health exposure across all lifecycle stages, keeping metals in safe use

Reduce GHG emissions, allowing metals to fully enable energy transition in their applications

Maintain lifetime of permanent resources, mitigating the need for additional extraction

Ensure access to a secure, diversified, affordable and sustainable supply of critical raw materials


Green Deal Industrial Plan
Policy framework for transforming the EU's economy for the net-zero age
Critical Raw Materials & Net Zero Industry Act
Lists initiatives to achieve climate goals and decarbonisation
Climate neutrality
Green Deal
Financing the transition
Taxonomy Regulation
Classification system for environmentally sustainable economic activities to steer investments
Industrial Emissions Directive revision
Scope potentially extended to extraction of industrial and metallic minerals. Stricter emission limit values
Makes IED more ambitious
Compatible ?
Zero Pollution ambition
Circular Economy
Batteries regulation
Substance restrictions via specific procedure
Chemicals Strategy for Sustainability
Tighter control of hazardous chemicals and simplification
Ecodesign regulation
Making sustainable products the norm
Waste legislation*
Avoid presence of hazardous chemicals in the waste stream
Zero Pollution Action Plan (ZPAP)
Revising measures to address pollution from large industrial installations
Updated Industrial Strategy
List of actions to support the green and digital transitions of EU industry
Transition Pathways
Concrete plans for each industrial ecosystem (e.g., chemicals) to achieve the twin transitions
Missing link and policy coherence
Urban Wastewater Treatment Directive
Water Framework Directive (lists of water pollutants)
Revision of the Ambient Air Quality Directives
Soil Health Law*
CLP revision
REACH Revision*
Link and procedure unknown
New hazard classes
To incorporate:
Generic approach to risk management (GRA)*
Essential Uses*
Mixture Assessment Factor (MAF)*
Restriction of substances hindering recycling & tracking of substances
Definition of Substances of Concern
Considered Group B in SSbD hazard assessment step
Help identify substitutes
Safe and Sustainable by Design (SSbD)
* Proposal under preparation
One Substance One Assessment*

Take Home messages

Take home messages

- REACH and CLP will bring in some changes on top of daily compliance but the extent is not well known yet when it comes to REACH (e.g., environmental footprint? Essential uses?) **Q4 2023**
- The challenge comes also from the increasing links and integration of ‘risk management’ tools
- The overall landscape is complex and requires monitoring, technical work and advocacy
- MEED, 4Cs concept, contributing to guidance(s) helps defending metal specificities

THANK YOU

Violaine Verougstraete and Hugo Waeterschoot

Eurometaux – European Metals Association

@Eurometaux

www.eurometaux.eu

Avenue de Tervueren 168, Box 13 | B-1150 Brussels | Tel: +32 (0) 2 775 63 11 | eurometaux@eurometaux.be

Exponent®

Endocrine Disruption – Fact or Fiction?

Manganese REACH Conference

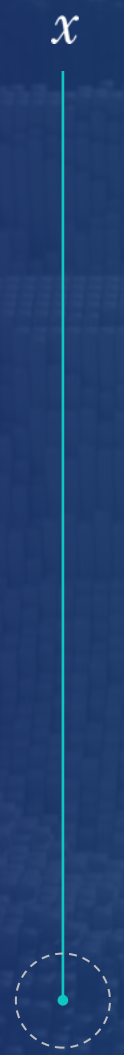
28 September 2023

Emily Richmond MSc, CBiol, MRSB, ERT

Senior Managing Toxicologist
Chemical Regulation and Food Safety

- 18+ years in regulatory toxicology, specialist in DART and Endocrine toxicity
- Worked on >50 ED assessments under the ECHA/EFSA ED guidance, including MoA.
- Frequent ECHA RAC stakeholder expert representation and member of the ECHA partner expert group for revision of the CLP guidance for ED
- Consultant toxicologist for numerous metals

Agenda



ARN recap

What is endocrine disruption (ED)?

How is ED regulated for in Europe?

The weight of evidence for human hazard from Mn induced endocrine disruption (regulatory data vs literature)

The way forward?

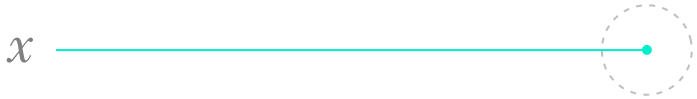
ED Assessment for manganese compounds

- ECHA Assessment of Regulatory Needs (ARN) report was published 7 December 2021, version 1.0. The report covers “Simple Manganese Compounds”

Six sub-groups are listed:

- Group I is a large group (14 substances) and includes soluble and poorly soluble manganese salts as well as manganese metal itself.
- Group II contains only sodium and potassium permanganate.
- Stated regulatory risk management action is strongest for substances in sub-groups I and II. For Endocrine disruption it specifically states:

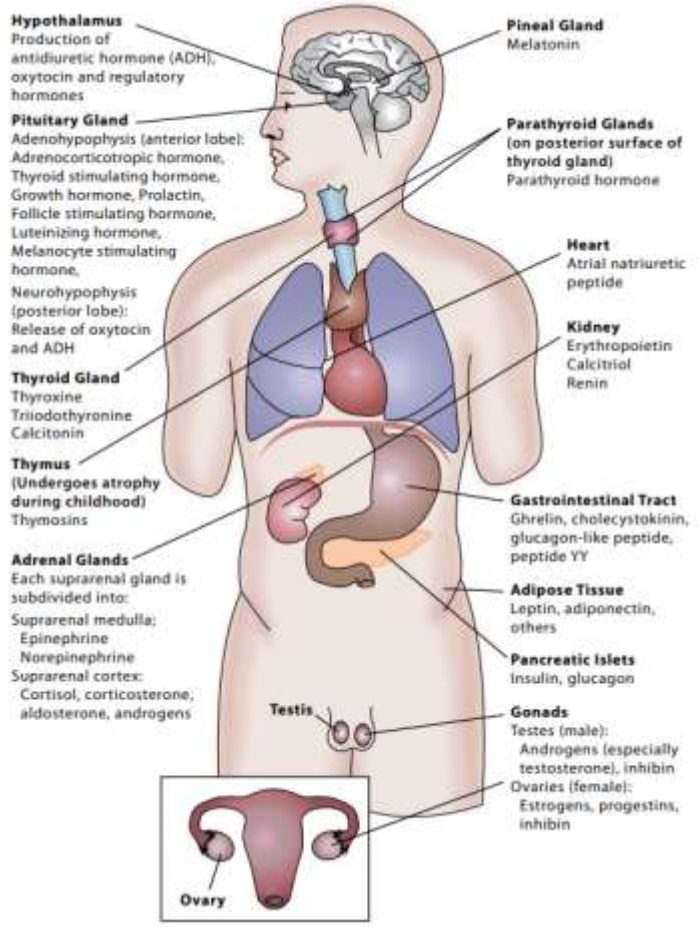
‘For all substances in the group, there is inconclusive evidence on human health ED hazard due to very limited relevant findings. The evidence is not considered sufficient to raise a concern or to suggest follow-up with further testing (and it is expected that the suggested classification for reproductive hazards will lead to efficient RMMs). However, in several studies reproductive effects are indicated, and an ED mode of action cannot be excluded. The mode of action can be considered in the context of preparation of the CLP report’



What is Endocrine Disruption (ED) and how is this regulated for in Europe?

What is the endocrine system?

- A complex system made up of glands and organs that produce, store, secrete and respond to hormones
- Hormones are endogenous chemicals that are produced in an organism and transported in tissue fluids to stimulate specific cells or tissues into action. i.e. a chemical messenger
- Hormones affect most body functions such as: growth, development, reproduction, sexual function, blood pressure, sleep, metabolism, mood



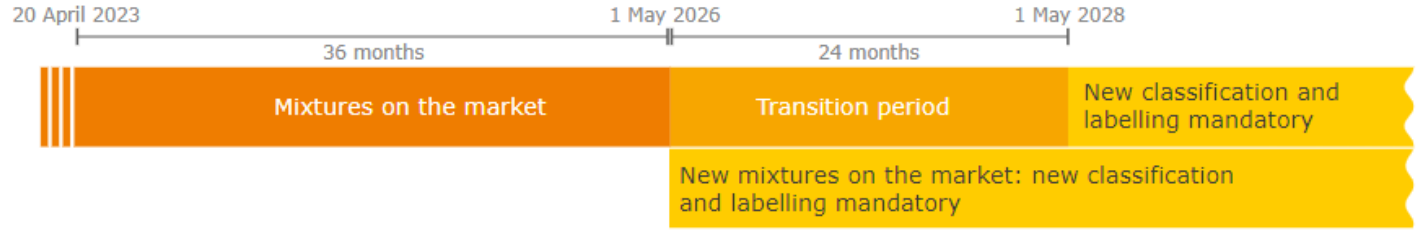
What is Endocrine Disruption (ED)?

- *'An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations'* (IPCS, 2002)
- Endocrine disrupting chemicals (EDC) interfere with the hormonal system and thereby produce harmful effects in both humans and wildlife
- EDC can be naturally occurring or man-made chemicals
- Growing global concern has resulted in changes in legislation

ED under REACH and CLP

- Under REACH (Regulation EC 1907/2006) – substances having ED properties identified as SVHC and subject to authorisation
- Amendment of CLP Regulation (EC) No 1272/2008 to include new hazard classes for ED (in force from 20 April 2023)
- Mandatory classification for ED from Nov 2026 for existing substances on the market

Hazard class and category code	Hazard statement code	Hazard statement
ED HH 1	EUH380	May cause endocrine disruption in humans
ED HH 2	EUH381	Suspected of causing endocrine disruption in humans
ED ENV 1	EUH430	May cause endocrine disruption in the environment
ED ENV 2	EUH431	Suspected of causing endocrine disruption in the environment



But how to identify ED under REACH?

- Up until 2018, there was no formal EU guidance on how to identify an EDC
- In 2018, EFSA and ECHA finalised:

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (published June 2018)

- Interim advice from ECHA is to follow this guidance for evaluating ED criteria under CLP
- ECHA/EFSA Update of the Guidance on the Application of the CLP criteria to include guidance on the new hazard classes is in preparation – expected mid-2024

ECHA GUIDANCE efsa

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC)

Abstract

This Guidance describes how to perform hazard identification for endocrine-disrupting properties by following the scientific criteria which are outlined in Commission Delegated Regulation (EU) 2017/2100 and Commission Regulation (EU) 2018/605 for biocidal products and plant protection products, respectively.

Procedures taken to investigate endocrine disruptor potential of manganese?

- Exponent have prepared a Weight of Evidence evaluation on the ED potential of manganese substances in Group I
- Followed principles of ECHA/EFSA ED Guidance to reach conclusions on ED scenario and whether any true concerns for ED MoA as indicated in ARN
- Included an extensive review of regulatory data AND a systematic literature review to determine if there are reliable conclusions which can be drawn on ED in the wider literature

ED assessment strategy

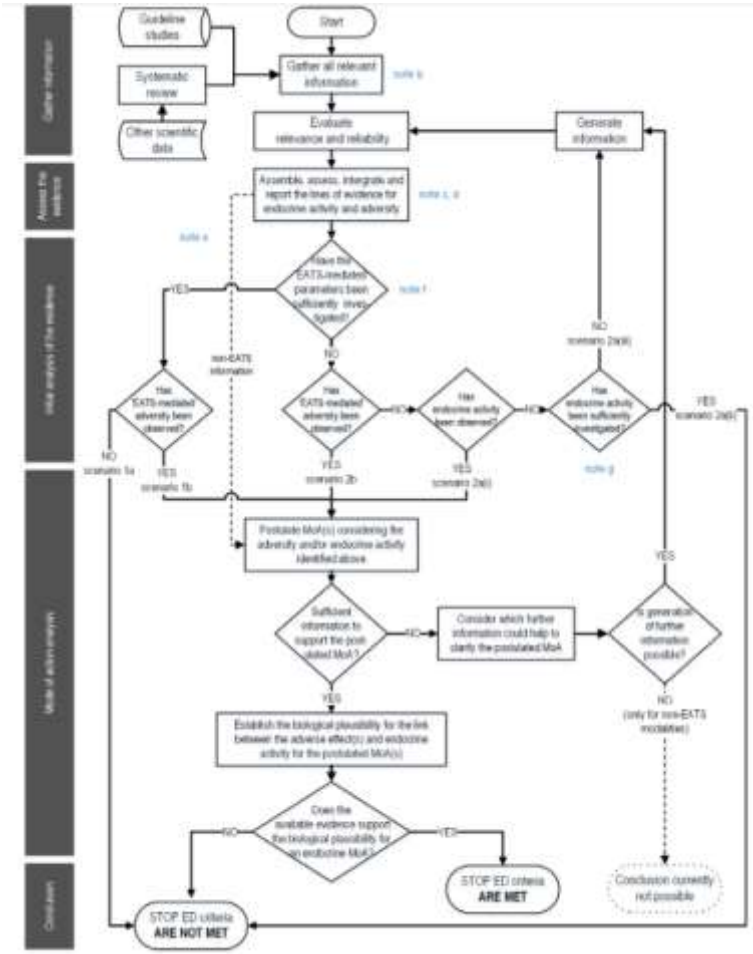
Gather information

Assess the evidence

Initial analysis of the evidence

MoA analysis (if triggered)

Conclusion on ED criteria



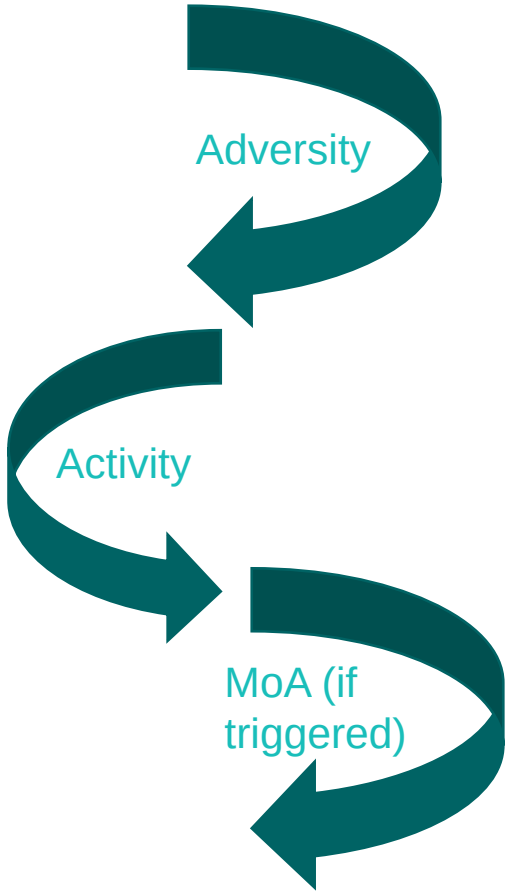
Following the ECHA/EFSA ED assessment strategy

- Focus on estrogen (E), androgen (A), steroidogenesis (S) and thyroid (T) modalities
- EAS and T assessed separately
- For each modality the following stepwise approach applies:

- Assessment for adversity
- Assessment for activity

→ Data gathering from regulatory studies and from focused ED systematic literature review (considering data sufficiency for conclusions)

Generate Weight of Evidence (WoE) to reach ED scenario conclusions



ED literature search strategy

- ED guidance specifies either a single concept or targeted search strategy should be developed to conduct a systematic literature review. The time scale is not predefined
- Exponent approach – Initial targeted search strategy:
  - Time scale: All data up to 01 February 2023.
  - All relevant toxicology and life sciences databases on the STN and ProQuest DIALOG search services were searched.
  - Each Group I substance (by Name and CAS number, not trade name) was searched separately.
    - System algorithms were used to remove as many duplicate citations as possible and to sort records in reverse chronological order.
    - Individual substance searches were merged into one result to also remove duplications across the substances

STN DATABASES:

Toxicology Database Cluster

CAplus (Toxicology focus)
TOXCENTER

Life Sciences Database Cluster

BIOSIS
CABA
EMBASE
ESBIOBASE
MEDLINE
SCISEARCH

PROQUEST DIALOG DATABASES:

AGRICOLA
AGRIS
Analytical Abstracts
Aqualine
Aquatic Science & Fisheries Abstracts (ASFA)
BIOSIS® Toxicology
CAB ABSTRACTS
Ecology Abstracts
Embase
Endocrinology Abstracts
Environment Abstracts
Foodline®: SCIENCE
FSTA®
GEOBASE
GeoRef
MEDLINE®
Meteorological & Geoastrophysical Abstracts
Oceanic Abstracts
Pollution Abstracts
ToxFile®
Toxicology Abstracts
TOXLINE
Water Resources Abstracts

Additional
National Center for Biotechnology Information (2023). PubChem Compound Summary
PubMed

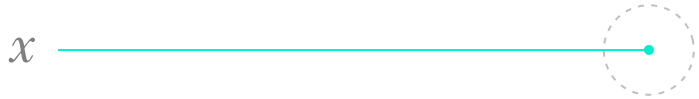
ED search terms (based on ECHA/EFSA ED guidance)

- *estradiol
- *testosterone
- accessory sex*
- Adren*
- Amphibian
- Androg*
- anogenital-distance; AGD
- Aromatase
- basolateral separation;
- corticotrop*
- Cryptorchid*
- Endocrine
- endocrine disrupt*
- epididym*
- Estrog* or Oestrog*
- Estrus or Oestrus or estrous
- Feminization
- Fish life cycle
- Fish short term reproduction
- *glucocorticoid*
- GnRH
- gonad*
- hershberger
- Hormone (- to catch “growth hormone”, FSH, LH!)
- Hypospadi*
- Hypothal* (for hypothalamus, hypothalamic…)
- Masculinization
- metamorph*
- Neurodevelopment
- ovarian follicle;
- oviduct; ovary
- Pituitary
- preputial separation
- Progestagen* or Progesterone or gestagen*
- prostate
- Pubertal
- Retinoid
- Secondary sexual
- seminal vesicles
- silurana
- sperm
- spiggin*
- steroid*
- T3
- T4
- Testis or Testes
- Thyro*
- Toxcast
- Triiodo*
- TSH
- tubercles
- Uterotrophic
- uterus
- vagina
- vaginal opening or vaginal patency
- vitellogen*
- Xenopus

Results of searches

Titles reviewed	29,153	10,540 with duplicates removed
Abstracts reviewed after title screening	353	254 discounted after initial review

- Systematic process for discounting literature:
  - Is the exposure scenario controlled?
  - Is the focus on normal biological process rather than actual endocrine disturbance?
  - Are the data from humans, rats, mice, rabbits or dogs (following OECD approach for literature reviews)?
  - Can the abstract be accessed and is it in English?
  - Further criteria for full paper review:
    - From 1990 onwards (allowing 23 years of research)
    - Focus on most soluble/bioavailable as 'worst case scenario' (where solubility unknown paper purchased)
    - Only relevant dose routes for human exposure (e.g. Intravenous routes not relevant)
    - Precedence given to in vivo or ex vivo rather than in vitro data
    - Novel research data rather than review articles



The Weight of Evidence for human hazard from Mn induced Endocrine Disruption (regulatory data vs literature)

Key findings of the ED Weight of Evidence

- Data sufficiency:
  - For both T and EAS modalities, across the data set for Group I substances, there is considered a sufficient regulatory data set to draw ED adversity conclusions (note this is based on ECHAs grouping, assuming Mn is the toxophore – data insufficient without grouping)

- OECD 408 (v. 1998): Silico-Manganese Slag (SiMn Slag): Toxicity Study by Oral Administration to Sprague-Dawley Rats for 13 Weeks including Proof of Absorption Analysis [Cooper, 2016; report amended 2019]
- OECD 414 (v. 2001): Ferromanganese Slag (FeMn Slag): Study for Effects on Embryo-Fetal Development in the Rabbit by Oral Gavage Administration
- OECD 414 (v. 2001): Ferromanganese Slag (FeMn Slag): Study for Effects on Embryo-Fetal Development in the Rat by Oral Gavage Administration
- OECD 414 (v. 2001): Manganese Carbonate ($MnCO_3$): Combined Pilot Study and Preliminary Embryofoetal Development Study in the New Zealand White Rabbit by Oral (Gavage) Administration
- OECD 414 (v. 2001): Trimanganese tetraoxide ($Mn3O_4$): Study for Effects on Embryo-Fetal Development in the Rat by Oral Gavage Administration
- OECD 414 (v. 2001): Manganese dichloride($MnCl_2$): Prenatal Developmental Toxicity Study in the Han Wistar Rat
- OECD 414 (v. 2001): Manganese dichloride($MnCl_2$): Developmental Neurotoxicity Toxicity Study in the Han Wistar Rat
- Broadly OECD 408 and 453 compliant (v. 1998 or 2009, respectively): Manganese sulphate ($MnSO_4$): National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Manganese (II) Sulfate Monohydrate in F344/N Rats and B6C3F1 Mice
- OECD 416 (v. 2001) Manganese dichloride ($MnCl_2$): Two Generation Reproduction Inhalation Toxicity Study of Manganese Dichloride in Rats

Key findings of the ED Weight of Evidence cont.

EAS modalities (regulatory data set)

- SiMn Slag (insoluble) - No adversity or target organ toxicity identified after subchronic exposure up to the regulatory limit dose (reflecting the lack of systemic bioavailability proven)
- Data consistent with 90 day exposure to manganese sulphate (soluble) which also identified no changes in any endocrine sensitive organs in rats
- No adversity in any endocrine sensitive organs after chronic exposure of rats to manganese sulphate
- No developmental effects reported after exposure of rats to SiMn Slag, FeMn Slag, $MnCO_3$, Mn_3O_4
- No reproductive toxicity (including developmental neurotoxicity) changes in rats after $MnCl_2$ inhalation (soluble)
- In rabbits, some inconsistent changes in post-natal implantation loss after exposure to ferrous manganese slag but only at maternally toxic doses with confounding vehicle effects. Foetal abnormalities were not of endocrine origin (Visceral abnormalities of head, heart and blood vessels)
- No evidence of post-implantation loss in rabbits exposed to non-lethal doses of Mn Carbonate in a preliminary pilot study

Key findings of the ED Weight of Evidence cont.

Thyroid modality

- SiMn Slag (insoluble) - No thyroid adversity identified after subchronic exposure up to the regulatory limit dose (reflecting the lack of systemic bioavailability)
- No thyroid histopathological changes after 90 day or chronic exposure to manganese sulphate (soluble) in rats
- In mice, after chronic exposure to manganese sulphate, marginal increase in thyroid follicular cell adenoma, very similar to historical control data and lacking dose response. Doses were far in excess of the OECD limit dose.
- In rats after prenatal exposure to $MnCl_2$ inhalation (soluble), slight increase in foetal thyroid size which correlated with diffuse follicular hypertrophy at the highest dose tested.
  - No thyroid toxicity in the subsequent reproductive toxicity study (note only histopathology conducted) which exposed at similar doses for longer durations through two generations. No reproducibility of effect.
  - No developmental neurotoxicity detected in a OECD 426 compliant study at the same dose level.

Systematic literature review outcome

- Large volume of literature – Mn is a large area of research
- Academic data conflict with regulatory study outcomes
  - Mn is associated with normal sexual development, normal sperm function and thyroid function
  - Concern arises from disturbed function which might come from abnormal exposure
    - Main focus areas of ED concern are:
      - **Onset of precocious puberty**
      - **Thyroid disturbance**
      - **Reproductive function**
  - Human data
    - All human data obtained have no controlled exposure scenario

353 Abstracts reviewed – 48 full paper reviews for relevance and reliability
11 relevant articles
Only 1 was reliable (with limitations) using Klimisch scoring
All remaining articles were considered Klimisch 3 or 4 due to severe limitations for regulatory purposes

What did the systematic literature review find?

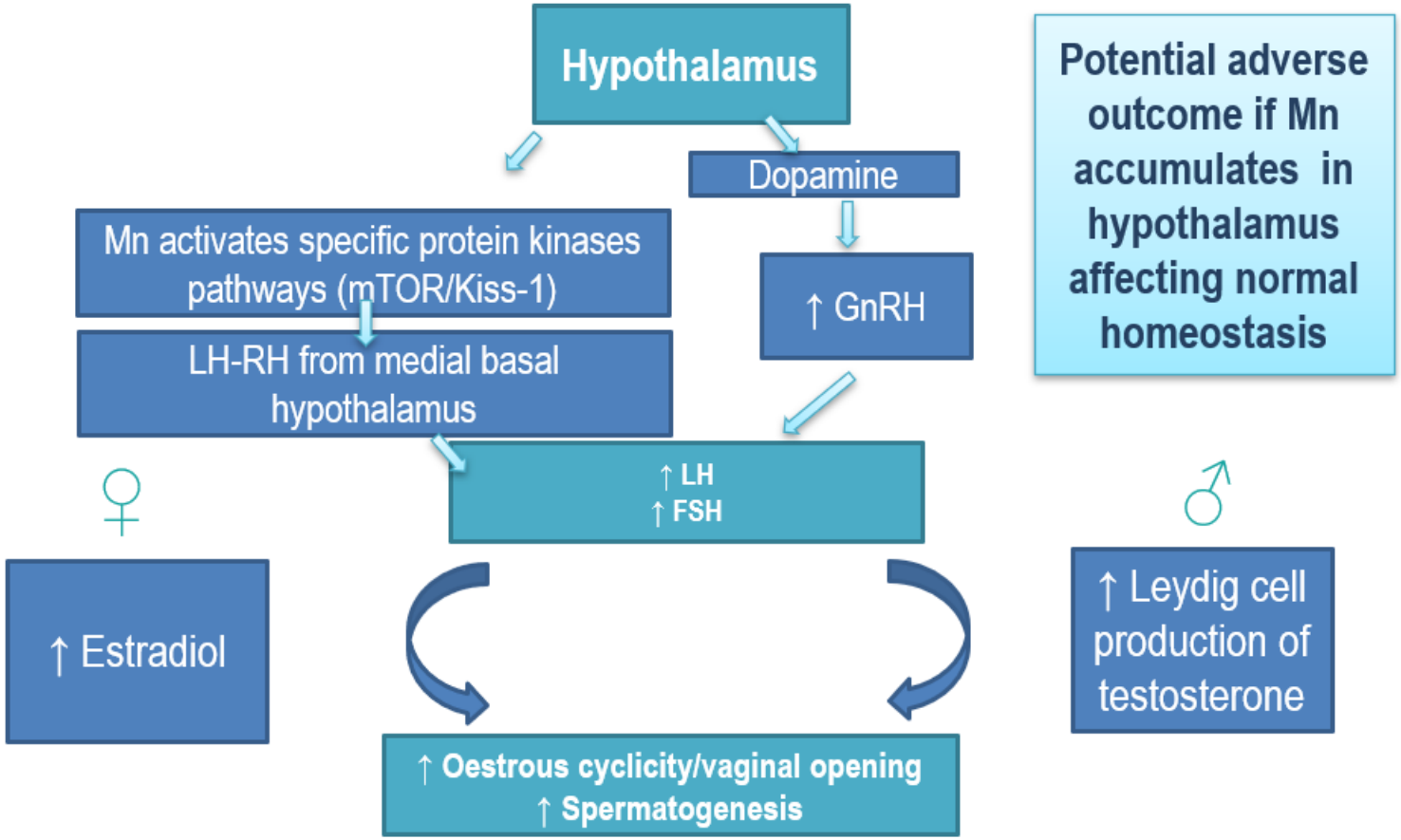
- Academic publications
  - In some cases, series of publications from same researchers based on ED and repro effects in rats and mice
  - Regardless of reliability - a large body of research is available, heightening concern (ARN!)
  - Key information weakens reliability, e.g. control of endogenous Mn exposure from diet, Mn characterisation, robust group sizes, no HCD

Neuroendocrine disturbance?

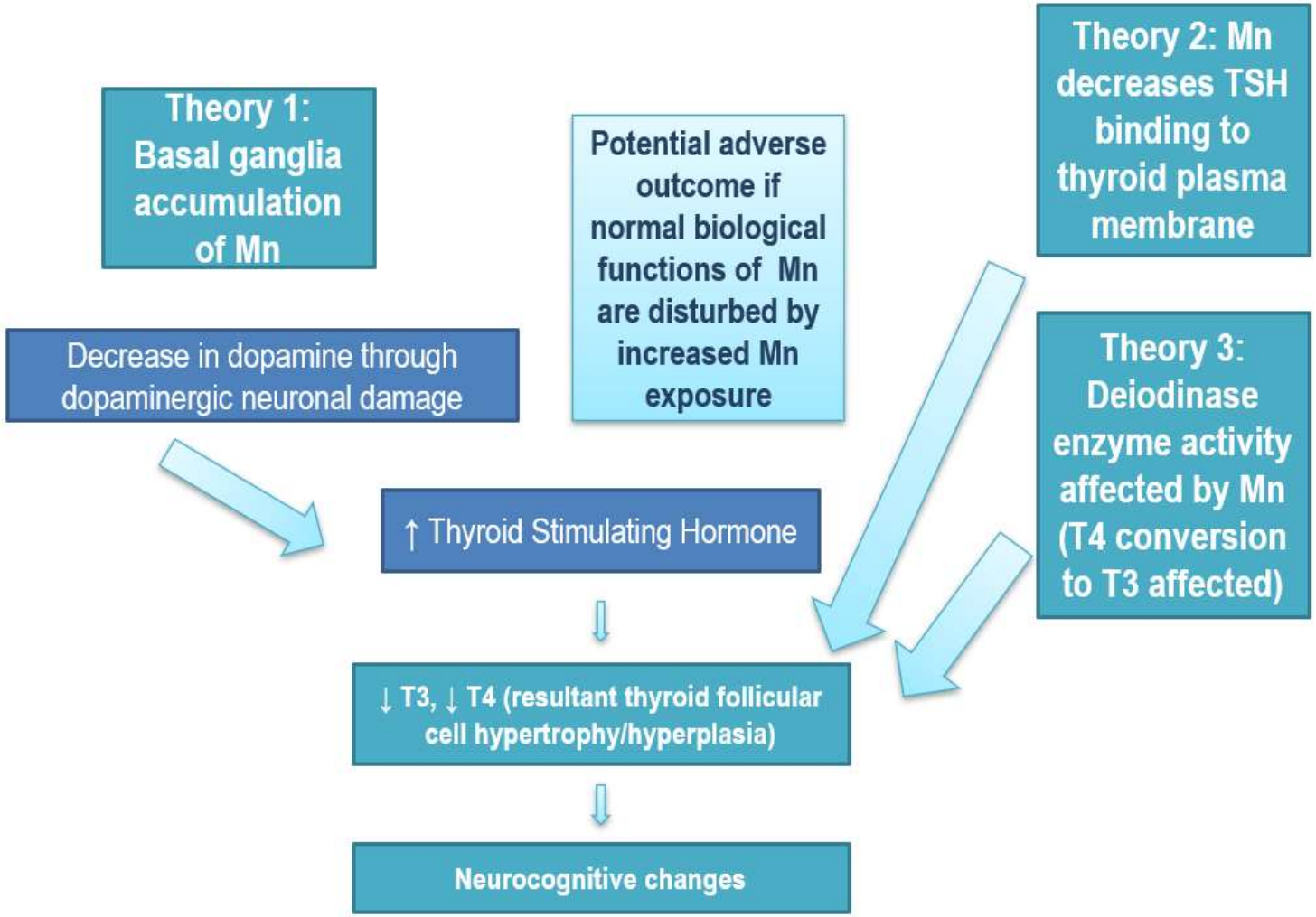
- Mn is an essential element associated with normal sexual development, normal sperm function, oestrous cycling and thyroid function

Potential neuroendocrine link though hypothalamic disturbance and dopaminergic control

Postulated reproduction and precocious puberty affects in literature

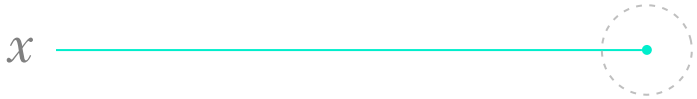


Postulated Thyroid Disruption in literature



Conclusions from ED Weight of Evidence

- ED scenario from regulatory data indicate no compelling evidence of mammalian EAS or T adversity. Very slight indications of T adversity in two studies ($MnSO_4$ and $MnCl_2$) but not reproducible, and lack dose-response
- Literature data support that Mn is responsible for normal mammalian biological processes under neuroendocrine control, e.g. reproductive function, sexual development and thyroid homeostasis
- Conflicting conclusions between literature and regulatory data with regard to endocrine disruption
  - Note absence of reliable literature data, despite relevancy
- Biologically feasible that significant changes in systemic Mn concentrations would disturb normal homeostatic functions BUT adverse outcomes not identified in the regulatory data



Ways forward for Mn and ED

ED – fact or fiction? Classification outcomes?

- Remaining uncertainty on how ED Classification criteria will be applied (note mandatory classification from Nov 2026)
  - Cat 1: may cause ED
  - Cat 2: suspected to cause ED
- How do you classify for neuroendocrine changes? neurotoxic or endocrine or both?
  - Potential argumentation that the primary site of toxic insult would be the brain and the endocrine change would be the secondary consequence
  - Indicate neurotoxicity classification warranted rather than endocrine but data would be required to prove this theory under the ED guidance approach
    - *In vitro* and *in vivo* ED activity assays are feasible for EATS to investigate direct thyroidal, estrogenic, androgenic and steroidogenic effects
    - Indications that change to Annex VII information requirements would necessitate these assays regardless

Way forward?

- Substantial academic data (unreliable but relevant) indicates Mn is could be an ED through neuroendocrine disturbance in excessive concentrations
- A strong justification will be necessary to lower concern as regulators prefer to use " the precautionary" principle – this could lead to some Mn substances being classified as suspected ED
- Under ED criteria, additional studies can be required to investigate the direct endocrine activity potential of different inorganic Mn-based substances
  - ED activity assays are feasible for EATS to investigate direct thyroidal, estrogenic, androgenic and steroidogenic effects
  - Indications that change to Annex VII information requirements would necessitate these assays regardless

Potential path forward = conduct studies to discount concern and strengthen argumentation that Mn is not an ED with regulatory compliant studies

No classification for ED until additional data is generated to enable appropriate classification

Prepare for potential ED classification for some substances – precautionary principle

Thank you for your attention

Emily Richmond

erichmond@exponent.com

Assessment of regulatory needs – what you need to know

Manganese REACH conference

28 September 2023

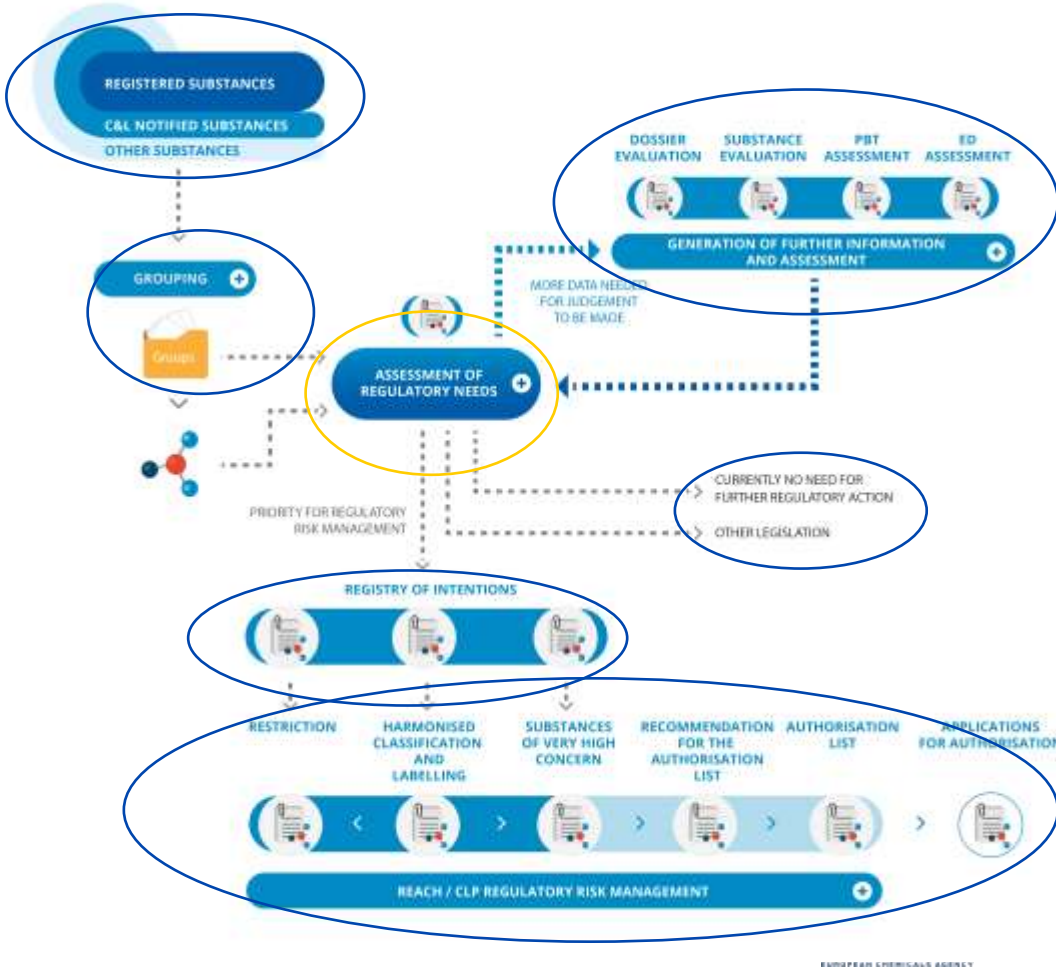
Chrystele Tissier, prioritisation unit
Maarten Roggeman, risk management unit
European Chemicals Agency, ECHA

Contents

ECHA’s integrated regulatory strategy

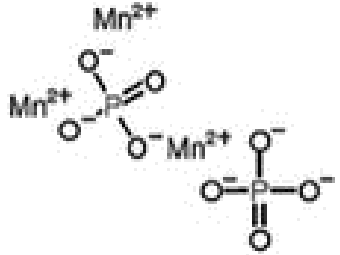
ECHA's Integrated Regulatory Strategy

- → Regulatory processes connected
- → Work on groups is central to finding substances needing actions
- → Transparent:
  - Annual IRS Report
  - Chemical Universe
  - Assessments of Regulatory Needs published
- → See details in IRS infographic



Grouping and assessment of regulatory needs

Why do we work on groups of substances?



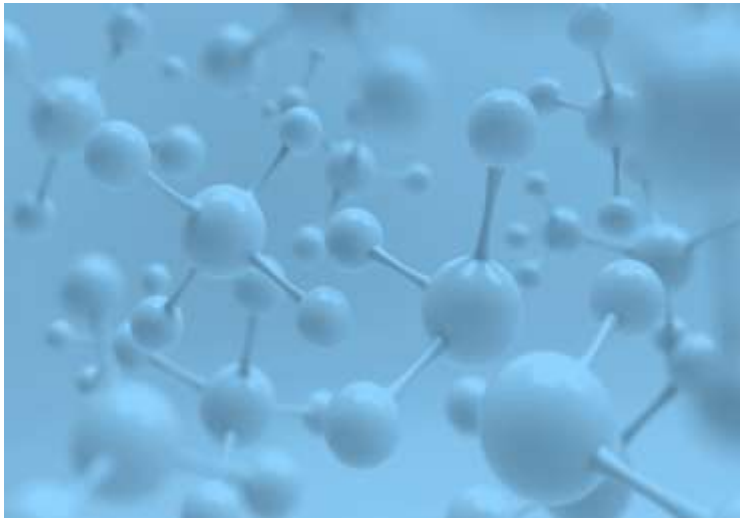
→ Increased **efficiency** and **effectiveness**

→ Benefits:

- Treats related substances consistently
- Efficient use of (requests for) data and faster action:
  - pooling information
  - targeting data requests
- Focus on substances of concern to target the right substances at the right time
- Increases predictability of authorities' actions
- Support informed substitutions, avoid regrettable substitutions

Assessments of Regulatory Needs (ARN) in brief

- → **Informal**, **screening** level assessment of groups of structurally related registered substances
- → Helps authorities consider optimal way to address potential concern (combination of exposure and hazard) for group of substances
- → Assessment finds substances or groups that need potentially RRM but also those that don't need
- → More clarity on concern after follow-up processes



Preparatory work to support REACH & CLP processes

How do we assess groups of substances?

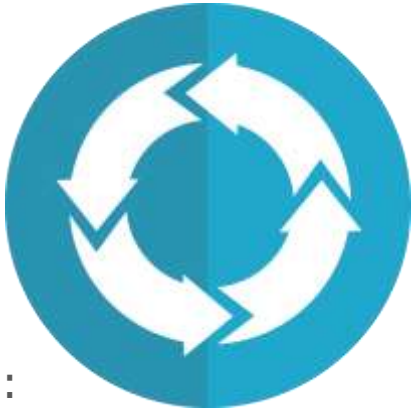
→ Identify **most appropriate way to address the identified concerns** (iteratively)

→ Main source of information: registration dossiers (both hazard and exposure information) – holistic view

→ Group of chemically similar substances

- Various group sizes: from <10 to >50 substances
- Grouping uses IT algorithms based on structural similarity, registrants read-across/category approaches, external category associations.
- ARN-groups are not registrants' read-across/ categories, nor groups in regulatory processes
- Different from Section 1.5 of Annex XI to REACH

An iterative assessment



- → Immediate regulatory action proposed.
- → Further data generation through compliance check often suggested to clarify the potential hazard identified.
- → Data generation on the most relevant substances based on:
  - Hazard
  - Data gaps
  - Tonnage
  - Use/exposure potential
  - Relevance for other group members
- → Ultimate potential risk management action proposed if hazards confirmed for the whole group, for a subgroup or for individual substances.
- → Assessment of read-across/category approach done later during official processes (e.g. compliance check)

Transparency and predictability

Transparency and predictability of IRS related actions

- → Publication of ARN's reports to make clear and transparent what will be the next (potential) actions for a (group of) substance(s)
- → Increases predictability for industry:
  - Time for industry to update their registration dossiers
  - Plan for the upcoming regulatory work
- → Supports informed substitution (avoid regrettable substitution)

Transparency and predictability of IRS related actions

→ Informal process –conclusions of ECHA in ARN do not mean initiation of a formal regulatory process:

- Interaction with industry/stakeholders is only foreseen in the formal processes

→ "See a problem or have feedback" button added on ARN webpage: please use in case of factual errors

≠ Not for discussion on new information on hazards or uses, not for disagreements on assessments conclusions or plans

≠ The feedback will be considered

Achievements – what’s new

Status of ARN work

- → Since 2019: >6000 substances assessed in >230 groups
- → Most common immediate regulatory step: CCH with ~300 substances identified for CCH per year (nearly all CCHs come from ARN work)
- → EU regulatory risk management actions expected for **~35%** of assessed substances
- → ARN work is one source of candidates for the Restrictions Roadmap (e.g. Mn)

What's new?

→ ARN report template enhanced to clarify
- the focus and basis of ECHA's work
- the sequence of the different steps before RRM action
- Softer wording in the conclusions and better reflection on the uncertainties in particular related to the potential hazard identified

→ New notification system via REACH IT informing registrants about the publication of the ARN report

Coming soon

- → Webinar “Towards faster regulatory action: ECHA's approach to assessing chemicals in groups” – 3rd October
- → New ECHA strategy being prepared by the end of 2023 with new priorities for coming years
- → IRS review being initiated, starting with a stakeholder survey and followed by stakeholder discussions early March 2024

The simple Manganese compounds

Assessment of regulatory needs – Simple Manganese compounds

→ 29 manganese compounds

→ Uses as reported in the registration dossiers

- Mining and metallurgical operations for iron, steel, ferrous and non-ferrous alloys, manufacturing of dry-cell batteries, additives, pigments and dyes, feed additives, fertilisers……
- Widespread uses with potential for exposure to humans and releases to environment

→ Hazards: Repr., STOT RE, neurotox

→ Actions proposed at subgroup level

- Subgroups 1 and 2: simple inorganic salts, oxides and manganese metal and permanganates
  - Step 1: CLH
  - Step 2 (if hazard confirmed): restriction combined with authorisation if hazard confirmed

- All remaining substances
  - Step 1: CCH
  - Step 2 (if hazardous): CLH
  - Step 3 (if hazard confirmed): Restriction combined with authorisation if hazard confirmed

Restrictions Roadmap entry

	Subject of restriction proposal	Numbers of substances in group for regulatory action (if applicable)	Hazards in scope	Uses				Additional information	(Anticipated) year of submission of mandate to ECHA
			Confirmed or suspected hazards	Industrial	Professional	Consumer	Article service life		
	Groups where CLH or candidate listing to be carried out with restriction as suggested risk management								
2.	Simple manganese compounds	Group (15)	R, STOT RE, Neurotox.		x	x	x	The need for further regulatory risk management measures (e.g. combination of authorisation and restriction) is under discussion, focusing on subgroups 'Simple inorganic salts, oxides and manganese metal' and 'Permanganates'. Might apply to other substances in the group following steps taken to generate data in order to clarify the hazard.	TBD

Key messages

Key messages

- → Assessment of regulatory needs (ARN) is an iterative, informal process, linking the REACH and CLP regulatory processes to enable faster RMM.
- → The aim of ECHA grouping is manyfold:
  - ensure consistency and coherence in the regulatory actions proposed for similar substances
  - ensure that the risk management actions are taken in a timely manner and whenever possible at group level, avoiding thereby regrettable substitution
  - avoids unnecessary animal testing and use all data available.
- → Publication of ARNs brings transparency and makes it easier for companies to predict the actions regulators are planning
- → ARN is preparatory work to support REACH & CLP formal processes
- → CLH first steps for subgroups 1 and 2 for the simple manganese compounds, for all other substances data generation is first.

Where to find more information?

- → IRS infographic
- → The annual IRS report (July 2023) and the chemical universe updates
- → Assessment of regulatory needs page
- → General page to explain the grouping approach
- → PACT
- → List of assessments of regulatory needs (including also RMOAs)
- → Assessment of regulatory needs - Simple manganese compounds
- → Chemical universe
- → Q&As on assessments of regulatory needs
- → Webinar 14 December 2021
- → Webinar 3 October 2023

Thank you!
Any questions?

arn@echa.europa.eu

echa.europa.eu/subscribe

Connect with us

---

echa.europa.eu/podcasts

European Chemicals Agency

@one_healthenv_eu

@EU_ECHA

@EUECHA

EUchemicals

Manganese REACH Conference

Sept. 26-28, 2023

The Thon Hotel
Brussels, Belgium

DAY 2

Mn Aquatic toxicity – an overview

Manganese REACH Conference

28 September 2023

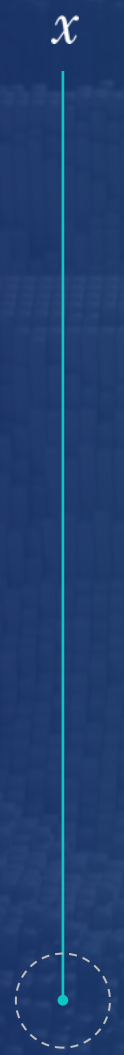
Katie Hill

Senior Managing Scientist
Head of Industrial Chemical Notification Services

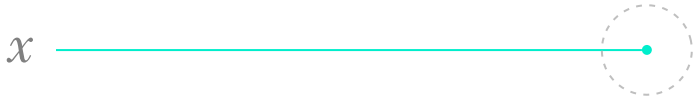
Chemical Regulation and Food Safety

- BSc (Chemistry), LLM
- 18+ years in Regulatory Affairs
- 9+ years at Exponent
- Working on REACH since 2007
- Previous experience in metals REACH consortium and industry

Agenda



- A brief look back
- Environmental hazard classification methodology
- Summary of current Mn substance classifications
- Relation to ARN
- Current and future work



A brief look back

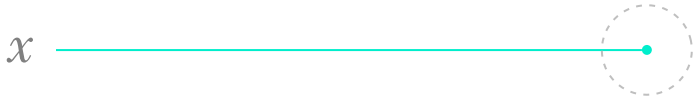
A brief look back

- Testing strategy designed by CRO in *ca.* 2008
  - Consideration of published data ('solubles') and REACH information requirements
- Ecotox studies performed on specific Mn substances
  - Suite of short-term fish, daphnia, algae and long-term invertebrate studies for Mn oxides, sulphide, FeMn slag
  - Limited read across (only used between soluble substances; from FeMn slag to sinter ore; from MnO to $MnCO_3$)
- Original submission in 2010
  - 'Solubles': data on $MnSO_4$ and $MnCl_2$ used and classification by molecular weight correction of L(E)C50/NOEC → standard
  - Sparingly soluble substance-specific data: aquatic hazard information requirements and TDp data
  - Sparingly soluble classification based on comparison of the above → non-standard
  - Aim: to prevent regulatory authorities grouping together manganese and its insoluble compounds with the classifications of its soluble compounds (HH and ENV)

A brief look back, cont.

- Exponent involvement - 2012
  - Early task: consideration of new guidance on environmental C&L (April 2012 release), relating to 2nd ATP to CLP Regulation. (Additional loading rates (0.1 mg/L and 0.01 mg/L) over 28 days)
- Overview of MARA substance environmental classifications
  - Original classification (hazard data on substance ↔ TDp data on substance)

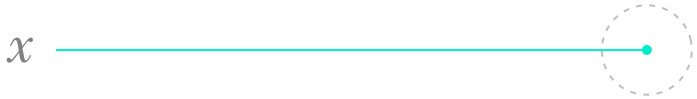
    vs.
  - Standard approach (hazard data on Mn ion ↔ TDp data on substance)
- Further consideration of standard approach but with chronic ERV based on:
  - Lowest relevant NOEC as identified in ARCHE report (2013) → approach for limited datasets
  - HC5 value as previously determined from 13 NOECs over 11 species → approach for extensive datasets
- Outcome: following standard approach using lowest relevant NOEC considered advantageous and carried forward in subsequent dossier updates



How are metals and metal compounds classified?

Metal and metal compound classification

- Driven by toxicity of metal ion (ecotoxicity data of soluble compounds)
  - Acute and chronic Ecotoxicity Reference Values (ERV) in mg Mn/L
- Soluble metal compounds
  - Molecular weight correction on ERV and comparison with classification cut off levels
- Sparingly soluble metals and metal compounds
  - ERVs compared to levels of metal ion release from Transformation/ Dissolution protocol (TDp) testing



Overview of Mn substance classifications

Soluble compounds

- $MnSO_4$
  - Harmonised C&L (Aquatic Chronic 2, H411)
  - Base data not known or available to us
  - Only applies to $MnSO_4$. Not been read-across to other substances
- $MnCl_2$ and $Mn(NO_3)_2$

  Current acute ERV from short-term fish test on $MnSO_4$ (LC50 3.2 mg Mn/L)
  - Equivalent to 7.33 mg $MnCl_2$/L
  - Equivalent to 10.41 mg $Mn(NO_3)_2$/L

  Current chronic ERV from long term fish test on $MnSO_4$ (NOEC 0.55 mg Mn/L)
  - Equivalent to 1.26 mg $MnCl_2$/L
  - Equivalent to 1.79 mg $Mn(NO_3)_2$/L

  All > 1 mg/L and hence no classification for acute or chronic effects

Sparingly soluble compounds

- MnO, MnO_2, Mn_3O_4, $MnCO_3$, MnS, Mn sinter ore, FeMn slag, SiMn slag
- TDp study information
  - Screen: Maximum release at pH 6
  - Full study (2010): 1 mg/L (7 and 28 d), 10 and 100 mg/L (7 d) loadings
- Current ERVs
  - Acute: 3.2 mg Mn/L; Chronic: 0.55 mg Mn/L
- Interpretation of data
  - Acute ERV > 1 mg/L → Not classified (acute)
  - Chronic ERV > 28d TDp conc at 1 mg/L loading → Not classified (chronic)

Metal

- Original study with smallest representative particle size on market
  - 585.6 µg Mn/L (after 28 days, 1 mg/L loading) > chronic ERV = Chronic 2
- Subsequent TDp study on greater particle sizes to remove classification for coarser grades of Mn

Sample particle size	Conc in TDp after 28d, 1 mg/L loading (mg/L)	Comparison with chronic ERV (0.55 mg/L)	Classification required?
< 0.45 µm	0.5856	Higher	Chronic 2
96.6 % between 45 and 425 µm 3.4 % <45 µm	0.162	Lower	None
> 1 mm (massive form)	0.0115	Lower	None

Threshold of particle size for classification: 425 µm

Mn Metal

- Use of Table 4.1.2 from CLP to determine how other particle sizes can be classified

Table 4.1.2

Classification of a mixture for long-term (chronic) hazards, based on summation of the concentration of classified components

Sum of components classified as:	Mixture is classified as:
Chronic 1 × M (a) ≥ 25 %	Chronic 1
(M × 10 × Chronic 1) + Chronic 2 ≥ 25 %	Chronic 2
(M × 100 × Chronic 1) + (10 × Chronic 2) + Chronic 3 ≥ 25 %	Chronic 3
Chronic 1 + Chronic 2 + Chronic 3 + Chronic 4 ≥ 25 %	Chronic 4

(a) For explanation of the M-factor, see 4.1.3.5.5.5.

- ≥ 25% of particles < 425 µm
  - Chronic 2
- Between 2.5 and 25% of particles < 425 µm
  - Chronic 3
- < 2.5% of particles < 425 µm
  - Not classified

Summary of Mn substance environmental classifications in JS

- None of the consortium substances ($MnCl_2$, $Mn(NO_3)_2$, $MnSO_4$, MnO, MnO_2, Mn_3O_4, $MnCO_3$, MnS, FeMn slag, SiMn slag, sinter ore) have an environmental classification except:

- $MnSO_4$ (harmonised classification) – Chronic 2

- Mn metal (self-classification)

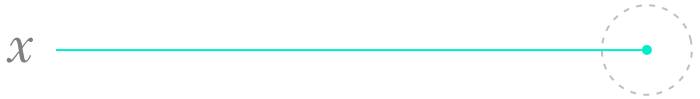
≥ 25% of particles < 425 µm - Chronic 2

Between 2.5 and 25% of particles < 425 µm - Chronic 3

< 2.5% of particles < 425 µm - Not classified

Mn mixtures (alloys)

- Alloys considered special mixtures under REACH and CLP
  - Alloys are not simple mixtures of metals – have distinctive properties compared to metal components
  - Metal release from alloys can differ to constituent metals
- FeMn and SiMn alloys submitted to TDp testing (2010)
  - measurement of Mn release only
- Mn release < Mn ERV values
  - no classification in relation to Mn
- Other constituent metals would need to be considered in similar way
- Possibility for ecotoxicity validation step where additivity approach invalid (eg competitive Me+ binding)
  - test on sensitive species at dissolved concs measured in TDp



Relation to ARN

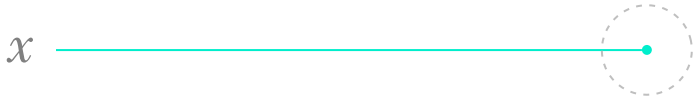
ARN and Environmental hazard

- Aquatic toxicity is one of the hazards in scope of an ECHA ARN
- Known or potential hazard for aquatic toxicity indicated (all Mn sub-groups)

- "***Concern that the self-classification in many of the registration dossiers may not be adequately reflecting the ecotoxicological data***"

- First step of ARN – hazard confirmation via CLH
  - Any CLH proposals would cover aquatic toxicity in addition to human health endpoints
- ECHA also expects registrants to adequately self-classify substances for aquatic toxicity after CCH

(High environmental RCRs noted for $MnCl_2$, $MnSO_4$, $Mn(NO_3)_2$, MnO_2, Mn)



Current and future work

Consideration of issues and potential weaknesses

- Reliability and selection of key studies appears to be being questioned by ECHA
- Some existing data on soluble salts
  - of variable quality (several non-guideline, unknown GLP compliance, non-standard species)
  - datasets not extensive but might not be considered data poor
  - HC5 method requires > 10 and ideally > 15 data points (HC5 previously calculated based on 13 NOECs of variable quality)
  - Use of lowest NOEC can represent the worst case
- Concern:
  - Same data used as ERVs to derive the C&L of the other Group I ARN substances (by comparison with TDp data) → Any revision to ERVs could impact environmental C&L of all Group I substances
  - ECHA could argue the data are not reliable enough to justify avoiding the CLH in the case of $MnCl_2$ and $Mn(NO_3)_2$ (and possible other ARN Group I substances)

Complications

- Sparingly soluble salts complicated (different oxidation states)
- Some aquatic toxicity data on the substances themselves - the validity of which can be challenged on scientific grounds (e.g. exposure period in long-term Daphnia studies 8 rather than 21 days, some issues with analysis of solutions)
- Available aquatic toxicity data limited in terms of range of abiotic factors that could impact Mn bioavailability (eg pH)
- Mn is naturally occurring (importance of acclimatisation)
- Mn an essential element (tests within organisms' homeostatic ranges)
- etc…

Way forward

- Review all aquatic toxicity data in light of current guidance (focus on chronic data on soluble salts)
  - No L(E)C50 < 1 mg/L and hence no impact on acute hazard classification
- Review of methods followed and conclusions drawn
  - Individual studies (relevance, reliability, and use in ERV setting)
  - Revisit ERV derivation in light of data re-assessment
  - Assess any potential impact on substance C&L
- Update reporting
  - Latest standards (guidance, best practise, updated IUCLID software)
  - Clear and robust conclusions
- Dossier updates - prioritisation for $MnSO_4$, $MnCl_2$ and $Mn(NO_3)_2$

But for now…

Substance	Environmental classification	Signal word	Pictogram	Transport classification
$MnSO_4$	Chronic 2	None		Class 9
Mn (≥25% particles < 425 µm)	Chronic 2	None		Class 9
Mn (2.5-25% particles < 425 µm)	Chronic 3	None	None	None
Mn (< 2.5% particles < 425 µm)	None	None	None	None

Thank you for your attention

Katie Hill

khill@exponent.com

Harmonising the categorisation of manganese slag as a by-product

Presentation to

Manganese REACH conference

28 September 2023

David Lever

Principal Consultant

Agenda

- Context and motivation
  - What are the benefits of categorising manganese slags as by-products?
- Methodology
- Uses of manganese slags
- Regulatory status
- Socio-economic assessment - harmonising the categorisation of manganese slag as a by-product
- Conclusions

Risk & Policy Analysts Ltd

- We help companies prepare data-driven, balanced and credible arguments in support of continued market access
- Independent, specialist consultancy with an established reputation and proven expertise in chemicals, environment, economics, EU policy, and sustainability
- Chemicals and economics team specialised in Analysis of Alternatives (AoA) and Socio-Economic Analysis (SEA) for REACH Authorisation and Restriction, and engaging with the extended supply chain to obtain relevant data
- Clients in private and public sector

Motivation: What are the benefits of categorising manganese slags as by-products?

- Ferromanganese (FeMn) slag and silicomanganese (SiMn) slag are categorised as either waste or by-products in different Member States and their local authorities – no harmonisation
- Different regulatory requirements are in place for waste and for by-products
- Best Available Techniques (BAT) for non-ferrous metals[1] – intention to reduce the quantities of slag sent for disposal
- Identify any socio-economic benefits of European-wide categorisation of manganese slags as by-product

[1] BAT implementing decision of 13 June 2016, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.174.01.0032.01.ENG

Methodology

- Review of present regulatory status and past research [1]
- Stakeholder consultation facilitated by MARA Secretary General
  - Production volumes
  - Uses, benefits, and revenue generated
  - How the slags are categorised
  - Advantages and disadvantages of each categorisation
- Data aggregated and anonymised

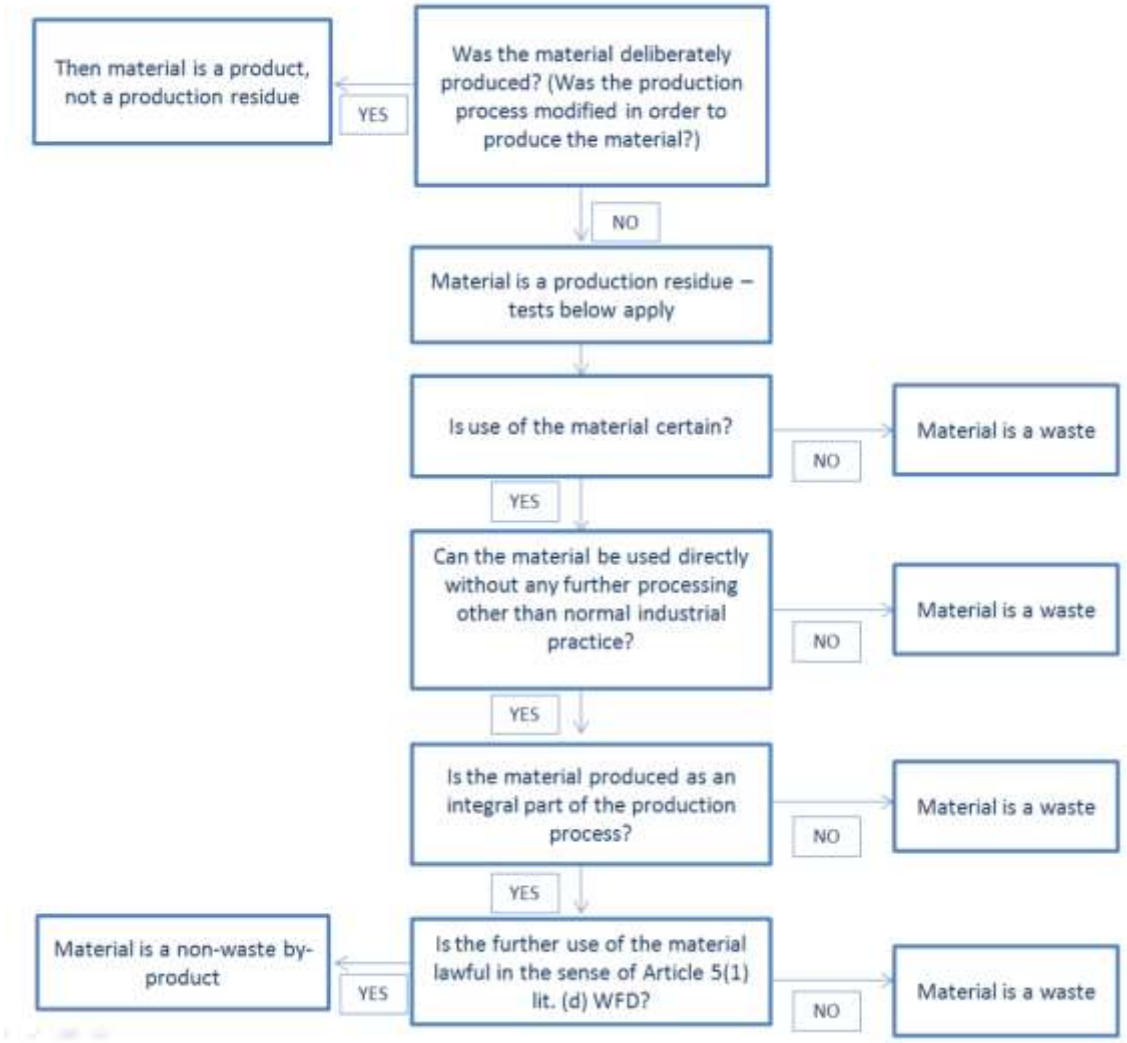
[1] For example, Manganese Slag SEA Part 2: Regulatory Status Report produced by RPA for IMnI (2018)

Definition of waste and by-products according to Waste Framework Directive 2008/98/EC[1]

- Article 3(1): "*'waste' means any substance or object which the holder discards or intends or is required to discard*"
- Article 5(1) states a substance may be regarded as a by-product if:
  - Further use of the substance is certain;
  - The substance can be used directly without any further processing other than normal industrial practice;
  - The substance is produced as an integral part of a production process; and
  - Further use is lawful, i.e., the object fulfils all relevant product, environmental and health protection requirements for the specific use and will not lead to overall adverse environmental or human health impacts."

[1] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32008L0098

Definition of waste and by-products



https://ec.europa.eu/environment/pdf/waste/framework/guidance_doc.pdf

Uses and benefits of manganese slags

- Feedstock into ferromanganese or silicomanganese alloy production
  - Good source of manganese; reduces extraction and consumption of virgin materials
- Construction (aggregate or pozzolanic material)
  - aggregate, offering good drainage, stability, light weight, low leaching in various environments e.g., road and rail, dies, restoration
  - can be used without additional processing, competitive price compared to virgin material
  - Clinker and concrete
- Fertiliser production
  - Good source of manganese (one of seven essential micronutrients)

https://inductotherm.com.au

https://tarmac.com

https://yara.co.uk

Regulatory status of manganese slags

	Slags, ferromanganese-manufg.	Slags, silicomanganese-manufg.
CAS number	69012-28-8	69012-33-5
EC Number	273-728-1	273-733-9
Hazard classification and labelling	According to the classification provided by companies to ECHA in REACH registrations this substance is suspected of damaging fertility or the unborn child	
		Repr. 2 H361
Symbol		

Regulatory status of manganese slags

- Waste BAT 161 states manganese slags should be recycled for silicomanganese production, or for construction applications
- Communications from the European Commission[1] in principle provide a supporting framework for harmonised categorisation as a by-product
- Largely up to national competent authorities and national judges to decide whether a substance should be considered a waste or a by-product
- Variation in how slags are categorised in the countries investigated in the study

[1] "A New Circular Economy Action Plan For A Cleaner And More Competitive Europe", March 2020; "On the implementation of the circular economy package: options to address the interface between chemical, product and waste legislation", Jan 2018; European Parliament resolution 13 September 2018 concerning uncertainties about how materials can cease to be waste

Benefits of harmonised classification

- A significant proportion of manganese slag is re-used on-site for SiMn alloy production
- Out of 500+ workers that are employed in plants producing manganese slags investigated in the study, between 25-50 of these workers are directly involved in the handling and processing of FeMn and SiMn slags
- In cases where slag is sold off-site, a net revenue more than €2 million was generated (2021)

Conclusions

- Advantages of categorising manganese slags as a by-product:
  - Diversion of slags from landfill and its associated costs;
  - Slag replaces virgin material (in production of alloys, construction aggregates, and fertiliser) and therefore reduces depletion of natural resources and contributes to the circular economy; and
  - In some cases, revenue generation from sales of slags.
- If manganese slag is classified as a waste, potential risks and threats identified by stakeholders in the consultation process include:
  - Risk of metallurgical production having to pause if slag cannot be suitably reused or diverted;
  - Costs of disposal to landfill.

Thank you

david.lever@rpaltd.co.uk

+44 203 988 4671

Risk & Policy Analysts Ltd

Suite C, 2nd floor, The Atrium

St Georges Street

Norwich, NR3 1AB

United Kingdom

www.rpaltd.co.uk

CARBON BOARDER ADJUSTMENT MECHANISM (CBAM):
IMPACT ON FERRO-ALLOYS IMPORTS AND PRODUCTION IN EUROPE

Manganese REACH Conference

Brussels, 26-28 September 2023

Carbon Boarder Adjustment Mechanism (CBAM)

Start:2026
(transitional period 2023-2026)

CBAM is expected to be a tool to counter carbon leakage (shift production outside EU with lower climate policy standards)

Sectors involved: Aluminium, Electricity generation, Fertilizers, Cement, Iron and Steel **and precursors like some ferro-alloys.**

Application to **imports from all non-EU countries**, but exemptions will be made for countries that have ETS linked to the EU ETS (e.g. EEA countries – Norway, Liechtenstein, Iceland and Switzerland). **The UK is not exempted.**

Emissions include CO2, NOx and PFCs (Scope 1), whereas **indirect emissions are provisionally excluded** (Scope 2).

EU Free allowances and CBAM: once the mechanism is applied to a EU product, its free allocation will be **reduced by 10% each year until it hits zero**.

CARBON BOARDER ADJUSTMENT MECHANISM (CBAM)

Ferro Manganese included

Ferro-chromium

CN Codes 7202 41
7202 49

Ferro-Manganese

CN Code 7202 11

Ferro-Nickel

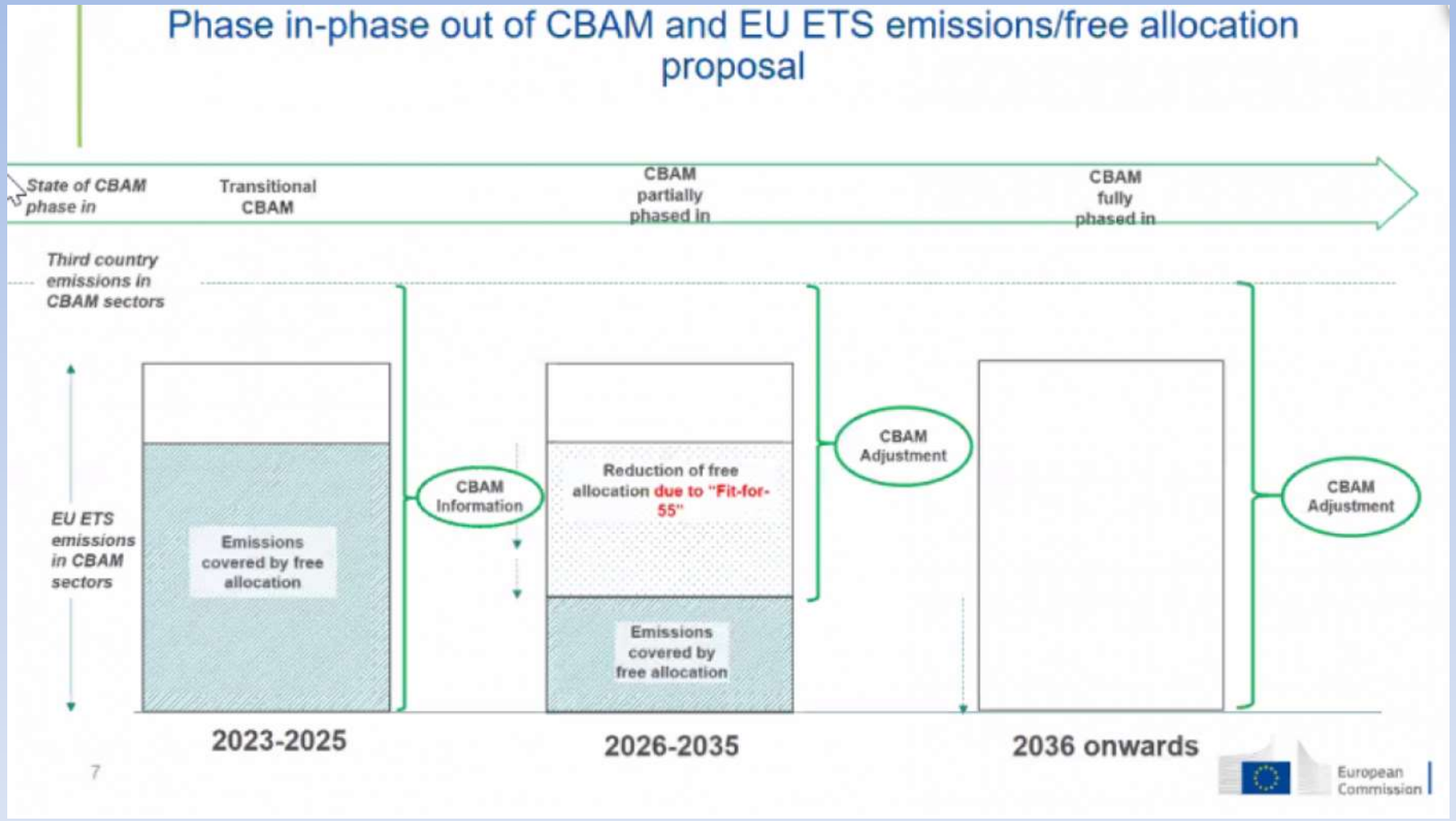
CN Code 7202 6000 00

Iron and Steel

CN code	Greenhouse gas
72 – Iron and steel Except: ***7202 2 – Ferro silicon*** ***7202 3 – Ferro-silico-manganese*** ***7202 50 00 – Ferro-silico-chromium*** ***7202 70 00 – Ferro-molybdenum*** ***7202 80 00 – Ferro-tungsten and ferro-silico-tungsten*** ***7202 91 00 – Ferro-titanium and ferro-silico-titanium*** ***7202 92 00 – Ferro-vanadium*** ***7202 93 00 – Ferro-niobium*** ***7202 99 – Other:*** ***7202 99 10 – Ferro-phosphorus*** ***7202 99 30 – Ferro-silico-magnesium*** ***7202 99 80 – Other*** 7204 – Ferrous waste and scrap; remelting scrap ingots and steel	Carbon dioxide
2601 12 00 – Agglomerated iron ores and concentrates, other than roasted iron pyrites	***Carbon dioxide***

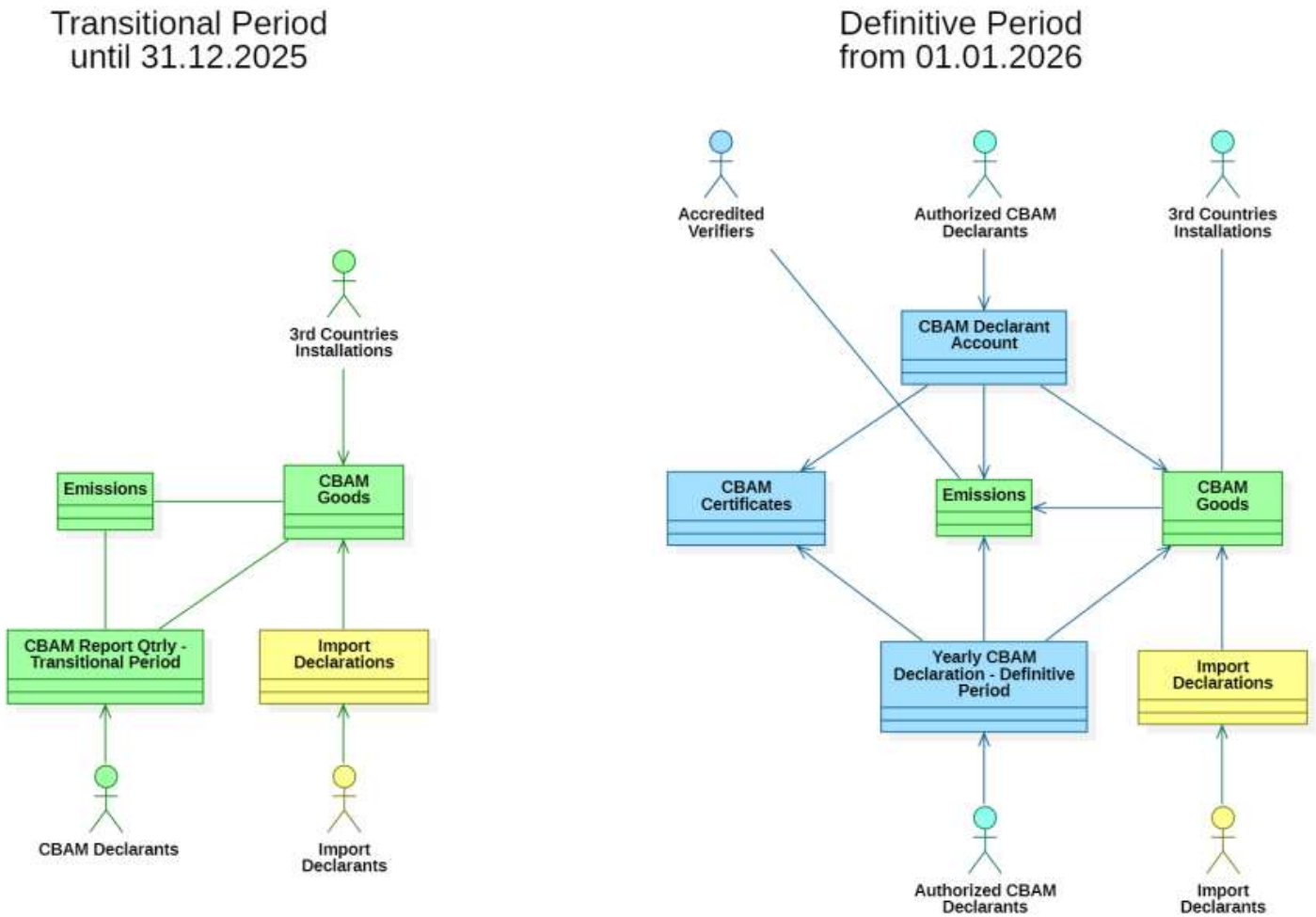
CARBON BOARDER ADJUSTMENT MECHANISM (CBAM)

CARBON BOARDER ADJUSTMENT MECHANISM (CBAM)



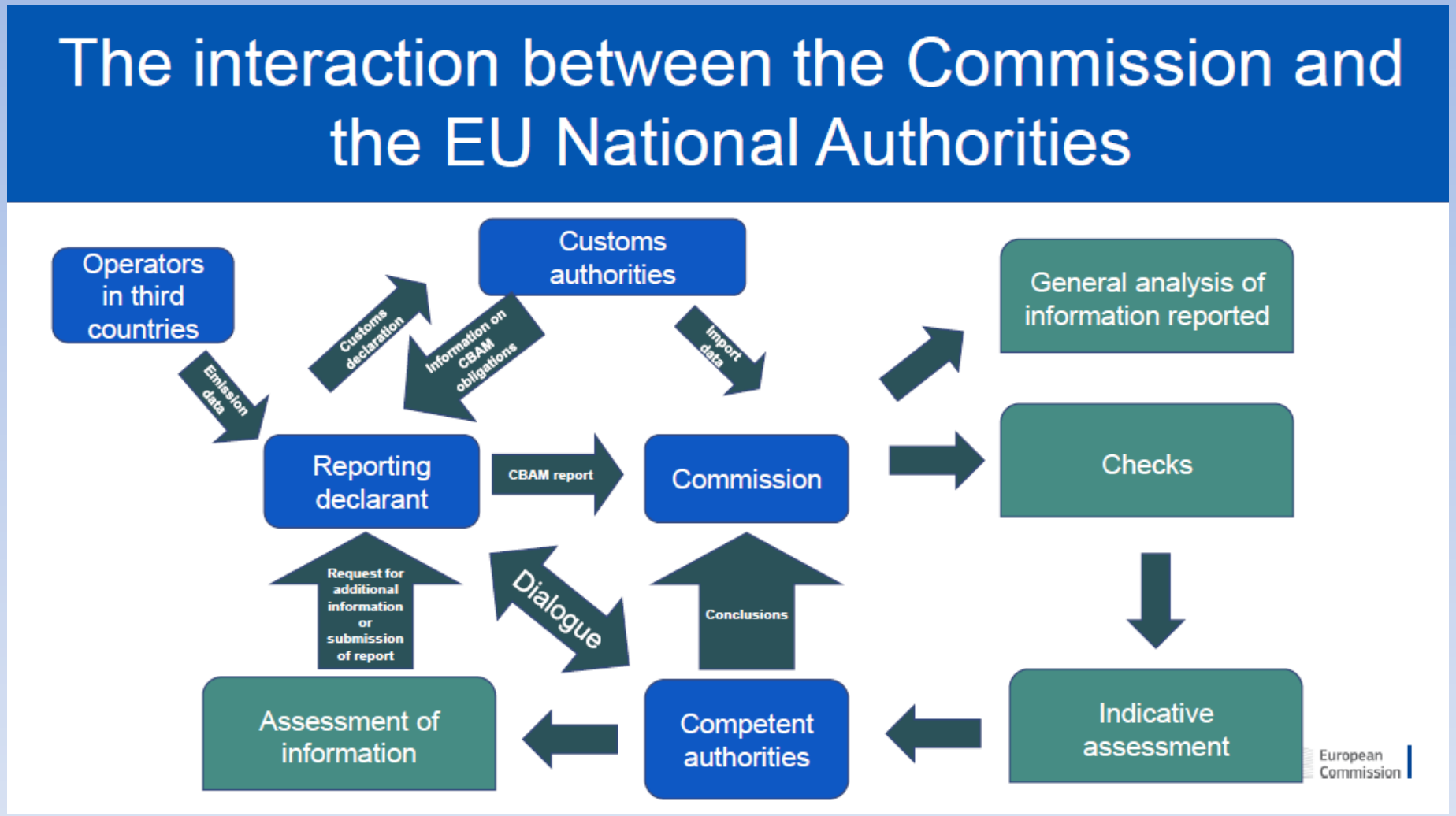
CARBON BOARDER ADJUSTMENT MECHANISM (CBAM)

The administrative system



European Commission

CARBON BOARDER ADJUSTMENT MECHANISM (CBAM)



CARBON BOARDER ADJUSTMENT MECHANISM (CBAM)

The administrative system

Transitional phase
October 2023 - December 2025

- CBAM report containing the following:
  - Total quantity of goods imported during the preceding quarter
  - Total embedded direct and indirect emissions in those goods
  - The carbon price due in the country of origin for the embedded emissions

→ Report to be submitted each quarter

Post transitional phase
January 2026 onwards

- CBAM declaration containing the following:
  - Total quantity of goods imported during the preceding calendar year
  - Total embedded emissions in those goods
  - Emissions to be verified by EU accredited verifier
  - Total number of CBAM certificated to be surrendered
  - The carbon price effectively paid in the country of origin for the embedded emissions

→ Declaration to be submitted each year

European Commission

CARBON BOARDER ADJUSTMENT MECHANISM (CBAM)

Upcoming

- implementing acts defining calculation methods for CO2 footprint

Obligations

- Direct and embedded emissions, otherwise "default " data is used
- Verification by the accredited person in accordance with EC requirements

CBAM Certificates

- Companies buy and surrender certificates to cover carbon content via annual declarations
- Purchase: throughout the year (the price would be the average of the weekly ETS EU price)

CBAM Online interface platform

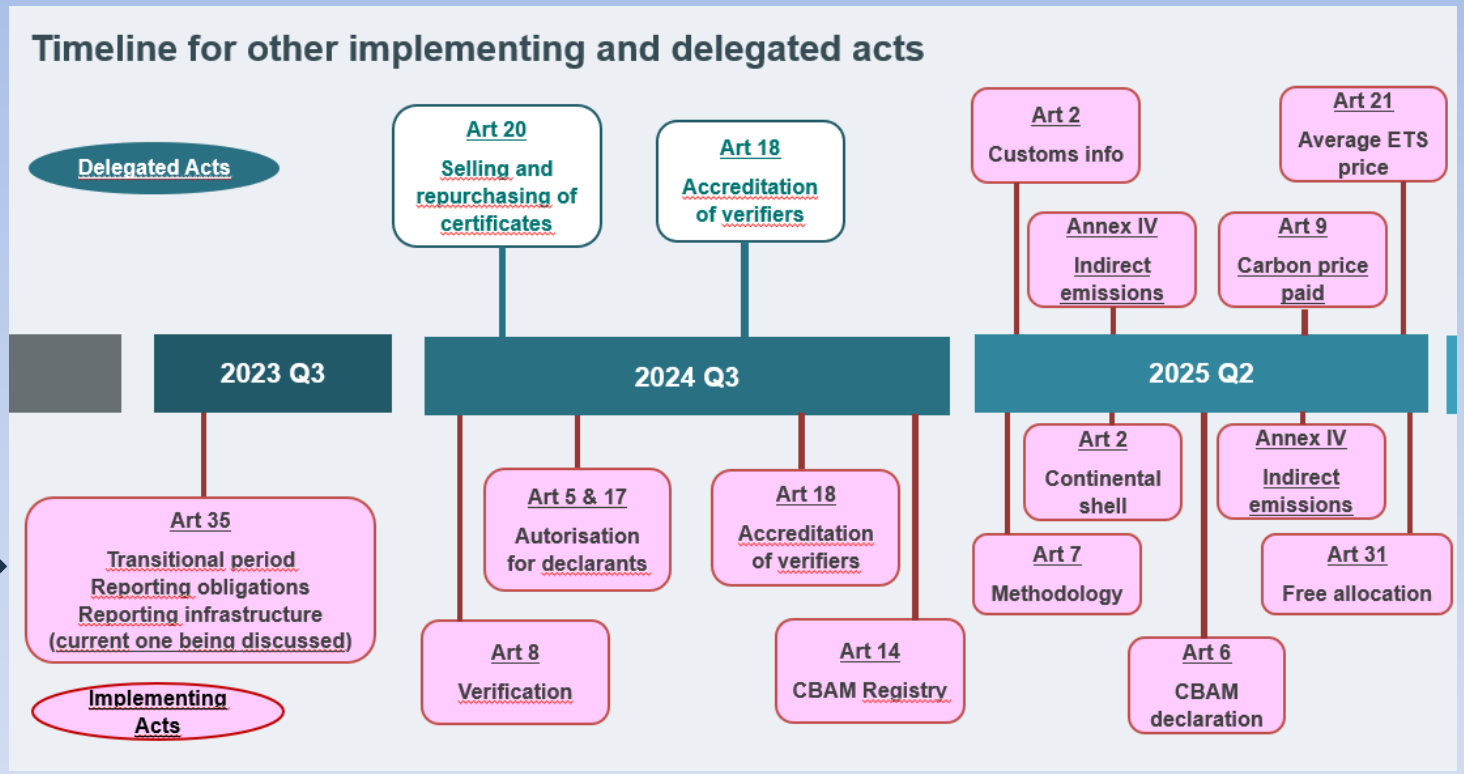
- Filing CBAM authorization requests
- Declaring CBAM quarterly emission reports during the transitional period (starts this year)
- Effective after 1 January 2024
- MS Customs authorities: reaching out to importers & training , ahead of 1 October 2023

Timing

- Importers need the CBAM authorization as of 1st January 2026 to be compliant.

CBAM: NEXT STEPS

CBAM published mid-March 2023. Implementing/delegated acts are prepared at full speed.



The implementing regulation on reporting obligations during the transitional period and its annexes has been published on 17 August 2023 : here and here

The EU Commission guidelines, tutorials, and seminars are being prepared in urgency mode.

CBAM: COMMENTS

- **Need to conduct a full impact assessment on CBAM prior adding any new sector to the CBAM**, with consultation of the sectors targeted.
- A full impact assessment and a workable methodology will need to be addressed for **indirect carbon costs** which are different from indirect emissions embedded in traded products due to the electricity market design in Europe.
- The carbon border adjustment proposal **fails to address carbon leakage risks**, and the envisaged rules will probably not ensure the global reduction of CO2 emissions
  - Shift to increasing share of imports of products based on renewable/nuclear energy
  - Declining EU exports because of higher EU cost levels
- The CBAM proposal is complex & open to loopholes and circumvention (resource shuffling, transshipment strategies etc.)

CBAM: FUTURE ?

- EC aims to expand very fast the scope (goods from the sectors on the Delegated Act on carbon leakage list)

- But many unhappy:

  - In the EU: not yet clear at national level which authority will be responsible for handling the paperwork.
  - CBAM will require a significant overhaul in customs administration

- Also unhappy —Poland is asking the General Court, to annul the mechanism, arguing that the law should have been passed unanimously and not by a qualified majority.

- Potential challenge at the WTO: India, China ?

THANK YOU FOR YOUR ATTENTION !

NADIA VINCK
EUROALLIAGES

Keller & Heckman

Manganese Alloys and the Upcoming European Critical Raw Materials Act

September 28, 2023

Marie Escornebouleu

Associate

Brussels, Belgium

+32 (0) 2 645 5092

escornebouleu@khlaw.com

Marie Escornebouеu

- Marie Escornebouеu counsels clients on EU product regulatory law, with an emphasis on chemicals legislation, food and drug packaging, cosmetics, and environmental issues.
- She advises companies on sustainability initiatives; REACH matters; the Classification, Labelling, and Packaging (CLP) Regulation; and Biocidal Products Regulation (BPR). She also assists companies in obtaining regulatory clearances for food-contact materials at the European Union (EU) and Member State level and advises clients with respect to mutual recognition.

1. Status of Adoption & Timing

- **March 2023**: Proposal for a Regulation establishing a framework for ensuring a secure and sustainable supply of critical raw materials
- **Followed by Commission's communication**: 'A secure and sustainable supply of critical raw materials in support of the twin transition' – shows what initiatives are in the pipeline related to e.g., financial support, strategic partnerships, and sustainability and circularity
- Proposal now **pending** before the European Parliament and Council (adoption foreseen 2025/2026)
- **Latest**: European Parliament adopted its Report on 14 September

2. Critical Raw Materials

- **Scope:** non-energy, non-agricultural raw materials, referred to as 'critical raw materials'
  - Crucial for strategic technologies used for the green, digital, defense, and space applications, the supplies of which are subject to a high level of supply risk
- **Critical vs. strategic raw materials**
  - *Strategic:* materials that score the highest in terms of strategic importance, forecast demand increase and difficulty of production
  - *Critical:* includes all strategic raw materials + over RM of high importance
- **'Manganese'** listed in Annex II as 'critical' and '**Manganese – battery grade**' is listed in Annex I as 'strategic'
- Review clause – 4 years

3. Framework Regulation

- **Goals**:
  - Face increased demand induced by green and digital transition
  - Address issue of overconcentration of supply sources
  - Ensure a secure and sustainable access to CRMs

- **Framework Regulation:** details will be set in delegated and implementing acts
  - E.g., future amendment to the list of CRMs, criteria for Strategic Projects
  - COM granted a significant power

4. Strategic Projects & Benchmarks (1)

- **Strategic RM**: EU to set benchmarks for domestic capacities to be reached by 2030
  - At least 10% of domestic demand for extraction
  - At least 40% of domestic demand for processing
  - At least 15% of domestic demand for recycling capacity
  - In parallel, diversification of sources in third states
- To reach these objectives, focus on '**Strategic Projects**'

4. Strategic Projects & Benchmarks (2)

- **Criteria**:
  - Meaningful contribution to the security of the EU's supply
  - Project technically feasible within a reasonable timeframe
  - Production volume can be estimated
  - Sustainable implementation
  - Cross-border benefits (if EU), mutually beneficial (if non-EU)
- **Procedure**:
  1) Application submitted by Project Promoter to COM
  2) COM decides taking into consideration European Critical Raw Materials board opinion
  3) Possibility for MS to object

4. Strategic Projects & Benchmarks (3)

- **Benefits conferred by this status**
  - Projects are regarded as of public interest or serving public safety and health, therefore benefitting from tolerances (for instance re biodiversity impact)
  - MS required to contribute to timely and effective implementation
  - Prioritization re permits
  - Regular reporting and exchanges with the Board

5. Obligations for Member States

- **One-stop-shop for permits for critical RM projects**
  - Single point of contact for applicants
  - Procedures shall be transparent, efficient, and predictable

- **Prioritization of Strategic Projects**
  - Time limits for permit granting
    - 24 months for extraction projects, 12 months for processing or recycling projects
    - For processing or recycling projects, permit automatically granted if time limit exceeded

- **Financial aspects**
  - MS shall foster investment in the Strategic Projects

6. Sustainability Aspects

- **Adoption of national programmes promoting circularity:**
  - Collection of waste with a high critical raw materials recovery potential
  - Integration in the recycling system
  - Secondary market and reuse
  - COM to identify products with a high CRM recovery potential via implementing acts

- **Recognition of certification schemes at EU level**

- **Rules for the calculation and verification of the environmental footprint**

7. Monitoring

- **Risk assessment and mitigation:**
  - COM to conduct stress tests for each strategic raw material
  - Support to research and innovation
  - Information exchange
  - Joint purchasing system between Member States

- **Duties for operators**
  - Report on their use of critical raw materials and their sources to the COM and authorities (for largest CRM operators, for others voluntary)
  - Company risk preparedness: MS shall identify large companies that manufacture strategic technologies: will have to perform an audit every two years of their supply chain

8. Challenges for the Manganese Industry

- More admin: monitoring, reporting, and due diligence activities
- Eco-design criteria, minimum content of recycled content
- More R&D into substitution of critical raw materials incl. manganese (?)

9. Opportunities for the Manganese Industry

- Build-up of strategic stockpiles may secure EU supply chains
- Access to finance in the scope of Strategic Projects
- Access to funding and collaboration platforms
- Better circularity by fostering recycling and reuse of critical raw materials
- Support to research and innovation in critical raw materials
- Smoother permitting
- Listing expansion?

Thank You

Any questions?

Marie Escornebouleu

Associate

Brussels, Belgium

+32 (0) 2 645 5092

escornebouleu@khlaw.com

fieldfisher

Interaction between REACH and EU sanctions on Russia: how registrants should comply?

28 September 2023

Natalie Konings

Summary

- **Introduction**
- **First Part : Applicable legislation**
  - **International sanctions: background**
  - **Types of sanctions**
  - **Liability**
  - **Enforcement**
  - **Penalties**
- **Second Part: Impact Assessment**
  - **Risk areas for consortia**
  - **Compliance program**
- **Conclusion**

Introduction

Impact of EU sanctions on REACH consortia

- General prohibition to provide business and management consulting services to Russian entities (Article 5n of Council Regulation 833/2014)
- Asset freezes and trade sanctions
- ORs and Third Party Representatives

REGULATIONS

First Part: Applicable Legislation

International: Background

Overview

- Sanctions are adopted by UN Security Council -> limited impact due to Chinese and Russian vetoes
- UK, US and EU adopted additional national sanction measures (generally coordinated, differences between e.g. lists of designated persons and sanctioned products)
- UK, EU and US sanctions typically must be observed by:
  - their nationals, wherever they are in the world;
  - all business done, in whole or in part, within their territory or airspace; and
  - all legal entities incorporated or constituted under their law, including foreign branches.
- US/UK sanctions may apply to non-US/UK persons outside the US/UK if a transaction involves a 'US/UK nexus' e.g. a transaction conducted in US dollars

Impact assessment: Consortium established for EU-REACH purposes is considered as « doing business in the EU »

Types of sanctions

Asset Freeze (Council Regulation 269/2014)	Trade sanctions (Council Regulation 833/2014)
Freezing the assets of sanctioned individuals and entities ("Designated persons or entities")	Restrictions on **exporting** listed goods and services to Russia / Belarus
Designated parties are set out in a list published by the EU Commission (other governments publish similar lists).	Restrictions on **importing** listed goods and services from Russia / Belarus
Entities not designated in the sanctions list may nevertheless be sanctions if they are **more than 50% owned or controlled** by a designated party	Restrictions affect chemicals and derived products: Manganese dioxide, silico-Manganese steel, Oil, Polymers, Ethyleneamines (see list of prohibited goods)

Liability

- Sanctions in the UK and EU are a '**strict liability**' offence: penalties can be imposed for breaches with no requirement to prove that the offender had knowledge or reasonable cause to suspect its activity breached sanctions (so long as it can prove that on a balance of probabilities a breach has in fact occurred)
- It remains important to design a **compliance program** and attempt to screen out sanctioned entities from involvement in joint registration to demonstrate that reasonable steps were taken to comply -> mitigating circumstances in the framework of criminal proceedings
- Most consortia have **no legal personality**, in any breach of sanctions it is likely that the authorities would prosecute the member companies and/or the management company

Enforcement

Regulator responsible for enforcing sanctions :

- Vary from country to country
- Sometimes more than one relevant authority authority – depending upon the exact nature of the alleged sanctions breach

The EU

Relevant competent authorities in each EU member state:

- **Ministry of Finance** in Belgium
- **Dutch Fiscal Information and Investigation Service** in the Netherlands

The UK

- Office of Financial Implementation (' **OFSI** ')

- Export Control Joint Unit (' **ECJU** ') and/or His Majesty's Revenue and Customs (**'HMRC** ')

Penalties (1/3)

- Any penalties for breach of UK and/or EU sanctions depend upon the **particular circumstances** of each case. Factors impacting on the penalties are: compliance program, the size/scale of any breach, the longevity of the breach, efforts to hide the purported breaches, and the level of cooperation with any investigation
- Non-compliance can amount to a criminal offence subject to **fines** and **imprisonment**. OFSI has the power to impose civil penalties of up to £ 1 million or 50% of the value of the breach, whichever is higher

Penalties (2/3)

- Recent publication of fines include Hong Kong International Wine and Spirits Competition Ltd – an organisation responsible for hosting an annual international wine fair in Hong Kong – fined **£ 30,000** for receiving three payments (totalling £3,919.62) and 78 bottles of wine from sanctioned entity (Massandra) between 2017 and 2020.
- Largest reported instance of a monetary penalty occurred in February 2020: Standard Chartered Bank was fined a total of **£20.47 million** – notwithstanding a voluntary disclosure to OFSI that reduced the initial penalty by 30% – for non-compliance with the UK's Russia sanctions regime. The bank was in breach by making funds available in the form of loans to a sanctioned entity (Denizbank A.Ş) without a licence

Penalties (3/3)

- In the EU, next to fines, competent authorities may impose penalties on individuals. Belgian law foresees imprisonment penalties (up to 5 years), while fines may amount to € 22 million
- Beyond financial damage, non-compliance can engender serious reputation risks for a company. Some competent authorities are entitled to publicly disclose details of the fines it imposed and have powers to "name and shame" individuals or corporates who have failed to comply with their sanctions obligations (even where that party has not been fined)

Second Part: Impact Assessment

Risk areas for consortia

Data sharing activities, granting proprietary rights on studies to designated parties or compensating designated parties for access to data is no longer permitted

Cost sharing activities, any compensation to and from designated parties can no longer be accepted, any remaining balance that may belong to designated parties should be kept on an escrow account

Asset Freeze

Dossier preparation and submission - providing or facilitating access to registration to designated parties (through, e.g. third party representative services) may be qualified as a provision of prohibited economic benefits

Any **contractual relation** should be reviewed, such as with a supplier to the Consortium (e.g. laboratories located in Russia)

Risk areas for consortia

Design a compliance program

Identify and suspend activities with Russian / Belarusian entities
(EU Regulations foresee that contractual claims (especially claim for damages) made by designated parties will not be satisfied)

Screen payments and bank accounts

Request compliance statements, in particular for only representatives and third party representatives

Report to ECHA

Concluding remarks

Recent and rapid expansion of UK, EU and US sanctions

- EU 11th package of sanctions - prohibition to sell, license, transfer or refer intellectual property rights (including studies and REACH data) to an entity established in Russia
- New EU guidance on due diligence expectations to prevent the circumvention of Russia sanctions
- Enforcement Coordination Mechanism at G7 level

Thank you and questions

Claudio Mereu

Joint Managing Partner
Regulatory & Trade Group

+32 2 742 70 60

claudio.mereu@fieldfisher.com

Natalie Konings

Counsel
Regulatory & Trade Group

+32 2 742 70 12

natalie.konings@fieldfisher.com