INTERNATIONAL MOLYBDENUM ASSOCIATION
THE VOICE OF THE MOLYBDENUM INDUSTRY

SUMMIT COUNTY, COLORADO, USA

STAKEHOLDER MEETING

18 September 2019

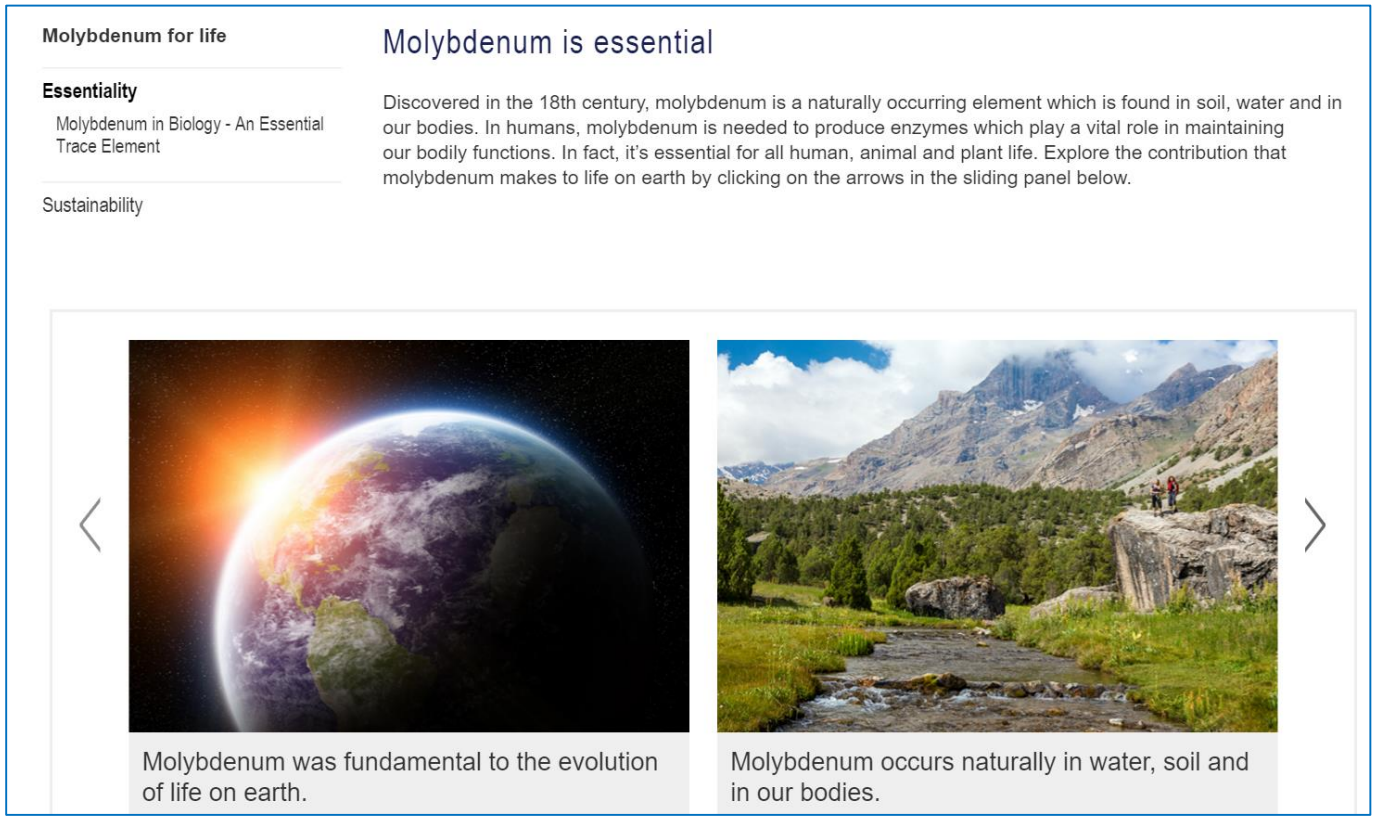
Presented by: Sandra Carey
IMOA Health, Safety & Environment Executive

Molybdenum Science:

Data generation by the International Molybdenum Association and its increasing uptake and adoption within the global regulatory community

Molybdenum (Mo-LIB-den-um) – basics:

- Inorganic naturally-occurring substance in the earth's crust, in the form of molybdenite ore.
- Mo is an essential element for humans, animals and plants …… no survival without it



http://www.imoa.info/essentiality/essentiality-in-action.ph

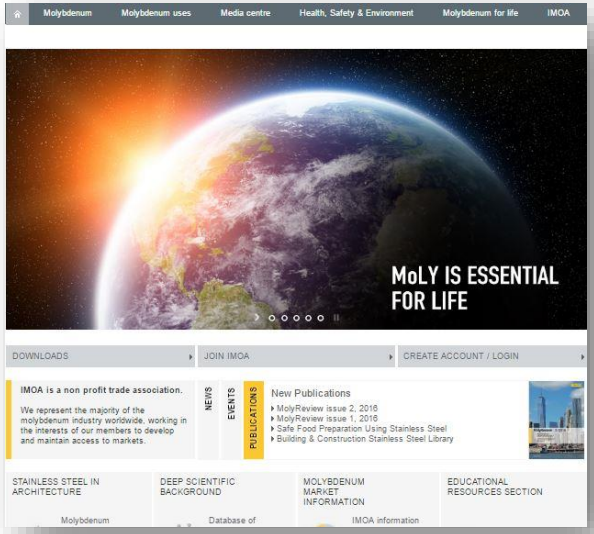
Essentiality: Section on IMOA website:

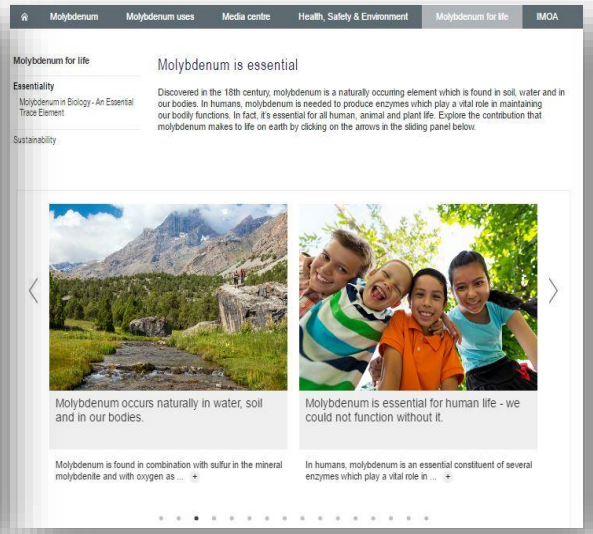
https://www.imoa.info/essentiality/essentiality-in-action.php

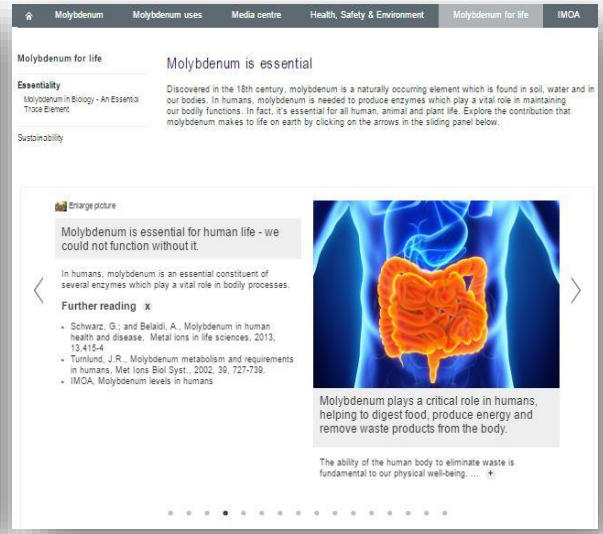
Website homepage refresh

High-level messages

Evidence-based references

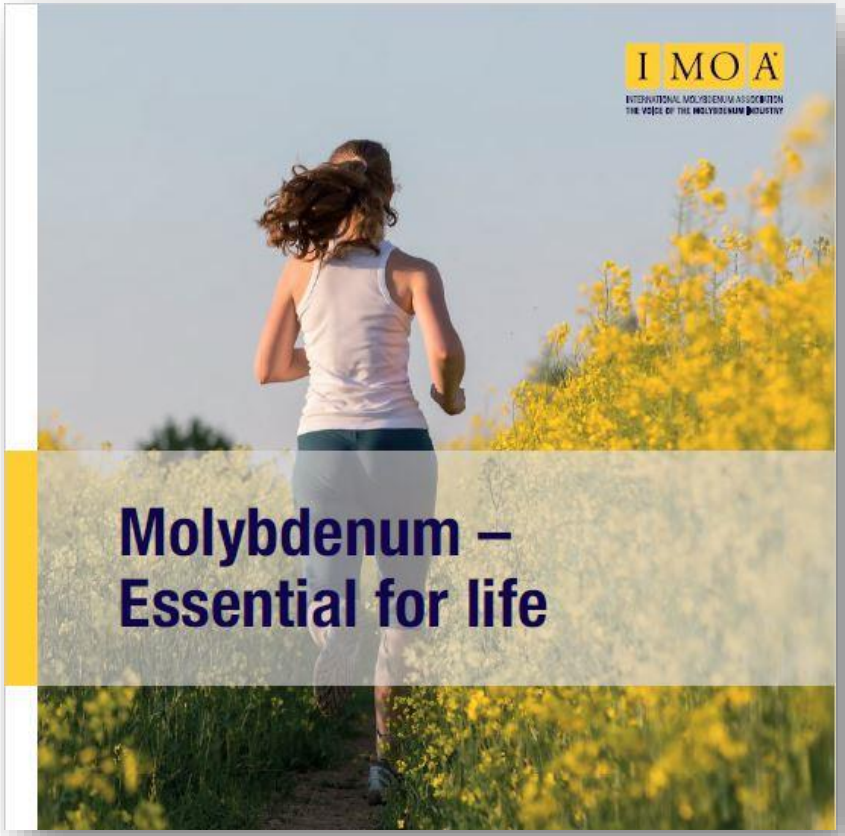


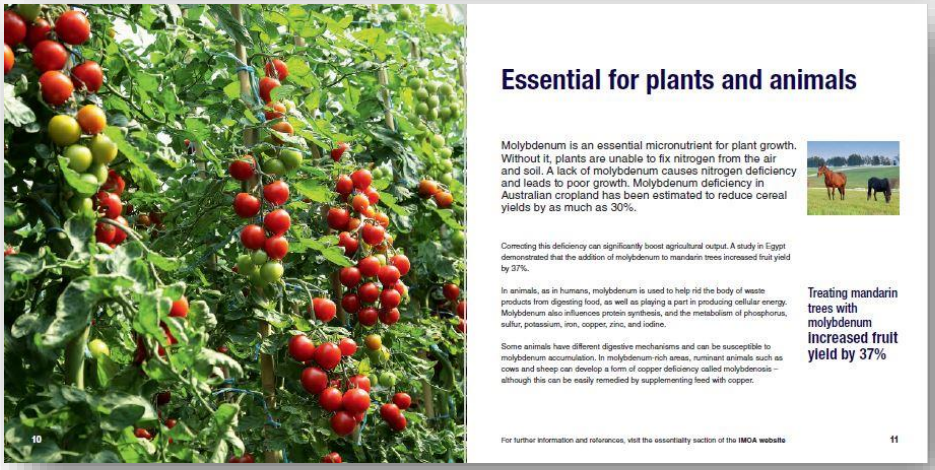




Mo is bio-essential to humans, animals and plants.

Essentiality Info: in pdf format



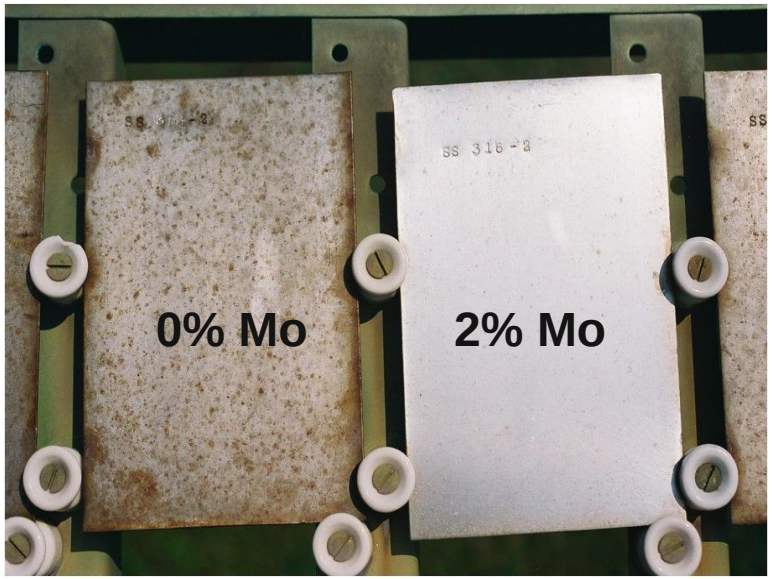


Available in English and Spanish

Molybdenum – basics:

- Molybdenum makes products for a more sustainable world, including stainless steel that is recyclable, longer lasting, corrosion resistant, and stronger.

- Moly has a much higher melting point than most other metals, making it a critical component in the transportation, construction, and renewable energy industries.



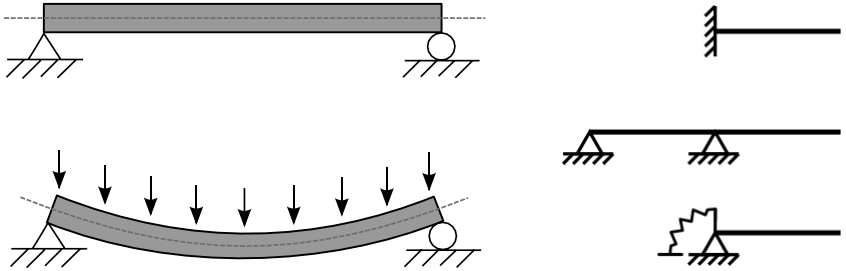
Toronto bridge nearing completion

- Garrison Crossing (formally Ft. York) 2205 duplex stainless steel pedestrian bridges designed by Pedelta
- Opening late summer 2019

Despite a budget reduction to $19 million Canadian, the bridges stayed duplex

Examples of structural applications

- Structural elements
  - Columns
  - Beams
  - Plates
  - Arches
  - Shells
  - Catenaries



- Example: beam
  - I-beam
  - H-beam
  - Rectangular
  - Cylindrical tube
  - L-beam (angle)
  - C-beam (channel)

Washington DC – structural Type 316L

- Significant recent commitment to Type 316L structural stainless steel & glass in “Great Streets” program
- $100 million will be spent over 20-years to replace all metro bus shelters on major transportation corridors (demo project in 2013)
- 24 large subway entrance or landmark station canopies finished or in process and others expected (demo project about 20 years ago)

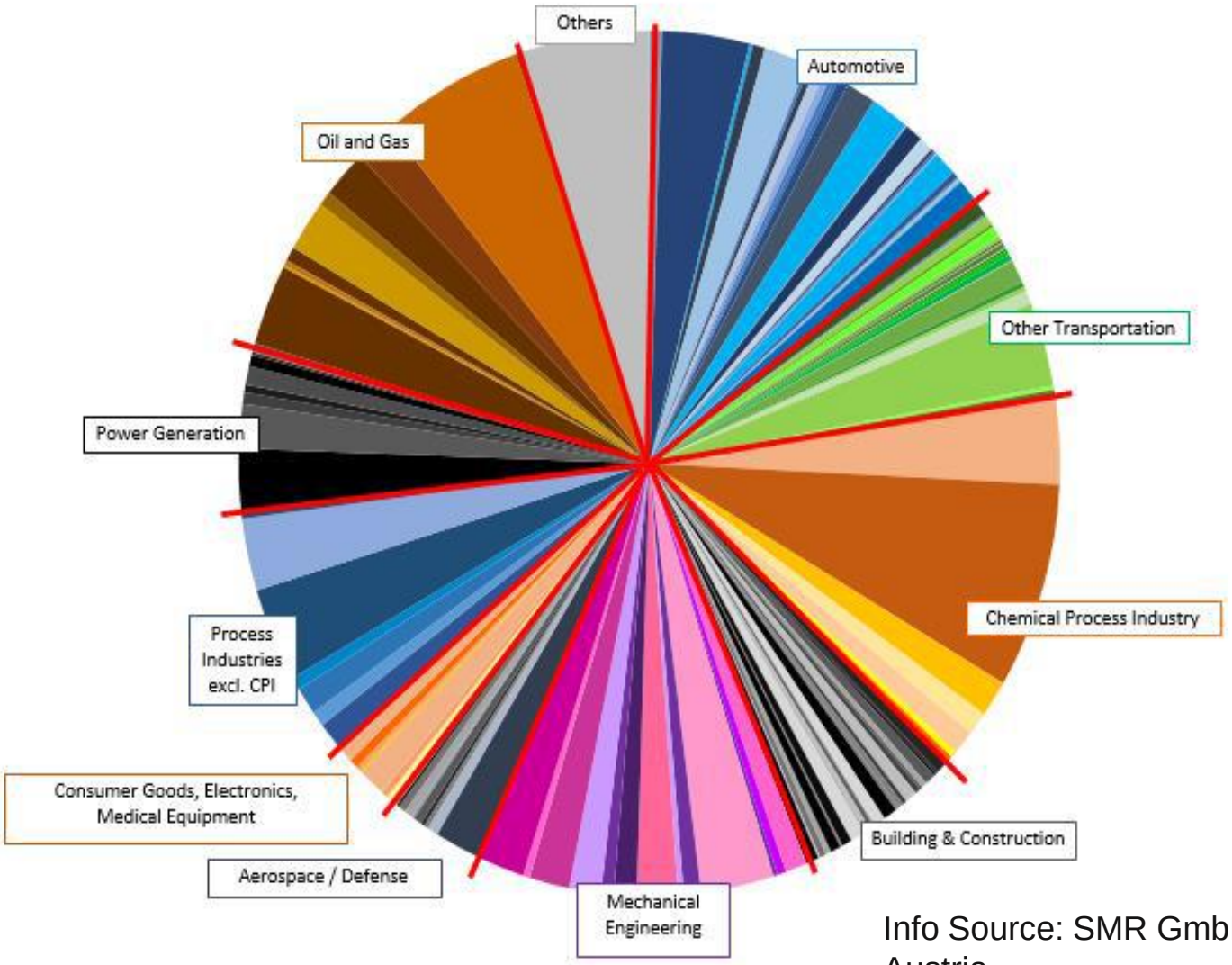
Molybdenum is:

- ✓ Found in foods like legumes and grains as well as daily vitamin & mineral supplements

- ✓ Used to:
  - build solar panels and wind turbines (Greener/Cleaner energy)
  - manufacture flat screen televisions and stainless steel food processing equipment
  - in catalytic processes to remove sulfur from fuel to improve air quality
  - in lubricants and greases

- an essential component of equipment necessary for US national defense. Its original, primary use was in Allied efforts during World War II.

Mo sectors of Use:



Info Source: SMR GmbH, Austria

Global Annual Mo production volume: ca. 280,000 tonnes.

Cu: 18M

Sourced from primary and co-product mines.

IMOA – Who we are:

Established: 1989 Based: London, U.K.
Global, not regional. 5 FTE's + external technical support

Members: 59 from 18 countries. Molybdenum primary & co-producers, processors and downstream users.

Main Committees:

- ❑ Executive Committee
- ❑ Health, Safety & Environment
- ❑ Market Development
- ❑ Sustainability & Communications

IMOA is a member of the North American Metals Council (NAMC) & several European metals trade associations

Health, Safety, and Environment Committee

- Primary scope and objectives: Develop high-quality environmental and human health science to address regulatory issues; fill critical data gaps in the molybdenum effects dataset

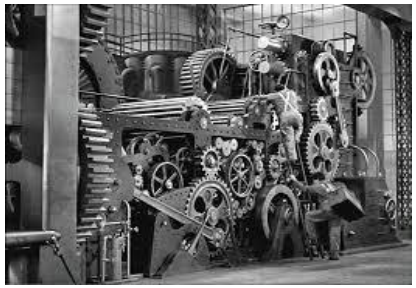
- 15 member companies from Austria, Belgium, Chile, Peru, Germany, Netherlands, UK, and USA providing technical experts

- Recent significant accomplishments:
  - Develop molybdate effects dataset and risk assessment for EU REACH
  - 90-day Repeated-Dose Toxicity Study
  - Prenatal Developmental Toxicity Study
  - Organization for Economic Cooperation and Development - mutual acceptance of study data
  - Two-Generation Reproduction Toxicity Study

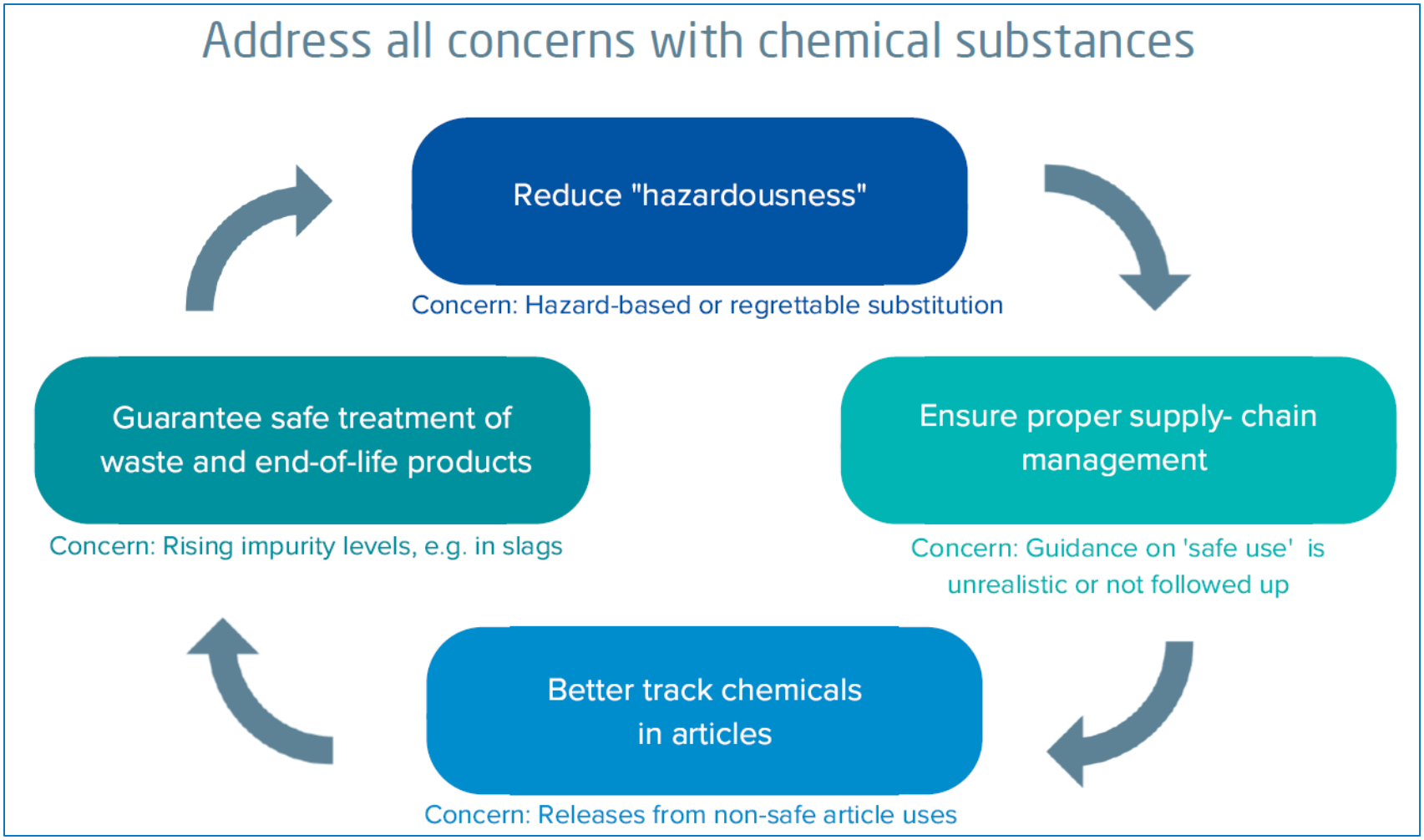
- **Data resource for all interested parties**

Trend: societal/regulatory control over the supply chain

Primary materials	Manufac-turing	Industrial use	Consumer use	End of Life
Mining or Recycling	Refining & smelting	Manufac-turing of half-fabricates	Consumer use of articles	End of Life (recycling or disposal)



Global Regulatory Focus:



Chemicals Regulation in the EU: New Regulation in 2006 - REACH

Registration
Evaluation
Authorisation (and restriction) of
Chemicals

For “large scale improvement of human health and the environment in Europe”

ECHA
EUROPEAN CHEMICALS AGENCY

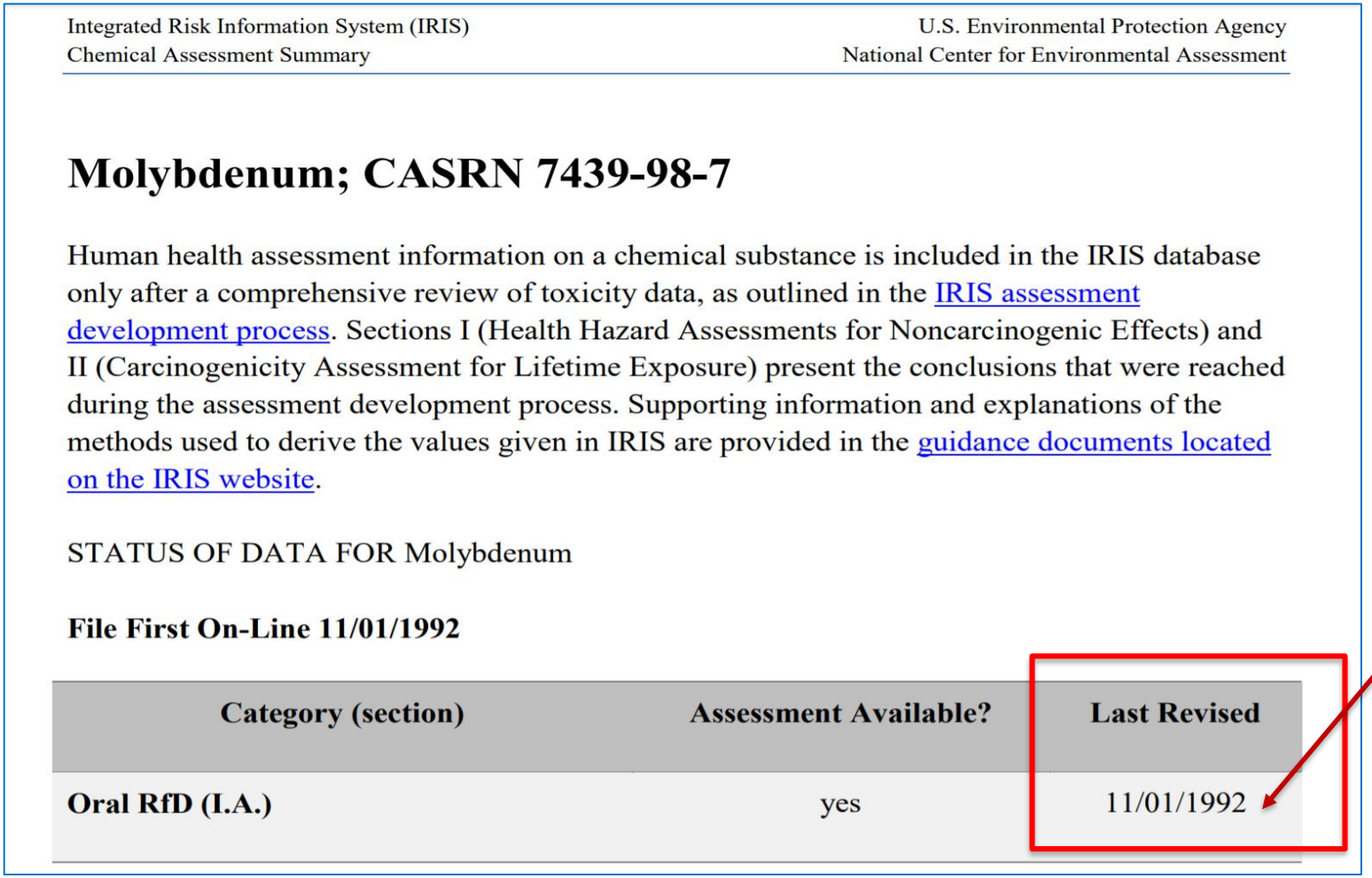
Hazard identification
Risk Assessment
Communication along the supply chain about safe handling and use of chemicals

Substance-specific legislation:
REACH Regulation no. 1907/2006

US EPA IRIS database on Molybdenum:

IRIS = Integrated Risk Information System

https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0425_summary.pdf



Integrated Risk Information System (IRIS)
Chemical Assessment Summary

U.S. Environmental Protection Agency
National Center for Environmental Assessment

Molybdenum; CASRN 7439-98-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Molybdenum

File First On-Line 11/01/1992

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	11/01/1992

Not updated for last 27 years

EU REACH Regulation Data Matrix – 9 pages – Human Health extract:

IUCLID 5 tree view	Section Name	REACH Annex	REACH Number	Specific rules for IUCLID-REACH relationships different to a 1 to 1 relationship	1 – 10T, physicochemical requirements, Annex 7	1 – 10T, standard requirements, Annex 7	10 – 100T, Annex 8	100 – 1000T, Annex 9	above 1000T, Annex 10	on-site isolated intermediates above 1T	transported isolated intermediates 1 – 1000T	transported isolated intermediates above 1000T, Annex 7	PPORD
		8	8.4.2 (in vitro cytogenicity in mammalian cells or in vitro micronucleus)	study must be provided. For >10T: This IUCLID 5 section corresponds to 3 REACH Annex numbers. However only 2 studies are sufficient for completeness (e.g. if there is a positive result in 8.4.1 or in 8.4.2, then 8.4.3 does not need to be provided).	o	o	r	r	r	o	o	o	o
		8	8.4.3 (in vitro gene mutation in mammalian cells)		o	o	r	r	r	o	o	o	o
7.8.1	Toxicity to reproduction	8	8.7.1 (screening)	For 10-100T, 1 screening study must be provided. For >100T, 1 two-generation study must be provided.	o	o	r	r	r	o	o	o	o
		9	8.7.3 (two-generation)		o	o	o	r	r	o	o	o	o
7.8.2	Developmental toxicity / teratogenicity	9	8.7.2		o	o	o	r	r	o	o	o	o

REACH dataset embedded into OECD dataset: Highly soluble molybdenum salts

http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?id=5c88d62f-4401-4cad-b521-521a4bd710f3

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Highly soluble molybdenum salts
Chemical Name(s) and CAS No(s).	Sodium molybdate: CAS 10102-40-6 for sodium molybdate dihydrate CAS 7631-95-0 for sodium molybdate (anhydrous) Ammonium dimolybdate: CAS 27546-07-2 Ammonium heptamolybdate: CAS 12054-85-2 for ammonium heptamolybdate tetrahydrate CAS 12027-67-7 for ammonium heptamolybdate (anhydrous)
Structural Formula(s)	$Na_2MoO_4 \cdot 2\ H_2O$ Na_2MoO_4 $(NH_4)_2Mo_2O_7$ $(NH_4)_6Mo_7O_{24} \cdot 4\ H_2O$ $(NH_4)_6Mo_7O_{24}$

SUMMARY CONCLUSIONS OF THE SIAR

Rationale for molybdenum salts category

The substances included in this category are the higher volume molybdate salts available on the market.

The category is based on a common moiety of concern, the molybdate anion $[MoO_4]^{2-}$. All category members are potential contributors of this moiety. The counter ions of the molybdate salts (i.e. sodium and ammonium), due to their ubiquitous presence in biota and/or their essential role in human physiology, are not addressed further as they are not considered to contribute to any toxicity of the molybdate salts.

The chemistry of molybdenum is complex, allowing a wide range of valences as summarised in the graph below:

The following aquatic chronic toxicity test results have been determined for the freshwater environment. Values are based on measured exposure levels unless mentioned otherwise.

Species	Endpoint	Value (mg Mo/L)	Type[a]	Guideline
Fish				
Oncorhynchus mykiss	78d-$EC_{10,biomass}$ 32d-$NOEC_{mortality}$ 32d-$NOEC_{mortality}$ 12m-$NOEC_{mortality,growth}$	43.2 200[b] 750[b] >17	f-t f-t s-s f-t	OECD TG 210 EPS 1/RM/28 EPS 1/RM/28 No guideline specified
Oncochynchus kisutch	20wk-$NOEC_{develop}$	≥ 19.5	f-t	No guideline specified
Pimephales promelas	34d-$EC_{10,biomass}$ 32d-$EC_{10,biomass}$	39.9 90.9	f-t n.s.	OECD TG 210 ASTM E1241-98
Invertebrates				
Daphnia magna	21d-$EC_{10,reproduction}$	62.8 105.6 108	s-s s-s s-s	OECD TG 211 OECD No 211 ASTM, 1997
Ceriodaphnia dubia	7d-$EC_{10,reproduction}$	50.8-78.2	s-s	EPA-821-R-02-013
Chironomus riparius	14d-$EC_{10,growth\ rate}$	121.4	s-s	OECD TG 218
Brachyonus calyciflorus	48h-$EC_{10,reproduction}$	193.6	s	conform to APHA 8420, 1998
Gastropods				
Lymnaea stagnalis	28d-$EC_{10,growth\ rate}$	221.8	s-s	No guideline specified
Amphibians				
Xenopus laevis	4d-$EC_{10,development}$	115.9	s-s	conform to APHA

Tools for determining Mo safe concentrations in the environment:

What is the IMOA molybdate effects dataset?:

Physico-chemical, environment and human health data generated from rigorously conducted studies about the molybdate ion, which is the moiety of concern that could cause a toxic effect (in humans, plants & animals).

The dataset has the quality endorsement of having achieved OECD Mutual Acceptance of Data Status.

To what extent can the IMOA molybdate effects dataset be relied upon?

Best indication are **examples** of regulatory bodies that are taking the IMOA molybdate effects dataset into account in their rule-making.

Data: Iterative approach to generate a scientifically-sound dataset for global use:

2007-2013: Molybdate Effects Dataset – Risk Assessment – Regulatory Compliance for EU REACH Regulation

2014: OECD Mutual Acceptance of Data Status – data quality endorsement

Dissemination for global regulatory data use:

EU + Australia, Canada, USA … Korea

OECD - ADHERENTS TO THE 'MUTUAL ACCEPTANCE OF DATA' (MAD) PROGRAM:

INTERNATIONAL MOLYBDENUM ASSOCIATION

OECD

Organisation for Economic Co-Operation and Development)
Intergovernmental Organisation grouping 34 industrialised countries

EU

- Austria
- Belgium
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Ireland
- Italy
- Luxembourg
- The Netherlands
- Poland
- Portugal
- Slovak Republic
- Slovenia
- Spain
- Sweden
- United Kingdom

EUROPEAN NON-EU

- Iceland
- Israel
- Norway
- Switzerlan
- Turkey

AMERICAS

- Canada
- Chile
- Mexico
- United States

ASIA - PACIFIC

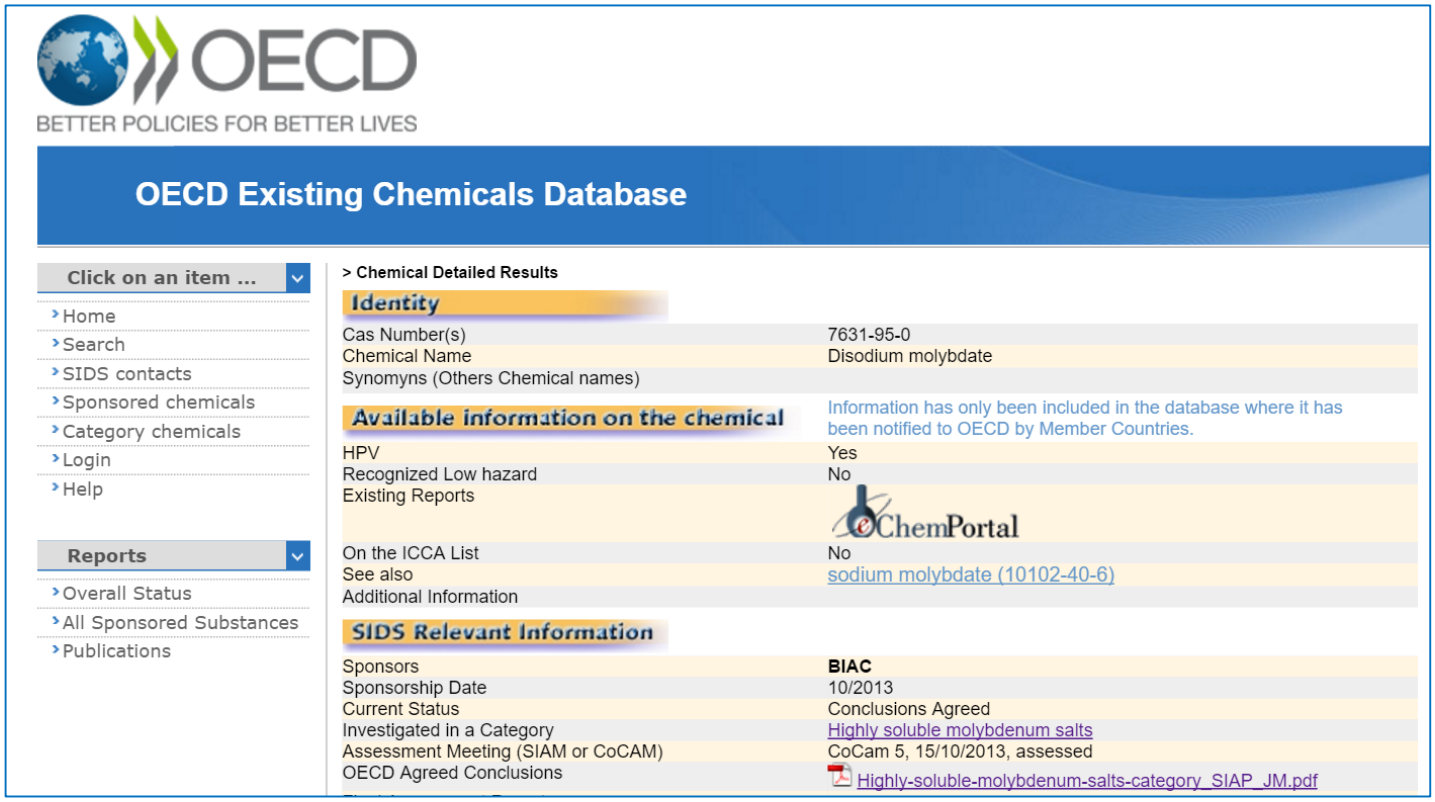
- Australia
- Japan
- New Zealand
- South Korea

– MAD and non-members:

- Argentina*, Brazil*, India, South Africa and Singapore (full MAD adherent)
- Thailand, Malaysia (provisional adherent)

A Mutually Accepted Dataset is the starting point for introducing or reviewing substance regulation in an OECD-member country

2014 – OECD Mutual Acceptance of Data status on highly soluble molybdenum salts dataset



OECD

BETTER POLICIES FOR BETTER LIVES

OECD Existing Chemicals Database

Click on an item ...

- Home
- Search
- SIDS contacts
- Sponsored chemicals
- Category chemicals
- Login
- Help

Reports

- Overall Status
- All Sponsored Substances
- Publications

> Chemical Detailed Results

Identity

Cas Number(s)	7631-95-0
Chemical Name	Disodium molybdate
Synomyns (Others Chemical names)	

Available information on the chemical

Information has only been included in the database where it has been notified to OECD by Member Countries.

HPV	Yes
Recognized Low hazard	No
Existing Reports	eChemPortal
On the ICCA List	No
See also	sodium molybdate (10102-40-6)
Additional Information	

SIDS Relevant Information

Sponsors	**BIAC**
Sponsorship Date	10/2013
Current Status	Conclusions Agreed
Investigated in a Category	Highly soluble molybdenum salts
Assessment Meeting (SIAM or CoCAM)	CoCam 5, 15/10/2013, assessed
OECD Agreed Conclusions	Highly-soluble-molybdenum-salts-category_SIAP_JM.pdf

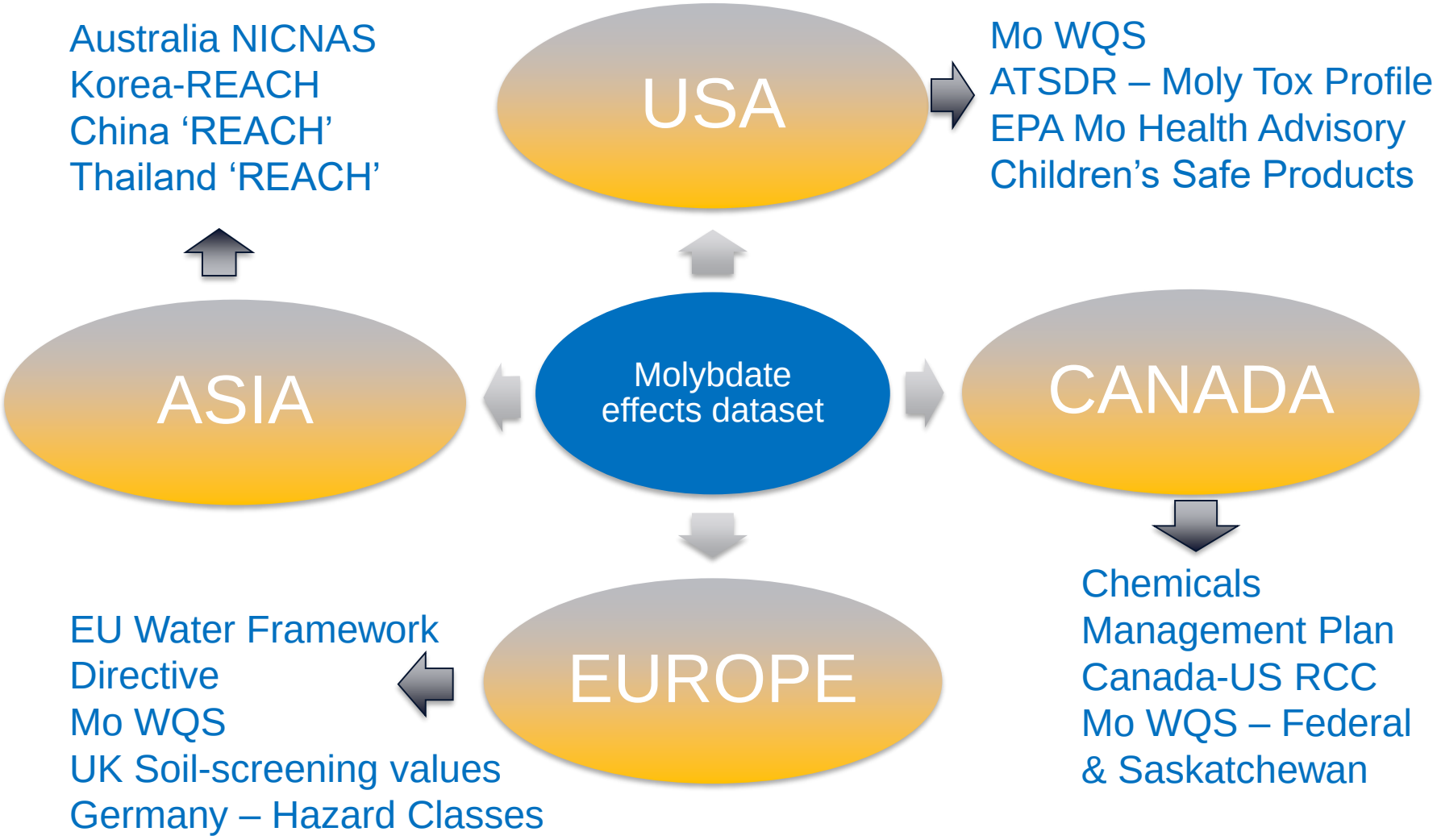
Highly soluble = worst case results = most precautionary approach

Scientific peer review panel of 6 OECD-member countries inc. USA plus Australia, Canada, Netherlands, Japan, UK & OECD Secretariat

http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?id=5c88d62f-4401-4cad-b521-521a4bd710f3

Examples of regulatory uptake of the IMOA molybdate effects dataset in risk assessment based rule-making:

IMOA's Molybdate Effects Dataset - OECD approved – for global Chemicals Management purposes



USA – Children's Safe Products Rule:

2017-2019: Molybdenum & Compounds **de-listed and de-regulated** from the Chemicals of High Concern to Children List, in Washington, Oregon, and most recently Minnesota.

Key assessment contributor: IMOA's (OECD MAD) molybdate effects dataset

Why did IMOA engage in regulatory dialogue?:

- Share the reality (and the correct perception) of moly toxicology to the authorities, based on today's scientific knowledge (not 1970's Reprotext database)
- Halts unwarranted substance stigmatization and substance phase-out
- Dissociates Mo from other so-called 'heavy metals' when meaning 'toxic' instead of it's physical property of 'density'

Washington State Children's Product Safety Rule 2017:

CODE REVISER USE ONLY

RULE-MAKING ORDER
PERMANENT RULE ONLY

CR-103P (August 2017)
(Implements RCW 34.05.360)

OFFICE OF THE CODE REVISER
STATE OF WASHINGTON
FILED

DATE: September 29, 2017
TIME: 10:25 AM

WSR 17-20-050

Agency: Department of Ecology AO 16-08

Effective date of rule:
Permanent Rules
☒ 31 days after filing.
☐ Other (specify) _____ **(If less than 31 days after filing, a specific finding under RCW 34.05.380(3) is required and should be stated below)**

Any other findings required by other provisions of law as precondition to adoption or effectiveness of rule?
☐ Yes ☒ No If Yes, explain:

Purpose: Ecology is amending Chapter 173-334 WAC Children's Safe Products Reporting Rule. The 2016 Washington State Legislature's amendment of RCW 70.240 identified six flame retardants to be considered for inclusion on the list of chemicals of high concern to children (CHCCs) in Chapter 173-334 WAC. Ecology and the Washington Department of Health evaluated recent scientific data for the six flame retardants and other chemicals. The rule amendment adds twenty chemicals, removes three chemicals, and splits one chemical listing into three individual listings on the list of CHCCs. The amendment also streamlines the rule: removes the phase-in reporting schedule, defines terms, and clarifies the reporting process.

List of CHCCs removed by Rule Amendment

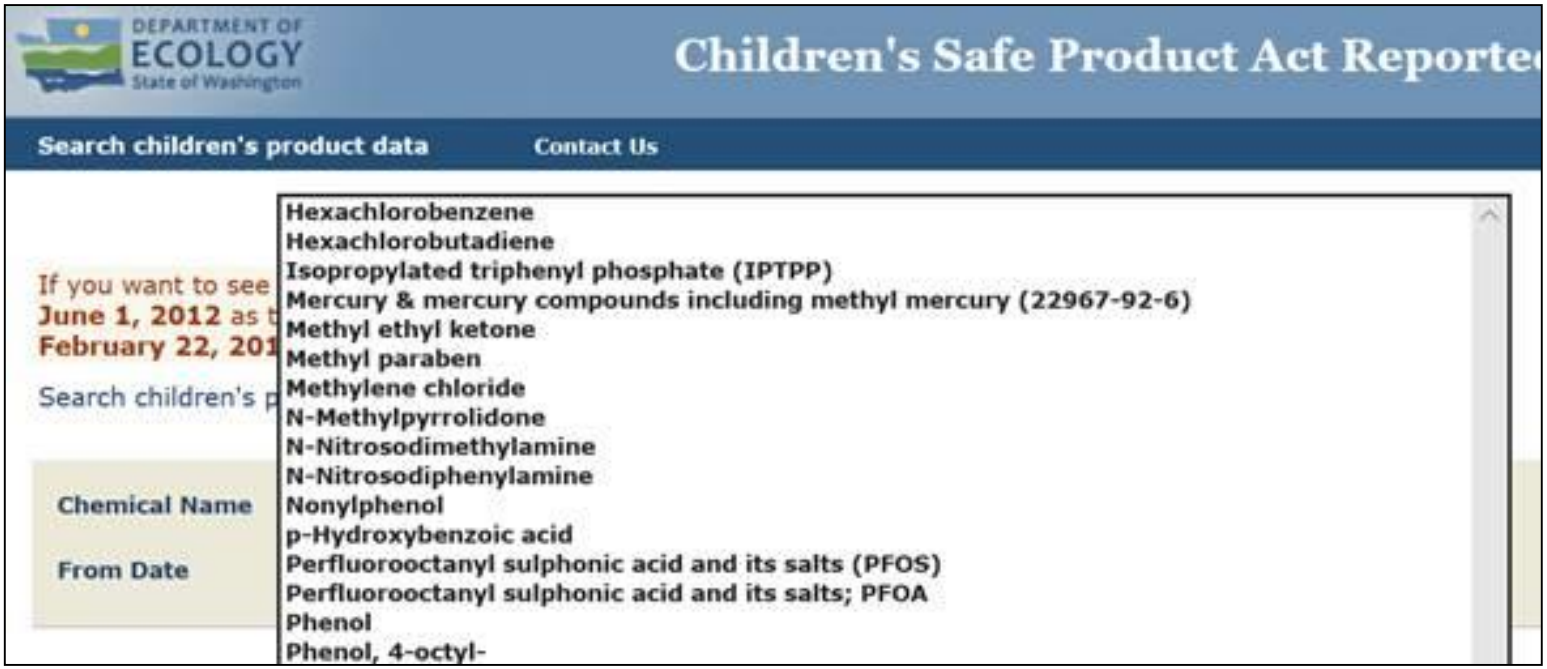
CAS	Chemical	Removed
71-36-3	1-Butanol	2013
85-44-9	Phthalic anhydride	2017
556-67-2	Octamethylcyclotetrasiloxane (D4)	2017
7439-98-7	Molybdenum & molybdenum compounds	2017

Extract of table from Rule filed on 29 September 2017

Mo & Compounds **de-listed and de-regulated** as from end September 2017

Washington CSPA:

2019 - Molybdenum no longer on the list of reported substances



For manufacturing reporting period ending 31 Jan 2019

Searchable database at:

https://apps.ecology.wa.gov/cspareporting/

Oregon State – Toxics-Free Kids Act

- Moly & compounds ***de-listed*** **& de-regulated** by Oregon Health Authority with effect from 1 January 2019
  - Process period: May – end September 2018

Start of process in May:

Ecology removed three chemicals after 2017 rulemaking.
OHA proposes to **remove** the same three chemicals from OAR 333-015-2020:

CAS	Chemical Name	Acronym
85-44-9	Phthalic anhydride	None
556-67-2	Octamethylcyclotetrasiloxane	D4
7439-98-7	Molybdenum & molybdenum compounds	Mo

For each of the three chemicals removed from Ecology's CHCC list, in addition to summaries of *toxicity*, *potential for exposure* and a list of references, Washington State's Chemicals of High Concern to Children Added or Delisted during the 2017 Rule Update provides a summary of the reason for removal. OHA's toxicology review concurs with Washington State's rationale for removal.

05022018ver Page 3 of 3

End of Process:

OFFICE OF THE SECRETARY OF STATE
DENNIS RICHARDSON
SECRETARY OF STATE

LESLIE CUMMINGS
DEPUTY SECRETARY OF STATE

ARCHIVES DIVISION
MARY BETH HERKERT
DIRECTOR
800 SUMMER STREET NE
SALEM, OR 97310
503-373-0701

PERMANENT ADMINISTRATIVE ORDER

PH 252-2018
CHAPTER 333
OREGON HEALTH AUTHORITY
PUBLIC HEALTH DIVISION

FILED
09/11/2018 2:18 PM
ARCHIVES DIVISION
SECRETARY OF STATE
& LEGISLATIVE COUNSEL

FILING CAPTION: Toxic Free Kids Rule Revision

EFFECTIVE DATE: 01/01/2019

AGENCY APPROVED DATE: 09/11/2018

AMEND: 333-016-2020

RULE TITLE: Chemicals of High Concern to Children

NOTICE FILED DATE: 07/14/2018

RULE SUMMARY: 1) Amend OAR 333-016-2020: Per ORS 431A.255, the Authority is to review and amend OAR 333-016-2020, Chemicals of High Concern to Children (CHCC) every three years from date rule first became effective (January 1, 2016). Specifically, ORS 431A.255 directs the Authority to consider adding or removing High Priority Chemicals of Concern for Children's Health (HPCCCH) that are added or removed from Washington State Department of Ecology's Reporting List of Chemicals of High Concern to Children (CHCC). Changes to Ecology's CHCC list were made through Washington Administrative Code rulemaking and took effect on October 30, 2017. Therefore, the Authority is adding (to OAR 333-016-2020) five of the 20 chemicals that were added to Ecology's list, and remove the three chemicals that Ecology removed from their list.

US-Canada Regulatory Cooperation Council Initiative – Mo case study

Purpose: To assess how US-Canada can work together to jointly risk assess substances. Focus on identifying differences/impediments to joint assessment, partly through conduct of 5 substance/substance group case studies.

Why was moly selected?

- A 'forward priority' for both US-EPA under Toxic Substances Control Act (TSCA), and Health Canada and Environment Canada under Chemicals Management Program (CMP)

Collaboration on common priorities

B. Identification of and collaboration on common priorities

(January 2015 to October 2016):

- Five substances/groups were selected as case studies:
  - TPP (Triphenylphosphate)
  - Phthalic anhydride
  - 4-tert-octylphenol
  - Cyanide Compounds
  - Molybdenum Compounds
- Formation of multi-stakeholder case study sub-groups
- Focus area(s) for each case studies and milestones will be determined during a workshop in late October 2015

Health Canada co-authored publication

Regulatory Toxicology and Pharmacology 77 (2016) 223–229

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Published 2016

Biomonitoring Equivalents for molybdenum

Sean M. Hays [a, *], Kristin Macey [b], Devika Poddalgoda [b], Ming Lu [b], Andy Nong [b], Lesa L. Aylward [c]

[a] Summit Toxicology, LLP, Lyons, CO 90540, USA
[b] Health Canada, Ottawa, ON, Canada
[c] Summit Toxicology, LLP, Falls Church, VA 22044, USA

The BEs were derived for the EAR, RDA and UL from IOM, RfD from EPA, TDI from RIVM, UL from EC SCF, and the lowest NOAEL identified for Mo in the OECD SIDS assessment profile from a 90-day toxicity study (Murray et al., 2014a), herein referred to as the OECD SIDS NOAEL (Table 1). The OECD SIDS NOAEL was included for BE derivation because the OECD SIDS assessment profile includes newer OECD test guideline compliant studies, which were not available at the time of the EPA, IOM, EC SCF or RIVM evaluations of Mo. Additionally, these studies have higher reliability than the studies used in above mentioned exposure guidance values because they were conducted according OECD test guidelines and good laboratory practices. The BEs associated with the IOM EAR,

Human Health Studies:

Lead Author of the 3 peer-reviewed published papers: Murray (J.)

OECD Protocol-compliant and GLP:

- 2011: 90-day Repeated Dose Toxicity (HLS,Princeton,USA)
  - *Hoffmann G. (2011): Sodium molybdate dihydrate: A 90-day oral dietary administration study in rats (GLP). Study No. 10-2225.*
- 2013: Prenatal Developmental Toxicity ((RTI, Raleigh, USA)
  - *Tyl, R. (2013): Developmental Toxicity Evaluation of Sodium Molybdate Dihydrate (CAS No. 10102-40-6) administered in the diet to CD® (Sprague Dawley) Rats*
- 2015-16: 2-Generation Reproduction (CRL, Pennsyl., USA)
  - *Hoberman A.(2017): Two generation (one litter per generation) reproduction toxicity study of sodium molybdenum dihydrate in rats*
  - *Peer-reviewed publication: March 2019*

Studies conducted according to OECD Test Protocol Guidelines:

Extract from OECD website:

The OECD Guidelines are a unique tool for assessing the potential effects of chemicals on human health and the environment.

Accepted internationally as standard methods for safety testing, the Guidelines are used by professionals in industry, academia and government involved in the testing and assessment of chemicals (industrial chemicals, pesticides, cosmetics, etc.).

These Guidelines are regularly updated with the assistance of hundreds of national experts from OECD member countries.

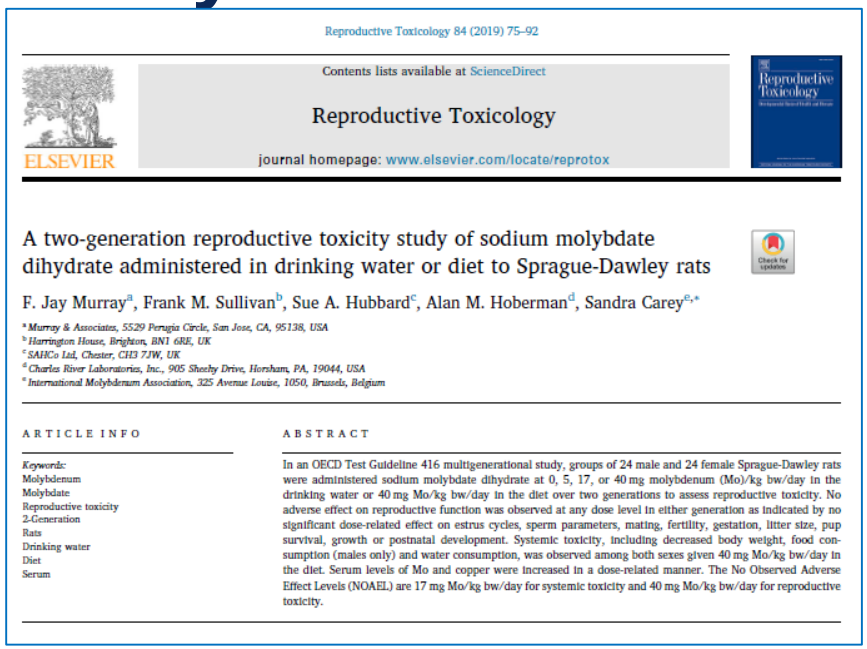
Why higher-tier human health studies?

- Critical data-gaps to fill
- Absence of OECD guideline compliant studies, and of GLP certification (GLP = good laboratory practice)
- Existing literature assessments of molybdenum (e.g. IOM, NAS) selecting reproductive toxicity as most sensitive human health endpoint, based on Fungwe 1990 study
- Water quality standards protective of human health (i.e. reprotox endpoint), using Fungwe – NOAEL at 0.9 mg Mo/kg bw/day

NAS (2001) Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc. Food and Nutrition Board, Institute of Medicine, National Academy Press, Washington, D.C.

Fungwe, T.V. et al. (1990): The role of dietary molybdenum on oestrous activity, fertility, reproduction and molybdenum and copper enzyme activities of female rats, Nutr. Res. 10, 515-524

2-Generation Reproduction Toxicity Study



Reproductive Toxicology 84 (2019) 75–92

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

A two-generation reproductive toxicity study of sodium molybdate dihydrate administered in drinking water or diet to Sprague-Dawley rats

F. Jay Murray[a], Frank M. Sullivan[b], Sue A. Hubbard[c], Alan M. Hoberman[d], Sandra Carey[e,*]

[a] Murray & Associates, 5529 Perugia Circle, San Jose, CA, 95138, USA
[b] Harrington House, Brighton, BN1 6RE, UK
[c] SAHCo Ltd, Chester, CH3 7JW, UK
[d] Charles River Laboratories, Inc., 905 Sheehy Drive, Horsham, PA, 19044, USA
[e] International Molybdenum Association, 325 Avenue Louise, 1050, Brussels, Belgium

ARTICLE INFO

Keywords:
Molybdenum
Molybdate
Reproductive toxicity
2-Generation
Rats
Drinking water
Diet
Serum

ABSTRACT

In an OECD Test Guideline 416 multigenerational study, groups of 24 male and 24 female Sprague-Dawley rats were administered sodium molybdate dihydrate at 0, 5, 17, or 40 mg molybdenum (Mo)/kg bw/day in the drinking water or 40 mg Mo/kg bw/day in the diet over two generations to assess reproductive toxicity. No adverse effect on reproductive function was observed at any dose level in either generation as indicated by no significant dose-related effect on estrus cycles, sperm parameters, mating, fertility, gestation, litter size, pup survival, growth or postnatal development. Systemic toxicity, including decreased body weight, food consumption (males only) and water consumption, was observed among both sexes given 40 mg Mo/kg bw/day in the diet. Serum levels of Mo and copper were increased in a dose-related manner. The No Observed Adverse Effect Levels (NOAEL) are 17 mg Mo/kg bw/day for systemic toxicity and 40 mg Mo/kg bw/day for reproductive toxicity.

Published early 2019!

Article link:
https://doi.org/10.1016/j.reprotox.2018.11.004

Manuscript:

- Passed Journal peer-review by 3 reviewers
- Published on-line 29 January 2019, Open Access (free to download)
- Published in hard copy Journal, March 2019

- Culmination of 5 years work 2014-2018:
- Palatability/range-finder/main study/publication

Fungwe et al study, 1990

Science Center, 874 Union Avenue, Memphis, TN 38163. This paper is part of work that was presented, in part, to fulfill the requirements for the degree of Doctor of Philosophy

ELSEVIER

Nutrition Research

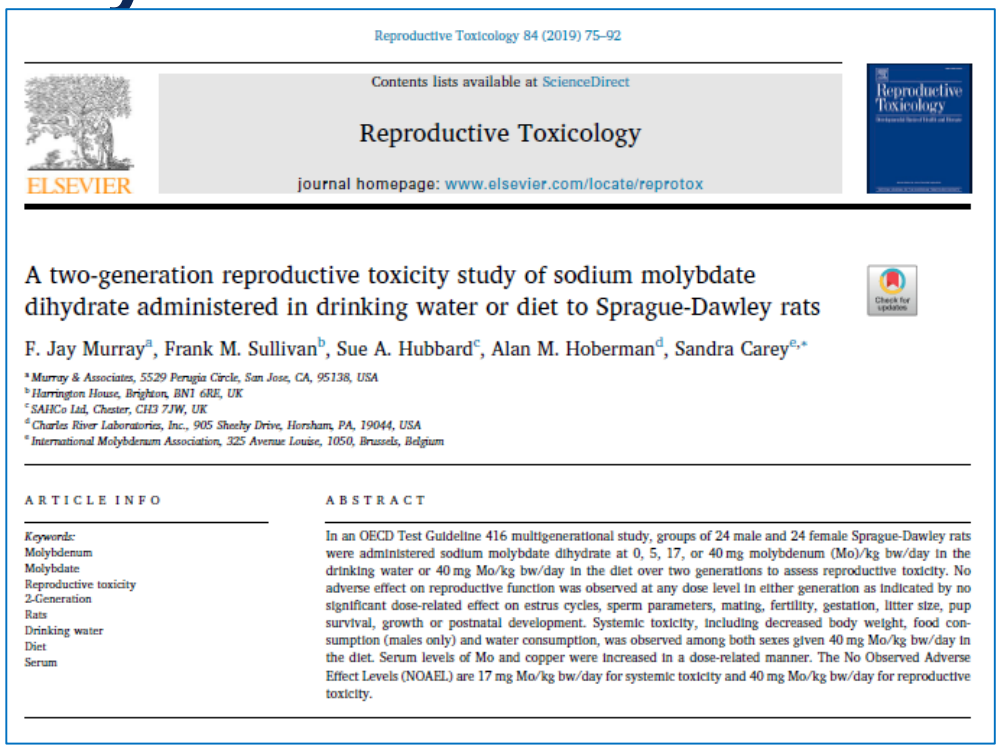
Volume 10, Issue 5, May 1990, Pages 515-524

The role of dietary molybdenum on estrous activity, fertility, reproduction and molybdenum and copper enzyme activities of female rats *

Ph.D. Thomas V. Fungwe [#, §, **], D.V.M., Ph.D. Fred Buddingh [#], D.V.M. Diane S. Demick [#], Ph.D. Charles D. Lox [##], Ph.D. Meiling T. Yang, Ph.D. Shiang P. Yang [**]

In the absence of an OECD protocol-compliant/GLP study, the Fungwe study was understandably used for regulatory purposes.
It was 'the only show in town', but that is no longer the case as 2-Generation reprotox study conducted and now peer-review published in 2019.

2-Gen study unable to reproduce findings reported in the Fungwe 1990 study



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Colorado State Mo WQS value of 210 micrograms/L is based on the Fungwe study.

Not possible to determine the exact dose levels of the test material consumed by the rats in the Fungwe study since neither the water intakes nor body weights are reported.

- **Discussion section** of the document **compares and contrasts** the recent 2-Generation study data with the data generated by Fungwe.
- The 2-Generation study was **not able** to reproduce the effects reported by Fungwe, 1990. Reproductive toxicity was not identified in the recent 2-Generation study.

NOAELs in 2-Gen., Developmental and 90-Day Toxicity Studies

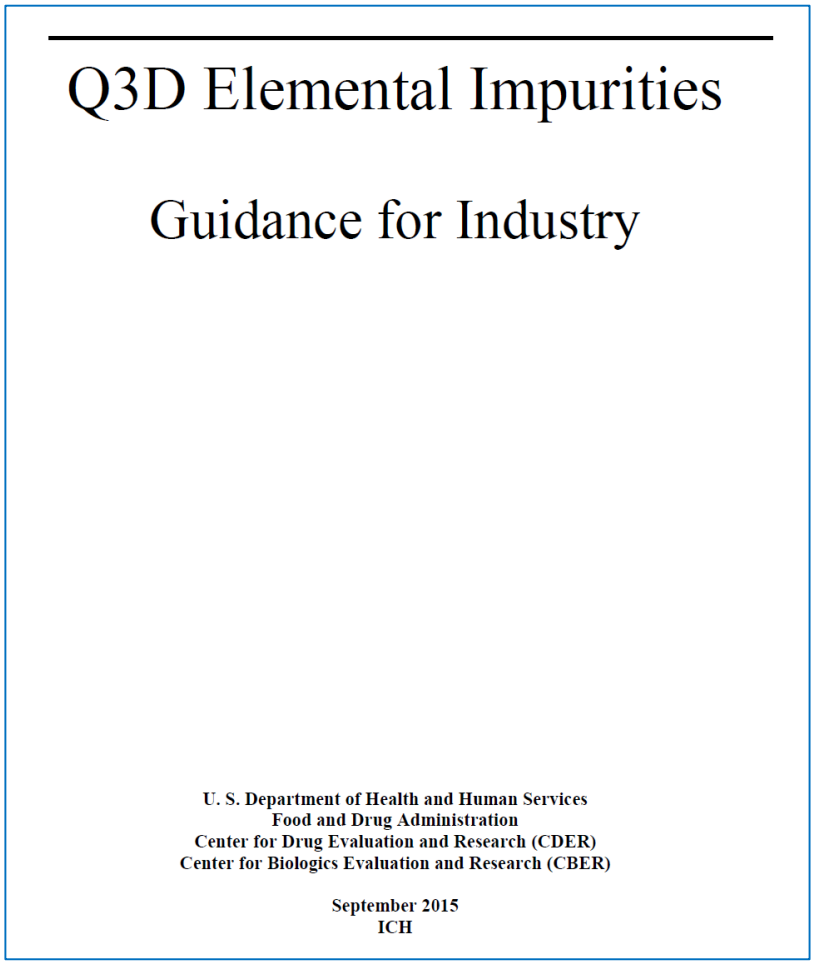
Study	Systemic Toxicity NOAEL, mg Mo/kg bw/day	Reproductive Toxicity NOAEL, mg Mo/kg bw/day
2-Gen. Reprotox Study	17	40
Developmental Tox. Study	40	40
90-Day Repeated Dose Tox. Study	17	60[a]

NOAEL = No Observed Adverse Effect Level

a = gonadal, sperm and estrous cycle effects

2-Gen results: No test substance-related effect on estrous cycle, semen evaluation, mating, pregnancy rate, duration of gestation, litter size, sex ratio, pup survival, pup weight, postnatal development, reproductive organ weights and histopathology in any generation. No adverse effects on reproductive function or development.

US FDA used 90-day repeated dose toxicity study:



Q3D Elemental Impurities

Guidance for Industry

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2015
ICH

An official website of the United States government

FDA U.S. FOOD & DRUG ADMINISTRATION

On January 1, 2018, new guidelines regarding elemental impurities in brand and generic drug products went into effect.

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf

Mo section pages 46-47:

Appendix 3: Individual Safety Assessments

MOLYBDENUM

Summary of PDE for Molybdenum

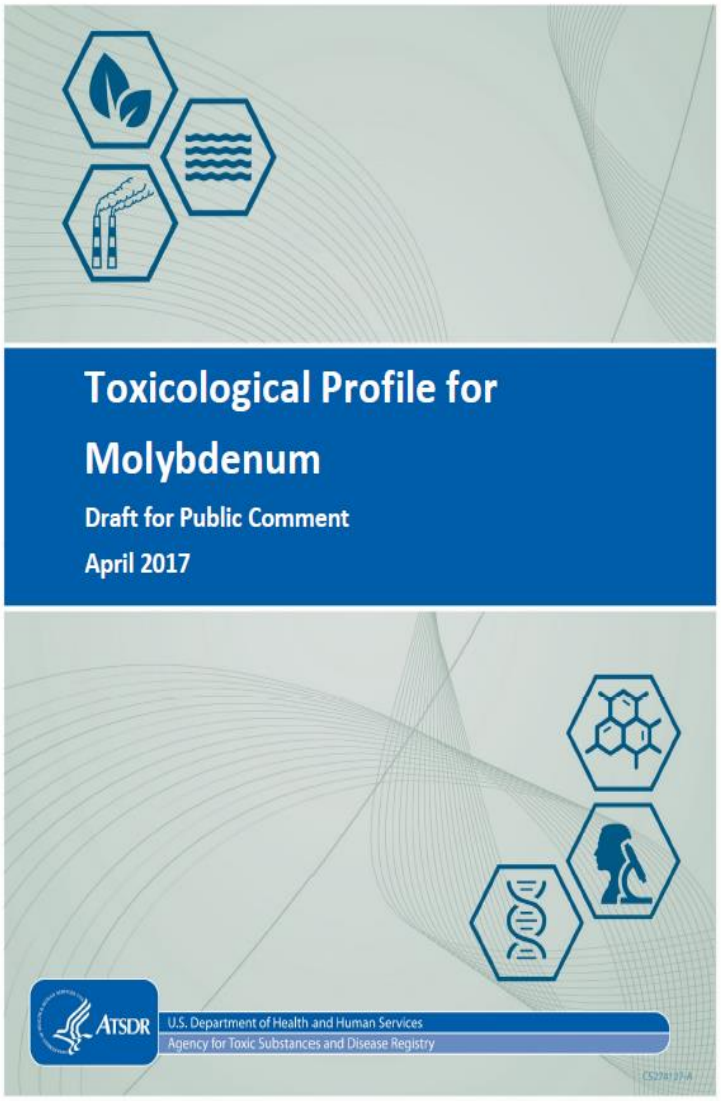
Molybdenum (Mo)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	3400	1700	11

PDE – Oral Exposure

A good laboratory practice compliant 90-day toxicology study that investigated the toxicity of sodium molybdate dehydrate administered in the diet of rats demonstrated effects at 60 mg Mo/kg/day, including effects on body weight, weight gain, food conversion efficiency, some organ weights (absolute and relative to body weight) and renal histopathology (slight diffuse hyperplasia in the proximal tubules in 2 females) (Murray *et al*, 2014). No adverse effects were noted after a 60-day recovery period, with the exception of reduced body weights in male rats. No adverse effects on reproductive organs, estrus cycles, or sperm parameters were noted. The authors conclude that the NOAEL for this study was 17 mg Mo/kg/day. No treatment-related toxicity was seen at this dose. Using modifying factors (F1-F5 as discussed in Appendix 1) the oral PDE is:

PDE = 17 mg/kg x 50 kg / 5 x 10 x 5 x 1 x 1 = 3.4 mg/d = 3400 µg/day

US ATSDR – Draft Toxicological Profile – IMOA Review



First-time this US Agency is generating a toxicological profile about Molybdenum.

Not a leaflet! ….. > 270 pages

IMOA technical submission September 2017
ATSDR ongoing review 2019
Takes account of IMOA Human Health studies (90-day repeated dose tox, Prenatal DevTox, 2-Generation Reprotox).

- Awaiting ATSDR finalization

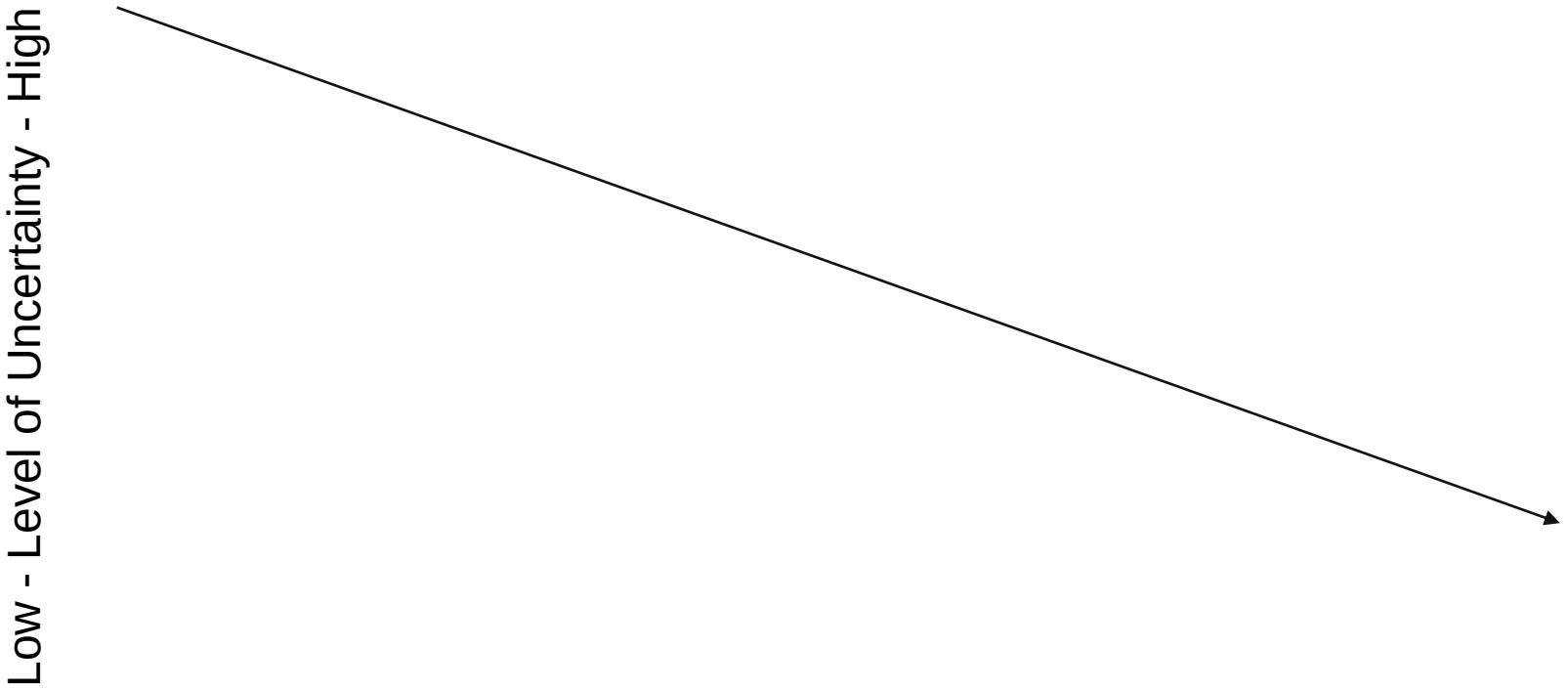
Human Health Studies:

OECD Protocol-compliant and GLP:

- 2011: 90-day Repeated Dose Toxicity (HLS,Princeton,USA)
  - *Hoffmann G. (2011): Sodium molybdate dihydrate: A 90-day oral dietary administration study in rats (GLP). Study No. 10-2225.*
- 2013: Prenatal Developmental Toxicity ((RTI, Raleigh, USA)
  - *Tyl, R. (2013): Developmental Toxicity Evaluation of Sodium Molybdate Dihydrate (CAS No. 10102-40-6) administered in the diet to CD® (Sprague Dawley) Rats*
- 2015-16: 2-Generation Reproduction (CRL, Pennsyl., USA)
  - *Hoberman A.(2017): Two generation (one litter per generation) reproduction toxicity study of sodium molybdenum dihydrate in rats*
  - *Peer-reviewed publication: March 2019*

Lead Author of the 3 peer-reviewed published papers: Murray (J.)

IMOA Studies – advancing science and reducing uncertainty levels



Kovalskiy 1961 Fungwe 1990 Hoffman 2011* Tyl 2013* Hoberman 2016*

* Studies commissioned by IMOA

Kovalski'y et al study, 1961

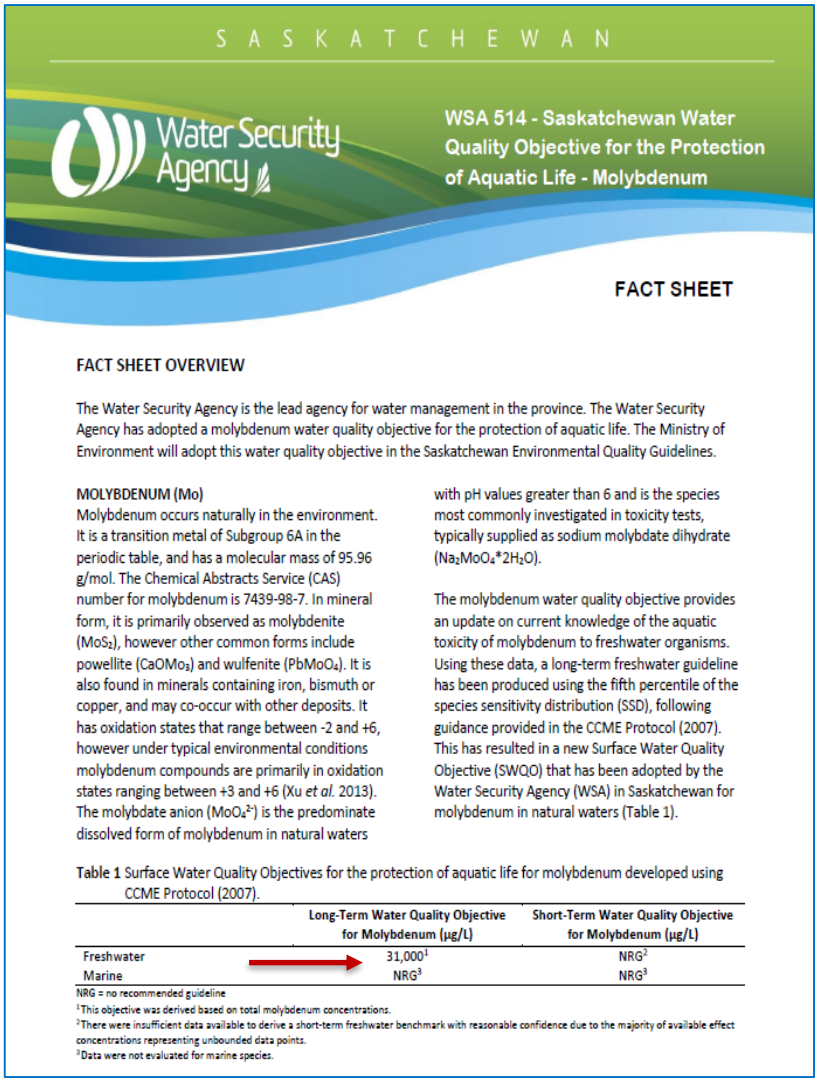
- US ATSDR Draft Moly Tox Profile concludes low confidence in this study and unsuitable as a basis for deriving a chronic oral Minimal Risk Level

- Panel on Micronutrients of the Institute of Medicine 2001 has similar concerns about poor reliability of the study. In its chapter on Molybdenum (page 434) it states:

> " ….. serious methodological difficulties are noted with this particular study including possible analytical problems in the assessment of blood and urinary copper levels and the very small size of the control group in contrast to the molybdenum-exposed group."

Despite this:
Kovalski'y is the key study in US EPA IRIS Database for Moly (1992), and also the still current EPA Molybdenum Health Advisory (latest edition 2018)

Canada-Saskatchewan Mo WQS review finalized:



SASKATCHEWAN

Water Security Agency

WSA 514 - Saskatchewan Water Quality Objective for the Protection of Aquatic Life - Molybdenum

FACT SHEET

FACT SHEET OVERVIEW

The Water Security Agency is the lead agency for water management in the province. The Water Security Agency has adopted a molybdenum water quality objective for the protection of aquatic life. The Ministry of Environment will adopt this water quality objective in the Saskatchewan Environmental Quality Guidelines.

MOLYBDENUM (Mo)

Molybdenum occurs naturally in the environment. It is a transition metal of Subgroup 6A in the periodic table, and has a molecular mass of 95.96 g/mol. The Chemical Abstracts Service (CAS) number for molybdenum is 7439-98-7. In mineral form, it is primarily observed as molybdenite (MoS_2), however other common forms include powellite ($CaOMo_3$) and wulfenite ($PbMoO_4$). It is also found in minerals containing iron, bismuth or copper, and may co-occur with other deposits. It has oxidation states that range between -2 and +6, however under typical environmental conditions molybdenum compounds are primarily in oxidation states ranging between +3 and +6 (Xu *et al.* 2013). The molybdate anion (MoO_4^{2-}) is the predominate dissolved form of molybdenum in natural waters with pH values greater than 6 and is the species most commonly investigated in toxicity tests, typically supplied as sodium molybdate dihydrate ($Na_2MoO_4*2H_2O$).

The molybdenum water quality objective provides an update on current knowledge of the aquatic toxicity of molybdenum to freshwater organisms. Using these data, a long-term freshwater guideline has been produced using the fifth percentile of the species sensitivity distribution (SSD), following guidance provided in the CCME Protocol (2007). This has resulted in a new Surface Water Quality Objective (SWQO) that has been adopted by the Water Security Agency (WSA) in Saskatchewan for molybdenum in natural waters (Table 1).

Table 1 Surface Water Quality Objectives for the protection of aquatic life for molybdenum developed using CCME Protocol (2007).

	Long-Term Water Quality Objective for Molybdenum (µg/L)	Short-Term Water Quality Objective for Molybdenum (µg/L)
Freshwater	31,000[1]	NRG[2]
Marine	NRG[3]	NRG[3]

NRG = no recommended guideline

[1] This objective was derived based on total molybdenum concentrations.

[2] There were insufficient data available to derive a short-term freshwater benchmark with reasonable confidence due to the majority of available effect concentrations representing unbounded data points.

[3] Data were not evaluated for marine species.

- ❑ Existing Mo Water Quality Standard: **73** micrograms Mo *(protective of aquatic life)*
- ❑ Proposed revision (by Cameco): 26,000 micrograms Mo, then upped to 31,000 micrograms Mo
- ❑ Duration of review: 2016 to end 2018
- ❑ Outcome: **31,000** micrograms Mo/L approved as the revised Mo WQS
- ❑ 424-fold increase in Mo WQS

Table heavily populated with IMOA data (De Schampheleare, and Heijerick & Carey):

Table 3. Toxicity data points used in the species sensitivity distribution to determine the long-term surface water quality objective for molybdenum.

Species	Duration	Endpoint	Observed Effect	Effects Concentration (mg/L Mo) Reported	Species Geometric Mean	Reference
Oncorhynchus mykiss (rainbow trout)	78 d	EC10	Biomass	43.2	43.2	De Schampheleare *et al.* (2010)
Pimephales promelas (fathead minnow)	34 d 32 d	EC10 EC10	Biomass Growth	39.3 90.9	59.8	De Schampheleare *et al.* (2010) GEI (2009)
Salmo trutta (brown trout)	86 d	EC10	Growth	202.0	202.0	Lucas et al. (2017)
Brachionus calyciflorus (rotifer)	48 h	EC10	Reprod.	193.6	193.6	De Schampheleare *et al.* (2010)
Ceriodaphnia dubia (cladoceran)	7 d 8 d 7 d	EC10 IC12.5 EC10	Reprod. Reprod. Reprod.	78.2 34.0 50.8	51.3	De Schampheleare *et al.* (2010) Naddy et al. (1995) GEI (2009)
Chironomus riparius (midge)	14 d	EC10	Biomass	121.4	121.4	De Schampheleare *et al.* (2010)
Daphnia magna (cladoceran)	21 d 21 d 21 d	EC10 EC10 EC10	Reprod. Reprod. Reprod.	105.6 62.8 108.0	89.4	De Schampheleare *et al.* (2010) De Schampheleare *et al.* (2010) GEI (2009)
Hyalella azteca (amphipod)	42-d	EC10	Reprod.	44.6	44.6	Heijerick and Carey (2017)
Lymnaea stagnalis (snail)	28 d	EC10	Growth	221.3	221.3	De Schampheleare *et al.* (2010)
Pseudokirchneriella subcapitata	72 h 72 h	EC10 EC10	Growth rate Growth rate	74.3 164.0	110.4	De Schampheleare *et al.* (2010) De Schampheleare *et al.* (2010)
Lemna minor (duckweed)	7 d	EC10	Growth rate	241.5	241.5	De Schampheleare *et al.* (2010)
Xenopus laevis (African clawed frog)	4 d	EC10	Malformation	115.9	115.9	De Schampheleare et al. (2010)

(Nautilus Environmental 2017)

Canada-Saskatchewan *Province*

Mo WQS review docs – IMOA & OECD acknowledgements

Saskatchewan

Ministry of Environment

3211 Albert Stree
Regina, Canada
S4S 5W6

May 9, 2017

Saskatchewan Environmental Quality Guideline Subscribers

Dear Saskatchewan Environmental Quality Guideline Subscribers:

Re: Revised Molybdenum Water Quality Guideline

The Ministry of Environment would like to adopt a new molybdenum value for the protection of aquatic life in the Saskatchewan Environmental Quality Guidelines.

(Davies et al. 2005; De Schamphelaere *et al* 2010). As well, we have been made aware that an extensive literature review and ecotoxicity data set is available, supported and published to provide key data and hazard conclusions to support the European Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) program. This information has been published in peer reviewed journals

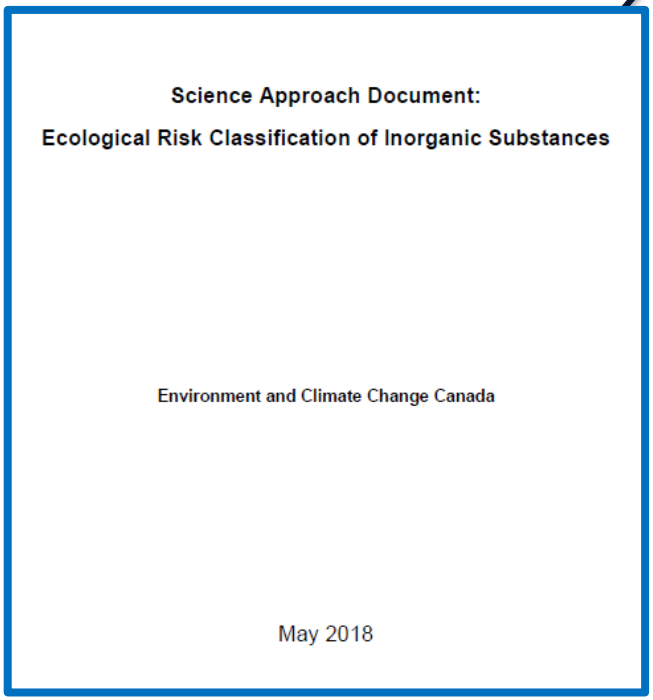
(De Schamphelaere *et al* 2010; Heijerick *et al* 2012) and in 2014 achieved Organization of Economic Co-operation and Development Mutual Acceptance of Data status, which is a data quality endorsement from scientists from member countries, including Canada.

Increased to 31 mg Mo →

The Ministry has reviewed the draft documents and is supportive of the revised long-term water quality guideline for the protection of aquatic life for molybdenum of 26 mg/L. The revised guideline is based on robust, scientifically defensible, current data and CCME guideline derivation guidance. The majority of the data used to re-derive the molybdenum water quality guidelines has also achieved Organization of Economic Co-operation and Development Mutual Acceptance of Data status. In addition, specialists from the International Molybdenum Association have reviewed the document and are also supportive of the revised guideline.

Water Quality Standards ….. Canada (Federal Level):

- WQS **Protective of Aquatic Life:**
  - Limit value traditionally < 350 micrograms Mo/L (sparse datasets)
  - EU REACH: IMOA derived PNEC (Predicted No Effect Concentration): 12,600 micrograms/L
  - 2014: OECD-endorsed IMOA molybdate dataset


Science Approach Document:

Ecological Risk Classification of Inorganic Substances

Environment and Climate Change Canada

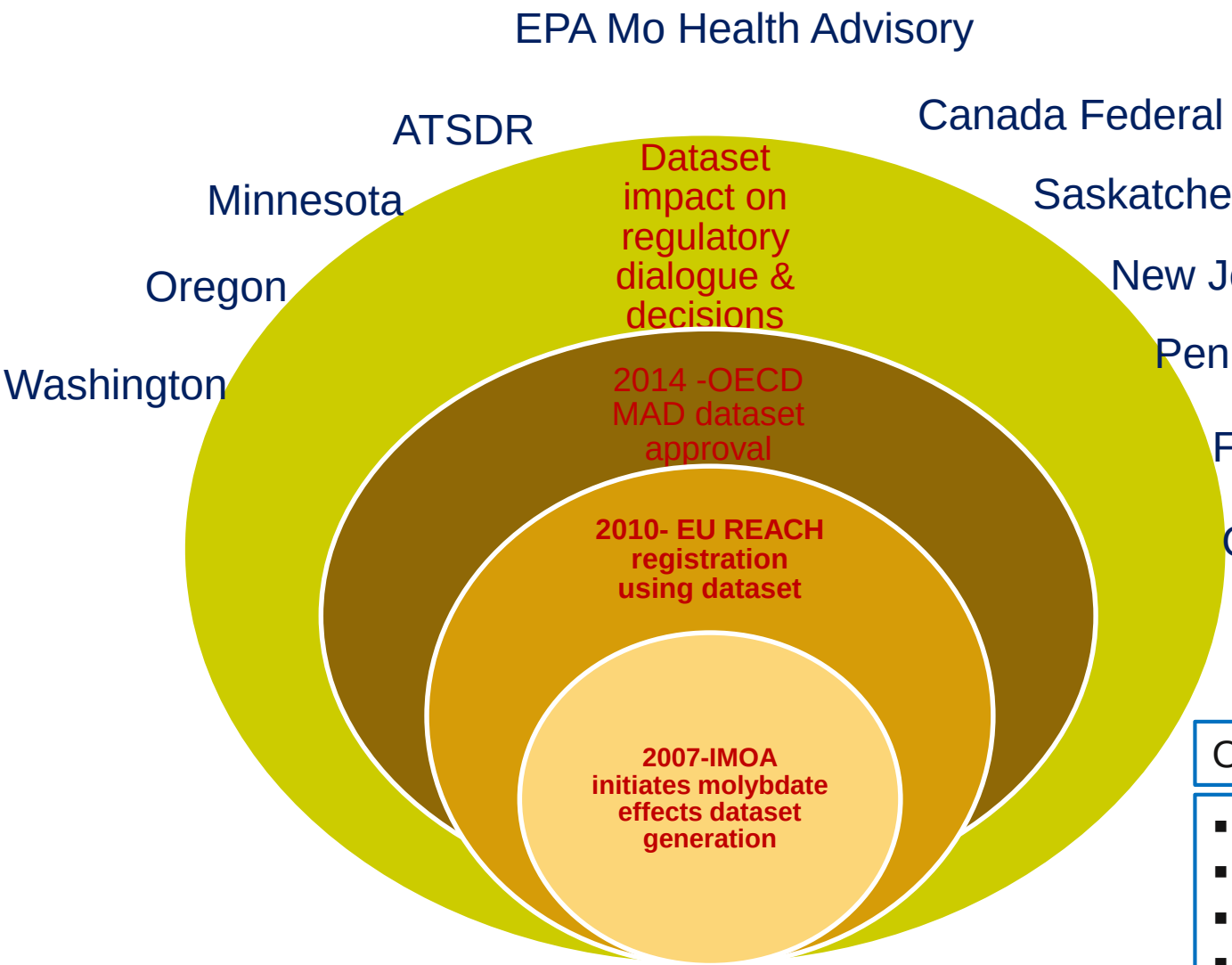
May 2018

Table 4-3. Derivation of aquatic PNEC values

ERC-I substance or group (number of substances)	Approach	Assessment factor	Derived $PNEC_{aq}$ (µg/L)
Barium (4)	CTV/AF	5	1780
Beryllium (1)	CTV/AF	10	6.7
Bismuth (7)	CTV/AF	50	0.5
Cerium (1)	CTV/AF	10	3.2
Deuterium oxide (1)	Categorization	1	1000
Germanium (1)	CTV/AF	20	10.5
Hydrogen peroxide (1)	CTV/AF	10	230
Iodine (5)	CTV/AF	100	16.7
Lanthanum (3)	CTV/AF	10	1.8
Lithium (16)	Acute SSD/AF	10	121.6
Molybdenum (2)	Chronic SSD	NA	26340
Neodymium (1)	CTV/AF	50	1.1
Praseodymium (1)	CTV/AF	50	0.7
Silicon carbide (1)	CTV/AF	100	40000
Talc (1)	CTV/AF	100	40000
Tellurium (2)	CTV/AF	10	25
Tin (2)	CTV/AF	5	300
Titanium (13)	CTV/AF	10	850
Yttrium (1)	CTV/AF	5	3.3

NA, not applicable; CTV, critical toxicity value; AF, assessment factor; SSD, species sensitivity distribution.

Robust scientific data in action:



On the horizon:

- Korea-REACH
- China
- Thailand
- EU REACH (more)

Way Forward:

Common goals:

- utilize high-quality human health and environmental science for the regulation of molybdenum
- Maintain and develop regulatory dialogue through knowledge-sharing and scientific study resources

Thank you for your kind attention this morning!

Sandra Carey
HSE Executive
International Molybdenum Association
Email: sandracarey@imoa.info
Tel: + 44 7778 813721

Views expressed in this presentation are those of the presenter and not necessarily those of IMOA.