

# IRIS Assessment Plan For Inorganic Mercury Salts

**Key Topic 3. Alternative methods or new approaches to inform data poor mercury salts (i.e., mercurous chloride and mercuric sulfide).**

*Lena Smirnova,  
Center For Alternatives to Animal Testing  
Johns Hopkins University  
[lena.smirnova@jhu.edu](mailto:lena.smirnova@jhu.edu)*





Food for Thought ...

### 3S – Systematic, Systemic, and Systems Biology and Toxicology

Lena Smirnova<sup>1</sup>, Nicole Kleinstreuer<sup>2</sup>, Raffaella Corvi<sup>3</sup>, Andre Levchenko<sup>4</sup>, Suzanne C. Fitzpatrick<sup>5</sup>  
and Thomas Hartung<sup>1,6</sup>

Smirnova et al., Altex 2018

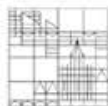
Chemical  
Research in  
Toxicology

Perspective  
pubs.acs.org/crt

#### Systems Toxicology: Real World Applications and Opportunities

Thomas Hartung<sup>1,2</sup>, Rex E. FitzGerald<sup>3</sup>, Paul Jennings<sup>4</sup>, Gary R. Mirams<sup>5</sup>, Manuel C. Peitsch<sup>6</sup>,  
Amin Rostami-Hodjegan<sup>7</sup>, Imran Shah<sup>8</sup>, Martin F. Wilks<sup>9</sup>, and Shana J. Sturla<sup>10</sup>

Hartung et al.,  
Chem Res Toxicol 2017



## Systematic -existing knowledge-

Systematic review → Bioengineering

## Systems biology/toxicology

MPS  
Experimental  
-body-on-chip-

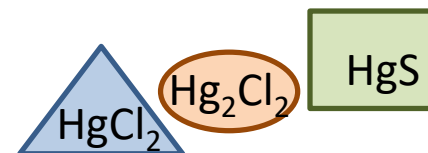
Computational  
-modeling-  
-virtual patient-

## Systemic studies

3S

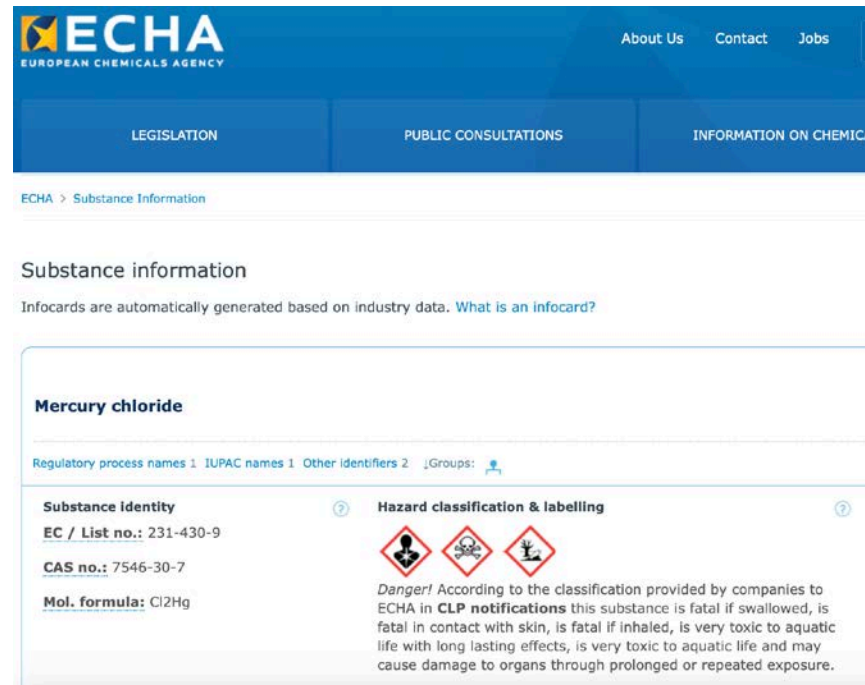
# Systematic review - a laudable approach

- Defined Inclusion/exclusion criteria
- Include studies from earlier than 1997. IRIS assessment only  $\text{HgCl}_2$  (RfD from 1995) and non-systematic
- *In vitro* and non-mammalian studies to be included in stream of evidence and not in supplement.
- OHAT scheme can be used for evidence integration, where *in vitro* mechanistic data are used to up-/down-grade the human and animal evidence.  
[https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookmarch2019\\_508.pdf](https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookmarch2019_508.pdf)
- QA: ToxRtool for *in vitro* and *in vivo* studies:  
<https://ec.europa.eu/jrc/en/scientific-tool/toxrtool-toxicological-data-reliability-assessment-tool>  
Quality scoring tools for *in vitro*, *in vivo*, QSAR, human data: Samuel et al. 2017  
<https://www.ncbi.nlm.nih.gov/pubmed/27039952>



# Regulation and registration of Mercury salts in Europe

- The use of mercury salts in EU is fundamentally banned
- No REACH registration of inorganic mercury salts
- All mercury compounds are included in PIC (prior Informed consent) list, which was derived from Rotterdam Convention (<http://www.pic.int>)



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ECHA > Substance Information

Substance information

Infocards are automatically generated based on industry data. [What is an infocard?](#)

**Mercury chloride**

Regulatory process names 1 IUPAC names 1 Other identifiers 2 Groups: 


**Substance Identity**

EC / List no.: 231-430-9

CAS no.: 7546-30-7

Mol. formula: Cl<sub>2</sub>Hg

**Hazard classification & labelling**



*Danger! According to the classification provided by companies to ECHA in CLP notifications this substance is fatal if swallowed, is fatal in contact with skin, is fatal if inhaled, is very toxic to aquatic life with long lasting effects, is very toxic to aquatic life and may cause damage to organs through prolonged or repeated exposure.*

Notified classification and labelling according to CLP criteria

## General Section

EC / List no. 	Name	CAS Number 	Additional Notif Information 
231-430-9	Mercury chloride	7546-30-7	State/Form IUPAC Names

Classification		Labelling	
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)
Acute Tox. 2	H300	H300	
Acute Tox. 1	H310	H310	
Acute Tox. 2	H330	H330	
STOT RE 2	H373	H373	
Aquatic Acute 1	H400		
Aquatic Chronic 1	H410	H410	



# Scientific issues

- No animal data included for  $\text{Hg}_2\text{Cl}_2$  but 30 for HgS
- Alternatives: *in vitro* and read-across
- Solubility
- Bioavailability and Exposure route (dermal excluded?!)

# Scientific issues - suggestions

- **No animal data included for  $\text{Hg}_2\text{Cl}_2$  but 30 for HgS**
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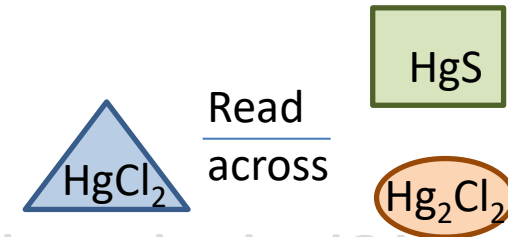
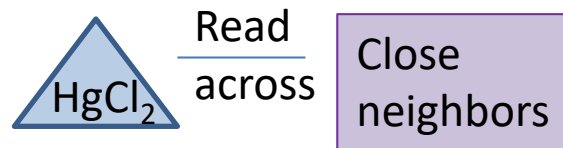
Include mechanistic studies from supplement into the main stream of systematic review and use OHAT recommendations of evidence integration

# Scientific issues - suggestions

- No animal data included for  $\text{Hg}_2\text{Cl}_2$  but 30 for  $\text{HgS}$

- **Alternatives: *in vitro* and read-across**

- Solubility



- Bioavailability and Exposure route (dermal excluded?!)

Automated read-across and QSAR are difficult due to the small size of the molecules

ECHA Guidance for Read-Across: RAAF (Read-Across Assessment Framework)

[https://echa.europa.eu/documents/10162/13628/raaf\\_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a](https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a)

Good Read-Across Practice (GRAP): Ball et al. 2016

<https://www.ncbi.nlm.nih.gov/pubmed/26863606>

# Automated Read-across. Testing Mercurous chloride

UL Cheminformatics Tool Kit

- Beta- version GenRA on EPA Comptox dashboard
- UL Cheminformatic Tool kit

Select Structure > Select Endpoints > Prediction Model: 1.7.0 > Download

Prediction

Download CSV XML JSON

Target	Name	Acute Oral Probability
<chem>Cl—Hg Cl—Hg</chem>	chloromercury 10112-91-1	<b>60% Hazardous</b> 40% Non-Hazardous

GHS Category	Probability
H300	26%
H301	22%
H302	3%
H303	10%
<b>Total</b>	<b>60%</b>

**EPA** United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads Copy Share Submit Comment

**Step Two: Data Gap Analysis**

Neighbors by: Chem: Morgan Fgrpts Filter by: invivo data Summary Data Gap Analysis

Chemical structure diagram showing Mercurous chloride (Hg<sub>2</sub>Cl<sub>2</sub>) at the center, surrounded by various chlorinated compounds and their analogs. The diagram includes chemical structures for Lindane, beta-Hexachlorocyclopentadiene, Hexachlorobenzene, 1,1-Dichloroethane, (E)-1,2-Dichloroethene, 1,1,2,2-Tetrachloroethane, 1,2-Dichloroethane, Lithium hypochlorite, and Chlorine. A table on the right lists the compounds and their associated data values.

Compound	bio h21	bio h22	chem ct	tox h2f
Mercury chloride (Hg <sub>2</sub> Cl <sub>2</sub> )	0	0	4	0
Chlorine	0	0	1	83
Lithium hypochlorite	0	0	3	95
1,2-Dichloroethane	6	0	9	168
1,1,2,2-Tetrachloroethane	5	0	8	168
(E)-1,2-Dichloroethylene	8	187	9	85
1,1-Dichloroethane	10	0	4	83
Hexachlorobenzene	6	0	10	139
beta-Hexachlorocyclopentadiene	20	714	8	82
Lindane	20	819	8	402

# of Analogs 10

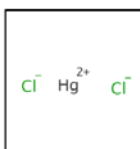
Next



# Scientific issues

- No animal data included for  $\text{Hg}_2\text{Cl}_2$  but 30 for  $\text{HgS}$

- Alternatives: *in vitro* and read-across: ToxCast** NO DATA on  $\text{Hg}_2\text{Cl}_2$  and  $\text{HgS}$



Mercuric chloride

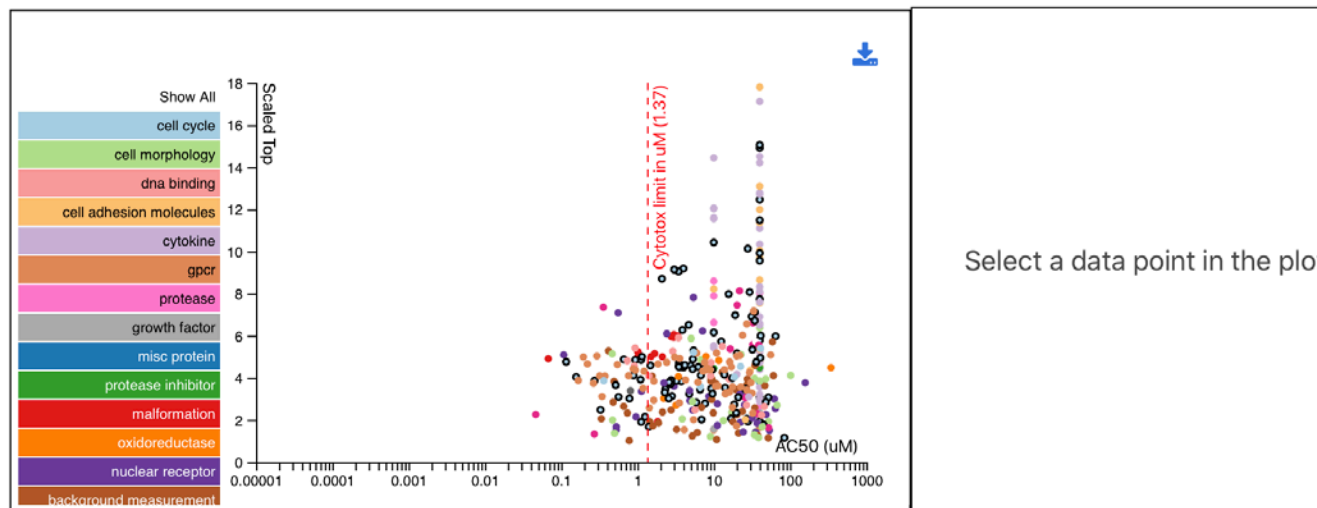
7487-94-7 | DTXSID5020811

Searched by DSSTox Substance Id.

## Chemical Activity Summary

 TOXCAST DATA

 ASSAY C



# Scientific issues

- No animal data included for  $\text{Hg}_2\text{Cl}_2$  but 30 for  $\text{HgS}$
- Alternatives: *in vitro* and read-across
- **Solubility poses a problem for cell culture based alternative approaches.**
  - Hg level in the medium should be assessed by MS to determine solubility and free concentrations. Medium composition should be taken into account (protein content, serum etc.)
  - *In vitro* systems of human digestive process to study bioaccessibility
  - Ideal *in vitro* models for main organs of mercury toxicity: liver organoids (Insphero) and kidney-on-chip (Nortis Inc.)
  - Developmental tox to be considered: Mercuric mercury accumulates in the placenta, fetal tissues, and amniotic fluid. Possible transport of mercuric mercury via one or more amino acid transporters - accumulation in the brain
- Bioavailability and Exposure route (dermal excluded?!)

# Scientific issues

- No animal data included for  $\text{Hg}_2\text{Cl}_2$  but 30 for HgS
- Alternatives: in vitro and read-across
- Solubility
- **Bioavailability (bioaccessibility, absorption and metabolism) and Exposure route (dermal excluded?!)**

[Int J Environ Res Public Health](#). 2017 Feb; 14(2): 169.

Published online 2017 Feb 10. doi: [10.3390/ijerph14020169](https://doi.org/10.3390/ijerph14020169)

## A Review of Mercury Bioavailability in Humans and Fish

[Mark A. Bradley](#),<sup>1</sup> [Benjamin D. Barst](#),<sup>2</sup> and [Niladri Basu](#)<sup>1,2,\*</sup>

New Approach methodologies: PBPK and IVIVE computational models

# Summary

- Systematic review – the right way to go with some improvement.
- Read-Across following pertinent guidance
- MPS and Organ-on-chip – ideal in vitro alternatives, but no data
- All in vitro studies should address solubility and bioaccessibility
- PBPK modeling for bioavailability
- Dermal route of exposure to be considered?



# THANK YOU!

*lena.smirnova@jhu.edu*

