

IRIS Assessment Plan For Inorganic Mercury Salts

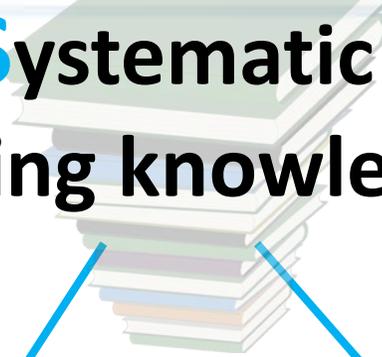
Key Topic 3. Alternative methods or new approaches to inform data poor mercury salts (i.e., mercurous chloride and mercuric sulfide).

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**Systematic
-existing knowledge-**

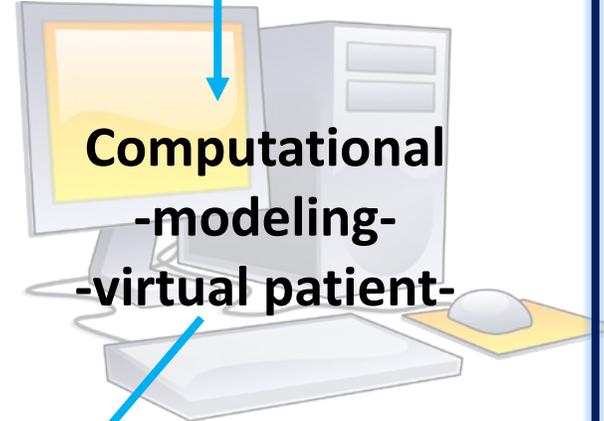
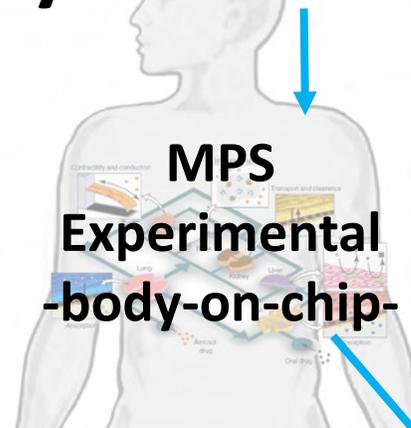


Systematic review

Bioengineering



Systems biology/toxicology



Systemic studies

Food for Thought ...

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

Lena Smirnova¹, Nicole Kleinstreuer², Raffaella Corvi³, Andre Levchenko⁴, Suzanne C. Fitzpatrick⁵
and Thomas Hartung^{1,6}

Smirnova et al., Altex 2018

**Chemical
Research in
Toxicology**

Perspective
pubs.acs.org/crt

Systems Toxicology: Real World Applications and Opportunities

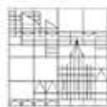
Thomas Hartung,^{1,2} Rex E. FitzGerald,³ Paul Jennings,⁴ Gary R. Mirams,⁵ Manuel C. Peitsch,⁶
Amin Rostami-Hodjegan,^{7,8} Imran Shah,⁹ Martin F. Wilks,³ and Shana J. Sturla¹⁰

Hartung et al.,

Chem Res Toxicol 2017

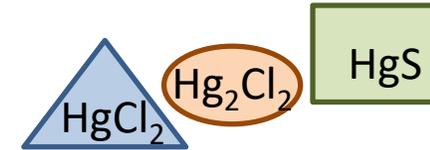


Universität
Konstanz



Systematic review - a laudable approach

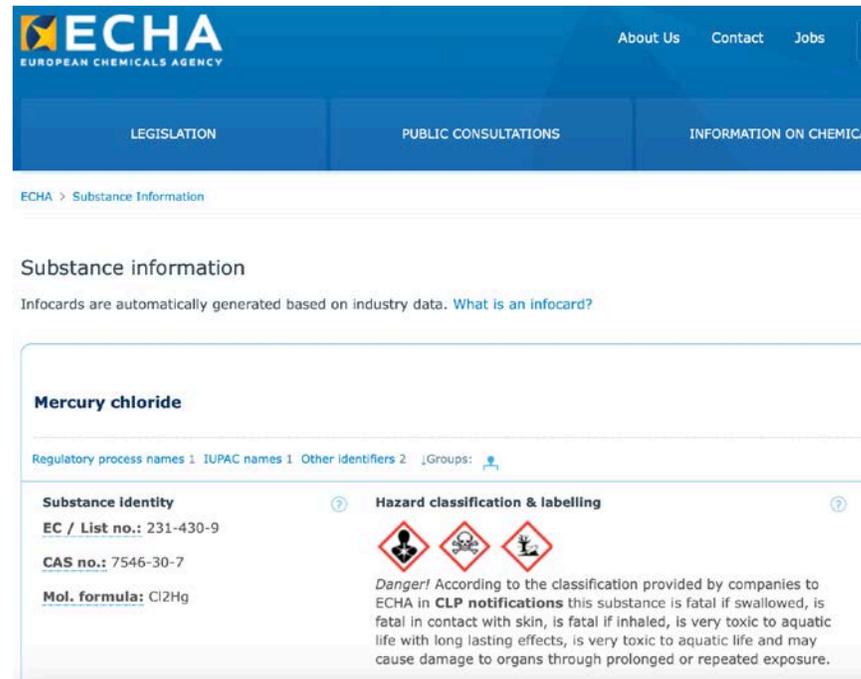
- Defined Inclusion/exclusion criteria
- Include studies from earlier than 1997. IRIS assessment only HgCl_2 (RfD from 1995) and non-systematic
- *In vitro* and non-mammalian studies to be included in stream of evidence and not in supplement.
- OHAT scheme can be used for evidence integration, where *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
- 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>)



ECHA
EUROPEAN CHEMICALS AGENCY

LEGISLATION PUBLIC CONSULTATIONS INFORMATION ON CHEMICALS

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: Cl₂Hg

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 Hg_2Cl_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 Hg₂Cl₂ but 30 for HgS**
- Alternatives: in vitro and read-across
- Solubility
- Bioavailability and Exposure route (dermal excluded?!)

Include mechanistic studies from supplement into the main stream of systematic review and use OHAT recommendations of evidence integration

Scientific issues - suggestions

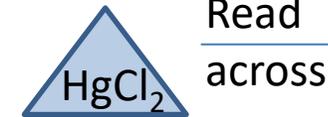
- No animal data included for Hg_2Cl_2 but 30 for HgS

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

- Solubility



Close neighbors



- 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

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

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

Scientific issues

- No animal data included for Hg_2Cl_2 but 30 for HgS

- Alternatives: *in vitro* and read-across: ToxCast** NO DATA on Hg_2Cl_2 and HgS

EPA United States Environmental Protection Agency

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

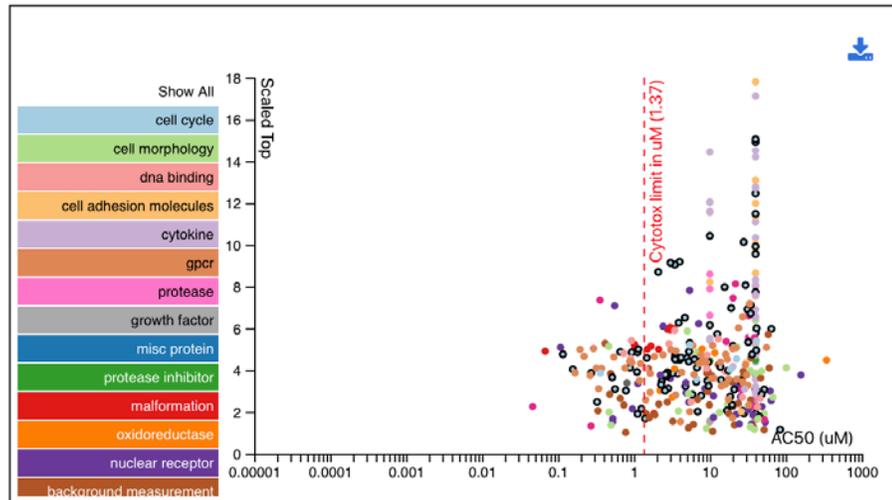
[Cl-].[Hg2+].[Cl-] Mercuric chloride
 7487-94-7 | DTXSID5020811
 Searched by DSSTox Substance Id.

Chemical Activity Summary

- DETAILS
- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- ADME
- EXPOSURE
- BIOACTIVITY
 - TOXCAST: SUMMARY
 - EDSP21
 - TOXCAST/TOX21

TOXCAST DATA

ASSAY C



Select a data point in the plot

Scientific issues

- No animal data included for Hg_2Cl_2 but 30 for 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 Hg_2Cl_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](#),¹ [Benjamin D. Barst](#),² and [Niladri Basu](#)^{1,2,*}

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!

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