Asia-Pacific
Economic Cooperation

2015/SOM3/CD/WKSP/024

Case Study - Using Bioaccessibility Data for Grouping Metal Compounds

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APEC
PHILIPPINES
2015

Workshop on Metals Risk Assessment
Cebu, Philippines
28-29 August 2015

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Problem Statement: While certain high volume metal compounds may have large amounts of toxicology data, experience with assessing chemicals in the Australian Inventory of Chemical Substances (AICS) have shown that many metal compounds have limited data. In order to fill data gaps, data could be read-across from data rich chemicals to data poor chemicals according to the OECD guidance on grouping of chemicals (OECD, 2014). However, in the past it has been usual to use water solubility of metal compounds as the basis for bioavailability of the metal ion and hence, read-across. This may over or under estimate the toxicity of the metal compounds in vivo.

Scientific Issues: Generally, it is expected that the metal ion is the moiety responsible for systemic toxicity and a significant contributor to local toxicity. Therefore, the toxicity of metal compounds is considered to be related to the in vivo bioavailability of metal ions. Use of water solubility as a surrogate for bioavailability in humans has drawbacks as the influences of pH, presence of various ligands or redox conditions are not reflected (OECD, 2014). However, the use of bioaccessibility data from bioelution studies utilising physiologically relevant fluids is considered to provide a better estimate of bioavailability at the target organ/site in humans.

Current risk /hazard assessment: The use of bioaccessibility data for grouping metal compounds for read-across purposes is specified in the updated OECD guidance on grouping of chemicals (OECD, 2014). Recently, the Inventory Multi-

tiered Assessment and Prioritisation (IMAP) programme in Australia has utilised bioaccessibility data for grouping a range of metal compounds, including a large number of nickel and cobalt compounds. Assessment information can be found at http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments.

Discussion questions:

Please discuss the following questions with regards to the information available on Mx compounds in Appendix A and B.

1) Do you consider Mx compound A to be a skin sensitiser? In order to read-across data to Mx compound A which chemical or chemicals will you include in your group?

2) Can you read-across data to Mx compound A for repeated dose toxicity via the oral route? What factors do you consider?

3) Do you consider Mx compound A to be hazardous under GHS criteria (refer Appendix C) for repeated dose toxicity via the inhalation route? Would you consider applying a read-across for this endpoint?

Reference

OECD (2014), Guidance on Grouping of Chemicals, Second Edition. Environment Directorate. Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Series on Testing and Assessment, No. 194. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en

APPENDIX A

Water solubility data for Mx compounds*

Chemical	Water solubility
$MxSO_4$	380 g/L
$MxCl_2$	510 g/L
Mx powder	Insoluble
MxO	Insoluble
Mx aluminate-spinel	Insoluble
Mx compound A	Insoluble

Bioaccessibility data for Mx compounds* in various biological fluids

Chemical	Bioaccessibility in gastric fluid (% Mx content released)	Bioaccessibility in alveolar fluid (% Mx content released)	Bioaccessibility in lysosomal fluid (% Mx content released)	Bioaccessibility in sweat (% Mx content released)
$MxSO_4$	94	90	92	90
$MxCl_2$	93	89	94	91
Mx powder	88	4	90	ND
MxO	91	6	90	4
Mx aluminate-spinel	0.06	0.007	0.01	0.009
Mx compound A	88	5	90	6

*fictitious chemicals; ND: not determined

APPENDIX B

Available toxicity data for Mx compounds

Chemical	Acute toxicity Oral (LD50)	Acute toxicity Inhalation (LC50)	Repeated Dose Toxicity Oral	Repeated Dose Toxicity Inhalation	Skin Sensitisation
$MxSO_4$	756 mg/kg bw 285 mg Mx/kg bw	4.3 mg/L/4 h 1.6 mg Mx/L/4 h	90 day rat study (OECD TG 408); doses tested: 0, 10, 30 or 100 mg/kg bw/day. NOAEL of 10 mg/kg bw/day based on kidney damage.	90 day rat study (OECD TG 413); exposed to aerosols containing 0, 0.3, 1, 3, 10 or 30 mg/m^3 for 6 h/day. LOAEC of 0.3 mg/m^3 based on lung fibrosis.	Sensitiser in several guinea pig maximisation tests.
$MxCl_2$	698 mg/kg bw 316 mg Mx/kg bw	4.1 mg/L/4 h 1.9 mg Mx/L/4 h	28 day rat study (OECD TG 407); doses tested: 0, 10, 30 or 100 mg/kg bw/day. NOAEL of 30 mg/kg bw/day based on kidney damage.	28 day rat study (OECD TG 412); exposed to aerosols containing 0, 3, 10 or 30 mg/m^3 for 6 h/day. LOAEC of 3 mg/m^3 based on lung fibrosis.	Sensitiser in a guinea pig maximisation test (OECD TG 406).
Mx powder	347 mg/kg bw	0.07 mg/L/4 h	ND	ND	ND
MxO	431 mg/kg bw 338 mg Mx/kg bw	0.09 mg/L/4 h 0.07 mg Mx/L/4 h	90 day rat study (OECD TG 408); doses tested: 0, 3, 10 or 30 mg/kg bw/day. NOAEL of 10 mg/kg bw/day based on kidney damage.	ND	Sensitiser in an OECD TG 429 local lymph node assay (LLNA) in mice.
Mx aluminate-spinel	>5000 mg/kg bw >1648 mg Mx/kg bw	>5 mg/L/4 h >1.6 mg/L/4 h	90 day rat study (OECD TG 408); doses tested: 0, 10, 30 or 100 mg/kg bw/day. NOEL of >100 mg/kg bw/day based on no effects observed.	90 day rat study (OECD TG 413); exposed to aerosols containing 0, 30, 100 or 300 mg/m^3 for 6 h/day. NOAEC of 300 mg/m^3 based on no adverse effects observed.	Not a sensitiser in a guinea pig maximisation test (OECD TG 406).
Mx compound A†	490 mg/kg bw 342 mg Mx/kg bw	0.09 mg/L/4 h 0.06 mg Mx/L/4 h	ND	ND	ND

†Assume counter ion has no contribution to toxicity.

bw: body weight; h: hour; ND: not determined; NOEL: no observed effect level; NOAEL: no observed adverse effect level; NOAEC: no observed adverse effect concentration; LOAEC: lowest observed adverse effect concentration