

Case Study Read Across Strategy for Molybdenum Compounds



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Read across for metal compounds some basic considerations



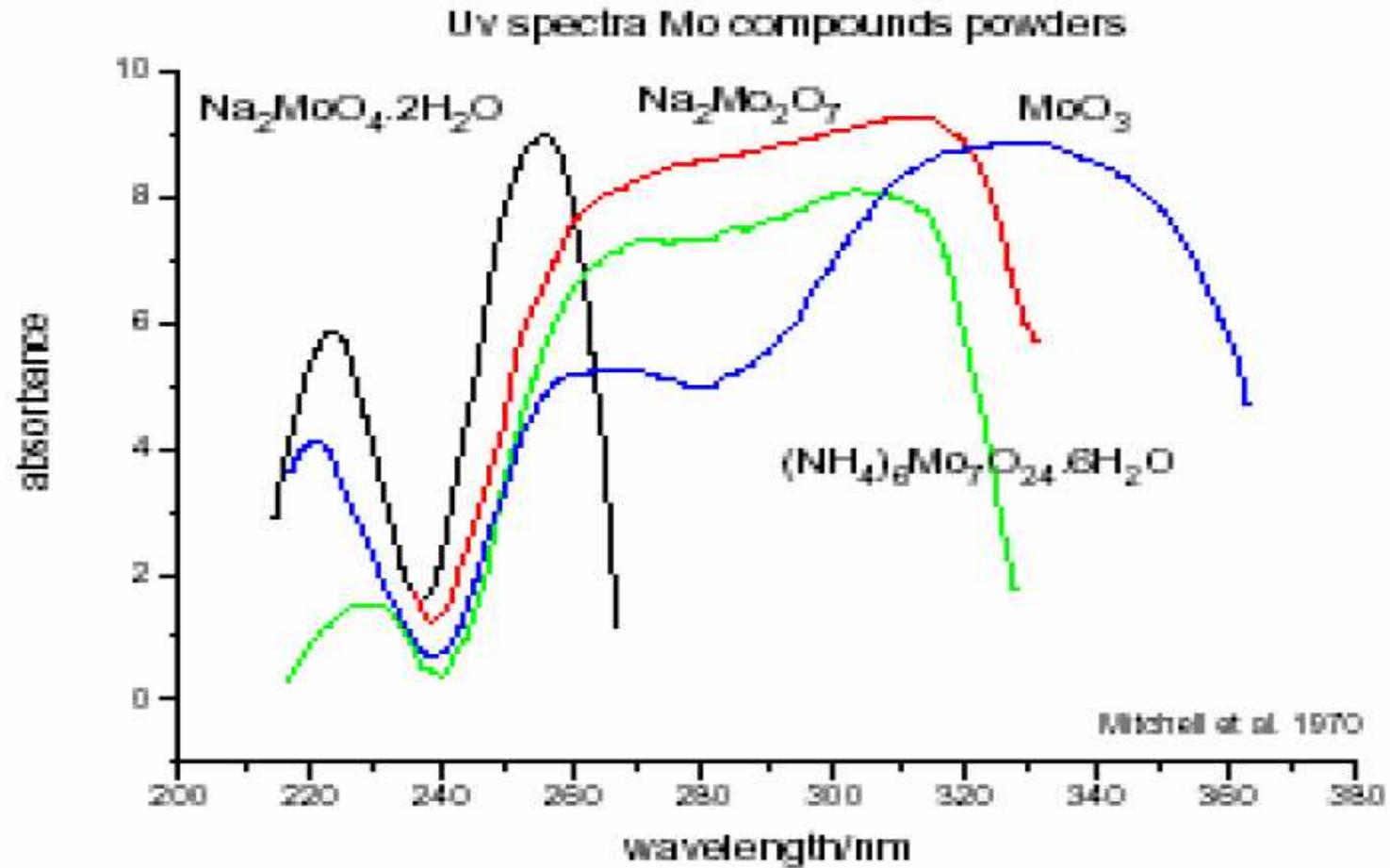
1. Which species is likely to be responsible for the toxicity?
2. Look at the metal cation and the possible toxicity of the anion.
3. Can complex anions be formed under environmental and physiological conditions?
4. Has the metal different oxidation states? If so can it be transformed easily under environmental and physiological conditions?
5. Consider stability of different oxidation states.
6. Can complexes be formed? Could they be relevant under physiological and environmental conditions and ameliorate toxicity?
7. Can insoluble “polymeric” species be formed under relevant conditions (Al-oxides, hydroxides)?
8. What are the relevant species for the compound to look at?
9. Define compounds which likely lead to the same toxicologically relevant species.
10. Define within that group domains of bioaccessibility

Basic data collected



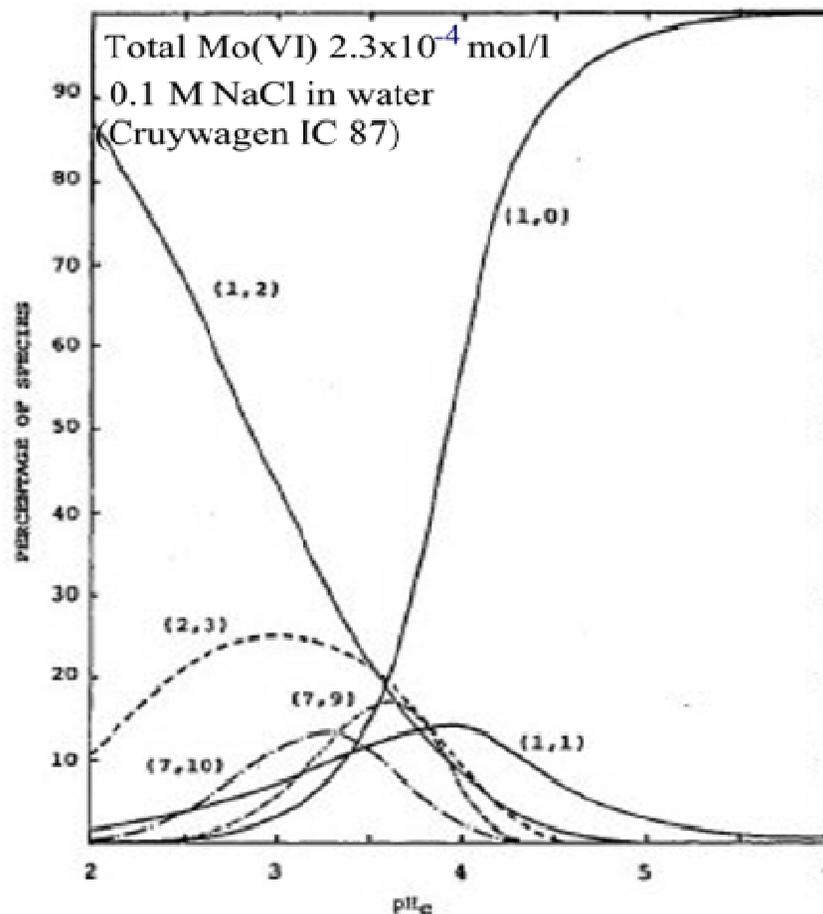
- **Water solubility with speciation of the dissolved species**
- **Dissolution under environmentally relevant conditions and speciation**
- **Speciation could be determined by UV spectroscopy**
 - Species identified by their characteristic UV spectra
 - peak positions
 - peak intensities.
 - The spectra were analysed by decomposition into Gaussian peaks
- **In vitro bioaccessibility studies in various physiological fluids**

UV spectra solids



pH dependent UV spectra

- At a total Mo concentration below ca 10^{-3} M (Figure), $[\text{MoO}_4]^{2-}$ is the only species at $\text{pH} \geq 4.5$



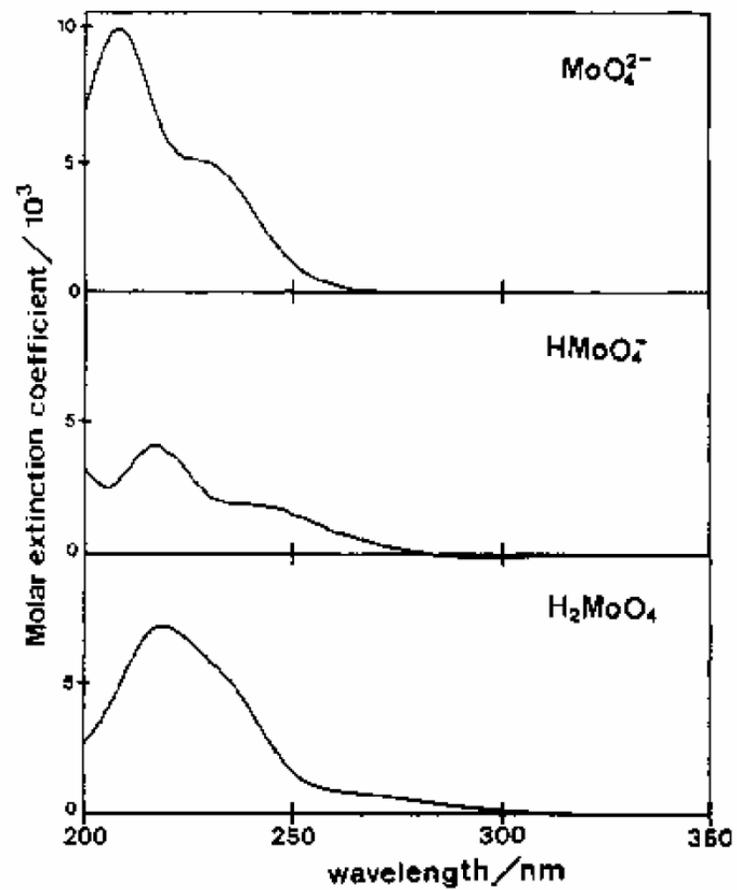
J. J. Cruywagen and J. B. B. Heyns,
Inorg. Chem. 1987, 26, 2569-2512.

UV analysis



- UV spectra of molybdenum compounds dissolved in water or stirred in suspension in water: identification of molybdenum species in solution.
- Water solutions of soluble molybdates: sodium and ammonium molybdates
- Supernatant solutions of suspensions of poorly soluble molybdenum substances: calcium molybdate, molybdenum metal, ferromolybdenum, molybdenum dioxide, molybdenum trioxide, roasted molybdenum concentrate and molybdenum disulfide.
- Particular species may be identified by the positions and intensities of peaks in the UV spectra
- Molybdate species in solution were identified by comparison with the literature spectra.
- The species in solutions of sodium molybdate at concentrations 1–10 mg/L and pH ca 7 is the molybdate ion, $[\text{MoO}_4]^{2-}$
- Absorption maximum (peak) at 207–208 nm (48000 cm^{-1}).
- At lower pH $[\text{MoO}_4]^{2-}$ ion is protonated to $[\text{HMoO}_4]^-$ and $[\text{H}_2\text{MoO}_4]$ species, the peaks in the UV spectra shift to lower energies (longer wavelengths)

Molybdate spectra



Results

- Spectra as data files of wavelengths and intensities
 - The spectra consist of overlapping peaks that were analyzed into Gaussian peaks using energy units (cm-1)
 - Results:
 - The spectra were identical with the reference spectra of sodium molybdate
 - The molybdate anion is the species present in aqueous solutions of all compounds
 - Concentration- and pH-dependent changes were identical
- (P.C.H. Mitchell, 2009)

Hypothesis for the analog approach



- Upon dissolution in aqueous solutions at physiologically relevant concentrations and pH conditions, the only aqueous molybdenum species emerging from all considered molybdenum substances is the molybdate $[\text{MoO}_4]^{2-}$ anion.
- For systemic toxicity, read-across between all molybdenum substances seems generally justified.
- Highly soluble molydates can be used as source chemicals.
- For poorly soluble Mo species, read-across from highly soluble/highly bioaccessible substances is likely to constitute a conservative overestimate.
- Impurities: separate analysis for every compound

Further differentiation for toxicological assessment

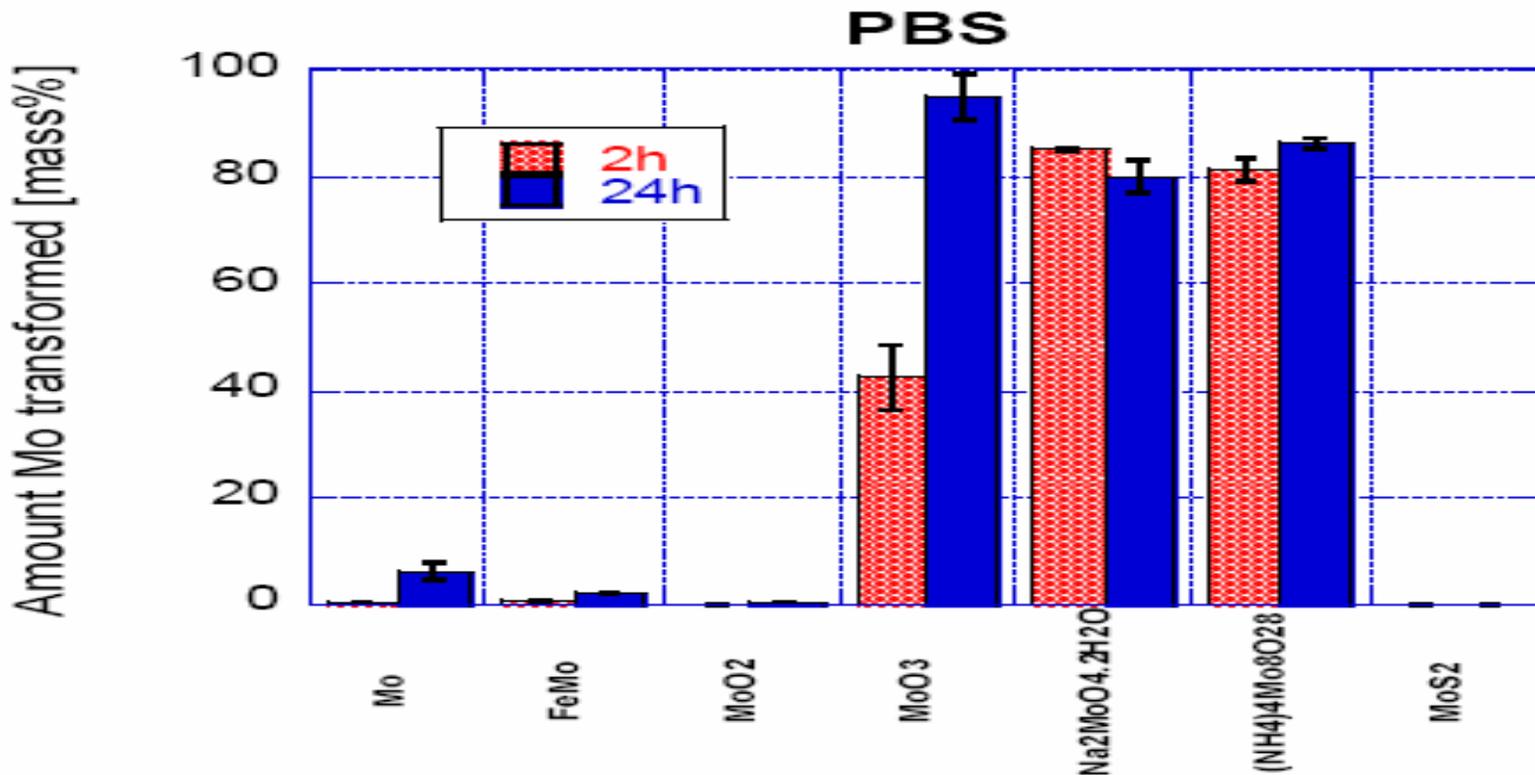


- Based on in vitro bioaccessability studies with artificial body fluids.
 - Loading 0.1 g/L fluid, normalization for particle size distribution, incubation 2 and 24 h.
 - Additional in vivo kinetic data and in vitro dermal absorption studies available.
- Molybdate as only relevant species confirmed.
- Two groups for read across:
 - Highly and moderately bioaccessible molybdenum compounds.
 - Poorly available molybdenum compounds: water solubility well below 10 mg/L, accessibility in physiological media: < 10%.
- Exemption: local inflammatory changes by molybdenum trioxide and species that can liberate H_3O^+ .

Bioaccessibility – results 1 (IMO/EBRC 2008)



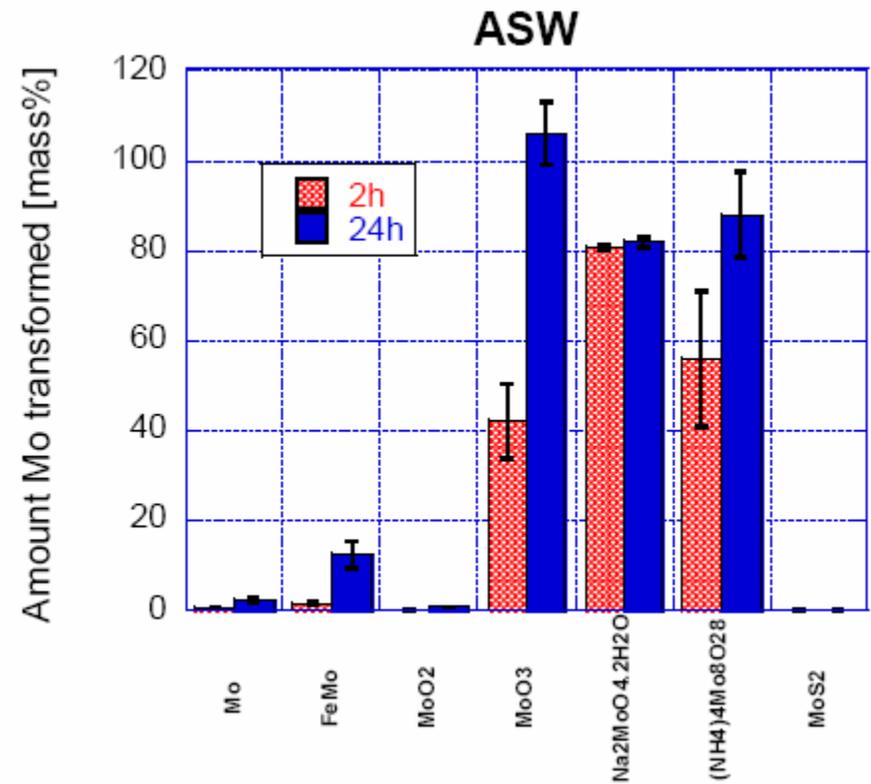
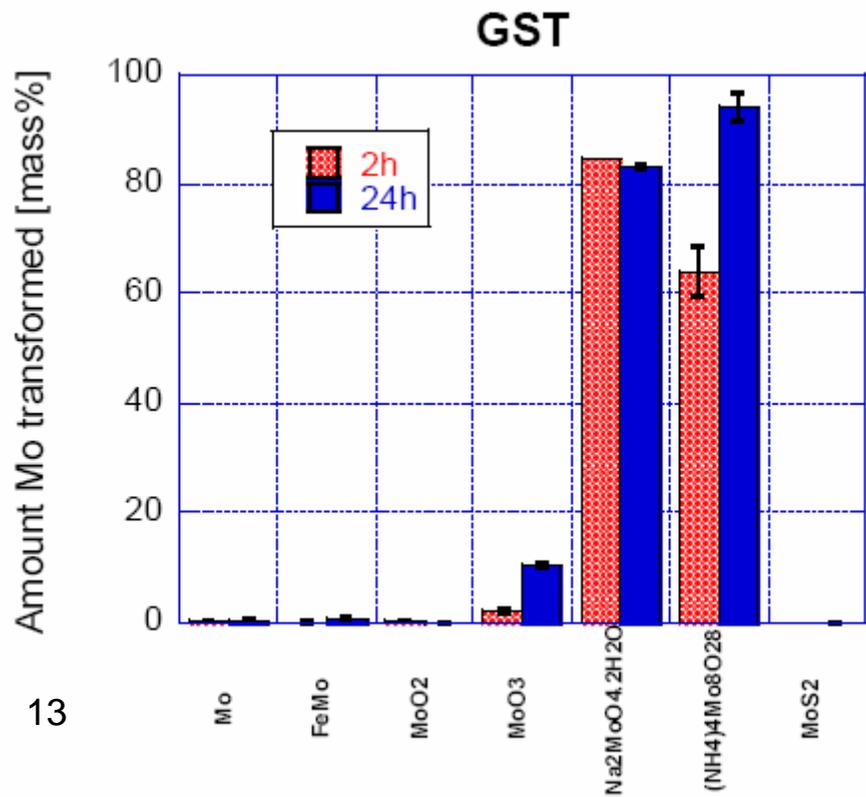
PBS, Phosphate-buffered saline (pH 7.4), is a standard physiological solution that mimics the ion strength of human blood serum. It is widely used in the research and medical health care community as a reference test solution for comparison of data under simulated physiological conditions.



Bioaccessibility – results 2 (IMO/EBRC 2008)



GST: gastric juice (pH=1.5-1.6)
ASW: Artificial sweat solution (pH 6.5)

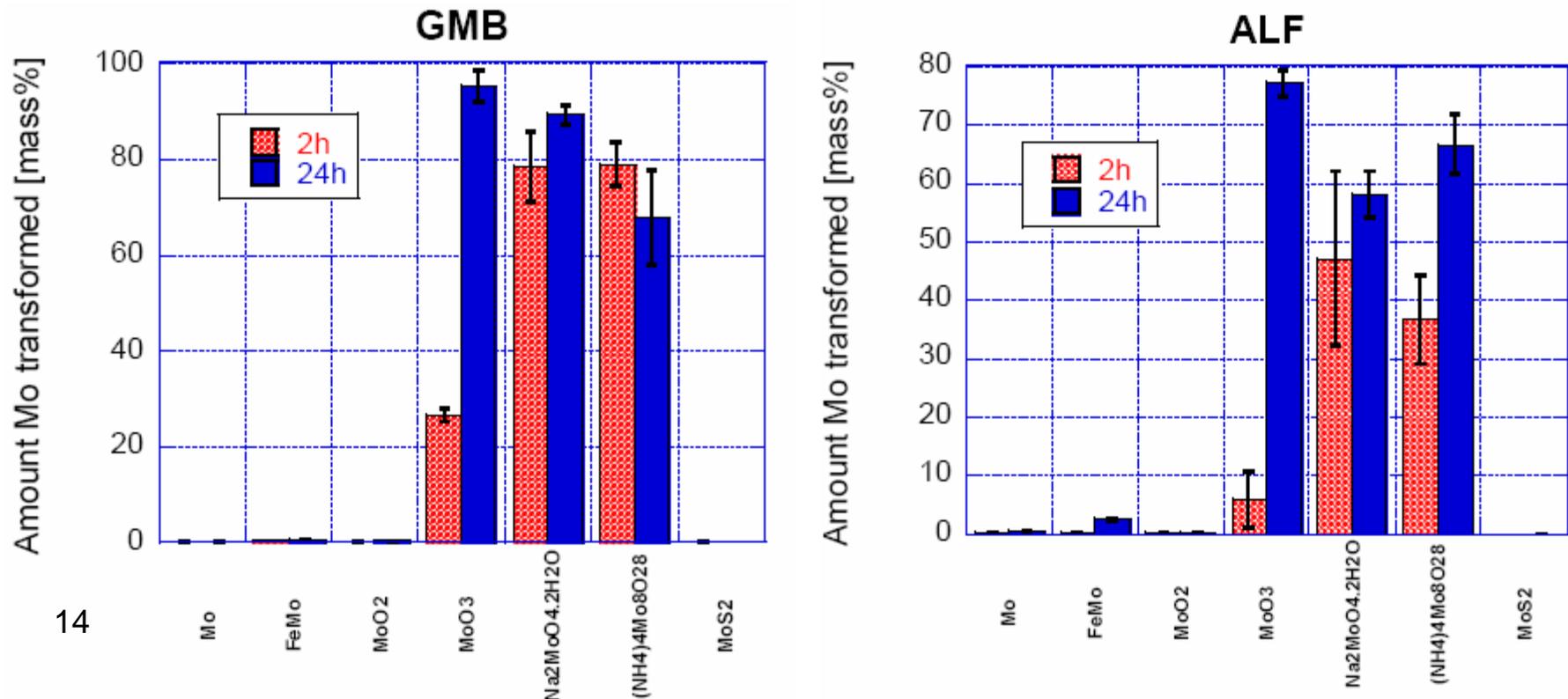


Bioaccessibility – results 3 (IMO/EBRC 2008)



GMB: Gamble’s solution (pH 7.4) mimics interstitial fluid within the deep lung under normal health conditions.

ALF: Artificial lysosomal fluid (ALF, pH 4.5) simulates intracellular conditions in lung cells occurring in conjunction with phagocytosis and represents relatively harsh conditions.



Bioaccessibility – summary of results



- Sodium and ammonium molybdate and MoO_3 dissolved almost completely within 24h in all fluids, with the exception of MoO_3 in gastric juice (only 10% because reaction equilibrium is shifted due to low pH)
- RMC (previous results) also dissolved almost completely within 24h
 - differentiation between MoO_3 and RMC not justified
- Mo metal, FeMo, MoO_2 dissolved to a much lesser degree (~ 0.1 % - 3 %), depending on the medium (one exception: 13% of FeMo dissolved in sweat after 24h)
- MoS_2 was the least bioaccessible compound (\ll 0.1 % dissolved)

Read across overview



Substance/Formula	CAS:	Properties ¹⁾	Read-Across-Grouping Long-term effects	Read-Across-Grouping Acute effects
Roasted Molybdenite Concentrate (formula not available)	86089-09-0	<p><u>soluble</u> molybdenum substances</p> <p>water solubility above ca. 100 mg/L</p> <p>solubility in biological fluids 30-100%</p> <p>"high bioaccessibility"</p>	Grouped based on chemical similarity for long-term, local effects via inhalation (suspected carcinogenicity via inhalation).	Grouped for all acute effects (local and systemic).
Molybdenum Trioxide MoO ₃	1313-27-5			
Sodium Molybdate Na ₂ MoO ₄	10102-40-6		Grouped for all long-term, systemic effects (all release MoO ₄ ²⁻ ion).	
Ammonium Dimolybdate, (NH ₄) ₂ Mo ₂ O ₇	27546-07-2			
Ammonium Heptamolybdate, (NH ₄) ₅ Mo ₇ O ₂₄	12027-67-7			
Ammonium Octamolybdate, (NH ₄) ₄ Mo ₈ O ₂₆	12411-64-2			
Calcium Molybdate CaMoO ₄	7789-82-4			
Iron Molybdate Fe ₂ (MoO ₄) ₃	13769-81-8			
Molybdenum (metal) Mo	7439-98-7	<p><u>Poorly/hardly soluble</u> molybdenum substances</p>	Grouped for all long-term, systemic effects (all release MoO ₄ ²⁻ ion).	Grouped for all acute effects (local and systemic).
Ferromolybdenum Slags (UVCB, formula not available)	84144-95-6	<p>water solubility well below ca. 10 mg/L</p> <p>solubility in biological fluids well below 10%</p>		
Molybdenum Dioxide MoO ₂	18868-43-4	"negligible bioaccessibility"		Conservative read-across to "high bioavailability" group above.

Conclusions



- The read-across strategy was justified by the identification of one species present under relevant physiological conditions in all investigated materials.
- The investigation of the most soluble compound releasing this species was considered a conservative approach.
- Further differentiation was reached considering two basic groups of bioavailability.
- Every endpoint was examined for the appropriateness of read across.
- Exemptions were identified and explained.

Acknowledgement



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