Human health effects of antimony – an update

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Public perception of HH effects of antimony

In the public domain, antimony is said to....
...be highly toxic
...cause cancer
...be a heavy metal
...be “similar” to arsenic

...poses risk to consumers when used as flame retardant in textiles etc.
...leach from PET bottles at dangerous levels

Are these statements true or not.....?
Human health effects of antimony – an update

1. Antimony in a regulatory context

2. EU Risk Assessment for Antimony trioxide
   - Background
   - Short term and chronic effects
   - Exposure assessment for workers and consumers – examples

3. Concluding remarks
## 1. Antimony in a regulatory context

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU RAR ATO concluded</td>
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<td>OECD review of ATO</td>
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<td>REACH registration of 3 antimony substances</td>
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<td>CLP notification</td>
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<td>Canadian review of ATO</td>
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<td>REACH dossiers of 5 antimony substances</td>
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<tr>
<td>US National Toxicology Program (NTP) : chronic testing in rodents ATO</td>
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<tr>
<td>GHS Implementation (Japan, EU, US, Others)</td>
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</tbody>
</table>
2. EU RAR for Antimony trioxide (ATO) Procedure

- Published on the 4th priority list of 793/93/EC on 25 October 2000 / Sweden was Rapporteur Member State, but 27 EU MS involved in detailed scientific discussions / approval

- RAR on ATO only, not considering metal or other Sb substances:
  - HH and ENV effects (hazards)
  - Exposure (occupational/consumer/indirect via the ENV)
  - Risk Characterisation

- ATO has in the meantime also completed review at OECD level

- Focus on this presentation is on ATO and its major uses
### 2. EU Risk Assessment for Antimony trioxide

#### Hazard profile*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Outcome</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin irritation</td>
<td>Not irritating</td>
<td>Not classified</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Not irritating</td>
<td>Not classified</td>
</tr>
<tr>
<td>Sensitisation</td>
<td>Not sensitising</td>
<td>Not classified</td>
</tr>
<tr>
<td>Acute oral</td>
<td>Not acutely toxic via oral route, LD50 &gt; 20000 mg/kg</td>
<td>Not classified</td>
</tr>
<tr>
<td>Acute dermal</td>
<td>Not acutely toxic via dermal route, LD50 &gt; 8300 mg/kg</td>
<td>Not classified</td>
</tr>
<tr>
<td>Acute inhalation</td>
<td>Not acutely toxic via inhalation route, LC50 &gt; 5.2 mg/L</td>
<td>Not classified</td>
</tr>
<tr>
<td>Repeated dose toxicity</td>
<td>No systemic toxicity, oral NOAEL = 1686 mg/kg/day</td>
<td>Not classified</td>
</tr>
<tr>
<td>Mutagenicity</td>
<td>Not mutagenic/clastogenic</td>
<td>Not classified</td>
</tr>
<tr>
<td>Reproductive toxicity</td>
<td>Not teratogen, Not toxic for reproduction</td>
<td>Not classified</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>Category 3 inhalation, local effects, NOAEC=0.51 mg/m³: suspected of causing cancer by inhalation</td>
<td>Category 3 (DSD)</td>
</tr>
</tbody>
</table>

* guideline, state-of-the-art data, mostly unpublished
2. EU Risk Assessment for Antimony trioxide
Short term effects – overall conclusions

- Prior to RAR phase, data base on ATO was fragmentary, of poor quality and many data gaps – now essentially complete

- Antimony trioxide is void of:
  
  acute toxicity via oral, inhalation or dermal routes
  sensitisation via skin or respiratory system
  eye irritation effects

- Some residual concerns over skin irritation in workers resolved as follows…
2. EU Risk Assessment for Antimony trioxide
Skin irritation - RAC conclusion

- Sweden proposed a legal classification for ATO as skin irritant

  - However, the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) concluded that a classification with “irritating to skin” was **not** warranted, since special conditions were required:
    - substantial heat, physical obstruction sweat glands
    - high (inert) dust exposure levels

  - Furthermore, it was unclear whether ATO was the only chemical substance to which these workers had been exposed (ECHA/PR/09/09, Helsinki, 06 July 2009).
2. EU Risk Assessment for Antimony trioxide chronic / repeated dose toxicity

- Repeated **inhalation** exposure to ATO = local effects in the lung
- NOAEC of 0.51 mg/m³ is derived from a 12 month inhalation exposure study in rat ("inflammation" at higher exp. concentrations)
- Pneumonia-like symptoms in a 19d inhalation development toxicity study

- 2 repeated dose oral studies => Q: ATO toxic to liver ?
  - absence of histological changes
  - no clinical signs of antimony intoxication whatsoever
  - conclusion: findings regarded as adaptive response, or merely incidental to treatment with Antimony trioxide, but not substance-specific

- NOAEL of 1686 mg/kg bw/d for repeated dose **oral** toxicity
2. EU Risk Assessment for Antimony trioxide Genotoxicity

ATO tested in wide array of genotoxicity assays *in vitro* and *in vivo*:

- no gene mutations in *in vitro test systems*
- chromosome aberrations seen in some *in vitro assays*
- re-testing *in vivo* incl. 21d repetitive oral testing at 1,000 mg/kg bw/d did not induce either chromosome aberrations or micronuclei (mouse and rat test systems)
- result verified by toxicokinetics/tissue distribution data (bone marrow exposed)

ATO = non-clastogenic and non-mutagenic
2. EU Risk Assessment for Antimony trioxide
Reproduction toxicity

Teratogenicity:
ATO tested negative for developmental toxicity (rats)

Fertility:
- detailed toxicokinetic study revealed no relevant extent of
distribution to organs of reproductive function
- no effects whatsoever seen on reproductive organs in 90d oral
toxicity study (rats) up to doses of approx. 1,6000 mg/kg bw/d

Overall conclusion:
- no concerns for reproduction toxicity
Three chronic inhalation studies with ATO in rats are available:

- two animal studies = neoplastic properties
- one animal study = negative results

- the assumed mechanism for carcinogenicity is **overload** with inert particles coupled with impaired lung clearance, followed by a secondary sequence of inflammatory response, fibrosis and tumours

- this mechanism is widely considered of **limited relevance for humans**

Quantitative risk characterisation = NOAEC of 0.51 mg/m³ derived for local repeated dose toxicity was also proposed for carcinogenicity
2. EU Risk Assessment for Antimony trioxide
Toxicokinetics

Oral absorption:
- studies via oral application => 1% oral absorption of Sb(III) substances

Dermal absorption:
- in vitro percutaneous study => 0.26% dermal absorption for ATO
  also applicable to other Sb(III) substances

Inhalation absorption:
- physical particle size and density for 8 different samples of ATO
  + MPPD model and values on gastrointestinal tract absorption
  => absorption factor of 6.82%
2. EU Risk Assessment for Antimony trioxide
Relevant exposure scenarios:

- Industry survey on occupational exposure
  - Development of sector-specific questionnaires covering environmental and human health issues (exposure scenarios)

- Consumer exposure
  - Assessment based on a detailed description of the use in consumer products, composition and market volume

- Indirect exposure / General population
  - Based on environmental emissions and resulting concentrations in air, water and food
  - Assessment based on „real“ emission-data as well as on model-predictions
2. EU Risk Assessment for Antimony trioxide Exposure of workers and consumers - examples

1. Workers exposure
   => Primary production of antimony substances

2. Consumer exposure
   1. Use of PET bottles
      - leaching of “Sb” into liquids
   2. Flame retardants used in textiles
      - skin and mouth (children) contact
   3. Exposure via indoor air (dust)
      - abrasion from textiles, “chalking” of plastics
2. EU Risk Assessment for Antimony trioxide Exposure of workers - examples

1 ES for production of diantimony trioxide

6 ES for industrial uses of ATO:
- PET production
- Flame retardant in plastics and rubber industry
- Flame retarded textiles
- Glass, enamels, functional ceramics and semi-conductors
- Pigments, paints, coatings, ceramics, brake pads, fine chemicals
- Wood adhesives

2 ES for professional uses of ATO:
- Use of ATO containing preparations
- Use of ATO containing articles

Jena, 22 August 2011
2. EU Risk Assessment for Antimony trioxide

Exposure estimates for the production of ATO

Inhalation exposure (RWC ) and RCR (in brackets):

<table>
<thead>
<tr>
<th>Workplace</th>
<th>Method used for inhalation exposure assessment</th>
<th>Inhalation exposure estimate (RCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion</td>
<td>measured data</td>
<td>0.29 mg/m³ (0.58)</td>
</tr>
<tr>
<td>Refuming</td>
<td>measured data</td>
<td>0.24 mg/m³ (0.47)</td>
</tr>
<tr>
<td>Packaging</td>
<td>measured data</td>
<td>0.21 mg/m³ (0.42)</td>
</tr>
</tbody>
</table>

Dermal exposure:

- Low dermal absorption of 0.26 % (ECB, 2008)
- Route is not a relevant exposure path and not assessed in ES
- Risk phrase in ES: “…dermal exposure has to be minimised to an extent as technically feasible when working under conditions of substantial heat and sweat…”


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2. EU Risk Assessment for Antimony trioxide Exposure: Use in production of PET bottles

Used as a catalyst in PET (~300 ppm), covalently bonded

Exempted from HH assessment under REACH acc. to Article 14 (5)a, but covered in EU-RAR

PET bottle (used as container for drinking water)

- Typical: 0.343 µg Sb/L => 0.014 µg Sb$_2$O$_3$/kg bw/day
- RWC: 0.879 µg Sb/L => 0.035 µg Sb$_2$O$_3$/kg bw/day

WHO drinking water guideline value = 20 µg Sb/L

Guideline derivation: allocation to water 10% of TDI

60 kg adult, 2 litres/day

TDI of 6 µg Sb/kg bw/day based on NOAEL of 6 mg Sb /kg bw/day, drinking water study with (highly soluble) APT, high uncertainty factor (1000)
2. EU Risk Assessment for Antimony trioxide

Exposure: Flame retardants used in textiles

Fabrics (including PET fibre): sitting on upholstery
- RWC (dermal) 1.8 μg Sb₂O₃/kg bw/day (RCR = 1.1 * 10⁻⁵)

Chewing on toys (including PET fibre)
- RWC (oral) 0.44 μg Sb₂O₃/kg bw/day (RCR = 2.6 * 10⁻⁵)

Service life/ Wearing of clothes containing antimony trioxide for fire resistance

<table>
<thead>
<tr>
<th>Route of exposure</th>
<th>Exposure estimate (RCR)</th>
<th>Method used, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (child)</td>
<td>0.036 μg/kg bw/d (2.1 * 10⁻⁶)</td>
<td>Exposure: (weight of textile mouthed * release rate)/ body weight/day</td>
</tr>
<tr>
<td>Dermal (child)</td>
<td>Local: 1.1 μg/cm²/d Systemic: 360 μg/kg bw/d (2.1 * 10⁻²)</td>
<td>Exposure (local): (weight of clothes * release rate)/ skin area/day Exposure (systemic): (weight of clothes * release rate)/ body weight/day</td>
</tr>
<tr>
<td>Inhalation</td>
<td>-</td>
<td>Inhalation exposure is insignificant due to the extremely low vapour pressure of diantimony trioxide. However, exposure due to wear debris was covered by the indoor air scenario.</td>
</tr>
</tbody>
</table>

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2. EU Risk Assessment for Antimony trioxide Exposure: Indoor air scenario

House-dust as surrogate for particles released from e.g. back-coated textiles (abrasion/wearing) or chalking from plastics

House dust:

- Typical = 13 µg Sb/g => 15.6 µg Sb₂O₃/g
- RWC = 50 µg Sb/g => 60 µg Sb₂O₃/g

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Oral (child)</td>
<td>RWC: 0.6 µg/kg bw/d (3.6 * 10⁻⁵)</td>
<td>ingested house dust * conc of Sb2O3 in house dust); considering hand-to-mouth behaviour of small children</td>
</tr>
<tr>
<td>Inhalation</td>
<td>RWC 3.15·10⁻⁶ mg Sb₂O₃/m³ (3.2·10⁻⁵)</td>
<td>concentration of Sb₂O₃ in house dust * indoor air dust levels (52.3µg/m³).</td>
</tr>
</tbody>
</table>

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Concluding remarks

1. Is antimony trioxide “highly toxic”…?
   - It is of low order of toxicity via the oral route;
   - Inhalation is of concern at high (occ.) exposure levels > above OEL;
   - Associated with overload because of inertness of ATO;
   - Threshold mechanism: overload ▶ inflammation ▶ secondary cancer

2. This particular mechanism is under discussion for its limited relevance to humans

3. Leaching of “Sb” into PET bottled liquids is within guideline limits, which in turn reflect inherently very conservative safety factors

4. Use as flame retardant has been shown to be associated with high safety margins
Thank you for your attention!