campine

committed and competent

ATO	ROC Assessment criteria
	Known Human carcinogen
Human studies	Sufficient evidence in human studies Causal relationship between ATO exposure and human cancer
	Reasonable anticipated human carcinogen
Human studies	Limited evidence Causal indications are credible ?
Animal studies	Increased incidence of malignant and-or malignant/ benign tumours
	In multiple species or multiple sites
	By multiple exposure routes
	Unusual degree : incidence, site, type, age of onset
	Less than sufficient data from human and animal - HOWEVER
	Structurally related to compound with carcinogenic properties
	Convincing ATO acts through mechanism indicating likely to be cancerogenic

Campine's data

100 years in production business
No cases of lung cancer

Health monitoring workers by independent health service

- Very weak relationship between changes in pulmonary function parameters and years of exposure.
- No clear relationship between mean urinary antimony concentration and
  - Liver function
  - Changes in pulmonary function parameters
- Chest X-ray's (> 20 year for ATO workers)
  - No pulmonary lesions detected

Evidence from animal studies ?

NTP TR590

Body weights – Clinical signs

	Rat male	Rat female	Mice male	Mice female
Body weights >10% reduction controls Mid study	30 mg/m^3	3, 10 , 30 mg/m^3	30 mg/m^3	30 mg/m^3
Body weights >20% reduction controls end study	30 mg/m^3	10 , 30 mg/m^3	30 mg/m^3	30 mg/m^3 3 (and 10) mg/m3 gained weight /control
	Overdosing	Overdosing		

Clinical findings: abnormal breading, cyanosis, thinness in males and females

Evidence from animal studies ?

TR590

Blood Sb burden

	µg Sb/g blood	Female rats time dependent increase	Female mice Independent of time
3mg/m³	Day 61	7± 0.4	0.04 ± 0.002
	Day 124	16 ± 1.0	0.06 ± 0.001
	Day 271	40 ± 4.0	0.05 ± 0.006
	Day 369	51 ± 2.3	0.05 ± 0.003
	Day 551	63 ± 4.0	0.06 ± 0.010
10mg/m³	Day 61	18 ± 0.8	0.083 ± 0.021
	Day 124	40 ± 1.5	0.089 ± 0.002
	Day 271	89 ± 2.2	0.091 ± 0.002
	Day 369	102 ± 2.7	0.088 ± 0.003
	Day 551	149 ± 8.5	0.087 ± 0.004

Blood Sb burden: mice < rat

Evidence from animal studies ?

Focus entirely on one inhalation study

- ATO (toxicokinetics) species specific behaviour

  rat /mice (supported by many studies *)

  - Mice do not mimic the human situation
    almost no absorption
    no time dependent systemic increase

*Goodwin, L. G., & Page, J. E. (1943). A study of the excretion of organic antimonials using a polarographic procedure. *Biochemical Journal*, *37*, 198–209.

*Dieter, M. P. (1992). *Toxicity studies of antimony potassium tartrate in F344 / N Rats and B6C3F 1 Mice (Drinking Water and intraperitoneal injection studies) National Toxicology Program*.

Evidence from animal studies ?

TR590

Lung tissue Sb burden

	µg Sb/g lung	Female rats	Female mice	Mice/Rat %
3mg/m3	Day 61	437± 14	561 ± 12	128
	Day 124	689 ± 49	683 ± 59	99
	Day 271	838 ± 41	802 ± 22	96
	Day 369	765± 179	979 ± 54	128
	Day 551	978 ± 86	1,472 ± 116	151
10mg/m3	Day 61	1,203± 52	1,233 ± 42	102
	Day 124	1,571 ± 59	1,476 ± 33	94
	Day 271	1,983 ± 92	2,678 ±135	135
	Day 369	1,976 ± 93	3,798 ± 232	192
	Day 551	1,801 ± 278	4,188 ± 609	233

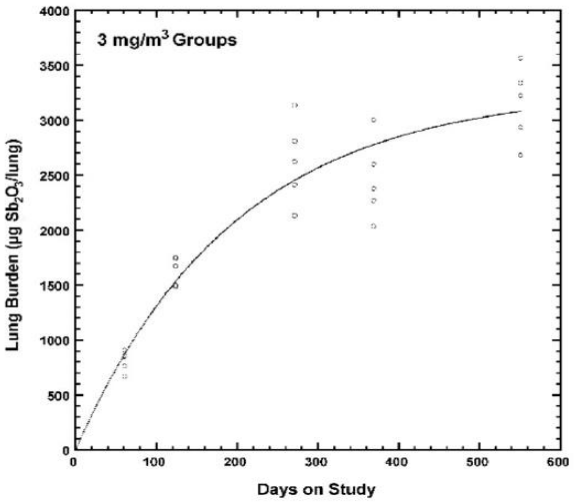
ATO Lung tissue burden in mice and rats (From table G8/ G3 - NTP 2017a)

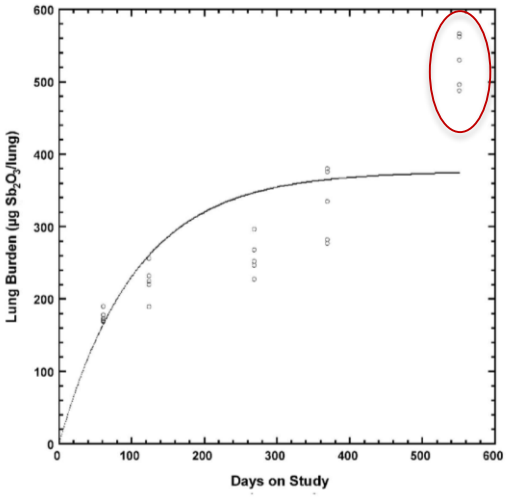
Evidence from animal studies ?

TR590

Sb lung clearance

Rat 3mg/m^3 Mice





Lung tissue burden: mice > rat

TR590

Lung effects

Per 50 0/3/10/30 mg/m³	Rat male	Rat female	Mice male	Mice female
Alveolar /bronchiolar adenoma	3/ 4/ 6/ 8	0/ 2 / 6/ 5	NR	1 / 10 / 19/ 8
Alveolar /bronchiolar adenoma or carcinoma	3/ 4/ 8/ 8	NR		
Alveolar /bronchiolar carcinoma	NR	NR	4/18/20/ 27	2/ 14 / 11/ 11
Historical incidence	**0 -3 (0-6%)**	**0**	**13-16 (26-32%)**	**3-9 (6 -18 %)**

Thomas, A. C., & Mattila, J. T. (2014). “Of mice and men”: Arginine metabolism in macrophages. *Frontiers in Immunology*, *5*(OCT), 1–7.

Martinez, F. O., Helming, L., Milde, R., Varin, A., Melgert, B. N., Draijer, C., … Gordon, S. (2013). Genetic programs expressed in resting and IL-4 alternatively activated mouse and human macrophages: Similarities and differences. *Blood*, *121*(9), 57–70.

Evidence from animal studies ?

Focus entirely on one inhalation study

- highest doses cause overt toxicity and cannot be taken into account

- Toxicokinetics mice is different from rat/human

- lung overload (rat and mice)
  - ATO accumulation in lung mice > rat
  - condition not occurring in human

- lung lesions (adenoma and or carcinoma)
  - rat is over sensitive and not relevant for human
  - mice natural high background
    (male mice at same level as historical controls)

* Warheit, D. B., Kreiling, R., & Levy, L. S. (2016). Relevance of the rat lung tumor response to particle overload for human risk assessment—Update and interpretation of new data since ILSI 2000. *Toxicology*, *374*, 42–59
* ECETOC (2013) Technical report 122