Bundesanstalt für Arbeitsschutz
und Arbeitsmedizin

May TiO_2 be carcinogenic to humans?

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Current RAC recommendation on TiO_2 classification

Category 2: *Suspected* of *causing cancer (inhalation)*

not *Category 1B: sufficient evidence in experimental animals*

– **restricted to inhalation route**

– **caused by respirable fraction only**

– **covers all forms of respirable TiO_2**

including nano-TiO_2 but excluding WHO fibres

RAC, Risk Assessment Committee of EU Chemicals Agency

Status of discussion before RAC

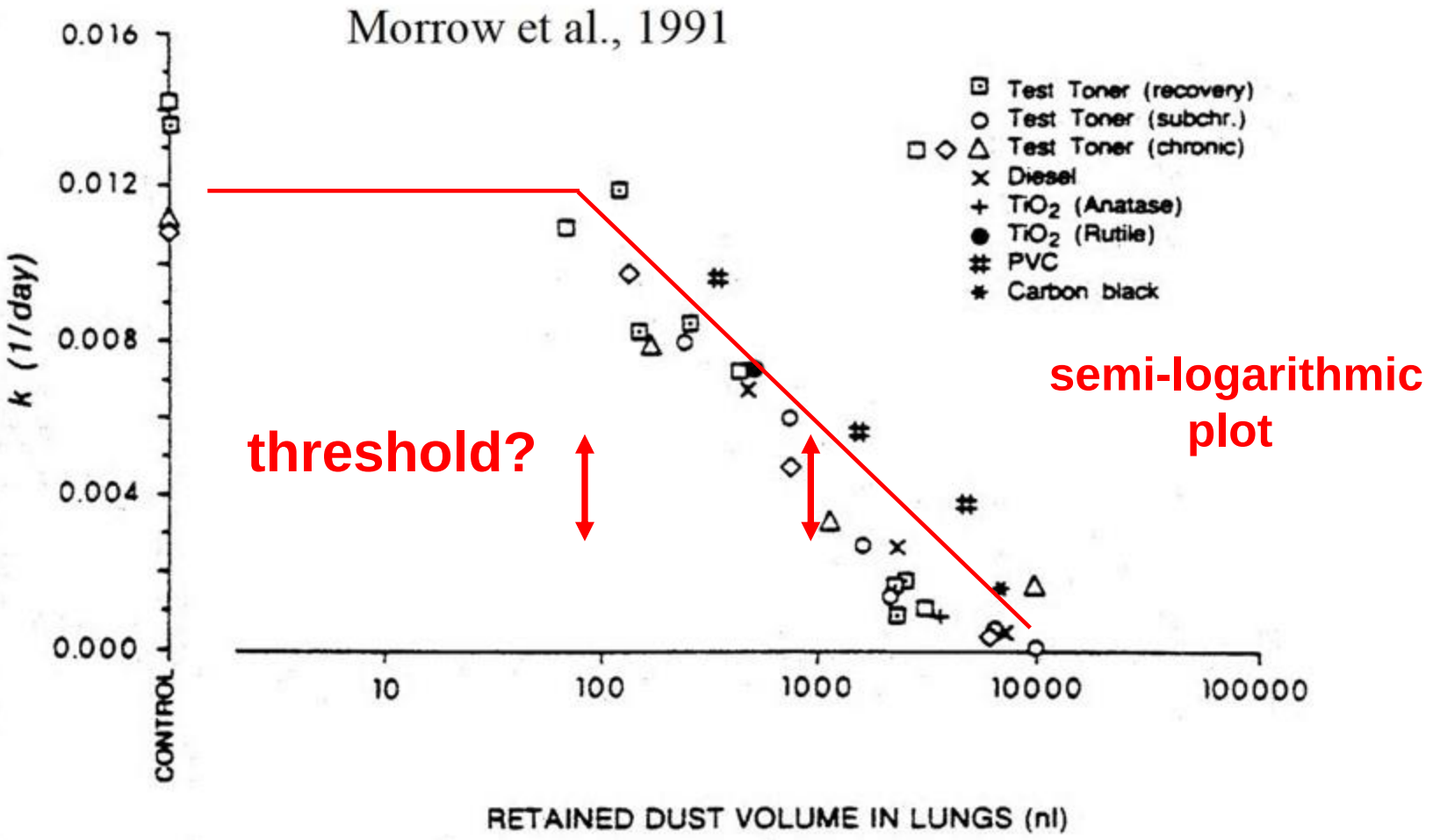
- IARC 2006: titanium dioxide & carbon black:
  sufficient evidence in experimental animals *(rat)* for *(inhalation)* carcinogenicity *(Baan et al., 2007)*

- opposing position….

  rat is no adequate species to study GBP carcinogenicity

  lung tumours only due to lung overload

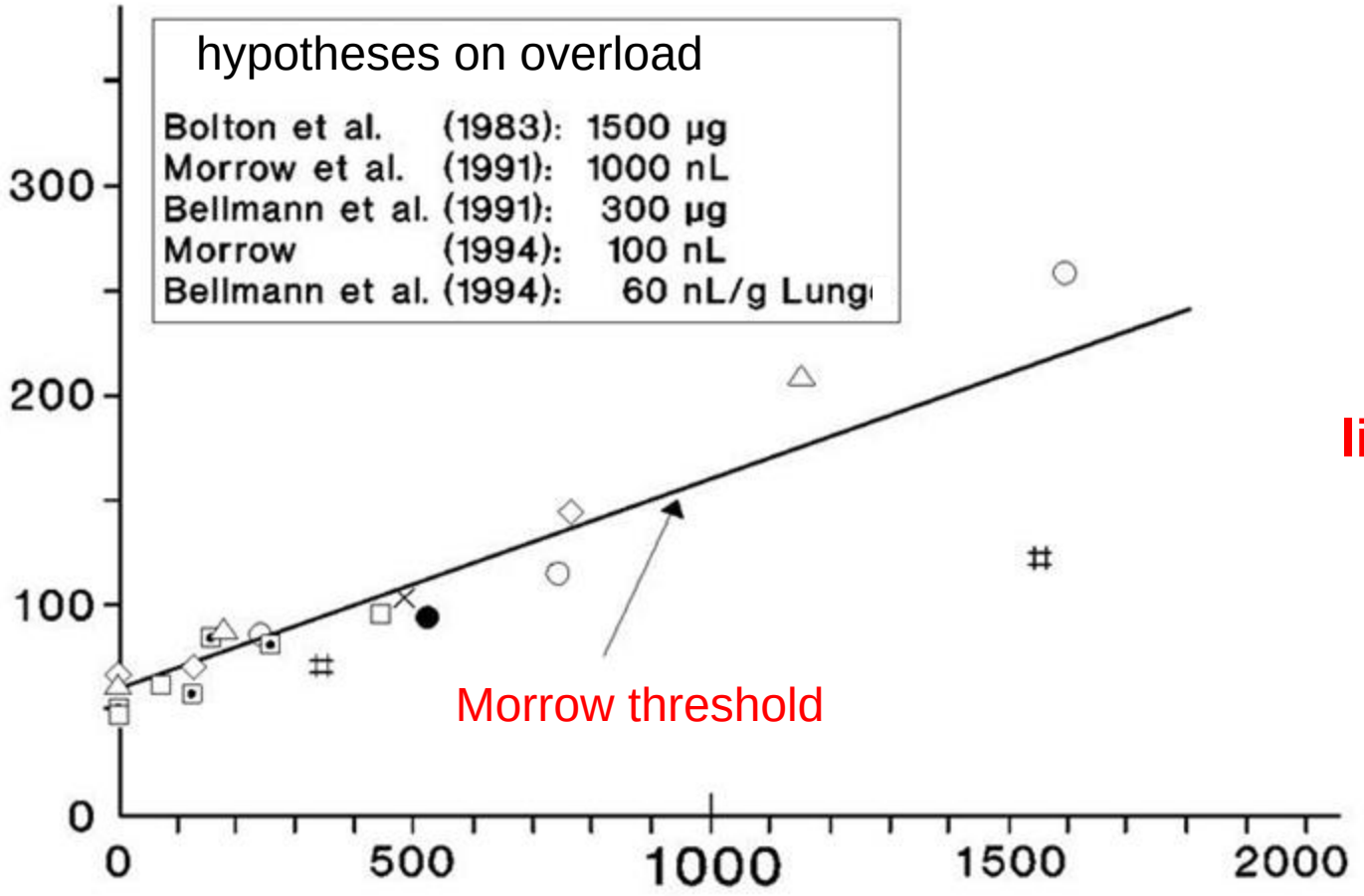
Lung clearance of PSLT : where is the threshold?



PSLT, poorly soluble low toxicity particles

No threshold in ↓ clearance with increasing lung dust load!

elimination half-life (days)



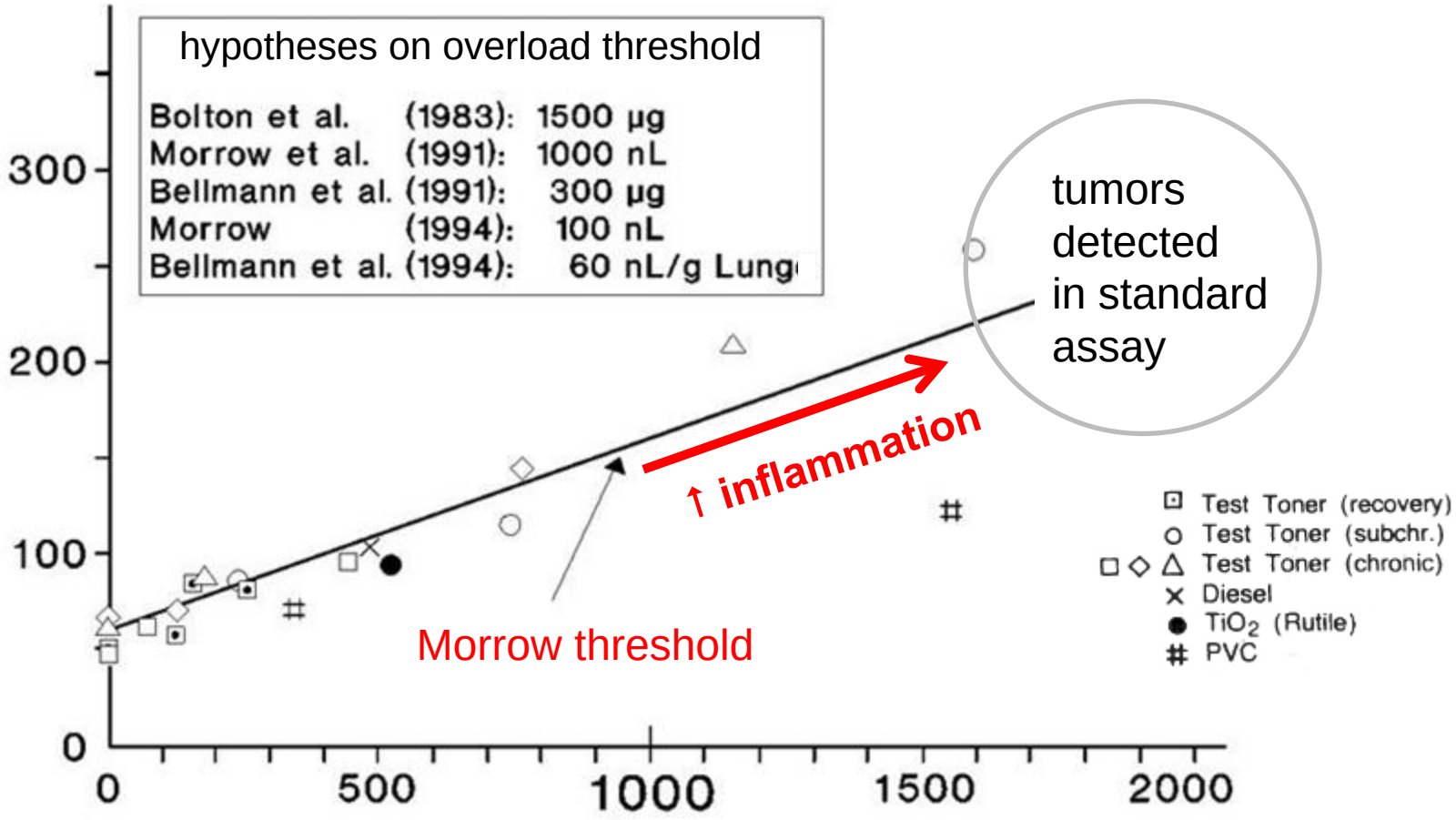
linear plot

retained dust volume per rat lung (nl)

Roller et al. 2003

No threshold in ↓ clearance with increasing lung dust load

elimination half-life (days)



retained dust volume per rat lung (nl)

graph: Roller et al. 2003 Eur J Oncol 8(4), 277, changed,
symbols in Roller taken from Morrow et al (1991) J Am Coll Toxicol 10 No.2

Table 2. Nonfibrous particles causing intrapulmonary lung tumors in rodents exposed by inhalation.

Nonfibrous particles	Rat	Mouse	Hamster	IARC[a]	Reference
Alpha-emitting particulate radionuclides	+	+	±	X	(16–19)
Antimony ore	+	ND	ND	X	(20)
Antimony trioxide	+	ND	ND	2B	(20)
Beryllium fluoride	+	ND	ND	1[b]	(21,22)
Beryllium hydrogen phosphate	+	ND	ND	1[b]	(22,23)
Beryllium metal	+	±	ND	1[b]	(22,24)
Beryllium sulfate	+	ND	ND	1[b]	(13,22)
Beryl ore	+	ND	–	X	(25)
Beta-emitting particulate radionuclides	+	+	–	X	(26–28)
Cadmium chloride	+	–	–	1[b]	(22,29,30)
Cadmium oxide	+	+	–	1[b]	(22,29,30)
Cadmium sulfate	+	–	–	1[b]	(22,29,30)
Cadmium sulfide	+	–	–	1[b]	(22,29,30)
Calcium chromate	+	+	ND	1[b]	(8,31,32)
Chromium dioxide	±	ND	ND	3[b]	(8,33)
Carbon black	+	–	ND	2B	(5,6,34)
Coal dust	±	ND	ND	X	(35)
Coal tar aerosol	+	+	ND	1	(3,36,37)
Nickel carbonyl	+	ND	ND	1[b]	(8,38)
Nickel metal	+	–	ND	1[b]	(8,39)
Nickel oxide	+	±	–	1[b]	(8,10,16)
Nickel subsulfide	+	–	ND	1[b]	(8,11)
Oil shale dust	+	ND	ND	X	(40,41)
Polymeric methylene diphenyl diisocyanate	+	ND	ND	3	(3,42)
Silica (crystalline)	+	–	ND	2A	(43–45)
Solvent-refined coal solids	+	ND	ND	X	(46)
Talc (asbestos-free)	+	–	–	3	(3,16,47)
Titanium dioxide	+	–	ND	3	(6,48,49)
Titanium tetrachloride (hydrolysis products)	+	ND	ND	X	(50)
Volcanic ash	+	ND	ND	X	(51)
Zinc manganese beryllium silicate	+	ND	ND	X	(23)

Abbreviations: ±, limited; +, positive; –, negative; X, not classified by IARC. [a]IARC classification for human carcinogenesis, regardless of target organ or exposure route. [b]IARC classification for family of compounds rather than individual compound.

Lung carcinogenicity:

mice & hamster adequate species?

ND, no data

Mauderly et al. 1997

baua:

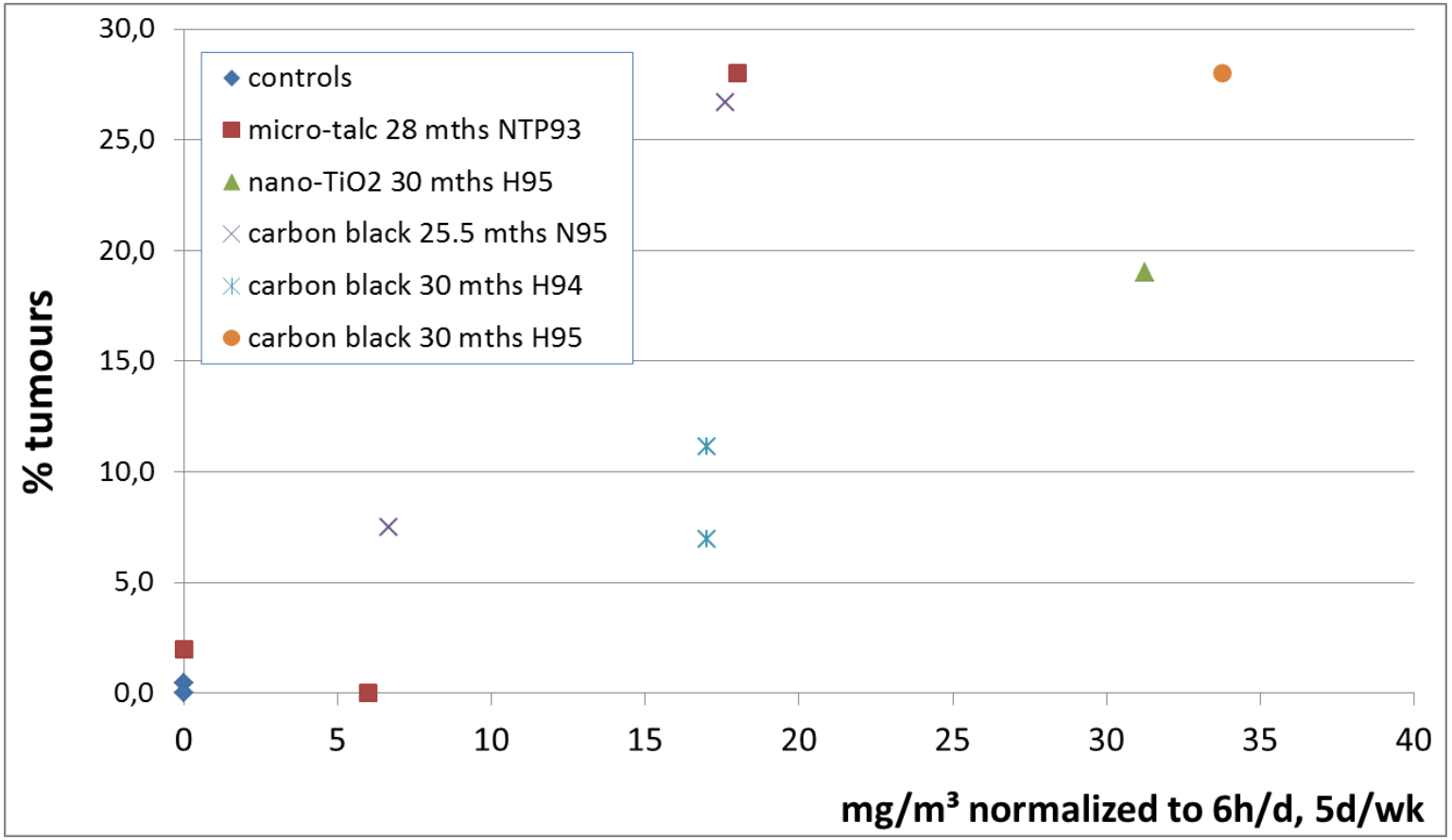
PSLT lung carcinogenicity (data) in different species?

hamster:
negative with e.g. benzo(a)pyrene & vinyl chloride.

mouse:
negative with crystalline silica

monkeys
negative:
to few animals studied, only 2 years duration.

PSLT inhalation carcinogenicity in female rats



selected data, lower concentration range, cystic keratinizing lesions excluded

H94 Heinrich et al. 1994; H95 Heinrich et al. 1995; N95 Nikula et al. 1995; NTP93, NTP 1993 TR

Be aware…..

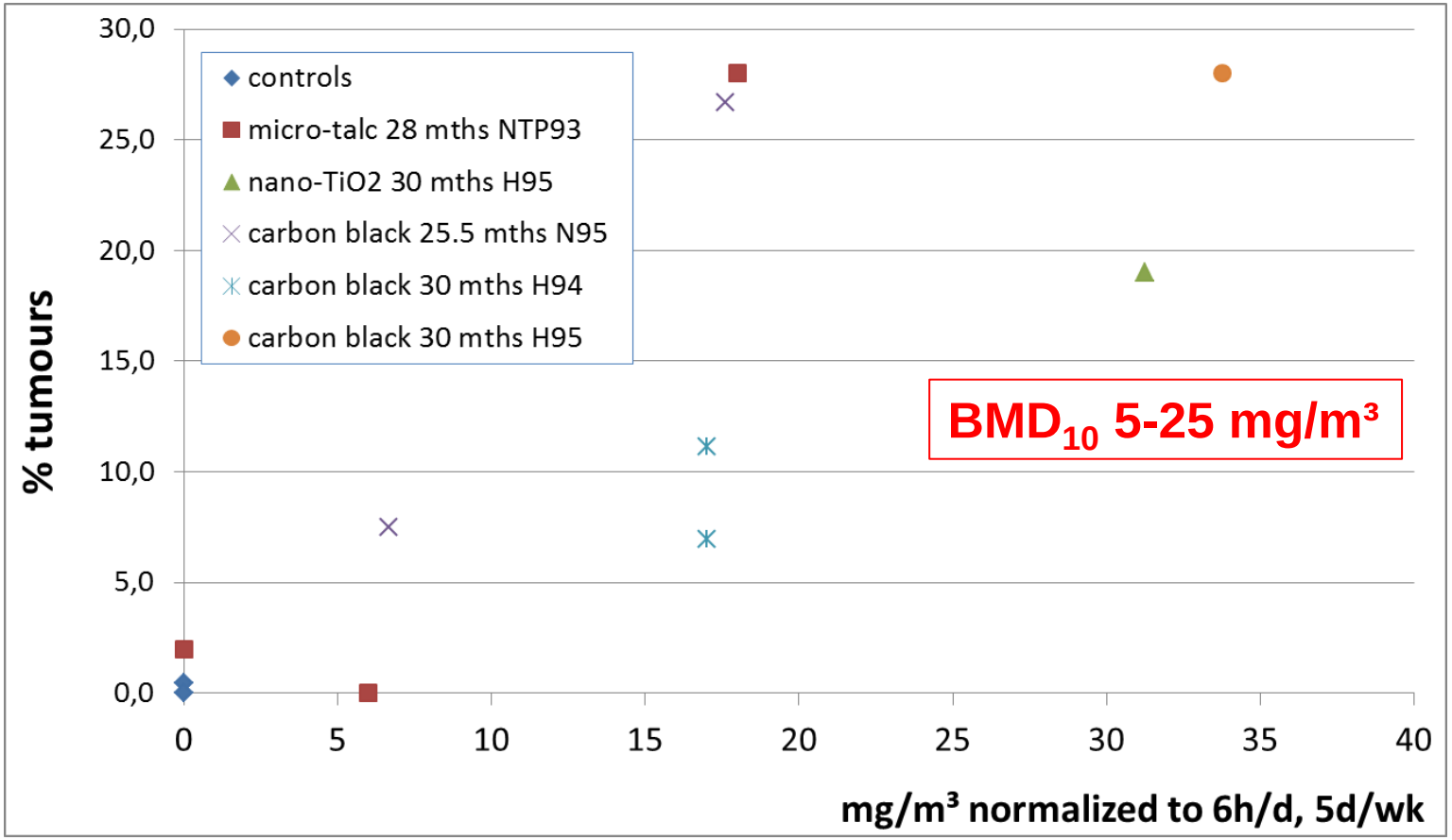
…..that RAC did not (and could not)

consider and review all data

relevant to (PSLT) classification:

- **focus was on TiO_2 classification**
- **allowed to include only data fed into RAC discussion (classification dossier, public consultation)**

PSLT inhalation carcinogenicity in female rats



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Why is epidemiology not positive?

TiO_2: occupational exposures low/generally below OELs

respirable fraction <1 mg/m³ (TWA)

(Hext et al. 2005; Boffetta et al. 2004)

coal mine dust

respirable fraction ~1.5 mg/m³

mean average work-life exposure (Graber et al. 2014)

- lung cancer prevalence in humans relatively high (5-7%)
- rather low carcinogenic potency including nanosized PSLT even in rat (https://www.baua.de/DE/Aufgaben/Geschaeftsfuehrung-von-Ausschuessen/AGS/pdf/Nanoscaled-GBP.pdf?__blob=publicationFile&v=2; Gebel Arch Tox 2012)
- humans likely less sensitive compared to rats

Type of PSLT induced lung tumours in rats

- **squamous cell carcinoma**
- **bronchio-alveolar adenoma and adenocarcinoma**
- **cystic keratinizing lesions** *(Boorman et al. 1996)*

i) squamous metaplasia with marked keratinization (non-neoplastic lesion)
ii) pulmonary keratinizing cysts (not yet considered as neoplasms)
iii) cystic keratinizing epithelioma (benign tumours)
iv) cystic keratinizing pulmonary squamous cell carcinoma (malignant tumours)

grey colour: not relevant for human cancer evaluation

PSLT tumours and CLP classification criteria

- **mainly female rats**
- **majority of tumours occurred late in life**
- **tumours at higher exposure levels (low potency)**
- **practical threshold** *(inflammation-mediated genotoxicity)*
- **no multisite carcinogen**
- **monkeys and humans presumably less sensitive**
- **species-specificity / AOP difference rat vs humans not proven**

Summary

- **TiO_2 is a PSLT particle**
- **PSLT particles share mode of toxic action**
- **rat develops lung tumours at high exposure conc.**

  (low potency carcinogen)
- **currently not conclusively proven that rat tumours are species specific, i.e. not relevant to humans**
- **lung tumours:**

  1 species, mainly 1 sex, not multisite

⇒ **suspected to cause cancer in humans**

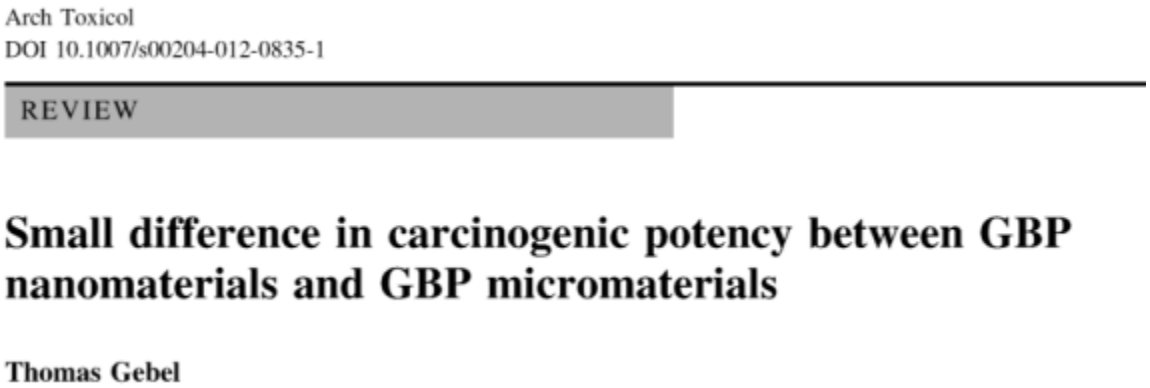
backup

Comparative carcinogenic potency

- rat inhalation studies: PSLT nanomaterials are ~ 2-3 times more potent cf. PSLT micromaterials related to mass conc.

- no relevant difference +/- diesel data: particle is toxic principle

conclusion: potency difference between PSLT nanomaterials and PSLT micromaterials for OEL derivation is low when using the rat carcinogenicity studies



Arch Toxicol
DOI 10.1007/s00204-012-0835-1

REVIEW

Small difference in carcinogenic potency between GBP nanomaterials and GBP micromaterials

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Gebel (2012) Arch Toxicol. 2012; 86(7):995-1007.