

**Comments on the draft NIOSH CURRENT
INTELLIGENCE BULLETIN:
Evaluation of Health Hazard and Recommendations
for Occupational Exposure to Titanium Dioxide**

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Aim of presentation

- To draw attention to the strengths of all 3 cohort studies (the CIB evaluation focuses too much on “*methodologic and epidemiologic limitations*”)
- To draw attention to the limitations of the quantitative risk assessment which is driven by tumor responses at very high doses and ignores the evidence from more relevant levels of exposure

Evaluation of Human Studies

1. Boffetta et al (2004)

- Study covers 2/3 of the total 22,000 subjects, but no methodological limitations are listed.
- CIB Summary states “Nonmalignant respiratory disease was not increased significantly (i.e., $p < 0.05$) in any of the studies”.

In fact, deficits of nonmalignant respiratory disease in all 3 studies including the 202 obs versus 228 exp deaths in this study.

- CIB comments about lack of power of studies to detect possible TiO₂ pneumoconiosis deaths and lack of reporting of such deaths (line 719) but only mentions the two US studies.

The Boffetta study had much greater power, and is certain to have commented on an unusual pattern of pneumoconiosis deaths given the evident interest in a possible association between TiO₂ exposure pleural plaques and thickening (see discussion of pleural cancer by Boffetta et al).

Evaluation of Human Studies

1. Boffetta et al (2004)

Low Power?

Lines 3141-50 argue that a significant dose-response relationship for TiO₂ exposure and lung cancer would not be expected to be observed in the European study because the upper confidence limit on excess risk at the median cumulative exposure is estimated to be quite low.

Power of Boffetta study

- Cumulative exposure in the highest quartile group is much more relevant (mid point estimated to be 56.5 and 78.1 mg/m³ years i.e.29 and 39 times higher than the median cumulative exposure value)
- 78.1 mg/m³ years equate to average lifetime exposures of 1.74 mg/m³ and Table E-2 indicates that the upper confidence limits on excess risk at that concentration correspond to a relative risk of 1.5 to 1.7
- The CIB correctly states that Boffetta et al. (2004) does not provide information on study power, but the full report of the European study (Boffetta et al, 2003) does discuss the power of the study and states that *“in the internal analysis, the power of the study to detect (at a level of 0.05) a relative risk of 1.7 in the highest versus the lowest quartile of cumulative exposure was 90% ... and 1.5 was 74%”*.

Hence there was adequate power to detect a dose response

Evaluation of Human Studies

2. Fryzek et al (2003)

- The CIB states that “*company records from the early period were destroyed or lost for the companies*”. Fryzek states “it is possible that some company records from the early periods in the plants may have been destroyed or lost. Although we found no evidence to support such an assumption ...”

Evaluation of Human Studies

2. Fryzek et al (2003) cont

- The CIB states “*the RRs may have been artificially low*” and “*questionable modeling methods [Beaumont et al. 2004]*”. However, comments by Beaumont related only to analyses in one table and Fryzek clearly shows that the effect of the possible bias raised by Beaumont is negligible.
- It is unclear why the CIB draws attention to a non significant hazard ratio of 1.3 in the medium cumulative exposure group but doesn't mention the hazard ratio of 0.7 in the high cumulative exposure group.

Evaluation of Human Studies

3. Chen and Fayerweather (1988)

- The CIB states that serious limitations of the study by Fayerweather and Chen (1988) precluded any conclusions (line 567).

Many of the limitations listed (e.g. possible confounding by asbestos) are less relevant to the mortality component of the study and do **not** invalidate the lung cancer findings (SMR = 0.52).

- For example, the CIB states that the “study reported the number of observed deaths for the period 1935–1983; the source for deaths prior to 1957 is not clear”.

The investigators clearly state that they used the SSA and NDI to obtain vital status information not available in the DuPont registry and there is no evidence of under ascertainment of lung cancer deaths.

Conclusions from epidemiologic studies

- No evidence of exposure effect in over 20,000 workers exposed since 1930s in US and Europe
- No evidence of effect in highest cumulative exposure group of the 2 multicenter studies
 - a) In European study, equivalent mean lifetime exposures ranged from 0.3 – 3.2 mg/m³ fine TiO₂ in highest exposure group
 - b) Range not known for US multicenter study, but probably similar to European. Highest exposed group had mean exposure of 6.2 mg/m³ total dust over last half of study period
- Studies not informative about ultrafine

Quantitative Risk Assessment

Key mechanistic conclusions (section 4.3)

- NIOSH has determined that a plausible mechanism of action for TiO₂ in rats can be described as the accumulation of TiO₂ in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses, tumorigenesis
- These effects are better described by particle surface area than mass dose
- The observed inflammatory response is consistent with a threshold mechanism
- The weight of evidence suggests that the tumor response observed in rats exposed to fine and ultrafine TiO₂ results from a secondary genotoxic mechanism involving chronic inflammation and cell proliferation, rather than via genotoxicity of TiO₂ itself.

Lung tumor modeling approaches used to generate risk estimates

- Benchmark dose (BMD) modeling with linear extrapolation (1/10 dose divided by 100)
- Linearized multi-stage modeling

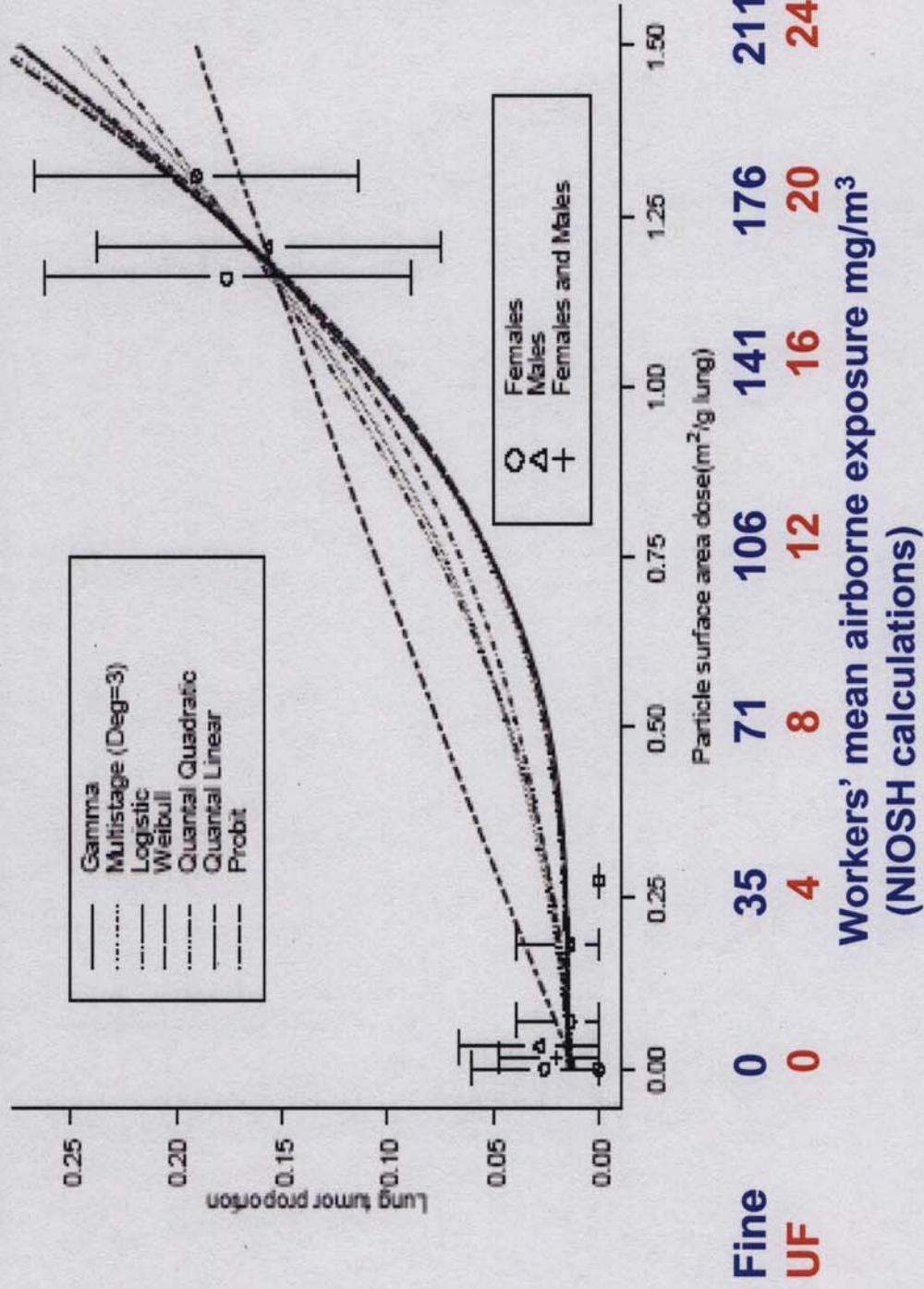
Usual approach for a genotoxic carcinogen with no threshold - why use for TiO₂?

- Bayesian model averaging (BMA) of all model estimates

Potentially better approach, but results ignored

Why does the rat model lead to RELs of 1.5 mg/m³ fine and 0.1 mg/m³ UF?

Fig 4-4 with equivalent mean worker exposure

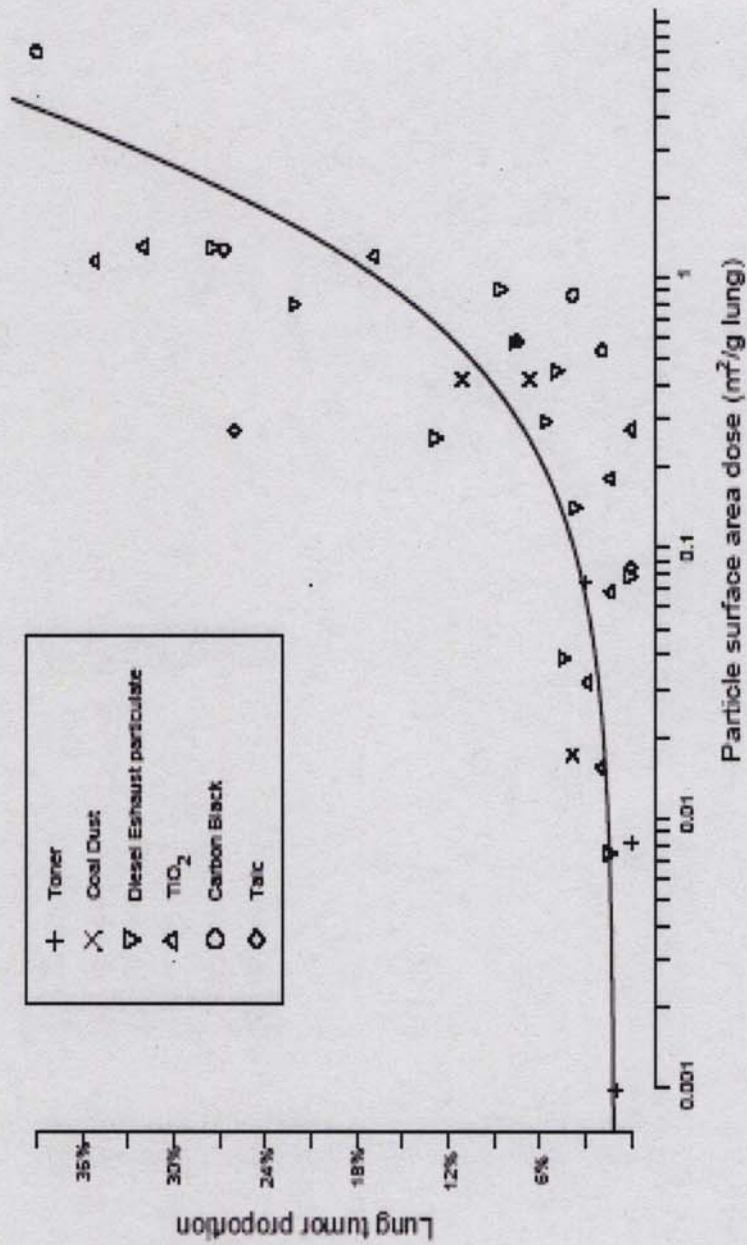


Limitations of tumor modeling approach

1. No Threshold

- The mechanistic conclusions suggest that NIOSH should have used a threshold modeling approach
- NIOSH notes that the best-fitting dose-response curves for the tumorigenicity of TiO₂ are nonlinear (e.g., multistage model is cubic with no linear term), but the threshold seen and modeled for pulmonary inflammation is also clearly apparent in the tumorigenicity data shown in Fig 3-4
- Morfeld (personal communication) has successfully fitted a threshold model to the data in Fig 3-4

Fig 3-4 Relationship between particle surface area dose and tumor proportion in rats for various PSLT dusts



Threshold model

All dusts

Threshold estimate = 0.18 m²/g (95% CI 0.063 – 0.32)

TiO₂

Threshold estimate = 0.32 m²/g (95% CI 0.13 – 1.00)

Threshold modeling approach of Morfeld

“The methodology used is described in Appendix B of the NIOSH document (the results are based on the likelihood profile). No weights were applied in this aggregated re-analysis. The thresholds are clearly significant.” (Peter Morfeld, University of Cologne)

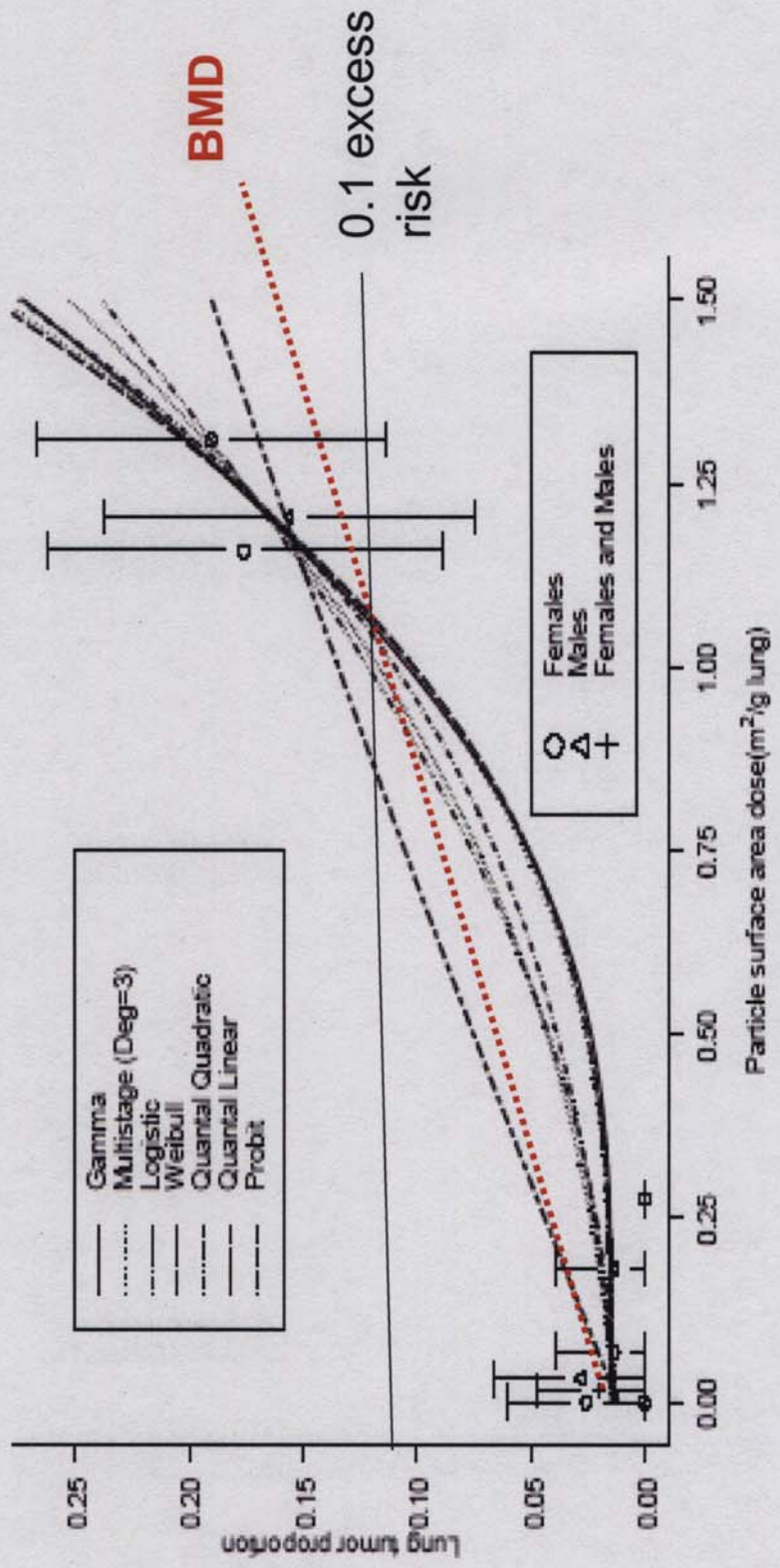
See also Morfeld et al. (2006) Dose-response and threshold analysis of tumor prevalence after intratracheal instillation of six types of low- and high-surface-area dusts in a chronic rat experiment. Inhalation Toxicology (in press)

Comments on tumor modeling approaches

2. Benchmark dose (BMD)

- Essentially model (and science) free
- Risk estimate and upper bound would be almost identical if just the high dose tumor responses had been used to perform the calculation
- BMD effectively gives the same answer as the quantal linear model – easily the worst fitting model

BMD driven entirely by tumor response at high doses



Fine 0 35 71 106 141 176 211
 Workers' mean airborne exposure mg/m3
 (NIOSH calculations)

Limitations of tumor modeling approaches

3. Linearized multistage model

- The linearized multistage model is also very sensitive to the high dose response (see Lovell and Thomas, 1996)
- Using the upper confidence interval of the linear term (the linearized upper bound on risk) to obtain an upper bound on risk effectively ignores the data at the more relevant low doses
- The best fitting multistage model is as close to a threshold model as it can get (a zero linear term and a zero quadratic term) – why ignore this and calculate the linearized upper bound on risk?

Limitations of tumor modeling approaches

4. Nonlinear models ignored

- The multistage, Gamma and Weibull clearly model the low (and more relevant) dose behaviour best.
- Why not obtain the lower confidence limit for the 1 in 1000 excess risk dose directly from the multistage model (i.e. not using the upper confidence limit for the slope term as in the linearized multistage approach)?
- Lower limit dose obtained this way is not supplied in Table 4-5, but would be expected to be much closer to the dose from the Gamma (0.042 m²/g) and Weibull (0.036 m²/g) models than the linearized multistage estimate of 0.014 m²/g

Limitations of tumor modeling approaches

5. Bayesian model averaging (BMA)

- The CIB correctly notes that *“BMA provides an approach for summarizing the risk estimates from the various models, which differ in the low-dose region of interest for human health risk estimation. BMA also provides an approach for addressing the uncertainty in choice of model in the BMD approach.”*
- Nevertheless, the BMA is given little weight by the CIB.
- However, it is surprising that the 3 best fitting models have easily the lowest posterior probabilities - what prior probabilities were used?

Summary of most plausible risk estimates from rat tumor modeling for fine TiO₂

	Best estimate mg/m ³	Lower conf limit mg/m ³
Threshold (all dusts model)	45 (25)	18 (2 mg/m ³ UF) (9)
BMA (1 in 1000)	8.7 ^a	6.5 ^a
Nonlinear ^b (1 in 1000)	31 - 39	5 - 6

^a Will increase if threshold models included, and given appropriate prior probability

^b Multistage, Weibull and Gamma models

Limitations of Quantitative Risk Assessment approach

– use of epidemiology data

- In section 4.4. NIOSH states that “the epidemiologic studies lacked the power to detect an excess risk of 1/1000”.

They do not have sufficient power to detect an SMR for lung cancer of 1.02, but does an effect seen in rats at exposures equivalent to 150 mg/m³ indicate power?

- The CIB states that “For quantitative risk assessment, dose-response data are needed, either from human studies or extrapolated to humans from animal studies. The epidemiologic studies on lung cancer have not shown a dose-response relationship in TiO₂ workers [Fryzek et al. 2003; Boffetta et al. 2004]. However, dose-response data are available in rats ...”

It seems odd to favor the rat data over human because there is no evidence of dose response in the human studies

Limitations of Quantitative Risk Assessment approach – use of epidemiology data cont.

- The main use made of the negative epidemiologic data is to test an hypothesis derived from implausible animal models
- However, a finding of no difference in excess risks from the rat and human model at 1.5 mg/m³ cannot be interpreted as meaning that the rat has the same sensitivity as man (and that predictions can be made using the rat model – see lines 3044-9).
- In fact, no evidence of an exposure effect in either species at that level.

Overall conclusions

- No evidence of an exposure effect in over 20,000 workers exposed since the 1930s in US and Europe
- Strong evidence from human and animal studies of no effect at low levels of exposure, but human data provides limited information about ultrafine
- Strong evidence that rat is far more sensitive than mice, hamsters and primates
- Threshold models are needed to reflect mechanism of action conclusions (BMD and linearized multistage are not appropriate)
- BMA may be a useful approach to deal with uncertainty in model assumptions **but** must have sensible prior weightings and include threshold models

Rat threshold model indicates that the lower limit for the critical dose of ultrafine may be as high as 2 mg/m³. Hence, REL of 1.5 mg/m³ would be protective for fine and ultrafine exposures.