From:
Sent: Sunday, April 30, 2006 11:22 PM
To: NIOSH Docket Office
Subject: Peer Review of Titanium Dioxide Document - NIOSH-033

Attachments: NIOSH titanium dioxide 2006-4-30.doc; 2005 bio professional.DOC

NIOSH titanium   2005 bio
dioxide 2006-4...   professional.DOC (.. Enclosed are my peer review comments and a summary resume.

cc: Chron file, comments file

1

Risk Assessment for Titanium Dioxide and other Poorly Soluble "Low" Toxicity Particles

April 30, 2006

These comments review the NIOSH draft Current Intelligence Bulletin for titanium dioxide, a pigment widely used in paints.

The bulletin's conclusion that pigment grade, large particle titanium dioxide (TiO_2) should not be considered to pose a carcinogenic threat by inhalation is incorrect and should be withdrawn. The NIOSH statement that "low concentrations" pose a "negligible risk of lung cancer" [line 48] is not supported by the evidence and should be withdrawn.

NIOSH classified TiO_2 as an OSHA Category I Human Carcinogen years ago, based on an inhalation study of pigment grade material.(Lee; Trochimowicz, and Reinhardt 1985) NIOSH notes that since then, a bioassay of ultrafine TiO_2 found it to be carcinogenic, but much more potent than the pigment grade material.(Heinrich U ; Fuhst R ; Rittinghausen S ; Creutzenberg O ; Bellmann B ; Koch W , and Levsen K. 1995)

Since the draft was released, an IARC working group has classified titanium dioxide as Group 2B, "possibly carcinogenic to humans" based on inadequate data in humans and sufficient data in laboratory animals.(Baan; Straif; Grosse; Secretan; El Ghissassi, and Cogliano 2006) Sufficient data in laboratory animals is equivalent to an OSHA Class I human carcinogen.

NIOSH has incorrectly interpreted the available epidemiology as implicitly providing evidence for safety.

This reviewer concurs with NIOSH that a common approach to setting occupational exposure limits to all poorly soluble low toxicity (PSLT) particles is appropriate. The new data suggests that inhalation of fine particles at prevailing exposure levels in many industries may be a major cause of occupational cancer and respiratory illness, and perhaps cardiac effects as well. This reviewer applauds NIOSH as the only public agency taking up this issue.

1. NIOSH correctly states that titanium dioxide and its appropriate exposure limit should be considered in the context of all PSLT data. NIOSH has failed to synthesize that data set, especially human evidence.

2. The large body of epidemiological findings documenting increased community mortality and hospital admissions from pulmonary and cardiac causes with fluctuations of fine particulate matter in ambient air – community air pollution – must be taken into account. These community effects – which include frank mortality – occur with fluctuation in ambient exposure *below* established EPA ambient air standards for particulate matter.(Krewski; Burnett; Goldberg; Hoover; Siemiatycki; Jerrett; Abrahamowicz, and White 2003;Becker; Soukup; Sioutas, and Cassee 2003;Vedal; Brauer; White, and Petkau 2003;Pope; Burnett; Thun; Calle; Krewski; Ito, and Thurston 2002;Dockery; Schwartz, and Spengler 1992;Oberdorster; Gelein; Ferin, and Weiss 1995;Schwartz; Dockery, and Neas 1996) Lung cancer is also increased with particulate exposure.(Krewski; Burnett; Jerrett; Pope; Rainham; Calle; Thurston, and Thun 2005) These effects are seen both for PM_{10} [particulate matter 10 microns and less, essentially equivalent to thoracic particulate or total particulate collected with a closed face filter] or $PM_{2.5}$ [particulate matter 2.5 microns and below, a somewhat smaller size fraction than respirable particulate which is essentially 4 microns and below.] These effects are directly relevant to a risk assessment for titanium dioxide.

3. The rat *is* the appropriate animal model for evaluating particulates for potential lung carcinogenicity in people. The mouse resists the effects of known human lung cancer agents such as silica and tobacco smoke. The hamster is very resistant to particulate agents; although the hamster provided the first clear evidence for carcinogenicity of tobacco smoke in an animal inhalation model, laryngeal tumors were generated, not lung tumors. The mouse and hamster produce false negatives for known human carcinogens, so null studies in the bioassay in these species should be given little weight.(Mauderly 1997) The rat is not "sensitive," it is "less resistant."

4.   The Lee study of pigment grade titanium dioxide has been incorrectly discounted because of the supposed high exposure levels, 250 mg/M3. The Lee study was analyzed without benefit of mortality adjusted statistics, as would be routine in National Toxicology Program bioassays. Animals were terminated at two years. Tobacco smoke doesn't produce a meaningful lung tumor yield in rates at exposures less than 100 mg/M^3.(Finch GL 1995) A second study reports an effect level of 250 mg/M3, when animals were held 6 months after the two year exposure period. Similar exposure levels were needed to produce lung tumors in mice. Thus, pigment grade titanium dioxide has a similar potency to cigarette smoke in the animal models.

Silica and asbestos levels of 20 mg/M^3 or greater are needed to generate a substantial tumor yield. Unit risks of silica at mg/M^3 exposure levels in people are extremely high. If TiO2 is 1/10 as potent as silica, it will still extrapolate to significant risks at mg/M^3 exposure levels.

Various commenters have emphasized that the effect dose for pigment grade large particle TiO_2 is 250 mg/M^3. Beyond frank carcinogenicity, 250 mg/M^3 exposures to tobacco smoke are routinely used to evoke respiratory effects in rodents.(March; Barr; Finch; Hahn; Hobbs; Menache, and Nikula 1999;Finch; Lundgren; Barr; Chen; Griffith; Hobbs; Hoover; Nikula, and Mauderly 1998)

5. Titanium dioxide of any particle size is an OSHA Category I carcinogen. The data available, and the "lung overload" hypothesis, do not support a threshold model. A threshold model predicts there is a dose level below which there is no dose response relationship.

The rat-specific "lung overload" mechanism is at best an unproven hypothesis to be applied to quantitative risk assessment. At worst, "lung overload" as an excuse to depart from more standard risk assessment methods is an unsubstantiated "Houdini Risk Assessment" scheme. Similarly, the argument that exposure-response relationships are "non-linear" – a code word for threshold, even though "non-linear" includes supra-linear – is unsubstantiated, especially for exposure levels which prevail in the occupational environment.

The scientific issue is whether "lung overload," impaired clearance, macrophage hyperplasia and other non-malignant pathology are separate processes from carcinogenesis. If impaired clearance simply acts to increase residence time and exposure of lung tissue to PSLT particles, resulting in carcinogenic results, then the PSLT particles must have some carcinogenic potential in themselves. By contrast, if PSLT particles have no carcinogenic potential in themselves, then macrophage hyperplasia and impaired clearance from any cause have carcinogenic potential in the absence of PSLT particles. Since human PSLT exposure is ubiquitous, in the latter case, any condition that causes macrophage hyperplasia should be considered carcinogenic.

Imagine that impaired clearance and macrophage hyperplasia are, regardless of cause, carcinogenic. This might be biologically plausible if PSLT particles, which are ubiquitous, and also exist in the laboratory air breathed by bioassay animals, initiate lung tumors. Decreased clearance, and increased macrophage hyperplasia, will be linear with increased carcinogenesis, regardless of whether these effects are sub- or supra-linear with the exposure.

Imagine, in addition and contrast, that contact of PSLT with lung tissue by itself initiates carcinogenesis. Plausibly contact concentration and time will be first order with target cell initiation. Where PSLT exposure also impairs clearance and causes macrophage hyperplasia, the exposure response relationship will be steeper than first order, since concentration of exposure to PSLT is involved in two steps. This will be true even if both steps are first order. Therefore, an exposure response relationship that is linear in initiation [holding clearance constant], and linear in impaired clearance [holding PSLT contact with tissue constant], will be supra-linear for both in concert.

3

Perversely, if PSLT exposure causes both initiation, and impaired clearance, then the exposure response relationship in the high dose range will be greater than first order [steeper] than in the low dose range. Thus, the apparently steeper and higher order exposure response relationship in the high dose range will *underestimate* risk in the lower dose range.

6. By contrast to the laboratory studies, people may experience impaired clearance and macrophage hyperplasia from causes other than TiO2 exposure, along with TiO$_2$ exposure from occupational sources. Risk assessment models must take this into account. Thus, TiO$_2$ in humans doesn't have to be the complete carcinogen it needs to be in the laboratory studies.

7. The cited mortality studies in occupational settings are inadequate to provide evidence of lack of risk from TiO2 at prevailing exposure levels.(Fryzek; Chadda; Marano; White; Schweitzer; McLaughlin, and Blot 2003) At best it provides evidence that no greater than 5% of workers will perish from lung cancer attributable to titanium dioxide pigment exposure at 6.2 mg/M^3. The following summary should be substituted for the section following line 581.

Fryzek and coworkers at the International Epidemiology Institute studied 4241 TiO$_2$ workers at four unidentified TiO$_2$ plants in the United States. The study sponsor was unidentified. The highest exposed job category, where about ¼ of the cohort was ever employed, endured a geometric mean exposure of 2.7 mg/M^3. The arithmetic mean for this skewed distribution was 6.2 mg/M^3 due to high exposures before 1985. Only 112 total and 11 respiratory cancer deaths were observed among this group. Other exposed categories endured geometric mean exposures below 1.0 mg/M^3. Standardized mortality ratios (SMRs) were presented for both races (22% of the cohort was non-white) and genders (10% women) combined. The combination of SMR's for white and non-white workers will narrow the SMR because of the stronger healthy worker effect among non-whites. The analysis apparently included non-administrative salaried personnel, which would also lower the SMR. A separate analysis for white, male, hourly workers should have been presented.

The noted lower overall mortality observed [SMR = 0.8] is expected in an occupational cohort, and is of no health significance for evaluating effects of titanium dioxide. Given that overall mortality was only 13%, and the dilution of SMR by inclusion of non-whites and salaried personnel, this SMR is notable Despite these obstacles, deaths from lung cancer were as high as expected, therefore proportional mortality from lung cancer was increased.

The investigators opined that "Internal analyses revealed no significant trends or exposure-risk associations for total cancers, lung cancer, or other causes of death" and that "workers with likely higher levels of TiO$_2$ exposure had similar mortality patterns to those with less exposure." However, workers in each

4

employment duration stratum and overall showed a distinct increase in SMR for lung cancer comparing those with less than 20 years latency to those with more than 20 years of latency. Increased mortality in the long latency, shorter duration strata is consistent health related termination of employment. This effect has been observed in other, much larger industrial cohorts.(Delzell; Brown, and Matthews 2003;Mirer 2003)

This study provides some evidence for an exposure related effect, given the latency effect, which is a measure of exposure response. It is inadequate to support a conclusion of "not likely to be carcinogenic in humans." The upper confidence interval for respiratory cancer among those ever employed in the high exposure job category was 1.6, and among all exposed employees with greater than 20 years latency it was 1.5. Thus, at the prevailing exposure levels, we can possibly rule out a greater than 50% increase in lung cancer, or a unit risk of about 2.5 per 100. In some groups the upper confidence interval was two fold. This observation is entirely consistent with conventional extrapolation from the animal bioassay.

8. The Boffetta Montreal study(Boffetta; Gaborieau; Nadon; Parent; Weiderpass, and Siemiatycki 2001) is a population based case control study. The same power limitation applies. The upper confidence interval of the odds ratio is 1.5. No trend was apparent according to the estimated frequency, level, or duration of exposure. The upper confidence interval was 2.7 for medium or high exposure for at least 5 years.

9. The Boffetta European Study(Boffetta; Soutar; Cherrie; Granath; Andersen; Anttila; Blettner; Gaborieau; Klug; Langard; Luce; Merletti; Miller; Mirabelli; Pukkala; Adami, and Weiderpass 2004) provides evidence for an exposure related effect, contrary to the conclusions of the investigators and the NIOSH review. The investigators and the review note, correctly that lung cancer among males was increased to a significant level; the upper confidence limit was a 38% increase, corresponding to about 2% mortality attributable to exposure. The review fails to note that the SMR for lung cancer increased with latency [duration from first exposure] in all employment duration strata, becoming statistically significant only after 20 years latency. The absence of exposure response carries less force since the top quartile of exposure begins at 13 mg/M3-years, equivalent to 0.3 mg/M3 over 45 years.

5

Table 5. Standardized mortality ratios of lung cancer by duration of employment and time since first employment

Years of employment		Years since first employment				
		1-10	10.01-20	20.01-30	30.01 +	Total
1-5	Obs Exp	7.0/7.1	12.1/9.7	45.9/16.6	17.8/15	77.7/48.4
	SMR	0.99	1.24	2.47	1.19	1.61
	95% CI	0.4-2.03	0.64-2.15	1.78-3.36	0.71-1.90	1.27-2.01
5.01-10	Obs Exp	9.0/9.2	10.1/7.7	11.2/9.7	3.2/7.2	33.5/33.7
	SMR	0.98	1.31	1.15	0.44	0.99
	95% CI	0.45-1.86	0.62-2.4	0.57-2.03	0.09-1.22	0.67-1.37
10.01-15	Obs Exp	-	17.5/18.6	9.1/11.8	7.5/4.7	34.4/35.1
	SMR	-	0.96	0.77	1.6	0.98
	95% CI	-	0.57-1.53	0.35-1.45	0.74-3.26	0.67-1.35
15.01-20	Obs Exp	-	13.3/14.7	20.7/15.2	11.4/8.6	45.4/38.3
	SMR	-	0.90	1.36	1.34	1.18
	95% CI	-	0.47-1.51	0.85-2.11	0.64-2.30	0.85-1.56
20.01 +	Obs Exp	-	-	38.8/34.7	76.7/57.8	115.5/92.5
	SMR	-	-	1.12	1.33	1.25
	95% CI	-	-	0.80-1.54	1.05-1.67	1.03-1.47
Total	Obs Exp	16.0/16.3	53.2/50.9	120.6/88.0	116.6/93.9	306.5/249.3
	SMR	0.98	1.05	1.37	1.25	1.23
	95% CI	0.56-1.59	0.78-1.37	1.14-1.64	1.04-1.50	1.10-1.38

SMR, standardized mortality ratio; CI, confidence interval.
* Observed deaths are not integer values because of correction factors for missing causes of death.

10. This reviewer concurs that smaller particle size is likely to increase toxicity per unit weight as well as increased penetration. Per unit weight, surface area increases as the square of the reduction in diameter, while particle count increases as the cube. We question whether available data can distinguish between surface area and particle number as the best measure. We note that particle counts were the basis for exposure limits prior to the 1970's, were phased out as mass became the easier technology for analysis. Now that direct reading real time particle counting and sizing is technologically feasible, it may be a better basis for a standard. This reviewer urges NIOSH to clarify terminology.

11. A departure point for setting a REL should be the benchmark dose, or no effect level, for lung inflammation, probably in the rat. The benchmark dose is equivalent to about a 10% attack rate for the effect.(Gaylor; Ryan; Krewski, and Zhu 1998) The REL should be set below that by some extrapolation factor.

The lowest statistically significant effect level observed was 2 mg/M^3 for 13 weeks for alveolar cell replication in rats exposed to ultrafine TiO$_2$.(Bermudez; Mangum; Wong; Asgharian; Hext; Warheit, and Everitt 2004) This elevation persists, although it is not statistically significant, for 13 weeks post exposure. This reviewer recommends that NIOSH calculate the benchmark dose for this and the other array of inflammation parameters, and then apply an appropriate extrapolation factor.

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7

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8

TABLE 4
Alveolar Cell Replication

Weeks postexposure	Dose group (mg/m³)	Mice		Rats		Hamsters	
		Labeling index[a] mean	SD	Labeling index mean	SD	Labeling index Mean	SD
0	0	6.20	1.93	4.53	1.78	9.67	0.74
	0.5	5.34	1.43	6.23	2.42	10.25	0.48
	2	5.51	2.39	7.81*	1.22	10.60	3.81
	10	8.98	3.63	12.18*	2.53	12.87	5.22
4	0	7.28	2.64	4.59	1.05	11.85	2.43
	0.5	5.36	1.02	6.30	1.18	12.51	9.06
	2	5.91	1.53	7.15	1.44	9.88	2.01
	10	9.21	2.18	10.06*	0.96	12.03	2.53
13	0	5.64	1.12	5.09	1.83	12.02	2.40
	0.5	7.06	2.36	5.48	2.06	12.77	1.43
	2	6.09	1.88	7.17	4.37	10.01	3.70
	10	10.21*	1.99	9.40*	2.66	11.89	3.48
26	0	4.91	1.17	5.44	1.68	10.13	2.45
	0.5	6.53	1.91	4.18	1.28	12.36	2.66
	2	5.92	1.81	5.49	0.33	7.71	2.54
	10	9.46*	2.45	7.48	2.37	10.95	2.39
52(49)[b]	0	5.34	0.77	6.29	0.98	17.04	3.76
	0.5	8.04	2.08	6.61	0.96	16.95	3.10
	2	7.28	1.64	3.97	0.67	13.89	3.11
	10	8.09	2.75	7.21	1.40	15.92	3.39

[a] Labeling indices are reported as the percentage of BrdU-labeled cells of the cells counted (minimum of 400 cells counted).

[b] Hamsters were sacrificed at 49 weeks postexposure.

* Significantly different from the concurrent control ($p < 0.05$).