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DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ-10-17941	88100000270	5/13/10

COMMENTS:

DOES NOT CONTAIN CBI

326871

8EHQ-10-17941

8EHQ-0510-17941A

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for Health and Environmental Sciences
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May 12, 2010

Via Federal Express

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Dear 8(e) Coordinator:

Titanium Dioxide and Titanium Tetrachloride
13463-67-7 and 7550-45-0

This letter is to inform the Agency of preliminary results from an epidemiology study titled "Occupational Exposure and Mortality Among Workers at Three Titanium Dioxide Plants". The research results are from an ongoing retrospective cohort study conducted by epidemiologists at Oak Ridge Associated Universities (ORAU) that has been previously described in a published paper (Ellis *et al.*, 2010).

The current research assesses all-cause and all-cancer mortality as well as cause-specific mortality from lung cancer, heart diseases, and non-malignant respiratory diseases for 3,607 employees exposed for at least 6 months to titanium dioxide (TiO_2) production processes at three U.S. facilities from 1935 through 2005. Since the three plants (Edge Moor Plant (Delaware); New Johnsonville Plant (Tennessee) and De Lisle Plant (Mississippi)) ran identical processes using the same starting materials, data for workers were combined to increase statistical power. Vital status follow-up was ascertained through December 31, 2005, and causes of death were obtained through various sources including the U.S. National Death Index (NDI *Plus*) as described in Ellis et al. (2010). Standardized mortality ratios (SMR) were calculated using expected mortality counts based on both the U.S. general population reference rates and reference rates calculated from national and regional DuPont worker populations. In addition, statistical analyses using Poisson regression models for time-dependent cumulative exposures for both TiO_2 and an intermediate chemical, titanium tetrachloride ($TiCl_4$), provided exposure-response comparisons for the five mortality outcomes (all causes, all cancer, lung cancer, heart diseases, and non-malignant respiratory diseases).

First, there are significant SMRs for all mortality causes (SMR = 1.23, 95% confidence interval (CI): 1.15, 1.32); for all cancers (SMR = 1.17, 95% CI: 1.02, 1.33); and for lung cancer (SMR = 1.35, 95% CI: 1.07, 1.66) for TiO_2 exposed workers at the 3 combined plant sites compared to reference population mortality rates based on all U.S. DuPont employees. These results are heavily influenced by the mortality experience of workers at the Edge Moor Plant. The Edge Moor group has the longest follow-up periods of cohort members due to an entry year as early as 1935 and an average entry year of 1960 for workers at this facility. This group accounts for 711 of the 833 total deaths (85%) ascertained for the combined cohort.

Evidence of the disproportionate mortality effect due to longer follow-up for workers at the Edge Moor Plant is seen in significant SMRs for all mortality causes (SMR = 1.40, 95% CI: 1.30, 1.50); for all cancers (SMR = 1.34, 95% CI: 1.16, 1.53); for lung cancer (SMR = 1.68, 95% CI: 1.32, 2.11), and for heart diseases (SMR = 1.17, 95% CI: 1.03, 1.31) when only workers from this facility are compared to reference population rates for regional DuPont employees from mid-Atlantic states (Delaware, Maryland, New Jersey, New York, and Pennsylvania).

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The use of national and regional DuPont reference rates by the ORAU investigators was designed to reduce the influence of the healthy worker effect, a widely noted bias in occupational mortality studies (Checkoway *et al.*, 2004). However, there are limitations to the interpretability of SMRs calculated using DuPont reference rates due to differing demographic distributions and individual risk factors (e.g. tobacco smoking), the excessive proportion of mortality among cohort members at the longest operating plant site (as noted the Edge Moor Plant accounted for 85% of the total cohort deaths), and the lack of consistency with general U.S. population-based SMRs which show no significantly increased mortality ratios (Ellis *et al.* 2010). Also, for this study, there is no consistent increase for mortality ratios calculated separately for workers from the New Johnsonville and De Lisle Plants. SMRs for these workers are significantly decreased for all mortality causes (SMR = 0.76, 95% CI: 0.63, 0.90); for all cancers (SMR = 0.65, 95% CI: 0.45, 0.91); and for heart diseases (SMR = 0.66, 95% CI: 0.50, 0.85) when compared to reference population rates for regional DuPont employees from Southeastern states (Alabama, Florida, Georgia, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia). Additionally, lung cancer mortality was decreased for workers at these two plants (SMR = 0.75, 95% CI: 0.40, 1.25).

Second, relative risks (RR) were calculated for cumulative exposure categories using statistical models based on Poisson regression. For these analyses, four cumulative exposure categories (5 to 15, 15 to 35, 35 to 80, 80 plus mg/m^3-years) are compared to a referent category of workers with less than 5 mg/m^3-years of cumulative exposure. In addition, analyses were conducted for lagged exposures determined after the removal of the most recent 10 years of work history for each worker's cumulative exposure estimate (Salvan *et al.*, 1995). An important observation is that there is no monotonic increase for the relative risks from any mortality outcome that is associated with increasing cumulative exposure; however, several cumulative exposure categories have significantly increased RRs when compared to workers in the lowest cumulative exposure category.

Notable significant results from these analyses include increased risk estimates for all mortality causes for workers with cumulative TiO_2 exposure categorized as 15 to 35 mg/m^3-years (RR = 1.32, 95% CI: 1.06, 1.64) and as 80 plus mg/m^3-years (RR = 1.30, 95% CI: 1.02, 1.66) compared to workers with cumulative exposure less than 5 mg/m^3-years. A significant RR for heart disease mortality for workers with cumulative TiO_2 exposure categorized as 15 to 35 mg/m^3-years (RR = 1.61, 95% CI: 1.13, 2.31) compared to workers with cumulative exposure less than 5 mg/m^3-years.

For the lagged analyses, significant RRs for all mortality causes for workers with 10-year lagged cumulative TiO_2 exposure categorized as 5 to 15 mg/m^3-years (RR = 1.27, 95% CI: 1.02, 1.58); as 15 to 35 mg/m^3-years (RR = 1.36, 95% CI: 1.10, 1.69); and as 80 plus mg/m^3-years (RR = 1.42, 95% CI: 1.11, 1.81) compared to workers with 10-year lagged cumulative exposure less than 5 mg/m^3-years. A significant RR for all cancer mortality for workers with 10-year lagged cumulative TiO_2 exposure categorized as 80 plus mg/m^3-years (RR = 1.60, 95% CI: 1.02, 2.50) compared to workers with 10-year lagged cumulative exposure less than 5 mg/m^3-years. Significant RRs for heart disease mortality for workers with 10-year lagged cumulative TiO_2 exposure categorized as 5 to 15 mg/m^3-years (RR = 1.47, 95% CI: 1.02, 2.11); as 15 to 35 mg/m^3-years (RR = 1.65, 95% CI: 1.16, 2.34); and as 80 plus mg/m^3-years (RR = 1.51, 95% CI: 1.00, 2.25) compared to workers with 10-year lagged cumulative exposure less than 5 mg/m^3-years.

Finally, a significant RR for lung cancer mortality for workers with cumulative $TiCl_4$ exposure categorized as 5 to 25 mg/m^3-years (RR = 2.00, 95% CI: 1.07, 3.76) compared to workers with no cumulative exposure to $TiCl_4$.

Important limitations of these preliminary results include the lack of information describing tobacco smoking or other individual characteristics that may influence risk estimates for mortality, specifically those for lung cancer and heart disease mortality. Further, no monotonically increasing trend was observed for RRs for mortality outcomes by increasing cumulative exposures to TiO_2 or $TiCl_4$ for four categories compared to the referent category. Moreover, no monotonically increasing trend was observed for relative risks for mortality outcomes by increasing 10-year lagged cumulative exposure categories for both substances (same quantitative ranges). Finally, only 1 of 40 relative risk estimates for cumulative exposure to $TiCl_4$ is significantly increased. This indicates that the single RR result may be due to the multiple comparisons conducted for categorized cumulative exposures. Based on the investigators' use of a default p-value of 0.05 as indicative of statistical significance, this result is within the expectation of random chance for a statistically significant finding (Goodman, 1998).

Given the intention of the ORAU study investigators to publish this report in a peer-reviewed journal, a copy of the final manuscript interpreting the complete results of the study will be sent to the Agency when available.

This information is submitted in accordance with current guidance issued by EPA indicating EPA's interpretation of Section 8(e) of the Toxic Substances Control Act or, where it is not clear that reporting criteria have been met, it is submitted as a precautionary measure and because it is information in which EPA may have an interest.

Sincerely,

A. Michael Kaplan

A. Michael Kaplan, Ph.D.
Director – Regulatory Affairs

AMK/JMS: clp
(302) 366-5260

REFERENCES

Checkoway H, Pearce N, Kriebel D. Research Methods in Occupational Epidemiology, 2nd edition. Oxford University Press, Oxford, United Kingdom: 2004.

Ellis ED, Watkins J, Tankersley W, Phillips J, and Girardi D. Mortality among titanium dioxide workers at three DuPont plants. Journal of Occupational and Environmental Medicine 2010;52(3):303-9.

Goodman SN. Multiple comparisons, explained. American Journal of Epidemiology 1998;147(9):807-812.

Salvan A, Stayner L, Steenland K, and Smith R. Selecting an exposure lag period. Epidemiology 1995;6:387-390).

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