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Titanium Dioxide Nanoparticles: Grassian et al. Respond.

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In their study of inhalation exposure of titanium dioxide particles, Grassian et al. (2007) presented a transmission electron micrograph (TEM) (their Figure 2A) as an image of “dispersed” TiO$_2$ nanoparticles. Yet, the TiO$_2$ nanoparticles in this TEM do not appear to be dispersed. There is clear evidence of self-organization of the nanoparticles into distinct assemblages, separated by relatively large regions devoid of any particle. This spatial pattern, very unlikely to occur randomly, is even more apparent when Grassian et al.’s TEM is contrast-enhanced, sharpened, and thresholded (Figure 1A) to eliminate the initial grainy background. With this image, one can demonstrate quantitatively the extent of clustering by calculating the radial distribution function (Torquato 2002), defined as the probability of finding a nanoparticle, in any direction, at various distances away from the center of a given nanoparticle. We compared the values obtained for this function with those associated with an image in which the same nanoparticles have been artificially dispersed (with image processing software). In the dispersed case (Figure 1B), the probability of finding a black pixel drops precipitously when the distance exceeds the apparent radius of nanoparticles, and then stays close to zero thereafter. In the “original” case (Grassian et al.’s Figure 2A), there is also a drop, but the radial distribution function never gets to zero. It progressively increases again as the radial distance increases. This quantitative difference between the curves in Figure 1B leads to the conclusion that the nanoparticles in Figure 1A are clustered.

However, this conclusion is intriguing in itself. Indeed, before obtaining their TEM, Grassian et al. (2007) suspended the TiO$_2$ nanoparticles in methanol and sonicated the suspension for an unspecified, but presumably appreciable “period of time.” Given this strongly dispersive treatment, it is remarkable that aggregation still occurred to the extent it did. This observation suggests that the 2- to 5-nm size of the primary TiO$_2$ “nano”-particles may be somewhat irrelevant to environmental and toxicologic concerns because in nature, under conditions far more conducive to aggregation than those imposed by Grassian et al. (2007), nanoparticles may never be found alone, but are part of significantly larger-sized aggregates. In a recent study, French et al. (French RA, Jacobson AR, Kim B, Isley SL, Penn RL, Baveye PC, unpublished data) observed that in aqueous suspensions under a range of environmentally relevant conditions of pH and ionic strength, TiO$_2$ nanoparticles form aggregates of several hundred nanometers to several micrometers in diameter within minutes.

This aggregation may have toxicologic implications. In any given system (e.g., aerosols), it is possible that even a slight change in pH or ionic strength may cause TiO$_2$ nanoparticles to cluster differently, and therefore to have very dissimilar biological activity. In general, this might explain mixed results found in the literature on the toxicity of TiO$_2$ nanoparticles to environmentally relevant species. Until now, these inconclusive results have been explained (Oberdörster et al. 2005) by arguing that the high biological activity of TiO$_2$ nanoparticles, caused by their large specific surface area, creates a high potential for inflammatory, pro-oxidant, and antioxidant activity. Yet, conflicting observations may perhaps be imputable instead to compounding factors due to nanoparticle aggregation, which so far has not been given serious consideration.

The authors declare they have no competing financial interests.

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Baveye and Laba have further analyzed the transmission electron micrograph (TEM) image shown in Figure 2A of our article (Grassian et al. (2007b) to quantitatively determine the extent of titanium dioxide nanoparticle clustering in the image by calculating the radial distribution function. The main point of doing this calculation was to demonstrate that TiO$_2$ nanoparticle aggregates will not completely deaggregate even when subjected to harsh conditions.

We completely agree with the statement of Baveye and Laba that “aggregation may have toxicologic implications.” We disagree with their suggestion that “nanoparticle aggregation … so far has not been given serious consideration.” There is growing consensus that nanoparticle aggregation is an important factor in understanding the health implications of nanoparticles. This has been described by researchers working in the area of nanoparticle toxicity (Balbus et al. 2007; Powers et al. 2006), as well as by us. In addition to Grassian et al. (2007b), we refer to another study in which we further investigated TiO$_2$ nanoparticle aggregation in inhalation and instillation studies (Grassian et al. 2007a). In that study we demonstrated that the size and nature of
DDT and Breast Cancer

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In a recent article, Cohn et al. (2007) noted an association between increased breast cancer risk and \( p,p'\)-DDT \( [1,1,1\text{-trichloro-2,2-bis(p-chlorophenyl)ethane}] \) exposure early in life. Their article should be interpreted with caution, particularly the estimated 5-fold increase in risk for women born after 1931—since this value was repeated in the news article by Manuel (2007). Cohn et al. (2007) evaluated three DDT congeners—that is, \( p,p'\)-DDT, \( o,p'\)-DDT \( [1,1,1\text{-trichloro-2(p-chlorophenyl)-2-(p-chlorophenylethane)} \), and \( p,p'\)-DDE \( [1,1\text{-dichloro-2,2-bis(p-chlorophenylethane)} \)—by various categories of year of birth, yet they found no significantly increased risk estimates for any of the three DDT congeners in multiple comparisons that were not adjusted for the other DDT-related chemicals either in all women or in women born after 1931. The estimated 5-fold increase in risk for the upper tertile of \( p,p'\)-DDT serum levels was only observed in subgroup analyses that were both restricted to women born after 1931 and adjusted for serum level of \( o,p'\)-DDT. The impact of the adjustment for \( o,p'\)-DDT on the risk estimate for \( p,p'\)-DDT is remarkable in view of the low \( o,p'\)-DDT levels observed (35% were below the limit of detection). A significant inverse association between \( o,p'\)-DDT level and breast cancer risk, which was interpreted by Cohn et al. in terms of length of time since DDT exposure, became stronger after adjustment for \( p,p'\)-DDT levels; presumably this does not indicate a protective effect of recent DDT exposure.

In view of the absence of evidence for an association between \( p,p'\)-DDE levels and breast cancer risk (López-Cervantes et al. 2004), it seems unlikely that DDT exposure increases the risk of breast cancer. Nonetheless, if the effect of DDT exposure early in life on breast cancer risk is large (a possibility suggested by Cohn et al. (2007)), then the decreasing birth cohort trend in breast cancer risk that has been observed for U.S. baby boomers is even more remarkable (Chu et al. 1999; Tarone 2006, 2007; Tarone and Chu 2000). Women born after 1945 would have been exposed to DDT for each of the first 13 years of life, with increasing exposure through the late 1960s (Wolff et al. 2005), but the birth cohort risk of breast cancer showed a marked decrease among U.S. women for over two decades after 1945. DDT exposure would join a list of other breast cancer risk factors predicting increasing breast cancer risk in baby boomers (Tarone 2006); yet the birth cohort risk of breast cancer decreased for women born after 1945. That the hypothesized association between DDT exposure and breast cancer risk has received far more attention than the paradoxical decreasing risk of breast cancer that has actually occurred among young U.S. women says much about the priorities and focus of environmental epidemiology. The author declares he has no competing financial interest.

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DDT and Breast Cancer: Cohn et al. Respond
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We thank Tarone for his letter, as it provides an opportunity to elaborate on analytic strategies for the study of DDT associations with breast cancer. One feature of our study (Cohn et al. 2007)—assessment of exposure in blood samples collected during active DDT use in the 1960s—provided a unique opportunity to examine three DDT-related compounds singly and in combination. The three DDT-related compounds studied represent distinct aspects of exposure. \( p,p'\)-DDT \( [1,1,1\text{-trichloro-2,2-bis(p-chlorophenyl)ethane}] \) is the primary ingredient of commercial grade DDT, \( p,p'\)-DDE \( [1,1\text{-dichloro-2,2-bis(p-chlorophenylethane)} \), the most persistent DDT-related compound, is a metabolite of \( p,p'\)-DDT that is both made by humans during active exposure, and also ingested directly from food sources where it can be stored for long periods in fat (Morgan and Roan 1975). \( o,p'\)-DDT \( [1,1,1\text{-trichloro-2(p-chlorophenyl)-2-(p-chlorophenylethane)} \) is a low-concentration contaminant of commercial DDT that is eliminated by humans most quickly, making it a marker of recent exposure (Morgan and Roan 1975). Therefore, absolute and relative DDT/DDE isomer levels may represent different windows of exposure (Wolff et al. 2007).

Unlike our investigation, most other breast cancer studies were conducted long after active use of DDT ceased. Thus the preponderance (> 95%) of their exposure was only \( p,p'\)-DDE [see our Figure 1 and Table 1 (Cohn et al. 2007)]. Hence, our study provides new information. An additional
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...and functional activity may differ for each
p,p' association between... function of liver cancer was enhanced when p,p' DDE
was low. We also reported that a higher propor-
tion of p,p' DDE to p,p' DDT in maternal serum
samples was associated with longer time to
pregnancy in their daughters 30 years after exposure in utero (Cohn et al. 2003). In another
other breast cancer study, Romieu et al. (2000)
demonstrated a significant effect for p,p' DDE—after
adjustment for p,p' DDT—for predicting breast
cancer, particularly in postmenopausal women.
We believe that simultaneous adjustment
for DDT-related compounds is a strength of
our study.

Tarone suggests that subgroup analyses
weaken the results of our article (Cohn et al.
2007). However, we pointed out in our article
that subgroup analyses, by birth cohort,
were planned a priori and were a primary
objective of our study. In this set-
ing, subgroup analyses are a strength
that enabled us to examine whether age at DDT
exposure may be of importance in human breast
cancer.

The trends in breast cancer incidence
in young women previously presented by
Tarone in Table 1 of his article (Tarone
2006) do not refute a possible effect of
DDT exposure in childhood. Successive
birth cohorts of women diagnosed at
20–39 years of age between 1975 and 2002
(Table 1; Tarone 2006) experienced
decreasing DDT exposure in childhood
(birth years 1941–1982) because DDT use
began in 1945, peaked in 1959, and was
banned in 1972 in the United States (U.S.
Environmental Protection Agency 1975).
Successive birth cohorts of women
examined at 40–49 years of age between 1990
and 2002 (Table 1 in Tarone 2006) were
all exposed to DDT in childhood (birth
years 1941–1962); therefore, breast cancer
trends for these birth cohorts are not
informative for investigating effects of DDT
exposure in childhood. Further, we agree
with Weiss (2007) that trends in invasive
disease and mortality cannot be interpreted
without consideration of the rising inci-
dence of in situ disease and its successful
treatment, which would reduce incidence
of invasive disease and mortality.

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Comments on “The Sweet Scent on Baby’s Breath?”
doi:10.1289/ehp.10993

The stated mission of Environmental Health
Perspectives (EHP) is
to serve as a forum for the discussion of the inter-
relationships between the environment and
human health by publishing in a balanced and
objective manner the best peer-reviewed research
and most current and credible news of the field.
(EHP 2008)

We would like to focus on the part of
your mission statement, regarding “a balanced
and objective manner.” For the third time in
about as many years, we find ourselves writ-
ting to EHP to correct inaccuracies in its
reporting of the state of the science regard-
ing fragrance ingredients and our under-
standing of their fate and effects in the
environment and human health.

Your news item “The Sweet Scent on
Baby’s Breath?” (Potera 2007) is yet another
example of information conveyed by your
journal in a manner that is neither balanced
nor objective. For example, you quote the
work of Luckenbach and Epel (2005), yet
omit the clarifications from the Research
Institute for Fragrance Materials (RIFM) that
EHP published in a follow-up letter to the
to the editor (Salvito 2005).

You continue to allow reiteration of the
inaccurate statement that there is little
known about the polycyclic musks, when in
fact a robust body of scientific studies pub-
lished in a number of peer-reviewed journals
are in fact available, and have been used to
support a thorough evaluation in Europe of
the risks of these ingredients to human
health and environment.

6-Acetyl-1,1,2,4,4,7-hexamethyldiolaline
(AHTN) and hexahydro-hexamethy-
cyclopenta (g)-2-benzopyran (HHCB)
have been assessed by the Scientific
Committee on Cosmetic and Non-Food
Products (SCCNFP 2002a, 2002b) of the
European Union and were determined to be safe
to human health for their use in cosmetic
products. This was noted by Salvito (2005)
in his response to the work of Luckenbach
and Epel (2005). These ingredients have
even been evaluated by the European
Chemicals Bureau (ECB) for determination of
their environmental hazards [persistence,
bioaccumulation, and toxicity (PBT)], and
the ECB has determined that these materials
are not PBTs (European Chemical Bureau
2004). In addition, the SCCNFP issued
favorable opinions on both AHTN and
HHCB, finding them safe for use in cos-
metic products (SCCNFP 2002a, 2002b).
Further, there have been > 40 publications
in peer-reviewed scientific journals pertaining
to the human health and environmental
safety of polycyclic musks (references avail-
able upon request).

As a peer-reviewed journal whose stated
mission is to present the best science in an
objective manner, we are disappointed with
your continued lack of objectivity and
inability to collect the necessary information
to present a true perspective of the science.
It would appear that your news staff needs
to perform more thorough research in
preparing their reports and that your peer-
review process may be incomplete.

The RIFM, a nonprofit organization
whose research is governed by an independent
expert panel, was established to provide the research and testing necessary to assure the safety of ingredients used in the creation of fragrances. The RIFM has been in existence for > 40 years and has well-established relationships with academia; it is also well known among many regulatory agencies around the world for publishing its work in the peer-reviewed literature. Our organization, as well as others from our industry, are listed on the U.S. Environmental Protection Agency’s website under related links (U.S. EPA 2007).

The authors are employed by the Research Institute for Fragrance Materials, which publishes its work in the peer-reviewed literature under the guidance of an independent scientific panel and receives support from the private sector.

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Editor's note: Forum articles are short and cannot be all-inclusive of a topic. “The Sweet Scent on Baby’s Breath? [Environ Health Perspect 115:A491 (2007)]” focused on the presence of polycyclic musks in breast milk in the United States, which had never been measured before the study by Kannan and colleagues [Environ Sci Technol 41(11):3815–3820 (2007)]. That said, Smith and Salvito are correct that current from an industry source should have been included in this article.

Both researchers interviewed for this article [Environ Health Perspect 115:A491 (2007)] expressed concern about the impact of long-term bioaccumulation of polycyclic musks, as well as the lack of full understanding thereof. This concern is shared by others in the field; for example, the most recent Lake Michigan Lakewide Management Plan (http://www.epa.gov/lakemich/2006/index.html) includes six polycyclic musks—including AHTN and HHCB—one a watch list of pollutants to be reviewed in 2008. As researchers look at different end points (such as efflux transporters) or sentinel species (such as mussels), new data will continue to emerge that warrant further investigation, as well as reporting.

The Interaction of Agricultural Pesticides and Marginal Iodine Nutrition Status as a Cause of Autism Spectrum Disorders
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Roberts et al. (2007) recently reported on the results of their investigation into the relationship between agricultural pesticides and autism spectrum disorders (ASD) and found an association between organochlorines and ASD. One possible mechanism for this relationship is through thyroid disruption (Cheek et al. 1999). There is evidence to suggest that iodine deficiency might be associated with some of the increase in the reported prevalence/incidence of autism (Sullivan and Maberly 2004). For pregnant women who have a marginal iodine nutrition status, the disruption of the thyroid due to exposure to organochlorines could induce iodine deficiency and result in negative effects on the brain of the developing fetus. The U.S. iodine nutrition status has declined markedly over the last three decades, with the current iodine nutrition status among pregnant women being marginal (Caldwell et al. 2005; Hollowell et al. 1998). Because of the current iodine status of pregnant women, the public health Committee of the American Thyroid Association (2006) has recently recommended that all pregnant and lactating women take daily iodine supplements. It is interesting that the ASD case mothers tended to be older and more likely to be non-Hispanic white and non-Hispanic black than controls, which is consistent with a poorer iodine nutrition status in older women and in non-Hispanics in the United States (Caldwell et al. 2005; Hollowell et al. 1998).

Ensuring adequate iodine nutrition status of women, especially throughout pregnancy, is an extremely important public health goal. Given the negative effects of a number of environmental chemicals on the thyroid (Zoeller and Crofton 2000), it becomes increasingly important to ensure that all women have an adequate iodine intake and that the recommended approach to assuring adequate iodine nutrition is through a comprehensive iodized salt program (International Council for Control of Iodine Deficiency Disorders/United Nations Children’s Fund /World Health Organization 2001; Sullivan 2007).

The author is a board member of the International Council for the Control of Iodine Deficiency Disorders.

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Editor’s note: In accordance with journal policy, Roberts et al. were asked whether they wanted to respond to this letter, but they chose not to do so.