Comments on/Suggestions for the NTP's proposed tire-derived crumb rubber research program

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1) As a toxicologist who has examined exposures to, and health risks from, crumb rubber used as infill in synthetic turf fields, I should like to offer the following suggestions for the proposed study of this material by scientists at the National Toxicology Program.
2) First, because of the physical nature of crumb rubber, the oral route of exposure is likely to be the most significant for people, especially children, who play on crumb rubber-filled fields. Crumb rubber is unlikely to be intentionally ingested, but unintentional ingestion cannot be ruled out.
3) Thus, oral bioassays of crumb rubber in laboratory rats could be quite informative.
    a) I recommend that crumb rubber be tested as a whole, suspended in distilled water and administered by gavage.
    b) The NTP research outline mentions testing *extracts* of crumb rubber instead, but I believe that testing any such extracts – whether aqueous and biologically-based, or, worse in my opinion, organic solvent-based – could well yield false-negative results, false-positive results, and/or less meaningful results than tests of the solid material itself.
    c) I also recommend that three dose-rates of crumb rubber be tested. Low, medium, and high dose-rates might be based on estimates of inadvertent soil ingestion by children (on the order of 50 to 500 milligrams per child per day), scaled by body-weight to rats.
    d) The NTP program outline does not mention testing different dose rates, but I believe that doing so would be critical. Prior genetic and other toxicity studies of road tire-debris from ambient air have found that small doses of tire-debris appear to be adaptive and health-protective -- because of the induction of protective levels of heat shock proteins -- even as large doses appear to be toxic (Gualtieri et al., 2008).
    e) Such dose-dependency (with protective effects at low doses, and toxic effects at high doses) has also been observed for zinc (Truong-Tran et al., 2001; Carter et al., 2002; Szuster-Ciesielska et al., 2008; Andreau et al., 2012),

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which constitutes some 1 to 2% of tires by weight (because of the use of zinc oxide in rubber vulcanization).

4) Next, given the ability to detect toxicity, including genotoxicity, and changes in gene expression *in vivo* (using laboratory rats), it is not clear, to me at least, what additional benefit would be gained by performing any *in vitro* assays -- especially since (i) the material at issue is a solid, and (ii) no *in vitro* test can account for the combined effects of absorption, distribution, metabolism, and excretion that occur in people and other animals.
5) Moreover, some *in vitro* testing has already been undertaken. For example, Birkholz et al. (2003) subjected crumb rubber to aggressive extraction, and tested the extract for both aquatic toxicity and mutagenicity. Finding no toxic or mutagenic activity, the authors wrote, "We conclude that the use of tire crumb in playgrounds results in minimal hazard to children and the receiving environment."
6) The NTP research outline also suggests studying, *in vitro*, "specific marker chemicals that are identified as components of the tire crumb rubber (e.g. benzothiazoles)", but it is not clear that this would yield relevant information, especially since it is not known whether ingestion of crumb rubber results in any significant absorption of such compounds.
   a) Prior studies of leachate from crumb rubber have detected only trace, less than part per billion concentrations of benzothiazole (Li et al., 2010).
   b) Moreover, since several pharmaceuticals are benzothiazole-based, existing toxicological data (either published or internal to the U.S. FDA) may provide useful insights, obviating the need for additional study.
   c) More generally, studying crumb rubber as a whole, *in vivo*, necessarily involves studying all of the "marker chemicals" of crumb rubber, and does so in ways that are more relevant and holistic than *in vitro* tests of any individual constituent.
7) Next, the NTP research outline suggests that both respiratory and dermal routes of exposure to crumb rubber may be significant, but the physical and chemical natures of crumb rubber, and empirical data, suggest otherwise.
8) With regard to inhalation, I would point out that crumb rubber infill is in the size range of 10 to 30 mesh, which equates to particle-sizes ranging from 2,000 microns to 600 microns. Such particles are far too large to be inhaled.
   a) Further, tests of existing synthetic turf fields, with crumb rubber that had been weathered, found no rubber particles smaller than 1,000 microns in size (Lim and Walker, 2009).
   b) Small amounts of some VOCs and occasionally sVOCs can sometimes be detected from crumb rubber off-gassing, but numerous studies have found that such emissions result in no significant impact on the quality of ambient

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air, and do not pose health risks any different from those posed by ambient air in general (Lim and Walker, 2009; California Office of Environmental Health Hazard Assessment, 2010; Ginsberg et al., 2011; Schilirò et al., 2012).

   c) Laboratory studies of crumb rubber inhalation would require either (a) modification of the fill material, e.g. by grinding to inhalable particle sizes, or (b) the testing of vapors emitted by crumb rubber under ambient conditions. Modifications such as (a) would result in unrealistic exposures -- since the testing would be of something other than the material of interest. Testing of field-vapors (b) would require extensive efforts to detect and characterize these vapors, and then to somehow concentrate them for bioassaying. I doubt that such efforts would be worthwhile.

9) Next, with regard to risks from dermal contact, I would note that the (i) physical nature of vulcanized rubber, (ii) limited opportunities for sustained, intimate, and substantial dermal contact, (iii) results of "synthetic sweat" extraction studies (Pavilonis et al., 2013), and (iv) results of biomarker studies in athletes playing on crumb rubber-filled fields (Van Rooij and Jongeneelen, 2010) combine to indicate that dermal absorption of constituents of crumb rubber-infill is negligible.
   a) I would add that for soil and grass surfaces, the same may not be true -- grass and soil-smears on skin may persist for some time, so that contact with these materials might result in non-trivial dermal exposures.

10) This brings up another point. There are of course alternatives to crumb rubber-filled fields: these are synthetic fields filled with non-crumb rubber materials, and, of course, natural grass and dirt fields. I think it vitally important that NTP subject these materials to the same sorts of bioassays to which crumb rubber will be subjected.
   a) After all, soils are much more complex than crumb rubber, in that they contain myriad chemicals, both natural and pollution-derived, countless microorganisms, and other biological and biochemical materials.
   b) And other synthetic field infills, such as sand, cork, and/or coconut husks, also contain heterogeneous and largely untested mixtures of chemicals and biochemicals (and, after some time in the environment, would also harbor countless microorganisms).
   c) I urge NTP to test these other materials, in addition to crumb rubber, for their toxic potentials. Wouldn't this sort of comparative information help OEHHA in its evaluation, and help school departments, athletic groups, towns, and cities to make informed choices with regard to playing fields? I believe so.
      i) For example, we might well expect that crumb rubber could induce one pattern of gene expression, while ordinary soils might induce other

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patterns of gene expression. Why focus only on the former, to the exclusion of the latter? What is the basis for simply assuming that playing field soils present no health-risks?

d) Of course, bioassaying soils and other materials would increase the scope and cost of the NTP research program. Fortunately, though, if NTP agrees with my prior comments, then it will have saved considerable time and money by not bothering with extraction, *in vitro* tests, individual constituent tests, or tests meant to mimic inhalation or dermal exposures.

11) Next, I would note that all playing fields and field-materials confer both health benefits and health and safety risks.
   a) Talk with athletes and coaches, and you will hear many of them say that synthetic fields with crumb rubber infill are, empirically, safer than many natural grass and dirt fields, which can become compacted, uneven, muddy, dusty, and otherwise less-than-optimal.
   b) Given the frequency and severity of injuries among athletes, both recreational and professional, it may well be that the chemical properties of infills and sports-fields matter far less than their physical properties, especially with regard to shock-absorption.
   c) Of course, it is not NTP's remit to study shock absorption. In the realm of toxicology, I believe that NTP's agreeing to study crumb rubber, and, again, I hope, its alternatives, is a much-welcomed event. I know that I speak for many in saying that I am glad that NTP will be doing this work. I hope that my comments will prove useful as NTP refines and begins to implement its scope of work.

12) Finally, given the substantial publicity surrounding the issue of crumb rubber in playing fields, I urge NTP to provide clear and written guidance as to the meaning of the types of test-results it expects to obtain. I suggest that before undertaking any specific tests, NTP consider whether and how the likely range of test-results could address the fundamental question, "Does crumb rubber infill pose a significant risk to health?" If specific laboratory tests are not likely to address this question, then they may not be responsive to California OEHHA's request, and may not otherwise be worth conducting.

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