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June 20, 2017

EWG Comments to the National Toxicology Program Board of Scientific Counselors

Beyond Single Chemicals: Evaluating Chemical Mixtures in Consumer Products, Mixture Toxicity, and Exposures in Human Populations

The Environmental Working Group, a nonprofit research and policy organization, is pleased to testify in support of the work done by the National Toxicology Program that will help elucidate the effects of real world exposures to toxic chemicals Americans face. This effort sets the groundwork for a more scientifically robust approach to safety testing of chemicals and mixtures, and ultimately will lead to better protection of public health.

Traditional toxicity testing approaches, carried out one chemical at a time, struggle to account for the additive and synergistic effects of toxic chemicals. As a result, risk assessment paradigms that government agencies rely on fail to assess cumulative exposures to complex chemical mixtures. Meanwhile, Americans continue to be exposed to harmful contaminants via food, water, air and consumer products.

The National Toxicology Program is on the forefront of new methods to study people's exposures to complex chemical mixtures and their combined effects. In March 2016, EWG nominated for NTP to test the Halifax approach of assessing the carcinogenic potential of exposure to chemical mixtures at environmentally relevant levels. The Halifax framework emphasizes that numerous chemicals can trigger cancer development and progression even when these chemicals do not meet the traditional definitions of a carcinogen (Miller 2017).

EWG is eager to see NTP continue research on the potential for mixtures of environmental contaminants to cause cancer and non-cancer effects. The scientific understanding of mixtures effects will greatly benefit from the NTP studies and from expanded monitoring of real-life exposures people face.

With regard to understanding the health risks poses by chemical mixtures, EWG highlights four main messages to the NTP's Board of Scientific Counselors:

- NTP should continue to perform and fund studies of chemical mixtures for cancer and non-cancer effects.
- NTP should review data from biomonitoring studies like the National Health and Nutrition Examination Surveys to understand current human exposures to mixtures.
- EWG agrees that NTP should screen mixtures of chemicals in consumer products, synthetic turf, and household dust for their biological activity.

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- NTP's examination of transgenerational toxicity should consider mixture effects and the potential that humans may be more susceptible than suggested by earlier estimates based on laboratory animal studies.

Details and supporting information for these recommendations are provided below.

1. Research on the toxic effects of chemical mixtures

Animal toxicology studies and carcinogenic evaluations have long focused on administering relatively high doses of single agents, an approach that cannot represent the milieu of exposures that are experienced in reality. Decades of research demonstrated that chemicals associated with cancer initiation and development act via multiple mechanisms, affect multiple pathways and trigger distinct hallmark processes.

As described in an authoritative review written in 2015 by scientists working on the Halifax Project (Goodson 2015), “a series of complimentary exposures acting in concert might prove to be far more carcinogenic than predictions related to any single exposure might suggest.” This hypothesis fits within the current understanding of cancer as a multistage process that can be triggered by different exposures and stressors. From the public health and regulatory perspectives, the ‘Hallmarks of Cancer’ approach provides a systematic framework for identifying and testing the carcinogenicity of chemical mixtures.

EWG applauds NTP's efforts to adopt a more systems-based approach to toxicity testing for cancer and non-cancer effects. The testing of mixtures presents many challenges, but NTP is well-equipped to address them by leveraging the breadth of expertise available within and outside the program.

2. Exploring human exposures to mixtures through biomonitoring data

Biomonitoring data from the National Health and Nutrition Examination Surveys and other studies point to potential health harm from contaminants detected in the bodies of Americans even at the current levels of exposure.

EWG's 2005 body burden study found hundreds of chemicals in the cord blood of newborns, showing that exposures to toxic chemicals begin in the womb. And Tracey Woodruff and colleagues at the University of California, San Francisco, Program for Reproductive Health and the Environment analyzed NHANES data for pregnant women and found similar results (Woodruff 2011).

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The National Institute of Environmental Health Sciences contributed support for a follow up biomonitoring study of maternal and umbilical cord blood published in 2016 in the journal *Environmental Science & Technology*, which found that for many chemicals “fetuses may experience higher exposures than their mothers” (Morello-Frosch 2016). Authors of this study, an interdisciplinary group of scholars from San Francisco Bay Area, highlighted the need to characterize potential health risks of exposure to toxic chemicals during gestation, and called for policies aimed at reducing sources of exposure.

NHANES datasets still hold a lot of unexplored data that can help guide NTP research on mixtures. Up to now, most research projects that grew out of NHANES primarily focused on individual chemicals and chemical families, with little acknowledgement that all of the different classes of contaminants such as pesticides, flame retardants, phthalates, metals and perfluorinated chemicals, co-occur in the same study participants. An analysis of cumulative exposures would likely reveal even greater impact on health than observed from studies of individual contaminants.

EWG encourages NIEHS and NTP to utilize existing biomonitoring data to explore exposures to mixtures, and commission or support new biomonitoring studies that may better address exposures to mixtures for key populations where data is lacking, including pregnant and nursing women, newborns, and very young children.

3. Studying the effects of chemical mixtures in consumer products and household dust

EWG strongly supports the state of Connecticut’s nomination for NTP to screen consumer products using the Tox21 framework for biological effects. This would provide important information about the potential effects of combinations of chemicals that American children and adults face every day. The state of Connecticut proposes a pragmatic starting list of children’s products – including infant sleepwear, car seat padding, sleep mats, plastic bath toys, and baby bottles – as well as household dust. EWG recommends for NTP to pursue testing of these products and media and also include tests of leachate from synthetic turf.

Additionally, EWG urges NTP to consider screening consumer products and ingredients that are relevant for infants and children, even though these products might not be designated specifically for use by children, such as cosmetics, sunscreen ingredients, and household cleaners. For example, research has shown in-vitro estrogenic activity for some cosmetics and sunscreens, but the implications of these exposures for children’s health – and public health generally – are not well characterized. Further, ingredients are not fully disclosed for many consumer products such as cleaning products. NTP research in this important area will provide essential information to help fill a significant data gap.

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Assessing the potential presence and the biological effects of chemicals in consumer products, household dust and synthetic turf will give NTP useful information that can be applied when designing the mixtures research studies.

4. Transgenerational toxicity

NTP is forging new ground in its review of potential transgenerational effects of contaminant exposures. NTP scientists have done an excellent job identifying those human and animal studies that highlight the potential for chemical exposures to be passed down to unexposed great-grandchildren and subsequent generations. But the reality is that most transgenerational impacts will be challenging to examine in humans since people have chronic, multigenerational exposures to chemicals under scrutiny. In humans, it may be very difficult to tease apart the transgenerational effects from the effects of direct exposures during gestation, childhood and adulthood.

Experimental studies in laboratory animals can fill the data gap with respect to transgenerational toxicity and potential effects on people. At the same time, research increasingly shows that people can be more sensitive to the harmful effects of many xenobiotic chemicals than previously estimated from risk assessment based on studies in experimental animals. NTP should consider ways to evaluate whether humans may be more vulnerable to transmissible epigenetic disturbances than laboratory animals.

EWG encourages NTP to keep mixtures in mind when it evaluates potential for multi- and transgenerational effects of chemical exposures. Most studies of transgenerational effects administer individual chemicals, and additional studies could determine whether mixtures of chemicals exert influences on epigenetic programming.

Conclusion

If environmentally relevant mixtures of chemicals are causing or substantially contributing to cancer and the development of other diseases, then the public health consequences are profound. As described in a 2017 paper co-authored by scientists from the Environmental Protection Agency:

... traditional chemical risk assessment is faced with multiple challenges with respect to predicting and preventing disease in human populations, and epidemiological studies increasingly report observations of adverse health effects at exposure levels predicted from animal studies to be safe for humans. This discordance reinforces concerns about the adequacy of



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contemporary risk assessment practices for protecting public health.
(Gwinn 2017)

EWG applauds the Board of Scientific Counselors in its important role of guiding NTP towards implementation of a framework that examines human exposures to complex mixtures and consequences of these exposures on health.

NTP has proposed a variety of projects to achieve these goals, from measuring the activity of mixtures in consumer products and synthetic turf, to developing new tools to study mixture effects in-vivo. NTP's progress on systematic review also builds a framework for integrating available data from animal toxicology, epidemiology and high-throughput technologies. The true goal of this work is develop science and processes to support timely government decision-making about toxic chemicals. It is critical to consider the regulatory implications of this research and how the general public should be protected from the potential adverse health effects of exposures to contaminants mixtures.

We express our full confidence that NTP's findings will serve as a resource for the public interest sector, private sector leaders and officials at every level of government who are responsive to Americans' demands for more robust protection of human and environmental health.

Submitted on behalf of the Environmental Working Group,

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