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Supplemental Material

Community Approaches for Integrating Environmental Exposures into Human Models of Disease

Anne E. Thessen, Cynthia J. Grondin, Resham D. Kulkarni, Susanne Brander, Lisa Truong, Nicole A. Vasilevsky, Tiffany J. Callahan, Lauren E. Chan, Brian Westra, Mary Willis, Sarah E. Rothenberg, Annie M. Jarabek, Lyle Burgoon, Susan A. Korrick, and Melissa A. Haendel

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The objective of the Computable Exposures Workshop was to foster development of data reporting standards and a computational model that will facilitate the inclusion of exposure data in computational analysis of human disease. To this end, the workshop brought together a diverse community to discuss the nature of exposure data and how it might best be integrated with genomic and phenomic data. Workshop participants were asked to develop use cases and competency questions to ensure the resulting model will meet real-world user needs. Below are listed all types of use cases and competency questions developed by workshop participants.

Use Cases. Use cases are narratives written from the perspective of a user trying to complete a specific task in the proposed infrastructure. They are used to help constrain the features of the system so that development effort is focused on a user need.

1. Translate toxicological endpoint terms, like neurodevelopmental toxicity, into phenotype terms from HPO (Human Phenotype Ontology).
2. Use knowledge graph to try and fill in some of the AOP (Adverse Outcome Pathway) or AEP (Aggregate Exposure Pathway) pathways based on the start or end of the pathway.
3. Find out if myelination is affected by Propylthiouracil (PTU) exposure.
4. Find out which biomarkers can be used to examine exposure to metals and metalloids in soil that are ingested via dust.
5. Predict what a disease cluster would look like based on the structure and/or composition of a chemical or mixture that is similar to the chemical/mixture in question.
6. Starting with an endpoint and some possible processes, make a prediction about the possible exposure(s).
7. What levels of benzene exposure in the air over what period of time are likely to cause blood cancers? Which blood cancers?
8. What genetic variants are found in leukemias associated with exposure to Benzene in the air? Pre-leukemias?
9. What genetic variants are associated with greater sensitivity to altered neurologic function from exposure to polychlorinated biphenyls?
10. Can we cluster exposures by shared characteristics e.g., outcomes, chemical structure, etc.?
11. What are the developmental effects in animals and humans exposed prenatally to benzene over short or long periods of time?
12. What are the methylation tag pattern changes related to prenatal exposure to benzene in animals?
13. What is my biggest exposure risk based on my geographical location? How can I prevent or minimize that exposure?
14. What am I exposed to in my particular line of work? How might this impact my health?
15. For what components of X industrial emission do we need more information on health outcomes?
16. After Y policy was implemented, did population exposures to X chemical decrease?

Competency Questions. Competency questions are specific queries with known answers that function as a test of the infrastructure. They could be used to identify missing functionality and data.

1. What are the outcomes of exposure to perchlorate in humans, fish, rats, and frogs?
2. What are all the environmental agents that cause developmental delay in humans?

3. Do I get the expected number of instances based on the data that have been included and what should be inferred by the reasoner?
4. Do all instances of exposure to PTU or perchlorate result in biomarker increased Thyroid-stimulating Hormone or decreased Thyroxine and Triiodothyronine?
5. What are all the instances of PTU or perchlorate that do not result in the expected biomarker changes and return the ancillary data?
6. What are the health endpoints for iodine deficiency in infants and adults?
7. Does iodine deficiency increase susceptibility to PTU and perchlorate?
8. What are all the nutrient deficiencies that can cause iron deficiency anemia?
9. What is a safe amount of iron (daily intake) to consume for someone diagnosed with hereditary hemochromatosis (either heterozygous or homozygous for a certain variant).
10. What nutrients are needed to support a healthy pregnancy? What are the outcomes of deficiencies?
11. What fish species have reduced egg production or fecundity following sublethal pyrethroid exposure?
12. What are all the effects (endpoints and phenotypes) of parental exposure to a chemical stressor on development of the F1 generation in vertebrates?
13. Which chemicals in stormwater run-off have aquatic toxicity data available from assays done at different salinities?
14. List all of the endocrine disruptors known to reduce fecundity in vertebrates.
15. Does calcium supplementation decrease osteoporosis risk?
16. What diseases are prevented or reduced by consuming iodized salt?
17. How might I be exposed to lead? What might happen to me if I am?
18. Am I more susceptible to certain chemicals or disease outcomes because I take the prescription medication x?
19. What environmental contaminants exacerbate/trigger autoimmune disease?
20. Find me all the rare diseases that we know are caused by an environmental exposure.
21. What behaviors increase my exposure to lead?
22. What are all the possible adverse outcomes of having a diet that includes a lot of lead- and arsenic-contaminated plants?
23. What environmental exposures co-occur with traffic air pollution and what are the combined impacts on cardiovascular disease?
24. What chemicals cause liver toxicity?
25. I have elevated serum glutamic-pyruvic transaminase? What does it mean?
26. What pesticide formulations have substances known to be carcinogenic to mammals?
27. What are established biomarkers of exposure and what time-periods do they represent?
28. What is the effectiveness of environmental regulations for reducing health impacts from air and water contaminants?
29. What sources of chemical exposures exist in my community?
30. What vitamins are known to be preventative against the effects of pesticides? Other toxins?
31. What is the relative role of behaviors (diet, physical activity, etc.), environmental (chemical), clinical treatment, etc in disease development (think Patient Advocate Foundation here)
32. How does second hand smoke impact heart rate or other cardiovascular endpoints?
33. What drug/drug interaction or drug/nutrient interaction do I need to be aware of on my current prescription regimen? What non-medication ingredients should I be aware of? (complementary and alternative medicines, adverse outcomes)
34. What cancers are linked to multivitamin supplementation? Or single nutrient supplementation? No nutritive supplementation i.e. Complementary and Alternative Medicine therapies?
35. How do illicit drugs (or legal substances, cannabis, e-cigarettes/vaping, alcohol) impact nutrient absorption? Health status? Behavior? etc.

36. Do particular diseases occur due to environmental exposures following a natural disaster?
37. What types of environmental exposures (and at what frequencies/level) are associated with increased asthma exacerbation?
38. Exposure to what chemical and at what concentration during which time period can lead to macular degeneration and how does this susceptibility change with someone diagnosed with age-related macular degeneration?