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Strengthening Toxic Chemical Risk Assessments to Protect Human Health

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EXECUTIVE SUMMARY

The National Academy of Sciences (NAS) issued three groundbreaking reports over the past few years, but their major recommendations—that the U.S. Environmental Protection Agency (EPA) as well as other government agencies such as the U.S. Food and Drug Administration (FDA) should make several changes to strengthen their toxic chemical risk assessments—have not been heeded. In this paper, we make the case that federal agencies should immediately begin to incorporate these changes into their assessments. The public must be protected from diseases due to toxic chemicals in food, water, air, and consumer products.

The NAS released three reports between 2007 and 2009 that recommended modernizing chemical health evaluations in the United States.[1,2,3] Chemical evaluations, including chemical testing and risk assessment, set allowable levels of human exposure; if testing or assessments are done incorrectly or slowly, people can become ill. Legally-allowable levels of chemical exposures may be unsafe if they are based on outdated or inaccurate science, or on no data at all.

The NAS reports concluded that significant improvements in both chemical testing and risk assessment are needed to protect people from toxic chemicals. Unfortunately, these landmark recommendations are not widely known, and most have not been implemented, even though they would significantly improve current practices.

Risk assessments are used for many purposes, including setting legally-allowable levels of pollutants in the environment, food, and consumer products. Historically, risk assessments have included the following four steps:

1. **Hazard assessment**, which means determining the type of health effects associated with exposure to a chemical.
2. **Dose-response**, which consists of assessing the relationship between exposure and health effects.
3. **Determining the level of exposure** and how it varies across uses and individuals.
4. **Risk characterization**, which combines exposure and dose-response to estimate risks to people.[4]

Unfortunately, with the exception of pesticides, most chemicals used in industrial processes or commercial products are not tested for toxicity. No formal risk assessment is performed because most chemicals on the market today were grandfathered in under the Toxic Substances Control Act (TSCA) of 1976, and their safety has never been assessed. Unlike pharmaceuticals and pesticides, even new chemicals are rarely tested for toxicity and are only subject to a quick and very limited review.

The few chemicals that have been assessed have usually come to regulatory attention because of observed adverse health effects in animals or people. However, many of these assessments take decades to complete (see the NRDC report *The Delay Game* at www.nrdc.org/health/thedelaygame.asp). The NAS review concluded that the current chemical testing and risk assessment process has become "bogged down."[5]

This issue paper discusses and expands on key recommendations from the NAS reports, with the hope of increasing policymakers' understanding of the importance and urgency of adopting these recommendations.

KEY RECOMMENDATIONS

The NAS reports recommended that agencies start by identifying a set of options to reduce hazards or exposures at the earliest stages of decision-making, and then using risk assessment to evaluate the merits of the various options, with public involvement at all stages.[6] Furthermore, the NAS recommended that simplified guidelines and methods be developed to allow risk assessments to be done in a timely fashion, and to facilitate community participation.

The NAS reports recommended four main areas of reform:[3]

1. Identify and incorporate **variability** in human exposure and **vulnerability** into health assessments, so that all people are better protected.
2. When information is missing or unreliable, use **science-based default assumptions** that protect health, rather than waiting for more data, to speed up the chemical assessment and decision-making processes. There should be a clear set of criteria for when to depart from default assumptions.
3. In assessing the risk of chemicals, incorporate information about the potential impacts of exposure to **multiple chemicals**. Consider other factors, such as exposure to biological and radiological agents, and social conditions.
4. Because the population is exposed to multiple chemicals and there is a wide range of susceptibility to chemical exposures, it cannot be presumed that any—even low-level—exposures are risk-free. It should be assumed that **low levels of exposures are associated with some level of risk**, unless there are sufficient data to contradict this assumption.

Each recommendation reflects the most current scientific understanding of environmental chemical risks to better protect people from toxic chemicals. The EPA, the FDA, and other federal and state agencies should quickly incorporate these reforms into their guidelines and procedures, as well as into risk assessments that are currently underway.

The federal agencies charged with protecting our health and safety will help their mission and improve the scientific foundation of their decisions by making these sensible recommendations part of standard practice.

"Without additional modifications, risk assessment might become irrelevant in many decision contexts, and its application might exacerbate the credibility and communications gaps between risk assessors and stakeholders."

—Science and Decisions 2009, p. 213

I. VARIABILITY AND VULNERABILITY

Recommendation #1: Identify and incorporate *variability* in human exposure and *vulnerability* into health assessments, so that all people are better protected.

Important variations that exist between individuals affect their likelihood of developing a disease or other health problem following a chemical exposure. First, the exposure level varies; some people may be exposed to higher levels than others, depending on where they work or live, or what they eat. Second, factors such as age, genetic makeup, diet, socioeconomic status, and pre-existing diseases contribute to variability, making some individuals more susceptible to developing a health problem.

Multiple exposures and susceptibility factors may interact to increase an individual's risk from exposure to a particular chemical. For example, exposure at a critical age or during a critical stage of development, underlying health conditions, nutritional status, or genetic make-up can make it difficult to metabolize a chemical, and may increase susceptibility. Current risk assessment practices do not fully account for this variability, leaving many people inadequately protected by regulatory standards. Also, chemicals are assessed one at a time, not in combination, and the assessments do not incorporate nutritional deficiencies, pre-existing conditions, or genetic factors.

NATIONAL ACADEMY OF SCIENCES RECOMMENDATIONS SUMMARY

In its 2009 report *Science and Decisions: Advancing Risk Assessment*, the NAS recommended a process to address and communicate the uncertainty and variability inherent in a risk assessment—including uncertainty and variability in the measurement of chemical releases into the environment, environmental fate and transport, exposure assessment, dose-response assessment, and risk characterization.[3] The NAS also recommended that the types, sources, extent, and magnitude of vulnerability be explained for each step. In addition to fully characterizing the population at risk, the NAS stated that special attention should be paid to vulnerable individuals and populations that may be particularly susceptible or more highly exposed.

The NAS further recommended that agencies develop clear guidance to help individual risk analysts determine the appropriate level of detail and resources needed for uncertainty and vulnerability analyses, depending on the importance and nature of the decision to be made. This guidance should include an explanation of the process that can be easily understood by the public and decision makers.

A tiered approach, when selecting the level of detail included in the analysis, allows agencies to identify and address the most uncertain and variable factors first; the value of focusing on further details can be determined afterwards. In cancer assessments, for example, the NAS committee calculated that differences in median versus higher-end response to carcinogens differ by a factor of 25.[7] It would be appropriate to assume this level of variability for an early-tier assessment of most cancer-causing chemicals, unless a greater level of detail is needed. The committee also pointed out that variability (differences in exposure or vulnerability) is distinct from uncertainty (data gaps), and that each of these important issues should be addressed separately.

HOW DOES THIS DIFFER FROM CURRENT PRACTICE?

Currently, the EPA takes a narrow view of variability in the human population, and weighs human variability differently for cancer and non-cancer endpoints. In non-cancer risk assessments, variability in the human population is usually treated as just another element of uncertainty, addressed with one "default" factor (usually of 10 and sometimes less), without evaluating whether that adequately accounts for the full range of human variability. Reference values are usually defined without quantifying how disease incidence varies with exposure. In cancer risk assessments, in the absence of any chemical-specific evidence, the EPA generally assumes that there is no human variability. Although the agency does consider increased susceptibility in infants and children, it generally does not consider a fetus as a distinct and vulnerable life stage, and so implicitly assumes that the fetus faces the same cancer risk as an adult.[8] In addition, the EPA only considers early life vulnerability to mutagenic chemicals

(those that cause cancer by directly interacting with DNA), and not to increased risk from chemicals that have other mechanisms of action. One of the NAS recommendations, however, was that "special attention should be given to hormonally active compounds."[9]

Example: Hexavalent Chromium

Hexavalent chromium (also known as CrVI or hex chrome)—used in electroplating, leather tanning, and textile manufacturing—is a known drinking water pollutant and carcinogen, and can contaminate soil and water supplies for decades. Studies by the National Toxicology Program show that oral ingestion of hex chrome causes cancer of the intestine in lab animals; the chemical is a known human carcinogen when it is inhaled.[10]

Industry scientists argue that hex chrome is not carcinogenic to humans when it is ingested because they believe it is mostly detoxified by conversion into non-toxic trivalent chromium (CrIII) in the stomach. This argument presumes that everyone has a stomach capable of rapidly reducing CrVI to CrIII prior to any contact with cells, but is flawed since the reduction process relies on a very acidic gastric environment (a pH of less than 4), which is not present in all individuals.

The California EPA assessed the toxicity of hex chrome and concluded that, "[i]nfants' stomachs are near neutral pH during the first days to weeks after birth, and stomach pH levels generally remain higher than adults during the first three months of life."[11] Furthermore, millions of people take over-the-counter antacid medications or prescription medications to treat gastritis, ulcers, and gastrointestinal reflux disease. These medications, especially the proton pump inhibitors such as Prilosec® or Prevacid®, are designed to increase the pH of the stomach to higher than 4. In fact, in 1999, a national survey reported that there are about 20 million prescriptions for acid-reducing medications,[12] which means millions of people are more vulnerable to the carcinogenic effect of hex chrome. The assumption that everyone has a stomach pH below 4 is unrealistic, and would fail to protect a major vulnerable segment of the population. The NAS recommendations would require the EPA to assure that these people are protected by assuming that CrVI is not detoxified in the stomach.

"The committee encourages EPA to quantify more explicitly variations in exposure and in dose response relationships. The tiered approach to variability assessment discussed in the 2005 guidelines, with multiple risk descriptions for different susceptible subgroups, is a step in the right direction but falls short of what is needed. The guidelines embrace a default of no variability in the absence of chemical specific evidence to the contrary.... Thus, there is a need for a nonzero default to address the variation in the population expected in the absence of chemical-specific data."
—Science and Decisions 2009, p. 112

"The committee recognizes that EPA has the technical capability to do…very detailed and computationally intensive analyses of uncertainty and variability. But such analyses are not necessary in all decision contexts, given that transparency and timeliness are also desirable attributes of a risk assessment, and given that some decisions can be made with less complex analyses. The question is often not about better ways to do these analyses, but about developing a better understanding of when to do these analyses."
—Science and Decisions 2009, p. 112

"Improving characterization of uncertainty and variability in risk assessment comes at a cost, and additional resources and training of risk assessors and risk managers will be required. In the short term, EPA should build the capacity to provide guidance to address and implement the principles of uncertainty and variability analysis."
—Science and Decisions 2009, p. 112

II. SCIENCE-BASED ASSUMPTIONS

Recommendation #2: When information is missing or unreliable, use *scientifically-based default assumptions* that will protect health to improve the timeliness of the chemical assessment and decision-making process, and set clear scientifically-based criteria for when to depart from these assumptions.

Estimating the level of risk posed by a chemical entails considering how toxic or potent the chemical is, and the extent of the exposure. In both cases, there is likely to be substantial information that a scientist or government regulator would like to know, but that doesn't exist. For example, there may be data on effects in laboratory rodents, but not people; data from adults, but not infants and children; or data on the health effects from inhaling the chemical, but not on eating food contaminated with it. There may be studies on certain health outcomes such as cancer, but nothing on potential toxicity to other critical body systems, such as the immune, neurological, or endocrine systems. In the absence of complete data, the EPA must develop as robust an assessment as possible to protect human health and the environment from dangerous exposures to hazardous chemicals.

The EPA currently fills in the gaps with "default" adjustment factors to account for limitations in the data, based on standardized assumptions. For example, if the only available toxicity data is from adult animals, adjustments are made to account for the potentially increased susceptibility of humans compared to animals, and the higher susceptibility of children compared to adults. Typically, these adjustment factors are a mathematical factor of 3-fold or 10-fold, depending on the degree of missing information, and the judgment of the agency. Because there are always unknown variables (data gaps), there will always be assumptions. How these assumptions are applied, however, can make a hazardous chemical appear safe, or a safe chemical appear hazardous.

SUMMARY OF THE NATIONAL ACADEMY OF SCIENCES RECOMMENDATIONS

In *Science and Decisions*, the NAS committee concluded that "established defaults need to be maintained for the steps in the risk assessment that require inferences."[13] The NAS committee recommended that the EPA and other agencies update default factors and assumptions based on the best current science, identify where unstated or implicit assumptions are used, and replace these with explicit assumptions.

These recommendations push the EPA to, "continue and expand use of the best, most current science to support or revise its default assumptions,"[14] which make the assumptions stronger, rather than reducing reliance on them. In fact, the committee specifically recommended that the EPA develop "clear standards for departures from defaults."The committee also noted that establishing "clear criteria for departure from defaults can provide incentives for third parties to produce research" that can reduce uncertainty and, over time, result in more accurate assessments.[15] Importantly, by using the established defaults more often, the EPA avoids "the delay entailed by having to re-examine generic information with every new risk assessment."[16] The agency should also evaluate and quantify, when possible, the impact of the uncertainty associated with a default assumption, including a description of how using a default versus the chosen alternative assumption affects the decisions that protect both the environment and public health.

HOW DOES THIS DIFFER FROM CURRENT PRACTICE?

Some current default assumptions are based on actual numerical data, such as the breathing rate of an adult at rest or during exercise, body weight of a two-year-old toddler, or the amount of water that an adult drinks each day. Other assumptions are rooted in generally accepted scientific principles, such as that if a chemical is harmful to a lab animal it is likely harmful to humans. Other default assumptions include numbers with no quantitative scientific basis, such as assuming that there is a 10-fold range of vulnerability across the human population, or that the difference in vulnerability between a lab rat and a human is also 10-fold. All of the above examples are called explicit defaults because the EPA explicitly states when one is being applied, and identifies its numerical value. The NAS committee was generally very supportive of these default assumptions, and encouraged their continued use, but did note, however, that these defaults should be clearly stated, and their scientific basis updated, to assure they protect health and accomplish their specific goal.

In addition to explicit assumptions, the NAS committee identified unstated assumptions that are not acknowledged, but can be even more influential. The most significant missing default assumption the committee identified was of the safety of any chemical or health endpoint for which

no data exist. For example, most chemicals are not tested for their potential interference with delicate hormonal systems that are critical for normal growth and development, learning, and behavior; the assumption is that chemicals have no effect on hormones—an implicit default assumption that may or may not be true, and that does not protect health.

The NAS committee compiled a list of highly problematic, common implicit defaults in the EPA risk assessments, including:[17]

- For low-dose linear agents (chemicals for which there is no safe level of exposure), all humans are equally susceptible at the same life stage.
- Humans and rodents have the same "biologic clock," and thus tumor incidence from conventional, chronic rodent studies is representative of the effect of a lifetime human exposure after species dose-equivalence adjustments.
- Chemicals have no *in utero* carcinogenic activity.
- There is no difference in susceptibility at different ages for known or likely carcinogens that are not established mutagens.
- Chemicals that lack both adequate epidemiologic and animal bioassay data pose no health risk worthy of regulatory attention, with few exceptions.

NAS recommended that the EPA identify and quantify the implicit assumptions listed above, and use default values for these assumptions until data are available. These recommendations also apply to other federal agencies, such as the FDA and the Consumer Product Safety Commission, neither of which has dealt with this important set of issues.

"Defaults need to be maintained for the steps in risk assessment that require inferences beyond those that can be clearly drawn from the available data or to otherwise fill common data gaps"
—Science and Decisions 2009, p. 192

"EPA should continue and expand use of the best, most current science to support or revise its default assumptions."
—Science and Decisions 2009, p. 112

"Agents that have not been examined sufficiently in epidemiologic or toxicological studies are insufficiently included in or even excluded from risk assessments. Typically, there is no description of the risks potentially posed by these agents in the risk characterization, so their presence often carries no weight in the decision-making."
—Science and Decisions 2009, p. 193

"When EPA elects to depart from a default assumption, it should quantify the implications of using an alternative assumption, including describing how use of the default and the selected alternative influences the risk estimate for risk-management options under consideration."
—Science and Decisions 2009, p. 208

Example: Cancer-Causing Chemicals in Gulf Seafood

The British Petroleum Gulf of Mexico oil spill in 2010 released more than 200 million gallons of oil into U.S. waters. Federal agencies initially closed approximately 37 percent of the Gulf to commercial and recreational fishing. Polycyclic aromatic hydrocarbons (PAHs)—cancer-causing chemicals in crude oil—can accumulate in seafood, especially shellfish.[18] To establish criteria for reopening Gulf fisheries, the FDA calculated levels of concern (LOCs) for each specific type of seafood for the spill.[19]

There were numerous deficiencies in the FDA's seafood safety assessment; in particular, the agency used inappropriate default values, and did not incorporate any default adjustment factor for the susceptibility of a fetus or child.[20] The assessment used a default bodyweight of 80 kilograms (176 lbs.), despite the fact that 75 percent of the female population in the United States weighs less than 80 kg, and an average four- to six-year-old child weighs 21.6 kg (47.6 lbs.).[21] Other federal agencies, such as the national EPA and California EPA, use an adult default bodyweight of 60 kg (132 lbs.) and child-specific bodyweights to assess risks to children. Because risk is inversely proportional to bodyweight, using an excessively high weight estimate systematically underestimates real risks to a significant portion of the population.

Also, the FDA conducted only a risk assessment for adults and did not evaluate risks to developing fetuses or children, although exposure to PAHs during pregnancy causes genetic damage to a developing fetus, including DNA aberrations in specific chromosomes, low birth weight, and intrauterine growth restriction.[22] The increased vulnerability of a developing fetus and child to genotoxins and carcinogens is widely recognized, but the EPA uses an adjustment factor for mutagenic carcinogens for early life exposure, and not prenatal exposure.[23] California EPA's policy is to include an early-life adjustment factor for fetuses and children for all carcinogens, as recommended by the NAS.[24] The lack of the appropriate default adjustment factors means that the FDA's final assessment of Gulf seafood safety left the most vulnerable members of the population unprotected.

III. CUMULATIVE RISK

Recommendation #3: When assessing the risk of chemicals, incorporate the potential impacts of exposure to multiple chemicals. Consider other factors, such as exposure to biological and radiological agents, and social conditions.

Every day, people and wildlife eat, drink, breathe, and absorb through the skin a large variety of chemicals. There may be multiple sources of exposure to the same chemical, from, for example, air or water pollution, food, or product use; it is the aggregate exposure from all these sources that ultimately affects health. People also live in different communities, and their health status, nutrition, and social circumstances vary. The combination of chemicals, health, and lifestyle variables in addition to societal factors, influences the health effects that can result from a chemical exposure.

Unfortunately, risk assessments usually focus on only a single chemical at a time, and sometimes on only one or a few sources of exposure, generally ignoring the actual complexity of the world. Ignoring common, combined exposures to multiple chemical agents and other non-chemical stressors that affect human health can result in underestimating the health effects of chemicals in many individuals and communities. Aggregate and cumulative risk assessments can address these shortcomings by taking into account multiple sources of chemicals in combination with other contributing factors or background exposures.

SUMMARY OF THE NATIONAL ACADEMY OF SCIENCES RECOMMENDATIONS

In the 2008 NAS report *Phthalates and Cumulative Risk Assessment*, the NAS recommended that cumulative risk assessments should be completed for groups of chemicals that have the "same common adverse outcomes."[25] For example, phthalates—industrial chemicals that are used in a wide variety of consumer products—and other chemicals can result in the feminization of a developing male fetus and male genital birth defects, but have different mechanisms of action. Some chemicals mimic estrogen, while others block the androgen hormone receptor; still others affect the levels of androgens—such as testosterone—in the blood. In the EPA's 2006 draft assessment of one phthalate, dibutyl phthalate, the agency did not consider the risk from these chemicals as a group, and did not incorporate the possible effects of additional estrogenic and anti-androgenic chemicals.[26]

In the 2009 report *Science and Decisions*, the NAS underscored the key recommendations of the 2008 *Phthalates* report and added, "There is a need for cumulative risk assessments (CRA)…assessments that include combined risks posed by aggregate exposure to multiple agents or stressors; aggregate exposure includes all routes, pathways, and sources of exposure to a given agent or stressor."[27] The NAS definition of "agent or stressor" includes not only chemicals, but biological agents, radiologic agents, physical agents, and psychosocial stressors.[28] The committee recognized that a broad variety of factors, including nutrition, health status, and psychosocial stress, can increase individual vulnerability to toxic chemicals, and these factors—and their variability across a population—need to be considered in risk assessments to protect public health.

Features of cumulative risk assessment should include the following:

- Consideration of multiple stressors (chemical and non-chemical)
- How the stressors act in concert
- A population-focused assessment (the population and relevant sub-populations should be defined and multiple stressors assessed in terms of the impact on these populations)

Meanwhile, the NAS recommended that the EPA, to make the process more efficient, develop databases and science-based default approaches to incorporate key non-chemical stressors in the absence of population-specific data.[29]

HOW DOES THIS DIFFER FROM CURRENT PRACTICE?

Currently, most chemicals are evaluated individually by the EPA, with the unrealistic underlying presumption that nothing else in the environment interacts with a specific chemical to affect health risks. There are exceptions—the 1996 amendments to the Safe Drinking Water Act require consideration of chemical mixtures in drinking water; when registering food-use pesticides, the 1996 Food Quality Protection Act requires the EPA to consider "aggregate risks" of all uses of a single pesticide that contribute to human exposure and the "cumulative exposure" to people from different pesticides together, according to a shared "mode of

action" for their toxicity. These requirements only apply to pesticides that are registered for use on food crops, and are not currently used for all chemicals, or even for all pesticides.

But even the best of the current EPA approaches is not sufficiently health-protective. As described in the *Phthalates and Cumulative Risk Assessment* report, chemicals that contribute to the same adverse health outcome should be considered together in a cumulative risk assessment, not just those chemicals that cause the health outcome by the same specific biological pathway.[30] For example, through a variety of different pathways and mechanisms, a number of chemicals—lead, mercury, brominated flame retardants, and organophosphate pesticides—can interfere with normal brain development in children.[31,32] A cumulative risk assessment focused on the health endpoint of abnormal brain development and function would necessarily consider the impact of a chemical in the context of background exposures to other chemical and non-chemical stressors that also influence brain development, regardless of the specific mechanism involved.

The recommendation to assess chemicals together that share a common adverse health outcome, such as impaired brain development, has not yet been adopted at the EPA or any other agency, nor has the more far-reaching recommendation from *Science and Decisions*, to incorporate other non-chemical stressors.

Example: Male Reproductive Abnormalities from Mixtures of Pesticides and Plastic Additives, Exacerbated by Stress

Abnormal development of the male reproductive tract—which can result in birth defects, low sperm counts, impaired fertility, and increased risk of testicular cancer—is an increasing public health concern in many countries.[33] Laboratory animal research shows that fetal exposures to certain chemicals can increase the risk of these outcomes by interfering with a variety of developmental processes via different mechanisms. For example, one study reported that in test animals, a mixture of up to 10 chemicals that disrupt male reproductive development by multiple mechanisms resulted in more frequent and severe effects than with any of the chemicals individually.[34] This combined effect would be missed if only those chemicals that share the same mode of action were studied. Many of the chemicals in this test mixture are ones to which people and wildlife are regularly exposed, such as phthalates and certain pesticides. In addition, a study in laboratory rodents recently demonstrated that stress hormones can increase the frequency and severity of harm caused by prenatal exposure to phthalates.[35] Clearly, it is important to consider background exposures from both chemical and non-chemical agents when calculating the risk of exposure to a chemical of interest.

"For cumulative risk assessment, the committee strongly recommends that EPA group chemicals that cause common adverse outcomes and not focus exclusively on structural similarity or on similar mechanisms of action."

—Phthalates and Cumulative Risk Assessment 2008, p. 9

"EPA is increasingly asked to address broader public-health and environmental-health questions involving multiple exposures, complex mixtures, and vulnerability of exposed populations—issues that stakeholder groups (such as communities affected by environmental exposures) often consider to be inadequately captured by current risk assessments."

—Science and Decisions 2009, p. 266

"There is a need for cumulative risk assessments as defined by EPA (EPA 2003)—assessments that include combined risks posed by aggregate exposure to multiple agents or stressors; aggregate exposure includes all routes, pathways, and sources of exposure to a given agent or stressor. Chemical, biologic, radiologic, physical, and psychologic stressors are considered in this definition."

—Science and Decisions 2009, p. 266

IV. LOW-LEVEL EXPOSURES

Recommendation #4: Because the population is exposed to multiple chemicals and there is a wide range of susceptibility to chemical exposures, it cannot be presumed that exposures—even low ones—are risk-free. It should be assumed that *low levels of exposures are associated with some level of risk,* unless there are sufficient data to reject this assumption.

The current approach to evaluating risks for any health effects other than cancer is to assume that there is a "safe" exposure level below which negligible or no health effects will occur, otherwise known as a threshold of response. For carcinogens, the assumption is that there is no threshold unless shown otherwise. In practice, a single chemical is usually tested in a genetically homogeneous strain of rodent, where individuals are raised in the same highly controlled laboratory environment and are healthy, and the dose of the chemical that does not cause obvious harm is used to establish a "safe" threshold. This same threshold (after applying an animal-to-human adjustment factor) is then applied to a diverse human population. This results in levels of many chemicals in food, air, water, and workplaces being declared safe, although the opposite may be true.

According to the NAS, "small chemical exposures in the presence of existing disease processes and other endogenous and exogenous exposures can have linear dose response relationships at low doses."[36] In other words, there may be no safe threshold in the human population for many chemicals. Newer science shows many examples of chemicals that increase the risk of various non-cancer health effects—such as reproductive harm and neurological effects—at low doses, without any scientifically-identifiable threshold.[37,38] Even if a threshold is established in an individual, when risk is assessed across a diverse population, there is a diminishing likelihood that the same threshold exists because some people are more vulnerable than others.

SUMMARY OF THE NAS RECOMMENDATIONS

The NAS committee recommended that agencies use the same approach for addressing risks from both cancer and non-cancer health effects (such as developmental or reproductive effects). The committee also concluded that, "scientific and risk management considerations both support unification of cancer and non-cancer dose response assessment approaches."[39] The agency called for a "unified-dose response framework" that includes a systematic evaluation of factors such as background exposures, disease processes, and inherent vulnerabilities. This evaluation will inform the choice of the appropriate dose-response model.

The NAS also pointed out that the population differs due to age, disease status, nutrition, and other factors. Because of these differences, and the fact that people are exposed to multiple chemicals, science supports using a model that does not have an assumption of a threshold below which exposures cause zero risk in the population. The NAS recommended that a conceptual model be developed that is, "from linear conceptual models unless data are sufficient to reject low-dose linearity; and nonlinear conceptual models otherwise."[40]

In essence, the new NAS recommended approach is to assume that all exposures, even low level, are associated with some level of risk, unless there is sufficient data to the contrary, after accounting for background chemical exposures, biological make-up, and population variability. Neither the EPA nor any other federal or state agency has begun to follow this recommendation.

HOW DOES THIS DIFFER FROM CURRENT PRACTICE?

The EPA, the FDA, and other agencies have a very different approach to dose-response assessments for cancer than for non-cancer health effects. For carcinogens that are known to cause DNA mutations, the current assumption is that there is no safe (zero-risk) level of exposure, and the risk at low doses follows a linear dose-response relationship. In other words, any exposure is associated with some cancer risk and increasing exposure levels are associated with proportionately increasing risks. This linear dose-response model is assumed to apply to all mutagenic carcinogens, unless data show otherwise.

In contrast, for non-cancer health effects (such as neurologic damage, birth defects, immune dysfunction, reproductive abnormalities, and others), the current assumption is that the body's natural defense mechanisms will repair or reverse damage up to a certain point, and hence lead to a dose threshold below which damage will not occur. For these health effects, risk assessments focus on defining the reference dose (RfD) or reference concentration (RfC), which is defined as a dose "likely to be without an appreciable risk of deleterious effects" over a lifetime of exposure.[41] In actual fact, these levels may pose appreciable risks.

Example: Mercury

Prenatal exposure to organic mercury, a common contaminant in seafood, can cause adverse developmental and cognitive effects in children, even at low doses that do not result in effects in the mother. Infants and children are particularly sensitive to the effects of neurotoxins such as mercury because their brains are still developing; children who are exposed to even low concentrations of mercury prenatally are at increased risk of poor performance on neurobehavioral tests, such as those that measure attention, fine motor function, language skills, visual-spatial abilities (like drawing), and verbal memory.

There is evidence that mercury exposure can also affect the immune and reproductive systems. Current research indicates that there is no safe level of mercury in the blood, and an increasing number of studies find risks of health effects at lower and lower exposures.[42,43] Further, infants and children are exposed to multiple chemicals that can adversely impact brain development, including lead and polychlorinated biphenyl (PCBs). The EPA currently has an Oral reference dose (RfD) for mercury that is approximately equivalent to 5.8 parts per billion in blood.[44] Under the current approach, the EPA assumes that the risk of neurological effects below 5.8 parts per billion is zero, which may seriously underestimate the risk to all the women whose blood mercury levels are slightly below the threshold.

"The committee finds that the underlying science is more consistent with a new conceptual framework for dose-response modeling and recommends the agency adopt a unified framework…which includes background processes and exposures in considering risks on the individual and population scales."

—Science and Decisions 2009, p. 135

"Separation of cancer and non-cancer outcomes in dose-response analysis is artificial because non-cancer endpoints can occur without a threshold or low-dose nonlinearity on the population level and in some cases on the individual level. Similarly, the mechanisms of action (MOA) for carcinogens vary and require a flexible but consistent analytic framework. The separation not only is *scientifically unjustified* but leads to *undesirable risk-management outcomes,* including inadequate attention to non-cancer endpoints, especially in benefit-cost analyses"

—Science and Decisions 2009, p. 177 (italics added)

"…[L]ow-dose linearity can arise when the dose-response curves for individuals in the population are nonlinear or even have thresholds but the exposure to the chemical in question adds to prevalent background exposures that are contributing to current disease. The dose response relationship would be determined to a great extent by human variability and background exposure."

—Science and Decisions 2009, p. 141

V. CONCLUSION

The U.S. system for assessing chemicals for safety is broken:

- The vast majority of chemicals in use today have never been tested for their potential to harm human health or the environment.
- Chemicals that have been tested have numerous data gaps and uncertainties.
- The range of human exposures and vulnerability is large and poorly understood.
- The risk assessment process for common chemicals is convoluted and subject to decades of delay due to corporate interference and litigation.

Recent reports from the NAS offer important recommendations to address the problems with the current system and better protect human health from toxic chemicals. Yet these reports have been languishing without the focus and attention they deserve. The EPA, the FDA, and other federal and state agencies must move quickly to incorporate the NAS recommendations into their own agency guidelines, and should begin immediately to incorporate these principles into risk assessments.

Currently, the policies that determine how industrial chemicals are regulated presume that the chemicals are safe in the absence of an assessment. This can be reversed by setting default, interim health-protective standards and restrictions pending completion of a risk assessment. Such a default would stimulate more research, reward chemical manufacturers for producing data instead of avoiding it, and remove many of the incentives that chemical manufacturers now use to delay final assessments. This could be done right away, while agencies plan how to implement the NAS' recommendations.

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