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The developmental origins of disease: implications for primary prevention of diseases in children (and the rest of us)

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Summary. Recent research into the developmental origins of disease, revealing risks to children, shows why the vast majority of laws in the U.S. and probably those of many other countries poorly protect children from toxic substances, and what we might learn from this to better protect other susceptible subpopulations and the rest of us. Once we recognize the numerous limitations of current laws, it becomes incumbent upon decision makers to find and adopt strategies to better protect children. Laws that permit exposure of children and adults to chemical substances without any knowledge of their toxicity should be modified. All of us including children are exposed to myriad chemicals that are toxic and carcinogenic. Yet they remain on the market, e.g., benzene, butadiene, formaldehyde, trichloroethylene, vinyl chloride, all known carcinogens. Current laws should be changed first, to serve the primary prevention of disease as the best means to protect the public's health. Second, this should lead a) to toxicity testing of new products prior to release, and b) to increasing the toxicity testing of products (and pollutants) already in commerce (many were previously grandfathered as "safe"). Third, because instituting much-needed political change will very likely be slow, in the short to intermediate term scientists should seek to use existing scientific tools to more quickly identify toxic products and to develop new types of studies with the goal of preventing harm to the public. Scientific research may to some extent compensate for legal inaction.

Key words: developmental origins of disease, postmarket laws, premarket laws, mechanistic data

«Le origini di malattia in età di sviluppo: implicazioni per la prevenzione primaria di malattie nei bambini (e per il resto di noi)»

Riassunto. Recenti ricerche sulle origini di malattia da ricercarsi nell'età dello sviluppo, hanno rivelato la presenza di rischi per i bambini e mostrato che la maggior parte delle leggi negli USA e probabilmente anche in molti altri stati, scarsamente riescono a proteggere i bambini dalle sostanze tossiche ambientali. Partendo da questa constatazione, dobbiamo imparare a proteggere in maniera migliore altre sotto-popolazioni più suscettibili e di conseguenza anche il resto delle persone. Quindi diventa incombente per i fautori delle leggi in ambito di salute pubblica, trovare ed adottare strategie per meglio proteggere i bambini. Le leggi che permettono l'esposizione dei bambini e degli adulti a sostanze chimiche senza alcuna conoscenza circa la loro tossicità, dovrebbero essere modificate. Tutti noi, compresi i bambini, siamo esposti a miriadi di agenti chimici dimostrati tossici e cancerogeni e che tuttora sono presenti sul mercato (ad esempio: benzene, butadiene, formaldeide, tricloroetilene, cloruro di vinile, tutti cancerogeni conosciuti). Al fine di attuare una migliore strategia per proteggere la salute pubblica, si dovrebbero innanzitutto cambiare le leggi correnti per consentire la prevenzione primaria delle malattie. In secondo luogo, questo dovrebbe condurre a: a) testare la tossicità dei prodotti prima della vendita e b) aumentare i tests di tossicità dei prodotti (ed inquinanti) già in commercio (poiché molti sono stati in precedenza certificati come "sicuri"). Terzo, poiché i cambiamenti più necessari in ambito politico-istituzionale avvengono in maniera piuttosto lenta, gli scienziati, nel breve-medio termine, dovrebbero diffondere l'utilizzo dei mezzi scientifici esistenti per identificare il più presto possibile i prodotti tossici e

sviluppare nuove tipologie di studi che abbiano come obiettivo la prevenzione della salute pubblica. La ricerca scientifica dovrebbe così in qualche modo compensare la mancanza di azione da parte degli organi legislativi.

Parole chiave: origini di malattia in età di sviluppo, leggi sui prodotti già in commercio, leggi sui prodotti pre-commercio, dati meccanicistici

Introduction

In recent decades scientific research has revealed that children are especially vulnerable to molecular invasion and particularly susceptible to diseases, dysfunction, or even premature death when transient molecular invaders become biologically embedded in their bodies (1). Children are typically at even greater risk than adults from a variety of diseases caused by chemical substances (2-4). If we care about our and others' children, this increases the urgency to reduce risks and to prevent harm to them.

This article discusses some research revealing risks to children, why the vast majority of laws in the U.S. and probably those of many other countries poorly protect children from toxic molecules, and what we might learn from this to better protect the public. Once we recognize some of the present limitations, it becomes incumbent upon decision makers to find and adopt strategies to protect children (and other susceptible subpopulations). Current laws should be changed first, to serve the primary prevention of disease as the best means to protect the public's health. Second, laws that permit exposure of children and adults to chemical substances without any knowledge of their toxicity should be modified: a) to demand toxicity testing of new products and b) to increase the toxicity testing on products (and pollutants) already in commerce. Third, because instituting much-needed political change will most likely be slow, in the short to intermediate term scientists should seek to use existing scientific tools to more quickly identify toxic products and to develop new types of studies with the goal of preventing harm to the public (5-7).

Generic legal strategies to protect the public health

In the United States laws governing chemical products are of two kinds: premarket and postmarket (3). These presumably resemble different approaches to protecting the public's health in other countries. *Premarket* laws seek to identify risks from products *before* they enter commerce and people are exposed, by requiring a battery of toxicity tests on the products and scientific review of the results. In the U.S. pharmaceuticals and pesticides (and to a lesser extent direct and indirect food additives) are the main chemical products governed by premarket laws. Under such laws chemical products must be routinely tested for their toxicity, subjected to independent scientific review and review by a public health agency - the Food and Drug Administration (FDA) for pharmaceuticals or the Environmental Protection Agency (EPA) for pesticides - before they may enter the market and be commercialized.

Premarket laws best serve the aims of primary prevention of cancer and other diseases and dysfunction as long as chemical agents are identified as toxic before they enter commerce (7). Even these laws have at least two limitations. Some data may be withheld from the public under provisions of confidential business information. Also, on occasion despite the best efforts testing may not reveal a toxicant and these products will have to be withdrawn from the market at a later stage.

Postmarket environmental health laws do not require manufacturers of products, or those who might have them in waste streams or who might use them, to routinely test for and identify risks from the products before they enter the environment and people are exposed. Under the Toxic Substances Control Act (TSCA, 1976) in the U.S., which governs an overwhelming percentage of new chemical creations (probably approaching 90%), companies need only submit the most minimal data (more below) (3, 8). Currently, this law is under review in the U.S. Congress for amendment and has passed the House of Representatives (9). However, whether both houses will agree on amendments it so that it becomes law and whether any

changes will better protect the public's health remains to be seen.

Under TSCA the U.S. Environmental Protection Agency (EPA) may legally require toxicity data about a proposed chemical product, but this is not an easy process to utilize because a fairly elaborate regulatory process burdens it. Postmarket laws seek to prevent health harm from occurring by identifying risks after products are in the market and exposures have occurred or are likely to exist, but ideally before risks materialize into harm (3). (It is unlikely that risk assessment would prevent all harm because such procedures are so time-consuming (3)).

One gesture in TSCA toward trying to detect the toxicity of chemicals before public exposure results led to a pre-market "premanufacture notification" provision for new chemicals. Companies seeking to manufacture new chemicals or use existing chemicals for substantial new purposes must submit a Premanufacture Notification (PMN) to the EPA before they may manufacture the product. The PMN must include "all available data on chemical identity, production volume, by-products, use, environmental release, disposal practices, and human exposures" (10). If a company has conducted any toxicity tests, it must submit them, but if it has not, there is nothing to submit. Beyond this the EPA "must take what it is given" (11). The EPA can request additional data, but in that case it must have data showing that a substance already poses an "unreasonable risk" to health or the environment (3, 8). Moreover, this is a burdensome process discouraging its use (3).

Unfortunately and quite importantly, the law requires *no* routine *toxicity* or *health effects data* before a product is proposed for manufacture and commercialization, unless it is likely to pose "unreasonable risks" to public health or the environment (8). Of course, a company is not likely to have this information unless it has conducted appropriate tests. At the time legislators and others perhaps hoped that companies would do more toxicity testing and report their results in order to protect the public (3). This voluntary option has not been taken and in fact many companies have ceased testing their creations at all. Some have closed down their toxicology departments (12, 13). Quite significantly, TSCA explicitly "forbids promulgation of blanket testing requirements for all new chemicals" (8).

Postmarket laws apply to occupational settings, drinking water, air pollutants, effluents released into rivers and navigable waters, toxic waste dumps, and general chemicals under the TSCA. The U.S. and most countries live in a postmarket world. These laws largely frame responses to potentially toxic industrial chemicals, as well ideas about preventing diseases and dysfunction to children and adults alike. Under them public health agencies have no choice but to *react* to the presence of risks or, more likely, to harm, before exposures and risks can be reduced or the products removed from commerce.

Importantly, recent research on the developmental origins of disease renders *postmarket* and reactive approaches to environmental health problems quite inadequate to protect children and adults alike.

The developmental origins of disease

Scientific research into the developmental origins of disease reveals that protection of the public from chemical exposure is much more complicated than perhaps it had been regarded in the past. This research has found that many diseases "may have their origin during development and not during adult life when the disease becomes apparent" (14). Typically, "*In utero* nutrition and/or *in utero* or neonatal exposure to environmental toxicants alter susceptibility to disease later in life [by affecting] the programming of tissue function that occurs during development… These toxicant-induced pathogenic responses are most likely the result of altered gene expression or altered protein regulation [instances of epigenetic changes, not a change in the genetic sequence] [resulting in] altered cell production and cell differentiation" (14). The consequence is that genes do not express themselves as they normally would or are caused to express themselves at inopportune times, possibly leading to disease or dysfunction, often later in life. While an epigenetic mechanism may not be the only one to account for such predispositions to disease during development, it appears to be quite important. The upshot is that such biological changes can "result in death, malformations, low birth weight or functional changes including increased susceptibility to diseases later in life" (14).

Humans readily absorb toxic chemicals

Concomitant with these developments, researchers have also found that humans and other mammals are exquisitely permeable to toxic chemicals. That is, when they are exposed they readily absorb the vast majority of substances into their bodies and then retain them for short or quite long periods of time. For instance, the U.S. Center for Disease Control and Prevention has developed reliable protocols revealing that as a totality U.S. citizens are contaminated by at least 265 human made chemical creations. Many are known toxicants (15). Pregnant women are typically contaminated with about 43 substances, and women's contamination is often shared with developing children *in utero* - the placenta is no significant barrier (16). The result is that babies have been born with numerous industrial chemicals in their bodies, most being known toxicants (17, 18).

The placenta is an inadequate barrier to most toxicants

It has been clear for some time that a pregnant woman shares exogenous chemical compounds in her body with a developing fetus (2, 3, 16-18). In the 1960s the womb was regarded as something like a protective capsule, relatively impermeable to circulating drugs or toxicants (19). However that view quickly changed with the public health catastrophes of Thalidomide (which caused shortened limb defects and other problems, 1960s) (3) the methylmercury contamination of Minimata Bay in Japan contaminating fish (ingestion of which caused a variety of neurological and other problems in people and animals, 1950s) (20) and the pharmaceutical diethylstilbestrol (taken by pregnant women, which caused vaginal/cervical cancer in their female children when they reached about twenty years of age, 1960-1970s) (2, 3, 21). Moreover, it has been known for some time that long-term studies in animals have shown that chemicals are more carcinogenic when given during gestation (22, 23).

Because of recent research into the developmental origins of disease, there is now much more evidence of this generic effect, influencing one leading researcher to note that there is "no placental barrier per se*:* the vast majority of chemicals given the pregnant animal (or woman) reach the fetus in significant concentrations soon after administration" (24). New technologies are beginning to show similar problems: nanoparticles can move from mom to baby through the placenta (25).

Children are exposed to larger doses per body weight than adults

Developing children are exposed to *larger doses of toxicants relative to the body weight* than the mother, via cord blood and breast milk (3). For example, mercury concentrations can be at least 5 times higher in fetal brain than in mother's blood (26), while lipophilic substances can be concentrated in cord blood and breast milk, with PCBs up to dozens of times greater (27). Lead stored in a pregnant mother's bones will be mobilized as part of the "calcium stream" that delivers calcium to a developing child (19). Recently, scientists have found that fetuses have near "universal exposure" to bisphenol A (BPA) with free BPA (a more harmful variant) found in higher concentrations in fetal livers than in maternal blood or urine (28, 29).

Once born children have higher metabolism, breathing, and absorption rates, along with higher fluid and food intake rates per body weight than do adults (30). They also play close to ground/floor, "mouth" everything they can get their hands on, and ingest much of what is present including any toxicants in dust or dirt. For instance, formaldehyde long used as an adhesive for pressed woods and carpeting results in higher body burdens in children (31).

Children have reduced defenses to toxicants

Children also have lesser defenses against many toxicants and diseases. They have *less developed* immune systems, blood brain barriers, livers, and detoxifying enzymes compared with adults (2, 3, 32, 33). In some instances lesser developed enzymes may provide protection against toxicants that require enzymatic reduction of a less harmful or nonharmful substance into a more harmful one, but lacking detoxifying enzymes tipically adds to their vulnerability.

Children are more sensitive to toxicants

In general, young children "tend to be more sensitive to adverse environmental influences... [with] tis-

sues undergoing rapid cell division, and [having] much less capacity to metabolize [and detoxify] xenobiotics than [do adults]" (2, 34). While this is in general true, it is especially critical for two organ systems: the brain and the immune system. If either is damaged early in life, it appears that the harm may last a lifetime. The developing brain has windows of "unique susceptibility," unlike adult brains-it must grow from a single cell into billions following "precise pathways" in the "correct sequence" connected in the "proper ways" to function properly (32). The brain has "one chance to get it right" (35). The immune system resembles the brain, damage to it being similarly permanent (30, 33). In fact Dietert and co-authors have found that immune system diseases in children increase the likelihood of later life deficiencies in their immune systems (36).

In sum, the generic picture is that developing children have greater exposures per body weight, are more susceptible to toxicants, and have lesser defenses than adults. Quite significantly, if children's diseases are triggered or predisposed early in life, they have a much longer lifespan than adults for the disease or dysfunction to appear or a much longer period of time for it to burden their lives.

Genetic variation increases vulnerability to diseases

Beyond this generic picture, genetic variation can increase children's vulnerability. Some children are more susceptible to polycyclic aromatic hydrocarbons (37) some are more susceptible to organophosphate pesticides (38), and some have special vulnerabilities to methylmercury (39). (Genetic variation can also render some more fortunate children less susceptible to disease). In addition, exposure can induce independent additive effects that can increase a person's vulnerability at the same endpoint. Substances can affect different "upstream" pathways producing jointly additive effects, but not affecting the same cellular receptors. For instance, dioxin-like PCBs, non-dioxin-like PCBs, perchlorate, and brominated fire retardants (PBDEs), each operating by different biological pathways, can reduce thyroid concentrations in pregnant women, potentially posing neurological risks to developing fetuses (40). Researchers have also found similar independent additive effects acting by different mechanisms that can affect the immune system (40, 41).

Tiny exposures can trigger diseases

In at least some instances, quite small exposures can cause adverse effects to children. While it is well-known that lead can contribute to lower IQs, violent behavior, motor skill problems and attention disorders, along with cardiovascular disease (42-44) it may be less well recognized that there appears to be no threshold for lead toxicity during development, early childhood, or even adulthood (45, 46). Similarly, mutagenic carcinogens appear to have no threshold for toxicity during development, early childhood, or even adulthood (47). And, at least for one thalidomide baby a single dose of a 50 mg or 100 mg pill caused malformations (48).

In animal studies brief, tiny exposures to DES (or to some other synthetic estrogens) are sufficient to cause obesity in mice as well as transplacental carcinogenesis (49-52). A single dose of valproic acid (anti-epileptic drug) was found in animal studies to cause autism-like behavior (53).

Moreover, some hormone-like substances do not follow dose-response curves that might be more typical of many carcinogens. Vandenberg *et al.* found that low doses of many hormones can cause greater harm than larger doses. For instance, high doses of tamoxifen inhibit growth of contralateral breast cancer, serving a therapeutic function when a woman has breast cancer and may prevent or delay the occurrence of breast cancer in women at increased risk for this disease (54). At lower concentrations it stimulates breast cancer cell growth. It can also increase risks for endometrial cancer. At the highest doses tamoxifen is acutely toxic (54). Similar dose-response curves are seen in DES-exposed mice (52).

Multigenerational and transgenerational effects

The above examples are more common instances of diseases or dysfunctions caused by *in utero* or early life exposure to toxicants. Both early animal research by Turusov *et al.* (1992) and more recent studies by Skinner reveal that exposure to the germ cells *in utero* can contribute to adverse effects that are multigenerational (spanning more than one generation) (55) or

even transgenerational (spanning generations out to great grand offspring or great, great grand offspring (56, 57).

In utero exposure of pregnant rats to some pesticides and bisphenol A (each individually) causes sperm damage, sterility, and a host of cancers in their male offspring (sons) and their son's offspring after being bred with wild types. These particular adverse effects are further associated with additional diseases: prostate disease, kidney disease, immune system abnormalities, testis abnormalities, and tumor development. Skinner's lab found that the effects persisted through four generations, making them transgenerational (56, 57).

Skinner also conducted animal experiments on a range of substances to determine how they affected female offspring. Each of 5 classes of substances - 1) vinclozolin, 2) permethrin and DEET, 3) a plastics mixture (BPA, dibulyphthalate and DEHP), 4) dioxin and 5) jet fuel - administered individually to pregnant rats during gestation days 8-15 when female reproductive organs were developing, caused the offspring through 4 generations to develop:

- Polycystic ovarian disease (infrequent ovulation, high androgen levels, multiple persistent ovarian cysts; often insulin resistance [seen in 6-18% women].
- Primary ovarian insufficiency (POI) - which decreases the primordial follicle pool of eggs (thus reducing chances of pregnancy over a lifetime) [seen in 1% of women] (58).

Transient exposures can become biologically embedded in people

The upshot of the research reviewed above is that what appear to be *transient, often tiny, but ill-timed* exposures can become biologically *embedded* in individuals, in their children or grandchildren (multigenerational), and, with appropriate timing, in family lines (transgenerational) (1, 3). That is, in many circumstances what seem to be brief, occasionally one-time, exposures can become entrenched biologically, causing diseases or dysfunctions in the affected animal or human offspring, or later generations. Thus, toxic exposures can have more permanent adverse effects by being fixed into our biology.

"Bad daddy" influences

Much of the focus has been on how *in utero* exposures can contribute to adverse effects. However, the contamination of fathers with what has been called "Bad Daddy" factors may also predispose offspring to diseases (59). Chemotherapeutic agents can degrade the quality of sperm, e.g., causing chromosome breaks, resulting in spontaneous abortion and abnormally slow growth. Lead and mercury can cause miscarriages. Paternal exposures to pesticides can trigger childhood leukemia. Solvents, cleaning solutions, dyes, paints and other chemicals contribute to birth defects, and childhood cancer (59).

Pharmaceuticals are not free from problems for males. Paxil (an antidepressant) can contribute to a five-fold increase in sperm fragmentation, which increases the chances of miscarriage. Exposure of either parent to lead can result in still-births or other fetal problems. Anesthetic gases can increase miscarriages. Morphine can lead to profoundly abnormal, chronic late blooming, underweight offspring (59). Even various forms of nutrition and stress in males can contribute to adverse effects in the offspring of humans or animals. A father's ingestion of betel nuts tends to create weight problems for sons and this may extend to grandsons (animal data). In animals, the stress of fathers can be passed to their offspring (60).

The evidentiary picture of the developmental basis of disease is something like a pointillist painting: parts of the picture filled with numerous data points, others partially filled, some blank, but the general background reasonably solid (3). Science points to a substantial range of problems in which exposure to toxicants can contribute to diseases, dysfunctions or premature death for developing children.

What do these findings suggest for public health policy?

Given the exquisite vulnerability of children during development and humans' substantial permeability to potentially toxic molecules in a world awash with some tested, but many untested, and some known and some unknown toxicants, this suggests that there

should be considerable urgency to protect children, other susceptible subpopulations, and, of course, less vulnerable adults. This seems to argue for a robust primary prevention strategy to set children on a healthy path so that they can be fully functioning and biologically fit over their lifetimes. At present failure to address these issues will likely result in unjust curtailing of some citizens' chances at fair equality of opportunities over a lifetime (3, 61).

In the U.S. and other countries for new substances proposed for commerce, a precautionary and primary prevention strategy should lead to premarket testing of products for various toxic endpoints and independent scientific evaluation of the tests before substances can enter commerce. Such testing would approach but not be identical to that of pharmaceuticals and pesticides, probably more closely resembling pesticides (3). The European Union appears to be on its way to better protecting the public's health with toxicity testing under its REACH [Registration, Evaluation, Authorisation and Restriction of Chemicals] legislation that applies to both new and existing chemicals and products in the market (62).

Moreover, just restricting attention to childhood diseases shows they are quite expensive - $76.6 billion in 2008 alone for the portion of diseases attributable to lead poisoning, childhood cancer, asthma, intellectual disability, autism, and attention deficit disorder (3.5% of all healthcare costs) (63). Given these costs, premarket toxicity testing of new substances seems quite reasonable and efficient. In the European Union under the REACH legislation the 11-year cost to test and review 30,000 chemicals is about $5 billion (€3.5 billion), or less than 1 euro per European citizen per year for 11 years (3, 64). Premarket testing to reduce adverse health effects, suffering and death would be a bargain at multiples of that amount (3).

For existing substances in commerce the current picture is much bleaker. For instance the U.S. EPA and the U.S. Occupational Safety and Health Administration (OSHA) have had a variety of known toxicants for which risk data were urgently needed to institute health protections. These have been in a queue for many years simply to estimate their theoretical risks. However, these substances have become mired in procrastination, obfuscation, and endless economic and political disputes - TCE (20+ years), dioxin (20+ years), perchloroethylene (13+ years), formaldehyde (11+ years), and naphthalene (9+ years) (65). There may have been some, but in general little, improvement since that 2008 report. Without risk estimations public health agencies cannot proceed to reduce toxic effects. Such postmarket laws afford the public quite poor protection.

However, in the U.S. and perhaps other countries that currently rely on postmarket laws it will not be easy to institute premarket toxicity testing because the creators of chemical products are likely to resist such efforts strenuously. New products are not the only problem; existing toxicants in commerce, in toxic waste dumps and in pollutants will remain in public spaces, almost certainly contaminating the populace until they are identified and their risks reduced or eliminated.

What can be done to protect the public from existing toxicants in the market?

If substances are in commerce and there are exposures via parents or direct exposure to young children, this increases the chances that some children will be vulnerable to diseases before even well-motivated, politically unencumbered, and well-funded public health officials can recognize the causal pathway and take steps to reduce or eliminate risks. Political efforts to frustrate public health efforts substantially add to the problems. Postmarket laws largely fail to prevent diseases and are far from precautionary in spirit or fact (3).

In this circumstance some scientific findings have the potential to assist and perhaps greatly assist identifying and assessing toxicants. The most promising evidence illustrating this issue concerns carcinogens and these are used as examples. However, scientists could begin to explore toxic endpoints of hormones and other toxicants by analogy with what has been learned from research into carcinogens.

For carcinogens the International Agency for Research on Cancer and the U.S. National Toxicology Program, utilizing mechanistic evidence, have upgraded numerous substances that previously had had less supportive evidence for their carcinogenicity. For instance, IARC now classifies substances as

known human carcinogens based on data other than sufficient human epidemiological studies; thus, if public health agencies can act on the IARC data, citizens will suffer fewer adverse effects before harm can be reduced. For instance, in addition to having evidence that a substance is a known human carcinogen based on epidemiological studies, that have "established a causal relationship between exposure to an agent and human cancer," a substance may now be classified as a "known" human carcinogen when: 1) evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and 2) strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity (66).

For instance, IARC has done this for Aristolochic acid, benzo[a]pyrene, ethylene oxide, and phenacetin (67).

Consequently, while there may be some evidence that a substance has been found in epidemiological studies to cause cancer in humans, but it is not definitive, both human and animal data can be importantly supplemented by mechanistic data to provide confidence that a substance is properly classified as a known human carcinogen. Mechanistic data include "data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents" (66). Moreover, finding mechanistic evidence for the carcinogenicity of a substance may be easier and quicker than awaiting the results of long-term human epidemiological or similar detailed, costly and labor-intensive animal data.

More important for public health purposes is that scientific data sufficient for "probable human carcinogens" assist in identifying carcinogens at an earlier stage and better protecting public health. The descriptor "probable human carcinogen" is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A (66).

Importantly, IARC regards both probable and known human carcinogens as "equally compelling cancer hazard[s]"; IARC's classification system simply distinguishes whether the data on which that conclusion is based include strong evidence in exposed humans (68). Thus, classification of a substance as a "probable human carcinogen" should suffice for public health purposes.

In addition, just as mechanistic evidence can substitute "for conventional epidemiological studies when there is less than sufficient evidence in humans" … [m]echanistic evidence can also substitute for conventional cancer bioassays when there is less than sufficient evidence in experimental animals" (68).

Because of the importance now given to mechanistic evidence in identifying carcinogens, IARC has recently upgraded six agents to "known human carcinogens" (Areca nut, benzo[a]pyrene, ethylene oxide, neutrons, NNN and NNK, 2,3,7,8-tetrachlorodibenzo-para-dioxin) and 38 to probable human carcinogens, including acrylamide, benzidine-based dyes, CCNU, epichlorohydrin, clycidol, MOCA, and styrene-7,8-oxide (68). This effort suggests that at least 38 substances, which previously would not have been considered as plausible for regulatory action by national regulatory bodies (because they were judged somewhat short of being "probable" human carcinogens), now are ripe for regulation. The greater scientific certainty about the toxicity of these substances may motivate governmental agencies to act on them quicker to protect the public, the workforce and children. Of course, even having authoritative scientific findings may not budge political and regulatory institutions, but with the backing of science they have good reason to pursue health protections.

Mechanistic data about substances is far from a cure-all to serve the public. However, IARC's use of such data points to one way to possibly quicker post-market public health protection and suggests that public health could benefit in major ways by similar

scientific advances that might find precursors to adverse effects in humans. Importantly, the IARC Monographs have made, and continue to make, major contributions to the scientific underpinning for societal action to improve the public's health (69).

The U.S. National Toxicology Program is a national institution analogous to IARC. It has the U.S.'s only official national listing of carcinogens. It currently lists 56 substances as known human carcinogens and 187 chemicals as reasonably anticipated to be human carcinogens to a total of 243. Its procedure for classifying substances as known or probable human carcinogens is reasonably similar of that of the IARC, although there are some differences: IARC has a much larger group of compounds identified as known human carcinogens (117 v. 56), while NTP has a much larger group classified as "probable" human carcinogens (74 v. 187) (70).

Finally, before closing, one other promising kind of mechanistic evidence should be mentioned. The National Academy of Sciences has recommended "a transformative paradigm shift" in toxicity testing in order to detect "upstream events," that is, early perturbations in biological processes that would lead to disease (71). It urges that researchers should look for "disruption of normal cellular pathways and biological programming" for reliable clues to diseases. A group of researchers has followed this up looking for precursors of breast cancer (72). While this approach seems promising and provides a possible new model for using mechanistic information to screen for carcinogens, further research is need in order to develop the ideas and implement them (72).

Conclusion

In the absence of slow to non-existent modifications in postmarket laws to better protect the public, the scientific community with imaginative research findings might better advance public health protection in the meantime. Moreover, for suspected toxicants in the market, in toxic waste dumps or in the air, water, or soil, mechanistic data may permit quicker identification of them as probable toxic hazards to humans and, one hopes, hasten their regulation. Scientific research may to some extent compensate for legal inaction. This would indeed be beneficial to public health.

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