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MiniReview

The Legal Failure to Prevent Subclinical Developmental Toxicity

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Abstract: Legal systems appear to function poorly to identify and prevent subclinical developmental toxic effects in children that can lead to long-term harm. In the USA, the vast majority of substances enter commerce without any legally required testing (under so-called 'post-market' laws). In 1984, less than 20% of all substances had been subject to pre-market testing and there has been little change since. Once substances are suspected of contributing to harm, an administration agency has the burden to show risks or harms and their causes, an increasingly difficult demonstration. Post-market laws tend to produce no data prior to exposures and any protections result after some harm may have occurred. *Pre-market screening* laws such as the US Toxic Substances Control Act provide little data or protection. *Pre-market testing and approval* laws, analogous to US drug and pesticide laws, offer better approaches for identifying and eliminating toxicants before they result in harm, but do not apply to many products and rarely include concerns for developmental toxicity. The Registration, Evaluation, Authorization and Restriction of Chemicals legislation in the European Union has greater promise for the identification of new or existing toxicants. However, the potential for serious, subtle subclinical developmental effects provides reasons to pursue a more precautionary approach to identifying potential toxicants and forestalling harms. This paper sketches a more robust precautionary law and a more substantial departure from existing laws that would treat chemical invasions as trespasses. The scientific community can assist legal efforts by credibly publicizing the seriousness of subclinical developmental effects.

The papers of this conference show that, 'the periods of embryonic, foetal and infant development are remarkably susceptible to environmental hazards. Toxic exposures to chemical pollutants during these windows of increased susceptibility can cause disease and disability in infants, children and across the entire span of human life' [1]. Such exposures during development can cause adverse effects in several major organ systems of the body. For example, the developing brain has windows of 'unique susceptibility' (more vulnerable than adult brains) with millions of changes in a short period of time following 'precise pathways' within 'tightly controlled time frame[s]' in the 'correct sequence' [2]. External insults to this precise process can cause adverse neurological events. Moreover, developing foetuses, newborns and young children may have greater exposures than adults on a unit weight basis, and they have reduced ability to detoxify invading substances. The result can be reduction in motor skills or IQ, and in some cases onset of Alzheimer's and Parkinson's diseases later in life. Other developing systems, the reproductive, immune and cardiovascular, can also be adversely affected [1].

It is very difficult for current laws to prevent these subtle, long-term and potentially quite substantial effects. The US legal system serves as the major example, because I know it best, but it is likely to be comparatively representative of other legal systems. I briefly consider some of the promising proposals under the European Union's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) legislation, sketch a more health protective model and suggest a different approach altogether on the model of a trespass or illegitimate invasion.

To date, the US legal system has not produced data about the toxicity of many substances nor regulated well chemicals that can cause subclinical toxicity. Moreover, it appears highly unlikely that existing legal structures could function very well to prevent such effects. Consequently, different legal approaches will be needed to prevent subclinical effects and their consequences in children.

Generic legal strategies

There are broadly speaking two generic legal strategies for trying to prevent harms to human health from environmental exposures to toxicants with one hybrid law from California (Proposition 65) combining aspects of each (fig. 1).

Post-market laws

The US legal system regulates the vast majority of chemical substances (between 80% and 90%) with *post-market* laws.

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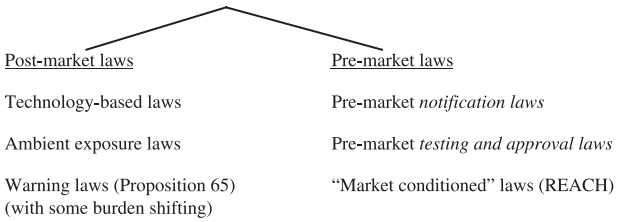

Fig. 1. Generic legal strategies for addressing toxic substances.

Under such laws, substances enter commerce without any legally required pre-market testing and remain there causing human exposure until there is sufficient harm or risks of harm to justify reducing exposures or removing them from the market [3] (since 1981, companies have been required to notify the US Environmental Protection Agency [EPA] of their intentions to manufacture new substances or create new uses for them, but this does not require testing [3]). Typically, before taking legal action to reduce toxic exposures an administrative agency must bear a burden of proof and *issue a regulatory rule* in accordance with legal procedures that can be more or less burdensome depending on the statute. Under some statutes – so-called technology-based laws – an agency must identify a substance as a toxicant (e.g. reproductive or carcinogenic), and then identify technologies (for certain classes of industries) that will reduce exposures to it as low as is technologically (and sometimes economically) feasible. Under more legally onerous statutes – so-called 'ambient exposure' laws – an agency has a burden to establish the particular exposure level at which a substance does not pose a risk of harm to human health (often with an 'adequate' or 'ample' margin of safety), a very science-intensive, time-consuming procedure [3]. Such post-market laws will largely apply to industrial chemicals that are of concern for causing adverse subclinical neurotoxic developmental effects (e.g. methyl mercury, arsenic, lead, solvents, manganese and perchlorate) [2,3]. There are warning or notification laws that inform the public of toxic releases (or for purposes of clean-up) or that they are in the presence of toxicants, but these generally do not provide much protection other than permitting informed citizens to possibly avoid them or lobby an industry to reduce exposures [3] – I discuss one more effective version of such laws under California's Proposition 65. Finally, there are some US post-market laws that address consumer products within the Consumer Product Safety Commission (the Consumer Product Safety Act and the Federal Hazardous Substances Act) [3], but legal procedures are cumbersome and the agency enforcing them is small and poorly funded. This reduces the efficacy of these laws in protecting the public from toxicants in consumer products.

Theoretically, most post-market laws permit the use of surrogates to identify the risks before they materialize into actual human health *harm*, for example, by utilizing animal studies and other non-human evidence [3]. However, agencies are under increasing pressures from regulated industries and some commentators to show actual human harm. For example, a US National Academy of Sciences Committee recommends 'the most stringent criteria and requires epidemiologic evidence for drawing any positive conclusions about potential carcinogenicity; animal evidence and other test information are used only to confirm cancer causation once epidemiological associations have been demonstrated' [4]. Although the US EPA still regulates using animal studies, it faces considerable pressure to utilize human data. Should this occur, it would lose any preventive effects that could come from early detection by means of non-human studies.

The post-market regulation of chemicals results in considerable ignorance of industrial and other chemicals. In 1984, the National Academy of Sciences found that for a significant majority of substances in commerce there was no toxicity information in the public record that would permit human health hazard assessments of them (table 1) (Chemicals subject to post-market laws are indicated) [5].

In the early 1990s, there was insufficient change in the data to justify updating the 1984 findings [6]. In 1998, the US EPA, industries and Environmental Defence initiated a voluntary effort to complete testing on about 2800 high production volume substances, but to date there are few updates [7,8]. Each year in the USA, about 1500–2000 new substances enter the market without legally required testing [9], although these probably do not represent significant portion of the total volume of chemicals in the market [10] (in the European Union, there appears to be greater testing of new substances [11]). Post-market laws will not identify subclinical developmental toxic effects before human exposures and prevent them. Agencies acting under such laws are also likely to be slow to remove toxicants from the market [3].

Table 1.

Percent of substances with no toxicity data for hazard assessment (National Research Council, Toxicity Testing [5]).

Category	Size of category	Percentage with no toxicity data	Post-market or pre-market
Chemicals in commerce: at least 1 million pounds/year	12,860	78	Post-market
Chemicals in commerce: less than 1 million pounds/year	13,911	76	Post-market
Chemicals in commerce: production unknown or inaccessible	21,752	82	Post-market
Cosmetic ingredients	3410	56	Post-market
Food additives	8627	46	Some post-market; some pre-market
Drugs and excipients used in drug formulations	1815	26	Pre-market
Pesticides and inert ingredients of pesticide formulations	3350	38	Pre-market; some grandfathered in

Pre-market laws

Pre-market notification statutes.

The 1976 Toxic Substances Control Act requires companies to submit to the EPA what they know about all *new* chemical substances or significant new uses of them proposed for manufacturing [3]. The agency has only 90–180 days to review the data or the substance can go into production. It can also stop the process and require further testing if it finds toxicity warnings in the data [3]. Ordinarily, these are data about physical and chemical properties. The EPA uses this information as part of a multidisciplinary approach to try to infer any biological and toxicological activity from the submitted data [10] (how well the agency reviews this data is not clear). However, this law does not legally require any testing of the product. If companies have conducted testing, they are required to submit the results. If they have not, they are only required to submit what they know. Most submissions contain no toxicity data [3,10]. Despite these shortcomings, this law likely motivates firms to examine their products for obvious toxic properties and probably has some deterrent effects. That is, given the history of substances that have posed problems, the EPA can provide guidance about products that are likely to cause problems. Moreover, if the EPA sees potential toxic effects in the chemical structure or other properties, firms may withdraw their products (or if they are very valuable, test them further). However, this law also has some tendency to invite scientific ignorance about the products. Because testing is not required, if a company tests a product, it risks regulatory trouble, so this may diminish firms' investigation of their products for toxicity. Finally, with such sparse information requirements, the EPA is unlikely to identify developmental toxicants.

Pre-market testing and approval statutes.

Drugs, pesticides and new food additives are subject to pre-market testing and approval laws. These laws impose a burden of proof on the firms submitting products for agency approval to do the required testing and to persuade a regulatory agency that the product is appropriately 'safe' or that it shows 'no unreasonable risk' to human health and so on [3]. Such laws could address subclinical developmental toxicity before there are exposures and risks posed to foetuses and newborns, if appropriate tests were required (at present, pesticide laws hold some promise on this issue). Legally required tests would likely need to be updated to address the developmental issues discussed in this journal issue.

Endocrine disrupter screening programme

The USA authorized an endocrine disrupter programme based on 1996 Food Quality Protection Act and the 1996 Amendments to the Safe Drinking Water Act, based on existing pre-market and post-market laws [12]. Its aims are to 'to identify potential endocrine disruptors, determine adverse effects, dose–response, assess risk and ultimately manage risk under current laws' [13]. Through screening and testing the agency seeks to identify chemicals that have the potential to interact with the endocrine system (Tier 1 screening) and then to 'determine the endocrine-related effects caused by each endocrine disruptor and obtain information about effects at various doses' (Tier 2 screening). As of September 2005, the agency still had not elected the first 50–100 chemicals to be screened (those with 'high potential for human exposure'), had not identified the administrative procedures to be followed, had not identified the validated tests or the battery of tests to be included, and had not identified the time frame for testing or receiving the data [14]. There appears to have been no successful regulatory action to date.

This overview suggests that there are poor resources in the USA to test industrial chemicals for subclinical developmental toxicity before there is actual exposure and before developing foetuses and young children are put at risk. The Endocrine Disrupter Screening Programme, 11 years in progress, has achieved no regulatory results to date and it is based on existing (largely post-market) laws. Moreover, even if this programme were completely successful for endocrine disrupters, it would only address those substances, not developmental toxicants that could affect other organ systems.

It appears that in the USA these laws have been developed as a result of political processes that have not necessarily had protecting the public health as their main goal. One might say that the public has been maneuvered into this institutional result, perhaps without fully recognizing where it led – poorly protecting the nation's children. Better alternatives are needed.

REACH: registration, evaluation, authorization and restriction of chemicals

The European Union's REACH legislation introduces registration and mandatory data requirements for new and an estimated 30,000 existing chemicals (for new substances since 1981, the European Union has required fuller data sets for assessing toxicity [15]. Whether the required data would permit adequate assessment of developmental toxicants is less clear). It transfers responsibility for risk assessment from government to the manufacturers and importers, and includes downstream uses in the registration and management process. It introduces authorization and restriction procedures for the most hazardous chemicals and creates a new European Chemicals Agency. One might think of this legislation as a 'market conditioned testing law'. If firms do not provide data required by the programme, their products will not be permitted to enter (or remain in) the market. The legal permission to market products is conditional on the firms testing them for toxicity ('no data, no market') [16]. This programme holds some promise for detecting developmental toxicants before they enter commerce and cause adverse effects. Whether or not this will work for subclinical neurotoxic and other developmental effects depends on tests the European Union requires.

The REACH testing strategy is to require fewer tests for products produced in lesser amounts and to require more tests and more detailed tests as the production volume increases. For substances produced in the highest volume, the cumulative tests that could be utilized to identify developmental toxicants would include a reproductive/developmental screen in one species, a second developmental test *in vivo*, together with a two-generation reproductive study, a long-term toxicity study of greater than 12 months, a study of reproductive toxicity over two generations and a carcinogenicity study [16]. The success of the testing battery for identifying developmental toxicants depends on the specific tests required and how they are administered, but basic toxicology tests are unlikely to identify specific developmental effects. However, REACH may provide sufficient authority to update and improve developmental tests because of its structure and legal provisions [16].

A modest step: California's Proposition 65

A post-market law in the USA, the state of California's Proposition 65, holds some promise for removing developmental toxicants from the market relatively quickly. It first specifies that no person doing business in California 'shall knowingly and intentionally expose any individual to a chemical *known to the state* to cause cancer or reproductive toxicity without first giving clear and reasonable warning to such individual' [17]. This provision applies to exposures from drinking water, the environment, the workplace, and consumer products, *inter alia*.

Second, substances are known to the state to cause cancer or reproductive/developmental toxicity because they have been *listed* by a Governor's agency, the Office of Environmental Health Hazard Assessment, assisted by two independent scientific committees: the Carcinogen Identification Committee and the Developmental and Reproductive Toxicant Identification Committee [18]. Provisions of the law also permit nearly automatic listing of substances if an appropriately designated 'authoritative agency' (e.g. the International Agency for Research on Cancer, or the US National Toxicology Programme) has already listed a substance as a reproductive/developmental or carcinogenic toxicant [19].

Third, once substances have been 'listed', businesses that expose the public have several options; they may

- issue clear and reasonable warnings about exposures,
- generate more information,
  - to show there is no significant risk, or
  - to show there is no exposure
- reduce exposure from it so there is no significant exposure or risk, or
- phase out the product [20].

That is, those who expose the public to listed substances must issue 'clear and reasonable warnings', or take one of the above courses of action, unless they are exempt. A firm may comply by showing exposures cause 'no significant risk assuming lifetime exposure at the level in question for substances known to the state to cause cancer [or reproductive/developmental toxicity]' [21]. Legally permissible risks are specified by law [21,22]. The firm has the burden of proof to show compliance [23,24]. If it does not comply with the law, it can face substantial fines, $2500 per exposure per person per day without warnings. The law would typically be enforced by the state, or, if it fails to act, by private citizens after informing the state and giving it an opportunity to act. In effect, Proposition 65 has some legal burdens of proof within it somewhat analogous to pre-market testing laws.

This law does not provide a guarantee for reducing exposures to toxicants, but it has had some success in reducing exposures to environmental tobacco smoke, engine exhaust near buildings, toluene, methylene chloride, mercury, ethylene oxide, di(2-ethylhexyl)phthalate, trichloroethylene and perchloroethylene [20]. Enforcement actions led to product reformulation (e.g. mercury removed from nasal spray, lead reduction in power cords, lead in calcium supplements, lead in dishes and glassware), permitted people to choose to avoid exposures (e.g. to alcoholic beverages, community exposure warnings, second-hand smoke), and provided useful educational information [20].

A strength of Proposition 65 is that it requires warnings on exposures that cause developmental problems whether in the endocrine, neurological or other organ systems. Listing a substance as a developmental/reproductive (or carcinogenic) toxicant is in principle possible as soon as the appropriate science is available. It can address consumer products, and, thus, is superior to US federal laws. More importantly, listing, thus enforcement, can be based *animal* studies; human data are not required.

Nonetheless, it is a post-market law and has no provisions to require pre-market testing of products. And, it has limitations for developmental toxicants by restricting evidence of toxicity only to exposures occurring during development (not postnatally) and by what substances the relevant scientific committee is prepared to list. Committee actions can vary with the political views of the governor who appointed it.

Precautionary steps

Elsewhere I suggested a model for remedying some of the shortcomings that exist in the USA and other legal systems (mainly in post market laws) that would include the following:

> [(a) placing] on the manufacturer a *reasonable burden to produce evidence* about the short and long-term human health and environmental effects of substances or products that would enter [or are in] commerce, [and (b) placing] a *burden . . . on* the firm to show to some [appropriate] *standard of proof . . .* to the satisfaction of an agency, analogous to the US [laws concerning pharmaceuticals], that the substance or product was appropriately '*safe*' or posed no '*significant risks*' (where these would need specification) to the public, the workforce or the environment. A substance would not enter commerce until it had *agency approval* and its *continued presence in the market would be conditioned on its being* '*safe*' or *exhibiting* '*no significant risk*.' It could be *expeditiously withdrawn* if evidence arose that falsified the condition of approval. Moreover, the firm would have *an affirmative legal duty . . . to report evidence of adverse effects* to the agency [25].

Moreover, testing could be 'tiered' as it is under REACH with more testing of products produced in greater volumes, and no or minimal testing of substances that were highly likely to pose no risks, for example, perhaps large polymers that could not enter human systems (tiered testing would reduce some of the costs of a pre-market testing law, but there would be additional costs compared with post-market laws). Such a law has several motivations. It seeks to generate information, and to identify and prevent harm before there are significant exposures.

> It better serves the aim of primary protection of the environment and public health than post-market laws. To this extent it resembles primary preventive aims in medicine and public health . . . [Moreover], [i]t is *fair* to make a firm to whom advantages will flow from introducing a product in uncertain circumstances and over which risks it has control to bear responsibility for removing uncertainty about the product and to bear losses that may occur if the uncertainties materialize into adverse outcomes. [Current laws impose] the costs of uncertainties (or actual harms) – in the form of disease and monetary costs – from substances [on the public and the workforce, but] . . . they have no knowledge and [little control] over them [25].

However, even a law that had such features would need appropriate testing of new and existing substances for developmental toxicity in different organ systems with special attention to the *timing* of *in utero* and postnatal exposures [2,26]. Where testing does not decisively determine easily identifiable toxic levels for *in utero* exposures or newborns, such laws could authorize more 'accurate' safety factors, if they could be determined on the basis of the science. If they cannot, as citizens we should utilize the analogues of legal presumptions to take action towards threats or harms presented to things we value (*legal presumptions* create legally required inferences, unless an opponent produces evidence to the contrary [25]). More generally, in setting public policies we need to recognize that science cannot provide all the answers even in science-intensive areas for policy purposes. By recognizing this, we can avoid a kind of 'science trap', where opponents of providing greater health protections try to persuade the appropriate governmental authorities that exquisitely detailed science is needed to justify each step of protective regulations.

The scientific basis for presumptions can be illustrated by exposures to subclinical neurotoxic developmental effects that can and have occurred in children. Industrial chemicals contribute to developmental disabilities in 5/1000 up to 42/1000 children [2]. Moreover, scientists are beginning to recognize that development is a more 'open' system than perhaps had been realized in the past. Not only is the womb not impermeable to exogenous factors, but also the developmental process can be invaded and disrupted in ways that scientists are only now beginning to understand [1,2,27]. As noted earlier, the developing brain follows a developmental process in which the right events must occur in the right pathway at the right time, which creates windows of 'unique susceptibility' (unlike adult brains) [2]. This continued vulnerability extends months beyond birth. Children also have 'increased exposures, augmented absorption rates, and diminished ability to detoxify exogenous compounds', compared to adults (adult exposure limits are inadequate for developmental purposes) [2]. Researchers also know of individual substances and classes of chemical substances that pose risks of neurotoxicity from which we can learn for the future: persistent lipophilic substances, including about 100 pesticides, halogenated industrial compounds and metals [2].

Thus, there are strong presumptions for testing to identify foetal and neonatal toxicants based on the above-scientific understanding of brain development and substances that can harm it. However, substantive moral considerations can augment this to form a social policy for protecting our children. For example, as citizens we should be entitled not to have our children subclinically *experimented on* or harmed by industrial chemicals. Moreover, we should seek to protect the next generation from risks and harms, and not underestimate the risks in our efforts to approximate any adverse effects. Finally, as a matter of fairness such diseases should be prevented from occurring so parents should not have to bear the future costs of children's care and losses imposed on them as a result of businesses' failure to understand their products and to ensure greater protection of the public.

A more substantial departure from existing approaches

Although this idea cannot be developed in detail, we should begin to think of a more extensive departure from existing legal structures and their underlying moral paradigms. Like trespass in the law or unauthorized invasions of our person, it should be considered a moral and legal wrong to create substances that can invade the uterus *without testing them for whether they cause risks or harm in utero*. Causing an actual harm is not a necessary condition of trespasses or invasions [28]. I am not legally permitted to enter your home without permission even if it causes no harm. It is a trespass for me to invade your land with invisible substances, if this will interfere with your use of your property (but not harm it or you) [29]. If a patient visits the dentist and unknown to her the dentist fluoridates her teeth or touches her in inappropriate places while she is anaesthetized, she has been morally and legally wronged. We are sovereigns over our bodies and our property in many ways [30], except when it comes to invasions of or trespasses on our developing children and ourselves from industrial chemicals. This should be remedied.

A practical consequence would be that like pre-market testing and approval laws (or REACH), a legal system should require that firms seeking to introduce new substances into commerce (or that have chemicals in the market) to test them to determine whether they can cross (trespass into) the placenta and whether they can invade neonates. If they cannot invade the womb, this would end the matter on the dimension of foetal exposure (there might still need to be tests for immediate postnatal exposure). If they can invade the womb, legal systems should require firms to show no harm (or no significant risks of harm) to developing foetuses or neonates. On one alternative, agencies could

design testing protocols and require testing to assure no significant risks of adverse effects in a reasonable array of animal or short-term tests. Or, on another alternative and perhaps more simply like REACH, if firms wanted to market their products in a country (or keep them in the market), they could have a burden of proof to ensure that substances would not invade the womb, or if they did, they could have a burden to show the chemicals would not pose significant risks to developing foetuses. Without such testing and assurances, they could not market their products ('no data, no market'). Moreover, there could be provisions for special tests of products that are closely analogous to substances that are already known or strongly suspected of causing subclinical developmental effects. Finally, another way of getting at this alternative is to recognize that because current scientific understanding strongly supports a presumption that the developmental process may be more fragile than researchers previously understood, and that substances that are present in the bodies of developing foetuses may have some adverse effects on development, this provides the basis of a legal presumption that would shift the burden of proof to a manufacturer to provide evidence to the satisfaction of an agency that a product does not pose risks to developing foetuses or neonates.

Of course, required testing of the kind suggested above would have costs for the firms involved and would likely occasion opposition. However, when there are developmentally caused adverse effects, there are costs to affected individuals and their families as long as the effects last; sometimes for a lifetime. Such dispersed human health, familial and monetary costs are less visible and receive less publicity than aggregated monetary product costs that are publicized by industry groups.

Conclusion

The public has been legally and politically maneuvered into the current institutions that appear inadequate to prevent developmental toxic effects. Those interested in protecting the health of a nation's children must diagnose existing laws and their shortcomings, and design counter proposals based on good science and good public health policy. In order to protect our children, public health scientists and legal scholars will need to collaborate to reform the existing legal structures to address more specifically developmental toxicity. Individual scientists and scientific organizations must publicly and credibly speak out about the developmental threats and potential harms because most of these risks are hidden from the public. Legislatures with guidance from scientists and legal scholars should move towards laws requiring more and better pre-market testing for developmental toxicants. The rationale could be based on traditional pre-market testing and approval laws, on models like REACH or on a trespass/invasion model.

Without significant legal changes in addressing subclinical developmental effects, public health agencies will have to rely on time-consuming, corroborative science in legally difficult circumstances to confirm on a case-by-case basis against powerful political groups and difficult burdens and standards of proof that there is actual (clinical?) human harm [25]. If this occurs, any subclinical developmental effects will be perpetrated for years and through many annual cohorts before they are identified and rectified. This is not a paradigm of precaution or for primary protection of a nation's children.

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