Potentials for exposure to industrial chemicals suspected of causing developmental neurotoxicity

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Summary
This brief report has been developed as an appendix to the article, "Developmental Neurotoxicity of Industrial Chemicals – A Silent Pandemic," by Philippe Grandjean and Philip Landrigan, published in the November 8 online edition of *The Lancet*. An expanded search for neurotoxic chemicals revealed that 278 additional chemicals are considered to be neurotoxic by the (U.S.) National Institute of Occupational Safety and Health. Even with this addition, the true number of chemicals that have caused damage to the human nervous system is likely much greater.
Most of the 201 neurotoxic chemicals listed in *The Lancet* article are commonly used. About half of them are considered high-volume production chemicals. Twenty-one are on the top-50 list of compounds from chemical waste and nearly half are priority substances in regard to releases to the environment. Methodological approaches to screening for neurotoxicity have improved only slowly, but new techniques include tests based on cell lines and brain tissue cultures. The risks to brain development caused by neurotoxic chemicals deserve national and international attention, and an action plan needs to be developed.

Known human neurotoxicants

The Lancet paper[1] identified 201 chemicals with the ability to cause neurological effects in humans, as described in the peer-reviewed scientific literature. Most of this literature deals with clinical poisoning cases, where the cause was obvious, and where the neurological effects were documented. Some of the literature is based on studies of exposed workers, but very little information is from populations with exposures to chemicals from environmental pollution, because attribution to a single toxic chemical is often impossible.

We have further examined published records from the (U.S.) National Institute of Occupational Safety and Health (NIOSH) on exposure limits for occupational toxicants[2]. NIOSH provides information on the target organs that are sensitive to these chemicals. By scrutinizing the information on exposure limits, we find that well over 200 substances (not included in *The Lancet* table) have been assigned an exposure limit to protect against effects that include nervous system damage (often conjointly with effects on other organs). In these cases, NIOSH has considered the evidence sufficient to warn against neurotoxicity if exposure limits are exceeded.

Thus, using less stringent criteria, many additional chemicals with less scientific documentation must be regarded as neurotoxic to humans. The documentation on these substances needs to be further scrutinized and expanded.

Exposures to the known human neurotoxicants

For the chemical compounds listed in *The Lancet* table, the risks to human health will depend on their likelihood of causing human exposures. The substances have therefore been compared with lists of the chemicals most frequently used in industry and produced in the highest amounts (see table below). The so-called high-volume production (HPV) chemicals

(almost 5,000 substances worldwide) are produced in volumes exceeding 1 million pounds per year [3,4,5]. Because of their importance in chemical production, they may well cause occupational exposures, releases to the environment, and exposures via consumer products. Almost one-half of the chemicals in *The Lancet* table are produced in high volumes.

In regard to environmental contamination, the U.S. Environmental Protection Agency (EPA) requires that the release to the environment of certain chemicals (Toxic Release Inventory, TRI) must be reported[6]. Slightly less than half of the substances included in *The Lancet* table are also priority substances regarding environmental releases.

A small number of the chemicals in *The Lancet* table are now banned, such as polychlorinated biphenyls (PCBs). However, this does not necessarily mean that these substances no longer present a hazard. Twenty-one of the chemicals appear among the top-50 hazardous compounds from chemical waste, selected by the (U.S.) Agency for Toxic Substances and Disease Registry in regard to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)[7].

*Table 1. Number of industrial chemicals considered toxic to the human brain (total number, 201) and their listing as regulatory agency priorities**

	# Listed in *Lancet* Table	# *Not* listed in *Lancet* Table	Total
HPV	97	4746	4843
TRI	93	488	581
CERCLA	21	29	50

*HPV, high-production volume; CERCLA, Comprehensive Environmental Response, Compensation, and Liability Act; TRI, Toxic Release Inventory

This information suggests that the neurotoxic chemicals in *The Lancet* table are mostly common chemicals, and very few of them, if any, could be considered laboratory oddities or substances of only historical interest. This finding is noteworthy, because the appearance of human poisoning cases, on which the table was based, may have led to stricter prevention. However, as indicated by *The Lancet* article, regulations to protect against neurotoxicity, especially developmental neurotoxicity, has usually been delayed.

The majority of the 201 compounds are therefore undoubtedly present in the environment, in food, or in consumer goods. Unfortunately, only a small number of these substances are currently included in biological monitoring efforts, such as those carried out by the (U.S.) Centers for Disease Control (CDC's most recent National Report on Human Exposure to Environmental Chemicals tested for the presence of 148 chemicals in humans)[8]. Methods for biological monitoring and other types of exposure assessment are available and, given human exposure to this high number of neurotoxic chemicals, a more inclusive evaluation would seem to deserve immediate attention.

Potential human neurotoxicants

The number of neurotoxic chemicals is likely to be much larger, as indicated by toxicology tests. Twenty years ago, about 750 chemicals had shown neurotoxic effects in laboratory animals[9]. The number is thought to exceed 1,000 today, although no authoritative estimate of the true number of neurotoxicants is available.

In 1998, the U.S. EPA found that a full set of basic toxicology information was available for only 7% of the HPV chemicals, including developmental/reproductive toxicity. Much of the missing information is now being gathered as part of a multi-national effort.

Although developmental toxicity information was available for 654 chemicals (23%), these data may not necessarily include neurotoxicity data beyond crude variables, such as brain weight. Under standard testing conditions, detailed level-3 neurotoxicity testing would be carried out only if indicated by the short-term tests or level-2 testing of subchronic neurotoxicity tests. Although not specifically covered by the U.S.EPA report, very few of the HPV chemicals have apparently been tested this way.

In 1998, the U.S.EPA estimated that developmental neurotoxicity test would cost approximately $150,000. Although this amount is possibly on the low side, better cell-based screening methods have since then been developed that would allow prioritizing of chemicals that need to be examined by full-scale developmental tests.

When a neurotoxicity test shows a positive outcome, a neurotoxic hazard is indicated. In past testing efforts, the proportion of positive tests among substances tested has varied according to the types of chemicals tested[10]. Perhaps as many as 25% can be expected to show neurotoxic properties. Thus, among the 80,000 to 100,000 chemicals in use worldwide, a substantial number must therefore be suspected of being capable of damaging the human brain, particularly during development.

The way forward

The incomplete information and the associated uncertainties can easily lead to underestimation of the pandemic of developmental neurotoxicity. Because of the vast societal importance of optimizing human brain development, we propose immediate action to protect the brains of future generations:

1. Documentation of chemicals that have caused toxic effects on the nervous system in humans to facilitate targeted preventive action against releases of these chemicals;
2. Documentation of human exposures to neurotoxic chemicals and identification of subgroups at risk due to residence, occupation, diet, and other factors;
3. Research on the consequences of developmental exposures to neurotoxic chemicals to expand our understanding of the long-term consequences of such exposures; and
4. Screening for neurotoxicity of commonly used chemicals to identify those that may present a hazard to brain development.

These efforts will require a substantial research effort, investment in safety by commercial enterprise, coordination of prevention by governmental authorities, and international collaboration. We will attempt to initiate and inspire such efforts.

References

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