Ethics Assessment as an Adjunct to Risk Assessment in the Evaluation of Developmental Neurotoxicants

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The conduct of experimental studies in humans is governed by a body of principles whose main precepts have evolved over the past few decades. Three of these provide the foundations for judging the ethical adequacy of such an experiment. One addresses the question of who receives the benefits of the research and who bears its burdens (justice). A second requires that the research maximize the potential benefits to the subjects and minimize the risk of harm (beneficence). The third, the source of guidelines for informed consent, requires that subjects enter into the research voluntarily and with adequate information (respect for persons). Unlike research conducted to evaluate drugs, however, environmental exposures to potentially toxic chemicals do not survey those exposed for their consent, nor do they provide an appropriate calculus for measuring risks and benefits, which typically involve two different populations. Especially for exposure to developmental neurotoxicants, where the risk–benefit incompatibility can be so striking, another element may need to be incorporated into risk characterization: a process of ethics assessment. A scheme for doing so can be derived from the procedures of fuzzy logic, which allow rules to be formulated that are applicable to ethical principles. Such an approach incorporates some of the tenets of the precautionary principle. *Key words:* Belmont report, brain development, developmental disabilities, ethics, fuzzy logic, precautionary principle, risk assessment. — *Environ Health Perspect* 109(suppl 6):905–908 (2001).
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In 1998, the U.S. Environmental Protection Agency (U.S. EPA) convened a special panel of its science advisory board to address the contentious issue of administering pesticides to volunteer subjects. The issue came to public attention because of provisions in the Food Quality Protection Act of 1996 (*1*) that called for an added 10-fold safety factor for children beyond safety factors already applied to animal data. Pesticide manufacturers, confronted by these more rigorous standards, sought to eliminate the 10-fold species extrapolation factor by providing experimental data from human subjects. The panel was charged with two main tasks: determining what characteristics of a human study were appropriate for regulatory decisions and defining the ethical implications of such a study. Because of the role that pesticides play in the food supply and in the control of disease, the panel also was asked to discuss potential risks and benefits of volunteer studies to both individuals and society.

The panel's report (*2*) emphasized that the threshold for justification of such studies should be set at a very high level and that deliberate exposure be approached with the greatest degree of caution. It also noted that agency policy must adequately consider vulnerable populations such as fetuses, children, pregnant women, the elderly, and those with already compromised health. The report's comments on risks and benefits urged consideration not of risk–benefit ratios in isolation, but of the distribution of risks and benefits across populations. Put another way, it insisted that risks should not be imposed on one population to secure benefits for another population.

A crucial issue obscured by the panel's charge to review the ethical framework governing treatment of volunteers was that of involuntary exposure. Exposure to environmental chemicals such as pesticides is largely beyond the control of those exposed and is governed by an entirely different set of practices and standards. This article argues that the panel's conclusions should also be seen from a much wider perspective: What ethical principles should control the deposition and dispersal in the environment of chemicals with potentially adverse effects on health, especially those identified as or suspected to be developmental toxicants? Should ethical questions be formally included in the process of risk assessment and risk management, especially within the boundaries of risk characterization? If so, how might the process be implemented?

Guides to Human Experimentation

The planning of clinical investigations accords a major role to informed consent. Institutional review boards review the design of the investigation and the risks it may pose to participants, but they just as carefully scrutinize how clearly and completely the subjects have been informed of the possible risks. Clinical investigations of drugs, particularly new ones, are only one phase in a long chain of investigations based on previous extensive animal research.

Except for pesticides, which are covered by the provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (*3*) and which undergo a defined series of toxicity tests before marketing, toxic chemicals can be introduced into the environment with relatively modest or even minimal toxicity testing. In essence, for many agents the most extensive testing is conducted in humans exposed after the agent has been introduced. Even those tested according to contemporary guidelines, however, introduce a troublesome ethical gap.

The ethical dilemmas stem from three pillars of protection of human subjects in research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, established in 1974, issued a document in 1979 known as the *Belmont Report*, which affirms the basic ethical principles, equivalent to those issued later, that guide the conduct of research with human subjects (*4*). One is beneficence, which requires that researchers maximize the potential benefits to the subjects and minimize the risks of harm. A second principle is justice, which embodies the question of who receives the benefits of research and who bears its burdens. A third is respect for persons, the source of the guidelines for informed consent. It requires that subjects enter into the research voluntarily and with adequate information. Here, children receive special consideration because they are held to lack adequate capacity for self-determination.

An ethical challenge is posed by the conflict between the Belmont principles and how society governs the discharge and dispersal of toxic substances into the environment, especially those that may endanger early development.

Justice

Most often, chemicals are discharged into the environment to benefit the discharger. Those who undergo the exposure do not participate

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in the profits, which are readily monetizable. The benefits to those exposed cannot be monetized except in vague terms; for example, the possibility of lower prices for commodities. The risks and benefits are almost totally mismatched.

Beneficence

This principle, whose axioms are *a*) do no harm and *b*) maximize benefits and minimize harms, holds that those who are responsible for imposing risks incur obligations to justify those risks and to distribute the benefits to those most in need of them. Again, we have no adequate framework for assessing benefits for those exposed except on an ambiguous economic scale.

Respect for Persons

Voluntariness is the key concept. It cannot be argued that most of us expose ourselves to environmental toxicants voluntarily. The exposures are inadvertent and often inescapable. An even more critical point is that we are not given the opportunity for informed consent. The fetus, infant, and child possess essentially no choice at all.

Developmental exposures heighten the disjunction between the ethical principles governing volunteer studies and the lack of corresponding principles governing environmental exposures. Of the over 80,000 chemicals used in commerce and industry, dismayingly few have been subjected to even superficial toxicity testing, and of the 3,000 produced or imported at over 1 million pounds per year, only about a quarter have undergone any testing for developmental toxicity (*5*). Even for those few, the depth of detail is inadequate to determine if they pose a health hazard, particularly to the developing brain. We are faced with a striking disparity between the community's concerns about developmental disabilities and our knowledge of their etiologies, a disparity so wide that it prompts questions about the ethical implications of allowing exposure to chemical agents with the potential to impair brain development.

Developmental Neurotoxicity

The dearth of information linking developmental disorders and their possible environmental etiologies is recognized by federal agencies. For example, the U.S. EPA, in collaboration with the International Life Sciences Institute (ILSI), recently launched an effort to develop a set of developmental neurotoxicity guidelines encompassing behavior, morphology, and pharmacokinetics (*6*). The National Institute of Environmental Health Sciences has issued a request for proposals for Children's Environmental Health Centers that will focus on environmental chemical contributions to developmental disabilities. Even the media have begun to pay attention to this problem. *U.S. News and World Report* featured a story in their issue of June 19, 2000, titled "Kids at risk. Chemicals in the environment come under scrutiny as the number of childhood learning problems soars" (*7*). It asked whether environmental chemicals might be responsible for current rates of learning disabilities, attention deficit hyperactivity disorder, and other developmental problems.

Although the effort by ILSI and the U.S. EPA will contribute toward resolving the question of how to identify developmental neurotoxicants, such efforts are destined to fall far short of inclusiveness. Even with pesticides, which are the environmental chemicals subject to the closest regulation, our knowledge of their potential to interfere with neurobehavioral development remains surprisingly elementary (*8*). The situation with other classes of chemicals is even less promising. Our ignorance of this potential creates a series of ethical quandaries, because in the absence of definitive information, we are in essence asking the most powerless members of society to participate in a massive experiment in which risks and benefits are not shared equitably and in which informed consent vanishes as an ethical principle.

Several special features of developmental exposure to neurotoxicants underscore the information dilemma. First, we now recognize that events occurring early in the course of brain development attain functional expression in different forms throughout a lifetime. These early events might even be predisposing factors for neurodegenerative diseases during advanced age, a problem phrased as "silent toxicity" (*9*). How is it possible to gauge such an outcome without complex longitudinal studies that are not seen as part of current guidelines? Furthermore, assays of functional expression also require more than minimal techniques and instruments; they may require, instead, painstaking, advanced, novel, and expensive techniques (*10*). Some leave legacies such as reduced earning capacity or may show their influence most clearly in subject populations already challenged by other kinds of stress such as poverty (*11*). Chemical risk assessment typically takes a position independent of other adverse, often interacting, influences.

Unforeseen Consequences: Endocrine Disruption

The discovery, described compellingly by Colborn et al. (*12*), that so many common commercial chemicals and chemical contaminants act as endocrine disruptors exemplifies the ethical predicament. Toxicologists paid little attention to endocrine function before Colborn and her collaborators assembled a huge volume of data to underscore its importance. But developmental neurotoxicity is now faced with a new set of questions arising from endocrine disruptors. Many different kinds of chemicals are recognized for their ability to interfere with endocrine function, particularly during early development (*13*). The array of endocrine-disrupting chemicals includes many different classes.

The endocrine disruptor issue demonstrated how little we knew about the chemicals emitted into our environment despite all the regulations and research that were supposed to protect public health. It would be ingenuous not to expect more surprises in the future. They can arise both from chemicals already in use and present in the environment and from new ones as well. The emergence of endocrine disruption as a health risk is a powerful example of how, because of incomplete and fragmentary information, the public was subjected to a massive clinical trial. It is an example of how we have bypassed the equivalents of the ethical tenets that govern the design and conduct of such trials.

Ethics Assessment for Environmental Exposures

Can the principles of the *Belmont Report*, which was devised primarily as guidance for clinical trials, be applied and justified in the wider context of environmental exposures? President Clinton's statement, made against the background of the Tuskegee Syphilis Study in a 1997 commencement address at Morgan State University, implies more than it says on the surface: "We must never allow our citizens to be unwitting guinea pigs in scientific experiments that put them at risk without their consent and full knowledge."

Commercial products released either deliberately or adventitiously into the environment are not the object of scientific research designed specifically to treat disease. To what standards of risk should they then be held? Should they meet the same standards as pharmaceuticals? Wier (*14*) put the question in this way:

> Guidelines for developmental toxicity testing of pharmaceuticals have required behavioral evaluations since 1975 . . . . Therefore, the safety assessment of new pharmaceuticals marketed internationally is made with consideration for all major end points of developmental toxicity, in contrast to the situation for chemicals other than drugs for which "triggers" specifically for behavioral evaluations have been proposed. . . . These "triggers" include demonstrated potential to produce central nervous system malformations; known neuropharmacologic, neurotoxic, or hormonal effects in adult animals; and structural analogy to compounds known to affect offspring behavior. In the case of the U.S. Toxic Substances Control Act, behavioral evaluations may be indicated based

> only on exposure potential . . . . The exposure-based "trigger" is consistent with the rationale for behavioral evaluations in the developmental toxicity testing of pharmaceuticals. Nevertheless, an important difference is that requirements for basic teratology and behavioral testing are not coincident for chemicals other than drugs.

Persuasive support for this statement comes from data showing that even drugs not designed to act primarily on central nervous system function may still induce developmental neurotoxicity in the form of aberrant behavior (*15*). They include classes such as vitamin analogs, hyperlipemic drugs, antibiotics, anticoagulants, antiallergens, and others. Food dyes fall into this category as well (*11*).

We have to assume, because we lack complete confidence in our ability to foresee the potential developmental neurotoxicity of environmental chemicals, that they pose a finite, undefined risk of harm. If we take the Belmont principles as our ethical guide to permitting such exposures, we confront another dilemma: how could a modern society function if decisions about the use of chemicals, which, even with limited use, will find their way into the communal environment, comply with requirements analogous to those governing clinical trials? As a substitute, we appoint surrogates such as the U.S. EPA and the U.S. Food and Drug Administration to enforce compliance with the conventional standards of risk assessment. Procedures for conducting an ethics assessment have not been defined for such situations. Is it possible to construct such a procedure by drawing upon techniques developed for other types of amorphous questions?

A Model for Ethics Assessment

Panels of experts or, for community risk initiatives, residents or other relevant parties, are often called upon to develop risk rankings or ratings for environmental hazards. Typically, such exercises strive for consensus. Consensus rankings or ratings, however, ignore an important component of such exercises: disagreements among raters (*16*). The extent of variability among raters might reflect the degree of uncertainty in the data available to them, or it might even reflect a rich data set that can support diverse interpretations (*17*). Much as we have enlisted such panels for risk ratings, we could also enlist experts or community members to assign ethical ratings to environmental exposures. A promising method for doing so rests on the principles of fuzzy logic. The term was chosen by its originator, Lotfi Zadeh, to contrast the principles of his multivalent logic with conventional binary or Boolean logic.

Fuzzy logic originated in an engineering context (*18*). For example, it can be applied to design a controller for maintaining the air temperature in a building at a constant level. Because it converts terms such as "low" and "high" to the operations of the controller, it turns out to be particularly useful for extracting operational precision from verbal imprecision. It calibrates vagueness by deriving decision rules (*19*). Its basic premise is that many things are described as degrees of something. For example, saying that a person is tall conveys only a relative, subjective measure of height. To an average woman, a man 180 cm in height would likely be described as tall. To a basketball coach, that term might be reserved for someone 210 cm in height. A fuzzy logic definition of tall would first create what is called a membership class whose limits are anchored at 0 and 1, as in Figure 1. Such a translation is termed "fuzzification."

For conversion into a fuzzy medium, ethical ratings could adopt the scheme illustrated in Figure 2. Judges would be asked, for example, to provide ratings of justice for a particular environmental condition. Rater 1 centers the rating at medium, and sets boundaries at very low and high. Rater 3 is centered at very low, with boundaries at extremely low (essentially zero) and low. Rater 2's judgments take the form of a trapezoid, with the highest degrees of membership assigned to high and very high, with boundaries at medium and extremely high (equivalent here to the maximum, set at 6. The abscissa's numerical scale is arbitrary). The ratings of a panel of judges can then be combined by one or more of several techniques described in the fuzzy logic literature [e.g., Klir and Folger (*19*)].

Assume that a panel has been requested to provide ethical ratings for a particular environmental condition, for example, aerial spraying of a special pesticide combination to control an invasive insect species in a community, or siting a power-generating plant in a certain area, or permitting the inclusion of a new gasoline fuel additive during specified seasons of the year. The panel, provided with toxicity, health, exposure, and economic data, is then requested to offer an ethical judgment about the appropriateness of the action by rating it on the basis of the three *Belmont Report* dimensions: justice (J), beneficence (B), and respect for persons (R). A variety of methods can be applied to calculate a group or consensus profile, which might have an irregular shape because of differences among judges. A "crisp," or single value for any of the three Belmont criteria may be calculated (defuzzification) to represent the profile. Once these have been computed, we next turn to the rule base typically generated by fuzzy logic models. Each rule consists of a fuzzy set denoting a range of values. One rule base is shown below. It is intended only as an illustration because it assumes that ratings are transformed or restricted to only the designated categories and do not include values that overlap two membership classes such as VL and L.

Rule 1: If J is VH and B is VH and R is VH
Acceptability is 1
Rule 2: If J is VH and B is VH and R is H
Acceptability is 2
…..
Rule 124: If J is VL and B is VL and R is L
Acceptability is 134
Rule 125: If J is VL and B is VL and R is VL
Acceptability is 135

Compiling such a list of rules makes ethical judgments about a course of action much more transparent and provides a standard for policy decisions by the community or its representatives.

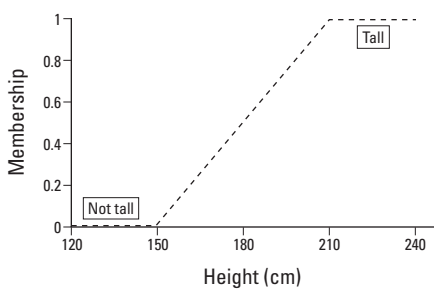

Figure 1. Schematic depiction of the fuzzy definition of tallness. A membership value of 1.0 denotes complete membership in the class, i.e., fuzzy set. Tall varies with measured height. Membership, as shown here, would be zero for heights 150 cm and below and 1.0 for heights 210 cm and above. A height of 180 cm would correspond to a membership value of 0.5.

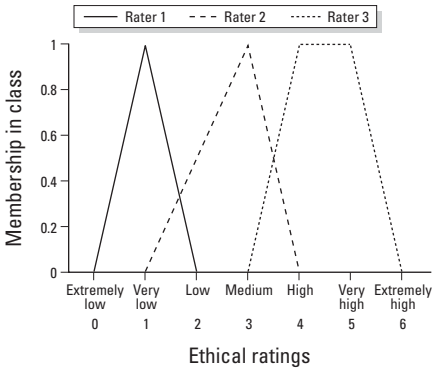

Figure 2. Showing how different raters might rate the ethical implications of a specified activity or exposure to a specified agent or class of agents. Rater 1 judges the designated criterion (justice, beneficence, or respect for persons) to be centered at medium, with asymmetrical boundaries at very low and high. Rater 2 assigns maximum membership to both very high and high. Rater 3 centers maximum membership at very low with symmetrical boundaries at extremely low (effectively zero) and low. The abscissa is anchored at zero and 6 and is arbitrary because it is simply incorporated into the decision rules.

Precautionary Principle

Although their congruence is far from complete, elements of ethics assessment and the precautionary principle reflect similar uneasiness about the scope of environmental hazards and evoke comparable quandaries in policy. The precautionary principle approaches environmental and public health policy decisions from a vantage point in conflict with the traditional position. At present, we base decisions about environmental policy on acceptable risk, which, in reality, translates to "How high can we afford to elevate exposure levels without inducing detectable adverse effects?" From this perspective, the burden of demonstrating adverse health effects at environmental exposure levels falls on the public itself. In essence, customary practice assumes that toxic agents and hazardous practices are entitled to more rights than the public and are innocent until proven guilty.

The precautionary principle, in effect, reverses this process. It thrusts the responsibility for proof on those who create the risks. Its guiding rule declares that we are obliged to initiate precautionary or preventive measures when a specified activity threatens to harm health or the environment, even if a direct cause-and-effect linkage has not been demonstrated unequivocally. Fulfilling the principle's rules also requires participation by the affected public, which expands decision powers to the community and even wider publics.

Ethics assessment and the precautionary principle intersect at this juncture. Where the precautionary principle shifts the burden of proof, ethics assessment poses questions of balance as well: Who creates and profits from the risks and who assumes them? To what degree do those creating risks share the benefits with those subjected to them? How effectively are the risks communicated to those at risk and to what extent do they undertake them voluntarily?

Ethics assessment would especially highlight how often the public is asked to accept inadequate information about many if not most of the toxic or potentially toxic chemicals pervading our environment. Such ignorance becomes particularly dismaying with every new bit of evidence that science uncovers about the vulnerability of the developing brain because here is where the ethical dimensions of justice, beneficence, and voluntariness clash with traditional practices. Endocrine disruptors are only the most recent and visible example (*20*) of how often risk has been overlooked or miscalculated or resisted. Endocrine disruption also underscores the problem that conventional risk assessment is based on investigations of single chemicals rather than their cumulative weight, and that our calculations of chemical risks generally ignore the social and economic circumstances, such as poverty, in which they are embedded (*11*). The process of risk characterization, conceived in the past simply as a conjunction of response probability and exposure level, is currently seen as a much broader effort that also involves community standards and perspectives (*21*). Perhaps it is time now to add one more element: ethics assessment.

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