Chemicals and Children’s Environment: What We Don’t Know about Risks
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Although we know that certain types of childhood cancers are increasing, we do not know why. With few exceptions, we know little about the role of environmental carcinogens in childhood cancer. Generally, we have adequate information to screen chemicals for potential hazard for only certain categories of chemicals—drugs, food additives, and pesticides. The U.S. Environmental Protection Agency (U.S. EPA) is implementing the 1996 Food Quality Protection Act, which provides added protections against pesticide risks, especially for children. But the situation is quite different for many industrial chemicals. We lack even basic toxicity data for a majority of the U.S. EPA’s list of approximately 3000 nonpolymeric high-production-volume industrial chemicals being produced in the United States each year that are found in consumer products and the workplace. We know even less about the remaining 70,000 chemicals on the U.S. EPA inventory. The U.S. EPA has initiatives underway to address the risks posed by some of these commercial chemicals, including efforts to reduce risks posed by indoor air pollutants and household products. These initiatives specifically address children’s risks. We are supporting toxicity screening of high-volume industrial chemicals on a cooperative international basis through the Organisation for Economic Co-operation and Development. Until more information is available, it is difficult to assess the possible role of these chemicals in childhood cancer and to take steps to reduce exposure to children. — Environ Health Perspect 106(Suppl 3):875–880 (1998).
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Introduction
The U.S. Environmental Protection Agency (U.S. EPA) Office of Children’s Health Protection held a conference in September on Preventable Causes of Cancer in Children. The conference helped us to evaluate our knowledge about and efforts in preventing environmentally related cancers in children and to determine the future directions of our additional efforts.

We know little about how chemicals in the environment relate to risks of childhood cancer. We do know that certain types of childhood cancers are increasing, but we do not know why. In general, the amount and quality of the information on carcinogenic and other risks depend on the chemicals being discussed. Generally, we have adequate data to screen chemicals for potential carcinogenic and other hazards for drugs, food additives, and pesticides. Although it is often necessary to obtain additional data for assessing children’s risks to these chemicals, we have little information about other chemicals regulated under the Toxic Substances Control Act (TSCA) (1) and the Consumer Product Safety Commission’s Hazardous Substances Act (2).

Addressing Children’s Susceptibilities
We have even less information on infants’ and children’s unique exposures and susceptibilities to chemicals, including carcinogens. Infants and children can be more vulnerable to some chemicals because of their unique exposures and susceptibilities, but so far, our testing and research have done little to answer questions that these key differences raise: What is the exposure to a chemical for the first year of life? What are the exposures to a toddler? What is the total cumulative lifetime exposure? And what health effects occur or could be attributed to exposures at each stage? What are the health effects for the integrated lifetime exposures? And how do children’s exposures to chemicals differ from adults’ as the result of their unique behavior patterns? We have only partial answers to these questions, and there is clearly a need for more information and research to ensure that we are providing children with a full measure of protection.

We have more knowledge of carcinogenic and other health effects of chemicals on fetuses, infants, and children for drugs than for any other class of chemicals, and it is to this body of knowledge that environmental regulators have looked to help screen similar environmental chemicals for potential carcinogenic and other toxic effects. An example of a carcinogenic drug that may be similar to other environmental chemicals that mimic hormones is diethylstilbestrol (DES), a strong estrogenic drug taken by thousands of women to avoid miscarriages. DES produced developmental changes in some of the fetuses that resulted in an unexpectedly large number of cervical and vaginal cancers in the adult daughters (3,4).

A 1992 compilation of research on how children differ from adults in their exposure and susceptibility to chemicals concluded that in some cases there may be no difference in the response of adults and children. In other cases, different physiological and metabolic factors, pharmacokinetics, and diet, behavior patterns, and other influences can make children either more or less susceptible to the effects of chemicals than adults (5).

For years, in setting tolerances for pesticides, the U.S. EPA had been adding an additional 10-fold uncertainty factor when toxicity tests showed fetal developmental effects, and we have taken into account
Table 1. Pesticidal chemicals classified as known, probable, or possible human carcinogens (includes both active and inert ingredients).a

| Cancer class | n | Pesticides                                                                 | Regulatory status                                                                 |
|--------------|---|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Group A—Human carcinogens | 5 | Benzene, inorganic arsenic, chromium VI, coal tar, ethylene oxideb           | All uses canceled except coal tar and chromium as wood preservative and E70 as a fungiant |
| Group B1—Probable with limited human evidence | 4 | Acrylonitrile, creosote, formaldehyde, cadmium                               | All uses canceled except creosote as wood preservative and formaldehyde             |
| Group B2—Probable | 64 | Acetaldehyde, acetalchlor, acifluorofen (Na), aldrin, amitrole, aniline, aramite, azobenzene, bis(chloroethyl)ether, cacodylic acid, captafol, captan, carbon tetrachloride, chlorodane, chlordimeform, chloroaniline, chloroform, chlorothalonil, cyproconazole, dimethoate, DBCP, DDT, 1,2-dibromoethane, 1,2-dichloroethane, dichloromethane, 1,3-dichloropropene, dieldrin, di(2-ethylhexyl) phthalate, epichlorohydrin, ethylene thiourea, fenoxycarb, folpet, furmecyclo, haloxyfop-methyl, heptachlor, heptachlor epoxide, hexachlorobenzene, hexachlorocyclohexane (tech), iprodione, lactofen, lindane, manoeful, maneb, metat sodium, MKG 326, mirex, orthophenylenephenol, oxythioquinox, pentachlorophenol, perchloroethylene, polychlorinated biphenyls, procymidine, B-propriolactone, pronamide, propargite, propoxur, propylene oxide, tertarzole, thidicarb, toxaphene, trichloroethylene, triphenyltin hydroxide, 2,4,6-trichlorophenol, UDMH | All or most uses canceled or never approved for 28; others have various food and other uses. All food uses to be reassessed by 1999 (some sooner) |
| Group C—Possible human carcinogen | 80 | Acrolein, amitraz, asulam, atrazine, benomyl, bifenthrin, bromacil, bromoxynil, calcium cyanamide, carbaryl, clofentezine, cyanazine, cypermethrin, daclath, dichlobenil, diclofop-methyl, dichlorvos, dicofol, difenoconazole, dimethenamid, dimethoat, dinoseb, ethalfluralin, ethofenprox, fuberconazole, fipronli, fluorometuron, fomesafen, hexachloroethane, hexaconazole, hexythiazox, hexadimethrin, hydrogen cyanamide, imazalil, isofenphor, isoxaben, linuron, MBC, 2-mercaptobenzothiazole, methidathion, 3-methylphenol, metolachlor, MKG-264, molinate, MON 21200, nitrofen, norflurazon, oxadiazon, oxadixyl, oxyfluorfen, parathion, pendimethalin, pentachloronitrobenzene, permethrin, phosmet, phosphamidon, piperyonyl butoxide, prochloraz, propamidine, propazine, propiconazole, pyrithiobac-sodium, simazine, TOCMB, tobeconazole, terbutryn, 1,1,2,2-tetrachloroethane, triadimenol, triadimefon, triallate, tribenuron methyl, 1,1,2-trichloroethane, tridihane, trifluralin, triflusulfuron methyl, uniconazole, vinclozolin | All or most uses canceled or never approved for 15; others have various food and other uses. All food uses to be reassessed by 2006 (some sooner) |
| Not applicable | 4 | Aliette, melamine, Rhodamine B |                                                                                     |

Classifications under proposed revised guidelines

- Likely: 3 Ethropoph, isoxaflutole, propachlor
- Known/likely: 1 Diuron
- Likely/high: 3 Alachlor, benoxacor, tribufos
- Exposure only

Abbreviations: DBCP, 1,2-dibromo-3-chloropropane; DDT, dichlorodiphenyltrichloroethane; E70, ethylene oxide; MBC, methyl 2-benzimidazolcarbamate; MKG-264, N-ethyl bicyclohexene dicarboximide; MGK 326, dipropyl isocinchomeronate; MON 21200, 4-pyrazidacarboxylic acid, 2-(4-chlorophenyl)-3-ethyl-2,5-dihydro-5-oxo, potassium salt; TCMFB, 2-thiocyamethylenthio)benzoiazole; UDMH, 1,1-dimethylthiatricyclodiazine, "as impurity only; no longer cleared as inert."

Note that all group A’s and group B1’s as well as 31 group B2’s and 6 group C’s were classified by entities other than the U.S. EPA Office of Pesticide Programs, i.e., U.S. EPA Office of Research and Development, the National Toxicology Program, and/or the International Agency for Research on Cancer (IARC). Because the evaluation of many of these chemicals is an ongoing process, the information on this list may change, i.e., classifications may change. Further details are given at www.epa.gov/pesticides.

Abbreviation: E70, ethylene oxide was classified as Group 2B by the IARC and Group B1 by the U.S. EPA Office of Health Effects Assessment.

estimates on children's greater consumption of certain foods, e.g., apples, peanuts, and some grains, among others. But the National Academy of Sciences (NAS) National Research Council's (NRC) 1993 landmark report Pesticides in the Diets of Infants and Children reviewed the scientific literature and concluded that children can be more susceptible not only to some of the carcinogenic hazards posed by some chemicals, but also to noncarcinogenic risks as well, and that we needed to give them even greater protection from pesticides (6).

Protection of children has been a priority since the beginning of the Clinton Administration. Risk assessments now must account for children's...
special susceptibilities and exposures. Last year U.S. EPA Administrator Carol Browner announced the agency's National Agenda to Protect Children's Health, mandating that the U.S. EPA major existing health standards be reviewed and new standards be set that ensure the protection of children (7). The new Food Quality Protection Act (FQPA) (8) added protections for all ages, but specifically requires that pesticides be safe for children. Last spring, President Clinton issued a historic executive order that expands the U.S. EPA's efforts government-wide: Executive Order 13045, "Protection of Children from Environmental Health Risks and Safety Risks" (9). The order requires every federal agency to make protection of children a consideration. For the first time, federal agencies will be required to ensure that every standard takes into account special risks to children. An interagency task force led by the U.S. EPA Administrator and Health and Human Services Secretary will coordinate priorities for research on children.

Carcinogenicity Testing of Pesticides and Chemicals

The U.S. EPA's pesticide program and other national and international bodies have classified approximately 165 pesticidal chemicals as "known," "probable," or "possible" human carcinogens (Table 1) (10). As shown in Table 1, the U.S. EPA has already taken action to ban or restrict the use of a number of these compounds. It is important to note that a pesticide's classification, or hazard, is only part of the risk equation. We must also consider the likely exposure to the pesticide. We will reassess all these pesticides under the FQPA, and those judged to be probable human carcinogens or possible human carcinogens with quantifiable risks will be in the first group reviewed (8). As overwhelming as this is, for the majority of the approximately 3000 high-production-volume industrial chemicals produced in the United States in 1996, we have little or no publicly available hazard screening data (11). These chemicals, nonpolymers produced in quantities of more than 1 million pounds per year, are found in the workplace and in thousands of consumer products. Even fewer data are available for the remainder of the some 70,000 chemicals on the U.S. EPA inventory.

1996 Food Quality Protection Act

A new era of protection from carcinogenic risks has arrived for children, and one of the major driving forces is the 1996 FQPA (8). Under the new food quality law, all tolerances must meet a "reasonable certainty of no harm" standard. To make this finding, the U.S. EPA now must take into account the aggregate impact of all non-worker-related sources and pathways of exposure to a pesticide, i.e., to the combined exposure to a pesticide through all dietary routes, including drinking water, as well as exposures resulting from use in households and on lawns. We must also consider cumulative effects of a pesticide and other substances that share common mechanisms of toxicity.

We now must add an additional 10-fold safety factor to account for prenatal or postnatal developmental toxicity. The U.S. EPA also must consider all available information on in utero effects. For threshold effects, risks generally must fall below one in a million (10-6). For nonthreshold effects, the U.S. EPA adds a 100-fold uncertainty factor where prenatal/postnatal toxicity and exposure data for children are such that the risks for children have not been well defined and may be greater than the risks for adults. The U.S. EPA may make a finding, based on reliable data, that a smaller uncertainty factor is protective. This situation arises either when hazards for children are well enough characterized that the U.S. EPA concluded that the pesticide is not more hazardous for children than for adults or when the risks for children are well understood and constitute the basis for the U.S. EPA's risk assessment. The agency also must screen for and take into account chemicals that mimic hormones, so-called endocrine disrupters, some of which are known to be probable or possible human carcinogens.

These were key steps the NAS said were needed to protect infants and children from carcinogenic and other risks posed by pesticides. For the past year, the U.S. EPA has been working with the scientific community to conduct new research and to establish new testing and risk assessment methods to take these factors into account. All the requirements took effect with the law's enactment in August 1996, so the U.S. EPA is using its best scientific judgment in making decisions as the new data and risk assessment methods are being developed.

For the past year, with guidance from its Science Advisory Panel (SAP), the U.S. EPA has been learning how to conduct risk assessments taking into account the new requirements. The SAP was established under the Federal Advisory Committees Act to review all U.S. EPA scientific work under the new food quality law.

The SAP has reviewed and approved our approach to assessing cumulative risks of pesticides that act via a common mechanism of toxicity. The International Life Sciences Institute is helping the U.S. EPA to identify organophosphate chemicals having common mechanisms of toxicity. We are also gathering this information on carbamate pesticides. We hope this year, working with our stakeholders, to establish a process to evaluate the risks from cumulative exposures to the organophosphate pesticides. In any case where we currently have reliable evidence that pesticides share common mechanisms of toxicity, we will perform a cumulative risk assessment and make a decision based on the results. This will be a powerful tool in avoiding preventable risks, including cancer risks.

Perinatal Testing for Carcinogenesis

Over the years there has been much concern about whether current cancer testing guidelines (12) adequately assess risks for children. These were highlighted by the NAS report, and even before the passage of the new food quality law the U.S. EPA had updated and improved guidelines for prenatal developmental and reproductive toxicity data. Last fall, both the SAP and the U.S. EPA Science Advisory Board approved the new guidelines.

In addition, concerns have been expressed that conventional cancer biosays do not adequately address childhood cancer risks. Cancer bioassays generally begin dosing animals at 2 weeks of age and at weaning. In 1993 the NAS report concluded that

Estimates of cancer risk should take into account both the higher exposures of infants and children to certain pesticides and the earlier age at which these exposures occur in comparison to adults. These factors can be taken into account using cancer risk estimation methods that allow for time-dependent exposure patterns and toxicological testing paradigms that include early exposure. (6)

U.S. EPA reviewed the scientific literature to determine whether prenatal testing should be required for assessment of carcinogenicity of pesticides and concluded that the need for perinatal carcinogenesis tests should be determined on a case-by-case basis. This follows a similar decision made by the U.S. Food and Drug...
Administration (U.S. FDA) for food color additives (13). Like the U.S. FDA, the U.S. EPA will be setting criteria to determine when in utero tests will be required (14). In both perinatal and standard carcinogenicity tests, we found that qualitatively the same tumors were produced, except in the case of DES (15–17). Quantitatively, we found that perinatal dosing may or may not result in a higher tumor incidence than standard carcinogenic tests. When there is a greater response, it is difficult to determine if the effect is due to an enhanced sensitivity during development or to a greater total dosing, but increases were in the range of 20 to 30%. We found also that combined perinatal and adult exposure sometimes reduces the latency period for tumors to develop, and that enhanced effects were generally seen for genotoxins and also for DES.

In addition, there were several other factors that the U.S. EPA considered in the development of its proposed policy. First, DES showed that induction of developmental abnormalities during gestation may predispose to differential carcinogenic effects. This leads to the conclusion that environmental endocrine disruptors may pose unique susceptibilities for children. Second, age-related differences in the ability to metabolize chemicals can alter the sensitivity to carcinogens. This difference can go in the direction of making a child either more susceptible (e.g., cannot metabolize the carcinogen) or less susceptible (e.g., cannot form the carcinogenic metabolite). Third, genetic toxicology test results do not consistently predict the need for perinatal testing. However, enhanced mutations may occur during development because of significant cell division or reduced DNA repair with immature repair systems. Fourth, the immune system is not fully functional throughout development, until the third month of life.

Based on these considerations and others, the U.S. EPA has proposed a set of criteria for which chemicals will require in utero testing, which were reviewed by the SAP along with reviewers from the U.S. EPA Science Advisory Board (14). The factors that the U.S. EPA is proposing to consider are

- Exposures during prenatal/postnatal periods are generally high.
- Structure–activity relationship analysis indicates an association with a chemical shown to increase sensitivity in perinatal carcinogenicity tests.
- Margins of exposures between doses producing adverse effects and anticipated exposure are smaller during development than during adulthood.
- Pesticide forms adducts with DNA of fetal tissue.
- Pesticide is transported via the placenta or breast milk from mother to baby.
- Pesticide is metabolized to the active carcinogenic moiety during prenatal/postnatal period.
- Pesticide causes relevant effects due to estrogenic or other hormonally related endocrine disruption.

In making decisions on the chemicals that will require in utero testing, the U.S. EPA will be using a weight-of-evidence approach based on a careful evaluation of factors in combination. We will consider the nature of the toxic response, the adequacy of the exposure assessment for infants, and the potential dose–response relationships.

Perinatal carcinogenicity study protocols will be designed on a chemical-by-chemical basis. This is because they pose unique problems, such as determination of appropriate dosage levels. The proposed factors will be evaluated from time to time for their adequacy; appropriate modifications will be made as new information becomes available. Additional testing could be required at any time, but an important opportunity will be registration renewal, which must occur for all pesticides every 15 years under FQPA. Clearly, however, more research is warranted in this area to develop better methods to predict carcinogenic risks due to prenatal and neonatal exposures.

**Pesticide Tolerance Reassessment**

More immediately, the new food law sets a 10-year schedule for the U.S. EPA to review about 10,000 existing tolerances for pesticide residues on food. Within the next 2 years, the U.S. EPA will review the first third, or about 3300 tolerances, that pose the worst risks. The first group will include the organophosphate, carbamate, and organochlorine classes, as well as chemicals that may be human carcinogens.

As the U.S. EPA reviews new and existing pesticide registrations under the new law, we will find that some—considering their aggregate exposures and cumulative effects on children—pose more than a negligible risk. So we will be canceling registrations for some existing pesticide uses and denying requests for new pesticides than may have been allowed under previous pesticide laws. The important point here is that over time, pesticides posing the greatest carcinogenic and other health risks will be replaced by safer conventional pesticides or alternatives, such as integrated pest management, biological controls, and biotechnology.

The new law's provisions are already prompting decisions that we probably would not have made under the previous law. For example, we denied the renewal of a tolerance for residues of the fungicide iprodione on cotton seed, because after adding the additional risk from drinking water, the cancer risk was too high (18). We also denied a request by the state of California for an emergency exemption to use iprodione on pistachio nuts due to too great a cancer risk. Similar actions are pending. As you can see, our greatest challenge is to develop the new information and scientifically valid risk assessment methods that we need to do the job that we have been given.

**Industrial Chemicals**

So we are succeeding in our efforts to assess and reduce carcinogenic risks posed by pesticides from children's diets, as well as from homes, schools, and other unintended pathways. However, we have made far less progress in defining carcinogenic and other risks posed by many other chemicals that our children are exposed to in their environments.

Our inability to judge the safety of so many environmental chemicals was outlined by the NRC in 1984 (19), and by the Office of Technology Assessment (OTA) (20) shortly before it was abolished. Using the NRC's test methods of sampling high-production-volume chemicals, the Environmental Defense Fund (EDF) recently came to the same conclusion—that we do not have basic health effects data for the majority of nonpesticidal industrial chemicals produced in the greatest quantities in the United States (11). Although we have not yet completed a detailed review of the EDF report, the results are very close to the U.S. EPA's statistics for chemicals.

The EDF study indicated that the most basic toxicity testing results cannot be found in the public record for 71% of the approximately 3000 high-production-volume
chemicals in commercial use. The study was based on a random sample of 100 chemicals imported or produced in quantities of more than 1 million pounds per year. In measuring whether a chemical had qualified as having hazard identification available, the study used the definition of minimum screening data required by the international chemical screening and testing program of the Organisation for Economic Co-operation and Development Program (OECD).

The study's sample also indicated that the majority of high-production-volume chemicals have been tested only for their ability to cause mutations and birth defects. Carcinogenicity tests have not been conducted on 63% of the high-production-volume chemicals sampled.

Of course, many of the exposures to these widely used chemicals can be chronic. But, while 90% of the high-production-volume chemicals had been tested for acute toxicity, less than half of them had been tested for any form of chronic toxicity.

The study contained other dismaying findings. Forty-seven of the 100 high-production-volume chemicals sampled were included in the Toxics Release Inventory (TRI) and therefore are being emitted into air, land, and water in quantities of more than 10,000 pounds per year. Toxicity data was available for less than half of the TRI chemicals. Also, almost 60% of the chemicals sampled that met the U.S. EPA criteria for bioaccumulation and persistence did not meet basic screening requirements for health hazard data.

The clear conclusion from the 1984 NRC study, the OTA, and recent EDF study is not that almost 75% of all the commercial high-production-volume chemicals are unsafe, but that we have no reliable basis on which to determine if they are safe or not. Therefore, we are flying blind, and do not know where we should be making efforts to reduce their use and potential risks, including carcinogenic risks. We know even less about the remainder of the 70,000 chemicals on the U.S. EPA inventory.

We need to find ways to move ahead with screening these high-production-volume chemicals. The U.S. EPA is developing a toxics agenda—a clear mission and coherent strategy to systematically identify and act on the most serious chemical risks. Our highest priority targets are those chemicals to which children are most exposed—chemicals in their homes, schools, and play areas. Through the Toxics Agenda we are seeking to lay the basis for initiatives from industry, the public, and government to assess chemicals and make toxicity data available.

Clearly the 3000 very high-production-volume (>1 million lb/year) nonpolymeric chemicals have the highest priority for action. Of these, only 500 have had testing under the TSCA—half of these since 1992 (21). Clearly more testing is needed. We would like to see the chemical industry increase its support of the OECD screening information data sets program, which is assessing high-volume chemicals on a cooperative international basis (22). The purpose of this effort is to target risks and those chemicals that require further study. A key advantage of this approach is that its testing costs are shared with other countries, which should speed the task. We also would like to see stronger authority for the U.S. EPA to require testing, and a more specific agenda for testing, Testing for endocrine disruptors, as required in the Safe Drinking Water Act (23) and the FQPA (8), is a good beginning.

This year, the U.S. EPA plans to focus several initiatives at reducing children's exposures to toxics and potential carcinogens. One is an agencywide effort to target reductions in all media environmental programs persistent bioaccumulative toxic chemicals, such as dioxin, polychlorinated biphenyls, and mercury, that also may be carcinogens. We also plan to expand our consumer labeling initiative (24) beyond pesticides to labels on household and other consumer products, such as cleaning agents and latex paint, with the goal of providing more readily understandable information on hazards, especially to children.

Along the same lines, the U.S. EPA plans to make protection of indoor environments a higher priority. This effort is gaining momentum. Almost every program and regional office is involved in planning a strategy that will make the most of our resources and existing legislative authorities. The effort will include protection from indoor air pollution as well as other indoor health hazards.

We know that radon is estimated to account for 7000 to 30,000 lung cancer deaths annually (25), and that environmental tobacco smoke is estimated to account for 3000 annual lung cancer deaths in nonsmokers (26). We know that some consumer and commercial products and building materials emit chemicals that are suspected carcinogens (27). We do not know how many cases of childhood cancers are caused by these exposures, but we are focusing our efforts on protecting children from exposures that pose the highest risks.

On another initiative that I mentioned, we plan to begin to screen chemicals for their ability to mimic hormones. We will be looking at pesticides, which I mentioned, and at water contaminants. A federal advisory committee, the Endocrine Disruptor Screening and Testing Advisory Committee, is developing an implementation plan that is due in August 1998. Screening is slated to begin in 1999.

These initiatives are promising, and we are taking major steps to give our children added protections against cancers from pesticides. But we have a long way to go in understanding cancer risks posed by industrial chemicals, and therefore, we are far from being able to effectively regulate their carcinogenic risks to children.

REFERENCES AND NOTES

1. Toxic Substances Control Act, January 1, 1977; Title 1 U.S. Code at Section 136, and following those pages as amended.
2. Federal Hazardous Substances Act, January 1, 1977; Title 1 United States Code at Section 136, and following those pages as amended.
3. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina; association of stilbestrol therapy with tumor appearance in young women. N Engl J Med 284: 878 (1971).
4. IARC. Evaluation of the carcinogenic risk of chemicals to humans: diethylstilbestrol dipropionate. In: IARC Monographs, Vol 21. Lyon: International Agency for Research on Cancer, 1979:173–231.
5. Guzelian PS, Henry CJ, Olin SS, eds. Similarities and Differences between Children and Adults: Implications of Risk Assessment. Washington: International Life Science Institute Press, 1992.
6. NRC. Board on Environmental Sciences and Toxicology. Pesticides in the Diets of Infants and Children. Washington: National Research Council Press, 1993.
7. U.S. EPA. Environmental Health Threats to Children. Washington: U.S. Environmental Protection Agency, 1996.
8. Food Quality Protection Act, August 3, 1996, Title 7 United States Code at Section 1261, as amended.
9. President. Protection of Children from Environmental Health Risks and Safety Risks. Executive Order 13045. April 21, 1997. Fed Reg 19883–19888 (April 23, 1997).
10. U.S. EPA. Personal communication.
11. EDF. Toxic Ignorance: The Continuing Absence of Basic Health Testing for Top-Selling Chemicals in the United States. New York: Environmental Defense Fund, 1997.
12. 40 CFR Pt. 158, Data Requirements for Registration.
13. U.S. FDA. Toxicological Principles for the Safety Assessment of the Direct Food Additives and Color Additives Used in Food. Washington: U.S. Federal Drug Administration, 1982; 41–42.
14. U.S. EPA. Unpublished observations.
15. U.S. EPA. Unpublished observations.
16. McConnell EE. Comparative responses in carcinogenesis bioassays as a function of age at first exposure. In: Similarities and Differences Between Children and Adults: Implications of Risk Assessment (Guzelian PS, Henry CJ, Olin SS, eds). Washington: International Life Sciences Institute Press, 1992; 66–78.
17. Chhabra RS, Bucher JR, Haseman MR, Elwell MR, Kurtz PJ, Carlton BD. Comparative carcinogenicity of polybrominated biphenyls with or without perinatal exposure in rats and mice. Fundam Appl Toxicol 21:451–460 (1993).
18. U.S. EPA. Personal communication.
19. National Research Council. Toxicity Testing. Washington: National Academy Press, 1984.
20. U.S. Congress. Screening and Testing Chemicals in Commerce. OTA-BP-ENV-166. Washington: Office of Technology Assessment, September 1995.
21. U.S. EPA. Personal communication.
22. OECD. Screening Information Data Set Manual of the OECD Programme on the Cooperative Investigation of High Production Volume Chemicals, Second Ed. Paris: Organisation for Economic Co-operation and Development Secretariat, 1996.
23. Safe Drinking Water Act, December 16, 1974, Title 42 United States Code at Section 3000f, as amended.
24. 61 FR 12011 (March 22, 1996). Voluntary Consumer Labeling Initiative. Fed Reg 61:12011 (1996).
25. U.S. EPA. Technical Support Document for the 1992 Citizen’s Guide to Radon. EPA 400-R-92-011. Washington: U.S. Environmental Protection Agency, 1992.
26. U.S. EPA. Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. EPA 600-6-90-006F. Washington: U.S. Environmental Protection Agency, 1992.
27. U.S. EPA. Unpublished observations.