United States Senate
Committee on Environment and Public Works
Toxic Substances Control Act and the Chemicals Management Program at EPA
Testimony of Gail Charnley, PhD
2 August 2006

Summary of Key Points

- In its 1997 final report, the Presidential/Congressional Commission on Risk Assessment and Risk Management recommended that a sustained stakeholder process be initiated to review TSCA and its implementation. Since the time of the Commission's final report, a variety of activities has taken place that is consistent with that recommendation, including but not limited to the National Pollution Prevention and Toxics Advisory Committee, the High Production Volume Challenge Program and the new Extended Program, and the Voluntary Children's Chemical Evaluation Program.

- Biomonitoring data that provide information solely about trace levels of substances in blood or urine cannot be used to draw conclusions about the likelihood of disease except in very rare cases. Biomonitoring data can be used to demonstrate trends in exposure over time, to establish that exposure has occurred, or to identify individuals with unusual exposures. To the extent they are available, environmental and biomonitoring trend data demonstrate that emissions and body burdens of contaminants continue to decline. In any case, focusing solely on trace levels of chemicals in blood and ignoring the substantial contributions that genetics and economic, social, cultural, behavioral, and psychological factors contribute to risk is unlikely to provide detectable benefits to public health.

- It is illogical to presume that any chemical exposure is dangerous and that any potential chemical hazard poses a risk. When exposures are below the levels that produce toxicity in children or adults, no toxicity will be produced. And, even if they were to occur, increases in childhood health problems would be unlikely to be associated with environmental contaminant concentrations that are declining.

- Current EPA methods for setting standards to limit chemical exposures are precautionary and account for the possibility that children can be more susceptible than adults to chemical toxicity. When information on developmental toxicity is available, it is considered. When developmental toxicity is the most sensitive end point of toxicity, it serves as the basis for standard-setting. When no information on developmental toxicity is available, a database uncertainty factor is used to make the standard more stringent than it would be otherwise, in order to be precautionary and account for the possibility that children might be more susceptible than adults. A database uncertainty factor of 10 covers the possibility that children are more sensitive than adults about 95% of the time.

- Studies show that evaluating the relative sensitivity of children and adults to chemical toxicity must be done on a case-by-case basis. Children may be more than, less than, or just as sensitive as adults, depending on the chemical and the exposure situation. The only unifying principle that has emerged thus far is, "It depends." Assuming that children are always more susceptible to chemical toxicity or that children's exposures always contribute disproportionately to adult disease is not supported scientifically.

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Since the early 1990s, our awareness and understanding of the special susceptibilities of children to chemical exposures has improved substantially. Our precautionary methods for setting limits on chemical exposures take children's unique exposure characteristics into account and provide margins of safety that protect children when greater susceptibility to toxicity is known or suspected. A variety of voluntary programs have been initiated under the umbrella of TSCA that have generated basic toxicity data for most of the chemicals in commerce by volume, including information about children's exposures and susceptibilities. These efforts will continue to produce data and chemical-specific exposure limits will continue to be generated and fine-tuned as new data on developmental toxicity become available. Meanwhile, to the extent they are available, environmental and biomonitoring data demonstrate that chemical emissions and body burdens continue to decline.

TSCA Progress

In its 1997 final report, the Presidential/Congressional Commission on Risk Assessment and Risk Management[1] (for which I served as executive director) evaluated and made recommendations regarding the risk assessment and risk management policies and practices across the federal government. With regard to TSCA, the Risk Commission concluded:

> Given the divergent views about the situation, the history of litigation, the advances in the world of testing and toxicologic interpretation, and the willingness of all parties to engage in dialogue, the Commission recommends that EPA, industry, academia, and worker, consumer, and environmental organizations be convened in a sustained stakeholder

[1] The Commission was mandated by the 1990 amendments to the Clean Air Act, comprised ten commissioners appointed in a bipartisan manner, and operated between 1994 and 1997.

process to review TSCA and its implementation, to propose criteria for developing test batteries, to seek consensus on making weight-of-evidence judgments about such data, [and] to define criteria for making data more accessible to the public.[2]

Since the time of the Commission's report, a variety of activities has taken place that is consistent with that recommendation. Among the prominent ones are:

- US EPA convened the National Pollution Prevention and Toxics Advisory Committee, a national advisory body that provides advice, information, and recommendations on the overall policy and operation of programs managed by the Office of Pollution Prevention and Toxics in performing its duties and responsibilities under TSCA. The Committee provides a forum for public discussion and the development of independent advice to the EPA Administrator by taking advantage of the experience, strengths and responsibilities of a broad range of Agency constituents and stakeholders.

- The High Production Volume (HPV) Challenge Program was launched in 1998 as a cooperative effort among EPA, the American Chemistry Council, and Environmental Defense. More than 300 companies and consortia volunteered for the program, providing safety information on nearly 95 percent of US chemical production by volume. The HPV program is a tiered testing program that generates a basic set of toxicity data first on key end points, including reproductive, developmental, systemic, and genetic toxicity. The results of the basic testing allow scientists to evaluate potential hazards and decide whether additional toxicity tests are needed and, if so, which specific tests would be appropriate. This tiered testing and evaluation framework promotes an efficient use of resources, including laboratory animals, by targeting substances posing the greatest potential hazards. The HPV Challenge Program is nearly complete and has greatly accelerated the public availability of hazard screening data and critical information used to evaluate the potential health and environmental effects of HPV chemicals. The HPV

[2] US Commission on Risk Assessment and Risk Management (1997). Final Report, Volume 2. *Risk Assessment and Risk Management in Regulatory Decision-Making*. GPO #055-000-00567-1, page 128. Available at http://www.riskworld.com/nreports/1996/risk_rpt/RR6ME001.HTM

program is now supplemented by the Extended High Production Volume Program, a voluntary, industry-led initiative that continues to generate toxicity screening data for newer HPV chemicals and to make those data publicly available.

- The Voluntary Children's Chemical Evaluation Program is a voluntary pilot program that is part of EPA's Chemical Right-to-Know Initiative. The goal of the pilot is to better understand potential health risks to children associated with certain chemical exposures. The key question of the program is whether the potential hazards, exposures, and risks to children have been adequately characterized and, if not, what additional data are necessary. EPA has asked companies that manufacture or import 23 chemicals found in human tissues and the environment to volunteer to sponsor chemical evaluations. Sponsorship requires the companies to collect or develop health effects and exposure information on their chemicals and then to integrate that information in a risk assessment and a data needs assessment. Like the HPV program, VCCEP uses a tiered testing scheme to generate a basic set of toxicity and exposure data and then uses the results to determine what types of further testing is needed. The results of the pilot program thus far illustrate how various parties can work together under a voluntary program and how toxicity and exposure data can be integrated to make decisions regarding the adequacy of risk information for children. The program has been in operation since 2002 and is currently being reviewed and fine-tuned.[3]

These programs demonstrate that voluntary, multi-stakeholder initiatives have been initiated and are succeeding under the umbrella of TSCA. Since the mid-1990s, basic toxicity data have been generated for most of the chemicals in commerce by volume and research efforts have provided information about children's exposures and susceptibilities that has been incorporated into risk assessment and chemical standard-setting. These efforts will continue to generate data that will contribute to better and better chemical regulation and to safer, healthier children.

[3] For a status report, see Williams PRD, Patterson J, Briggs DW (2006). VCCEP: Progress on evaluating children's risks and data needs. Risk Analysis 26:781-801

Biomonitoring and the Role of the Environment in Children's Health

Establishing a role for chemicals in public health in general or children's health in particular is complicated by the fact that "environment" includes many more complexities than just chemical contaminants, such as physical safety, nutrition, socioeconomic factors, infectious agents, naturally occurring substances, ultraviolet radiation, tobacco smoke, and natural disasters. The National Children's Study defines a child's environment broadly, including natural and man-made environment factors, biological and chemical factors, physical surroundings, social factors, behavioral influences and outcomes, genetics, cultural and family influences and differences, and geographic locations.[4] Notable among the varying definitions of environment and the various attempts to quantify environmentally attributable proportions of disease is the comparatively small role that chemical exposures evidently play against the backdrop of socioeconomic conditions, behavioral factors, psychological factors, infectious agents, nutrition, and other considerations.

Several studies have attempted to evaluate the role of environment in ill health. For example, one evaluation estimated the extent to which global ill health is attributable to environmental risk factors, excluding genetics, diet, smoking, and some component of injuries but including food additives, infectious agents, pesticides, passive smoking, behavioral factors related to personal and household hygiene, some malnutrition, and the natural environment (e.g., dust and natural disasters).[5] That study concluded that 12% of disease in established market economies is potentially attributable to environmental factors. Compared to all ages, the proportions of children's environmentally attributable disease burden is about 0.8%.

This is not to say that chemical exposures do not play a role or that their contribution should be ignored; even if their contribution is small, it could constitute a public health problem by virtue of the numbers of people affected. However, given their relatively small contribution, chemical contaminants should not be treated in isolation from other factors if an effective

[4] US EPA/Environmental Protection Agency (2001). The National Children's Study. Conducted in partnership with the US Department of Health and Human Services. Available at http://www.nationalchildrensstudy.gov/

[5] Smith KR, Corvalan CF, Kjellstrom T (1999). How much global ill health is attributable to environmental factors? Epidemiology 10:573-84

environmental strategy for protecting and improving public health—and especially children's health—is desired.

Attributing specific health outcomes to specific chemicals at environmentally relevant levels of exposure is, except in the rarest of cases, unlikely to be either possible or defensible. For example, while the cause of childhood asthma may be traced to genetic influences, its occurrence may be triggered by environmental tobacco smoke or urban air pollution. An environmental health strategy that targets specific exposures without considering the contributions of other risk factors and the multifactorial etiology of disease will not be effective. In any case, dissecting out the contributions of genetics and economic, social, cultural, behavioral, and psychological factors for the purpose of identifying and reducing environmental risks in general, or chemical risks in particular, is unlikely to be straightforward. As EPA put it recently:[6]

> One of the greatest challenges to elucidating the connection between environmental exposure and disease is the fact that exposure to an environmental pollutant or stressor is rarely the sole cause of an adverse health outcome . . . Other factors include, for example, diet, exercise, alcohol consumption, heredity, medications, and whether other diseases are present . . . Also, different people have different vulnerabilities . . . All these factors make it difficult to establish a causal relationship between exposure to environmental pollutants and disease outcome . . .

For the reasons discussed above, biomonitoring data that provide information solely about trace levels of chemicals in blood or urine at a single point in time cannot be used to draw conclusions about the likelihood of disease except in very rare cases. Biomonitoring data can be used to demonstrate trends in exposure over time, to establish that exposure has occurred, to identify individuals with unusual exposures, or to help clarify the relationship between exposure and dose in some cases, but generally do not provide an indication with regard to the likelihood

[6] EPA/Environmental Protection Agency (2003). Draft Report on the Environment 2003. Technical Document. EPA-600-R-03-050. Office of Research and Development and Office of Environmental Information. Washington, DC. Available at http://www.epa.gov/indicators/roe/index.htm

of ill health. As the recent National Academy of Sciences report *Human Biomonitoring for Environmental* Chemicals put it:

> The ability to generate new biomonitoring data often exceeds the ability to evaluate whether and how a chemical measured in an individual or population may cause a health risk or to evaluate its sources and pathways of exposure . . . For some chemicals (such as mercury and lead), the health risks and effects are well known; but for most of the chemicals currently measured, the risks cannot be interpreted.[7]

As the Centers for Disease Control and Prevention puts it in its *National Report on Human Exposure to Environmental Chemicals*:

> The presence of a chemical in a blood or urine specimen does not mean that the chemical causes a health risk or disease.[8]

Our analytic abilities increasingly permit the detection of substances in biological samples in smaller and smaller trace quantities. That does not mean we are increasingly at risk of chemical-related disease. Trace levels of chemicals in the body are unlikely to overwhelm the body's natural ability to detoxify and eliminate them. Given our incomplete knowledge of the inter-relationships among multiple chemical and non-chemical, environmental and non-environmental stressors, interpretation of the potential impact of exposure to trace levels of chemicals, if any, will probably be dependent on eventual decoding of the human genome map. Meanwhile, using laboratory animals to provide information on chemical toxicity can help us identify target organ systems and target risk management strategies, but is unlikely to provide insight with regard to the potential impact of trace levels of chemicals.

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[7] National Academy of Sciences/National Research Council (2006). *Human Biomonitoring for Environmental Chemicals*. National Academy Press. Washington, DC. Page 2

[8] Centers for Disease Control and Prevention (2005). *National Report on Human Exposure to Environmental Chemicals*. Third Report. Atlanta, GA. Available at http://www.cdc.gov/exposurereport/

The good news is that, to the extent that they exist, environmental and biomonitoring trend data demonstrate that emissions and body burdens of contaminants continue to decline. EPA emissions data show that pollutant levels have generally declined while our economy has grown.[9] For example, dioxin and furan concentrations in the environment and human tissues have been declining since the 1970s. Samples taken of sediments from remote lakes impacted purely by atmospheric deposition and transport and of archived soils and herbage show low background levels of naturally occurring dioxins and furans prior to 1900 followed by a sharp rise after 1930, coinciding with the onset of industrialization and the large-scale production and use of organochlorine compounds, peaking in the 1970s, with a slow decline until the present day. Evidence for this decline has also been found in studies on archived sewage sludge, air measurements, and biological samples.[10] Human tissue concentrations of 2,3,7,8-TCDD taken from residents of Germany, France, the US, and Canada show that exposure has declined by more than 95% since 1972.[11] Other data show that if exposure to dioxin-like compounds stays at present levels (which is unlikely), current body burdens will fall by more than 50% by 2020.[12]

Studies show that the levels of contaminants in breast milk are also declining. For example, data from Germany, Norway, and the Netherlands indicate that concentrations of dioxins and furans have decreased by at least 50% since 1980.[13] Other substances for which trend data are available show continued declines as well. The extent to which chemicals present in breast milk present a health risk to the breastfeeding infant is not known. Virtually all national and international expert committees have concluded that, on the basis of available information, the benefits of breastfeeding outweigh the possible risks from chemical contaminants present in human milk at normal levels.[14] In fact, epidemiologic research shows that human milk and breastfeeding of infants provide advantages with regard to general health, growth, and

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[9] See, for example, EPA (2000). *National Pollutant Emission Trends, 1900-1998*. EPA-454/R-00-002. Office of Air Quality Planning and Standards. Research Triangle Park, NC. Available at http://www.epa.gov/ttn/chief/trends/trends98/trends98.pdf

[10] Euro Chlor (2003). *Dioxins and Furans in the Environment*. Science Dossier. Brussels, Belgium. Available at www.eurochlor.org

[11] Aylward LL, Hayes SM (2002). Temporal trends in human TCDD body burden: Decreases over three decades and implications for exposure levels. Journal of Exposure Analysis and Environmental Epidemiology 12:319-328

[12] Lorber M (2002). A pharmacokinetic model for estimating exposure of Americans to dioxin-like compounds in the past, present, and future. The Science of the Total Environment 288:81-95

[13] LaKind JS, Berlin C, Naiman DQ (2001). Infant exposure to chemicals in breast milk in the United States: What we need to learn from a breast milk monitoring program. Environmental Health Perspectives 109:75-88

[14] La Leche International (1994). *Pesticides and breastfeeding*. LEAVEN 30:37-40

development, while significantly decreasing risk for a large number of acute and chronic diseases.[15]

An expert committee was convened by the European Centre for Ecotoxicology and Toxicology of Chemicals to review trends over time in chemical exposures and in children's health.[16] That committee drew a number of conclusions that are germane to evaluating the role of chemical exposures and children's health:

- In comparing time trends of disease improved reporting systems, changes in diagnostic criteria/procedures, a more active approach to early detection of cases to improve prognosis and a better health care system in general must be taken into account. There is clear evidence of increasing rates of asthma in children, although rates in some countries may now have stabilized. There is no convincing evidence of widespread trends in other acute or chronic childhood respiratory diseases. Indoor air quality appears to be related to both asthma and, in some cases, to other respiratory-related diseases (such as otitis media). Interpretation of the available information on asthma and allergies is made difficult by inconsistent application of diagnostic criteria over place and time. Contemporaneous with the increasing frequency of asthma, data also suggest that other atopic disorders such as upper respiratory and food allergy may be increasing. Atopic dermatitis remains the leading skin disorder in young children.

- Although the frequency of neurodevelopmental disorders such as autism and attention deficit disorder is commonly believed by the public to be increasing, the limited data available do not support this perception.

- Data on reproductive effects are also limited and often suffer from serious data quality issues. Whilst geographic heterogeneity is apparent, broad population trends for these

[15] American Academy of Pediatrics (1997). Policy statement on breastfeeding and the use of human milk. Pediatrics 100:1035-1039

[16] European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) 2005. Trends in Children's Health and the Role of Chemicals: A State of the Science Review. Brussels. Available at

outcomes (sperm quality, hypospadias, cryptorchidism) are difficult to identify except for decreasing age at puberty in females.

- There is no evidence for major trends in the frequency of childhood cancer. Data indicate that developed countries tend to have a gradually increasing incidence of leukaemia with a corresponding drop in the incidence of lymphoma. Increases in brain tumour frequency are possibly related to the development of new diagnostic capabilities rather than to a true change in the incidence in the rate of malignant disease. With the increasing number of childhood cancer survivors, secondary cancers following chemotherapy appear to be on the increase.

- A wide range of environmental factors is thought to have an impact on children's health, extending well beyond industrial chemicals. These factors include nutrition (protein, vitamins, anti-oxidants), lifestyle and behavior choices such as tobacco and alcohol use, parental health, socio-economic status, choice of living environment (urban vs. rural, etc.), and parent-sibling behavior. From the available data, no general conclusions on the contribution of specific chemicals can be drawn across the multiple health outcomes addressed in [the committee's] report.

It is illogical to presume that any chemical exposure is dangerous and that any potential chemical hazard poses a risk. And, even if they were occurring, increases in childhood health problems would be unlikely to be associated with environmental contaminant concentrations that are decreasing. Even the New York Times notes that people alive today in developed countries are healthier than they used to be, live longer, get heart disease and other chronic illnesses later in life than they used to, experience less disability, and have higher IQs.[17] Much of those improvements is due not just to better medical care but also to better nutrition, higher birth weights, and fewer hazardous occupational and environmental exposures.

[17] New York Times, Sunday July 30, 2006

Limiting Chemical Exposures

Current EPA methods for setting standards to limit chemical exposures are precautionary and account for the possibility that children can be more susceptible than adults to chemical toxicity. When information on developmental toxicity is available, it is considered. When developmental toxicity is the most sensitive end point of toxicity, it serves as the basis for standard-setting. When no information on developmental toxicity is available, a database uncertainty factor is used to make the standard more stringent than it would be otherwise, in order to be precautionary and account for the possibility that children might be more susceptible than adults.

Traditionally, chemical risk assessment has been performed by comparing a measured or estimated human dose to a dose associated with a toxicity endpoint, such as a no-observed-adverse-effect level (NOAEL) or a benchmark dose, after adjustment by adequate uncertainty and/or safety factors. Adjusting for uncertainty generally involves dividing a NOAEL or benchmark dose derived from human data by 10 to yield a level of exposure that would be protective of individuals who might be more sensitive than those tested or observed. If no human data are available, a NOAEL or benchmark dose identified using laboratory animals is divided by 100—10 to protect sensitive individuals (intraspecies factor) and 10 to account for the possibility that humans could be more sensitive than the species tested (interspecies factor). The resulting lifetime exposure level is considered likely to be without adverse effects in humans, including sensitive subgroups or life stages, because the intraspecies uncertainty factor is meant to protect sensitive groups such as children or the elderly.

A number of scientists have attempted to investigate quantitatively whether the intraspecies uncertainty factor is adequate to account for the variability to chemical toxicity between the overall human population and its potentially more sensitive groups, including children. Dourson et al (2002) reviewed 17 studies that performed quantitative analysis of the extent of toxicodynamic and pharmacokinetic variability using different data and different

starting points, some specifically evaluating age effects in both humans and animals.[18] That analysis suggests that a high percentage of the population, including children, is protected by using a 10-fold uncertainty factor for human variability. Studies indicating that in some cases the young would not be protected by the standard uncertainty factor were those that evaluated acute lethality in laboratory animals (LD_{50}s) and are therefore less relevant to evaluating risks from environmental exposures. Based on specific comparisons for newborns, infants, children, and adults, the range of the population protected is between 67 and 100 %. Studies using larger populations that include sensitive individuals suggest that the value is closer to 100%.[19]

Other evaluations concur with those of Dourson et al (2002). For example, the German Research and Advisory Institute for Toxic Chemicals concluded that, based on toxicokinetic differences, the most susceptible group of neonates is protected by a 10-fold intraspecies uncertainty factor in most cases.[20] The authors also conclude, however, that the protection of neonates and infants may require consideration of their lower xenobiotic clearance rates and recommend using a log-normal density function, based on the differences in adult and neo-natal clearance rates, in the framework of probabilistic risk assessments.

Conclusions about the adequacy of the 10-fold intraspecies uncertainty factor do not mean that interindividual sensitivity varies 10-fold, as is often thought. Its application to a value in the low end of the distribution of human sensitivities, such as a NOAEL, and its use in conjunction with other uncertainty factors and conservative assumptions, actually cover total human sensitivity variations of 100 to 1,000 times (see Exhibit 4).

[18] Dourson M, Charnley G, Scheuplein R. 2002. Differential Sensitivity of Children and Adults to Chemical Toxicity. II. Risk and Regulation. Regulatory Toxicology and Pharmacology, 35:448-467

[19] Hattis D, Banati P, Goble R. 1999a. Distributions of Individual Susceptibility Among Humans for Toxic Effects. How Much Protection Does the Traditional Tenfold Factor Provide for What Fraction of Which Kinds of Chemicals and Effects? Annals of the New York Academy of Sciences 895:286-316;
Hattis D, Banati P, Goble R, and Burmaster D. 1999b. Human Interindividual Variability in Parameters Related to Health Risks. Risk Analysis 19:705-720; Renwick AG and Lazarus NR. 1998. Human variability and noncancer risk assessment an analysis of the default uncertainty factor. Reg Toxicol Pharmacol 27:3-20

[20] Schneider KI, Gerdes H, Hassauer M, Oltmanns J, Schulze J. 2002. Berücksichtigung der Risikogruppe Kind bei der Ableitung gesundheitsbezogener Umweltstandards. UFOPLAN-Nr. 201 61 215. Forschungs- und Beratungsinstitut Gefahrstoffe GmbH (FoBiG), Freiburg

In the absence of important data on a substance's toxicity, such as reproductive or developmental toxicity, standard EPA practice has been to use a "database uncertainty factor" in addition to the other factors. The database uncertainty factor is generally a factor of 10 that is added to the calculation of an exposure limit, making it ten times more stringent than it would be otherwise. In other words, EPA uses an extra uncertainty factor when there is inadequate information about developmental effects, reproductive effects, or developmental neurotoxicity in order to be precautionary and health-protective.

Age and chemical exposures

Children's exposures to chemicals from their environment are qualitatively and quantitatively different from those of adults. For example, children are likely to be exposed to different levels of chemical contaminants in foods than adults because they consume more calories of food per unit of body weight, fewer types of foods, and more processed foods.[21] The National Academy of Sciences report *Pesticides in the Diets of Infants and Children*[22] concluded that differences in diet and thus in dietary exposure to pesticide residues account for most of the potential differences in pesticide-related health risks that may exist between children and adults.

Normal childhood behaviors such as hand-to-mouth activity and crawling on the floor or ground can increase children's exposures to potential toxicants through ingestion and contact with dusts and residues. Greater risk of lead poisoning from lead-based paint is a well-known example of that problem. Children breathe more than adults on a body-weight basis, so may be exposed to higher doses of air pollutants. Children consume more water than adults on a body-weight basis, so may be exposed to higher doses of water pollutants. Infants consume breast milk, an important source of nutrition and immunologic protection, but sometimes a source of fat-soluble contaminants such as PCBs. Children may not perceive hazards as quickly or effectively as adults, so may experience some greater exposures by not avoiding them as readily. In contrast, adults have higher exposures than children to chemicals associated with activities

[21] US Department of Agriculture (1985). *Nationwide Food Consumption Survey: Continuing Survey of Food Intakes by Individuals, Women 19-50 Years and Their Children 1-5 Years*. Human Nutrition Information Service. Washington, DC

[22] National Academy of Sciences/National Research Council (1993). *Pesticides in the Diets of Infants and Children*. National Academy Press. Washington, DC

such as home car repair, cleaning, home painting, and other recreational or maintenance activities. Occupational exposures also would be greater for adults than children, although there are situations, such as pesticide application, where parents' exposures result in children's exposures when applicators return home after working.

Exposure is not the only determinant of toxicity, however. Once exposure has occurred, age-related differences in the body's ability to absorb, distribute, metabolize, and eliminate chemicals can produce different doses from the same exposures. Risks to health are determined by exposure, dose, and susceptibility. Even if children's exposures or doses of substances exceed those of adults on a body-weight basis, they will still not be at risk unless the doses are high enough to produce toxicity. The dose or level of exposure that is capable of producing toxicity is determined by children's inherent susceptibility, which may be greater than adults in some cases and less in others.

Age and susceptibility

There are many physiologic and pharmacologic reasons why the susceptibility of children and adults to the impacts of chemical exposures may differ. The developing organism experiences many complex, integrated events involving the regulation of cell growth, differentiation, and morphogenesis. Interfering with those events through mutation or through altered cell division, enzyme function, or energy sources can have significant adverse impacts on development.[23] Many environmental factors can have an impact on normal development, including nutrition and folic acid availability, maternal smoking and alcohol consumption, prescription drugs, and chemical contaminants such as lead and organic mercury.

Children are more sensitive than adults to the toxic effects of many chemicals, such as lead. At the same time, children are often less sensitive to many chemicals than are adults. For example, unlike the situation in adults, liver toxicity and death from acetaminophen poisoning is

[23] Wilson J (1977) Current Status of Teratology; General Principles and Mechanisms Derived from Animal Studies. In: *Handbook of Teratology; General Principles and Etiology*, ed. J Wilson and F Fraser. New York: Plenum Press; Faustman EM, Silbernagel SM, Fenske RA, Burbacher TM, Ponce RA (2000). Mechanisms underlying children's susceptibility to environmental toxicants. *Environmental Health Perspectives* 108:13- 21

extremely rare in children.[24] The metabolism and elimination rates of many drugs and other substances are known to be higher in children than adults. As a result, children will often have lower body burdens of drugs or chemicals than adults for the same exposures, when expressed on a body-weight basis. For example, as Exhibit 1 shows, morphine is cleared about 2-3 times faster by children than by adults. The chemotherapy drug methotrexate is cleared six times faster by children than by adults. The antipsychotic drug Thorazine® is cleared five times faster by children than by adults. As a result, kids require higher pharmacologic doses than adults of those drugs to achieve efficacy.

Thus, while some chemicals may be metabolized to toxic metabolites more quickly by children, those metabolites are likely also to be deactivated and eliminated more rapidly, presumably becoming less toxic by decreasing their effective doses. Children's generally more rapid elimination rates may compensate in part for any increased sensitivity during development.[25] A number of environmental exposures, including pesticides, parental occupational exposures, and infectious organisms have been suggested as possible precursors to cancer or other health effects in children; however, the considerable research conducted to date has yielded inconsistent or limited evidence identifying those factors as disproportionate threats to children's health.[26]

Rodent bioassays show that younger animals are less susceptible to chemical carcinogens in some cases and more susceptible in others. *Pesticides in the Diets of Infants and Children* included a table summarizing the results of studies that had been performed through 1983 in which the effects of age on chemically induced carcinogenesis in rodents had been evaluated. That list was updated in 2001.[27] As can be seen in Exhibit 2, the data indicate that there are a similar number of studies showing that younger animals are less susceptible than adults to chemically induced carcinogenesis as there are showing that they are more susceptible under the

[24] Penna A, Buchanan N (1991). Paracetamol poisoning in children and hepatotoxicity. British Journal of Clinical Pharmacology 32:143-149
[25] Renwick AG (1998). Toxicokinetics in infants and children in relation to the ADI and TDI. Food Additives and Contaminants 15S:17-35
[26] Public Health Policy Advisory Board (1999). *Health and the American Child. Part 1: A Focus on Mortality Among Children. Risks, Trends, and Priorities for the Twenty-First Century*. Washington, DC
[27] Charnley G, Putzrath RM (2001). Children's health, susceptibility, and regulatory approaches to reducing risks from chemical carcinogens. Environmental Health Perspectives 109:187-192

conditions of the bioassays. A number of studies showed that age played no role at all in susceptibility.

The National Academy of Sciences report concluded that those results clearly demonstrate that age may be an important factor in susceptibility to chemically induced carcinogenesis, but they do not support the conclusion that younger animals are always more susceptible than older animals. The database also illustrates the difficulty associated with assessing quantitatively the extent of the differences in susceptibility due to age. Virtually all of the studies evaluated used only one dose level, so the underlying dose-response relationships are unknown and comparison of sensitivities is possible only at the relatively high, single dose levels used. Generalizations about the effect of age on susceptibility to chemical carcinogens are thus difficult to make.

Data on acute chemical toxicity show similar results. Exhibit 3 shows how the lethal dose of DDT varies with age, indicating that in this case, infant rats are much less susceptible to toxicity than adult rats. A review by Ed Calabrese of the data available on LD_{50}s showed only small differences due to age. In some cases, young animals were more susceptible and, in some cases, adult animals were more susceptible.[28] In only a few cases did the differences exceed an order of magnitude, however, and in many cases, there were no differences. Data on the maximum tolerated doses of chemotherapeutic agents in humans show that they were frequently higher for children than adults, indicating greater susceptibility of adults, although the differences between age groups were usually less than or equal to two.[29] Studies of pesticide acute toxicity also show variability. In one study, no more than 2- to 3-fold differences in sensitivity were observed, with the younger animals more sensitive to toxicity than older animals in only four out of 36 cases.[30] In another study, however, 14 of 15 organophosphate pesticides showed greater acute toxicity to young rats than to adult rats.[31]

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[28] Calabrese EJ (1986). *Age and Susceptibility to Toxic Substances*. New York: John Wiley & Sons

[29] Bruckner JV (2000). Differences in sensitivity of children and adults to chemical toxicity: the NAS panel report. Regulatory Toxicology and Pharmacology 31:280-285

[30] Gaines TB, Linder RE (1986). Acute toxicity of pesticides in adult and weanling rats. Fundamental and Applied Toxicology 7:299-308

[31] Brodeur J, DuBois KP (1963). Comparison of acute toxicity of anticholinesterase insecticides to weanling and adult male rats. Proceedings of the Society for Experimental Biology and Medicine 114:509-511

Chemical exposures can affect normal prenatal or childhood development by interfering---either directly or indirectly---with the large network of regulatory genes that control growth and development. In contrast to physiological responses, which can vary in response to exposures or other stimuli and then return to normal, developmental systems move inexorably forward. Perturbation of critical components of the regulatory gene network can have two possible outcomes. The consequences of interference may not be repaired as development moves forward or the complexity of the system may confer the ability to compensate for perturbations, should they occur, illustrating again the difficulty of making generalizations about age and susceptibility.[32]

What the scientific evidence on age-related susceptibility to the effects of chemical contaminants does show is that children may be more than, less than, or just as sensitive as adults, depending on the chemical and the exposure situation. Children may be less sensitive to the effects of a chemical than adults if they do not absorb it as readily, if they clear it more rapidly, if they lack the enzymes required to activate it, if they detoxify it more quickly, or if they compensate more readily for any damage. Most of the available information on age-related differences in sensitivity comes from experiments using single, high doses of chemicals that produced short-term, acute toxicity, however. Those observations may be poor predictors of what occurs when low doses of chemicals are received over long periods of time or of developmental toxicity. Long-term exposure to low doses of chemicals can produce different types of toxicity than short-term exposure to high doses. On the other hand, low environmental exposures to chemicals are less likely to overwhelm developing detoxification and other defense mechanisms, so age-related differences at low doses may be quantitatively less pronounced than at high doses.[33] For example, data for the insecticide chlorpyrifos show that young animals are more sensitive than adults to its nervous system toxicity at high doses, but are less or similarly

[32] Davidson EH, Rast JP, Oliveri P, Ransick A, Calestani C, Yuh CH, Minokawa T, Amore G, Hinman V, Arenas-Mena C, Otim O, Brown CT, Livi CB, Lee PY, Revilla R, Rust AG, Pan Z, Schilstra MJ, Clarke PJ, Arnone MI, Rowen L, Cameron RA, McClay DR, Hood L, Bolouri H (2002). A genomic regulatory network for development. Science 295:1669-1678

[33] Scheuplein R, Charnley G, Dourson M (2002). Differential sensitivity of children and adults to chemical toxicity. I. Biological basis. Regulatory Toxicology and Pharmacology 35:429-447

sensitive than adults at low doses.[34] The reason for the difference in this case is that young animals can compensate for toxicity faster than adult animals can at lower doses by synthesizing replacement cholinesterase faster, but cannot compensate for it fast enough at higher doses.

The effect of age on susceptibility to chemical toxicity appears to depend on the chemical of concern, the toxic effect that is observed, the dose that is received, and the period of development during which exposure occurred, with infants, children, or the developing fetus more sensitive than adults in many cases but less sensitive in others. Susceptibility to chemical toxicity is the result of extremely complex biological interactions and there is no systematic method or model to predict age-related susceptibility.[35] There is no scientific support for any statement implying that children are always more sensitive than adults to environmental chemical exposures.

[34] Mattson JL, Maurissen PJ, Nolan RJ, Brzak KA (2000). Lack of differential sensitivity to cholinesterase inhibition in fetuses and neonate compared to dams treated perinatally with chlorpyrifos. Toxicological Sciences 53:438-446

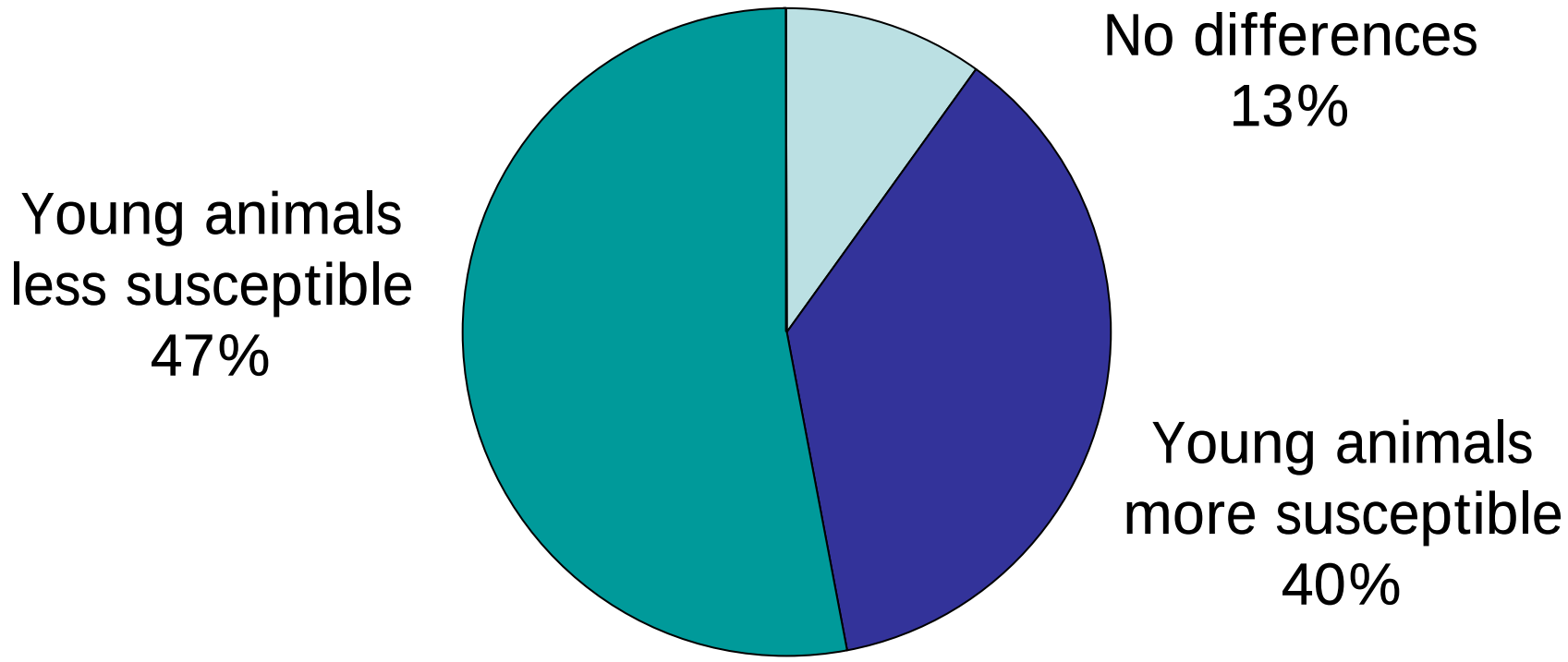
[35] Wargo J (1996). *Our Children's Toxic Legacy*. New Haven: Yale University Press

Exhibit 1
Age and Drug Clearance Rates

Compound	Age	Clearance Rate
• Morphine	children	20 - 25 ml/min/kg
	adults	6 - 15 ml/min/kg
• Methotrexate	children	0.6 l/kg/hr
	adults	0.1 l/kg/hr
• Thorazine	children	3.1 l/hr/kg
	adults	0.6 l/hr/kg
• Lidocaine	newborns	0.3-1.1 l/hr/kg
	adults	0.3-1.1 l/hr/kg

Source: ECETOC (2005)

Exhibit 2
Effects of Age on Laboratory Animal Carcinogenesis



Source: NAS/NRC (1993), Charnley & Putzrath (2001)

Exhibit 3
Example of Influence of Age:
DDT Toxicity in Rats

Age	**LD50 (mg/kg)**
Newborn	>4000
10 days	730
2 weeks	440
1 month	360
2 months	250
4 months	190
Adult	220

Exhibit 4
Response as a function of dose for humans of different sensitivities

