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**TOXICOLOGY DATA REQUIREMENTS
FOR ASSESSING RISKS OF PESTICIDE EXPOSURE TO
CHILDREN'S HEALTH**

**Report of the Toxicology Working Group of the
10X Task Force**

U.S. Environmental Protection Agency

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TOXICOLOGY DATA REQUIREMENTS FOR ASSESSING RISKS OF PESTICIDE EXPOSURE TO CHILDREN'S HEALTH

I. INTRODUCTION

The Food Quality Protection Act (FQPA) of 1996 states that for threshold effects, “an additional tenfold margin of safety for the chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of data with respect to exposure and toxicity to infants and children.

Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin of safety will be safe for infants and children.” In addition, FQPA lists several factors that must be considered when assessing risks to children,¹ such as available information concerning the special susceptibility of children to pesticide chemical residues, neurological differences between children and adults, and effects of in utero exposure.

To address these requirements of FQPA and to provide guidance on the use of toxicity data in hazard characterization and dose-response analysis relevant to decisions about the FQPA 10X factor, a 10X Task Force was established. The Task Force was divided into three working groups, the Toxicology Group, the Exposure Group, and the Integration Group, in order to address the issues. This Report describes the deliberations and conclusions of the Toxicology Working Group. A separate Exposure Report is available, and these together with an early draft of the Integration Report were used by the Office of Pesticide Programs, to develop its Policy on Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance-Setting Process. The OPP Policy Document was developed with input from scientists in the Office of Research and Development, the Office of Children's Health Protection, the Office of Pollution Prevention and Toxics, the Office of Water, the Office of Solid Waste and Emergency Response, and the Office of General Counsel. The Policy Document incorporates many of the salient points made in the Toxicology and Exposure Reports. Differences between the two are delineated in the Policy Document.²

¹The term “children” will be used in this document to cover all aspects of pre- and post-natal development, including adolescence up to the time of sexual maturation, which in humans spans the age range from 18-21 years of age.

²The primary differences are in the definition of the core toxicology dataset and application of the database uncertainty factor. The Toxicology Working Group's definition of the core toxicology dataset is more inclusive than that proposed by OPP, at least in the interim as new data requirements are imposed. As a result, the Toxicology Working Group recommends that the database uncertainty factor be used generally in situations where data are missing. Under the

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In the present document, the Toxicology Working Group of the 10X Task Force considered the following:

- 1) a definition of pre- and postnatal toxicity;
- 2) definition of the core toxicology data set for pesticides;
- 3) criteria for determining the degree of concern for hazards to children's health; and
- 4) characterization of the assessment process used for setting exposure values for children, including the residual uncertainties remaining after the toxicity assessment is completed.

The Toxicology Working Group has made a number of recommendations in this report, but chose not to address details concerning implementation of these recommendations (e.g., phasing in of new studies and application of the database uncertainty factor in regard to newly required studies); rather, these issues are addressed in the OPP Policy Document. In addition, several recommendations are made here concerning issues related to children's health risk assessment that have implications for other regulatory programs and that require broader and more in-depth discussion on an Agency-wide basis.

II. DEFINITION OF PRE- AND POSTNATAL TOXICITY

The definition used here for pre- and postnatal toxicity is the same as that used for developmental toxicity in EPA's Guidelines for Developmental Toxicity Risk Assessment (1991). Although this document is specifically focused on pesticides, the definition applies to most chemical and physical agents, as well as to some biological agents. Pre- and postnatal toxicity (or developmental toxicity³) is defined as adverse effects on the developing organism that may result from exposure prior to conception (to either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism (e.g., spontaneous abortion, stillbirth, sudden infant death syndrome, or any shortening of lifespan as a result of developmental exposures), (2) structural abnormalities (e.g., birth defects such as neural tube, craniofacial, skeletal, or reproductive system defects), (3) altered growth (usually growth retardation either in utero or postnatally, including delayed or impaired development of secondary sexual characteristics in adolescence), and (4) functional deficiencies (e.g., mental retardation, learning deficits, respiratory disease including asthma, cardiovascular disease, immune dysfunction, infertility or other reproductive impairments). Cancer as a result of

OPP approach discussed in the Policy Document, missing data would either be addressed through application of the database uncertainty factor or through an additional factor applied in risk characterization to address residual concerns due to missing data.

³Pre- and postnatal toxicity and developmental toxicity will be used interchangeably to refer to toxicity to children of all ages (from conception to sexual maturity) in this document.

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developmental exposures is also considered part of developmental toxicity but has not been discussed to any extent in previous EPA risk assessment guidelines.

The manifestations of developmental toxicity will vary depending on the timing of exposure and the underlying processes that are occurring. As examples, exposure prior to conception may cause chromosomal or DNA changes in germ cells that result in heritable effects, including death, malformations, growth retardation, functional deficits, or cancer in the offspring. During very early embryogenesis, cells are multiplying at a rapid rate and are relatively undifferentiated; exposure during this time tends to result in death, or compensation and continued normal development. For several genotoxic agents, exposure during this period also has been shown to result in malformations and growth retardation. As organogenesis begins, cells become more and more differentiated and the major structure of organs is formed, although not all organs develop at the same time or rate. Exposure during this period may cause major structural defects, as well as death, growth retardation, or postnatal functional changes. As major organ structure is completed, organization at the histological level as well as physiological and biochemical differentiation proceeds; in most mammals, these processes occur to varying extents during pre- and postnatal development.^{4,5} Some systems continue this aspect of development during late childhood and adolescence. In particular, the skeletal and reproductive systems continue development into adolescence and do not become fully mature until young adulthood at 18-21 years of age. Exposure during this period of organ growth and cellular organization may result in alterations that are detected as histopathology, growth retardation, functional changes, or cancer. It is likely, that in many cases, exposure during this time will affect the same target organs as in adults (e.g., the cardiovascular system, kidneys, respiratory system), but with different consequences because of the lack of maturity.

From this discussion, two generalizations can be made about the endpoints of developmental toxicity. First, when an organism is exposed to a toxic agent prior to conception, during early embryonic development and/or critical stages of organogenesis, the potential exists for a variety of outcomes such as death, structural malformations, neurological deficits, growth retardation, infertility or other impairment in reproductive capacity, impaired immunological function, or cancer. In this situation, the nature and the consequences of the outcomes are very different from the outcomes experienced by an adult exposed to the same chemical simply because the organ systems of the adult are mature and are no longer subject to the same kinds of biological effects.

⁴There are important differences in the timing of developmental events at birth in experimental animal species and humans that must be recognized in designing studies and interpreting experimental animal data for potential human risk.

⁵Exposure during pregnancy may also affect the placenta, which can in turn affect the developing embryo/fetus. Effects on the placenta may include alterations in blood flow and perfusion, metabolism, or in extreme cases, necrosis and separation from the uterine wall.

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The effect on the developing child at these stages is likely to be serious, irreversible and may have lifetime consequences, while that on the adult may be serious but is more likely to be reversible.

The second generalization is that when organ systems of the child have sufficiently developed to be functional but have not fully matured to the extent that they are in adults, exposure to a toxic agent may result in effects on the same target organs as in the adult, but the degree of response in the child may be different than in the adult due to a variety of factors, including more rapid cell proliferation/growth or incomplete maturation of enzyme systems for activation or detoxification of potentially toxic agents. Thus, the child may be affected at a lower or higher exposure level to a pesticide, may show a different latency before the adverse effect develops, and/or the long-term consequences of the exposure may be different in the child than in the adult. This could result in a different level of response in children than in adults even at the same exposure level. Because organ systems become fully mature at different ages, some organ systems in the child, especially during the adolescent period, may respond similarly as in the adult.

III. CORE TOXICOLOGY DATA SET FOR ASSESSING RISKS OF PESTICIDE EXPOSURE TO CHILDREN

A. Introduction

The definition of a complete and reliable core toxicology data set for pesticides is a primary consideration relative to the FQPA safety factor. An analysis must be performed for each pesticide in order to arrive at a conclusion that the data are, or are not, complete and reliable. These conclusions are based upon an overall assessment of the data base that considers content and quality, within a framework of scientific judgement and expertise.

The completeness of the data set is a concept defined by many factors that include, but are not limited to, the availability of a core set of toxicology studies, along with any necessary conditionally-required or supporting data, that allow Agency scientists to arrive at a supportable conclusion regarding the toxicological potential of the chemical for children and the degree of concern attached to those findings. The reliability of the data set is based in part on the Agency's testing guidelines which have been designed to provide reliable data on the toxicity of agents. Reliability must also be evaluated through use of scientific judgment considering factors such as the quality of the testing and reporting, the concordance of findings among studies (including those conducted according to Agency guidelines as well as those found in the open literature), and the overall confidence in the available data.

B. Core Toxicology Data Set for Pesticides

In the evaluation of hazard and dose-response, a broad selection of toxicology studies is used to screen each chemical. The types of studies included in the core data set are intended to

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characterize toxicity after exposure for varying lengths of time (a single exposure, exposure over several days or weeks, and chronic or lifetime exposure), and by different routes of exposure (oral, dermal and inhalation), depending on the route of concern. In addition, the studies conducted attempt to screen for toxicity to various organ systems in adult and developing animals. More specific testing of organ system function is included for some organs, e.g., reproductive toxicity, neurotoxicity, immunotoxicity, that would not be adequately screened in the other toxicity studies included in the core data set.

It is important to note that OPP has the authority under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA) to require further toxicological testing of a pesticide (that is, in addition to those studies listed in Part 158.340) when the need for additional testing is adequately demonstrated. Further testing requirements are determined individually for each chemical. In this context, the additional testing is generally considered to be part of the core data set for that specific chemical, and uncertainty associated with the lack of such data should be considered in application of the database uncertainty factor as described in section V.C.3. It should also be noted that OPP has the authority to waive part or all of the core data set for a specific chemical (see 40 CFR 158.45). Where data are waived for a particular pesticide, those data would not be considered part of the core data set for that pesticide.

For the purposes of defining the toxicity in children of “conventional chemical” pesticide active ingredients or other pesticides for which there may be significant exposure in children, the following studies should be included in the core toxicology data set. These recommendations are based on the minimum requirements for pesticides specified in 40 CFR Part 158.340, as well as revisions to the CFR Part 158 discussed in 1994 by OPP with the Scientific Advisory Panel (SAP) that include acute and subchronic neurotoxicity studies as well as immunotoxicity studies in adults as part of the core data set. In addition, the developmental neurotoxicity test in rodents is included in this list as a part of the core data set based on the rationale set forth in Section III.C. This is different from past practice in which developmental neurotoxicity testing was triggered based on adult and developmental toxicity findings (see Makris et al., 1998).

Acute studies (acute oral, acute dermal, acute inhalation, primary eye irritation, primary dermal irritation, and dermal sensitization)

Subchronic (90-day) feeding studies in rodents and nonrodents

Chronic feeding studies in rodents and nonrodents

Oncogenicity studies in two species of rodents (rats and mice preferred)

Prenatal developmental toxicity studies in rodents and nonrodents (rats and rabbits preferred)

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Two-generation reproduction study in rodents

General metabolism study in rodents

Mutagenicity studies (in vivo and in vitro assays of gene mutation, structural chromosomal aberration, and other genomic effects)

Acute and subchronic neurotoxicity studies in rats

Immunotoxicity study in rodents

Developmental neurotoxicity study in rodents (usually rats)

Additionally, depending on potential use and exposure of the pesticide, chemical attributes, or findings in the core studies, specialized studies may be conditionally required for any chemical. In some cases, classes of chemicals have been designated for neurotoxicity testing, e.g., the organophosphates and carbamates, because of their mechanism of action in inhibiting cholinesterase activity. Conditionally required studies can include those listed below as well as additional studies for which there are no current testing guidelines (see section III.D.):

Dermal penetration study

Subchronic (90-day) inhalation study

Acute or subchronic (90-day) delayed neurotoxicity studies in hens

Chronic neurotoxicity study in rats

Scheduled controlled operant behavior

Peripheral nerve function

Sensory evoked potential

21-day dermal study

This core data set includes adult as well as developmental toxicity studies for several reasons. For example, adult data are important in delineating target organs that may also be affected when exposures occur in children whose major organ systems have already formed but are functionally less mature than in adults. Since children include adolescents up to 18-21 years of age, adult data will provide important information about potential target organs during this period as well. Adult

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data also may provide information on target organs to evaluate in the reproduction studies or other developmental studies for similar target organ effects, e.g., developmental immunotoxicity, developmental carcinogenesis, or endocrine toxicity studies. These targeted studies would then be considered part of the core data set for that chemical. In addition, adult data provide relative potency information in children and adults.

A required sequence of toxicological testing for new pesticides is not specified by the Agency. Rather, decisions regarding the order of testing are left up to the individual registrants, based upon the understanding that there are many factors that could affect the testing progression. It is recommended that the development of pharmacokinetic information, especially that relevant to developing systems, be encouraged early in the process of toxicity testing in order to aid in the appropriate design of toxicity studies and interpretation of adult and developmental effects (see further discussion in section III.D.1). Generally, testing will proceed from single to multiple exposures, from shorter to longer duration studies, and from the more simplistic to the more complicated protocols, e.g. acute to subchronic to chronic testing. Additionally, different studies are often conducted simultaneously in the laboratory. Various studies may be done in combination as well. For example, the developmental neurotoxicity study may be done in conjunction with the prenatal developmental toxicity study in rats or may be combined with the two-generation study with neurotoxicity testing in the second generation offspring. Knowledge gained from studies already conducted should be used to design subsequent study protocols, in order to attain the greatest confidence in results for the higher-order studies. For example, conducting the subchronic (90-day) feeding study prior to the two-generation reproduction study would provide information on target organs that may be affected and that need to be evaluated specifically in the two-generation study.

The route of exposure used for the prenatal developmental toxicity study, the two-generation reproductive study, and the developmental neurotoxicity study is typically oral because of the concern about dietary (food or drinking water) exposure. In a number of cases, oral gavage is used and this permits more precise dosing of animals; however, this may result in differences in uptake and distribution of the chemical from that in humans, and dietary exposure may be more appropriate despite the inability to control internal dose using this route during lactation and early postweaning life. When inhalation or dermal exposure is of concern, particularly from residential exposures, studies should be conducted using the relevant route, unless there are appropriate methods available based on pharmacokinetics to convert oral exposure data to the route of concern.

The core data set recommended here includes those studies for which the Agency has developed standardized testing protocols. As discussed further in section III.D, there is a need to develop additional specialized test guidelines that address specific target organs. These additional studies are not listed as part of the core data set recommended here to be conducted on a routine basis. However, when concerns are raised about the possibility of pre- and/or postnatal effects that are not assessed in the core data set but may be evaluated in the studies discussed in section III.D,

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OPP may ask for such studies. In that case, the studies become part of the core data set for that pesticide. When there is a need for such testing but it has not been conducted, the database uncertainty factor should be applied as described in section V.C.3.

C. Rationale for Including Developmental Neurotoxicity as Part of the Core Toxicology Data Set for Pesticides

1. Background

Developmental neurotoxicity testing can provide data that are useful in characterizing hazard and dose-response. In the past, developmental neurotoxicity studies have been conducted as a second tier evaluation and the need for a developmental neurotoxicity study was based on criteria or triggers from both adult and developmental toxicity data and a weight-of-the-evidence review of all available data for each chemical. Such triggers were probably a reasonable place to start; however, they were based on experience with a limited number of agents. More recent information suggests that these triggers may not be inclusive enough to signal all chemicals that have the potential to produce developmental neurotoxicity.

Based on the data currently available, it is impossible to predict how many neurotoxic agents will show developmental neurotoxicity, nor do we currently have sufficient information to predict how many agents that are not neurotoxic or that do not show CNS malformations will cause developmental neurotoxicity (see further discussion below). Therefore, it is recommended that developmental neurotoxicity testing be included as part of the minimum core toxicology data set for all chemical food-use pesticides for which a tolerance would be set.

2. A comparison of developmental neurotoxicity versus other endpoints of developmental toxicity

The question of whether developmental toxicity screens can also serve to detect developmental neurotoxicity has been addressed by Faber and O'Donoghue (1991), Goldey et al. (1995), Ulbrich and Palmer (1996), and more recently by Makris et al. (1998)⁶. Faber and O'Donoghue reported that, of 41 developmental neurotoxicants, 37 also produced positive effects on a developmental toxicity screen, the Chernoff-Kavlock assay (Chernoff & Kavlock, 1982), and thus, developmental neurotoxicity testing did not need to be done, but could be predicted from developmental toxicity studies. Goldey et al. (1995) criticized this claim on the grounds that these 41 chemicals were drawn from Shepard's Catalog of Teratogenic Agents so were biased toward agents that caused developmental toxicity. These authors re-examined the question by surveying a broader range of agents and sources (i.e., the primary literature). Their survey included 126 developmental neurotoxicants from eight chemical classes: antiproliferative agents,

⁶Report reviewed by the Science Advisory Panel, December 8-9, 1998.

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drugs, food additives, metals, polychlorinated biphenyls (PCBs), pesticides, solvents, and other. Overall, they found that only 65% of these agents produced positive effects on measures that are included in the Chernoff-Kavlock assay. They also found large differences between chemical classes in this effect. Nearly all antiproliferative agents produced developmental toxic as well as neurotoxic effects whereas only 46% of drugs did so (Goldey et al., 1995). The detection rate for pesticides ranged from 50-70%. Importantly, there were prominent exemplars from each chemical class that produced no positive effects on the Chernoff-Kavlock assay (Goldey et al., 1995; Table 3). These authors also pointed out that, because of differences in study design (e.g., exposure period, dose selection, maternal toxicity as a confounding factor), it is currently not possible to determine whether developmental toxicity versus developmental neurotoxicity assessments yield comparable dose-response functions. In particular, the fact that exposure continues during the postnatal period -- an important period of nervous system vulnerability -- in developmental neurotoxicity studies, raises serious questions about the ability to predict or estimate their outcome on the basis of developmental toxicity screens in which exposure is prenatal only.

Ulbrich and Palmer (1996) reviewed regulatory submissions for pharmaceuticals in Germany over a 10-year period during which developmental neurotoxicity testing was included with fertility and reproduction studies, embryotoxicity studies, and/or peri- and postnatal studies. Of 85 drugs that produced behavioral effects in the developmental neurotoxicity tests and had an adequate data base, 24 (28%)⁷ showed behavioral changes that were found either to be the only adverse effects detected at any dose, or that occurred at the LOAEL together with other signs of developmental toxicity. These drugs included a wide variety of therapeutic classes, not only those that are known to act on the central nervous system; seven of the 24 were antibiotics. The authors concluded that "since the effects [in many cases] were not expected, this shows the necessity of conducting developmental neurotoxicity tests for all substances to which the developing human will be exposed."

A recent survey by Makris et al. (1998) supports this conclusion. They compared the no-observed-effect-levels (NOELs)⁸ of twelve agents submitted to EPA that were tested for adult neurotoxicity, developmental and reproductive toxicity, and developmental neurotoxicity. Nine of the twelve were pesticides and three were solvents. Of the three solvents tested (1,1,1-trichloroethane-1,1,1-TCE, triethylene glycol monoethyl ether-TGME, and isopropanol), only

⁷Personal communication from Dr. Beate Ulbrich.

⁸NOELs (no-observed-effect levels) and LOELs (lowest-observed-effect levels), rather than NOAELs and LOAELs, are discussed here and are presented in Appendix A since the Data Evaluation Reports for most of the studies present the values in this manner. In some instances, NOELs may have been based upon effects which would not be considered adverse, but in most cases, these values will not be different.

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TGME showed minimal behavioral effects at a high dose that also showed other types of adult and developmental toxicity. Neither 1,1,1-TCE nor isopropanol showed any types of developmental neurotoxic effects.

Of the nine pesticides reviewed by Makris et al., the NOEL for developmental neurotoxicity was lower than that of the fetal NOEL from the prenatal developmental toxicity study for eight of the nine pesticides tested, and demonstrated an equivalent dose for one (Chemical X). The offspring NOEL for the developmental neurotoxicity study was lower than the offspring NOEL for the reproduction study for six of the nine pesticides (aldicarb, carbaryl, DEET, emamectin, fipronil, and Chemical X) and equivalent for one (chlorpyrifos). In light of the fact that the developmental neurotoxicity study measures neurobehavioral and histopathological endpoints that are not examined in either the prenatal developmental or the reproductive toxicity studies, this tendency is not unexpected, even though the animals in the reproduction study were treated over a longer period of time than those in the developmental neurotoxicity study.

3. Adult versus developmental neurotoxicity

The fact that developmental exposure to agents produces neurotoxic effects that differ qualitatively and quantitatively from those produced by adult exposure represents a major empirical and conceptual foundation for the field of developmental neurotoxicology (Riley & Vorhees, 1986; Kimmel et al., 1990). The massive amounts of literature on environmental lead, methylmercury, and PCB exposure, fetal alcohol syndrome, and antiepileptic agents provide several prominent examples in which well-documented developmental neurobehavioral effects in both animals and humans do not occur following comparable adult exposure (reviewed in Kimmel et al., 1990). This is borne out in the Makris et al. (1998) study. In their survey of data on nine pesticides that caused developmental neurotoxicity, it was found that the NOEL for developmental neurotoxicity was less than or approximately equal to the NOELs for acute and/or subchronic neurotoxicity in adult animals for six of the nine pesticides (carbaryl, carbofuran, chlorpyrifos, molinate, DEET, and emamectin). Overall, in two of nine cases (carbaryl, and emamectin), the NOEL for developmental neurotoxicity was lower than or equal to that for any adult or offspring endpoint from the prenatal developmental, reproduction, or neurotoxicity studies. Makris et al. (1998) indicate the possibility of confounding factors that contribute to these conclusions and discuss these in detail. Despite the possibility of such uncertainties in characterizing the developmental neurotoxic effects of this subset of chemicals, the data from this study and others cited above clearly indicate that there is a need for both adult and developmental neurotoxicity evaluations in EPA's toxicity testing strategy for adequately characterizing hazards and dose-response relationships related to children's health risk assessment.

D. Further Test Guideline Development

For most of the studies discussed in this section, there are no testing guidelines available as yet. It is important that work begin on developing guidelines in these areas, and that the criteria used to

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determine the need for these conditionally required (triggered) toxicology studies also be clearly delineated. This will ensure consistent application of testing paradigms from chemical to chemical. Such criteria should be developed concurrently with new testing approaches and guidelines that are adopted, as well as for new endpoints that are added to established guidelines.

The complete data base needed to assess pre- and postnatal toxicity may vary somewhat from chemical to chemical depending on the nature of the toxicity and the state of development of new testing guidelines. For some chemicals, the core data set described in section III.B. may be sufficient. For other chemicals, the complete data set may include the core data set as well as one or more conditionally required studies. Since development of new testing guidelines is an ongoing process, conditionally required studies that do not have test guidelines available will not be considered part of the complete data base on a routine basis until such time as they have been developed and accepted by the scientific community. However, for an individual pesticide, scientific concerns may be raised about the possibility of specific pre- and post-natal effects based on effects seen in other studies. When such concerns exist, the uncertainty may be incorporated into the RfD/RfC through the application of the database uncertainty factor as described in Section V.C.3.

1. Pharmacokinetics

Critical to the interpretation and extrapolation of data on developmental toxicity is an understanding of the pharmacokinetics of chemicals in the developing system and the complexities of direct and indirect developmental exposures during pregnancy, lactation, and to neonates by various routes of exposure. Gathering of such data should be encouraged early in the sequence of toxicity testing. Guidelines for appropriate pharmacokinetic information relevant to pre- and postnatal exposures are needed. These data should be collected as part of a tiered approach for overall pharmacokinetic evaluation of pesticides, and could be modeled after the approach developed specifically for developmental toxicity studies in a previous EPA workshop (Kimmel and Francis, 1990). Such guidelines incorporating pharmacokinetic evaluations specific to children's health also should be included in Part 158.

2. Direct dosing of neonates

Although the studies in the core data set include exposures throughout the developmental period and the evaluation of a number of endpoints of developmental toxicity, there currently are no studies that include direct exposure of neonates prior to weaning. Such studies are important because exposure through mother's milk can be much higher or lower than direct exposure via drinking water, food, dermal or inhalation exposure. In addition, the metabolic capacity of neonates can differ markedly from that of adults, and acute or short-term exposure studies during this time would allow evaluation of the differential susceptibility of neonates to pesticide exposures. Criteria for such testing and testing approaches need to be developed for direct exposure of neonates that take into account the differences in developmental timing in the

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neonatal period between experimental animal species and humans. Most rodents that are used for toxicity testing are more immature at birth than are humans, and studies need to be designed with appropriate timing of exposure to coincide with the neonatal period in humans.

3. Specialized developmental neurotoxicity studies

There are situations in which specialized developmental neurotoxicity studies may be recommended beyond the standard developmental neurotoxicity testing protocol. Specialized developmental neurotoxicity studies include experiments in which relatively sensitive measures of sensory and/or cognitive function are evaluated in the offspring of animals exposed to chemicals during pregnancy and/or postnatally. Examples of specialized tests of sensory function include sensory evoked potentials and determination of sensory thresholds using pre-pulse inhibition of startle reflexes or operant behavioral techniques. Examples of specialized tests of cognitive function include delayed-matched-to-sample operant behavior to assess accuracy and performance, measures of working and reference memory in the Morris water maze, and assessment of attention. Two examples of cases in which specialized studies may be recommended are: 1) presence of data in the literature or from other non-guideline studies indicating that the chemical or a close structural relative produces persistent sensory or cognitive effects in the offspring of animals exposed during development, and 2) alterations in startle reactivity or learning/memory in the developmental neurotoxicity screen.

4. Developmental immunotoxicity studies

In the recent final reproductive toxicity testing guidelines, spleen and thymus weights are evaluated for weanling pups, and these endpoints, as well as altered adult immune function, are expected to provide indications of the potential for effects on the developing immune system that should be pursued with further testing. There is as yet, however, no standardized guideline for developmental immunotoxicity testing, nor have the adequacy of these triggering criteria been explored in any depth by the Agency.

5. Developmental carcinogenesis studies

Likewise, no specific standardized guidelines exist for second tier testing on chemicals that are suspected to enhance carcinogenic response following perinatal exposure. Experience with testing agents for carcinogenic potential following exposure during development is very limited to date. Several authors have reviewed a number of studies that have been conducted to evaluate carcinogenesis following developmental exposures (Vesselinovitch et al., 1979; McConnell, 1992; OPP, 1996). In the OPP analysis, which was presented to the FIFRA Scientific Advisory Panel (SAP) in October, 1996, the results of 40 carcinogenesis studies which included some component of developmental exposure were reviewed. The source of the data for this analysis was: 1) 24 chemicals from the McConnell literature review, 2) three chemicals evaluated by NTP, and 3) 13 chemicals evaluated by the Food and Drug Administration's Center for Food Safety and Applied

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Nutrition. Only the studies conducted by the NTP were specifically designed to allow for the characterization of the carcinogenic hazard in developing versus adult animals as well as a characterization of potential age-related differences in tumor types and incidence, latency of tumor formation, and dose-response relationships. These studies included three exposure regimens: 1) developmental-only exposure in which the animals are dosed for one to two weeks prior to mating, throughout gestation and lactation and until the pups are 8 weeks of age; 2) developmental plus adult exposure in which the animals are dosed as above and for the duration of their life span; and 3) adult-only exposure in which the animals are dosed beginning at 6-8 weeks of age and continuing for the duration of their life span (traditional long-term bioassay). The OPP review (1996), based on the limited data available, made the following observations. Exposure during prenatal and/or postnatal development rarely identifies carcinogenic test agents that are not identified in traditional long-term bioassays. However, exposure during prenatal and/or postnatal development and continuing through the animal's life span can sometimes result in an increase in tumor incidence, reduce the latency period for tumor formation and/or influence the dose response relationships. More studies are needed to verify these observations. At this time, it would appear that developmental carcinogenesis data in rodents would be more likely to affect the quantitative evaluation rather than the qualitative evaluation. Since it was concluded that the available data do not support routinely incorporating a perinatal exposure component into the standard carcinogenesis bioassay, OPP proposed criteria for determining the need for a developmental carcinogenesis study of a pesticide (OPP, 1997). These criteria were reviewed by the SAP in June, 1997 (OPP, 1997). The factors to be considered in a weight-of-evidence evaluation of the need for a developmental carcinogenesis study include:

- a. The pesticide causes adverse effects in studies with dosing in utero or during early postnatal development that:
 - 1). Are qualitatively different from those produced in adults (e.g., liver effects in the adults and uterine or testicular effects in the offspring);
 - 2). Suggest potential carcinogenic effects (e.g., hyperplasia, dysplasia, inhibition of apoptosis, inhibition of terminal differentiation);
 - 3). Are quantitatively different from those in adults (i.e., occurring at significantly lower exposures).
- b. Anticipated pesticide exposures during in utero and/or postnatal developmental periods are generally high in comparison to those later in life.
- c. The structure-activity-relationship analysis indicates an association with a chemical that has shown increased sensitivity in perinatal carcinogenicity tests.
- d. Margins of exposures between doses producing adverse effects and anticipated human exposure are smaller during development than during adulthood.
- e. Pesticides that have been shown to form adducts with the DNA of fetal tissue.
- f. Data showing that the pesticide is transported from maternal circulation across the placenta to the developing fetus and is detected in breast milk.
- g. The developing animal can readily metabolize the pesticide to the expected active carcinogenic moiety.

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- h. The pesticide has been found to cause biologically relevant effects due to a modification of the biological activity of estrogenic and/or androgenic receptor complexes or other hormonally-related molecular targets that indicate a potential for endocrine disruption and increased sensitivity of the developing animal.

6. Endocrine disruptor testing and screening

Another useful source of toxicological information that can be used as a trigger for additional testing will be forthcoming from implementation of the endocrine activity screening program required under the FQPA and the 1996 Amendments to the Safe Drinking Water Act. The recommendations of EDSTAC, a formal EPA advisory committee, have been finalized. The basic elements of the proposed Tier 1 Screening Battery will provide important mode-of-action information to guide additional studies. For example, the High Throughput Screening component will evaluate the potential for chemicals to act as activators or repressors of the estrogen, androgen and thyroid receptor using in vitro cell reporter assays. Three of the five proposed in vivo screening procedures have direct relevance to whether potential endocrine activity is observed in the whole animal. These tests include a uterotrophic assay to examine effects mediated via the estrogen receptor, a Hershberger assay to examine effects on androgen receptor function, and a peripubertal test that monitors development of the hypothalamic-pituitary-thyroid-gonadal axis. Since the modes-of-action detected by these screening tests suggest a heightened concern for risks of exposures during developmental periods, positive responses merit additional toxicological efforts to characterize critical target(s), exposure windows and dose-response relationships.

The final EDSTAC report also provides recommendations for clarification of these issues using "Tier 2 Tests." The purpose of Tier 2 Testing is to characterize the nature, likelihood, and dose-response relationship of endocrine disruption of estrogen, androgen, and thyroid activity in humans and wildlife. Tier 2 Testing is the definitive phase of the screening and testing program and is intended to provide more detailed information regarding endocrine disruption activity. Primarily, this tier should assess the concentrations which elicit effects that may be due to endocrine disruption and the consequences of such effects to inform risk assessments. To fulfill this purpose, the proposed tests are multi-generation studies designed to encompass critical life stages and processes, a broad range of doses, and administration by a relevant route of exposure. This allows a more comprehensive profile of biological consequences of chemical exposure that can be identified and related to the dose or exposure that caused them. Effects associated with endocrine disruption may be latent and not manifested until later in life or may not appear until the reproductive period is reached. The two-generation reproduction study is expected to fulfill the requirements of Tier 2 testing with the possible future addition of some thyroid-specific endpoints.

IV. CRITERIA FOR DETERMINING DEGREE OF CONCERN FOR HAZARDS TO

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CHILDREN'S HEALTH

A. Introduction

Several approaches have been proposed for characterizing the database concerning the potential pre- and post-natal toxicity of a particular chemical and providing some guidance as to the weight of evidence or degree of concern for children's health. However, each approach has been developed for a slightly different purpose and, as such, is generally complementary to the other approaches but not the same. The EPA developmental toxicity (1991) and reproductive toxicity (1996) risk assessment guidelines describe an approach that characterizes a database as sufficient or insufficient to judge that a chemical does or does not pose a hazard within the context of dose, route, duration, and timing of exposure. These guidelines use a weight of evidence approach for determining potential risk to humans based on an overall evaluation of developmental toxicity and exposure data, but do not specifically address the issue of degree of concern for children's health in the broader context of the entire toxicity data base. The issue of degree of concern was addressed by the International Programme on Chemical Safety (IPCS, 1995), which proposed an approach that was limited to the information gathered through developmental and reproductive toxicity studies. The approach recommended here provides a framework to evaluate the overall degree of concern for children's health that encompasses a review of all available toxicity information. This approach represents an evolution and further harmonization of the approaches previously described by EPA (1991, 1996) and IPCS (1995).

For the purposes of determining the adequacy of a database on a pesticide and making judgments about degree of concern, several criteria are proposed. These basically fall into four categories of information: 1) human data on pre- and post-natal toxicity; 2) pre- and postnatal toxicity in animal studies; 3) the dose-response nature of the experimental animal data; and 4) the relevance of the experimental animal data for humans. The degree of concern for potential hazards to children may be taken into account in the uncertainty and modifying factors applied to the RfD, although there is currently no formal process for doing so (see further discussion in Section V).

Table 1. Criteria to be considered in estimating a degree of concern for children's health risks

Issue	Criteria	Degree of Concern		
		Higher	Moderate	Lower
Human data on pre- and postnatal toxicity	Sufficient data to judge effect or no effect ⁹	Effects related to exposure		No effects related to exposure
Pre- and postnatal toxicity in animal studies ⁹	Effects of a different type with different consequences in young and adults	Effects at lower dose levels than in adults	Effects at similar dose levels as in adults	No effects or effects at higher doses, minor effects (e.g., judged to be normal variations), or effects secondary to generalized toxicity
	Effects of a similar type in young and adults	Effects at lower doses and/or shorter latency than in adults	Effects at similar dose and/or similar latency as in adults	No effects or effects at higher doses and with longer latency than in adults
Dose-response nature of the experimental animal data	Dose-related incidence of response	Incidence and intensity of response increases with dose		Effects only at high doses and secondary to generalized toxicity
	Relative potency of response	Effects at several doses including those lower than adult toxicity	Effects only at highest dose and minimal/low adult toxicity	Effects only at highest dose; clear adult toxicity at or below that dose
	Slope of the dose-response curve ¹⁰	Very steep or very shallow curve		Intermediate slope
	Definition of the NOAEL or BMD	Poor; e.g. no NOAEL, no experimental doses in the range of the BMD	Moderate; e.g., LOAEL, only two doses, experimental doses in the range of the BMD	Good; e.g., NOAEL, several doses, some in the range of the BMD
Relevance of the experimental animal data to humans	Toxicokinetics	Evidence suggesting similar qualitative and quantitative metabolism in humans		Evidence suggesting that the metabolic profile differs in important aspects between animal model and humans
	Biological response	Same types of effects in more than one species	Different types of effects in more than one species	Effects seen in one species, but not in others
	Mechanism-of-action studies	Demonstration of homologous mechanism of action in animal model and humans		Evidence suggesting the mechanism of action is species-specific and irrelevant to humans

⁹Assumes a sufficient database as described in EPA (1991, 1996).

¹⁰See text for discussion of this criterion.

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B. Human Data on Pre- and Postnatal Toxicity

Adequate human data are the most relevant data for assessing risk to humans. When sufficient human data are available to judge that an adverse developmental outcome is clearly related to exposure, the degree of concern is high. Sufficient data to show that there are no effects are more difficult to obtain because they usually require more data and evaluation of a wide range of endpoints. Sufficient data to judge that exposure to a pesticide does not cause pre- or postnatal toxicity would lead to a low degree of concern. Criteria for sufficiency of data are indicated in the EPA developmental toxicity (1991) and reproductive toxicity (1996) risk assessment guidelines.

C. Pre- and Postnatal Toxicity in Animal Studies

The degree of pre- and postnatal toxicity relative to adult toxicity impacts the degree of concern. Pre- and postnatal toxicity are defined and discussed in Section II. Two generalizations are made about the endpoints of developmental toxicity: 1) when exposure occurs during early embryonic development and/or critical stages of organogenesis at the gross or histological level, the nature and consequences of the outcome are very different from the outcome experienced by an adult; and 2) when exposure occurs after organ systems of a child have sufficiently developed and matured to be functional, the toxic outcomes that result are similar to that experienced by an adult, but the degree of response may be different, have a different latency before the adverse effect develops, and/or the long-term consequences may be greater or lesser than in adults. Data on adults to be used in comparison to developmental effects should come not only from the reproductive and developmental toxicity studies, but should be evaluated from the core data set as a whole. In particular, the acute, short-term, and subchronic toxicity (including neurotoxicity and immunotoxicity) studies can be compared with the prenatal developmental toxicity study. The subchronic toxicity studies are a source of adult toxicity data to be used in conjunction with the adult data from the two-generation reproduction study for comparison with developmental effects seen in this study. As shown in Table 1, when developmental effects from sufficient animal studies of a different or similar type are seen at doses lower than those causing effects in adults, the degree of concern would be highest. When developmental effects of either type are seen at similar dose levels as those in adults, the degree of concern would be moderate. When no developmental effects are seen or effects are seen at higher doses than in the adult, when effects are judged to be minor or secondary to generalized toxicity or have a longer latency than in the adult, the degree of concern would be lower.

D. Dose-Response Nature of the Experimental Animal Data

The dose-response nature of the experimental data also impacts the degree of concern. For example, when data are **dose-related**, that is, the incidence and intensity of response increases with increasing dose, the degree of concern is much greater than if effects are seen only at very high doses and information is available to show that they are secondary to more generalized

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toxicity. Also, the **relative potency** of the response may impact degree of concern; if developmental effects are seen at several doses including those at lower doses than for adult toxicity, the degree of concern will be much greater than if clear adult toxicity is shown that is at or below the developmentally toxic dose. The **slope of the dose-response curve** is of concern when either a very steep or very shallow curve occurs. For example, a very steep dose-response curve reflects the fact that even a small increase in dose can lead to a marked increase in toxicity. On the other hand, a very shallow dose-response curve reflects a situation in which there is uncertainty about the shape of the dose-response curve at low dose levels and thus the level below which there would not be expected to be any effect (i.e., the biological threshold). An intermediate slope would be of less concern. Ultimately, the degree of concern about the slope of the dose-response curve is related to the anticipated exposure levels and this should be considered as part of risk characterization when the toxicity and exposure assessments are integrated. Finally, if **definition of the NOAEL or BMD** is poor, i.e., there is no NOAEL or the increment between the LOAEL and NOAEL is very large, or there are no experimental doses in the range of the BMD, the degree of concern will be higher than in the case where the NOAEL or BMD are well-defined.

E. Relevance of the Experimental Animal Data to Humans

The risk assessment guidelines for developmental and reproductive endpoints indicate as one of the major default assumptions that animal data are relevant for humans. Such defaults are intended to be used only in the absence of experimental data that can provide direct information on the relevance of animal data. The advent of physiologically-based pharmacokinetic models and biologically-based dose-response models provides a framework for incorporating mode of action data into the risk assessment process, and thus allows movement away from the default considerations.

Several types of information can be considered in determining the relevance or non-relevance of effects observed in animal models for humans. This information is utilized in a variety of ways, from determining the role of metabolism in toxicity (Is the parent chemical or a metabolite responsible for the toxicity?), to assessing whether homologous activity would be expected across species (Do humans share the sensitivity of the animal model, or is the response due to some species-specific idiosyncratic reaction?), to the basic determination of whether or not a threshold is likely to exist for the response (Are repair mechanisms capable of maintaining a homeostatic process?), to lending credence to the criteria of biological plausibility in evaluation of the epidemiological evidence (Does the exposure window match the known critical period for the key developmental process?). All of this information must be weighed in light of the known heterogeneity of the human population versus relatively inbred strains of laboratory animals used in toxicity testing studies and housed under carefully controlled environmental conditions.

The availability of data that can be used in determining the relevance of a toxicology dataset to

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humans can have a major impact on degree of concern, although such data are often outside the range of the core toxicology data set defined in Section III. For example, comparative **toxicokinetic** data suggesting qualitative and quantitative metabolism similar to that in humans would support the relevancy of animal data and result in a greater degree of concern.

Toxicokinetic evidence suggesting that the metabolic profile differs in important aspects between the animal model and humans would indicate less relevancy and therefore could result in low or no cause for concern.

Similarities in **biological response** in more than one species could also result in a higher degree of concern, even though such data were not available in humans. In contrast, response data showing effects in one species, but not others, might result in a lower degree of concern, but would need to be balanced by what is known about toxicokinetics and mechanism of action in humans.

Mechanism of action information is also important in understanding whether a particular effect is adverse or not. For example, a transient reduction in anogenital distance in the postnatal animal following perinatal exposure is more significant if the chemical is also known to be an anti-androgen. Likewise, the interpretation of increased skeletal variants observed following exposure to many chemicals would be enhanced by data indicating the mechanistic pathways for these agents and the overall biological significance defined. Mechanism-of-action data are also important in determining whether various chemicals work by common mechanisms of action which would then be considered in a cumulative risk assessment.

V. CHARACTERIZATION OF THE ASSESSMENT PROCESS FOR CHILDREN'S HEALTH RISKS

A. Dose-Response Analysis for Children's Health Effects

A dose-response analysis for children's health effects of pesticides should be done as part of the overall dose-response analysis for health effects in general. That is, the data on developmental toxicity should be evaluated along with the data on adult exposures and the NOAEL or BMD for the lowest level effects should be based on consideration of all health effects. By doing this, children's health is protected along with that of other sensitive populations. In some situations, children are the only or the predominant population exposed (e.g., daycare centers, schools, drinking water used in infant formulas). In such cases, the risks to children may be evaluated separately from those for the rest of the population.

The dose-response analysis for pre-and postnatal toxicity involves defining a no-observed-adverse-effect level (NOAEL), or a lowest-observed-adverse-effect level (LOAEL), if a NOAEL is not available. The dose-response data also may be fit using a modeling approach and an effective dose (ED) estimated for a given level of response, e.g., the ED05 is the effective dose

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that produces a 5% response level. A lower confidence limit on the ED (the LED) is called the benchmark dose (BMD). There are several levels of response that may be used to calculate the BMD, e.g., 10%, 5%, 1% (BMD10, BMD05, BMD01), and there is ongoing discussion in the Agency about the appropriate level to use for extrapolation to lower dose levels.

Although data on pesticides from inhalation exposures are rarely available at present, there is a need to do residential exposures for children that include inhalation exposures. For most endpoints of toxicity except for developmental toxicity, the NOAEL or BMD for inhalation exposures is adjusted for the interval of exposure used in the toxicity study to a 24-hour per day exposure (e.g., 6/24 if inhalation exposure was 6 hours per day in the toxicity study). This adjustment, which is based on Haber's Law, has been questioned by a number of authors, and reviewed in a recent EPA-sponsored workshop (Eastern Research Group, 1998). Since developmental toxicity endpoints are assumed to be due to short intervals of exposure above a certain threshold level, this rationale did not seem to apply and was not recommended for use in calculating the RfC for developmental toxicity (EPA, 1991). This may have resulted, in some cases, in a less conservative approach being taken for developmental toxicity data than for other health effects. However, if a particular compound bioaccumulates, an adjustment for duration of exposure may be appropriate. The optimal situation is to develop PBPK data that can be used for duration adjustments. It is recommended that appropriate duration adjustment of inhalation data on developmental toxicity be further evaluated.

The NOAEL or BMD can be used in two ways in risk assessment: First, it can be divided by uncertainty factors to account for various uncertainties in the data (see below) and this value used to set the RfD/RfC. Second, the NOAEL or BMD can be divided by the human exposure estimate (actual or projected as a goal) to derive a margin of exposure (MOE) that can be used to determine whether there are adequate controls on exposure of humans.

B. Application of Developmental Toxicity Data to Various Duration Reference Doses

The Office of Pesticide Programs currently sets acute and chronic oral RfDs for dietary exposure to pesticides. The data available on developmental toxicity usually come from studies using repeated dosing regimens that can be characterized as subchronic dosing. For example, in the prenatal developmental toxicity study, dosing covers a period of development equivalent to the first and most of the second trimester of human gestation. In the developmental neurotoxicity study, the dosing period is both prenatal and postnatal to cover most of nervous system development. In the two-generation reproduction study, animals are exposed continuously through two generations. Data from the two-generation reproduction study are currently used for setting the chronic RfD, but prenatal developmental toxicity and developmental neurotoxicity data are not routinely considered. The NOAELs and BMDs for all developmental toxicity studies should be compared with all other toxicity data available so that in the relatively few cases where the NOAEL/BMD for developmental toxicity is lower than the NOAEL/BMD for chronic

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toxicity, it can be used as the basis for the RfD and be protective of children's health.

Although there are no developmental studies in which an acute (single) dosing regimen is used, a central premise in developmental toxicology is that adverse developmental outcomes may result from a single exposure (pre- or postnatally) to a chemical. Data are available to show that most of the types of developmental endpoints from studies used to evaluate pre- and postnatal toxicity (i.e., the prenatal developmental toxicity, developmental neurotoxicity, and 2-generation reproduction studies) can result from single exposures. It is recognized that some outcomes may result only from repeated exposure to a given chemical, and the degree of reversibility of the effect may be dependent on the duration of exposure. Whether or not a particular developmental outcome results from a single acute exposure or repeated exposures requires additional studies that are not often available. Information on toxicokinetics and/or mechanism of action may be helpful in interpreting the data but, again, such information is not typically available. As a default, data from all studies that evaluate developmental toxicity should be considered in determining acute RfDs.

The setting of intermediate duration RfDs (e.g., 10-14 days, 90 days, etc.) for dietary pesticide exposure should be considered since children may be differentially exposed to pesticides during critical stages of development that are less than lifetime (e.g., prenatally, neonatally via breast milk, and at various ages when dietary patterns differ markedly from adults). Intermediate RfDs are likely to be impacted to a greater extent by developmental toxicity data than is the chronic RfD. Exposures as well as susceptibility to developmental toxicity can change dramatically with stage of development, age, and behavior patterns. RfDs should be set that are relevant to these factors. Given the requirement under FQPA for aggregate exposure and cumulative risk, the calculation of intermediate duration hazard values seems likely and appropriate.

Short-term (1-7 days), intermediate (1 week to several months), and long-term (several months to lifetime) residential and occupational exposure hazard values are set for dermal and inhalation exposures to pesticides. Most developmental toxicity studies (of all types) are conducted using the oral route of exposure. In some cases, dermal exposure is used and, rarely, inhalation exposure. Thus, the optimal data to use in residential settings for assessing children's risk are not often available. Route-to-route extrapolation is done in some cases to allow consideration of developmental toxicity data. Pharmacokinetic data on different routes of exposure can be extremely useful in the extrapolation of data between routes.

The use of developmental toxicity (and other) data by the Office of Pesticide Programs in setting reference values for different durations and routes of exposure has been described in a document entitled "Hazard Identification - Toxicology Endpoint Selection Process," (OPP, 1998). It is recommended that an in-depth review and evaluation of this process be undertaken to ensure that developmental toxicity data are being used appropriately, given the type of data available.

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C. Uncertainty Factors Relevant to Protecting Children's Health

Several uncertainty factors have been defined for application to the NOAEL/BMD to derive the chronic reference dose (RfD). These include the interspecies uncertainty factor which is intended to account for the uncertainty involved in extrapolating from animal data to humans, the intraspecies uncertainty factor which is intended to account for the variation in sensitivity among the members of the human population including children, factors to extrapolate from subchronic to chronic data and from the LOAEL to the NOAEL, and other uncertainty and modifying factors. An uncertainty factor of interest here is one used to account for deficiencies in the database for a given chemical. Typically, a default value of 10 is used for each of these factors, but sometimes a factor of 3 is used, depending on the information available on the pesticide. The discussion here will focus on the intraspecies uncertainty factor and the database uncertainty factor which are especially relevant to protecting children's health. In addition, uncertainty and potential modifying factors related to degree of concern are discussed.

1. Intraspecies uncertainty factor

The intraspecies uncertainty factor is applied to account for variations in susceptibility within the human population. Various authors have evaluated the intraspecies uncertainty factor using data from animal or human studies, as summarized by Dourson et al. (1996). For example, Dourson and Stara (1983) suggested that a 10-fold factor would be adequate in lowering the dose from that for the median response level for about 92% of 490 chemicals with acute animal toxicity data. They indicated, however, that this might not be conservative for the human population which is more heterogeneous than animal strains. Calabrese (1985) reviewed the data on several metabolizing enzyme systems and found that the variability of a number of them exceeded a factor of 10 by several fold. He concluded, however, that the vast majority of responses fell clearly within a range of 10-fold, and that a 10-fold factor would protect about 80-95% of the population if considering the total range of human variability. Hattis et al. (1987) found that a 10-fold factor accounted for approximately 96% of the variation in toxicokinetic parameters for 49 chemicals (mostly drugs), again considering the total range of human variability. Dourson et al. (1996) concluded that the 10-fold default factor appeared to be protective when starting from a median response, by inference a NOAEL assumed to be from an average group of humans. Renwick and Lazarus (1998) considered data on toxicokinetics and toxicodynamics to support the idea that the 10-fold intraspecies factor can be divided into two factors to account for kinetics and dynamics. When they evaluated the composite 10-fold factor to account for variability in both kinetics and dynamics, they concluded that a 10-fold factor would cover the vast majority of the population (>99%).

Most of the values cited above did not specifically consider children as part of the range of human variability when evaluating the adequacy of the intrahuman variability factor and, in particular, did not consider the amount of variation that might be covered by a 10-fold intraspecies uncertainty

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factor if the RfD were based on developmental toxicity data. Three groups of authors did consider the adequacy of the 10-fold intraspecies uncertainty factor for both young and adults. Sheehan and Gaylor (1990) compared the LD₅₀ ratios of adult to newborn mammals for 238 chemicals and found that about 86% of the values were less than a 10-fold ratio. Renwick and Lazarus (1998) evaluated the human variability factor for the general population as well as for specific subpopulations, including children. They indicated that, generally, infants and children do not represent a special subgroup from a kinetic point of view as young children frequently eliminate drugs and other chemical agents more readily than adults. They also showed, however, that marked differences in kinetic parameters for some agents, for example, as much as a 5-fold reduction in clearance rates of theophylline in preterm infants versus adults, might result in a number of children not being covered by half the 10-fold factor that accounts for kinetic variability. Given that such differences between children and adults (or children of various ages) may exist because of differences in metabolic capacity or developmental stage of specific organ systems, these authors suggested that the focus should be on delineating the differences in sensitivity of developing organisms and on the variability in sensitivity compared with adults, as well as differences in the sources and extent of exposure. Renwick (1998) further evaluated the similarities and differences between children and adults as well as between young and adult animal models and humans, and reviewed comparative data on toxicokinetics. He suggested that the 10-fold inter- and intra-species factors may be sufficient if developmental toxicity data are available. Because children tend to have a higher clearance rate for many xenobiotics compared with adults, this may compensate to some extent for the potential increased sensitivity of the young during development. Continued evaluation of such data is needed to characterize the similarities and differences between children and adults and the adequacy of the intraspecies uncertainty factor for protecting children.

Dourson et al. (1996) documented the number of cases in which the intraspecies uncertainty factor has been reduced from the default of 10-fold (2/46 RfCs, 13/346 RfDs, overall frequency 3.6%). In those cases where developmental effects were the most sensitive endpoint (0 RfCs, 6 RfDs), reduction of the intraspecies uncertainty factor from 10 to 3 was based on data derived either from human data showing which age groups or time periods were most sensitive (e.g., methyl mercury exposure to the developing fetus), or from an animal study but when strong human or other data also were available to support the decision (e.g., Aroclor 1016 in utero exposure in monkeys, strontium-induced rachitic bones in young rats). In three cases, the intraspecies uncertainty factor has been reduced to 1 based on very specific data about the particular vulnerability of infants and children within certain age ranges to an agent (e.g., nitrate, nitrite, fluorine/soluble fluoride). The Toxicology Working Group recommends that reduction of the intraspecies uncertainty factor from a default of 10 be considered only if data are complete and the age group or window of vulnerability during development has been clearly delineated, preferably based on human data or on animal data with supporting human data. Rarely can the intraspecies uncertainty factor be reduced to 1, and only if variability in children at various ages due to genetic, lifestyle, and other influences can be shown not to be a factor.

2. Use of the database uncertainty factor

While the NRC report on Pesticides in the Diets of Infants and Children (1993) indicated that the current 10-fold intraspecies factor adequately protects for socioeconomic, nutritional, and health status factors that influence the vulnerability of children to environmental toxicants, it also indicated that additional protection for developmental toxicity (essentially an additional 10-fold factor) may be required, depending on the toxicant of interest and the amount of testing that has been conducted. Schilter et al. (1996) discussed the issues related to health risks for infants (defined as 4 months to 2 years of age), and why infants may be more vulnerable than adults to pesticide residues in foods, based both on exposure and on critical developmental processes occurring in infancy. They recommended an additional 10-fold uncertainty factor to be applied to the ADI for pesticide residues in food to protect infants unless specific data on developmental toxicity, including developmental neurotoxicity, reproductive development, or other data such as immunotoxicity which may be indicated from adult immunotoxicity data, are available. Their paper supported the idea that if adequate data to characterize potential toxicity to infants is available, it would not be necessary to apply an additional factor beyond the 10-fold intraspecies factor. They also advocated evaluating the data base for each pesticide, considering mechanism of action and other relevant data, on a case-by-case basis.

In many respects, the additional 10-fold factor for infants recommended by the NRC (1993) and by Schilter et al. (1996) is similar to the database uncertainty factor applied when data on pre- and postnatal toxicity are incomplete. As indicated above, an uncertainty factor has sometimes been applied to the chronic RfD to account for deficiencies in the available dataset. In particular, if data on children's health are not adequate, then an uncertainty factor has been used to account for these deficiencies (Dourson et al., 1996). Often a factor of 3 is applied if either a prenatal toxicity study or a two-generation reproduction study is missing, or a factor of 10 may be applied if both are missing. Dourson et al. (1992) examined the use of the database uncertainty factor by analyzing ratios of NOAELs for chronic dog, rat, and mouse studies and reproductive and developmental toxicity studies in rats. They concluded that reproductive and developmental toxicity studies provide useful information in establishing the lowest NOAEL, and that if one or more bioassays are missing, a factor should be used to address this scientific uncertainty. The database uncertainty factor has not been used in the past to account for the lack of a developmental neurotoxicity study, but should be used for this purpose in the future based on the recommendation in this report to include developmental neurotoxicity testing as part of the core toxicology data set for pesticides. In addition, if there are data from the core set of toxicology studies that signal the need for other types of testing, e.g., specialized developmental neurotoxicity studies, developmental immunotoxicity studies, developmental carcinogenesis studies, or developmental endocrine toxicity studies, then the database factor should take into account whether or not these data have been collected and used in the assessment. The size of the factor to be applied will depend on other information in the database and how much impact the

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missing data may have on determining the toxicity of a chemical. Good scientific judgment must be used in determining the appropriate size of the database factor to apply based on the core toxicology data set for pesticides recommended in this report. Further discussion about the appropriate use and size of the uncertainty factor to account for additional required studies is needed.

3. Uncertainty factors related to degree of concern

As discussed in section IV, there is no formal process for accounting for degree of concern in the RfD process. However, some aspects of degree of concern are currently taken into account. For example, human and animal data are currently considered in the process of calculating the RfD, and are used as the critical effect when data indicate that developmental effects are the most sensitive endpoints. When a complete database (as defined in this document) is not available, a database uncertainty factor should be applied to account for inadequate or missing data. The dose-response nature of the data are considered to a certain extent in the RfD process, especially when the BMD approach is used to model data and to estimate a low level of response; however, there is no approach currently for including concerns about the slope of the dose-response curve. Since concerns about the slope of the dose-response curve are related to some extent to human exposure estimates, this is an issue to be considered in risk characterization, i.e., if the margin of exposure is small and the slope of the dose-response curve is very steep, there may be residual uncertainties that must be dealt with in risk characterization to account for the concern that even a small increase in exposure could result in a marked increase in response. On the other hand, a very shallow slope could be a concern even with a large MOE, since definition of the biological threshold will be more difficult and an additional factor may be needed to insure that the RfD is below this threshold. The NOAEL approach does not allow for considerations of variability in the data, but use of the lower confidence limit on dose in the BMD approach does account for variability in the animal or human data on which it is based. Both the interspecies and intraspecies uncertainty factors include consideration of potential toxicokinetic and toxicodynamic similarities and differences among species and within humans, and these factors can be adjusted when data are available to more appropriately account for similarities and differences among species and within human subpopulations, including different age groups. Although various means of accounting for degree of concern are described here, there is no formal process for doing so, and it may be appropriate to consider use of an additional modifying factor to account for a very high degree of concern. This issue should be considered further for the appropriate calculation of the RfD to protect children's health.

4. Application of uncertainty/modifying factors for protecting children's health

It appears from the data available that when a complete developmental toxicity database is available, the default intraspecies 10-fold uncertainty factor will be adequate in the majority of cases for protecting children's health. The Toxicology Working Group recommends that only in

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cases where data are complete and the age group or window of vulnerability during development has been clearly delineated, preferably based on human data or on animal data with supporting human data, should there be consideration of reducing the 10-fold intraspecies factor. However, when data specific to children's health are missing or inadequate for a particular pesticide, application of the database uncertainty factor in addition to the 10-fold intraspecies variability factor is considered appropriate to account for the possibility that children may be significantly more sensitive than adults. The size of the database uncertainty factor applied will depend on other information available in the database and how much impact the missing data may have on determining the toxicity of the pesticide for children. An additional modifying factor may be considered for application when the degree of concern is particularly high.

D. Characterization of the Assessment - Does the Current Process Compensate Adequately for Data Deficiencies and Toxicity?

Once the hazard characterization and dose-response evaluation are completed, the toxicity assessment process overall can be characterized relative to how well it accounts for the uncertainties in the database and the degree of concern about the potential toxicity of a pesticide for children. This is especially important in evaluating the conservative nature of the process and if there are any residual uncertainties left that should be accounted for in risk characterization.

1. Quality of the assessment

The following types of assessments would be considered of high quality and provide a high level of confidence in the toxicity assessment:

If the core toxicology data set (including developmental neurotoxicity and conditional data triggered from other information) is complete and the hazard characterization and dose-response assessment have taken into account all of the data, including those on children's health, and incorporated all the uncertainties.

If the data set is incomplete (as defined in this document), but the database uncertainty factor has been adequately applied to account for this deficiency.

If the degree of concern is high for the potential of a pesticide to cause children's health effects and this information has been accounted for in calculating the RfD. This could include setting the NOAEL/BMD based on the most sensitive endpoint and accounting for bioaccumulation, the steepness of the dose-response curve when the anticipated exposure level is high or is expected to be poorly controlled, or a very shallow dose-response curve when exposure is not expected to be high but the actual no effect level may be far below the NOAEL or BMD.

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The conditions described by these statements result in a high level of confidence based on the approaches discussed in this document relative to what constitutes a complete data set, the quality and reliability of data, and factors to be considered in the degree of concern. Using the types of approaches exemplified here and outlined in this report, we believe that the toxicity assessment process can adequately compensate for data deficiencies and potential toxicity in children.

2. Residual uncertainties

For the most part, the RfD process takes into account deficiencies in the toxicity database and the potential for toxicity of a pesticide to children. If an assessment did not meet the standards of rigor described in this document culminating in the types of statements described in section V.D.1 the assessment would be considered to contain residual uncertainties. In these cases, an additional conservatism might be built into the risk characterization phase of the process by, for example, retaining part or all of the FQPA 10X factor.

Characterizations of the toxicity assessment should be integrated with similar characterizations of the exposure assessment during risk characterization to determine the level of confidence in the overall assessment and to make decisions about retention, reduction or removal of the FQPA 10X factor. The exposure assessment process is described in an accompanying document, and the integrative process is described in a third over-arching document that summarizes the deliberations and conclusions of the 10X Task Force relative to implementation of the FQPA 10X factor.

VI. RECOMMENDATIONS

The following recommendations are made concerning data requirements for determining potential hazard to children's health:

- 1) The core toxicology data set requirements for pesticides should include adult neurotoxicity and immunotoxicity studies, developmental neurotoxicity studies, and other triggered studies as defined in this document for all "conventional chemical" food use pesticide active ingredients for which a tolerance would be set, or other pesticides for which there may be significant exposure in children.
- 2) 40 CFR Part 158.340 should be updated as soon as possible to include the adult and developmental neurotoxicity guidelines and the adult immunotoxicity guidelines and to refer to the revised two-generation reproduction and prenatal developmental toxicity testing guidelines finalized in March 1998.
- 3) Developmental toxicity endpoints from all types of developmental and reproductive toxicity studies should be considered in setting RfDs, both acute and chronic.

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- 4) Guidelines for pharmacokinetic studies should be developed that include considerations of exposure during pregnancy and lactation, and of infants and children. These data can be developed as part of a tiered approach to overall pharmacokinetic evaluations and should be required for assessment of effects on infants and children in Part 158.
- 5) Specific testing guidelines for other types of functional or latent effects (e.g., developmental immunotoxicity, developmentally-induced cancer) do not currently exist. As well, guidelines for direct dosing of neonates and appropriate interpretation and application of such data are not available. Efforts should be made to develop these guidelines as well as criteria for when such studies should be conducted.
- 6) It appears from the data available that when a complete developmental toxicity database is available, the default intraspecies 10-fold uncertainty factor will be adequate in the majority of cases for protecting children's health. The Toxicology Working Group recommends that only in cases where data are complete and the age group or window of vulnerability during development has been clearly delineated, preferably based on human data or on animal data with supporting human data, should there be consideration of reducing the 10-fold intraspecies factor. However, when data specific to children's health are missing or inadequate for a particular pesticide, application of the database uncertainty factor in addition to the 10-fold intraspecies variability factor is considered appropriate to account for the possibility that children may be significantly more sensitive than adults. The size of the database uncertainty factor applied will depend on other information available in the database and how much impact the missing data may have on determining the potential toxicity of the pesticide for children.
- 7) Several topics relative to the RfD/RfC process discussed in this document for pesticides need further discussion on an Agency-wide basis. It is recommended that the Risk Assessment Forum and Science Policy Council consider these issues. They include:
 - a) Application of the database uncertainty factor for additional required developmental and adult toxicity studies;
 - b) How to account for the degree of concern for potential toxicity to children's health in the RfD/RfC process;
 - c) As indicated in this document, the current default recommended for using developmental toxicity data for different duration reference values is to apply all endpoints for all durations. Further consideration of the appropriate application of developmental toxicity endpoints to various duration reference values is recommended. As part of this recommendation, an in-depth review of the HED document on Hazard Identification - Toxicology Endpoint Selection System should be undertaken;

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- d) The appropriate setting of intermediate RfDs for pesticides;
 - e) Appropriate adjustment of the NOAEL or BMD from inhalation studies for extrapolation of developmental toxicity data among different durations of exposure.
- 8) Evaluation and possible updating of the developmental neurotoxicity protocol as recommended by the SAP.

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APPENDIX A

Comparison of NOELs from Selected Studies in Rats and NOELs Selected for Dietary Risk¹

Chemical	Developmental Neurotoxicity		Developmental Rat		Reproduction		Neurotoxicity		NOEL for Study Used in Risk Assessment ²	
	Mater	Offspring	Mater.	Fetal	Paren.	Offspring	Acute	Subchronic	Acute	Chronic
Aldicarb	0.05	0.05	0.125	0.125	0.4	0.7	<0.05	<0.05	0.01	0.01
Carbaryl	1.0	1.0	10	10	100	≥200	<10	1.0	1.0	1.4
Carbofuran	1.7	1.7	1	3	1	1	NS	<2.4	0.5	0.05
Molinate	6.9	<1.8	35	2.2	<0.4	0.4	<25	<4.0	<1.8	<0.3
DEET	90	90	250	250	<25	≥250	50	90	NR	100
Emamectin	0.6	0.1	2	4	0.6	0.6	<27.4	1.0	0.075	0.075
Fipronil	0.9	0.9 ^a	4	20	0.25	2.5	2.5	0.3	0.5	0.019
Chlorpyrifos	<0.3	1	0.1	≥15	0.1	1	10	≥15	0.1	0.03
Chemical X	40	125	40	125	5.7	>197.9	NS	5.7	40 ^b	1.35 ^b
1,1,1-TCE ^c	750	>750	1000	3000	NR	NR	NR	630	ND	ND
TGME ^d	1650	300	1250	625	NR	NR	NR	400	ND	ND
Isopropanol ^d	700	>1200	400	400	100	100	4150	4150	ND	ND

NOELs expressed as mg/kg/day. When separate dose values were obtained for each generation, sex, etc., the lowest value was used in the table. NS = Not submitted to the Agency; NR - Not required; ND = Not determined.

a) A separate developmental NOEL was established at 0.05 mg/kg/day, based on decreased pup body weight at 0.9 mg/kg/day.

b) Non-dietary, short- and intermediate-term residential oral exposure to children (hand-to-mouth).

c) NOAEL expressed as ppm; the developmental neurotoxicity study was a gavage study, and for purposes of comparison with all other studies which were dosed via inhalation, the oral doses used were converted to ppm.

d) NOAEL expressed as mg/kg/day; adult neurotoxicity studies were conducted by inhalation and the concentration in ppm were converted to mg/kg/day for purposes of comparison.

¹From Makris et al., 1998.

²The study used in the risk assessment may be different from any of the other studies shown in this table, e.g., the 90-day feeding study, the two-year bioassay, etc.