

US EPA ARCHIVE DOCUMENT

**PRESENTATION FOR FIFRA SCIENTIFIC ADVISORY PANEL BY OFFICE OF
PESTICIDE PROGRAMS, HEALTH EFFECTS DIVISION ON
FQPA SAFETY FACTOR FOR INFANTS AND CHILDREN:**

I. Executive Summary

This draft document has been prepared by the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) for submission to and peer review by the Scientific Advisory Panel. It discusses the application of the 10-fold safety factor to risk assessments, as mandated by the 1996 Food Quality Protection Act (FQPA), to ensure the protection of infants and children. As described herein, HED proposes a science-based and science-informed application of information to a risk management decision. The document is designed to be consistent with the position and public policy that is mandated by the FQPA: to tolerate less risk for infants and children. This HED document represents a significant effort to refine and articulate the thinking of the scientists within HED and is ready to be considered and reviewed by scientists and others outside HED. This document is also being distributed to other EPA offices for review, and will assist Agency offices in responding to a February 25th charge from Administrator Carol Browner and Deputy Administrator Fred Hansen to develop a framework for applying the 10-fold safety factor and for determining the appropriate child-specific information needed to make decisions under the FQPA. Accordingly, the thinking in this paper is likely to be further informed, adjusted and revised as a result of the Agency's continuing development of public policy in this area and the process of scientific peer review.

Pursuant to the language and intent of the FQPA, a 10-fold safety factor, referred to in this document as the "FQPA safety factor" or the "FQPA factor," will initially be employed for threshold effects, to ensure the protection of infants and children, unless the determination can be made, on the basis of reliable data, that a lesser margin of safety will be safe for infants and children. HED proposes that this safety factor be used in risk assessment following the establishment of the acute and/or chronic reference dose (RfD) values, which, in accordance with standard Agency policy, are based upon appropriate studies, endpoints, and dose levels, and include the application of uncertainty and modifying factors.

Under this approach, for each pesticide, the determination of the final FQPA safety factor for use in risk assessment would be made during the process of risk characterization. Hazard identification, dose-response evaluation, and exposure assessment are used in this determination and inform the process.

Under the approach set forth here, hazard and dose-response evaluation are used to identify the presence or lack of concerns in the areas of: 1) **uncertainty** related to the completeness of the toxicity data base for the assessment of potential effects on infants and children, and 2) special **susceptibility** of infants and children.

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Exposure assessment addresses the potential for exposure to infants and children, based upon the evaluation of use patterns, along with actual exposure data or estimates and the completeness of the data pertaining to exposure of infants and children.

This document recommends that the FQPA safety factor be retained when, in the presence of exposure to infants and children, significant issues of uncertainty and/or susceptibility are identified in the hazard assessment. A lack of completeness in exposure data would generally be addressed by using conservative exposure assumptions or through retaining the additional safety factor, as appropriate.

If there is no exposure to infants and children, or if no hazard concern for infants and children (either from incompleteness of data or from susceptibility) has been identified and data on exposure to infants and children are complete, the 10-fold FQPA safety factor would not be retained.

Under the approach discussed here, reduction or removal of the FQPA safety factor would be based upon a weight-of-evidence evaluation of all applicable data and reflect sound scientific judgement and principles, in the context of the language and intent of the statute.

This document sets forth in more comprehensive detail the types and nature of evaluations which would be applied in the weight-of-evidence approach. In general terms, the analysis considers such elements as (1) the extent and nature of exposure to infants and children and any likelihood that exposure evaluations may understate such exposure; (2) the extent of availability of data on the toxicity and effects of the pesticide to infants and children, and the probity and reliability of those data; (3) the evidence contained in available data of adverse effects specific to infants and children and/or of susceptibility of infants and children to the pesticide; and (4) the extent to which the exposure to children and/or the effects of concern for children represent the elements of the risk assessment relevant for the setting of protectiveness levels for acceptable exposure. Each of these considerations is elaborated in the document.

II. Introduction and background

This document describes the views of OPP's Health Effects Division on the following: 1) the contribution of hazard and dose-response evaluations in determining whether the FQPA safety factor for risk assessments can be removed or reduced, 2) the contribution of exposure assessment in evaluating whether application of the FQPA safety factor to the risk assessment is appropriate, 3) examples of risk characterization determinations, and 4) application of the FQPA safety factor to risk assessment. The document focuses on the decision logic for each of these processes. Although the document makes an attempt to identify circumstances which may differentiate the decision to remove the safety factor from a decision to retain it, much of the discussion of the circumstances appropriate to retention of the FQPA safety factor does not differentiate between the use of a 10-fold factor or some other value such as a 3-fold factor.

Under this approach, decisions on the magnitude of an additional safety factor are based on the weight of the evidence supporting the retention and application of that safety factor.

In any hazard assessment which uses animal data to predict possible toxicity to the human population, a certain level of uncertainty inherently exists. Traditionally, in the risk assessment process, an interspecies extrapolation factor (generally 10X) is applied to the appropriate study No-Observed-Effect-Level (NOEL) to adjust for this uncertainty. In addition, an intraspecies variability factor (also generally 10X) is applied to the calculation to adjust for individual differences in response, including those attributed to age and sex. Other factors, between 3- and 10-fold, can be utilized to adjust the risk assessment for uncertainties such as those introduced by the use of a study that does not identify a NOEL, or the use of a short-term study to extrapolate to long-term effects. This approach, as described by Barnes and Dourson (1988) has been used by the Office of Pesticide Programs (OPP) in the regulation of pesticides, including the calculation of the RfD(s), for well over a decade.

Pursuant to the 1996 Food Quality Protection Act (FQPA), which amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetics Act (FFDCA), OPP is now operating under a new policy framework. Section 408(b)(2)(C) of FFDCA now requires that, in the case of threshold effects, in order to ensure a reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide 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 the data with respect to exposure and toxicity to infants and children." This statutory provision further provides that "[n]otwithstanding such requirements 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 will be safe for infants and children."

In addition to the instructions embodied under FQPA, EPA announced on 20 October 1995 that it would consistently and explicitly evaluate risks to infants and children as a part of all potential regulatory actions. This was followed on 21 April 1997 by Executive Order 13045 which directs Federal agencies to identify and assess environmental health and safety risks to children. These actions set forth expectations that Federal actions will adequately consider risks to children as part of decision making activities. The present paper represents an effort by OPP's HED to advance for external peer review a proposed framework of procedures and expectations for EPA's use in implementing these policies pursuant to the FQPA.

III. Policy

Under the approach set forth here, the Office of Pesticide Programs would continue to initially employ, as a default, the additional FQPA 10X safety factor for threshold effects to ensure that its actions are protective of infants and children. Where reliable data are available, this presumption could be amended and the FQPA safety factor reduced or removed as long as the

alternative remains adequately protective of infants and children. This position was reviewed and approved by a Scientific Advisory Panel (October, 1996). For each action on a pesticide, both the hazard (toxicity) assessment (including dose response) and exposure assessment are considered in the final determination on the use of an additional safety factor.

This proposed policy framework, under the directives of FQPA and viewed in the context of the Executive Order and the intentions of the Agency policy on infants and children, **can** be implemented consistent with the National Academy of Sciences (NAS) paradigm, which defines risk assessment as a four-step process consisting of hazard identification, dose-response evaluation, exposure assessment, and risk characterization. Hazard- and dose-response assessments can be performed, including the derivation of the traditional RfD and acute RfD, if appropriate, and identification of critical toxicity endpoints to be used in risk assessments. In addition, uncertainties and susceptibilities to infants and children would be characterized. Concurrently, exposure assessment can be conducted and can include characterization of uncertainties in the data base related to exposure to infants and children. Risk characterization summarizes the critical information from the hazard, dose-response, and exposure assessments. At this stage, all assumptions and uncertainties used in the hazard and exposure assessments are clearly articulated. Decisions regarding the appropriate FQPA safety factor would be made based on this information.

Under this approach there are two primary concerns, related to toxicity, that need to be addressed in the risk assessment process: 1) safety concerns derived from **uncertainty** related to the completeness of the data for the assessment of potential effects on infants and children, and 2) safety concerns based on special **susceptibility** of infants and children. These two factors are not separate and distinct entities, but rather represent two aspects of an information continuum that defines the uncertainties in the scientific knowledge of the effects of any pesticide on the human population. A weight-of-the-evidence approach would be used in the process of characterizing the hazard that contributes to the final determination of whether or not to retain the FQPA safety factor. In addition to an evaluation of the quality, probity, reliability, and adequacy of available studies, this would include factors relating to the nature of the observed effects. An assumption is made in the process of evaluating these data: that the toxicity observed in animals is predictive of the potential toxicity in humans. This presumption includes the endpoints observed, age groups affected (fetuses, infants and children, and/or adults), and relative susceptibilities. It is recognized that there are inherent uncertainties in this assumption, which are considered in the case-by-case analysis and weight-of-evidence assessment.

The consideration of the exposure assessment in tandem with the hazard and dose-response assessments and knowledge of uncertainties already identified in the data base, provides additional information concerning the retention of the FQPA safety factor for risk assessments. The exposure assessment can provide information that might sway the determination in either direction. For example, if no exposure is anticipated for the susceptible subpopulation of

infants and children, then a finding to support removal of the FQPA factor could be appropriate. If, however, uncertainties exist in the exposure assessment due to the inability to develop a reliable and/or conservative estimate of exposure for the susceptible population subgroup of infants and children, the FQPA safety factor generally should be retained.

If sufficient data are available that indicate no significant special susceptibility to infants and children, a removal of the FQPA safety factor may be justified. If it is determined that there is evidence of significant special susceptibility for infants or children, or that there are incomplete data to make the determination of whether special susceptibility exists, the FQPA safety factor would likely be retained (depending on the weight of evidence and in the presence of exposure to infants and children) for the appropriate risk assessments.

Should retention of the FQPA safety factor be recommended following adequate risk characterization, the safety factor may, nevertheless, not apply to all risk assessments for the pesticide. Specific risk assessments to which the safety factor would apply can be considered from two perspectives: 1) the population or subpopulation being considered (e.g., infants, children, females of child-bearing age), and 2) the exposure scenario for the risk assessment (e.g., acute dietary, chronic dietary, occupational/residential). These aspects are described below, in the section on application to risk assessment.

IV. Hazard identification and dose-response assessment

Under this framework, an evaluation of all available information is used to fully characterize the toxicity profile, with emphasis on effects noted in offspring following pre- and/or postnatal exposure.

A. The toxicity data base

In the evaluation of hazard and dose-response, major studies that provide critical data pertinent to this assessment include prenatal developmental toxicity studies in rodents and nonrodents, multigeneration reproduction studies in rodents, and, in some cases, developmental neurotoxicity studies in rats, in conjunction with the rest of the toxicity database. Special non-core studies that further discuss the pharmacokinetics or the mode or mechanism of action of the chemical, as pertaining to effects observed in the offspring following pre- and/or postnatal exposure, are occasionally available. In addition, information from other sources, such as the open literature, should be considered.

For a food-use chemical, core data requirements are specified in 40 CFR Part 158. These consist of a prenatal developmental toxicity study in two species (one rodent and one nonrodent), and a multigeneration reproduction study in rodents. These studies are designed to evaluate the effects of pre- and postnatal exposure of the offspring to a chemical. In the prenatal developmental toxicity study, maternal animals are exposed to the chemical (generally by gavage) during gestation, and toxicity to the dams is assessed. The fetuses are removed by cesarean section; the uterine contents are evaluated for evidence of *in utero* death, and fetuses are weighed, examined for external anomalies, and evaluated further for alterations in

development to the soft tissue and skeletal structure. In the reproduction study, rodents are exposed to the chemical, generally in the diet, over the course of two generations. The first generation parental animals are placed on study at approximately 6 weeks of age and maintained on test diet for approximately 10 weeks, at which time they are mated. Exposure is maintained throughout the mating, gestation, and lactation periods. Resulting litters are examined for alterations in clinical observations, growth (body weight and day of sexual maturation), and survival. At weaning (postnatal day 21), the parental animals for the second generation are selected and all other parental animals and offspring are killed and subjected to postmortem examinations. The second generation is conducted in the same manner; the second generation adults are considered to be a unique population of animals, however, since they have been exposed to the test chemical since conception.

In addition, based upon the consideration of all available data against specific triggering criteria, a developmental neurotoxicity study may also be required. The developmental neurotoxicity testing guideline was finalized in 1991, following extensive scientific review, including an Agency-sponsored Workshop on the Qualitative and Quantitative Comparability of Human and Animal Developmental Neurotoxicity that was held on April 11-13, 1989 (Kimmel, Rees, and Francis, 1990) and evaluation by the Scientific Advisory Panel (SAP, 1989). In the developmental neurotoxicity study, pregnant rats are exposed to the chemical from gestation day 6 through to postnatal day 11. The offspring are therefore exposed to the chemical, via the maternal circulation and/or milk, during *in utero* and early postnatal development. The offspring are assessed for evidence of deficits in functional development. Endpoints evaluated between birth and day 60 of age include measures of physical development, reflex ontogeny, motor activity (including habituation), motor function, sensory function, and learning and memory. At postnatal day 11 and at study termination, the rats are subjected to extensive neuropathological examination.

Recommendations regarding procedures designed to trigger the need for conducting a developmental neurotoxicity study had been proposed by the Agency (Timm, 1987 and Rees, 1988), and by the 1989 workshop (Levine and Butcher, 1990). These approaches included the presumption that the developmental neurotoxicity study would be conducted as a second tier evaluation, and that the need for a developmental neurotoxicity study would be based on a weight-of-the-evidence review of all available data for each chemical, including the prenatal developmental toxicity studies and multigeneration reproduction study. The criteria generally used in the determination are listed in Appendix A. These criteria were reviewed and approved by a Scientific Advisory Panel in 1987 and were reconfirmed by a 1995 SAP.

Additionally, since the developmental neurotoxicity study has not yet been included in 40 CFR Part 158, the Office of Management and Business (OMB) has specified (OMB No. 2070-0107, 5/8/91) that larger-scale Data-Call-Ins (DCIs) can be issued for developmental neurotoxicity studies only if certain criteria are met. These criteria are also listed in Appendix A.

In response to concerns regarding the completeness of data available for assessing hazard to infants and children, OPP's Health Effects Division (HED) proposes that requirement of the developmental neurotoxicity testing for pesticides be based on whether the chemical profile meets one or more of the following criteria.

The substance has been shown to:

1. cause CNS malformations following prenatal exposure;
2. affect brain weight in offspring, which does not appear to be related solely to general growth retardation, following pre- and/or postnatal exposure;
3. cause neuropathology in developing or adult animals or neuropathy in humans;
4. cause persistent functional changes in the offspring which may be the result of effects on the nervous system;
5. act to significantly modify hormonal responses associated with the development of the nervous system, leading to significant developmental effects (e.g., effects on sexual maturation).

In addition, a weight-of-evidence assessment of the data base should be conducted, and all information pertinent to the assessment of neurotoxic potential of the chemical should be considered when determining the need for a developmental neurotoxicity study. This could include factors such as: a) acute behavioral/functional changes are produced in adult animals by an effect of the compound on the nervous system; b) the compound exhibits a structure-activity relationship to a known neurotoxicant or neuroactive chemical; c) evidence of developmental toxicity to fetal tissues, organs, and/or systems (other than the CNS) generates concern regarding potential effects on functional development of affected fetuses; or d) the potency of the chemical, the persistence of neurotoxic effects, or the partitioning of effects in the animal model (e.g., brain cholinesterase inhibition that occurs at a much lower dose than elicits plasma cholinesterase inhibition) generates an additional level of concern. Even in the absence of one or more of the specific criteria listed in items 1-5 above that would trigger the need for a developmental neurotoxicity study, the weight-of-evidence assessment could provide sufficient concern to result in this conclusion.

B. Hazard and dose-response characterization

Characterization of the data, used in the weight-of-the-evidence assessment for each chemical, can include some of the considerations that follow.

1. The breadth, depth, validity and consistency of the hazard data base help to inform the confidence in hazard and dose response judgments.
2. Absent or inadequate hazard studies that are core for evaluation of risk to infants and children by themselves generally argue for retention of the FQPA 10X default, unless

this has been accounted for by the use of a modifying factor in the derivation of a reference dose or reference concentration (RfD/RfC). Information on structurally-related chemicals can modify or reinforce uncertainties attributed to inadequate or absent hazard studies

3. The critical health effect helps determine the point of departure for risk estimation and calculation of the RfD/RfC.
 - a. Adverse effect: Usually the critical effect is an adverse health effect. Evaluation of the relationship between animal and human effects needs to be carefully evaluated. In some cases there is correspondence between effects in animals and humans (e.g., liver toxicity), whereas in others, minor effects in animals may signal more severe effects in humans (e.g., developmental).
 - b. Precursor effect: Sometimes a precursor effect that occurs at a dose below an adverse effect can be identified and used in assessments.
4. Mode of action information addresses the way a chemical induces adverse effects. As such, it aids in determining (a) whether an effect in animals might be a hazard to humans, (b) critical precursor effects of the adverse effect, and (c) the shape of the dose response curve.
5. The characterization of the dose response curve, including the shape of the curve, can provide information on doses that are expected to be associated with effects.
6. No Observed Adverse Effect Level or Concentration (NOAEL/NOAEC) or Benchmark Dose or Concentration (BMD/BMC):
 - a. Data sets vary as to whether a NOAEL(NOAEC)/BMD(BMC) for the critical effect has been determined or whether one may need to rely on a LOAEL.
 - b. Determination of whether the embryo/fetus/infant/child NOAEL (NOAEC)/BMD (BMC) is below the adult value helps to determine the need for an extra FQPA safety margin.
7. Comparative metabolism and pharmacokinetic data of pesticide chemicals can help determine (in conjunction with additional experimentation) potential target tissue dose. The Agency can request such data when investigating target organ toxicity. Data that evaluate maternal versus fetal and child versus adult doses or concentrations of the agent are useful.

V. Exposure assessment

In exposure assessment, an evaluation of all available information is conducted to characterize the potential exposure to susceptible subpopulations. The following characteristics would be considered, as well as any uncertainties associated with use patterns or the data:

1. Evaluations of the populations at risk characterize the size, composition, and age distribution. Application of the FQPA safety factor to the risk assessment is would not be required if the subpopulation of concern is not expected to receive any exposure to the pesticide. However, if exposure to susceptible subpopulations is indicated, further evaluation of this exposure is required.
2. Information on the patterns of exposure can include the expected magnitude, frequency, and duration. The potential for bioaccumulative exposure to the pesticide should be evaluated in light of known pharmacokinetic data and the toxicological profile. Additionally, cumulative exposure to other pesticides should be considered, if appropriate.
3. Sources of the exposure are characterized and analyzed to determine if single (point) or multiple (aggregate) exposures are anticipated. It is generally assumed that as the number of sources of exposure rises, the prediction of total exposure will be less accurate.
4. The availability of realistic exposure data for the susceptible subpopulation should be evaluated. Lack of adequate and acceptable data that have been generated to characterize the exposure to these subgroups frequently requires the use of conservative assumptions in the risk assessment process.

Exposure information is used for an initial determination of risk to susceptible subpopulations such as pregnant women (fetuses) or infants and children. Also considered is conservatism in the exposure assessment when it is based on models and Standard Operating Procedures (SOPs) that contain certain assumptions.

VI. Risk characterization

The approach set forth in this paper recommends that determination of the appropriateness of retaining an FQPA safety factor for risk assessment be performed during risk characterization for each pesticide on a case-by-case basis and always employ a weight-of-the-evidence approach (SAP, 1996). Information on hazard, dose-response, and exposure is factored into this determination.

A. The contribution of hazard and dose-response characterization in determining if it is appropriate to remove or reduce the FQPA factor

A complete characterization of the hazard and dose-response assessment, as it relates to infants and children, would be provided for the risk characterization and risk management process. The final determination for each individual chemical would rely on the weight-of-the-evidence and reflect the extent to which the uncertainty regarding effects on infants and children is

tolerable, given the severity of the effects observed.

Two important and co-critical factors would be considered in determining the level and importance of uncertainty regarding the effects of the pesticide on infants and children: the presence or absence of special susceptibility in developing organisms and the adequacy of the data base. Because of the complexity in making these determinations, particularly in the consideration of the weight-of-the-evidence, which can differ substantially for each chemical, HED believes that development of inviolate rules which will define the outcome for every pesticide is not possible. Additionally, although these determinations are based upon the available science, the resulting recommendations are significantly influenced by a policy favoring enhanced protectiveness for infants and children under the new regulatory framework. The following proposed guidance provides general direction which would apply under most circumstances.

- When increased susceptibility to developing organisms is exhibited, and especially when there are other factors which lead to increased concern for the safety of children, the FQPA factor would not be removed, even if the data base is complete and the hazard is well characterized. Increased concern is determined using a weight-of-evidence approach.
- When concerns about apparent increased susceptibility to developing organisms are lessened because of the nature of the toxic effects, the FQPA factor can be reduced or, if the concerns are sufficiently addressed, may be removed. Lessened concern is also determined using a weight-of-evidence approach.
- If required core studies related to determination of special susceptibility are not available (e.g., rat or rabbit developmental toxicity studies or multi generation reproduction studies), the FQPA factor would not be removed but may be reduced if there is sufficient evidence to support a finding that the remaining margin will be safe for infants and children, based on reliable data.
- If it is determined, based upon the results of required core studies and the weight-of-the-evidence, that additional studies are necessary to more adequately characterize the hazard to infants and children (e.g., developmental neurotoxicity studies), the FQPA factor would not be removed, but may be reduced, again depending on the basis of reliable data to support the required safety finding.
- If there is an absence of any apparent susceptibility issues in the studies required to adequately characterize the hazard to offspring, but other data or information in the peer reviewed literature suggest susceptibility concerns, and a weight-of-evidence assessment confirms the susceptibility concerns, then the FQPA factor would not be removed, but may be reduced, based on the reliable data available in the required

studies.

- When the data base is judged to be sufficient for evaluating potential susceptibility for the particular pesticide, there are no issues of susceptibility, and no other information increases the level of concern, the safety factor would be removed.

B. The contribution of exposure assessment in determining the need to apply the FQPA factor to the risk assessment

Information about the potential exposure to infants and children, together with full characterization of the exposure assessment, should inform the decision regarding the FQPA safety factor. The following approach generally applies, assuming that hazard evaluation has identified an issue of concern for infants and children:

- Evaluation of the populations at risk would characterize the size, composition, and age distribution. Retention of the FQPA safety factor to the risk assessment would not be required if the subpopulation of concern is not expected to receive any exposure to the pesticide.
- If there is reason to believe that there is the potential for exposure of infants and children to a pesticide with toxicity concerns, the starting point would be to recommend retention of the FQPA factor. However, further characterization of the exposure (i.e., generally high quantity and quality of information), or the use of conservative models and assumptions, may reduce or negate the concern.
- If the hazard evaluation has not identified an issue of concern as to infants and children, and the toxicology data base is complete, the safety factor may be retained due to incompleteness of the exposure data. However, where the general approach to gaps in the data concerning exposure is to make conservative assumptions, based on the existing reliable data, that ensure that exposure to infants and children is not underestimated, there may be a reliable basis to reduce or remove the safety factor.

C. Examples of risk characterization determinations for the retention of the FQPA safety factor

HED believes that it is not possible to give specific criteria that will be used to evaluate the various factors and make the final determination, based upon hazard/dose-response and exposure assessments, for retention of the FQPA 10X safety factor for infants and children. As an alternative, a few examples are given to depict the ways in which weight of evidence determinations would be conducted.

Example 1. When there is an inadequate hazard and exposure data base for infants and

children---the FQPA 10X safety factor generally would be retained.

- Example 2. When hazard testing is complete; when toxicity and susceptibility are identified for infants and children of a type or extent which is of concern and there is exposure of the young---the FQPA 10X safety factor generally would be retained.
- Example 3. When hazard testing is complete; when toxicity issues of concern are identified for infants and children; and when there are uncertainties concerning the degree of susceptibility and/or exposure of the young---the FQPA 10X safety factor generally would be retained.
- Example 4. When there is an adequate hazard data base; when toxicity and susceptibility are identified for infants and children but toxicity is not of high concern; when there are multiple exposure sources; when exposure is characterized for only one source---the FQPA 10X safety factor generally would be retained, unless highly conservative screening exposure estimates are used for the unaccounted exposures.
- Example 5. When hazard testing is complete; when toxicity is identified for infants and children but when dose response analysis indicates that adults are more sensitive than the young; and when exposures to infants and children are ably estimated--the FQPA 10X safety factor could be reduced or removed, depending upon the overall data base.
- Example 6. When hazard testing for infants and children is complete; when no issues of concern regarding toxicity or susceptibility are identified for infants and children---the FQPA 10X safety factor would be removed, assuming that exposure data are complete and/or there is little or no likelihood that exposure is underestimated.
- Example 7. When hazard testing identifies a health concern for infants and children; but when there is clearly no opportunity for childhood exposure---the FQPA 10X safety factor would be removed.

VI. Application of the FQPA safety factor to risk assessment

The use of the FQPA safety factor, based upon susceptibility and/or uncertainty issues, adds a new consideration: that of characterizing the risk to specific subpopulations. To simplify the following discussions regarding the populations and exposure scenarios to which the FQPA safety factor would apply, it is assumed that exposure data are adequate or uncertainties in the exposure data have been resolved by the application of conservative assumptions. It is also

assumed that hazard characterization indicates that either because of uncertainty in the data base or because of susceptibility, the FQPA safety factor would be retained.

A. Populations to which an FQPA safety factor would apply

In the context of FQPA, the subpopulations evaluated in the risk assessment process are: females of child-bearing age (age 13+), adult males, and infants and children (ages 0-1, 1-6, 6-12). Under certain circumstances, two separate endpoints, which pertain to two distinct populations, will be selected and used in calculations for the risk assessment on a single exposure scenario. If an acute dietary endpoint is selected based on a fetal finding in a prenatal developmental toxicity study and applied to the subpopulation of females 13+, the data base would be reviewed for the selection of a non-developmental acute endpoint for application to other populations, including infants and children.

The appropriate FQPA safety factor should be used only for risk assessments that address the specific susceptible subpopulation or the subpopulation for which there is uncertainty. In the case in which a developmental endpoint is selected for use in risk assessment, the FQPA safety factor would be retained for the subpopulations of females 13+.

B. Duration of exposure and application of the FQPA safety factor

The FQPA safety factor should be retained for acute exposure risk assessments, for chronic exposure risk assessments, or for both, depending on the toxicity profile of the chemical. An FQPA factor which is based on an acute toxicity profile, would not be retained for a risk assessment for long-term exposure, because repeated exposures generally will result in effects at much lower doses, based on a different toxicity endpoint. However, if the same endpoint were selected for the acute and chronic exposures, the FQPA safety factor then should generally be retained for both risk assessments. Under this approach the FQPA safety factor would be retained only in cases where it is needed to assure the safety of infants and children.

C. Non-dietary exposures (excluding occupational exposures) and application of the FQPA safety factor

The FQPA provision regarding a safety factor for infants and children applies to setting a tolerance for a food use under the Federal Food, Drug, and Cosmetic Act (FFDCA) and to unreasonable adverse effect determinations under FIFRA that involve human dietary risk. In setting tolerances, all sources of exposure, including dietary and nondietary, are to be considered, except for occupational exposures. In keeping with this exclusion, occupational exposures are not addressed in this paper, although with the acknowledgment that the occupational workforce may include pregnant women.

Appendix A

Criteria currently in use by OPPTS in determining the need for a developmental neurotoxicity study based on a weight-of-evidence consideration of the data base for each chemical:

Developmental neurotoxicity testing should be:

- a) mandatory if the substance has been shown to cause CNS malformations;
- b) strongly considered if the substance has been shown to cause neuropathology/neurotoxicity in adults or affect brain weight in weanlings;
- c) strongly considered if the substance is a hormonally-active compound (pituitary, thyroid, sex hormones), or affects sexual maturation;
- d) considered if the substance causes other types of developmental toxicity.

Criteria specified by OMB in 1991 that determine if a OPP can issue a DCI for a developmental neurotoxicity study for a pesticide:

- a) neurotoxicity is observed in developing or adult animals following exposure to the compound;
- b) behavioral/functional changes are produced by direct effect of the compound on the nervous system;
- c) the compound acts to significantly modify hormonal responses associated with the development of the nervous system leading to significant developmental effects; or
- d) the compound exhibits a strong structure-activity relationship to a known neurotoxicant