APPENDIX E

ADDITIONAL DEVELOPMENTAL TOXICITY ISSUES

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Several chemicals, including lead, PCBs, methylmercury, and some pharmaceuticals, are known to cause developmental toxicity in humans. This information comes from large-scale poisoning incidents that resulted in serious developmental effects in a large number of offspring. Human dose-response studies cannot be carried out with planned dosing for developmental toxicants. However, developmental toxicity studies have been carried out on many environmental contaminants in animals. Many of these have yielded positive results (U.S. EPA, 1991). It is difficult to specifically interpret the dose-response relationship between effects in animal studies and anticipated observable effects in the human population. Research has been conducted to evaluate the relationship between known human developmental toxicants and animal testing results; many similarities in response were found. Alternatively, chemicals that caused developmental effects in animals were studied for effects in humans. These evaluations have yielded mixed results. It has been theorized that the lack of concurrence in results may be due in part to the limited nature of the human data differences in exposure route and the timing and duration of exposure (U.S. EPA, 1991). Further analysis has indicated that:

> The minimally effective dose for the most sensitive animal species was generally higher than that for humans usually within 10-fold of the human effective dose, but sometimes was 100 times or more higher (U.S. EPA, 1991).

The Guidelines go on to state that:

> Thus, the experimental animal data were generally predictive of adverse developmental effects in humans, but in some cases, the administered dose or exposure level required to achieve these adverse effects was much higher than the effective dose in humans. (U.S. EPA, 1991)

A number of assumptions are made in approaching developmental toxicity risk assessment in the absence of specific information:

- Adverse effects in experimental animals may pose a hazard to humans.
- The four manifestations of developmental toxicity (death, structural abnormalities, growth alterations, and functional deficits) are all of concern rather

than only malformations and death, which were the primary effects considered in the past.

- The type of developmental effects seen in animals is **not** necessarily the same as that produced in humans.
- The most appropriate species is used to estimate human risk when data are available (e.g., pharmacokinetic). In the absence of such data, the most sensitive species is used.
- A threshold is assumed based on the capacity of the developing organism to repair or compensate for some amount of damage (U.S. EPA, 1991).

Although it is assumed there is a threshold for developmental toxicity, EPA has stated that:

> . . . a threshold for a population of individuals may or may not exist because of other endogenous or exogenous factors that may increase the sensitivity of some individuals in the population (U.S. EPA, 1991).

The Agency is currently sponsoring research to better characterize the dose-response relationship for developmental toxicants. This includes an evaluation of the threshold concept (U.S. EPA, 1991). The process of risk assessment, as recommended in the 1991 EPA guidelines, generally follows the four-step process described in this document. However, hazard identification and dose-response evaluation are combined in the developmental toxicity guidelines because "the determination of hazard is often dependent on whether a dose-response relationship is present" (U.S. EPA, 1991).

E. 1 DEFINITIONS

There is no one consistent definition of developmental toxicity (U.S. EPA, 1986a). Developmental toxicity may include the range of effects from early pregnancy loss to cognitive disorders detectable only long after birth. The severity of developmental effects ranges from minor alterations in enzyme levels, with no known associated pathology, to death. Developmental toxicity also encompasses health endpoints having genetic and nongenetic bases. EPA's 1986 guidelines (U.S. EPA, 1986a) provide useful definitions that are used in this document to classify different types of developmental effects and to define the scope of effects included under the overall heading of developmental effects.

- **Developmental Toxicology—**The study of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism, (2)

structural abnormality, (3) altered growth (defined below), and (4) functional deficiency.

- **Functional Developmental Toxicology—**The study of alterations or delays in the physiological and/or biochemical functioning of the individual during critical pre- or postnatal development periods.

- **Embryotoxicity and Fetotoxicity—**Any toxic effect on the conceptus as a result of prenatal exposure. The distinguishing feature between the two terms is the stage of development during which the injury occurs (the embryonic stage lasts until approximately 8 weeks postconception followed by the fetal stage). The terms include malformations and variations, altered growth, and in utero death.

- **Altered Growth—**An alteration in offspring organ or body weight or size. These alterations may or may not be accompanied by a change in crown-rump length and/or in skeletal ossification. Altered growth can be induced at any stage of development and may be reversible or may result in a permanent change.

- **Malformations—**Permanent structural changes that may adversely affect survival, development, or function. The term teratogenicity is used to describe only structural abnormalities.

- **Variations—**Divergences beyond the usual range of structural constitution that may not adversely affect survival or health. Distinguishing between variations and malformations is difficult because responses form a continuum from normal to extremely deviant. (U.S. EPA, 1986a, 1991).

Other terminology is often used (e.g., anomalies, deformations, and aberrations) but definitions may vary.

For purposes of this guidance document, the definition of developmental toxicology given above will be used to describe the range of effects considered in this section. This provides a broad scope for evaluation of developmental effects, including those resulting from both prenatal and preconception exposures and effects that are observable pre- and postnatally. This section does **not** include a discussion of reproductive system effects (i.e., damage to the reproductive system), such as sterility, that result from exposure **during** adulthood and that may prevent conception from occurring but that do not affect the development of another individual. This type of toxicity is included under the Chronic Toxicity heading in each profile in Section 5.

Carcinogenic effects occurring prior to adulthood may be considered developmental effects under some circumstances. These can be evaluated using the methods described in the previous section on carcinogenicity in keeping with EPA recommendations (U.S. EPA, 1986b, 1996) and, similarly, mutagenic effects

can be evaluated using criteria discussed in *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c), as described in Appendix D.

E.2 SPECIAL ISSUES IN EVALUATING DEVELOPMENTAL TOXICANTS

Studies of developmental toxicants that are most useful in quantitative risk assessment include human epidemiological studies and animal toxicology studies. Epidemiological studies have been conducted on very few chemicals. Animal studies, which are more readily available, pose problems related to interspecies extrapolation (see statements in Sections 2.3.5 and 5 regarding uncertainty). The *Guidelines for the Health Assessment of Suspect Developmental Toxicants* (U.S. EPA, 1991) provides guidance on evaluating various types of developmental toxicity studies.

Some aspects of the evaluation of developmental toxicity studies differ from the approaches and data that would be sought from most other types of toxicity studies. One area of concern is the need to ascertain overall reproductive performance, not only adverse effects on developing individuals. Exposure to a toxicant often results in developmental damage at a very early stage of growth. This may prevent implantation or lead to very early fetal loss. Such losses are usually only detectable in animal studies by comparing the number of individuals per litter or the number of litters produced to the same outcomes in control populations. Very early losses are often absorbed and are not identifiable via other means. In human studies such losses are not usually identified, although prospective studies have used the monitoring of pregnancy markers, such as human chorionic gonadotropic (HCG) hormone, to identify very early post-implantation pregnancy losses (see U.S. EPA, 1991, for further discussion).

Another area of concern in developmental toxicity studies that is not usually of significant interest in other types of toxicity studies is the importance of weight changes. According to the federal guidelines, "A change in offspring body weight is a sensitive indicator of developmental toxicity . . ." (U.S. EPA, 1991). A relatively small weight change is not generally considered important in toxicological studies of adult subjects; however, this is considered an important effect during development. For example, the human corollary to decreased weight in animals may be low birth weight, although this cannot be directly implied from animal studies. Low birth weight in infants is a significant and often serious public health problem. Weight gain or loss may also be organ-specific and may be indicative of organ toxicity. For example, decreased brain weight may be indicative of retarded or neurological development.

An issue that is often raised in developmental toxicity studies is maternal toxicity. Although some researchers have suggested that the presence of maternal toxicity undermines the validity of results observed in offspring, some level of maternal toxicity should be observed in this type of study at the high end of the dose regimen (U.S. EPA, 1991). The EPA health assessment guidelines describe appropriate endpoints of maternal toxicity. One reason that identification of

maternal toxicity is an important component of a developmental toxicity study is that it can provide information on the likelihood of developing individuals being more or less susceptible than adults to an agent. Agents that produce developmental toxicity in offspring at doses that do not cause maternal toxicity are of greatest concern because these dynamics suggest that developing individuals are more sensitive or selectively affected (U.S. EPA, 1991). Those that produce effects in parent and offspring at the same dose are also of concern; it should not be assumed that offspring toxicity results from maternal toxicity because both may be sensitive to the given dose level (U.S. EPA, 1991).

E.3 REFERENCES

U.S. EPA (U.S. Environmental Protection Agency). 1986a. Guidelines for the health assessment of suspect developmental toxicants. *Federal Register* 51(185):34028-34040.

U.S. EPA (U.S. Environmental Protection Agency). 1986b. Guidelines for carcinogen risk assessment. *Federal Register* 51(185):33992-34003.

U.S. EPA (U.S. Environmental Protection Agency). 1986c. Guidelines for mutagenicity risk assessment. *Federal Register* 51(185):34006-34012.

U.S. EPA (U.S. Environmental Protection Agency). 1991. Guidelines for the health assessment of suspect developmental toxicants. *Federal Register* 56:63798-63826.

U.S. EPA (U.S. Environmental Protection Agency). 1996. *Proposed Guidelines for Carcinogen Risk Assessment*. EPA/600/P-92/003C, Office of Research and Development, Washington, DC.