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# **Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens**

Risk Assessment Forum  
U.S. Environmental Protection Agency  
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## **AUTHORS AND CONTRIBUTORS**

This document was prepared by a Technical Panel of the Risk Assessment Forum.

### **AUTHORS**

Hugh Barton, National Health and Environmental Effects Research Laboratory, ORD

Jim Cogliano, National Center for Environmental Assessment, ORD

Michael P. Firestone, Office of Children's Health Protection, OA

Lynn Flowers, National Center for Environmental Assessment, ORD

R. Woodrow Setzer, National Health and Environmental Effects Research Laboratory,  
ORD

Larry Valcovic, National Center for Environmental Assessment, ORD

Tracey Woodruff, Office of Policy, Economics, and Innovation, OA

### **CONTRIBUTORS**

Neepa Choksi, Fellow to the Office of Solid Waste and Emergency Response

Resha M. Putzrath, Risk Assessment Forum Staff, National Center for Environmental  
Assessment, ORD

William P. Wood, Risk Assessment Forum Staff, National Center for Environmental, ORD

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## PREFACE

U.S. Environmental Protection Agency (EPA or the Agency) cancer risk assessments may be conducted differently than envisioned in this Supplemental Guidance for many reasons including, for example, new information, new scientific understanding, or different science policy judgment. The practice of risk assessment with respect to accounting for early-life exposures to toxicants continues to develop, and specific components of this Supplemental Guidance may become outdated or may otherwise require modification in individual settings. It is EPA's intent to use, to the extent practicable and consistent with Agency statutes and regulations, the best available science in its risk assessments and regulatory actions, and this Supplemental Guidance is not intended to provide any substantive or procedural obstacle in achieving that goal. Therefore, the Supplemental Guidance has no binding effect on EPA or on any regulated entity. Where EPA does use the approaches in the Supplemental Guidance in developing risk assessments, it will be because EPA has decided in the context of that risk assessment that the approaches from the Supplemental Guidance are suitable and appropriate. This judgment will be tested through peer review, and the risk assessment will be modified to use different approaches if appropriate.

This Supplemental Guidance is intended for guidance only. It does not establish any substantive "rules" under the Administrative Procedure Act or any other law and has no binding effect on EPA or any regulated entity, but instead represents a non-binding statement of policy.

The Supplemental Guidance addresses a number of issues pertaining to cancer risks associated with early-life exposures generally, but provides specific guidance on potency adjustment only for carcinogens acting through a mutagenic mode of action. This guidance recommends for such chemicals, a default approach using estimates from chronic studies (i.e., cancer slope factors) with appropriate modifications to address the potential for differential risk of early-lifestage exposure. Default adjustment factors are meant to be used only when no chemical-specific data are available to assess directly cancer susceptibility from early-life exposure to a carcinogen acting through a mutagenic mode of action.

The Agency considered both the advantages and disadvantages of extending the recommended, age dependent adjustment factors for carcinogenic potency to carcinogenic agents for which the mode of action remains unknown. EPA recommends these factors only for carcinogens acting through a mutagenic mode of action based on a combination of analysis of available data and long-standing science policy positions that set out the Agency's overall approach to carcinogen risk assessment, e.g., the use of a linear, no threshold extrapolation procedure in the absence of data in order to be health protective. In general, the Agency prefers

to rely on analyses of data rather than on general defaults. When data are available for a susceptible lifestage, they should be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis. In the case of nonmutagenic carcinogens, when the mode of action is unknown, the data were judged by EPA to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied. In this situation per the Agency's *Guidelines for Carcinogen Risk Assessment*, a linear low-dose extrapolation methodology is recommended. It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach (without further adjustment) provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life susceptibility or when the mode of action is not mutagenicity.

The Agency expects to produce additional supplemental guidance for other modes of action, as data from new research and toxicity testing indicate it is warranted. EPA intends to focus its research, and to work collaboratively with its federal partners, to improve understanding of the implications of early life exposure to carcinogens. Development of guidance for estrogenic agents and chemicals acting through other processes resulting in endocrine disruption and subsequent carcinogenesis, for example, might be a reasonable priority in light of the human experience with diethylstilbesterol and the existing early-life animal studies. It is worth noting that each mode of action for endocrine disruption will probably require separate analysis.

As the Agency examines additional carcinogenic agents, the age groupings may differ from those recommended for assessing cancer risks from early-life exposure to chemicals with a mutagenic mode of action. Puberty and its associated biological changes, for example, involve many biological processes that could lead to changes in susceptibility to the effects of some carcinogens, depending on their mode of action. The Agency is interested in identifying lifestages that may be particularly sensitive or refractory for carcinogenesis, and believes that the mode of action framework described in the Agency's *Guidelines for Carcinogen Risk Assessment* is an appropriate mechanism for elucidating these lifestages. For each additional mode of action evaluated, the various age groupings determined to be at differential risk may differ from those described in this Supplemental Guidance. For example, the age groupings selected for the age-dependent adjustments were initially selected based on the available data, i.e., for the laboratory animal age range representative of birth to < 2 years in humans. More limited data and information on human biology are being used to determine a science-informed policy regarding 2 to < 16 years. Data were not available to refine the latter age group. If more data become available regarding carcinogens with a mutagenic mode of action, consideration may be given to further refinement of these age groups.



Access to data and other information relating to the Cancer Guidelines (U.S. EPA, 2005) and this Supplemental Guidance will be through EPA's Risk Assessment Forum website, under Publications, Guidelines, Guidelines for Cancer Risk Assessment. The URL is <http://www.epa.gov/cancerguidelines>. The data and results of analyses are available in spreadsheets.

## 1. INTRODUCTION

Cancer risk to children in the context of the U.S. Environmental Protection Agency's cancer guidelines (U.S. EPA, 2005) includes both early-life exposures that may result in the occurrence of cancer during childhood and early-life exposures that may contribute to cancers later in life. The National Research Council (NRC, 1994) recommended that "EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults." This document focuses on cancer risks from early-life exposure compared with those from exposures occurring later in life. Evaluating childhood cancer and childhood exposures resulting in cancer later in life are related, but separable, issues.

Historically, the focus on cancer has been as a disease associated with aging, resulting from extended exposure duration with prolonged latency periods before the cancers appear. Because much of cancer epidemiology addresses occupational exposures and because rodent cancer studies are designed to last approximately a lifetime (two years) beginning after sexual maturity, the cancer database used by EPA and other agencies for risk assessment focuses on adults. However, extensive literature demonstrates that exposures early in life (i.e., transplacental or *in utero*, early postnatal, lactational) in animals can result in the development of cancer (reviewed in Toth, 1968; Della Porta and Terracini, 1969; Druckery, 1973; Rice, 1979; Vesselinovitch et al., 1979; Rice and Ward, 1982; Vesselovitch et al., 1983; Anderson et al., 2000). Thus, one element in extending analyses to children is to evaluate the extent to which exposures early in life would alter the incidence of cancers observed later in life, compared with the incidence observed with adult-only exposures (Anderson et al., 2000; NRC, 1993).

The causes of cancer encompass a variety of possible risk factors, including genetic predisposition (Tomlinson et al., 1997), diet, lifestyle, associations with congenital malformations (Bosland, 1996), and exposure to biological and physical agents and chemicals in the environment. In some cases, tumors in adults and children have been compared (Anderson et al., 2000; Ginsberg et al., 2002). Children and adults generally develop the same spectrum of tumors when they have inherited gene and chromosomal mutations, such as Li-Fraumeni syndrome (Birch et al., 1998). With ionizing radiation, which operates through a mutagenic mode of action, both the young and the old develop many of the same tumors, with the difference being that children are more susceptible for a number of tumor types (NRC, 1990; U.S. EPA, 1994; UNSCEAR, 2000). Studies with anticancer drugs (cytotoxic and immunosuppressive) demonstrate a similar spectrum of tumors (Hale et al., 1999; Kushner et al., 1998; Larson et al., 1996; Nyandoto et al., 1998). Various viral infections, such as Epstein Barr and hepatitis B, lead to lymphoma and liver cancer, respectively, in both age groups (Lindahl et

al., 1974; Mahoney, 1999). These observations in humans indicate that the mode of action for these agents would be the same or similar for adults and children.

Although there are similarities between childhood and adult tumors, significant differences are also known to exist (Grufferman, 1998; Israel, 1995). Tumors of childhood generally consist more of embryonic cell tumors, while adults have more carcinomas. Leukemias, brain and other nervous system tumors, lymphomas (lymph node cancers), bone cancers, soft tissue sarcomas, kidney cancers, eye cancers, and adrenal gland cancers are the most common cancers of children, while skin, prostate, breast, lung, and colorectal cancers are the most common in adults (Ries et al., 1999; U. S. Cancer Statistics Working Group, 2002). Some tumors are unique to the young, including several with well established genetic bases, such as tumors of the kidney (Wilms' tumor) or eye (retinoblastoma) (Anderson et al., 2000; Israel, 1995).

The relative rarity in the incidence of childhood cancers and a lack of animal testing guidelines with perinatal<sup>1</sup> exposure impede a full assessment of children's cancer risks from exposure to chemicals in the environment. Unequivocal evidence of childhood cancer in humans occurring from chemical exposures is limited (Anderson et al., 2000). Established risk factors for the development of childhood cancer include radiation and certain pharmaceutical agents used in chemotherapy (Reise, 1999). There is some evidence in humans for adult tumors resulting from perinatal exposure. Pharmacological use of diethylstilbesterol (DES) during pregnancy to prevent miscarriages induced clear cell adenocarcinoma of the vagina in a few daughters exposed *in utero* though this tumor was not observed in exposed mothers (Hatch et al., 1998; Robboy et al., 1984; Vessey, 1989). In addition to the limited human data, there are examples of transplacental carcinogens in animal studies, such as recent studies with nickel and arsenic (Diwan et al., 1992; Waalkes et al., 2003), as well as studies suggesting that altered development can affect later susceptibility<sup>2</sup> to cancer induced by exposure to other chemicals (Anderson et al., 2000; Birnbaum and Fenton, 2003).

Infrequently, perinatal exposure in animals has been shown to induce tumors of different types than those observed with adult exposures. Studies with saccharin (Cohen et al., 1995; Whysner and Williams, 1996; IARC, 1999) and ascorbate (Cohen et al., 1998; Cohen et al., 1995; NTP, 1983) found cancer when exposures were initiated in the perinatal period. In

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<sup>1</sup> Perinatal is defined as the time around birth and may include both prenatal (prior to birth) and postnatal (after birth) periods.

<sup>2</sup> Susceptibility is defined here as an increased likelihood of an adverse effect, often discussed in terms of relationship to a factor that can be used to describe a human subpopulation (e.g., lifestage, demographic feature, or genetic characteristic). The terms "susceptibility" and "sensitivity" are used with a variety of definitions in published literature making it essential that readers are aware of these differences in terminology across documents.

contrast, studies submitted to the Food and Drug Administration of approximately a dozen other food additives and colorings that were not adult carcinogens did not indicate cancer, even when perinatal exposures occurred (U.S. EPA, 1996). When observed, the differences between childhood and adult cancers suggest the importance of evaluating the impacts of maternal exposures during pregnancy as well as exposures to children (Anderson et al., 2000). The effects of maternal exposures and transplacental carcinogens require separate evaluation and are not quantitatively evaluated in the analysis presented below.

The limited human information described briefly above is supported by a number of animal bioassays that include both perinatal and adult exposures to chemicals. Standard animal bioassays generally begin dosing after the animals are 6-8 weeks old, when many organs and systems are almost fully developed, though substantial growth in body size continues thereafter (as more fully discussed in Hattis et al., 2005). The literature can be divided roughly into three types of exposure scenarios: those that include *repeated* exposures for the early postnatal to juvenile period, as compared with chronic later-life dosing; *lifetime* (i.e., combined perinatal and adult) exposure as compared with chronic later-life dosing; and those that include more *acute* exposures, such as a single intraperitoneal (ip) or subcutaneous injection, for both early-life and later-life dosing. In the early-life exposure studies that are available, perinatal exposure usually induces higher incidence of tumors later in life than the incidence seen in standard bioassays where adult animals only were exposed; some examples include diethylnitrosamine (DEN) (Peto et al., 1984), benzidine (Vesselinovitch et al., 1979), DDT (Vesselinovitch et al., 1979), and polybrominated biphenyls (PCBs) (Chhabra et al., 1993a). Reviews comparing early-life carcinogenesis bioassays with standard bioassays for a limited number of chemicals (McConnell, 1992; Miller et al., 2002; U.S. EPA, 1996) have concluded:

- The same tumor sites usually are observed following either perinatal or adult exposure.
- Perinatal exposure in conjunction with adult exposure usually increases the incidence of tumor bearing animals or reduces the latent period before tumors are observed.

There is limited evidence to inform the mode(s) of action leading to differences in tumor type and tumor incidence following early-life exposure and exposure later in life. Differences in the capacity to metabolize and clear chemicals at different ages can result in larger or smaller internal doses of the active agent(s), either increasing or decreasing risk (Ginsberg et al., 2002; Renwick, 1998). There is reason to surmise that some chemicals with a mutagenic mode of action, which would be expected to cause irreversible changes to DNA, would exhibit a greater effect in early-life versus later-life exposure. Several studies have shown increased susceptibility

of weanling animals to the formation of DNA adducts following exposure to vinyl chloride (Laib et al., 1989; Morinello et al., 2002a; Morinello et al., 2002b). Additionally, even though not used quantitatively in the analyses in this document, a recent analysis of *in vivo* transplacental micronucleus assays indicated that fetal tissues generally are more sensitive than maternal tissues for induction of micronuclei from mutagenic chemicals (Hayashi et al., 2000), providing qualitative support for the early-life susceptibility. Similarly, the neonatal mouse model for carcinogenesis, which uses two doses prior to weaning followed by observation of tumors at one year, shows carcinogenic responses for mutagenic agents (Flammang et al., 1997; McClain et al., 2001). These results are consistent with the current understanding of biological processes involved in carcinogenesis, which leads to a reasonable expectation that children can be more susceptible to carcinogenic agents than adults (Anderson et al., 2000; Birnbaum and Fenton, 2003; Ginsberg, 2003; Miller et al., 2002; Scheuplein et al., 2002). Some aspects potentially leading to childhood susceptibility include the following issues.

- More frequent cell division during development can result in enhanced fixation of mutations due to the reduced time available for repair of DNA lesions and clonal expansion of mutant cells gives a larger population of mutants (Slikker et al, 2004).
- Some embryonic cells, such as brain cells, lack key DNA repair enzymes.
- Some components of the immune system are not fully functional during development (Holladay and Smialowicz, 2000; Holsapple et al., 2003).
- Hormonal systems operate at different levels during different lifestages (Anderson et al., 2000).
- Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life (Anderson et al., 2000; Birnbaum and Fenton, 2003; Fenton and Davis, 2002).

The methodology that has been generally used by the U.S. EPA to estimate cancer risk associated with oral exposures relies on estimation of the lifetime average daily dose, which can account for differences between adults and children with respect to exposure factors such as eating habits and body weight. However, susceptibility differences with respect to early lifestages are not taken into consideration because cancer slope factors<sup>3</sup> are based upon effects

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<sup>3</sup> Cancer slope factor – An upper bound estimate of the increased cancer risk from a lifetime exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per unit exposure (e.g., mg/kg-day or ug/m<sup>3</sup>), is generally reserved for use in the low-dose region of the dose-response relationship. It is often the statistical upper bound on the potency and therefore the risk. “Upper bound” in this context is a plausible

observed following exposures to adult humans or sexually mature animals. Since a much larger database exists for chemicals inducing cancer in adult humans or sexually mature animals, it is necessary to determine whether adjustment of such adult-based cancer slope factors would be appropriate when assessing cancer risks associated with exposures early in life. The analysis undertaken here addresses this issue, focusing upon studies that define the potential duration and degree of increased susceptibility that may arise from childhood, defined as early-life (typically postnatal and juvenile animal) exposures. Some of these analyses, along with a more complete description of the procedures used, have been published (Barton et al., 2005). The analysis presented in this Supplemental Guidance and in the published article form the basis for developing Supplemental Guidance for evaluating cancer susceptibility associated with early-life exposures.

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upper limit to the true probability.

## 2. PROCEDURES

This section describes the steps taken to assess potential susceptibility to early-life exposure to carcinogenic compounds compared with adult and whole-life exposure. The readily available literature was reviewed to identify animal studies that compared tumor incidence between early-life and adult-only exposures or between early-life-and-adult and adult-only exposures. Studies were categorized by length of exposure; those studies with quantitative information to estimate tumor incidence over time for early-life and adult exposures were identified. These studies provided the basis for quantitatively estimating the difference in susceptibility between early-life and adult exposures, as described below. Finally, summaries of available human data for radiation exposure were reviewed in the context of tumor incidence from early-life versus later-in-life exposure.

### 2.1. DATA SOURCES FOR ANIMAL STUDIES

Studies in the literature included in this analysis are those that report tumor response from experiments that included both early-life and adult exposure as separate experimental groups. Initial studies for consideration were identified through review articles and a search of the National Toxicology Program (NTP) database. Reviews of the literature regarding cancer susceptibility from early-life exposure in animals include McConnell (1992), Ginsberg (2003), Anderson et al. (2000), Miller et al. (2002) and U.S. EPA (1996). A literature search was conducted utilizing key words and MeSH headings (Medline) from studies identified in the available reviews. The list of chemicals included in this analysis for quantitative evaluation is shown in Table 1a and 1b.

Abstracts or papers were reviewed to determine if a study provided information that could be used for quantitative analysis. The criteria used to decide if a study could be included in the quantitative analysis were:

- Exposure groups at different post-natal ages in the same study or same laboratory, if not concurrent (to control for a large number of potential cross-laboratory experimental variables including pathological examinations),
- Same strain/species (to eliminate strain-specific responses confounding age-dependent responses),
- Approximately the same dose within the limits of diets and drinking water intakes that obviously can vary with age (to eliminate dose-dependent responses confounding age-dependent responses),

- Similar latency period following exposures of different ages (to control for confounding latency period for tumor expression with age-dependent responses), arising from sacrifice at >1 year for all groups exposed at different ages, where early-life exposure can occur up to about 7 weeks. Variations of around 10 to 20% in latency period are acceptable,
- Postnatal exposure for juvenile rats and mice at ages younger than the standard 6 to 8 week start for bioassays; prenatal (*in utero*) exposures are not part of the current analysis. Studies that have postnatal exposure were included (without adjustment) even if they also involved prenatal exposure,
- “Adult” rats and mice exposure beginning at approximately 6 to 8 weeks old or older, i.e. comparable to the age at initiation of a standard cancer bioassay (McConnell, 1992). Studies with animals only at young ages do not provide appropriate comparisons to evaluate age-dependency of response (e.g., the many neonatal mouse cancer studies). Studies in other species were used as supporting evidence, because they are relatively rare and the determination of the appropriate comparison ages across species is not simple, and
- Number of affected animals and total number of animals examined are available or reasonably reconstructed for control, young, and adult groups (i.e., studies reporting only percent response or not including a control group would be excluded unless a reasonable estimate of historical background for the strain was obtainable).

Tables 2 and 3 include information on the methods and results from the animal studies identified in Table 1b. Pertinent information on species, sex, dosing regimen, and tumor incidence is given. Additionally, the “Notes” column includes general information about the relationship between tumor incidence, animal age at first dosing, and sex. The data in Tables 2 and 3 were used for the calculations, described below, for estimating potentially increased cancer risk from early-life exposure.

The available literature includes a wide range of exposure scenarios. This range is due in part to the lack of a defined protocol for early-life testing and the difficulty of standardizing and administering doses preweaning. As noted previously, the literature can be divided roughly into three types of exposure scenarios: those that include repeated exposures for the early postnatal to juvenile period, as compared with chronic later-life dosing; lifetime (i.e., combined perinatal and adult) exposure as compared with chronic later-life dosing; and those that include more acute exposures, such as a single intraperitoneal (ip) or subcutaneous injection, for both early-life and later-life dosing. Table 2 includes the studies that had early postnatal to juvenile exposures, adult chronic exposures, and lifetime exposures. Table 3 includes studies with acute exposures. A discussion of the implications of the different exposure scenarios is included in Section 3.



Studies were identified for more than 50 chemicals not included in Tables 2 and 3 that demonstrated carcinogenesis following perinatal exposure, but did not directly compare exposures at different ages. A large number of studies address *in utero* exposures only. More than 100 chemicals (with both negative and positive findings) have been studied in the neonatal mouse assay, but this assay does not have a comparable adult exposure (Flammang et al., 1997; McClain et al., 2001; Fujii, 1991). Studies across laboratories often varied in their use of animal strains (e.g., for AZT studies, Diwan et al., 1999 used CD-1 mice, while NTP, 1999 used B6C3F<sub>1</sub> mice). Studies of tamoxifen use two Wistar-derived strains and had very different periods for tumor expression, i.e., sacrifice at 20 months for adult-exposed rats and natural death up to 35 months for juvenile-exposed rats, with uterine tumors observed in animals dying after 22 months (Carthew et al., 2000; Carthew et al., 1996; Carthew et al., 1995). Due to these factors, the chemicals that belong to this group were not evaluated quantitatively. In addition, there were studies assessing radiation in animals (Covelli et al., 1984; Di et al., 1990; Sasaki et al., 1978). The radiation data were not analyzed in depth, in part because there are recognized differences in toxicokinetics and toxicodynamics between radiation and chemicals with a mutagenic mode of action for carcinogenesis. Even though the data on A-bomb survivors provide information for many different cancer sites in humans with a single exposure involving all ages, a number of national and international committees of experts have analyzed and modeled these data to develop risk estimates for various specific applications. Furthermore, lack of uniformity regarding radiation doses, gestational age at exposure, and the animal strains used make it difficult to make comparisons across studies (Preston et al., 2000).

## **2.2. EVALUATING THE MODE OF ACTION OF CARCINOGENS**

Evaluation of the mode of action of a carcinogen was based upon a weight-of-evidence approach. Multiple modes of action are associated with the chemicals in this database, but a number are associated with mutagenicity (i.e., benzo(a)pyrene, benzidine, dibenzanthracene, diethylnitrosamine, dimethylbenz(a)anthracene, dimethylnitrosamine, ethylnitrosourea, 3-methylcholanthrene, methylnitrosourea, safrole, urethane, and vinyl chloride). Determination of carcinogens that are operating by a mutagenic mode of action entails evaluation of short-term testing results for genetic endpoints, metabolic profiles, physicochemical properties, and structure-activity relationship (SAR) analyses in a weight-of-evidence approach (Dearfield et al., 1991; U.S. EPA, 1986, 1991; Waters et al., 1999), as has been done for several chemicals (e.g., Dearfield et al., 1999; McCarroll et al., 2002; U.S. EPA, 2000a). Key data for a mutagenic mode of action may be evidence that the carcinogen or a metabolite is DNA reactive and/or has the ability to bind to DNA. Also, such carcinogens usually produce positive effects in multiple test

systems for different genetic endpoints, particularly gene mutations and structural chromosome aberrations, and in tests performed *in vivo* which generally are supported by positive tests *in vitro*. Additionally, carcinogens may be identified as operating via a mutagenic mode of action if they have similar properties and SAR to established mutagenic mode of action.

### 2.3. QUANTITATIVE METHODS

To estimate the potential difference in susceptibility between early-life and adult exposure, we calculated the estimated ratio of the cancer potency from early-life exposure compared to the estimated cancer potency from adult exposure. The cancer potency was estimated from a one-hit model, or a restricted form of the Weibull model, which is commonly used to estimate cumulative incidence for tumor onset. The general form of the equation is:

$$P(\text{dose}) = 1 - [1 - P(0)] \exp(-\text{cancer potency} * \text{dose})$$

The ratio of juvenile to adult cancer potencies were calculated by fitting this model to the data for each age group. The model fit depended upon the design of the experiment that generated the data. Two designs should be handled separately: experiments in which animals are exposed either as juveniles or as adults (with either a single or multiple dose in each period), and experiments in which exposure begins either in the juvenile or in the adult period, but once begun, continues through life.

For the first case, the model equations are:

$$\begin{aligned} P_A &= P_0 + (1 - P_0)(1 - e^{-m_A \delta_A}) \\ P_J &= P_0 + (1 - P_0) \left(1 - e^{-m_A e^\lambda \delta_J}\right) \end{aligned} \quad (1)$$

where:

subscripts *A* and *J* refer to the adult and juvenile period, respectively,  
 $\lambda$  is the natural logarithm of the juvenile:adult cancer potency ratio,  
 $P_0$  is the fraction of control animals with the particular tumor type being modeled,  
 $P_x$  is the fraction of animals exposed in age period *x* with the tumor,  
 $m_A$  is the rate of accumulation of “hits” per unit of time for adults, i.e., the cancer potency, and  
 $\delta_x$  is the duration or number of exposures during age period *x*.

For a substantial number of data sets (acute exposures),  $\delta_J = \delta_A = 1$ . We are interested in

determining  $\lambda$ , which is the logarithm of the estimated ratio of juvenile to adult cancer potencies, a measure of potential susceptibility for early-life exposure.

For the second kind of design, the model equations should take into account that exposures that were initiated in the juvenile period continue through the adult period. The model equations for the fraction of animals exposed only as adults with tumors in this design are the same as in the first design, but the fraction of animals whose first exposure occurred in the juvenile period is:

$$P_J = P_0 + (1 + P_0) \left( 1 - e^{-m_A e^{\lambda} (\delta_J - \delta_A) - m_A \delta_A} \right) \quad (2)$$

All symbols in (eq. 2) have the same interpretation as their counterparts in (eq. 1), but now  $\delta_J$  includes the duration of exposure during the juvenile period as well as the subsequent adult period.

Parameters in these models were estimated using Bayesian methods (see, for example, Carlin and Louis, 2000), and all inferences about the ratios were based on the marginal posterior distribution of  $\lambda$ . Some of these analyses, including a more complete description of the procedures (including the potential effect of alternative Bayesian priors that have been examined) have been published (Barton et al., 2005). The data for estimating each ratio were in the form of numbers of animals tested and number affected for each of control, juvenile-exposed, and adult-exposed animals, and duration of exposure for each of the juvenile-exposed and adult-exposed groups. A few data sets had separate control groups for the juvenile-exposed and adult-exposed groups, and equations 1 and 2 were modified accordingly. The likelihood for the parameters in the model was the product of three (or four, if there were two control groups) binomial probabilities: for the number of animals with tumors in the control group(s), for the juvenile-exposed group, and for the adult-exposed group. The prior for  $P_0$  (the fraction of control animals with a particular tumor) was right triangular (right angle at the origin), based on the assumption that control incidences should be relatively low. (The base of the distribution is one, as  $P_0$  can not exceed one. As this is a probability distribution, the area of the triangle is one. Therefore, its height at the origin must be 2.) The effect of exposure in adults is quantified by the extra risk,  $Q$ , where the probability that an animal has a tumor is  $P_0 + (1 - P_0)Q$ . So, from equations 1,  $Q = 1 - e^{-m_A \delta_A}$ ,  $Q$  was given a uniform prior on the interval (0,1), reflecting total ignorance about the extra risk of adult exposure. Finally, the prior for  $\lambda$  was Gaussian with mean 0 (corresponding to a median or geometric mean ratio of one) and standard deviation 3. The prior for the log ratio of juvenile to adult cancer potency has some influence over the posterior estimates for the ratio of juvenile to adult potency. The magnitude of that influence depends on

the amount of support in the data for different values of the log ratio. The prior also effectively downweights extremely large or small values for the juvenile to adult potency ratio. Three priors for the standard deviation were evaluated (Barton et al., 2005, see Appendix), with the intent of finding the largest prior, i.e., one that would contain the least informative assumption for the prior. A standard deviation of 9 was tried, but some of the intervals would not converge. A standard deviation of 3 worked well, allowed ratio estimates to be derived, with all of the data of interest. An intermediate value of 6 was also examined to ascertain if a less informative prior could be used. While the intervals converged, a sensitivity analysis showed that this value for the standard deviation resulted in sufficient down-weighting of the ratios with limited information that these data would not influence the result. This was considered an unreasonable bias, so a standard deviation of 3 was used for the further analyses. A further discussion of these analyses can be found in Barton et al. (2005).

The posterior distribution for the unknown parameters in these models is the product of the likelihood from the data and the priors (the “unnormalized” prior), divided by a normalization constant that is the integral of the unnormalized prior over the ranges of all the parameters. This normalization constant was computed using numerical integration, as were posterior means and variances and marginal posterior quantiles for the log-ratio  $\lambda$ . All numerical computations were carried out in the R statistical programming language (version 1.8.1; R Development Core Team, 2003).

This method produced a posterior mean ratio of the early-life to adult cancer potency, which is an estimate of the potential susceptibility of early-life exposure to carcinogens. If the ratio was greater than one, this indicated that the experiment found that there was greater susceptibility from early-life exposure. If the ratio was less than one, this indicated that the experiment found that there was less susceptibility from early-life exposure. Summaries of the individual ratios from each of the dose groups from the different experiments for different groupings were also calculated (for example for all acute exposures of chemicals that are carcinogenic by a mutagenic mode of action). The summary ratios were constructed from the individual ratios within a group, by variance-weighting the means of each ratio. The individual, posterior means were weighted by using reciprocals of their posterior variance. This weighting procedure is commonly used because it gives greater weight to those studies for which the variances, i.e., the uncertainties, are smaller. Because the ratios were calculated as log ratios (see eq. 1), exponentiating the resulting inverse-variance-weighted mean yielded inverse-variance-weighted geometric means of ratios.

## 2.4. IONIZING RADIATION

A supporting role was assigned to the available human radiation data, where cancer incidence in adults who were children at the time of the atomic bomb (A-bomb) exposure was compared with cancer incidence in adults who were older at the time of exposure. Although there are recognized differences in toxicokinetics and toxicodynamics between radiation and chemical carcinogens with a mutagenic mode of action, the data on A-bomb survivors provide information for many different cancer sites in humans with a single exposure involving all ages. In addition to the richness of the data, a number of national and international committees of experts have analyzed and modeled these data to develop risk estimates for various specific applications.

The report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2000, with Scientific Annexes) lists more than 80 studies, in addition to the reports of the Japanese A-bomb survivors, in which at least one type of cancer was measured in humans who were exposed either intentionally or accidentally to some form of ionizing radiation. However only the A-bomb survivor reports have relevant information on incidence of early-life exposures. One of the more recent papers cited in the UNSCEAR report, by Thompson et al. (1994), contains detailed data on the incidence of 21 different cancers in 37,270 exposed A-bomb survivors (42,702 unexposed). Also, EPA has used data from the A-bomb survivors to develop age-specific relative risk coefficients using various methods for transporting the risk from the Japanese population to the U.S. population (U.S. EPA, 1994). It is beyond the scope of this effort to present all of the radiation data or a discussion of the various analyses and modeling efforts. Rather, information relevant to comparing cancer risks from juvenile versus adult exposure from UNSCEAR (2000) and U.S. EPA (1994; 1999) is presented as representative findings to determine whether the radiation data are similar qualitatively to the chemical findings. More detailed data on the A-bomb survivors can be found in Delongchamp et al. (1997) and Preston et al. (2000).

As previously noted, several studies have assessed radiation in animal studies (Covelli et al., 1984; Di et al., 1990; Sasaki et al., 1978). However, lack of uniformity regarding radiation doses, gestational age at exposure, and the animal strains used make it difficult to compare the experimental data on cancer induction after prenatal irradiation (Preston et al., 2000).

### 3. RESULTS

#### 3.1. QUALITATIVE EVALUATION OF THE DATABASE

The question addressed in this analysis was whether, and how, available quantitative scientific data could inform risk assessment policy choices for adjusting cancer slope factors when they are used in the assessment of cancer risk from childhood exposure. Cancer slope factors are, with few exceptions, based on adult human epidemiology or standard chronic adult rodent bioassays, which do not address the impacts of early-life exposures. Thus, the critical data are either human epidemiological data on childhood exposures resulting in adult cancer or research studies with rodents involving early postnatal exposures. The major human data available are from radiation exposures (studies summarized in Tables 9-11), with very limited data available for humans exposed during childhood to chemicals (reviewed in Anderson et al., 2000; Miller et al., 2002).

A review of the literature identified several hundred references reporting more than 50 chemicals that have been shown to be able to cause cancer following perinatal exposure (Table 1a) (reviewed in Toth, 1968; Della Porta and Terracini, 1969; Druckery, 1973, Rice, 1979; Vesselovitch et al., 1979; Rice and Ward, 1982; Vesselovitch et al.; 1983; Fujii, 1991; Anderson et al., 2000). Studies (or groups of studies from a single laboratory on a given chemical) that directly provided quantitative data on carcinogenesis following early postnatal exposures and adult exposures to chemicals in animals were identified for 18 chemicals, listed in Table 1b, 2, and 3. Of the identified studies, there were 11 chemicals involving repeated exposures during early postnatal and adult lifestages (Table 1b) and 8 chemicals using acute exposures (typically single doses) at different ages (Table 1b). Some of the studies evaluated single tissues or organs for tumors (e.g., only liver), while others evaluated multiple tissues and organs (Tables 2 and 3). Mice, rats, or both species and sometimes multiple strains were tested. These studies serve as the basis for the quantitative analyses presented later in the results.

In addition to the studies identified in Table 1b, studies were identified with early postnatal and early-life exposures that were evaluated qualitatively but not quantitatively. Some of these studies are notable and provide important supporting information. Two recent studies used transgenic mouse models for human tumors. Increased multiplicity of colon tumors was observed following earlier versus later azoxymethane exposures (Paulsen et al., 2003). Shortened mammary tumor latency following estradiol exposure occurred when exposures occurred between 8 and 18 weeks as opposed to earlier or later, which is generally consistent with the incidence results analyzed for DMBA (Yang et al., 2003). Several notable examples exist of developmental windows leading to cancer susceptibilities that were not observable in

adults. Several potent estrogenic chemicals including DES, tamoxifen, and genistein produce uterine tumors with early postnatal exposures of mice, though there also appear to be strain-dependent differences in the tumor sites in adult mice (Gass et al., 1964; Greenman et al., 1990; Newbold et al., 1990, 1997, 1998, 2001). Developmental susceptibilities are believed to play a key role in effects observed with saccharin (Cohen et al., 1995; Whysner and Williams, 1996) and ascorbate (Cohen et al., 1998; NTP, 1983), with bladder tumors arising when early-life exposures occurred. Studies with several species, including rat, mouse, and opossum, indicate that nervous systems tumors associated with exposures to ENU and several other chemicals appear to be highly dependent upon exposures occurring within certain windows, particularly prenatal ones (Rice, 1979; Rice and Ward, 1982; Jurgelski et al., 1979).

Analyses of the difference in cancer risk from exposures during different lifetime periods ideally should address both the period of potential susceptibility and the magnitude of the susceptibility. Available studies used a variety of study designs (see Tables 2 and 3), which can be valuable because they provide different information (Figure 1). However, variations in study design can result in a lack of comparability across chemicals, and can limit information on the consistency of effects with different chemicals acting through different modes of action. The acute dosing (largely single dose) studies (Table 3) are valuable because they involve identical exposures with explicitly defined doses and time periods demonstrating that differential tumor incidences arise exclusively from age-dependent susceptibility. These studies address both the period and magnitude of susceptibility. They were not as appropriate for quantitative adjustments for the cancer potency estimates because of their limitations, including that most used subcutaneous or ip injection that historically have not been considered quantitatively relevant routes of environmental exposure for human cancer risk assessment by EPA, and that these routes of exposure are expected to have only partial or a complete absence of first pass metabolism that is likely to affect potency estimates.

The repeated dosing studies with exposures during early postnatal or adult lifetime provide useful information on the relative impact of repeated exposures at different lifestages and may be more likely to have exposure occur during a window of susceptibility, if there is one. One notable difference in study designs was that studies with repeated early postnatal exposure were included in the analysis even if they also involved earlier maternal and/or prenatal exposure, while studies addressing only prenatal exposure were not otherwise a part of this analysis. Another notable difference among studies involved the tissues that were evaluated for tumors: some studies focused on a single tissue, particularly liver, while others evaluated multiple tissues.

Comparisons within a single repeated dosing study may have limitations for evaluating

differential susceptibility because exposures to the chemical can differ during the different lifestages, particularly when dietary or drinking water exposures are involved. A notable example is the PCB study (Chhabra et al., 1993a), in which mobilization of such lipid-soluble chemicals into mother's milk would be expected to result in infants receiving much larger exposures than other lifestages. While lactational transfer is just as relevant to human nursing offspring, this difference in exposure obscures the extent to which the early lifestage is quantitatively more susceptible (i.e., part of the increased early-life cancer risk arises from higher exposure than during the adult period). Maternal metabolism of compounds such as diphenylhydantoin (DPH) (Chhabra et al., 1993b) also may result in lower exposure during lactation, potentially underestimating the early-lifestage risk, if the parent compound is the active form of the chemical. Similar issues exist due to normal age-dependent changes in food and water consumption. Ascribing differential effects observed in animal studies solely to lifestage susceptibility must be done carefully as there may also be differences in the exposures. There are substantial and clear benefits, therefore, from experimental consistency when comparisons are made directly within a study (e.g., same species and strain, consistent pathological evaluation).

One issue to note is the rationale for the organization of the available data. It was observed that the results across a broad range of chemicals with a variety of modes of action were somewhat variable. Therefore, consistent with the approach of the EPA cancer guidelines (U.S. EPA, 2005), an approach based on mode of action appeared to be a common framework for analysis. Variability in lifestage-dependent susceptibility and susceptibility across a range of modes of action was further supported by theoretical analyses using multistage and two-stage models of carcinogenesis (Goddard and Krewski, 1995; Murdoch et al., 1992).

### **3.2. QUANTITATIVE EVALUATION OF THE DATABASE**

As described in the Section 2.3, the potential difference in susceptibility between early-life and adult exposure was calculated as the estimated ratio of cancer potency from early-life exposure over the cancer potency from adult exposure. Tables 4-7 present the results of the quantitative analysis using the studies that were determined qualitatively to have appropriate study designs (Tables 2 and 3) containing sufficient information to analyze. Based on the studies available, the calculations were organized into four tables: (1) compounds acting through a primarily mutagenic mode of action, where the compound was administered by a chronic dosing regimen to adults and repeated dosing in the early postnatal period (Table 4); (2) compounds acting through a primarily nonmutagenic mode of action, where the compound was administered by a chronic dosing regimen to adults and repeated dosing in the early postnatal period (Table 5);



(3) compounds acting through a primarily mutagenic mode of action, where the compounds were administered by an acute dosing regimen (Table 6); and (4) compounds acting primarily through either a mutagenic or nonmutagenic mode of action with chronic adult dosing and repeated early postnatal dosing (Table 7). In these tables, the 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses. The results are discussed below, followed by a description of results from analyses of studies of humans exposed to radiation.

### **3.2.1. Carcinogens with a Mutagenic Mode of Action**

The most informative database on early-lifestage susceptibility exists for chemicals with a well-accepted mutagenic mode of action (e.g., diethylnitrosamine, vinyl chloride). This database includes both single-dose studies and repeated-dose studies involving periods of postnatal and/or chronic exposure. These studies help define the periods of increased vulnerability and the magnitude of the susceptibility. The acute dosing studies demonstrate that the age-dependent responses are not due to differences in exposure, because these studies explicitly control the exposure.

#### ***3.2.1.1. Early Postnatal, Juvenile, and Adult Repeated Dosing Studies of Chemicals with a Mutagenic Mode of Action***

Studies comparing repeated dosing for early-life, adult, or lifetime exposures exist for six carcinogens with a mutagenic mode of action [benzidine, diethylnitrosamine (DEN), 3-methylcholanthrene, safrole, urethane, and vinyl chloride]; DEN also had acute dosing studies. Lifetime (i.e., combined juvenile and adult) compared to adult exposure studies were analyzed for DEN, safrole, and urethane, while studies comparing juvenile with adult exposures were analyzed for benzidine, 3-methylcholanthrene, safrole, and vinyl chloride. These chemicals all require metabolic activation to the active carcinogenic form. Analysis of the tumors arising per unit time of exposure found that juvenile exposures with each chemical could be more effective than adult exposures were at inducing tumors (Tables 4 and 7; Figure 2, a graphic representation of the posterior, unweighted geometric means and their 95% confidence intervals, for the ratios of juvenile to adult cancer potency for carcinogens acting through a mutagenic mode of action). The weighted geometric mean for repeat and lifetime exposures is 10.4; for acute exposures the weighted geometric mean value is 1.5. For benzidine and safrole, there was a notable sex difference, with high liver tumor incidence observed for early postnatal exposures of male, but not female, mice. For both the acute and the repeated/lifetime data, the 95<sup>th</sup> percentile of the individual, unweighted geometric means is above 10 (Figure 2).

This analysis focused upon the duration of exposure as a surrogate for dose, essentially assuming that the doses animals received during the different periods of these studies were similar. This assumption is a limitation of the analysis because these studies involved exposures via lactation (i.e., dosing the mother prior to weaning), drinking water, diet, or inhalation, which have the potential to deliver different doses at different lifestages. However, the range of the magnitudes of the tumor incidence ratios of juvenile to adult exposures is similar (Table 8) for the repeated dosing studies (0.12 – 111, weighted geometric mean 10.5, 42% of ratios greater than 1), lifetime dosing studies (0.18 – 79, weighted geometric mean 8.7, 67% of ratios greater than 1), and acute dosing studies (0.01 – 178, weighted geometric mean 1.5, 55% of ratios greater than 1), suggesting that these differences in dosing are not the sole determinant of the increased incidence of early tumors, i.e., uncertainty and variability remain. Because these comparisons include different chemicals with different tissue specificities, it may be informative to consider liver as a target organ affected by all of these chemicals. The range of the magnitudes of the liver tumor incidence ratios of juvenile to adult exposures is similar for the repeated dosing studies (0.12 – 111, weighted geometric mean 41.8, 86% of ratios greater than 1, Table 4), lifetime dosing studies (0.47 – 79, weighted geometric mean 14.9, 80% of ratios greater than 1, Table 7), and acute dosing studies (0.1 – 40, weighted geometric mean 8.1, 77% of ratios greater than 1, Table 8). Thus, the repeated dose studies support the concept that early-lifestage exposure to carcinogenic chemicals with a mutagenic mode of action would lead to an increased tumor incidence compared with adult exposures of a similar duration and dose.

### ***3.2.1.2. Acute Dosing Studies of Chemicals with a Mutagenic Mode of Action***

Acute dosing studies are available for eight carcinogens with a mutagenic mode of action that were administered to mice or rats [benzo[a]pyrene (BaP), dibenzanthracene (DBA), Diethylnitrosamine (DEN), dimethylbenzanthracene (DMBA), dimethylnitrosamine (DMN), ethylnitrosourea (ENU), methylnitrosourea (NMU), and urethane (also known as ethyl carbamate)] (Table 1b). Except for ENU and NMU, these compounds require metabolic activation to their active carcinogenic forms. These acute dosing studies generally compared a single exposure during the first few weeks of life with the identical or similar exposure in young adult animals (Tables 3 and 6). Many of these studies compared exposures during the preweaning period (i.e., approximately day 21 for rats and mice) with effects around week 6, which is approximately the age at which typical chronic bioassays begin dosing animals. These studies largely were by subcutaneous or ip injection, which historically have not been considered quantitatively relevant routes of environmental exposure for human cancer risk assessment by EPA. For purposes of comparing age-dependent susceptibilities to tumor development, these

data are highly relevant. The injection route typically alters the pharmacokinetic time courses of the parent compound and the metabolites compared with oral or other exposures due to altered kinetics of absorption and metabolism. However, for these compounds and the systemic organ effects observed, there are several pharmacokinetic reasons to believe that the age-dependent trends would be similar with other routes of exposure. These compounds are expected to be reasonably well absorbed orally, comparable with injection routes, and largely require metabolic activation, so partial or complete absence of first pass metabolism in the injection studies would be similar to or underestimate metabolic activation when compared with oral exposure.

The early exposures often resulted in higher incidence of tumors than later exposures, with increased early susceptibilities up to 178-fold (unweighted ratios in Table 6 range from 0.011 to 178, with a weighted geometric mean of 1.5, and 55% of ratios greater than 1, Figure 2, Table 8). Examples of the general age-dependent decline in susceptibility of tumor response include BaP (liver tumors), DEN (liver tumors), ENU (liver and nervous system tumors), and urethane (liver and lung tumors). While generally the Day 1 and Day 15 time points were higher than later time points, in several cases similar tumor incidence was observed at both these early times (e.g., ENU-induced kidney tumors, Tables 6 and 8).

While the degree of susceptibility generally declines during the early postnatal period through puberty into early adulthood, there are exceptions due perhaps to pubertal periods of tissue development (e.g., mammary tissues) or very early development of xenobiotic metabolizing enzymes. One such exception was the increased incidence of mammary tumors in 5-8 week old rats given DMBA, compared with older or younger rats (Meranze et al., 1969; Russo et al., 1979). Meranze et al. (1969) reported 8% mammary tumors following a single dose of DMBA at less than two weeks, 56% if given once to animals between 5 and 8 weeks old, and 15% when given once to 26 week old rats. Thus, a ratio of 7.1 is obtained when comparing susceptibilities of 5–8 week and 26-week-old rats (Table 6) compared to a ratio of 0.2 when comparing the exposure at 2 weeks versus 26 weeks. A similar effect was observed by Russo et al. (1979); see Table 3. This observation corresponds well with pubertal development of the mammary tissue, with ovarian function commencing between 3 and 4 weeks (after the < 2 week time point in the Meranze et al., 1969 study), and mammary ductal growth and branching occurring such that it is approximately two-thirds complete by week 5, consistent with the 5–8 week susceptible period of Meranze et al. (Silberstein, 2001). While this differs from the general trend previously discussed, it indicates susceptibility later in the juvenile period rather than earlier. Another example of deviation from the general trend toward an age-dependent decline is DEN-induced lung tumors that were somewhat lower in incidence following exposure on day 1 than observed for the day 15 or day 42 exposures (Vesselinovitch et al., 1975) (Tables 3 and 6).

There are substantial differences in the early-life susceptibility of different tissues observed in the acute studies (Table 8). It should be noted that the target tissues vary with chemical, so the number of chemicals for which data are available varies for each tissue. Several tissues have weighted geometric mean ratios of greater than 1 including kidney, leukemia, liver, lymph, mammary, nerve, reticular tissue, thymic lymphoma, and uterus/vagina. Some of these, such as the nerve and mammary tumors, appear to have a very specific window of susceptibility, as noted above, and the ratios were much higher if the exposure occurred during this window. Tissues with weighted mean ratios less than 1 include forestomach, harderian gland, ovaries, and thyroid. Lung has a weighted geometric mean of 1. Many of the studies produced very high lung tumor responses regardless of age, so the results are difficult to interpret, as illustrated by the dose-response data with urethane in Rogers (1951) in which the increased early susceptibility is only apparent when the dose is low. The large numbers of studies with high lung tumor responses at all ages contribute to the differences in the weighted geometric means for the acute and for the repeated dosing studies.

Overall, the acute dosing studies support the concept that early-lifestage exposure to carcinogenic chemicals with a mutagenic mode of action would lead to an increased incidence of tumors compared with adult exposures of a similar dose and duration. These studies generally use the same dose and duration at all ages, and thus do not have the type of issues discussed for the repeated dosing studies. On the other hand, the acute dosing studies have limitations that were sufficient to decide that they should not be included in the quantitative adjustment of cancer potency. First, as mentioned in the previous paragraph, the large number of studies of lung tumors with almost 100% response observed at all doses and all ages would significantly bias the median ratio toward unity for a reason based on study design rather than biology. Second, cancer potency estimates are usually derived from chronic exposures. Therefore, any adjustment to those potencies should be, if possible, from similar exposures. Third, most exposures of concern to the Agency are from repeated or chronic exposures rather than acute exposures. Finally, many of the acute studies used ip exposures, which is not the usual route of exposure for environmental chemicals. Thus, the repeated and lifetime studies are more appropriate for the purpose of this analysis.

### **3.2.2. Carcinogens With Modes of Action Other Than Mutagenicity**

Studies comparing tumors observed at the same sites following early postnatal and chronic adult exposures in a single protocol were available for six chemicals that do not act through a mutagenic mode of action [amitrole, dichlorodiphenyltrichloroethane (DDT), dieldrin, ethylene thiourea (ETU), diphenylhydantoin (DPH), polybrominated biphenyls (PBB)] (Table 5).

These chemicals cause tumors through several different, not necessarily well defined, modes of action. For example, thyroid hormone disruption by ETU causes thyroid tumors; some PBBs act through aryl hydrocarbon (Ah) receptors, while others are phenobarbital-like pleiotrophic inducers of liver enzymes and liver tumors. Three of these studies evaluated only mouse liver tumors (amitrole, DDT, dieldrin), while the other three evaluated a large number of tissues in both mice and rats (ETU, DPH, PBB). These studies generally included a combined perinatal and adult exposure as well as the separate perinatal or adult-only groups. It should be noted that no acute perinatal dosing studies of carcinogenesis were identified for these agents; such protocols are generally considered largely non-responsive for modes of action other than mutagenicity and potent estrogenicity (e.g., DES).

For five chemicals (amitrole, DDT, dieldrin, PBB and DPH), the same tumors were observed from early and/or adult exposures, though the studies for amitrole, DDT, and dieldrin only evaluates the animals for liver tumors. With ETU, no tumors in mice or rats were observed following perinatal exposure alone (except a small, not-statistically-significant increase in male rat thyroid tumors), while thyroid tumors were observed in adult rats and thyroid, liver, and pituitary tumors in adult mice. Analysis of the incidence of tumors per time of exposure shows early-lifestage susceptibilities. The range of the magnitudes of the tumor incidence ratios of juvenile to adult exposures is similar for the repeated dosing studies (0.06–13.3, weighted geometric mean 2.2, 27% of ratios greater than 1, Tables 5 and 8) and lifetime dosing studies (0.15–36, weighted geometric mean 3.4, 21% of ratios greater than 1, Tables 7 and 8). These ranges and means are similar to those for chemicals with a mutagenic mode of action, though the means and maximums are somewhat lower. Again, liver tumors are common to these chemicals. The range of the magnitudes of liver tumor incidence ratios of juvenile to adult exposures also is similar for the repeated dosing studies (0.06–13.3, weighted geometric mean 2.6, 43% of ratios greater than 1, Tables 5 and 8) and lifetime dosing studies (0.15–36, weighted geometric mean 5.8, 33% of ratios greater than 1, Tables 7 and 8).

The major factor that complicates the interpretation of the results is that these studies, except with DDT and dieldrin, involved dietary feeding initially to the mother, which potentially could increase or decrease the dose received by the pups. Due to the maternal dosing during pregnancy and lactation, the extent to which offspring received similar doses during different early and adult lifestages is particularly uncertain for DPH, ETU, and PBBs. Oral gavage doses in young animals were selected to approximate the average daily dose in adult dietary studies based on standard estimates of feed consumption in the studies with DDT and dieldrin, while the amitrole study involved dietary feeding postnatally to the mother so the young were dosed via lactation. In addition, DDT, dieldrin, and some PBBs are more persistent in the body than are

most chemicals, leading to a prolonged exposure even following limited dosing. Thus, these studies provide evidence that early lifestages can be more susceptible to exposures to chemicals causing cancer through a variety of modes of action other than mutagenicity. However, the studies with ethylene thiourea, which acts via thyroid disruption, indicate that this is not necessarily the case for all modes of action.

### **3.2.3. Ionizing Radiation**

As mentioned previously, the UNSCEAR, Annex I (2000) includes information derived from a wide range of both intentional (generally diagnostic or therapeutic medical) and accidental radiation exposures. Only information derived from the Japanese population (referred to as the Life Span Study in the UNSCEAR Annex I) is presented here. A statistically significant excess cancer mortality associated with radiation has been found among the bomb survivors for the following types of cancer: esophagus, stomach, colon, liver, lung, bone and connective tissue, skin, breast, urinary tract, and leukemia. Tables 9 and 10 are extracted from the tables in UNSCEAR, Annex I. The excess relative risk (ERR) is the increased cancer rate relative to an unexposed population; an ERR of 1 corresponds to a doubling of the cancer rate. Because of the low numbers of cancers in individual sites within narrow age groups, the ERRs for the various solid tumors and leukemia were presented only as less than or greater than 20 years of age at the time of exposure. The larger number of thyroid tumors enable a more detailed breakout shown in Table 10. Most sites show greater risks in the younger than in the older ages.

The U.S. EPA (1994) document presents a methodology for estimation of cancer risks in the U.S. population due to low-LET (linear energy transfer) radiation exposures using data from the Atomic Bomb Survivor Study (ABSS) as well as from selected medical exposures. The report developed mortality risk coefficients using several models that took into account age and gender dependence of dosimetry, radiogenic risk, and competing causes of death as well as transporting of risks across populations. The risk projections were updated using more recent vital statistics in a report that also included an uncertainty analysis (U.S. EPA, 1999). Details of the derivation of these coefficients are available at [http://www.epa.gov/radiation/docs/rad\\_risk.pdf](http://www.epa.gov/radiation/docs/rad_risk.pdf).

Table 11 contains the calculated age-specific risk coefficients derived from the application of the various models to the ABSS data. For most of the sites in the table, the risk coefficients are higher in the earlier age groups; liver, bone, skin, and kidney coefficients are age-independent and only esophageal cancer coefficients increase with increasing age. Also of note is that the coefficients generally are higher for females. Similar to the information from the UNSCEAR (2000) Annex, most sites show greater risks in the younger ages than the older ages.

However, a comparison of the two tables seems to show reversal of risks for some sites as a function of age at exposure. While the high sampling variability in the epidemiological data for some ages may contribute to this apparent reversal, the choice of risk models and associated parameters also is a factor.

## 4. DISCUSSION

The challenge for this analysis was how to use the existing, but limited, scientific database on early postnatal and juvenile exposures to carcinogens to inform a science policy decision on whether, and if so how, to assess the risk from childhood exposures to chemicals for which we have evidence of carcinogenicity only in adult humans or sexually mature laboratory animals. The database overall is of limited size (particularly compared with the number of chemicals that have been studied in adult occupational epidemiological studies or chronic bioassays). The majority of the human data involves exposures to ionizing radiation or DES (Anderson et al., 2000). More than 50 chemicals have been demonstrated to cause cancer following perinatal exposures in animals (without adult exposures), but only a subset of the chemicals have comparative studies across ages. The comparative experimental studies used 18 chemicals, 12 of which had mutagenic modes of action and 6 of which had data from repeated or lifetime exposures. Other analyses of similar data have found similar results (Hattis et al. 2005), but have focused on other aspects of the data, e.g., gender differences.

Previously published or internal U.S. EPA analyses have concluded that the standard animal bioassay protocols usually do not miss chemicals that would have been identified as carcinogens if perinatal exposures had been undertaken (McConnell, 1992; Miller et al., 2002; U.S. EPA, 1996). Given the increased complexity and costs of chronic bioassays with perinatal exposures, a limited number of such studies have been performed. However, these are the studies that largely constitute the available database for this analysis. In addition to the chronic bioassays with perinatal exposures, there are studies with acute dosing at different lifestages and a large number of studies with perinatal exposures without a directly comparative adult study.

Two other kinds of information can contribute toward developing a scientifically informed policy: theoretical analyses and analyses of stop studies.<sup>4</sup> Theoretical analyses suggest that the differential susceptibility would depend in part on the mode of action (i.e., at what step in the cancer process(s) the chemical was acting) and that the use of the average daily exposure prorated over a lifetime may underestimate or overestimate the cancer risk when exposures are time-dependent (Goddard and Krewski, 1995; Murdoch et al., 1992). Evidence for old-age-dependent promotion of basophilic foci in rats by peroxisome proliferators appears to provide a concrete example consistent with these theoretical analyses (Cattley et al., 1991; Kraupp-Grasl et al., 1991). The stop studies performed by the National Toxicology Program began exposure at the standard post-weaning age, but stopped exposure after varying periods of months. Other groups of animals were exposed for a full two years; all animals were evaluated

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<sup>4</sup> Stop studies are studies in which exposure is halted after a predetermined period.



for tumors at the end of two years regardless of the duration of exposure (Halmes et al., 2000). Related data also are available from the stop studies with vinyl chloride (Drew et al., 1983). Analysis by Halmes et al. (2000) showed that, for six of the eleven chemicals and half the tumor sites, the assumption that the cancer risk would be equal when the product of concentration and time (i.e., C x T) was constant was incorrect, and usually underestimated risk, as more of the risk came from the beginning of the exposure rather than the end. This dependence of risk on both duration and intensity of exposure did not appear to be correlated with mutagenicity. It should be noted that these stop studies all involved exposures early in the life of the animal (as opposed to a limited number of cancer studies that looked at later periods of life; e.g., Drew et al., 1983), but the extent to which the differences in tumor outcome result from increased susceptibility in these early periods or the extended period for expression of the cancer cannot be evaluated. These stop studies also used doses as high as or higher than the highest dose used in the two-year exposure. This latter factor clearly had a significant effect for two chemicals, causing tumors at higher doses that were not observed at lower doses. These results suggest that pharmacokinetic or other dose-rate dependencies can make the effects of exposures at high doses different from those exposures at lower doses. While not directly informative about early childhood exposures, these studies provide a perspective on the common cancer risk assessment practice of averaging exposures over a lifetime, especially those that include earlier lifestages. Thus, alternative methods for estimating risks from short-term exposures during childhood should be considered.

Information on different lifestage susceptibilities to cancer risks for humans exists for ionizing radiation. The effects of chemical mutagens at different lifestages on cancer induction are derived from laboratory animal studies. While the induction of cancer by ionizing radiation and the induction of cancer by chemical mutagens are not identical processes, both involve direct damage to DNA as critical causal steps in the process. In both cases, the impacts of early exposure can be greater than the impacts of later exposures, probably due to some combination of early-lifestage susceptibility and the longer periods for observation of effects. As indicated in Tables 9 and 10, A-bomb survivors exhibited different lifestage dependencies at different tumor sites, though the total radiation-related incidence of tumors showed a general slow decline with age at exposure. However, as previously noted, there are apparent differences at some sites between the two tables. In addition to the sampling and modeling differences, the excess risk values in Table 9 are based on Japanese baselines while the coefficients in Table 10 reflect UNSCEAR's effort to transport the risks from the Japanese population to that of the United States. However, it is clear that the total radiation-related tumor incidence showed a general slow decline with age at exposure.

The studies in rodents of chemicals with mutagenic modes of action similarly support a

general decline in induced cancer risk with age at exposure and similarly show some differences for individual tumor sites. In general, the earliest two or three postnatal weeks in mice and rats appeared to be the most susceptible, though some degree of increased susceptibility through puberty in rats (beginning around 5–7 weeks) and mice (beginning around 4–6 weeks) for some types of tumors exists.

All the acute dosing studies that demonstrated carcinogenicity with animals of different ages used chemicals with a mutagenic mode of action (Tables 4 and 6). These studies provide the clearest demonstrations of periods of differential susceptibility because the exposure rate is constant at the different ages. The repeated dose studies also include several of the most informative studies for assessing perinatal carcinogenesis, notably those on vinyl chloride and DEN (Tables 2 and 4). The vinyl chloride studies by Maltoni and colleagues are part of a large series of studies on this compound that included exposures to different concentrations for varying durations, including some at early lifestages (Maltoni et al., 1984). The DEN study by Peto et al. (1984) used a unique chronic study design in which groups of rats were exposed to multiple drinking water concentrations starting at 3, 6, or 20 weeks of life. This design provides information on the susceptibility of early exposure periods within a nearly lifetime exposure.

Beyond the analysis described here, there are conceptual biological rationales that would suggest DNA-damaging agents would have greater impacts on early lifestages. Growth involves substantial levels of cell replication, even in organs that in adults are only very slowly replicating, thus increasing the likelihood that a cell will undergo division before the DNA damage caused by the mutagen has been repaired. Increased replication also can lead to a greater division of initiated cells, leading to a larger number of initiated cells per specified dose. These periods of cell replication can vary for different tissues. For example, DMBA appears to be more effective at initiating mammary tumors in 6–8 week old rats, which are undergoing development of that tissue, than during earlier or later periods (Meranze et al., 1969). While tumor promotion processes can be very dependent upon the duration of promotion, initiation processes can occur in relatively brief periods (e.g., the single-dose studies in animals or radiation exposure in humans). Most tumors take extended periods to develop, making damage that occurs earlier in life more likely to result in tumors prior to death than would exposures that occur later in life. While some of these observations may also pertain to other modes, all of them (with some differences among tumor sites) appear to be potentially relevant to a greater susceptibility to mutagenic modes of action during early-life stages (vs. later-life stages).

The information on lifestage susceptibility for chemicals inducing cancers through modes of action other than direct DNA interaction is more varied, showing an increase in tumor incidence during perinatal exposure versus exposures of mature animals (e.g., polybrominated

biphenyls induced liver tumors), no tumors from perinatal exposure (e.g., ethylene thiourea induced thyroid tumors), no effect of combined perinatal and adult exposure (e.g., DPH liver tumors in rats and female mice), and different tumors from perinatal exposure versus adult exposure (e.g., DES, ascorbate). These variations are likely a result of the modes of action of these chemicals and the pharmacokinetic differences in doses during different periods of life. No studies were evaluated that were directly comparable to the single-dose studies with mutagens, which clearly show significant differences in tumor responses after explicitly controlled doses at different lifestages.

Some evidence for an effect of early-lifestage exposures on tumor incidence was observed in studies with polybrominated biphenyls, amitrole, DDT, dieldrin, and diphenylhydantoin. These studies show increased incidence of tumors in mice from perinatal exposure, though only those for polybrominated biphenyls were statistically significant. (A nonstatistically significant increase also was observed in male rats with polybrominated biphenyls.) Combined perinatal and adult exposures generally gave statistically significant increases, though not necessarily for each sex and species (rat and mice) in the diphenylhydantoin and polybrominated biphenyl studies.

There are important demonstrations of chemicals acting through modes of action other than mutagenic to cause different tumor types with early-lifestage exposures compared with exposures for adults, e.g., tamoxifen and DES (Carthew et al., 2000; Carthew et al., 1996, Gass et al., 1964; Newbold et al., 1990, 1997, 1998). In addition, studies with *in utero* exposure to atrazine (Fenton and Davis, 2002), DES, and arsenic (Waalkes et al., 2003) indicate that early-life exposures to compounds can alter susceptibility of endocrine and reproductive organs. Three of these compounds (i.e., DES, genistein, and tamoxifen) bind to the estrogen receptor. Ongoing studies on ethinyl estradiol, nonylphenol, and genistein by the National Toxicology Program will add to this database for estrogens (Laurenzana et al., 2002; Newbold et al., 2001). These studies will evaluate cancer incidence in offspring exposed *in utero*, during lactation, and through adulthood via diet. A study with genistein found uterine tumor development to be dependent upon early-lifestage exposures (Newbold et al., 2001). Another recent study of estrogen found a shorter latency for mammary tumors in mice exposed at 8 and 12 weeks as compared to mice exposed at 4 or 18 weeks, indicating a susceptible period between 8 to 12 weeks of exposure (Yang, 2003). Thus, there is an actively growing database from which to consider issues of childhood exposure and cancer for compounds acting through the estrogen receptor or other mechanisms of endocrine disruption.

The ability to estimate with any accuracy the juvenile to adult cancer potency ratio depends very much on the experimental design used. The lifetime design has less ability to

distinguish increased susceptibility from early-life exposure than the other types of designs. Consider two different experimental designs. In the first, the “lifetime” design, a group of animals are exposed starting as juveniles, and exposure continues through adulthood. A second group are exposed only in adulthood, and the juvenile:adult ratio results from a comparison of tumor incidences in the two groups. In the second, the “repeated” design, one group of animals is exposed only during the juvenile period, and is then followed through adulthood to assess tumor incidence, and a second group of animals is exposed only through adulthood. The lifetime design turns out to be a particularly insensitive design for estimating the juvenile:adult ratio.

The following example demonstrates the magnitude of the problem: Suppose the risk per day of exposure of a chemical is ten fold greater in the juvenile period as in the adult period, and animals exposed through adulthood at a particular dose level have an extra risk of 60% for having at least one tumor, while 1% of control animals have tumors. The adult exposure period is 94 weeks, while the juvenile exposure period is 4 weeks. Thus, in the lifetime design, the group of animals exposed as juveniles will receive a total of 98 weeks of exposure, (4 in juvenile and 94 in adult), while those receiving the adult-only exposure receive 94 weeks of exposure. In the repeated design, animals exposed as juveniles receive only 4 weeks of exposure, while the adults receive 94 weeks, just as in the lifetime design. Each group starts with 50 animals. Under these assumptions, using equations (1) and (2) from Section 2.3, the expected number of animals with tumors in the three treatment groups (control, juvenile-exposed, adult-exposed groups) in the two designs is:

|                 | <u>Number of animals with tumors</u> |                            |                       |
|-----------------|--------------------------------------|----------------------------|-----------------------|
|                 | <u>Control</u>                       | <u>Early-life exposure</u> | <u>Adult exposure</u> |
| <b>Lifetime</b> | 1                                    | 36                         | 30                    |
| <b>Repeated</b> | 1                                    | 16                         | 30                    |

Notice that in the “lifetime” design, only six more juvenile-exposed animals have tumors than in the adult-exposed group, whereas in the “repeated” design, 16 juvenile-exposed animals have tumors. The data in the lifetime design are consistent with the hypothesis of no tumors being induced during the juvenile period: the ratios 36/50 and 30/50 are not statistically significantly different. In other words, the data from the lifetime design are statistically consistent with the hypothesis of *no risk at all* during the juvenile period, even though the real response is a 10 times greater risk from early-life exposure. The difference between the results from the two different study designs is due to the one-hit model: each additional week of a long exposure contributes less than the previous week to the total number of animals with tumors.

Note that, even if the one-hit model is not correct, chronic exposure probably results in a non-statistically significant increase for the lifetime exposure including juveniles as compared with only adult exposure.

The proper measure of relative potency of an exposure in the juvenile period relative to an exposure in the adult period is the ratio of doses in the two periods that give the same incidence of tumors. However, most of the data sets used in this report contained only one non-control dose, precluding the extensive dose-response modeling that would be required to estimate this ratio of doses. However, this document largely considered chemicals for which a mutagenic mode of action has been established and for which a linear, no-threshold dose-response function is assumed for the low-dose range being considered for risk assessment. In the case of the linear dose-response function, the analysis of the relative response from the same dose will produce the same value as ratio of doses that produces the same incidence of tumors.

For a one-hit dose-response equation, the probability of developing a tumor after the same dose and duration in the juvenile or adult period is

$$P_a = 1 - (1 - P_0)e^{-m_a x}$$

$$P_j = 1 - (1 - P_0)e^{-m_j x}$$

for dose  $x$ . Suppose we want to calculate the dose  $D_a$  or  $D_j$  that results in a given incidence of tumors after an adult or juvenile exposure. From equation 1,  $D_a$  and  $D_j$  equal:

$$D_a = \frac{-\ln\left(\frac{1 - P_c}{1 - P_0}\right)}{m_a}$$

$$D_j = \frac{-\ln\left(\frac{1 - P_c}{1 - P_0}\right)}{m_j}$$

Thus, the ratio  $D_a/D_j = m_j/m_a$ , the ratio calculated in this document.

In summary, this analysis supports the conclusion that there can be greater susceptibility for the development of tumors as a result of exposures to chemicals acting through a mutagenic mode of action, when the exposures occur in early lifestages as compared with later lifestages. Thus, this Supplemental Guidance recommends for chemicals with a mutagenic mode of action for carcinogenesis when chemical-specific data on early-life exposure are absent, a default

approach using estimates from chronic studies (i.e., cancer slope factors) with appropriate modifications to address the potential for differential risk of early-lifestage exposure. For chemicals acting through a non-mutagenic mode of action, e.g., hormonally mediated carcinogens, the available data suggest that other approaches may need to be developed for addressing cancer risk estimates from childhood exposures. This is a particular concern because the tumors arising from hormonally active chemicals appear to involve different sites when exposure is during early-life versus adulthood, an effect that has been observed relatively infrequently. Development of such approaches would require additional research to provide an expanded scientific basis for their support, including additional research and the possible development of new toxicity testing protocols that consider early lifestage dosing.

The current data do also not allow analysis of some issues of potential interest for risk assessment, e.g., potential increased risk of childhood cancer, from *in utero* or childhood exposures. Assessing the role of environmental exposures on childhood cancers is difficult, but additional research could include epidemiological studies or experimental studies with animals genetically designed to express cancers analogous to human childhood cancers. Rigorous quantification of exposure doses at different lifestages and in rodent pups in experimental studies would be useful for evaluating whether there is greater childhood susceptibility. Pharmacokinetic modeling could better define the internal doses to improve determination of the magnitude of increased susceptibility.

## 5. GUIDANCE FOR ASSESSING CANCER RISKS FROM EARLY-LIFE EXPOSURE

Consistent with the approach and recommendations of the U.S. EPA cancer risk assessment guidelines (U.S. EPA, 2004), any assessment of cancer susceptibility will begin with a critical analysis of the available information. Figure 3 shows the proposed steps in the process. The potential for increased susceptibility to cancer from early-life exposure, relative to comparable exposure later in life, generally warrants explicit consideration for each assessment.

When developing quantitative estimates of cancer risk, the Agency recommends integration of age-specific values for both exposure and toxicity/potency where such data are available and appropriate. Children, in general, are expected to have some exposures that differ from those of adults (either higher or lower), due to differences in size, physiology, and behavior. For example, children are generally assumed to eat more food and drink more water relative to their body weight than adults. Children's normal activities, such as putting their hands into their mouths or playing on the ground, can result in exposures to contaminants that adults do not encounter. Moreover, children and adults exposed to the same concentration of an agent in food, water, or air may receive different (higher or lower) internal doses due to differences, for example, in intake, metabolism, or absorption rates. Children are less likely than adults to be exposed to products typically used in industrial settings and often have more limited diets than adults. When assessing risks, if the data are available and relevant, it is important to include exposure that is measured or modeled for all lifestages, including exposures during childhood and during adulthood. EPA continues to develop better tools for assessing childhood exposure differences, such as the *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2002a), and models, such as Stochastic Human Exposure and Dose Simulation (SHEDS) and Consolidated Human Activity Database (CHAD) (McCurdy et al., 2000; Zartarian et al., 2000)

Mode-of-action studies can be a source of data on quantitative differences between children and adults (Figure 3, Box 1). If the available information is sufficient to establish the agent's mode of action for early-life and adult exposures, then the implications for early-life exposure of that mode of action are used to develop separate risk estimates for childhood exposure. Pertinent information can be obtained both from agent-specific studies and from other

studies that investigate the general properties of the particular mode of action. All data indicating quantitative differences between children and adults are considered in developing those portion(s) of the risk estimates for exposure estimates that include childhood exposure. Some examples include the potential for children to have a different internal dose of the active agent or a change in a key precursor event (see Section 2.4.3.4 of the *Guidelines for Cancer Risk Assessment*).

When the mode of action cannot be established (Figure 3, Box 2), the policy choice would be to use linear extrapolation to lower doses such that risk estimates are based on a lifetime average daily exposure without further adjustment. No general adjustment is recommended at this time. This policy choice is consistent with past U.S. EPA practice that has been favorably evaluated over the years. The result would be expected to produce plausible upper bound risk estimates, based on the use of linear extrapolation as a default in the absence of information on the likely shape of the dose-response curve.

When a mode of action other than mutagenicity is established, if it is nonlinear (Figure 3, Box 3) or linear (Figure 3, Box 4), no general adjustment is recommended at this time. Although the available studies (discussed previously) indicates that higher or lower cancer risks may result from early-life exposure, there is insufficient information or analyses currently available to determine a general adjustment at this time. As other modes of action become better understood, this information may include data on quantitative differences between children and adults. If such data are available, an analysis of the differences could be used to adjust risk estimates for childhood exposure. EPA expects to expand this Supplemental Guidance to specifically address modes of action other than mutagenicity when sufficient data are available and analyzed.

When the data indicate a mutagenic mode of action,<sup>5</sup> the available studies (discussed

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<sup>5</sup> Determination of chemicals that are operating by a mutagenic mode of action entails evaluation of test results for genetic endpoints, metabolic profiles, physicochemical properties, and structure-activity analyses in a weight-of-evidence approach (Waters et al., 1999). Established protocols are used to generate the data (Cimino, 2001; OECD, 1998; U.S. EPA, 2002b); however, it is recognized that newer methods and technologies such as those arising from genomics can provide useful data and insights to a mutagenic mode of action. Carcinogens acting through a mutagenic mode of action generally interact with DNA and can produce such effects as DNA adducts and/or breakage. Carcinogens with a mutagenic mode of action often produce positive effects in multiple test systems for different genetic endpoints, particularly gene mutations and structural chromosome aberrations, and in tests performed *in vivo*, which generally are supported by those performed *in vitro*. This mode of action is addressed in more detail in Section 2.3.5 of EPA's cancer guidelines (U.S. EPA, 2005).



above) indicate higher cancer risks resulting from a given exposure occurring early in life when compared with the same amount of exposure during adulthood. However, chemical-specific data relating to mode of action (e.g., toxicokinetic or toxicodynamic information) may suggest that even though a compound has a mutagenic mode of action, higher cancer risks may not result. Such data should be considered before applying the age-dependent adjustment factors.

If the available, chemical-specific information includes an epidemiologic study of the effects of childhood exposure or an animal bioassay involving early-life exposure (Figure 3, Box 5), then these studies are analyzed to develop risk estimates (i.e., cancer slope factors) that specifically address any potential for differential potency in early lifestages. An example is the IRIS assessment of vinyl chloride (U.S. EPA, 2000b; c).

In the absence of early-life studies on a specific chemical under consideration (Figure 3, Box 6), the extrapolation from the point of departure to lower doses employs linear extrapolation (see Section 3.3.1 of the U.S. EPA [2005] cancer guidelines). This choice is based on mode-of-action data indicating that mutagens can give rise to cancers with an apparently low-dose linear response. Adjustments to the resultant risk estimates are specified with regard to childhood exposures. This approach is adopted because risk estimates based on an average daily exposure prorated over a lifetime do not consider the potential for higher cancer risks from early-life exposure.

The adjustments described below reflect the potential for early-life exposure to make a greater contribution to cancers appearing later in life. The 10-fold adjustment represents an approximation of the weighted geometric mean tumor incidence ratio from juvenile or adult exposures in the repeated dosing studies (see Table 8). This adjustment is applied for the first 2 years of life, when toxicokinetic and toxicodynamic differences between children and adults are greatest (Ginsberg et al., 2002; Renwick, 1998). Toxicokinetic differences from adults, which are greatest at birth, resolve by approximately 6 months to 1 year, while higher growth rates extend for longer periods. The 3-fold adjustment represents an intermediate level of adjustment that is applied after 2 years of age through <16 years of age. This upper age limit represents middle adolescence following the period of rapid developmental changes in puberty and the conclusion of growth in body height in NHANES data (Hattis et al., 2005). Efforts to map the approximate start of mouse and rat bioassays (i.e., 60 days) to equivalent ages in humans ranged from 10.6 to 15.1 years (Hattis et al., 2005). Data are not available to calculate a specific dose-response adjustment factor for the 2 to <16-year age range, so EPA selected the 3-fold

adjustment because it reflects a midpoint, i.e., approximately half the difference between 1 and 10 on a logarithmic scale ( $10^{1/2}$ ), between the 10-fold adjustment for the first two years of life and no adjustment (i.e., 1-fold) for adult exposure. EPA also recognizes that exposures occurring near the end of life may have little effect on lifetime cancer risk, but lacks adequate data at present to provide an adjustment for this "wasted dose" effect. Similarly, since most of the studies involved only one latency period, the potential effect of early-life exposure on latency for the observed tumors could not be evaluated. The lack of data on effect on latency also limited the types of analyses that could be performed, e.g., more complex dose-response functions, such as multi-stage or clonal expansion models, could not be evaluated. Thus, the potential effects of early-life exposures on latency were not evaluated. Finally, as the adjustment factors are derived from a weighted geometric mean of the data evaluated, these adjustment will both over-estimate and under-estimate the potential potency for early-life exposure for chemicals with a mutagenic mode of action for carcinogenesis. An examination of the data in the tables demonstrates that some of the ratios were less than one, while others exceeded 10. For this reason, the Supplemental Guidance emphasizes that chemical-specific data should be used in preference to these default adjustment factors whenever such data are available.

The following adjustments represent a practical approach that reflects the results of the preceding analysis, which concluded that cancer risks generally are higher from early-life exposure than from similar exposure durations later in life:

- For exposures before 2 years of age (i.e., spanning a 2-year time interval from the first day of birth up until a child's second birthday), a 10-fold adjustment.
- For exposures between 2 and <16 years of age (i.e., spanning a 14-year time interval from a child's second birthday up until their sixteenth birthday), a 3-fold adjustment.
- For exposures after turning 16 years of age, no adjustment.

Clearly other age groups, such as an age group experiencing pubertal changes in physiology, or approximately ages 9 - 15, may experience changes in biological processes that could lead to modifications in the susceptibility to the effects of some carcinogens, depending on the mode of action. This Supplemental Guidance focuses on carcinogens with a mutagenic mode

of action. For any mode of action, the Agency is interested in identifying lifestages that may be particularly sensitive or refractory for carcinogenesis, and believes that the mode of action framework as described by EPA's cancer guidelines (U.S. EPA, 2005), is an appropriate mechanism for elucidating these lifestages. In general, the Agency's analyses of lifestages that may be susceptible will depend on three factors: (1) establishing the mode of action for carcinogenesis; (2) using knowledge about the biological and toxicological key events in that mode of action that are likely to be affected by lifestages; and (3) the availability, or development, of data that allow analysis of the effects of chemicals acting by that mode of action during the relevant ages. For each mode of action evaluated, therefore, the various age groupings determined to be at a differential risk, which may differ significantly from those proposed for the mutagenic mode of action, are expected to be evaluated independently of other modes of action. When data, including well established mode of action data, are available that allow specific evaluation of lifestage differences in toxicokinetics or toxicodynamics that would lead to lesser or greater susceptibility from early-life exposures to carcinogens, then those data should be used, as generally discussed in EPA's cancer guidelines (U.S. EPA, 2005), in preference to the default procedures described in this Supplemental Guidance.

The 10-fold and 3-fold adjustments in slope factor are to be combined with age-specific exposure estimates when estimating cancer risks from early life exposure to carcinogens that act through a mutagenic mode of action. It is important to emphasize that these adjustments are combined with corresponding age-specific estimates of exposure to assess cancer risk. For example, for a 70-year lifetime, where there are data showing negligible exposure to children, the estimated cancer risk from childhood exposure would be also negligible and the lifetime cancer risk would be reduced to that resulting from the relevant number of years of adult exposure (in the absence of specific information, 55 years). Where there are data (measured or modeled) for childhood exposures, the age-group specific exposure values are used along with the corresponding adjustments to the slope factor. Where there are no relevant data or models for childhood exposures and only lifetime average exposure data are available, the lifetime exposure data are used with the adjustments to the slope factor for each age segment.

It is recognized that, when the exposure is fairly uniform over a lifetime, the effect of these adjustments on estimated lifetime cancer risk are small relative to the overall uncertainty of

such estimates. These adjustments can be applied when estimating the cancer risk resulting from childhood exposure. These adjustments are applied when developing risk estimates from conventional animal bioassays or epidemiologic studies of effects of adult exposure. Some examples follow in the next section.

The Agency has also carefully considered both the advantages and disadvantages to extending the default potency adjustment factors to carcinogenic chemicals for which the mode of action remains unknown. It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach (without further adjustment) provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life susceptibility. At the present time, therefore, EPA is recommending these age-dependent adjustment factors only for carcinogens acting through a mutagenic mode of action based on a combination of analysis of available data and the above-mentioned science policy position. In general, the Agency prefers to rely on analyses of data, rather than general defaults. When data are available for a susceptible lifestage, they should be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis. In this analysis, the data for non-mutagenic carcinogens, when the mode of action is unknown, were judged to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied.

## 6 COMBINING LIFESTAGE DIFFERENCES IN EXPOSURE AND DOSE-RESPONSE WHEN ASSESSING CARCINOGEN RISK - SOME EXAMPLES FOR CARCINOGENS THAT ACT THROUGH A MUTAGENIC MODE OF ACTION

It is important for the risk assessor to consider lifestage differences in both exposure and dose-response when assessing cancer risk resulting from early-life exposures. As discussed in Section 5, age dependent adjustments factors (ADAFs) in dose response (i.e., slope factors) are combined with age specific exposure estimates when assessing cancer risks. This is a departure from the way cancer risks have historically been based upon the premise that risk is proportional to the daily average of lifetime dose. This Supplemental Guidance recommends an integrative approach that can be used to assess total lifetime risk resulting from lifetime or less-than-lifetime exposure during a specific portion of a lifetime.

The following examples can help demonstrate how to apply this guidance by integrating potential lifestage differences in exposure and/or dose-response (potency), and also demonstrate what the resulting impacts are on calculated risks. These hypothetical examples consider risks from both lifetime, as well as less-than-lifetime oral exposures. Risks associated with inhalation exposure to carcinogens that act via a mutagenic mode of action are calculated in similar fashion by applying the appropriate ADAF(s) along with the corresponding inhalation unit risk estimate, using pertinent estimates of exposure concentration.

Note again, ADAFs are only to be used for agents with a mutagenic mode of action for carcinogenesis when chemical-specific data are absent. For all modes of action, when chemical-specific data are available for early-life exposure, those data should be used.

### 6.1 CALCULATING LIFETIME RISKS ASSOCIATED WITH LIFETIME EXPOSURES

**Example 1:** Consider a scenario of exposure to a carcinogen with a **nonmutagenic** mode of action. Suppose the oral cancer slope factor derived from a typical animal study (i.e., where dosing begins after puberty) is estimated to be 2 per mg/kg-d, and the exposure rate remains constant throughout life at 0.0001 mg/kg-d (this is equivalent to saying the daily average of lifetime dose rate is equal to 0.0001 mg/kg-d). The risk from lifetime exposure is calculated by multiplying the slope factor and the exposure rate:

$$\text{Risk} = (2 \text{ per mg/kg-d}) \times (0.0001 \text{ mg/kg-d})$$

$$= 2 \times 10^{-4}$$

**Example 2:** Now consider the same exposure scenario for a carcinogen with a **mutagenic** mode of action for which the oral cancer slope factor, derived from a typical animal study where dosing begins after puberty, is also estimated to be 2 per mg/kg-d. In this case, ADAFs are used, as follows.

a. To calculate lifetime risk for a population with average life expectancy of 70 years, sum the risk associated with each of the three relevant time periods:

- Risk during the first 2 years of life (where the ADAF = 10);
- Risk for ages 2 through < 16 (ADAF = 3); and
- Risk for ages 16 until 70 years (ADAF = 1).

Thus, risk equals the sum of:

- Risk for birth through < 2 yr = (2 per mg/kg-d) x 10 (ADAF) x (0.0001 mg/kg-d)  

$$\times 2\text{yr}/70\text{yr}$$

$$= 0.6 \times 10^{-4}$$
- Risk for ages 2 through < 16 = (2 per mg/kg-d) x 3 (ADAF) x (0.0001 mg/kg-d)  

$$\times (13\text{yr}/70\text{yr})$$

$$= 1.1 \times 10^{-4}$$
- Risk for ages 16 until 70 = (2 per mg/kg-d) x 1 (ADAF) x (0.0001 mg/kg-d)  

$$\times (55\text{yr}/70\text{yr})$$

$$= 1.6 \times 10^{-4}$$

$$\text{Risk} = 0.6 \times 10^{-4} + 1.1 \times 10^{-4} + 1.6 \times 10^{-4}$$

$$= 3.3 \times 10^{-4}$$

b. If exposure varies with age, then such differences are also included. Now suppose the same example as immediately above, except that exposure for ages 1 through <12 was twice as high as exposure for all other ages. In this case, sum the risk associated with each of the five relevant time periods in which exposure rates and/or potencies (slope

factors) vary:

Risk equals the sum of:

- Risk for birth through < 1 yr (1yr) = (2 per mg/kg-d) x 10 (ADAF) x 0.0001 mg/kg-d  
x 1yr/70yr  
=  $0.3 \times 10^{-4}$
- Risk for ages 1 through < 2 (1yr) = (2 per mg/kg-d) x 10 (ADAF) x 0.0002 mg/kg-d  
x 1yr/70 yr  
=  $0.6 \times 10^{-4}$
- Risk for ages 2 through < 12 (10yr) = (2 per mg/kg-d) x 3 (ADAF) x 0.0002 mg/kg-d  
x 10yr/70yr  
=  $1.7 \times 10^{-4}$
- Risk for ages 12 through < 16 (4yr) = (2 per mg/kg-d) x 3 (ADAF) x 0.0001 mg/kg-d  
x 4yr/70yr  
=  $0.3 \times 10^{-4}$
- Risk for ages 16 until 70 years (55yr) = (2 per mg/kg-d) x 1 (ADAF) x 0.0001 mg/kg-d  
x 55yr/70yr  
=  $1.6 \times 10^{-4}$

$$\begin{aligned} \text{Risk} &= 0.3 \times 10^{-4} + 0.6 \times 10^{-4} + 1.7 \times 10^{-4} + 0.3 \times 10^{-4} + 1.6 \times 10^{-4} \\ &= 4.5 \times 10^{-4} \end{aligned}$$

## 6.2 CALCULATING LIFETIME RISKS ASSOCIATED WITH LESS THAN LIFETIME EXPOSURES

If exposure only occurs for a limited number of years (for example, consider a family that lives near a source of exposure for a five-year period of time before moving away), it is critical to combine lifestage differences in exposure and dose-response for the relevant time interval. The examples presented below demonstrate how adjusting potency and/or exposure can affect the assessment of cancer risk.

**Example 3:** If exposure to a carcinogen with a mutagenic mode of action with an oral slope factor equal to 2 per mg/kg-d occurs during adulthood for only 5 years, the daily average of lifetime dose is time weighted to apportion risk for the number of years of exposure by a factor of 5/70:

$$\begin{aligned} \text{Risk} &= (2 \text{ per mg/kg-d}) \times (0.0001 \text{ mg/kg-d}) \times (5\text{yr}/70\text{yr}) \\ &= 1.4 \times 10^{-5} \end{aligned}$$

**Example 4:** If this 5-year exposure occurs during childhood, the risk calculations are adjusted to consider the potential for higher potency from early-life exposure. Assessors should remember that the age dependent adjustment factors for carcinogens with a mutagenic mode of action are applied only to exposure periods occurring up to age 16.

- a. For a child exposed between ages 5 and 10, only a 3-fold ADAF is applied because the exposure occurs entirely between ages 2 and <16 years:

$$\begin{aligned} \text{Risk} &= 3 \text{ (ADAF)} \times (2 \text{ per mg/kg-d}) \times (0.0001 \text{ mg/kg-d}) \times (5 \text{ yr}/70 \text{ yr}) \\ &= 4.3 \times 10^{-5} \end{aligned}$$

- b. For an exposure between ages 13 and <18, a 3-fold ADAF is applied only to the 3-year portion occurring before age 16:

Risk equals the sum of:

- Risk for ages 13 through < 16 (3yr) = 3 (ADAF) x (2 per mg/kg-d) x (0.0001 mg/kg-d) x (3 yr/70 yr) = 2.6 x 10<sup>-5</sup>
- Risk for ages 16 through < 18 (2yr) = 1 (ADAF) x (2 per mg/kg-d) x (0.0001 mg/kg-d) x (2 yr/70 yr) = 0.6 x 10<sup>-5</sup>

$$\text{Risk} = 2.6 \times 10^{-5} + 0.6 \times 10^{-5}$$





- Risk for birth through < 2 (2yr) = 10 (ADAF) x (2 per mg/kg-d) x (0.0002 mg/kg-d)  
x (2 yr/70 yr)  
= 11.4 x 10<sup>-5</sup>
- Risk for ages 2 through < 5 (3yr) = 3 (ADAF) x (2 per mg/kg-d) x (0.0001 mg/kg-d)  
x (3 yr/70 yr)  
= 2.6 x 10<sup>-5</sup>

$$\begin{aligned} \text{Risk} &= 11.4 \times 10^{-5} + 2.6 \times 10^{-5} \\ &= 1.4 \times 10^{-4} \end{aligned}$$

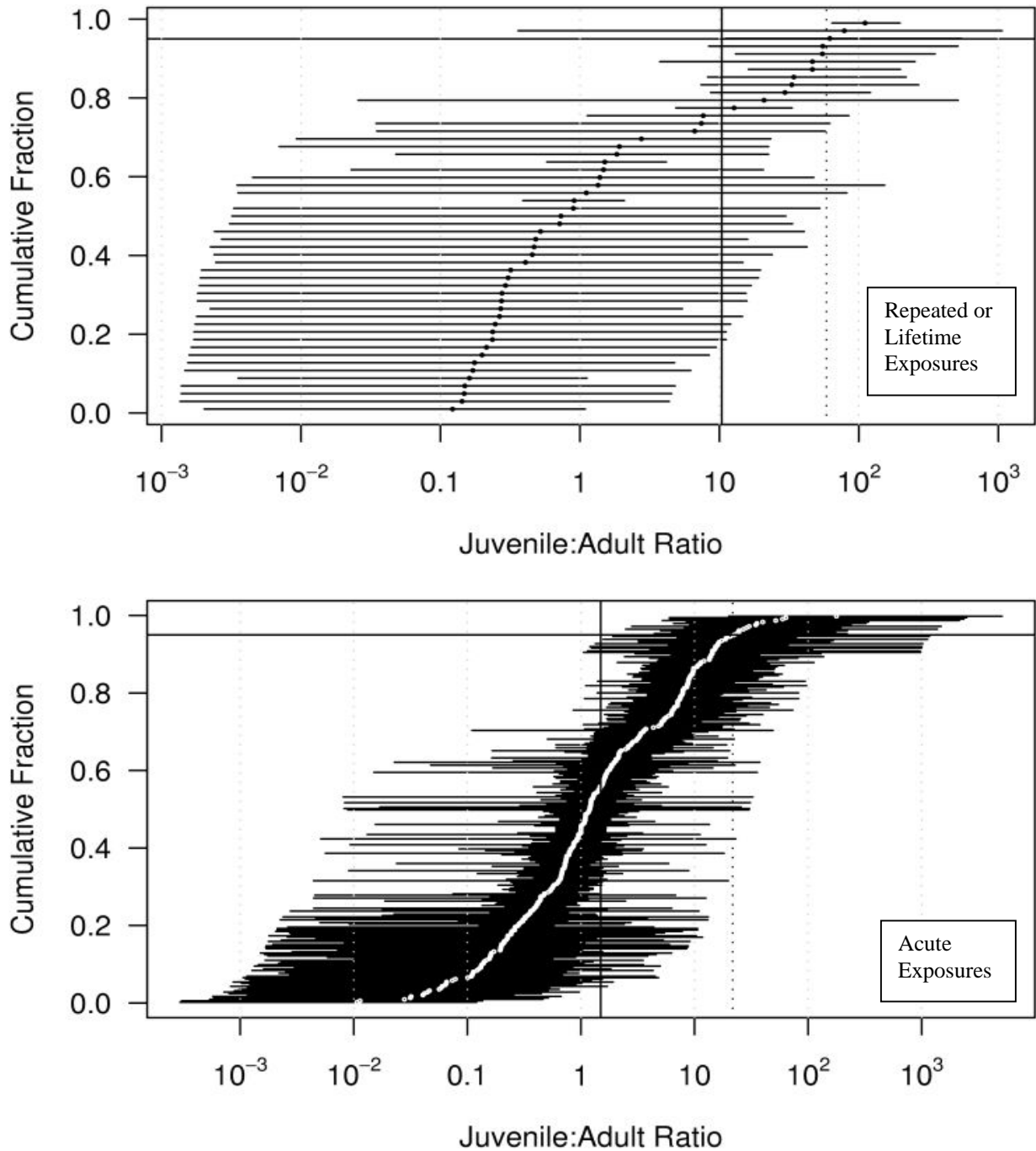
b. For comparison, a similar risk calculation for 5 years of exposure later in life (after age 16) in which the first 2 years of exposure are double that of the next 3 years are carried out without any adjustment for potency:

Risk equals the sum of:

- Risk for first 2 years of adult exposure = 1 (ADAF) x (2 per mg/kg-d)  
x (0.0002 mg/kg-d) x (2yr/70yr)  
= 1.1 x 10<sup>-5</sup>
- Risk for final 3 years of adult exposure = 1 (ADAF) x (2 per mg/kg-d)  
x (0.0001 mg/kg-d) x (3yr/70yr)  
= 0.9 x 10<sup>-5</sup>

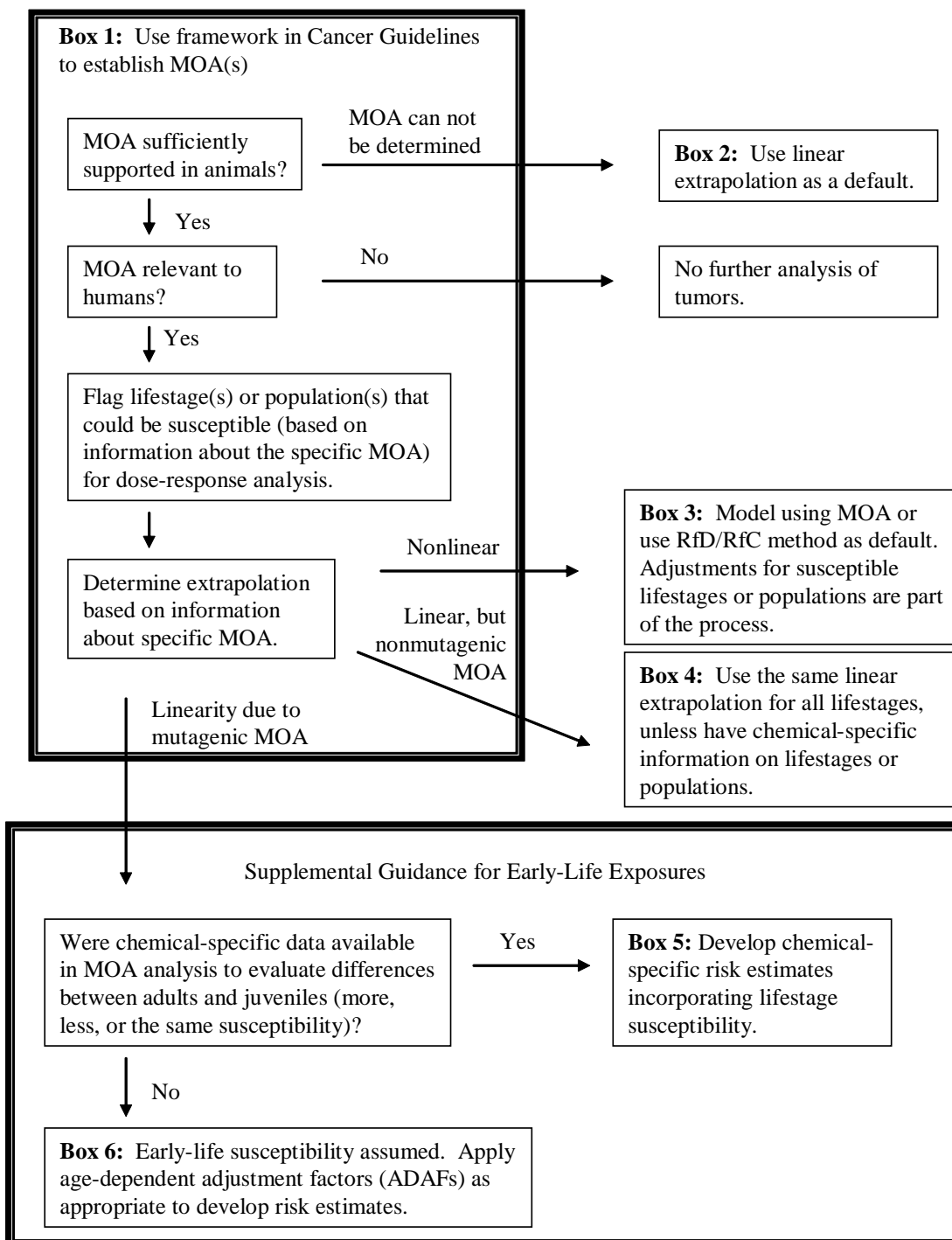
$$\begin{aligned} \text{Risk} &= 1.1 \times 10^{-5} + 0.9 \times 10^{-5} \\ &= 2 \times 10^{-5} \end{aligned}$$





**Figure 2: Posterior, unweighted geometric means and 95% confidence intervals for the ratios of juvenile to adult cancer potency for carcinogens acting primarily through a mutagenic mode of action.** The top panel is for repeated and lifetime exposure studies (geometric mean in black), the bottom panel is for acute exposure studies mutagens (geometric mean in white). The horizontal lines to the left and right of each geometric mean correspond to 95% confidence limits. The vertical dark line represents the inverse-variance weighted geometric mean of the posterior geometric means. The horizontal dark line represents the 95th percentile of the unweighted distribution, with the vertical, dotted line establishing its value.

**Figure 3. Flow chart for early-life risk assessment using mode of action framework**



**Table 1a. Chemicals that have been found to have carcinogenic effects from prenatal or postnatal exposure in animals as identified in different review articles**

| Chemical name   | Review articles including prenatal and postnatal exposure |                       |                        |                                  |                  | Chemicals selected for quantitative analysis |
|---|---|-----------------------|------------------------|----------------------------------|------------------|--|
|   | Fujii (1991)  | McClain et al. (2001) | Anderson et al. (2000) | Della Porta and Terracini (1969) | Other literature |  |
| 4-Acetylamino-biphenyl (AAB)                                      | X   |                       |                        |                                  |                  |  |
| 4-Aminoazobenzene (AB)  | X   |                       |                        |                                  |                  |  |
| 3-Amino-1,4,-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)            | X   |                       |                        |                                  |                  |  |
| 2-Aminodipyridol[1,2-a:3',2'-d]imidazole (Glu-P-2)                | X   |                       |                        |                                  |                  |  |
| 2-Amino-6-methyldipyridol[1,2-a:3',2'-d]imidazole (Glu-P-1)       | X   |                       |                        |                                  |                  |  |
| 3-Amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2)                 | X   |                       |                        |                                  |                  |  |
| Amitrole  |   |                       |                        |                                  |                  | X  |
| Arsenic   |   |                       |                        |                                  | X                |  |
| 5-Azacytidine   |   |                       | X                      |                                  |                  |  |
| 3'-Azido-3'-deoxythymidine (AZT)                                  |   |                       | X                      |                                  |                  |  |
| Azoxymethane  |   |                       | X                      |                                  |                  |  |
| Benz[ <i>a</i> ]anthracene  |   |                       |                        | X                                |                  |  |
| Benzidine   |   |                       | X                      |                                  |                  | X  |
| Benzo[ <i>a</i> ]pyrene (BaP)                                     | X   |                       |                        | X                                |                  | X  |
| 1-(4'Bromophenylazo)-1-phenyl-1-hydroperoxymethane (BPH)          | X   |                       |                        |                                  |                  |  |
| N-Butyl-N-(3-carboxypropyl)nitrosamine (BCPN)                     | X   |                       |                        |                                  |                  |  |
| N-Butyl-N-(3 hydroxybutyl)nitrosamine (BBN)                       | X   |                       |                        |                                  |                  |  |
| Butylnitrosourea (BNU)  | X   |                       |                        |                                  |                  |  |
| Cyclophosphamide  |   | X                     |                        |                                  |                  |  |
| Dibenz[ <i>a,h</i> ]anthracene (DBA)                              |   |                       |                        | X                                |                  | X  |
| Dibutylnitrosamine (DBN)  | X   |                       |                        |                                  |                  |  |
| Dichlorodiphenyltrichloroethane (DDT)                             |   |                       |                        |                                  |                  | X  |
| Dieldrin  |   |                       |                        |                                  |                  | X  |
| 2-Diethylaminoethyl-2,2-dephenylvalerate hydrochloride (SKF 525A) | X   |                       |                        |                                  |                  |  |

**Table 1a. Chemicals that have been found to have carcinogenic effects from prenatal or postnatal exposure in animals as identified in different review articles (continued)**

| Chemical name   | Review articles including prenatal and postnatal exposure |                       |                        |                                  |                  | Chemicals selected for quantitative analysis |
|---|---|-----------------------|------------------------|----------------------------------|------------------|--|
|   | Fujii (1991)  | McClain et al. (2001) | Anderson et al. (2000) | Della Porta and Terracini (1969) | Other literature |  |
| Diethylnitrosamine (DEN)                                  | X   |                       | X                      |                                  |                  | X  |
| Diethylstilbesterol (DES)                                 |   |                       | X                      |                                  |                  |  |
| 4-Dimethylaminoazobenzene                                 |   |                       |                        | X                                |                  |  |
| 1,2-Dimethylhydrazine (DMH)                               | X   |                       |                        |                                  |                  |  |
| 7,12-Dimethylbenz[ <i>a</i> ]anthracene (DMBA)            | X   |                       | X                      | X                                |                  | X  |
| Dimethylnitrosamine (DMN)                                 | X   |                       | X                      | X                                |                  | X  |
| 5',5'-Diphenylhydantoin (DPH)                             |   |                       |                        |                                  |                  | X  |
| Estradiol   | X   | X                     |                        |                                  |                  |  |
| 6-Ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (Santoquin) | X   |                       |                        |                                  |                  |  |
| Ethylene thiourea (ETU)                                   |   |                       |                        |                                  |                  | X  |
| Ethyl methane sulphonate                                  |   |                       |                        | X                                |                  |  |
| Ethylnitrosobiuret  |   |                       | X                      |                                  |                  |  |
| Ethylnitrosourea (ENU)                                    |   |                       | X                      |                                  |                  | X  |
| N-2-Fluorenylacetamide (FAA)                              | X   |                       |                        | X                                |                  |  |
| Genistein   |   |                       |                        |                                  | X                |  |
| 3-Hydroxyl-4-acetylamino-biphenyl (N-OH-AAB)              | X   |                       |                        |                                  |                  |  |
| N-2-Hydroxy-N-2-fluorenylacetamide (N-OH-FAA)             | X   |                       |                        |                                  |                  |  |
| 2-Hydroxypropyl-propylnitrosamine                         |   |                       | X                      |                                  |                  |  |
| 9-Methylantracene   |   |                       |                        | X                                |                  |  |
| Methyl-2-benzylhydrazine                                  |   |                       | X                      |                                  |                  |  |
| Methylcholanthrene  |   |                       | X                      | X                                |                  |  |
| 3-Methyl-4-dimethylaminoabenzene (3'ME-DAB)               | X   |                       |                        |                                  |                  |  |
| 4-(Methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)     |   |                       | X                      |                                  |                  |  |
| Methylnitrosourea (NMU)                                   |   |                       | X                      |                                  |                  |  |
| Methylnitrosourethane                                     |   |                       | X                      |                                  |                  |  |
| 1-Methyl-3-nitro-1-nitrosoguanidine (MNNG)                | X   |                       |                        |                                  |                  |  |

**Table 1a. Chemicals that have been found to have carcinogenic effects from prenatal or postnatal exposure in animals as identified in different review articles (continued)**

| Chemical name   | Review articles including prenatal and postnatal exposure |                       |                        |                                  |                  | Chemicals selected for quantitative analysis |
|---|---|-----------------------|------------------------|----------------------------------|------------------|--|
|   | Fujii (1991)  | McClain et al. (2001) | Anderson et al. (2000) | Della Porta and Terracini (1969) | Other literature |  |
| 2-Naphthylamine   |   |                       |                        | X                                |                  |  |
| 2-Naphthylhydroxyamine  |   |                       |                        | X                                |                  |  |
| Nickel acetate  |   |                       | X                      |                                  |                  |  |
| N-Nitrosobuylamine  |   |                       | X                      |                                  |                  |  |
| 4-Nitroquinoline-1-oxide  |   |                       | X                      | X                                |                  |  |
| N-Nitrosomethyl(2-oxopropyl)amine   |   |                       | X                      |                                  |                  |  |
| 2-Oxopropyl-propylnitrosamine   |   |                       | X                      |                                  |                  |  |
| 1-Phenyl-3,3',-dimethylhydrazine  |   |                       | X                      |                                  |                  |  |
| 1-Phenyl-3,3,-dimethyltriazene  |   |                       | X                      |                                  |                  |  |
| Polybrominated biphenyls (PBBs)   |   |                       |                        |                                  |                  | X  |
| Safrole (3,4-methylenedioxyallyl benzene)                                       | X   |                       | X                      |                                  |                  | X  |
| Soot  | X   |                       |                        |                                  |                  |  |
| Sterigmatocystin  | X   |                       |                        |                                  |                  |  |
| Tamoxifen   |   |                       |                        |                                  | X                |  |
| 1,3,5-Trimethyl-2,4,6-tris[3,5-di-tert-butyl-4-hydroxybenzyl]benzene (Ionox 33) | X   |                       |                        |                                  |                  |  |
| Urethane (ethyl carbamate)  |   |                       | X                      | X                                |                  | X  |
| Vinyl chloride  |   |                       |                        |                                  |                  | X  |



**Table 1b. List of chemicals considered in this analysis. (These are chemicals for which both early-life and adult exposure are reported in the same animal experiment.)**

| Chemical                                  | References                       | Study type                          | Mutagenic mode of action |
|---|----------------------------------|-------------------------------------|--------------------------|
| Amitrole                                  | Vesselinovitch (1983)            | Repeat dosing                       |                          |
| Benzidine                                 | Vesselinovitch et al. (1975b)    | Repeat dosing                       | X                        |
| Benzo[ <i>a</i> ]pyrene (BaP)             | Vesselinovitch et al. (1975a)    | Acute exposure                      | X                        |
| Dibenzanthracene (DBA)                    | Law (1940)                       | Acute exposure                      | X                        |
| Dichlorodiphenyltrichloroethane (DDT)     | Vesselinovitch et al. (1979)     | Repeat dosing<br>Lifetime exposure  |                          |
| Dieldrin                                  | Vesselinovitch et al. (1979)     | Repeat dosing<br>Lifetime exposure  |                          |
| Diethylnitrosamine (DEN)                  | Peto et al. (1984)               | Lifetime exposure                   | X                        |
|   | Vesselinovitch et al. (1984)     | Acute exposure                      |                          |
| Dimethylbenz[ <i>a</i> ]anthracene (DMBA) | Meranze et al. (1969)            | Acute exposure                      | X                        |
|   | Pietra et al. (1961)             | Acute exposure                      |                          |
|   | Walters (1966)                   | Acute exposure                      |                          |
| Dimethylnitrosamine (DMN)                 | Hard (1979)                      | Acute exposure                      | X                        |
| Diphenylhydantoin, 5,5- (DPH)             | Chhabra et al. (1993b)           | Repeat dosing<br>Lifetime exposure  |                          |
| Ethylnitrosourea (ENU)                    | Naito et al. (1981)              | Acute exposure                      | X                        |
|   | Vesselinovitch et al. (1974)     | Acute exposure                      |                          |
|   | Vesselinovitch (1983)            | Acute exposure                      |                          |
| Ethylene thiourea (ETU)                   | Chhabra et al. (1992)            | Repeat dosing<br>Lifetime exposure  |                          |
| 3-Methylcholanthrene (3-MU) <sup>a</sup>  | Klein (1959)                     | Repeat dosing                       | X                        |
| Methylnitrosourea (NMU)                   | Terracini and Testa (1970)       | Acute exposure                      | X                        |
|   | Terracini et al. (1976)          | Acute exposure                      |                          |
| Polybrominated biphenyls (PBBs)           | Chhabra et al. (1993a)           | Repeat dosing<br>Lifetime exposure  |                          |
| Safrole                                   | Vesselinovitch et al. (1979)     | Repeat dosing<br>Lifetime exposure  | X                        |
| Urethane                                  | Chieco-Bianchi et al. (1963)     | Acute exposure                      | X                        |
|   | Choudari Kommineni et al. (1970) | Acute exposure                      |                          |
|   | De Benedictis et al. (1962)      | Acute exposure                      |                          |
|   | Fiore-Donati et al. (1962)       | Acute exposure                      |                          |
|   | Klein (1966)                     | Acute exposure<br>Lifetime exposure |                          |
|   | Liebelt et al. (1964)            | Acute exposure                      |                          |
|   | Rogers (1951)                    | Acute exposure                      |                          |
| Vinyl chloride (VC)                       | Maltoni et al. (1984)            | Repeat dosing                       | X                        |

<sup>a</sup> Formerly known as 20-methylcholanthrene.

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures**

| Chemical                                | Species (strain)           | Target site | Age when first dosed | Dose route, # doses                       | Dose                     | Duration of exposure            | Age at death | Tumors <sup>a</sup>       |                          | Comments  | Reference  |
|---|----------------------------|-------------|----------------------|---|--------------------------|---------------------------------|--------------|---------------------------|--------------------------|---|--|
|   |                            |             |                      |   |                          |                                 |              | M                         | F                        |   |  |
| Amitrole                                | Mice (B6C3F <sub>1</sub> ) | liver       | Control              | None                                      | Control: 0 ppm           | N/A                             | 90 weeks     | 1/98 (1%)                 | 0/96 (0%)                | Incidences are mice with adenomas or carcinomas.                                  | Vesselinovitch (1983)  |
|   |                            |             | Gestation day 12     | Diet, to mothers                          | 500 ppm                  | Gestation day 12 to delivery    |              | 6/74 (8%) <sup>b</sup>    | 0/83 (0%) <sup>b</sup>   |   |  |
|   |                            |             | Newborn              | Diet, to mothers                          | 500 ppm                  | Birth until weaning             |              | 10/45 (22%) <sup>b</sup>  | 0/55 (0%) <sup>b</sup>   |   |  |
|   |                            |             | At weaning           | Diet, to offspring                        | 500 ppm                  | From weaning to 90 weeks        |              | 20/55 (36%) <sup>b</sup>  | 9/49 (18%) <sup>b</sup>  |   |  |
| Benzidine                               | Mice (B6C3F <sub>1</sub> ) | liver       | Control              | None                                      | Control: 0 ppm           | N/A                             | 90 weeks     | 1/98 (1%)                 | 0/100 (0%)               | Higher sensitivity in males during perinatal period, in females during adulthood. | Vesselinovitch et al. (1975b)<br>Vesselinovitch et al. (1979a) |
|   |                            |             | Gestation day 12     | Diet, to mothers                          | 150 ppm                  | Gestation day 12 to delivery    |              | 17/55 (31%) <sup>c</sup>  | 2/62 (3%) <sup>d</sup>   |   |  |
|   |                            |             | Newborn              | Diet, to mothers                          | 150 ppm                  | Birth until weaning             |              | 62/65 (95%) <sup>c</sup>  | 2/43 (5%) <sup>d</sup>   |   |  |
|   |                            |             | At weaning           | Diet, to offspring                        | 150 ppm                  | From weaning to 90 weeks        |              | 22/50 (44%) <sup>c</sup>  | 47/50 (94%) <sup>c</sup> | Incidences are mice with adenomas or carcinomas.                                  |  |
|   |                            |             | Gestation day 12     | Diet, to mothers                          | 150 ppm                  | Gestation day 12 until weaning  |              | 49/49 (100%) <sup>c</sup> | 12/48 (25%) <sup>c</sup> |   |  |
|   |                            |             | Gestation day 12     | Diet, to mothers                          | 150 ppm                  | Gestation day 12 until 90 weeks |              | 50/50 (100%) <sup>c</sup> | 47/50 (94%) <sup>c</sup> |   |  |
| DDT<br>Dichlorodiphenyl-trichloroethane | Mice (B6C3F <sub>1</sub> ) | liver       | Control              | None                                      | Control: 0 ppm           | N/A                             | 90 weeks     | 1/50 (2%)                 | —                        |   | Vesselinovitch et al. (1979b)                                  |
|   |                            |             | Week 1               | Gavage, daily                             | 230 µg                   | Weeks 1–4                       |              | 5/49 (10%) <sup>d</sup>   | —                        |   |  |
|   |                            |             | Week 5               | Diet, daily                               | 150 ppm                  | Weeks 5–90                      |              | 8/49 (16%) <sup>d</sup>   | —                        |   |  |
|   |                            |             | Week 1               | Gavage, daily until 4 weeks, then in diet | 230 µg<br>150 ppm (diet) | Weeks 1–90                      |              | 10/50 (20%) <sup>c</sup>  | —                        |   |  |

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical                               | Species (strain)           | Target site | Age when first dosed | Dose route, # doses                       | Dose                                     | Duration of exposure     | Age at death     | Tumors <sup>a</sup>         |   | Comments  | Reference                     |
|--|----------------------------|-------------|----------------------|---|--|--------------------------|------------------|-----------------------------|---|---|-------------------------------|
|  |                            |             |                      |   |  |                          |                  | M                           | F |   |                               |
| Dieldrin                               | Mice (B6C3F <sub>1</sub> ) | liver       | Control              | None                                      | Control: 0 ppm                           | N/A                      | 90 weeks         | 1/58 (2%)                   | — |   | Vesselinovitch et al. (1979b) |
|  |                            |             | Week 1               | Gavage, daily                             | 12.5 µg                                  | Weeks 1–4                |                  | 3/46 (7%) <sup>b</sup>      | — |   |                               |
|  |                            |             | Week 5               | Diet, daily                               | 10 ppm                                   | Weeks 5–90               |                  | 7/60 (12%) <sup>b</sup>     | — |   |                               |
|  |                            |             | Week 1               | Gavage, daily until 4 weeks, then in diet | 12.5 µg<br>10 ppm                        | Weeks 1–90               |                  | 21/70 (30%) <sup>a</sup>    | — |   |                               |
| DEN <sup>c</sup><br>Diethylnitrosamine | Rats (Colworth)            | liver       | Control              |   | Control                                  | N/A                      |                  | 29/384 (8%)                 |   | Highest tumor rate when dosed at earlier ages.<br><br>Incidents are rats with adenomas or carcinomas. | Peto et al. (1984)            |
|  |                            |             | Week 3               | Diet (in drinking water), daily           | 16 different doses combined <sup>f</sup> | From week 3 until death  | 6 months–3 years | 105/180 (58%) <sup>b</sup>  |   |   |                               |
|  |                            |             | Week 6               |   |  | From week 6 until death  |                  | 714/1440 (50%) <sup>b</sup> |   |   |                               |
|  |                            |             | Week 20              |   |  | From week 20 until death |                  | 76/180 (42%) <sup>b</sup>   |   |   |                               |
|  |                            | esophagus   | Control              |   | Control                                  | N/A                      |                  | 0/384 (0%)                  |   |   |                               |
|  |                            |             | Week 3               | Diet (in drinking water), daily           | 16 different doses combined <sup>g</sup> | From week 3 until death  |                  | 77/180 (43%) <sup>b</sup>   |   |   |                               |
|  |                            |             | Week 6               |   |  | From week 6 until death  |                  | 663/1440 (46%) <sup>b</sup> |   |   |                               |
|  |                            |             | Week 20              |   |  | From week 20 until death |                  | 88/180 (49%) <sup>b</sup>   |   |   |                               |

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical                          | Species (strain)              | Target site               | Age when first dosed | Dose route, # doses | Dose                        | Duration of exposure      | Age at death | Tumors <sup>a</sup>         |   | Comments   | Reference                 |
|-----------------------------------|-------------------------------|---------------------------|----------------------|---------------------|-----------------------------|---------------------------|--------------|-----------------------------|---|--|---------------------------|
|                                   |                               |                           |                      |                     |                             |                           |              | M                           | F   |  |                           |
| DPH<br>Diphenylhydantoin,<br>5,5- | Rats<br>(F344/N)              | liver                     | Control              | Control             | 0 ppm                       | N/A                       | 2 years      | 0/50<br>(0%)                | 0/50<br>(0%)  | In rats, perinatal exposure ranged from 63 to 630 ppm, and adult exposures ranged from 240 to 2,400 ppm. | Chhabra et al.<br>(1993b) |
|                                   |                               |                           | Perinatal            | Diet,<br>daily      | 630 ppm                     | Perinatal through 8 weeks |              | 1/50<br>(2%) <sup>d</sup>   | 0/49<br>(0%) <sup>d</sup>                                 |  |                           |
|                                   |                               |                           | 8 weeks              |                     | 800 ppm                     | 8 weeks–2 years           |              | 2/50<br>(4%) <sup>d</sup>   | 1/50<br>(2%) <sup>d</sup>                                 |  |                           |
|                                   |                               |                           | 8 weeks              |                     | 2,400 ppm                   | 8 weeks–2 years           |              | 4/50<br>(8%) <sup>d</sup>   | 1/50<br>(2%) <sup>d</sup>                                 |  |                           |
|                                   |                               |                           | Perinatal            |                     | 630–800                     | Perinatal through 2 years |              | 1/49<br>(2%) <sup>d</sup>   | 0/50<br>(0%) <sup>d</sup>                                 |  |                           |
|                                   |                               |                           | Perinatal            |                     | 630–2,400 ppm               | Perinatal through 2 years |              | 5/49<br>(10%) <sup>c</sup>  | 0/50<br>(0%) <sup>d</sup>                                 |  |                           |
|                                   |                               |                           |                      |                     |                             |                           |              |                             |   |  |                           |
|                                   | Mice<br>(B6C3F <sub>1</sub> ) | liver                     | Control              | Control male        | 0 ppm                       | N/A                       | 2 years      | 29/50<br>(58%)              | Tumor incidences are animals with adenomas or carcinomas. |  |                           |
|                                   |                               |                           | Perinatal            | Diet, male          | 210 ppm                     | Perinatal through 8 weeks |              | 33/50<br>(66%) <sup>d</sup> |   |  |                           |
|                                   |                               |                           | 8 weeks              |                     | 100 ppm                     | 8 weeks–2 years           |              | 29/49<br>(59%) <sup>d</sup> |   |  |                           |
|                                   |                               |                           | 8 weeks              |                     | 300 ppm                     | 8 weeks–2 years           |              | 26/49<br>(53%) <sup>d</sup> |   |  |                           |
|                                   |                               |                           | Perinatal            |                     | 210–100 ppm                 | Perinatal through 2 years |              | 35/49<br>(71%) <sup>d</sup> |   |  |                           |
|                                   |                               |                           | Perinatal            |                     | 210–300 ppm                 | Perinatal through 2 years |              | 41/50<br>(82%) <sup>c</sup> |   |  |                           |
|                                   |                               |                           |                      |                     |                             |                           |              |                             |   |  |                           |
|                                   |                               |                           | Control              | Control female      | 0 ppm                       | N/A                       | 2 years      |                             |   | 5/48<br>(10.4%) <sup>d</sup>   |                           |
|                                   |                               |                           | Perinatal            | Diet,<br>female     | 210 ppm                     | Perinatal through 8 weeks |              |                             |   | 12/49<br>(24.5%) <sup>d</sup>  |                           |
|                                   |                               |                           | 8 weeks              |                     | 200 ppm                     | 8 weeks–2 years           |              |                             |   | 14/49<br>(28%) <sup>c</sup>  |                           |
|                                   |                               |                           | 8 weeks              |                     | 600 ppm                     | 8 weeks–2 years           |              |                             |   | 30/50<br>(60%) <sup>c</sup>  |                           |
| Perinatal                         |                               |                           | 210–200 ppm          |                     | Perinatal through 2 years   |                           |              | 16/50<br>(32%) <sup>c</sup> |   |  |                           |
| Perinatal                         | 210–600 ppm                   | Perinatal through 2 years |                      |                     | 34/50<br>(68%) <sup>c</sup> |                           |              |                             |   |  |                           |
|                                   |                               |                           |                      |                     |                             |                           |              |                             |   |  |                           |

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical                 | Species (strain)              | Target site     | Age when first dosed        | Dose route, # doses | Dose                        | Duration of exposure      | Age at death | Tumors <sup>a</sup>           |                             | Comments  | Reference                |
|--------------------------|-------------------------------|-----------------|-----------------------------|---------------------|-----------------------------|---------------------------|--------------|-------------------------------|-----------------------------|---|--------------------------|
|                          |                               |                 |                             |                     |                             |                           |              | M                             | F                           |   |                          |
| ETU<br>Ethylene thiourea | Rats<br>(F344/N)              | thyroid         | Control                     | Control             | 0 ppm                       | N/A                       | 2 years      | 1/49<br>(2%)                  | 3/50<br>(6%)                | Tumor incidences are animals with adenomas or carcinomas. | Chhabra et al.<br>(1992) |
|                          |                               |                 | Perinatal                   | Diet,<br>daily      | 90 ppm                      | Perinatal through 8 weeks |              | 4/49<br>(8%) <sup>d</sup>     | 3/50<br>(6%) <sup>d</sup>   |   |                          |
|                          |                               |                 | 8 weeks                     |                     | 83 ppm                      | 8 weeks–2 years           |              | 12/46<br>(26%) <sup>c</sup>   | 7/44<br>(16%) <sup>d</sup>  |   |                          |
|                          |                               |                 | 8 weeks                     |                     | 250 ppm                     | 8 weeks–2 years           |              | 37/50<br>(74%) <sup>c</sup>   | 30/49<br>(61%) <sup>c</sup> |   |                          |
|                          |                               |                 | Perinatal                   |                     | 90–83 ppm                   | Perinatal through 2 years |              | 13/50<br>(26%) <sup>c</sup>   | 9/47<br>(19%) <sup>d</sup>  |   |                          |
|                          |                               |                 | Perinatal                   |                     | 90–250 ppm                  | Perinatal through 2 years |              | 48/50<br>(96%)                | 37/50<br>(74%)              |   |                          |
|                          | Mice<br>(B6C3F <sub>1</sub> ) | liver           | Control                     | Control             | 0 ppm                       | N/A                       | 2 years      | 20/49<br>(41%)                | 4/50<br>(8%)                |   |                          |
|                          |                               |                 | Perinatal                   | Diet,<br>daily      | 330 ppm                     | Perinatal through 8 weeks |              | 13/49<br>(26.5%) <sup>d</sup> | 5/49<br>(10%) <sup>d</sup>  |   |                          |
|                          |                               |                 | 8 weeks                     |                     | 330 ppm                     | 8 weeks–2 years           |              | 32/50<br>(64%) <sup>c</sup>   | 44/50<br>(88%) <sup>c</sup> |   |                          |
|                          |                               |                 | 8 weeks                     |                     | 1,000 ppm                   | 8 weeks–2 years           |              | 46/50<br>(92%) <sup>c</sup>   | 48/50<br>(96%) <sup>c</sup> |   |                          |
|                          |                               |                 | Perinatal                   |                     | 330–330 ppm                 | Perinatal through 2 years |              | 34/49<br>(69%) <sup>c</sup>   | 46/50<br>(92%) <sup>c</sup> |   |                          |
|                          |                               |                 | Perinatal                   |                     | 330–1,000 ppm               | Perinatal through 2 years |              | 47/49<br>(6%) <sup>c</sup>    | 49/50<br>(98%) <sup>c</sup> |   |                          |
|                          |                               | thyroid         | Control                     | Control             | 0 ppm                       | N/A                       |              | 1/50<br>(2%)                  | 0/50<br>(0%)                |   |                          |
|                          |                               |                 | Perinatal                   | Diet,<br>daily      | 330 ppm                     | Perinatal through 8 weeks |              | 1/46<br>(2%) <sup>d</sup>     | 1/49<br>(2%) <sup>d</sup>   |   |                          |
| 8 weeks                  | 330 ppm                       | 8 weeks–2 years | 1/49<br>(2%) <sup>d</sup>   |                     | 2/50<br>(4%) <sup>d</sup>   |                           |              |                               |                             |   |                          |
| 8 weeks                  | 1,000 ppm                     | 8 weeks–2 years | 29/50<br>(58%) <sup>c</sup> |                     | 38/50<br>(76%) <sup>c</sup> |                           |              |                               |                             |   |                          |

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical                                | Species (strain) | Target site | Age when first dosed | Dose route, # doses | Dose                      | Duration of exposure      | Age at death | Tumors <sup>a</sup>      |                          | Comments | Reference |
|---|------------------|-------------|----------------------|---------------------|---------------------------|---------------------------|--------------|--------------------------|--------------------------|----------|-----------|
|   |                  |             |                      |                     |                           |                           |              | M                        | F                        |          |           |
| ETU<br>Ethylene thiourea<br>(continued) |                  |             | Perinatal            |                     | 330–330 ppm               | Perinatal through 2 years |              | 2/48 (4%) <sup>d</sup>   | 10/49 (20%) <sup>c</sup> |          |           |
|   |                  |             | Perinatal            |                     | 330–1,000 ppm             | Perinatal through 2 years |              | 35/49 (71%) <sup>c</sup> | 38/50 (76%) <sup>c</sup> |          |           |
|   |                  | pituitary   | Control              | Control             | 0 ppm                     | N/A                       |              | 0/44 (0%)                | 11/47 (23%)              |          |           |
|   |                  | Perinatal   | Diet, daily          | 330 ppm             | Perinatal through 8 weeks | 0/42 (0%) <sup>d</sup>    |              | 11/48 (23%) <sup>d</sup> |                          |          |           |
|   |                  | 8 weeks     |                      | 330 ppm             | 8 weeks–2 years           | 0/42 (0%) <sup>d</sup>    |              | 19/49 (39%) <sup>d</sup> |                          |          |           |
|   |                  | 8 weeks     |                      | 1,000 ppm           | 8 weeks–2 years           | 8/41 (19.5%) <sup>c</sup> |              | 26/49 (53%) <sup>c</sup> |                          |          |           |
|   |                  | Perinatal   |                      | 330–330 ppm         | Perinatal through 2 years | 0/45 (0%) <sup>d</sup>    |              | 26/47 (55%) <sup>c</sup> |                          |          |           |
|   |                  | Perinatal   |                      | 330–1,000 ppm       | Perinatal through 2 years | 4/39 (10%) <sup>d</sup>   |              | 24/47 (51%) <sup>c</sup> |                          |          |           |

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical   | Species (strain) | Target site  | Age when first dosed | Dose route, # doses | Dose      | Duration of exposure | Age at death |          | Tumor incidence            |                            | Reference    |
|--|------------------|--------------|----------------------|---------------------|-----------|----------------------|--------------|----------|----------------------------|----------------------------|--------------|
|  |                  |              |                      |                     |           |                      | M            | F        | M                          | F                          |              |
| 3-Methylcholanthrene (formerly known as 20-methylcholanthrene) | Mice (Albino)    | liver        | Control              | gavage, 3× per week | NA        | NA                   | 475 days     | 480 days | 3/39 (7.7%)                | 0/36 (0%)                  | Klein (1959) |
|  |                  |              | 8 days               |                     | 0.25 mg/g | 10×                  | 311 days     | 321 days | 21/25 (84%) <sup>b</sup>   | 7/30 (23.3%) <sup>b</sup>  |              |
|  |                  |              | 90 days              |                     | 0.25 mg/g | 10×                  | 330 days     | 366 days | 1/26 (3.8%) <sup>b</sup>   | 0/29 (0%) <sup>d</sup>     |              |
|  |                  | lung         | Control              |                     | NA        | NA                   | 475 days     | 480 days | 17/39 (43.6%)              | 14/36 (38.9%)              |              |
|  |                  |              | 8 days               |                     | 0.25 mg/g | 10×                  | 311 days     | 321 days | 25/25 (100%) <sup>b</sup>  | 28/30 (93.3%) <sup>b</sup> |              |
|  |                  |              | 90 days              |                     | 0.25 mg/g | 10×                  | 330 days     | 366 days | 25/26 (96.2%) <sup>b</sup> | 27/29 (93.1%) <sup>b</sup> |              |
|  |                  | fore-stomach | Control              |                     | NA        | NA                   | 475 days     | 480 days | 0/39 (0%)                  | 0/36 (0%)                  |              |
|  |                  |              | 8 days               |                     | 0.25 mg/g | 10×                  | 311 days     | 321 days | 12/25 (48%) <sup>b</sup>   | 12/30 (40%) <sup>b</sup>   |              |
|  |                  |              | 90 days              |                     | 0.25 mg/g | 10×                  | 330 days     | 366 days | 13/26 (50%) <sup>b</sup>   | 8/29 (27.6%) <sup>b</sup>  |              |
|  |                  | skin         | Control              |                     | NA        | NA                   | 475 days     | 480 days | 0/39 (0%)                  | 0/36 (0%)                  |              |
|  |                  |              | 8 days               |                     | 0.25 mg/g | 10×                  | 311 days     | 321 days | 4/25 (16%) <sup>b</sup>    | 4/30 (13.3%) <sup>b</sup>  |              |
|  |                  |              | 90 days              |                     | 0.25 mg/g | 10×                  | 330 days     | 366 days | 1/26 (3.8%) <sup>b</sup>   | 1/25 (4%) <sup>b</sup>     |              |

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical                         | Species (strain)           | Target site                      | Age when first dosed | Dose route, # doses | Dose      | Duration of exposure | Age at death | Tumors <sup>a</sup>          |                              | Comments   | Reference              |
|----------------------------------|----------------------------|----------------------------------|----------------------|---------------------|-----------|----------------------|--------------|------------------------------|------------------------------|--|------------------------|
|                                  |                            |                                  |                      |                     |           |                      |              | M                            | F                            |  |                        |
| PBBs<br>Polybrominated biphenyls | Rats (F344/N)              | liver <sup>e</sup>               | Control              | Control             | 0 ppm     | N/A                  | 2 years      | 1/50<br>(2%)                 | 0/50<br>(0%)                 | Findings suggest that combined perinatal and adult exposure increases PBB-related hepatocellular carcinogenicity relative to adult-only exposure in mice and female rats.<br><br>Apparent association between increasing incidences of MCL and exposure to PBB in male and female rats.<br><br>Tumor incidences are animals with adenomas or carcinomas. | Chhabra et al. (1993a) |
|                                  |                            |                                  | Perinatal            | Diet                | 10 ppm    | Perinatal–8 weeks    |              | 5/50<br>(10%) <sup>d</sup>   | 0/50<br>(0%) <sup>d</sup>    |  |                        |
|                                  |                            |                                  | 8 weeks              |                     | 10 ppm    | 8 weeks–2 years      |              | 12/49<br>(24%) <sup>c</sup>  | 12/50<br>(24%) <sup>c</sup>  |  |                        |
|                                  |                            |                                  | 8 weeks              |                     | 30 ppm    | 8 weeks–2 years      |              | 41/50<br>(82%) <sup>c</sup>  | 39/50<br>(78%) <sup>c</sup>  |  |                        |
|                                  |                            |                                  | Perinatal            |                     | 10–10 ppm | Perinatal–2 years    |              | 16/50<br>(32%) <sup>c</sup>  | 39/50<br>(78%) <sup>c</sup>  |  |                        |
|                                  |                            |                                  | Perinatal            |                     | 10–30 ppm | Perinatal–2 years    |              | 41/50<br>(82%) <sup>c</sup>  | 47/50<br>(94%) <sup>c</sup>  |  |                        |
|                                  |                            | Mono-nuclear cell leukemia (MCL) | Control              | Control             | 0 ppm     | N/A                  | 2 years      | 25/50<br>(50%)               | 14/50<br>(28%)               |  |                        |
|                                  |                            |                                  | Perinatal            | Diet                | 10 ppm    | Perinatal–8 weeks    |              | 31/50<br>(62%) <sup>d</sup>  | 13/50<br>(26%) <sup>d</sup>  |  |                        |
|                                  |                            |                                  | 8 weeks              |                     | 10 ppm    | 8 weeks–2 years      |              | 33/50<br>(66%) <sup>c</sup>  | 22/50<br>(44%) <sup>d</sup>  |  |                        |
|                                  |                            |                                  | 8 weeks              |                     | 30 ppm    | 8 weeks–2 years      |              | 31/50<br>(62%) <sup>d</sup>  | 23/50<br>(46%) <sup>c</sup>  |  |                        |
|                                  |                            |                                  | Perinatal            |                     | 10–10 ppm | Perinatal–2 years    |              | 37/50<br>(74%) <sup>c</sup>  | 27/50<br>(54%) <sup>c</sup>  |  |                        |
|                                  |                            |                                  | Perinatal            |                     | 10–30 ppm | Perinatal–2 years    |              | 37/50<br>(74%) <sup>c</sup>  | 25/50<br>(50%) <sup>c</sup>  |  |                        |
|                                  | Mice (B6C3F <sub>1</sub> ) | liver <sup>e</sup>               | Control              | Control             | 0 ppm     | N/A                  | 2 years      | 16/50<br>(32%)               | 5/50<br>(10%)                |  |                        |
|                                  |                            |                                  | Perinatal            | Diet                | 30 ppm    | Perinatal–8 weeks    |              | 40/50<br>(80%) <sup>c</sup>  | 21/50<br>(42%) <sup>c</sup>  |  |                        |
|                                  |                            |                                  | 8 weeks              |                     | 10 ppm    | 8 weeks–2 years      |              | 48/49<br>(98%) <sup>c</sup>  | 42/50<br>(84%) <sup>c</sup>  |  |                        |
|                                  |                            |                                  | 8 weeks              |                     | 30 ppm    | 8 weeks–2 years      |              | 48/50<br>(96%) <sup>c</sup>  | 47/48<br>(98%) <sup>c</sup>  |  |                        |
|                                  |                            |                                  | Perinatal            |                     | 10 ppm    | Perinatal–2 years    |              | 46/49<br>(94%) <sup>c</sup>  | 44/50<br>(88%) <sup>c</sup>  |  |                        |
|                                  |                            |                                  | Perinatal            |                     | 30–30 ppm | Perinatal–2 years    |              | 50/50<br>(100%) <sup>c</sup> | 47/47<br>(100%) <sup>c</sup> |  |                        |



**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical | Species (strain)            | Target site | Age when first dosed | Dose route, # doses   | Dose                 | Duration of exposure  | Age at death | Tumors <sup>a</sup>          |                          | Comments  | Reference                     |
|----------|-----------------------------|-------------|----------------------|---|----------------------|---|--------------|------------------------------|--------------------------|---|-------------------------------|
|          |                             |             |                      |   |                      |   |              | M                            | F                        |   |                               |
| Safrole  | Mice (B6C3F <sub>1</sub> )  | liver       | Control              | None  | None                 | N/A   | 90 weeks     | 3/100 (3%)                   | 0/100 (0%)               | Highest tumor rate in males due to preweaning treatment.          | Vesselinovitch et al. (1979b) |
|          |                             |             | Day 12 of gestation  | Gavage, to mothers  | 120 µg/g body weight | 4× (days 12, 14, 16, 18)  |              | 2/61 (3%) <sup>d</sup>       | 0/65 (0%) <sup>d</sup>   |   |                               |
|          |                             |             | Newborn              | Gavage, to mothers, on alternate days   | 120 µg/g body weight | From birth until weaning  |              | 28/83 (34%) <sup>c</sup>     | 2/80 (3%) <sup>d</sup>   | Highest tumor rate in females due to susceptibility in adulthood. |                               |
|          |                             |             | At weaning           | Gavage, to offspring, 2× weekly   | 120 µg/g body weight | From weaning until 90 weeks   |              | 4/35 (11%) <sup>d</sup>      | 22/36 (61%) <sup>c</sup> |   |                               |
|          |                             |             | Day 12 of gestation  | Gavage, to mothers, alternate days  | 120 µg/g body weight | From gestation until weaning  |              | 22/68 (32%) <sup>b</sup>     | 1/72 (1%) <sup>b</sup>   |   |                               |
|          |                             |             | Day 12 of gestation  | Gavage, to mothers, alternate days until weaning; Gavage, to offspring, 2× weekly | 120 µg/g body weight | From gestation until 90 weeks                                       |              | 19/37 (51%) <sup>b</sup>     | 37/46 (80%) <sup>b</sup> |   |                               |
| Urethane | Mice (B6AF <sub>1</sub> /J) | liver       | 1 week               | gavage  | 2.5 mg/pup           | 1×  | 39–40 weeks  | Tumor incidence <sup>a</sup> |                          | No tumor data for controls.                                       | Klein (1966)                  |
|          |                             |             |                      |   |                      |   |              | M                            | F                        |   |                               |
|          |                             |             |                      |   |                      |   |              | 12/37 (33%) <sup>b</sup>     | 0/40 (0%) <sup>b</sup>   |   |                               |
|          |                             |             | 1 week               |   | 2.5 mg/pup           | 16× (1× at 1 week; 3× weekly for 5 weeks beginning at 4 wks of age) | 39 weeks     | 11/33 (33%) <sup>b</sup>     | 0/31 (0%) <sup>b</sup>   |   |                               |
|          |                             |             | 4 weeks              |   | 2.5 mg/pup           | 15× (3× weekly for 5 weeks beginning at 4 weeks of age)             | 41 weeks     | 0/37 (0%) <sup>b</sup>       | 0/31 (0%) <sup>b</sup>   |   |                               |

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical             | Species (strain)      | Target site         | Age when first dosed | Dose route, # doses | Dose       | Duration of exposure           | Age at death | Tumors <sup>a</sup>      |                          | Comments   | Reference             |
|----------------------|-----------------------|---------------------|----------------------|---------------------|------------|--------------------------------|--------------|--------------------------|--------------------------|--|-----------------------|
|                      |                       |                     |                      |                     |            |                                |              | M                        | F                        |  |                       |
| VC<br>Vinyl chloride | Rats (Sprague-Dawley) | liver angio-sarcoma | Control              | Control             | 0 ppm      | N/A                            | 135 weeks    | 0/22 (0%)                | 0/29 (0%)                | Higher tumor risk when exposed at birth, higher for females. | Maltoni et al. (1984) |
|                      |                       |                     | Newborn              | Inhalation          | 6,000 ppm  | 4 hrs/day, 5 days/wk, 5 weeks  | 124 weeks    | 5/18 (28%) <sup>b</sup>  | 12/24 (50%) <sup>b</sup> |  |                       |
|                      |                       |                     |                      |                     | 10,000 ppm |                                |              | 6/24 (25%) <sup>b</sup>  | 9/20 (45%) <sup>b</sup>  |  |                       |
|                      |                       |                     | Week 13              |                     | 6,000 ppm  | 4 hrs/day, 5 days/wk, 52 weeks | 135 weeks    | 3/17 (18%) <sup>b</sup>  | 10/25 (40%) <sup>b</sup> |  |                       |
|                      |                       |                     |                      |                     | 10,000 ppm |                                |              | 3/21 (14%) <sup>b</sup>  | 4/25 (16%) <sup>b</sup>  |  |                       |
|                      |                       |                     | zymlal gland         | Control             | Control    | 0 ppm                          | N/A          | 135 weeks                | 0/28 (0%)                |  |                       |
|                      |                       | Newborn             |                      | Inhalation          | 6,000 ppm  | 4 hrs/day, 5 days/wk, 5 weeks  | 124 weeks    | 1/12 (8%) <sup>b</sup>   | 1/17 (6%) <sup>b</sup>   |  |                       |
|                      |                       |                     |                      |                     | 10,000 ppm |                                |              | 1/17 (6%) <sup>b</sup>   | 0/17 (0%) <sup>b</sup>   |  |                       |
|                      |                       | Week 13             |                      |                     | 6,000 ppm  | 4 hrs/day, 5 days/wk, 52 weeks | 135 weeks    | 3/29 (10%) <sup>b</sup>  | 4/30 (13%) <sup>b</sup>  |  |                       |
|                      |                       |                     |                      |                     | 10,000 ppm |                                |              | 10/30 (33%) <sup>b</sup> | 6/30 (20%) <sup>b</sup>  |  |                       |
|                      |                       | leukemia            |                      | Control             | Control    | 0 ppm                          | N/A          | 135 weeks                | 0/27 (0%)                |  |                       |
|                      |                       |                     | Newborn              | Inhalation          | 6,000 ppm  | 4 hrs/day, 5 days/wk, 5 weeks  | 124 weeks    | N/A                      | 1/7 (14%) <sup>b</sup>   |  |                       |
|                      |                       |                     |                      |                     | 10,000 ppm |                                |              | 2/6 (33%) <sup>b</sup>   | 0/15 (0%) <sup>b</sup>   |  |                       |
|                      |                       |                     | Week 13              |                     | 6,000 ppm  | 4 hrs/day, 5 days/wk, 52 weeks | 135 weeks    | N/A                      | 0/29 (0%) <sup>b</sup>   |  |                       |
|                      |                       |                     |                      |                     | 10,000 ppm |                                |              | 0/27 (0%) <sup>b</sup>   | 2/29 (7%) <sup>b</sup>   |  |                       |
|                      |                       |                     | nephro-blastoma      | Control             | Control    | 0 ppm                          | N/A          | 135 weeks                | 0/22 (0%)                |  |                       |
|                      |                       | Newborn             |                      | Inhalation          | 6,000 ppm  | 4 hrs/day, 5 days/wk, 5 weeks  | 124 weeks    | 0/15 (0%) <sup>b</sup>   | 0/21 (0%) <sup>b</sup>   |  |                       |
|                      |                       |                     |                      |                     | 10,000 ppm |                                |              | 0/19 (0%) <sup>b</sup>   | 0/17 (0%) <sup>b</sup>   |  |                       |

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical                            | Species (strain) | Target site                    | Age when first dosed                        | Dose route, # doses | Dose                        | Duration of exposure              | Age at death | Tumors <sup>a</sup>        |                           | Comments | Reference |
|-------------------------------------|------------------|--------------------------------|---|---------------------|-----------------------------|-----------------------------------|--------------|----------------------------|---------------------------|----------|-----------|
|                                     |                  |                                |   |                     |                             |                                   |              | M                          | F                         |          |           |
| VC<br>Vinyl chloride<br>(continued) |                  |                                | Week 13                                     |                     | 6,000 ppm                   | 4 hrs/day,<br>5 days/wk, 52 weeks | 135 weeks    | 4/18<br>(22%) <sup>b</sup> | 1/26<br>(4%) <sup>b</sup> |          |           |
|                                     |                  |                                |   |                     | 10,000 ppm                  |                                   |              | 3/21<br>(14%) <sup>b</sup> | 2/25<br>(8%) <sup>b</sup> |          |           |
|                                     |                  | angio-sarcomas:<br>other sites | Control                                     | Control             | 0 ppm                       | N/A                               | 135 weeks    | 0/29<br>(0%)               | 0/29<br>(0%)              |          |           |
|                                     |                  |                                |   |                     |                             |                                   |              | Newborn                    | Inhalation                |          |           |
|                                     |                  |                                | 10,000 ppm                                  | 0/19<br>(0%)        | 0/17<br>(0%) <sup>b</sup>   |                                   |              |                            |                           |          |           |
|                                     |                  |                                | Week 13                                     |                     | 6,000 ppm                   | 4 hrs/day,<br>5 days/wk, 52 weeks | 135 weeks    | 1/29<br>(3%) <sup>b</sup>  | 2/30<br>(7%) <sup>b</sup> |          |           |
|                                     |                  |                                |   |                     |                             |                                   |              | 10,000 ppm                 | 2/30<br>(7%) <sup>b</sup> |          |           |
|                                     |                  |                                | angiomas<br>and<br>fibromas:<br>other sites | Control             | Control                     | 0 ppm                             | N/A          | 135 weeks                  | 0/28<br>(0%)              |          |           |
|                                     |                  | Newborn                        |   |                     |                             |                                   |              |                            | Inhalation                |          |           |
|                                     |                  |                                |   | 10,000 ppm          | 2/19<br>(11%) <sup>b</sup>  | 1/17<br>(6%) <sup>b</sup>         |              |                            |                           |          |           |
|                                     |                  | Week 13                        |   |                     | 6,000 ppm                   | 4 hrs/day,<br>5 days/wk, 52 weeks | 135 weeks    | 2/29<br>(7%) <sup>b</sup>  | 2/30<br>(7%) <sup>b</sup> |          |           |
|                                     |                  |                                |   |                     |                             |                                   |              | 10,000 ppm                 | 2/29<br>(7%) <sup>b</sup> |          |           |
|                                     |                  | hepatoma                       |   | Control             | Control                     | 0 ppm                             | N/A          | 135 weeks                  | 0/19<br>(0%)              |          |           |
|                                     |                  |                                | Newborn                                     |                     |                             |                                   |              |                            | Inhalation                |          |           |
|                                     |                  |                                |   | 10,000 ppm          | 13/24<br>(54%) <sup>b</sup> | 7/20<br>(35%) <sup>b</sup>        |              |                            |                           |          |           |
|                                     |                  |                                | Week 13                                     |                     | 6,000 ppm                   | 4 hrs/day,<br>5 days/wk, 52 weeks | 135 weeks    | 0/10<br>(0%) <sup>b</sup>  | 1/17<br>(6%) <sup>b</sup> |          |           |
|                                     |                  |                                |   |                     |                             |                                   |              | 10,000 ppm                 | 1/8<br>(13%) <sup>b</sup> |          |           |

**Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)**

| Chemical                            | Species (strain) | Target site     | Age when first dosed | Dose route, # doses | Dose       | Duration of exposure                | Age at death | Tumors <sup>a</sup>        |                            | Comments | Reference |
|-------------------------------------|------------------|-----------------|----------------------|---------------------|------------|-------------------------------------|--------------|----------------------------|----------------------------|----------|-----------|
|                                     |                  |                 |                      |                     |            |                                     |              | M                          | F                          |          |           |
| VC<br>Vinyl chloride<br>(continued) |                  | skin carcinomas | Control              | Control             | 0 ppm      | N/A                                 | 135 weeks    | 0/20<br>(0%)               | 1/29<br>(3%)               |          |           |
|                                     |                  |                 | Newborn              | Inhalation          | 6,000 ppm  | 4 hrs/day,<br>5 days/wk,<br>5 weeks | 124 weeks    | 1/10<br>(10%) <sup>b</sup> | 1/14<br>(7%) <sup>b</sup>  |          |           |
|                                     |                  |                 |                      |                     | 10,000 ppm |                                     |              | 1/16<br>(6%) <sup>b</sup>  | 0/15<br>(0%) <sup>b</sup>  |          |           |
|                                     |                  |                 | Week 13              |                     | 6,000 ppm  | 4 hrs/day,<br>5 days/wk, 52 weeks   | 135 weeks    | 0/15<br>(0%) <sup>b</sup>  | 2/19<br>(11%) <sup>b</sup> |          |           |
|                                     |                  |                 |                      |                     | 10,000 ppm |                                     |              | 2/13<br>(15%) <sup>b</sup> | 1/21<br>(5%) <sup>b</sup>  |          |           |
|                                     |                  |                 | neuro-blastoma       | Control             | Control    | 0 ppm                               | N/A          | 135 weeks                  | 0/22<br>(0%)               |          |           |
|                                     |                  | Newborn         |                      | Inhalation          | 6,000 ppm  | 4 hrs/day,<br>5 days/wk,<br>5 weeks | 124 weeks    | 0/18<br>(0%) <sup>b</sup>  | 0/29<br>(0%) <sup>b</sup>  |          |           |
|                                     |                  |                 |                      |                     | 10,000 ppm |                                     |              | 0/22<br>(0%) <sup>b</sup>  | 0/19<br>(0%) <sup>b</sup>  |          |           |
|                                     |                  | Week 13         |                      |                     | 6,000 ppm  | 4 hrs/day,<br>5 days/wk, 52 weeks   | 135 weeks    | 2/21<br>(10%) <sup>b</sup> | 1/27<br>(4%) <sup>b</sup>  |          |           |
|                                     |                  |                 |                      |                     | 10,000 ppm |                                     |              | 2/22<br>(9%) <sup>b</sup>  | 5/26<br>(19%) <sup>b</sup> |          |           |

<sup>a</sup> Where not delineated by gender, data combined by study authors or gender not specified. Where percentages only are given, number of subjects not specified.

<sup>b</sup> Not evaluated by authors.

<sup>c</sup> Significant compared with controls.

<sup>d</sup> Evaluated but not significant compared with controls.

<sup>e</sup> Reported as NDEA (N-nitrosodiethylamine) in the original document.

<sup>f</sup> Results from each dose are not available.

<sup>g</sup> Tumors were adenomas or carcinomas.

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure**

| Chemical                       | Species (strain)           | Target site | Age when first dosed | Dose route, # doses | Dose                 | Duration of exposure   | Age at death                  | Tumors <sup>a</sup>      |                         | Comments  | Reference                     |  |
|--------------------------------|----------------------------|-------------|----------------------|---------------------|----------------------|------------------------|-------------------------------|--------------------------|-------------------------|---|-------------------------------|--|
|                                |                            |             |                      |                     |                      |                        |                               | M                        | F                       |   |                               |  |
| BaP<br>Benzo[ <i>a</i> ]pyrene | Mice (B6C3F <sub>1</sub> ) | liver       | Control              | Control             | None                 | N/A                    | 142 weeks                     | 7/100 (7%)               | 1/100 (1%)              | In general, hepatomas developed with significantly higher incidence (p<0.01) in mice that were treated within 24 hours of birth or at 15 days of age than they did in similarly treated animals at 42 days of age.<br><br>+ higher for males. | Vesselinovitch et al. (1975a) |  |
|                                |                            |             | Day 1                | i.p.                | 75 µg/g body weight  | 1×                     | 86 weeks (m)<br>129 weeks (f) | 26/47 (55%) <sup>b</sup> | 3/45 (7%) <sup>b</sup>  |   |                               |  |
|                                |                            |             |                      |                     | 150 µg/g body weight | 1×                     | 81 weeks (m)<br>121 weeks (f) | 51/63 (81%) <sup>b</sup> | 8/45 (18%) <sup>b</sup> |   |                               |  |
|                                |                            |             | Day 15               | i.p.                | 75 µg/g body weight  | 1×                     | 93 weeks (m)<br>116 weeks (f) | 36/60 (60%) <sup>b</sup> | 4/55 (7%) <sup>b</sup>  |   |                               |  |
|                                |                            |             |                      |                     | 150 µg/g body weight | 1×                     | 81 weeks (m)<br>90 weeks (f)  | 32/55 (58%) <sup>b</sup> | 4/55 (7%) <sup>b</sup>  |   |                               |  |
|                                |                            |             | Day 42               | i.p.                | 75 µg/g body weight  | 1×                     | 108 weeks(m)                  | 7/55 (13%) <sup>b</sup>  | 0/47 (0%) <sup>b</sup>  |   |                               |  |
|                                | 150 µg/g body weight       | 1×          |                      |                     | 87 weeks (m)         | 4/47 (9%) <sup>b</sup> | 0/46 (0%) <sup>b</sup>        |                          |                         |   |                               |  |
|                                | Mice (C3AF <sub>1</sub> )  | liver       | Control              | Control             | None                 | N/A                    | 142 weeks                     | 8/100 (8%)               | 1/100 (1%)              |   |                               | + higher for males.  |
|                                |                            |             | Day 1                | i.p.                | 75 µg/g body weight  | 1×                     | 80 weeks (m)<br>91 weeks (f)  | 21/62 (34%) <sup>b</sup> | 1/45 (2%) <sup>b</sup>  |   |                               | “Age at death” is the average age at which tumors were observed. |
|                                |                            |             |                      |                     | 150 µg/g body weight | 1×                     | 69 weeks (m)<br>701 weeks (f) | 24/52 (46%) <sup>b</sup> | 1/56 (2%) <sup>b</sup>  |   |                               |  |
|                                |                            |             | Day 15               | i.p.                | 75 µg/g body weight  | 1×                     | 90 weeks (m)<br>102 weeks (f) | 15/56 (27%) <sup>b</sup> | 1/49 (2%) <sup>b</sup>  |   |                               |  |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                      | Species (strain)              | Target site | Age when first dosed | Dose route, # doses     | Dose                    | Duration of exposure                 | Age at death                    | Tumors <sup>a</sup>         |                           | Comments   | Reference |
|---|-------------------------------|-------------|----------------------|-------------------------|-------------------------|--------------------------------------|---------------------------------|-----------------------------|---------------------------|--|-----------|
|   |                               |             |                      |                         |                         |                                      |                                 | M                           | F                         |  |           |
| BaP<br>Benzo[ <i>a</i> ]pyrene<br>(continued) |                               |             |                      |                         | 150 µg/g<br>body weight | 1×                                   | 77 weeks<br>(m)<br>62 weeks (f) | 12/53<br>(23%) <sup>b</sup> | 1/57<br>(2%) <sup>b</sup> | Both sexes developed lung tumors with higher incidence when treated with BaP at birth than at 15 or 42 days of age (p<0.05). |           |
|   |                               |             | Day 42               | i.p.                    | 75 µg/g<br>body weight  | 1×                                   |                                 | 0/30<br>(0%) <sup>b</sup>   | 0/32<br>(0%) <sup>b</sup> |  |           |
|   |                               |             |                      |                         | 150 µg/g<br>body weight | 1×                                   | 79 weeks<br>(m)                 | 1/32<br>(3%) <sup>c</sup>   | 0/40<br>(0%) <sup>b</sup> |  |           |
|   | Mice<br>(B6C3F <sub>1</sub> ) | lung        | Control              | Control                 | Control                 | N/A                                  | 142 weeks                       | 13/100<br>(13%)             | 9/100<br>(9%)             |  |           |
|   | Day 1                         |             | i.p.                 | 75 µg/g<br>body weight  | 1×                      | 103 weeks<br>(m)<br>126 weeks<br>(f) | 20/47<br>(43%) <sup>b</sup>     | 22/45<br>(49%) <sup>b</sup> |                           |  |           |
|   |                               |             |                      | 150 µg/g<br>body weight | 1×                      | 84 weeks<br>(m)<br>112 weeks<br>(f)  | 37/63<br>(59%) <sup>b</sup>     | 28/45<br>(62%) <sup>b</sup> |                           |  |           |
|   | Day 15                        |             | i.p.                 | 75 µg/g<br>body weight  | 1×                      | 103 weeks<br>(m)<br>122 weeks<br>(f) | 15/60<br>(25%) <sup>b</sup>     | 18/55<br>(33%) <sup>b</sup> |                           |  |           |
|   |                               |             |                      | 150 µg/g<br>body weight | 1×                      | 82 weeks<br>(m)<br>101 weeks<br>(f)  | 20/55<br>(36%) <sup>b</sup>     | 18/45<br>(40%) <sup>b</sup> |                           |  |           |
|   | Day 42                        |             | i.p.                 | 75 µg/g<br>body weight  | 1×                      | 119 weeks<br>(m)<br>131 weeks<br>(f) | 20/55<br>(36%) <sup>b</sup>     | 12/47<br>(26%) <sup>b</sup> |                           |  |           |
|   |                               |             |                      | 150 µg/g<br>body weight | 1×                      | 95 weeks<br>(m)<br>118 weeks<br>(f)  | 18/47<br>(38%) <sup>b</sup>     | 8/46<br>(17%) <sup>b</sup>  |                           |  |           |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                      | Species (strain)               | Target site | Age when first dosed | Dose route, # doses | Dose                                | Duration of exposure | Age at death                    | Tumors <sup>a</sup>          |                             | Comments  | Reference                     |
|---|--------------------------------|-------------|----------------------|---------------------|-------------------------------------|----------------------|---------------------------------|------------------------------|-----------------------------|---|-------------------------------|
|   |                                |             |                      |                     |                                     |                      |                                 | M                            | F                           |   |                               |
| BaP<br>Benzo[ <i>a</i> ]pyrene<br>(continued) | Mice<br>(C3AF <sub>1</sub> )   | lung        | Control              | Control             | None                                | N/A                  | 142 weeks                       | 60/100<br>(60%)              | 50/100<br>(50%)             | Of the two mouse strains tested, C3AF <sub>1</sub> mice developed significantly more tumors than did the B6C3F <sub>1</sub> mice (p<0.001). | Vesselinovitch et al. (1975a) |
|   |                                |             | Day 1                | i.p.                | 75 µg/g<br>body weight              | 1×                   | 78 weeks<br>(m)<br>82 weeks (f) | 58/62<br>(93%) <sup>b</sup>  | 42/45<br>(93%) <sup>b</sup> |   |                               |
|   |                                |             |                      |                     | 150 µg/g<br>body weight             | 1×                   | 70 weeks<br>(m)<br>73 weeks (f) | 48/52<br>(92%) <sup>b</sup>  | 52/56<br>(93%) <sup>b</sup> |   |                               |
|   |                                |             | Day 15               | i.p.                | 75 µg/g<br>body weight              | 1×                   | 87 weeks<br>(m)<br>98 weeks (f) | 52/56<br>(93%) <sup>b</sup>  | 46/49<br>(94%) <sup>b</sup> |   |                               |
|   |                                |             |                      |                     | 150 µg/g<br>body weight             | 1×                   | 75 weeks<br>(m)<br>79 weeks (f) | 50/53<br>(94%) <sup>b</sup>  | 52/57<br>(91%) <sup>b</sup> |   |                               |
|   |                                |             | Day 42               | i.p.                | 75 µg/g<br>body weight              | 1×                   | 91 weeks<br>(m)<br>93 weeks (f) | 28/30<br>(93%) <sup>b</sup>  | 28/32<br>(87%) <sup>b</sup> |   |                               |
|   |                                |             |                      |                     | 150 µg/g<br>body weight             | 1×                   | 85 weeks<br>(m)<br>83 weeks (f) | 28/32<br>(87%) <sup>b</sup>  | 36/40<br>(90%) <sup>b</sup> |   |                               |
| DBA<br>Dibenzanthracene                       | Mice<br>(Caracul × P<br>stock) | lung        | Control              | Control             | None                                | N/A                  | 228 days                        | 1/31<br>(3.2%)               |                             |   | Law (1940)                    |
|   |                                |             | Day 1                | i.p.                | 4 mg per<br>cm <sup>3</sup> vehicle | 1×                   | 181 days                        | 24/24<br>(100%) <sup>b</sup> |                             |   |                               |
|   |                                |             | 2 months             | s.c.                | 4 mg per<br>cm <sup>3</sup> vehicle | 1×                   | 189 days                        | 2/29<br>(6.9%) <sup>b</sup>  |                             |   |                               |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                  | Species (strain)              | Target site | Age when first dosed | Dose route, # doses               | Dose   | Duration of exposure | Age at death                            | Tumors <sup>a</sup>         |                             | Comments  | Reference                    |
|---------------------------|-------------------------------|-------------|----------------------|-----------------------------------|--|----------------------|---|-----------------------------|-----------------------------|---|------------------------------|
|                           |                               |             |                      |                                   |  |                      |   | M                           | F                           |   |                              |
| DEN<br>Diethylnitrosamine | Mice<br>(B6C3F <sub>1</sub> ) | liver       | Control              | Control                           | Vehicle<br>(0.01 mL<br>trioctanoïn/g<br>body weight) | 4×                   | 142<br>weeks<br>(m)<br>137<br>weeks (f) | 7/98<br>(7%)                | 1/100<br>(1%)               | Animals treated as newborns and infants developed significantly more liver tumors than animals that were treated as young adults.<br><br>Newborns and infant females developed liver tumors at a later age than similarly treated males.<br><br>Incidences for malignant tumors only. | Vesselinovitch et al. (1984) |
|                           |                               |             | Day 1                | i.p. (3-, 6- and 6-day intervals) | 1.5 µg/g body weight                                 | 4×                   | 67 weeks (m)<br>90 weeks (f)            | 37/51<br>(73%) <sup>b</sup> | 45/64<br>(70%) <sup>b</sup> |   |                              |
|                           |                               |             |                      |                                   | 3 µg/g body weight                                   | 4×                   | 65 weeks (m)<br>80 weeks (f)            | 40/58<br>(69%) <sup>b</sup> | 44/65<br>(68%) <sup>b</sup> |   |                              |
|                           |                               |             | Day 15               | i.p. (3-, 6- and 6-day intervals) | 1.5 µg/g body weight                                 | 4×                   | 86 weeks (m)<br>117 weeks (f)           | 41/57<br>(72%) <sup>b</sup> | 40/71<br>(56%) <sup>b</sup> |   |                              |
|                           |                               |             |                      |                                   | 3 µg/g body weight                                   | 4×                   | 76 weeks (m)<br>96 weeks (f)            | 48/69<br>(70%) <sup>b</sup> | 46/62<br>(74%) <sup>b</sup> |   |                              |
|                           |                               |             | Day 42               | i.p. (3-, 6- and 6-day intervals) | 1.5 µg/g body weight                                 | 4×                   | 117 weeks (m)<br>135 weeks (f)          | 9/49<br>(18%) <sup>b</sup>  | 1/47<br>(2%) <sup>b</sup>   |   |                              |
|                           |                               |             |                      |                                   | 3 µg/g body weight                                   | 4×                   | 123 weeks (m)<br>133 weeks (f)          | 6/38<br>(16%) <sup>b</sup>  | 4/57<br>(7%) <sup>b</sup>   |   |                              |



**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                 | Species (strain)              | Target site | Age when first dosed | Dose route, # doses               | Dose                                    | Duration of exposure | Age at death                   | Tumors <sup>a</sup>      |                          | Comments   | Reference                    |
|--|-------------------------------|-------------|----------------------|-----------------------------------|---|----------------------|--------------------------------|--------------------------|--------------------------|--|------------------------------|
|  |                               |             |                      |                                   |   |                      |                                | M                        | F                        |  |                              |
| DEN<br>Diethylnitrosamine<br>(continued) | Mice<br>(C3AF <sub>1</sub> )  | liver       | Control              | Control                           | Vehicle (0.1 trioctanoin/g body weight) | 4×                   | 123 weeks (m)<br>131 weeks (f) | 8/99 (8%)                | 1/97 (1%)                | Highest tumor rate when dosed at early ages.<br><br>Newborns and infant females developed liver tumors at a lower incidence than similarly treated males.<br><br>+ higher for males. | Vesselinovitch et al. (1984) |
|  |                               |             | Day 1                | i.p. (3-, 6- and 6-day intervals) | 1.5 µg/g body weight                    | 4×                   | 64 weeks (m)<br>84 weeks (f)   | 23/32 (72%) <sup>b</sup> | 11/39 (28%) <sup>b</sup> |  |                              |
|  |                               |             |                      |                                   | 3 µg/g body weight                      | 4×                   | 59 weeks (m)<br>76 weeks (f)   | 39/58 (67%) <sup>b</sup> | 26/50 (52%) <sup>b</sup> |  |                              |
|  |                               |             | Day 15               |                                   | 1.5 µg/g body weight                    | 4×                   | 82 weeks (m)<br>102 weeks (f)  | 22/46 (48%) <sup>b</sup> | 8/65 (12%) <sup>b</sup>  |  |                              |
|  |                               |             |                      |                                   | 3 µg/g body weight                      | 4×                   | 74 weeks (m)<br>94 weeks (f)   | 35/54 (65%) <sup>b</sup> | 22/62 (35%) <sup>b</sup> |  |                              |
|  |                               |             | Day 42               |                                   | 1.5 µg/g body weight                    | 4×                   | 105 weeks (m)<br>106 weeks (f) | 12/56 (22%) <sup>b</sup> | 0/53 (0%) <sup>b</sup>   |  |                              |
|  |                               |             |                      |                                   | 3 µg/g body weight                      | 4×                   | 105 weeks (m)<br>103 weeks (f) | 9/57 (16%) <sup>b</sup>  | 0/56 (0%) <sup>b</sup>   |  |                              |
|  | Mice<br>(B6C3F <sub>1</sub> ) | lung        | Control              | Control                           | Vehicle (0.1 trioctanoin/g body weight) | 4×                   | 142 weeks (m)<br>137 weeks (f) | 13/98 (13%)              | 9/100 (9%)               | The mice treated as newborns showed lung tumors earlier than animals exposed at other times. It is not known whether this was due to actual earlier emergence of tumors or           |                              |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                 | Species (strain) | Target site | Age when first dosed      | Dose route, # doses               | Dose                 | Duration of exposure              | Age at death                            | Tumors <sup>a</sup>      |                                | Comments   | Reference |                          |                          |  |  |
|--|------------------|-------------|---------------------------|-----------------------------------|----------------------|-----------------------------------|---|--------------------------|--------------------------------|--|-----------|--------------------------|--------------------------|--|--|
|  |                  |             |                           |                                   |                      |                                   |   | M                        | F                              |  |           |                          |                          |  |  |
| DEN<br>Diethylnitrosamine<br>(continued) |                  |             | Day 1                     | i.p. (3-, 6- and 6-day intervals) | 1.5 µg/g body weight | 4×                                | 70 weeks (m)<br>91 weeks (f)            | 29/51 (57%) <sup>b</sup> | 49/64 (77%) <sup>b</sup>       | to their earlier detection caused by shorter survival. |           |                          |                          |  |  |
|  |                  |             |                           |                                   | 3 µg/g body weight   | 4×                                | 68 weeks (m)<br>81 weeks (f)            | 34/58 (59%) <sup>b</sup> | 42/65 (65%) <sup>b</sup>       |  |           |                          |                          |  |  |
|  |                  |             | Day 15                    |                                   | 1.5 µg/g body weight | 4×                                | 87 weeks (m)<br>115 weeks (f)           | 51/57 (89%) <sup>b</sup> | 61/71 (86%) <sup>b</sup>       |  |           |                          |                          |  |  |
|  |                  |             |                           |                                   | 3 µg/g body weight   | 4×                                | 77 weeks (m)<br>97 weeks (f)            | 51/69 (74%) <sup>b</sup> | 53/62 (85%) <sup>b</sup>       |  |           |                          |                          |  |  |
|  |                  |             | Day 42                    |                                   | 1.5 µg/g body weight | 4×                                | 123 weeks (m)<br>129 weeks (f)          | 38/49 (78%) <sup>b</sup> | 38/47 (81%) <sup>b</sup>       |  |           |                          |                          |  |  |
|  |                  |             |                           |                                   | 3 µg/g body weight   | 4×                                | 121 weeks (m)<br>127 weeks (f)          | 33/38 (87%) <sup>b</sup> | 43/57 (75%) <sup>b</sup>       |  |           |                          |                          |  |  |
|  |                  |             | Mice (C3AF <sub>1</sub> ) | lung                              | Control              | Control                           | Vehicle (0.1 trioctanoin/g body weight) | 4×                       | 142 weeks (m)<br>137 weeks (f) |  |           | 60/99 (61%)              | 50/97 (52%)              | Of the two strains, C3AF <sub>1</sub> mice developed lung tumors with a higher incidence and multiplicity than B6C3F <sub>1</sub> hybrids. |  |
|  |                  |             |                           |                                   | Day 1                | i.p. (3-, 6- and 6-day intervals) | 1.5 µg/g body weight                    | 4×                       | 65 weeks (m)<br>84 weeks (f)   |  |           | 30/32 (94%) <sup>b</sup> | 38/39 (97%) <sup>b</sup> |  |  |
|  |                  |             |                           |                                   |                      |                                   | 3 µg/g body weight                      | 4×                       | 59 weeks (m)<br>76 weeks (f)   |  |           | 49/58 (84%) <sup>b</sup> | 46/50 (92%) <sup>b</sup> |  |  |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                 | Species (strain) | Target site              | Age when first dosed       | Dose route, # doses  | Dose                 | Duration of exposure              | Age at death                   | Tumors <sup>a</sup>      |                          | Comments   | Reference                     |                          |                          |  |                                       |
|--|------------------|--------------------------|----------------------------|----------------------|----------------------|-----------------------------------|--------------------------------|--------------------------|--------------------------|--|-------------------------------|--------------------------|--------------------------|--|---------------------------------------|
|  |                  |                          |                            |                      |                      |                                   |                                | M                        | F                        |  |                               |                          |                          |  |                                       |
| DEN<br>Diethylnitrosamine<br>(continued) |                  |                          | Day 15                     |                      | 1.5 µg/g body weight | 4×                                | 80 weeks (m)<br>101 weeks (f)  | 42/46 (91%) <sup>b</sup> | 61/65 (94%) <sup>b</sup> |  |                               |                          |                          |  |                                       |
|  |                  |                          |                            |                      | 3 µg/g body weight   | 4×                                | 74 weeks (m)<br>92 weeks (f)   | 50/54 (93%) <sup>b</sup> | 57/62 (92%) <sup>b</sup> |  |                               |                          |                          |  |                                       |
|  |                  |                          | Day 42                     |                      | 1.5 µg/g body weight | 4×                                | 104 weeks (m)<br>110 weeks (f) | 55/56 (98%) <sup>b</sup> | 52/53 (98%) <sup>b</sup> |  |                               |                          |                          |  |                                       |
|  |                  |                          |                            |                      | 3 µg/g body weight   | 4×                                | 101 weeks (m)<br>102 weeks (f) | 56/57 (98%) <sup>b</sup> | 54/56 (96%) <sup>b</sup> |  |                               |                          |                          |  |                                       |
|  |                  |                          | Mice (B6C3F <sub>1</sub> ) | liver                | Control              | Control                           | None                           | N/A                      | 90 weeks                 |  |                               | 1/98 (1%)                | 0/96 (0%)                | Infant animals of both sexes (Day 15) were more sensitive than similarly exposed adults. | Vesselinovitch and Mihailovich (1983) |
|  |                  |                          |                            |                      | Gestation day 18     | i.p.                              | 1.5 µg/g body weight           | 1×                       |                          |  |                               | 2/50 (4%) <sup>b</sup>   | 1/51 (2%) <sup>b</sup>   |  |                                       |
|  |                  |                          |                            |                      | Day 15               | i.p. (3-, 6- and 6-day intervals) | 1.5 µg/g body weight           | 4×                       |                          |  |                               | 47/51 (92%) <sup>b</sup> | 60/64 (94%) <sup>b</sup> |  |                                       |
|  |                  |                          |                            |                      | Day 42               |                                   | 1.5 µg/g body weight           | 4×                       |                          |  |                               | 13/49 (26%) <sup>b</sup> | 3/47 (6%) <sup>b</sup>   |  |                                       |
|  | Day 1            | i.p.                     | 1.5 µg/g body weight       | 1×                   | 73 weeks             | 15/59 (25%) <sup>b</sup>          | —                              |                          |                          |  |                               |                          |                          |  |                                       |
|  |                  |                          | 5 µg/g body weight         | 1×                   |                      | 29/45 (64%) <sup>b</sup>          | —                              |                          |                          |  |                               |                          |                          |  |                                       |
|  |                  |                          | 10 µg/g body weight        | 1×                   |                      | 24/25 (96%) <sup>b</sup>          | —                              |                          |                          |  |                               |                          |                          |  |                                       |
|  |                  | Day 15                   | i.p.                       | 1.5 µg/g body weight | 1×                   | 13/24 (54%) <sup>b</sup>          | —                              |                          |                          |  |                               |                          |                          |  |                                       |
| 5 µg/g body weight                       | 1×               | 40/54 (74%) <sup>b</sup> |                            | —                    |                      |                                   |                                |                          |                          |  |                               |                          |                          |  |                                       |
|  |                  |                          |                            |                      |                      |                                   |                                |                          |                          | At the 1.5-µg dose level, 1-day-old mice developed significantly fewer liver tumors than similarly treated infants (Day 15) (p<0.025). | Vesselinovitch et al. (1979a) |                          |                          |  |                                       |
|  |                  |                          |                            |                      |                      |                                   |                                |                          |                          | Tumor incidence in treated groups versus controls was not evaluated.   |                               |                          |                          |  |                                       |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical  | Species (strain)             | Target site                       | Age when first dosed        | Dose route, # doses | Dose                       | Duration of exposure      | Age at death   | Tumors <sup>a</sup>          |                             | Comments   | Reference                |
|---|------------------------------|-----------------------------------|-----------------------------|---------------------|----------------------------|---------------------------|----------------|------------------------------|-----------------------------|--|--------------------------|
|   |                              |                                   |                             |                     |                            |                           |                | M                            | F                           |  |                          |
| DEN<br>Diethylnitrosamine<br>(continued)        |                              |                                   |                             |                     | 10 µg/g<br>body weight     | 1×                        |                | 25/25<br>(100%) <sup>b</sup> | —                           |  |                          |
| DMBA<br>Dimethyl-<br>benz[ <i>a</i> ]anthracene | Rats<br>(Sprague-<br>Dawley) | mammary<br>adeno-<br>sarcoma      | Day 20                      | Gavage              | 10 mg/100 g<br>body weight | 1×                        | Week 25        | —                            | 3/6<br>(50%) <sup>b</sup>   | 36 of 42 (86%) animals<br>dosed at age 20 days<br>died soon after.<br><br>Highest number of<br>tumors per animal was<br>in the 46-day group,<br>with decreasing<br>numbers in the older<br>animals.<br><br>Animals were sacrificed<br>22 weeks after<br>treatment. | Russo et al. (1979)      |
|   |                              |                                   | Day 30                      |                     | 10 mg/100 g<br>body weight | 1×                        | Week 26        | —                            | 14/15<br>(93%) <sup>b</sup> |  |                          |
|   |                              |                                   | Day 40                      |                     | 10 mg/100 g<br>body weight | 1×                        | Week 27        | —                            | 8/9<br>(89%) <sup>b</sup>   |  |                          |
|   |                              |                                   | Day 46                      |                     | 10 mg/100 g<br>body weight | 1×                        | Week 28        | —                            | 8/8<br>(100%) <sup>b</sup>  |  |                          |
|   |                              |                                   | Day 55                      |                     | 10 mg/100 g<br>body weight | 1×                        | Week 29        | —                            | 33/34<br>(97%) <sup>b</sup> |  |                          |
|   |                              |                                   | Day 70                      |                     | 10 mg/100 g<br>body weight | 1×                        | Week 32        | —                            | 5/8<br>(63%) <sup>b</sup>   |  |                          |
|   |                              |                                   | Day 140                     |                     | 10 mg/100 g<br>body weight | 1×                        | Week 42        | —                            | 10/15<br>(67%) <sup>b</sup> |  |                          |
|   |                              |                                   | Day 180                     |                     | 10 mg/100 g<br>body weight | 1×                        | Week 47        | —                            | 14/26<br>(54%) <sup>b</sup> |  |                          |
|   | Rats<br>(Wistar)             | mammary<br>carcinoma <sup>d</sup> | Control<br>5–8<br>weeks     | Control             | None                       | N/A                       | 17<br>months   | 0/22<br>(0%)                 | 0/25<br>(0%)                | Highest tumor rate in<br>females exposed at 5–8<br>weeks.<br><br>Animals were observed<br>for 16 months following<br>treatment.  | Meranze et al.<br>(1969) |
|   |                              |                                   | Control<br>26 weeks         | Control             | None                       | N/A                       | 20<br>months   | 0/31<br>(0%)                 | 2/20<br>(10%)               |  |                          |
|   |                              |                                   | < Week 2                    | Gavage              | 0.5–1.0 mg                 | 1×                        | Week 40–<br>56 | 0/23<br>(0%) <sup>b</sup>    | 4/50<br>(8%) <sup>b</sup>   |  |                          |
|   |                              |                                   | Week 5–8                    |                     | 15 mg                      | 1×                        | Week 14–<br>55 | 0/23<br>(0%) <sup>b</sup>    | 14/25<br>(56%) <sup>b</sup> |  |                          |
|   |                              |                                   | Week 26                     |                     | 15 mg                      | 1×                        | Week 32–<br>73 | 0/34<br>(0%) <sup>b</sup>    | 4/26<br>(15%) <sup>b</sup>  |  |                          |
|   |                              |                                   | Rats (Wistar,<br>castrated) |                     | mammary<br>carcinoma       | Week 5–8                  | Gavage         | 15 mg                        | 1×                          |  |                          |
| Week 26   | 15 mg                        | 1×                                |                             | Week 32–<br>73      |                            | 0/33<br>(0%) <sup>b</sup> |                | 0/26<br>(0%) <sup>b</sup>    |                             |  |                          |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical   | Species (strain) | Target site  | Age when first dosed    | Dose route, # doses | Dose                       | Duration of exposure | Age at death               | Tumors <sup>a</sup>          |                              | Comments  | Reference      |
|--|------------------|--------------|-------------------------|---------------------|----------------------------|----------------------|----------------------------|------------------------------|------------------------------|---|----------------|
|  |                  |              |                         |                     |                            |                      |                            | M                            | F                            |   |                |
| DMBA<br>Dimethyl-<br>benz[ <i>a</i> ]anthracene<br>(continued) | Rats<br>(Wistar) | Total tumors | Control<br>5–8<br>weeks | Control             | None                       | N/A                  | 17<br>months               | 0/22<br>(0%)                 | 0/25<br>(0%)                 | Total tumors includes<br>leukemia.  |                |
|  |                  |              | Control<br>26 weeks     | Control             | None                       | N/A                  | 20<br>months               | 2/31<br>(6%)                 | 5/20<br>(25%)                |   |                |
|  |                  |              | < Week 2                | Gavage              | 0.5–1.0 mg                 | 1×                   | Week 40–<br>56             | 16/23<br>(70%) <sup>b</sup>  | 36/50<br>(72%) <sup>b</sup>  |   |                |
|  |                  |              | Week 5–8                |                     | 15 mg                      | 1×                   | Week 14–<br>55             | 7/23<br>(30%) <sup>b</sup>   | 16/25<br>(64%) <sup>b</sup>  |   |                |
|  |                  |              | Week 26                 |                     | 15 mg                      | 1×                   | Week 32–<br>73             | 12/34<br>(35%) <sup>b</sup>  | 13/26<br>(50%) <sup>b</sup>  |   |                |
|  | Mice<br>(BALB/c) | lung         | Control:<br>Day 1       | Control<br>s.c.     | Aqueous<br>gelatine        | 1×                   | 40 weeks                   | 0/12<br>(0%)                 | 7/23<br>(30%)                | 15 µg DMBA gave rise<br>to a significantly greater<br>incidence of lung<br>tumors when<br>administered to<br>newborn mice than to<br>suckling or young<br>adults. | Walters (1966) |
|  |                  |              | Day 1                   | s.c.                | 15 µg                      | 1×                   | 40 weeks <sup>f</sup>      | 14/14<br>(100%) <sup>b</sup> | 24/24<br>(100%) <sup>b</sup> |   |                |
|  |                  |              | Week 2–3<br>(suckling)  | s.c.                | 15 µg                      | 1×                   | 42–43<br>weeks             | 12/23<br>(52%) <sup>b</sup>  | 16/22<br>(73%) <sup>b</sup>  |   |                |
|  |                  |              |                         | s.c.                | 30 µg<br>(60 µg total)     | 2×                   | 42–43<br>weeks             | 14/14<br>(100%) <sup>b</sup> | 24/24<br>(100%) <sup>b</sup> |   |                |
|  |                  |              | Adult <sup>e</sup>      | s.c.                | 15 µg                      | 1×                   | 48–49<br>weeks             | 6/12<br>(50%) <sup>b</sup>   | 15/33<br>(45%) <sup>b</sup>  |   |                |
|  |                  |              |                         | s.c.                | 30 µg<br>(60 µg total)     | 2×                   | 48–49<br>weeks             | 9/10<br>(90%) <sup>b</sup>   | 21/23<br>(91%) <sup>b</sup>  |   |                |
|  |                  |              |                         | s.c.                | 30 µg<br>(180 µg<br>total) | 6×                   | 48–49<br>weeks             | 12/12<br>(100%) <sup>b</sup> | 13/13<br>(100%) <sup>b</sup> |   |                |
|  |                  |              | Mice (Swiss)            | lymphoma            | Control                    | Control              | None                       | N/A                          | 31–52<br>weeks               |   |                |
| Day 1  | i.p.             | 30–40 µg     |                         |                     | 1×                         | 13–33<br>weeks       | 6/31<br>(19%) <sup>b</sup> |                              |                              |   |                |
| Day 1  | s.c.             | 30–40 µg     |                         |                     | 1×                         | 12–27<br>weeks       | 8/27<br>(30%) <sup>b</sup> |                              |                              |   |                |
| Week 8   | s.c.             | 900 µg       |                         |                     | 1×                         | 30 weeks             | 1/13<br>(8%) <sup>b</sup>  |                              |                              |   |                |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical   | Species (strain) | Target site      | Age when first dosed   | Dose route, # doses | Dose     | Duration of exposure | Age at death | Tumors <sup>a</sup>         |   | Comments   | Reference   |
|--|------------------|------------------|------------------------|---------------------|----------|----------------------|--------------|-----------------------------|---|--|-------------|
|  |                  |                  |                        |                     |          |                      |              | M                           | F |  |             |
| DMBA<br>Dimethyl-<br>benz[ <i>a</i> ]anthracene<br>(continued) | Mice (Swiss)     | lung             | Control                | Control             | None     | N/A                  | 31–52 weeks  | 4/408<br>(0.9%)             |   |  |             |
|  |                  |                  | Day 1                  | i.p.                | 30–40 µg | 1×                   | 13–33 weeks  | 24/31<br>(77%) <sup>b</sup> |   |  |             |
|  |                  |                  | Day 1                  | s.c.                | 30–40 µg | 1×                   | 12–27 weeks  | 23/27<br>(85%) <sup>b</sup> |   |  |             |
|  |                  |                  | Week 8                 | s.c.                | 900 µg   | 1×                   | 30 weeks     | 2/13<br>(15%) <sup>b</sup>  |   |  |             |
| DMN<br>Dimethyl-<br>nitrosamine                                | Rats<br>(Wistar) | kidney carcinoma | Day 1                  | i.p.                | 20 mg/kg | 1×                   | ≥5 months    | 1/33 (3) <sup>b</sup>       |   | In the neonatal group, the dose was reduced to 20 mg/kg to achieve approximately equivalent numbers of survivors.<br><br>No control group. | Hard (1979) |
|  |                  |                  | Day 21                 |                     | 30 mg/kg | 1×                   |              | 5/39 (13) <sup>b</sup>      |   |  |             |
|  |                  |                  | Month 1                |                     | 30 mg/kg | 1×                   |              | 2/33 (6) <sup>b</sup>       |   |  |             |
|  |                  |                  | Month 1.5              |                     | 30 mg/kg | 1×                   |              | 1/28 (4) <sup>b</sup>       |   |  |             |
|  |                  |                  | Month 2                |                     | 30 mg/kg | 1×                   |              | 1/26 (4) <sup>b</sup>       |   |  |             |
|  |                  |                  | Month 3                |                     | 30 mg/kg | 1×                   |              | 10/27 (37) <sup>b</sup>     |   |  |             |
|  |                  |                  | Month 4                |                     | 30 mg/kg | 1×                   |              | 7/32 (22) <sup>b</sup>      |   |  |             |
|  |                  |                  | Month 5                |                     | 30 mg/kg | 1×                   |              | 0/14 (0) <sup>b</sup>       |   |  |             |
|  | Rats<br>(Wistar) | kidney adenoma   | Day 1                  | i.p.                | 20 mg/kg | 1×                   | ≥5 months    | 1/33 (3) <sup>b</sup>       |   |  |             |
|  |                  |                  | Day 21                 |                     | 30 mg/kg | 1×                   |              | 13/39 (33) <sup>b</sup>     |   |  |             |
|  |                  |                  | Month 1                |                     | 30 mg/kg | 1×                   |              | 11/33 (33) <sup>b</sup>     |   |  |             |
|  |                  |                  | Month 1.5              |                     | 30 mg/kg | 1×                   |              | 13/28 (48) <sup>b</sup>     |   |  |             |
|  |                  |                  | Month 2                |                     | 30 mg/kg | 1×                   |              | 11/26 (42) <sup>b</sup>     |   |  |             |
|  |                  |                  | Month 3                |                     | 30 mg/kg | 1×                   |              | 18/27 (67) <sup>b</sup>     |   |  |             |
|  |                  |                  | Month 4                |                     | 30 mg/kg | 1×                   |              | 17/32 (53) <sup>b</sup>     |   |  |             |
| Month 5  | 30 mg/kg         | 1×               | 6/14 (43) <sup>b</sup> |                     |          |                      |              |                             |   |  |             |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                       | Species (strain) | Target site                                | Age when first dosed | Dose route, # doses | Dose     | Duration of exposure | Age at death | Tumors <sup>a</sup>     |   | Comments  | Reference |
|--|------------------|--|----------------------|---------------------|----------|----------------------|--------------|-------------------------|---|---|-----------|
|  |                  |  |                      |                     |          |                      |              | M                       | F |   |           |
| DMN<br>Dimethyl-<br>nitrosamine<br>(continued) | Rats<br>(Wistar) | kidney<br>mesenchymal<br>tumors            | Day 1                | i.p.                | 20 mg/kg | 1×                   | ≥5<br>months | 8/33 (24) <sup>b</sup>  |   | Mesenchymal tumors<br>were most frequent in<br>the three youngest age<br>groups (z test,<br>p < 0.001). |           |
|  |                  |  | Day 21               |                     | 30 mg/kg | 1×                   |              | 18/39 (46) <sup>b</sup> |   |   |           |
|  |                  |  | Month 1              |                     | 30 mg/kg | 1×                   |              | 23/33 (70) <sup>b</sup> |   |   |           |
|  |                  |  | Month 1.5            |                     | 30 mg/kg | 1×                   |              | 5/28 (19) <sup>b</sup>  |   |   |           |
|  |                  |  | Month 2              |                     | 30 mg/kg | 1×                   |              | 2/26 (8) <sup>b</sup>   |   |   |           |
|  |                  |  | Month 3              |                     | 30 mg/kg | 1×                   |              | 3/27 (11) <sup>b</sup>  |   |   |           |
|  |                  |  | Month 4              |                     | 30 mg/kg | 1×                   |              | 7/32 (22) <sup>b</sup>  |   |   |           |
|  |                  |  | Month 5              |                     | 30 mg/kg | 1×                   |              | 0/14 (0) <sup>b</sup>   |   |   |           |
|  | Rats<br>(Wistar) | kidney<br>cortical<br>epithelial<br>tumors | Day 1                | i.p.                | 20 mg/kg | 1×                   | ≥5<br>months | 2/33 (6) <sup>b</sup>   |   |   |           |
|  |                  |  | Day 21               |                     | 30 mg/kg | 1×                   |              | 16/39 (41) <sup>b</sup> |   |   |           |
|  |                  |  | Month 1              |                     | 30 mg/kg | 1×                   |              | 12/33 (36) <sup>b</sup> |   |   |           |
|  |                  |  | Month 1.5            |                     | 30 mg/kg | 1×                   |              | 14/28 (52) <sup>b</sup> |   |   |           |
|  |                  |  | Month 2              |                     | 30 mg/kg | 1×                   |              | 11/26 (42) <sup>b</sup> |   |   |           |
|  |                  |  | Month 3              |                     | 30 mg/kg | 1×                   |              | 18/27 (67) <sup>b</sup> |   |   |           |
|  |                  |  | Month 4              |                     | 30 mg/kg | 1×                   |              | 21/32 (66) <sup>b</sup> |   |   |           |
|  |                  |  | Month 5              |                     | 30 mg/kg | 1×                   |              | 6/14 (43) <sup>b</sup>  |   |   |           |
|  | Rats<br>(Wistar) | Total tumors                               | Day 1                | i.p.                | 20 mg/kg | 1×                   | ≥5<br>months | 11/33 (33) <sup>b</sup> |   |   |           |
|  |                  |  | Day 21               |                     | 30 mg/kg | 1×                   |              | 25/39 (64) <sup>b</sup> |   |   |           |
|  |                  |  | Month 1              |                     | 30 mg/kg | 1×                   |              | 25/33 (76) <sup>b</sup> |   |   |           |
|  |                  |  | Month 1.5            |                     | 30 mg/kg | 1×                   |              | 17/28 (63) <sup>b</sup> |   |   |           |
|  |                  |  | Month 2              |                     | 30 mg/kg | 1×                   |              | 13/26 (50) <sup>b</sup> |   |   |           |
|  |                  |  | Month 3              |                     | 30 mg/kg | 1×                   |              | 18/27 (67) <sup>b</sup> |   |   |           |
|  |                  |  | Month 4              |                     | 30 mg/kg | 1×                   |              | 22/32 (69) <sup>b</sup> |   |   |           |
|  |                  |  | Month 5              |                     | 30 mg/kg | 1×                   |              | 7/14 (50) <sup>b</sup>  |   |   |           |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                | Species (strain)           | Target site    | Age when first dosed | Dose route, # doses | Dose                | Duration of exposure | Age at death | Tumors <sup>a</sup>       |  | Comments   | Reference                    |
|-------------------------|----------------------------|----------------|----------------------|---------------------|---------------------|----------------------|--------------|---------------------------|--|--|------------------------------|
|                         |                            |                |                      |                     |                     |                      |              | M                         | F  |  |                              |
| ENU<br>Ethylnitrosourea | Rats                       | nervous system | Day 1                | Injection           | 20 mg/kg            | 1×                   | 90 weeks     | 100% <sup>b</sup>         |  | Susceptibility to neuro-oncogenic effect declined with increasing age.                 | Maekawa and Mitsumori (1990) |
|                         |                            |                | Day 30               | Injection           | 20 mg/kg            | 1×                   |              | 61% <sup>b</sup>          |  |  |                              |
|                         | Mice (B6C3F <sub>1</sub> ) | liver          | Control              | Control             | None                | N/A                  | 90 weeks     | 1/98 (1%)                 | 0/96 (0%)  | Both male and female mice were responsive to exposure during prenatal and infant life. | Vesselinovitch (1983)        |
|                         |                            |                | Gestation day 18     | i.p.                | 60 µg/g body weight | 1×                   |              | 28/52 (54%) <sup>b</sup>  | 18/49 (37%) <sup>b</sup>   |  |                              |
|                         |                            |                | Day 15               |                     | 60 µg/g body weight | 1×                   |              | 41/50 (82%) <sup>b</sup>  | 28/51 (55%) <sup>b</sup>   |  |                              |
|                         |                            |                | Day 42               |                     | 60 µg/g body weight | 1×                   |              | 10/50 (20%) <sup>b</sup>  | 5/50 (10%) <sup>b</sup>  |  |                              |
|                         | Rats (Wistar)              | nerve tissue   | Control              | Control             | None                | N/A                  | 4–7 months   | 0/16 (0%)                 | 0/10 (0%)  | Highest tumor rate seen when exposed during gestation or soon after birth.             | Naito et al. (1981)          |
|                         |                            |                | Gestation day 16     | i.p.                | 40 mg/kg            | 1×                   |              | 26/26 (100%) <sup>b</sup> | 18/18 (100%) <sup>b</sup>  |  |                              |
|                         |                            |                | Day 1                | s.c.                | 40 mg/kg            | 1×                   |              | 12/12 (100%) <sup>g</sup> | 16/16 (100%) <sup>g</sup>  |  |                              |
|                         |                            |                | Week 1               |                     | 40 mg/kg            | 1×                   |              | 12/17 (71%) <sup>b</sup>  | 18/20 (90%) <sup>b</sup>   |  |                              |
|                         |                            |                | Week 2               |                     | 40 mg/kg            | 1×                   |              | 10/14 (71%) <sup>b</sup>  | 14/18 (78%) <sup>b</sup>   |  |                              |
|                         |                            |                | Week 3               |                     | 40 mg/kg            | 1×                   |              | 6/13 (46%) <sup>b</sup>   | 5/17 (29%) <sup>b</sup>  |  |                              |
|                         |                            |                | Week 4               |                     | 40 mg/kg            | 1×                   |              | 8/15 (53%) <sup>b</sup>   | 2/10 (20%) <sup>b</sup>  |  |                              |
|                         |                            |                |                      |                     |                     |                      |              |                           | Statistically significant decrease in tumor incidence with increasing age of exposure. |  |                              |



**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                               | Species (strain)              | Target site | Age when first dosed | Dose route, # doses | Dose                | Duration of exposure | Age at death | Tumors <sup>a</sup>          |                              | Comments | Reference                    |                             |
|--|-------------------------------|-------------|----------------------|---------------------|---------------------|----------------------|--------------|------------------------------|------------------------------|----------|------------------------------|-----------------------------|
|  |                               |             |                      |                     |                     |                      |              | M                            | F                            |          |                              |                             |
| ENU<br>Ethylnitrosourea<br>(continued) | Mice<br>(B6C3F <sub>1</sub> ) | lung        | Day 1                | i.p.                | 60 µg/g body weight | 1×                   |              | 49/55<br>(89%) <sup>b</sup>  | 49/50<br>(98%) <sup>b</sup>  |          | Vesselinovitch et al. (1974) |                             |
|  |                               |             | Day 15               |                     |                     | 1×                   |              | 50/55<br>(91%) <sup>b</sup>  | 47/55<br>(85%) <sup>b</sup>  |          |                              |                             |
|  |                               |             | Day 42               |                     |                     | 1×                   |              | 53/59<br>(90%) <sup>b</sup>  | 44/51<br>(86%) <sup>b</sup>  |          |                              |                             |
|  |                               |             | Day 1                |                     |                     | 120 µg/g body weight |              | 1×                           | 36/38<br>(95%) <sup>b</sup>  |          |                              | 54/60<br>(90%) <sup>b</sup> |
|  |                               |             | Day 15               |                     |                     | 1×                   |              | 45/49<br>(92%) <sup>b</sup>  | 43/50<br>(86%) <sup>b</sup>  |          |                              |                             |
|  |                               |             | Day 42               |                     |                     | 1×                   |              | 52/54<br>(96%) <sup>b</sup>  | 50/57<br>(88%) <sup>b</sup>  |          |                              |                             |
|  | Mice<br>(C3AF <sub>1</sub> )  | lung        | Day 1                |                     | 60 µg/g body weight | 1×                   |              | 46/47<br>(98%) <sup>g</sup>  | 51/51<br>(100%) <sup>g</sup> |          |                              |                             |
|  |                               |             | Day 15               |                     |                     | 1×                   |              | 49/49<br>(100%) <sup>g</sup> | 57/59<br>(97%) <sup>g</sup>  |          |                              |                             |
|  |                               |             | Day 42               |                     |                     | 1×                   |              | 59/59<br>(100%) <sup>g</sup> | 57/57<br>(100%) <sup>g</sup> |          |                              |                             |
|  |                               |             | Day 1                |                     |                     | 120 µg/g body weight |              | 1×                           | 63/64<br>(98%) <sup>g</sup>  |          |                              | 53/57<br>(93%) <sup>g</sup> |
|  |                               |             | Day 15               |                     |                     | 1×                   |              | 54/56<br>(96%) <sup>g</sup>  | 50/56<br>(89%) <sup>g</sup>  |          |                              |                             |
|  |                               |             | Day 42               |                     |                     | 1×                   |              | 59/59<br>(100%) <sup>g</sup> | 48/48<br>(100%) <sup>g</sup> |          |                              |                             |
|  | Mice<br>(B6C3F <sub>1</sub> ) | liver       | Day 1                | i.p.                | 60 µg/g body weight | 1×                   |              | 50/54<br>(93%) <sup>g</sup>  | 28/43<br>(65%) <sup>g</sup>  |          |                              |                             |
|  |                               |             | Day 15               |                     |                     | 1×                   |              | 55/56<br>(98%) <sup>g</sup>  | 33/54<br>(61%) <sup>g</sup>  |          |                              |                             |
|  |                               |             | Day 42               |                     |                     | 1×                   |              | 12/40<br>(30%) <sup>b</sup>  | 6/39<br>(15%) <sup>b</sup>   |          |                              |                             |
|  |                               |             | Day 1                |                     |                     | 120 µg/g body weight |              | 1×                           | 29/34<br>(85%) <sup>g</sup>  |          |                              | 32/53<br>(60%) <sup>g</sup> |
|  |                               |             | Day 15               |                     |                     | 1×                   |              | 45/48<br>(94%) <sup>g</sup>  | 29/43<br>(67%) <sup>g</sup>  |          |                              |                             |
|  |                               |             | Day 42               |                     |                     | 1×                   |              | 17/49<br>(35%) <sup>g</sup>  | 4/50<br>(8%) <sup>g</sup>    |          |                              |                             |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                               | Species (strain)              | Target site | Age when first dosed | Dose route, # doses | Dose                | Duration of exposure | Age at death | Tumors <sup>a</sup>         |                             | Comments | Reference |                             |
|--|-------------------------------|-------------|----------------------|---------------------|---------------------|----------------------|--------------|-----------------------------|-----------------------------|----------|-----------|-----------------------------|
|  |                               |             |                      |                     |                     |                      |              | M                           | F                           |          |           |                             |
| ENU<br>Ethylnitrosourea<br>(continued) | Mice<br>(C3AF <sub>1</sub> )  | liver       | Day 1                | i.p.                | 60 µg/g body weight | 1×                   |              | 42/45<br>(93%) <sup>g</sup> | 19/41<br>(46%) <sup>g</sup> |          |           |                             |
|  |                               |             | Day 15               |                     |                     |                      |              | 42/50<br>(84%) <sup>g</sup> | 19/48<br>(40%) <sup>g</sup> |          |           |                             |
|  |                               |             | Day 42               |                     |                     |                      |              | 7/29<br>(24%) <sup>b</sup>  | 4/50<br>(8%) <sup>b</sup>   |          |           |                             |
|  |                               |             | Day 1                |                     |                     | 120 µg/g body weight |              | 1×                          | 55/62<br>(89%) <sup>g</sup> |          |           | 19/45<br>(42%) <sup>g</sup> |
|  |                               |             | Day 15               |                     |                     |                      |              |                             | 35/45<br>(78%) <sup>g</sup> |          |           | 15/35<br>(43%) <sup>g</sup> |
|  |                               |             | Day 42               |                     |                     |                      |              |                             | 8/33<br>(24%) <sup>b</sup>  |          |           | 3/33<br>(9%) <sup>b</sup>   |
|  | Mice<br>(B6C3F <sub>1</sub> ) | kidney      | Day 1                | i.p.                | 60 µg/g body weight | 1×                   |              | 11/48<br>(23%) <sup>b</sup> | 5/49<br>(10%) <sup>b</sup>  |          |           |                             |
|  |                               |             | Day 15               |                     |                     |                      |              | 6/41<br>(15%) <sup>b</sup>  | 7/31<br>(23%) <sup>b</sup>  |          |           |                             |
|  |                               |             | Day 42               |                     |                     |                      |              | 4/40<br>(10%) <sup>b</sup>  | 3/37<br>(8%) <sup>b</sup>   |          |           |                             |
|  |                               |             | Day 1                |                     |                     | 120 µg/g body weight |              | 1×                          | 10/30<br>(33%) <sup>g</sup> |          |           | 14/53<br>(26%) <sup>b</sup> |
|  |                               |             | Day 15               |                     |                     |                      |              |                             | 17/37<br>(46%) <sup>g</sup> |          |           | 19/49<br>(39%) <sup>b</sup> |
|  |                               |             | Day 42               |                     |                     |                      |              |                             | 8/40<br>(20%) <sup>b</sup>  |          |           | 11/39<br>(28%) <sup>b</sup> |
|  | Mice<br>(C3AF <sub>1</sub> )  | kidney      | Day 1                | i.p.                | 60 µg/g body weight | 1×                   |              | 7/44<br>(16%) <sup>b</sup>  | 6/45<br>(13%) <sup>b</sup>  |          |           |                             |
|  |                               |             | Day 15               |                     |                     |                      |              | 7/41<br>(17%) <sup>b</sup>  | 8/46<br>(17%) <sup>b</sup>  |          |           |                             |
|  |                               |             | Day 42               |                     |                     |                      |              | 3/42<br>(42%) <sup>b</sup>  | 3/43<br>(7%) <sup>b</sup>   |          |           |                             |
|  |                               |             | Day 1                |                     |                     | 120 µg/g body weight |              | 1×                          | 4/52<br>(7%) <sup>b</sup>   |          |           | 6/29<br>(21%) <sup>g</sup>  |
|  |                               |             | Day 15               |                     |                     |                      |              |                             | 8/35<br>(23%) <sup>b</sup>  |          |           | 12/29<br>(41%) <sup>g</sup> |
|  |                               |             | Day 42               |                     |                     |                      |              |                             | 6/41<br>(71%) <sup>b</sup>  |          |           | 3/39<br>(8%) <sup>b</sup>   |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                               | Species (strain)              | Target site | Age when first dosed | Dose route, # doses | Dose                | Duration of exposure | Age at death | Tumors <sup>a</sup>         |                             | Comments | Reference |  |                             |                             |
|--|-------------------------------|-------------|----------------------|---------------------|---------------------|----------------------|--------------|-----------------------------|-----------------------------|----------|-----------|--|-----------------------------|-----------------------------|
|  |                               |             |                      |                     |                     |                      |              | M                           | F                           |          |           |  |                             |                             |
| ENU<br>Ethylnitrosourea<br>(continued) | Mice<br>(B6C3F1)              | Harderian   | Day 1                |                     | 60 µg/g body weight | 1×                   |              | 7/40<br>(17%) <sup>b</sup>  | 5/43<br>(12%) <sup>b</sup>  |          |           |  |                             |                             |
|  |                               |             | Day 15               |                     |                     |                      |              | 10/51<br>(20%) <sup>b</sup> | 17/59<br>(29%) <sup>b</sup> |          |           |  |                             |                             |
|  |                               |             | Day 42               |                     |                     |                      |              | 14/50<br>(28%) <sup>b</sup> | 14/45<br>(31%) <sup>b</sup> |          |           |  |                             |                             |
|  |                               |             | Day 1                |                     |                     |                      |              | 120 µg/g body weight        | 1×                          |          |           |  | 9/30<br>(30%) <sup>g</sup>  | 6/52<br>(12%) <sup>b</sup>  |
|  |                               |             | Day 15               |                     |                     |                      |              |                             |                             |          |           |  | 15/41<br>(37%) <sup>g</sup> | 8/31<br>(26%) <sup>b</sup>  |
|  |                               |             | Day 42               |                     |                     |                      |              |                             |                             |          |           |  | 25/48<br>(52%) <sup>g</sup> | 14/49<br>(29%) <sup>b</sup> |
|  | Mice<br>(C3AF <sub>1</sub> )  | Harderian   | Day 1                |                     | 60 µg/g body weight | 1×                   |              | 3/25<br>(12%) <sup>b</sup>  | 4/35<br>(11%) <sup>b</sup>  |          |           |  |                             |                             |
|  |                               |             | Day 15               |                     |                     |                      |              | 1/9<br>(11%) <sup>b</sup>   | 6/38<br>(16%) <sup>b</sup>  |          |           |  |                             |                             |
|  |                               |             | Day 42               |                     |                     |                      |              | 12/48<br>(25%) <sup>b</sup> | 5/33<br>(15%) <sup>b</sup>  |          |           |  |                             |                             |
|  |                               |             | Day 1                |                     |                     |                      |              | 120 µg/g body weight        | 1×                          |          |           |  | 3/52<br>(6%) <sup>b</sup>   | 1/25<br>(4%) <sup>b</sup>   |
|  |                               |             | Day 15               |                     |                     |                      |              |                             |                             |          |           |  | 6/46<br>(13%) <sup>b</sup>  | 2/52<br>(4%) <sup>b</sup>   |
|  |                               |             | Day 42               |                     |                     |                      |              |                             |                             |          |           |  | 5/29<br>(17%) <sup>b</sup>  | 2/11<br>(18%) <sup>b</sup>  |
|  | Mice<br>(B6C3F <sub>1</sub> ) | stomach     | Day 1                |                     | 60 µg/g body weight | 1×                   |              | 3/48<br>(6%) <sup>b</sup>   | 4/43<br>(9%) <sup>b</sup>   |          |           |  |                             |                             |
|  |                               |             | Day 15               |                     |                     |                      |              | 10/42<br>(24%) <sup>g</sup> | 7/45<br>(16%) <sup>b</sup>  |          |           |  |                             |                             |
|  |                               |             | Day 42               |                     |                     |                      |              | 9/51<br>(18%) <sup>g</sup>  | 8/36<br>(22%) <sup>b</sup>  |          |           |  |                             |                             |
|  |                               |             | Day 1                |                     |                     |                      |              | 120 µg/g body weight        | 1×                          |          |           |  | 2/29<br>(7%) <sup>b</sup>   | 9/53<br>(17%) <sup>b</sup>  |
|  |                               |             | Day 15               |                     |                     |                      |              |                             |                             |          |           |  | 10/35<br>(29%) <sup>g</sup> | 12/33<br>(36%) <sup>b</sup> |
|  |                               |             | Day 42               |                     |                     |                      |              |                             |                             |          |           |  | 12/53<br>(23%) <sup>g</sup> | 12/50<br>(24%) <sup>b</sup> |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                               | Species (strain)              | Target site         | Age when first dosed | Dose route, # doses | Dose                | Duration of exposure | Age at death | Tumors <sup>a</sup>         |                             | Comments | Reference |  |                             |                             |
|--|-------------------------------|---------------------|----------------------|---------------------|---------------------|----------------------|--------------|-----------------------------|-----------------------------|----------|-----------|--|-----------------------------|-----------------------------|
|  |                               |                     |                      |                     |                     |                      |              | M                           | F                           |          |           |  |                             |                             |
| ENU<br>Ethylnitrosourea<br>(continued) | Mice<br>(C3AF <sub>1</sub> )  | stomach             | Day 1                |                     | 60 µg/g body weight | 1×                   |              | 2/39<br>(5%) <sup>b</sup>   | 7/45<br>(16%) <sup>b</sup>  |          |           |  |                             |                             |
|  |                               |                     | Day 15               |                     |                     |                      |              | 7/45<br>(16%) <sup>g</sup>  | 7/38<br>(18%) <sup>b</sup>  |          |           |  |                             |                             |
|  |                               |                     | Day 42               |                     |                     |                      |              | 14/55<br>(25%) <sup>g</sup> | 7/49<br>(14%) <sup>b</sup>  |          |           |  |                             |                             |
|  |                               |                     | Day 1                |                     |                     |                      |              | 120 µg/g body weight        | 1×                          |          |           |  | 8/60<br>(13%) <sup>b</sup>  | 9/44<br>(20%) <sup>b</sup>  |
|  |                               |                     | Day 15               |                     |                     |                      |              |                             |                             |          |           |  | 16/51<br>(31%) <sup>g</sup> | 11/42<br>(26%) <sup>b</sup> |
|  |                               |                     | Day 42               |                     |                     |                      |              |                             |                             |          |           |  | 19/48<br>(40%) <sup>g</sup> | 13/37<br>(35%) <sup>b</sup> |
|  | Mice<br>(B6C3F <sub>1</sub> ) | malignant lymphomas | Day 1                |                     | 60 µg/g body weight | 1×                   |              | 2/55<br>(4%) <sup>b</sup>   | 6/52<br>(12%) <sup>g</sup>  |          |           |  |                             |                             |
|  |                               |                     | Day 15               |                     |                     |                      |              | 3/56<br>(5%) <sup>b</sup>   | 14/59<br>(24%) <sup>g</sup> |          |           |  |                             |                             |
|  |                               |                     | Day 42               |                     |                     |                      |              | 9/59<br>(15%) <sup>b</sup>  | 17/59<br>(29%) <sup>g</sup> |          |           |  |                             |                             |
|  |                               |                     | Day 1                |                     |                     |                      |              | 120 µg/g body weight        | 1×                          |          |           |  | 8/39<br>(20%) <sup>b</sup>  | 15/65<br>(23%) <sup>g</sup> |
|  |                               |                     | Day 15               |                     |                     |                      |              |                             |                             |          |           |  | 14/60<br>(23%) <sup>b</sup> | 17/58<br>(29%) <sup>g</sup> |
|  |                               |                     | Day 42               |                     |                     |                      |              |                             |                             |          |           |  | 12/59<br>(20%) <sup>b</sup> | 14/60<br>(23%) <sup>g</sup> |
|  | Mice<br>(C3AF <sub>1</sub> )  | malignant lymphomas | Day 1                |                     | 60 µg/g body weight | 1×                   |              | 6/49<br>(12%) <sup>b</sup>  | 8/49<br>(16%) <sup>g</sup>  |          |           |  |                             |                             |
|  |                               |                     | Day 15               |                     |                     |                      |              | 3/49<br>(6%) <sup>b</sup>   | 13/61<br>(21%) <sup>g</sup> |          |           |  |                             |                             |
|  |                               |                     | Day 42               |                     |                     |                      |              | 6/60<br>(10%) <sup>b</sup>  | 9/55<br>(16%) <sup>g</sup>  |          |           |  |                             |                             |
|  |                               |                     | Day 1                |                     |                     |                      |              | 120 µg/g body weight        | 1×                          |          |           |  | 3/66<br>(5%) <sup>b</sup>   | 10/58<br>(17%) <sup>g</sup> |
|  |                               |                     | Day 15               |                     |                     |                      |              |                             |                             |          |           |  | 10/56<br>(18%) <sup>b</sup> | 18/60<br>(30%) <sup>g</sup> |
|  |                               |                     | Day 42               |                     |                     |                      |              |                             |                             |          |           |  | 3/49<br>(6%) <sup>b</sup>   | 13/50<br>(26%) <sup>g</sup> |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                 | Species (strain)             | Target site          | Age when first dosed | Dose route, # doses | Dose                | Duration of exposure | Age at death               | Tumor incidence <sup>a</sup> |                             | Comments   | Reference                  |
|--------------------------|------------------------------|----------------------|----------------------|---------------------|---------------------|----------------------|----------------------------|------------------------------|-----------------------------|--|----------------------------|
|                          |                              |                      |                      |                     |                     |                      |                            | M                            | F                           |  |                            |
| NMU<br>Methylnitrosourea | Mice<br>(BC3F <sub>1</sub> ) | Total tumors         | Control              | Control             | N/A                 | N/A                  | 60 weeks                   | 1/20<br>(5%)                 | 0%                          | Control mice did not exhibit tumors in target sites except a single hepatoma in a male control mouse.  | Terracini and Testa (1970) |
|                          |                              | lung                 | Day 1                | i.p.                | 50 µg/g body weight | 1×                   | 60 weeks                   | 12/15<br>(80%) <sup>b</sup>  | 16/19<br>(84%) <sup>b</sup> |  |                            |
|                          |                              |                      | 5 weeks              |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 10/26<br>(39%) <sup>b</sup>  | 10/35<br>(29%) <sup>b</sup> |  |                            |
|                          |                              | lympho-sarcoma       | Day 1                |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 23/39<br>(59%) <sup>b</sup>  | 23/45<br>(51%) <sup>b</sup> |  |                            |
|                          |                              |                      | 5 weeks              |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 11/35<br>(31%) <sup>b</sup>  | 21/45<br>(47%) <sup>b</sup> |  |                            |
|                          |                              | liver                | Day 1                |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 10/12<br>(83%) <sup>b</sup>  | 1/17<br>(6%) <sup>b</sup>   |  |                            |
|                          |                              |                      | 5 weeks              |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 0% <sup>b</sup>              | 0% <sup>c</sup>             |  |                            |
|                          |                              | kidney               | Day 1                |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 3/15<br>(20%) <sup>b</sup>   | 3/18<br>(17%) <sup>b</sup>  |  |                            |
|                          | 5 weeks                      |                      | 50 µg/g body weight  |                     | 1×                  | 60 weeks             | 2/21<br>(10%) <sup>b</sup> | 0% <sup>c</sup>              |                             |  |                            |
|                          | fore-stomach                 | Day 1                |                      | 50 µg/g body weight | 1×                  | 60 weeks             | 0% <sup>b</sup>            | 4/17<br>(24%) <sup>b</sup>   |                             |  |                            |
|                          |                              | 5 weeks              |                      | 50 µg/g body weight | 1×                  | 60 weeks             | 8/22<br>(36%) <sup>b</sup> | 12/18<br>(67%) <sup>b</sup>  |                             |  |                            |
|                          | Rats<br>(Wistar)             | mammary              | Day 1                | i.p.                | 50 µg/g body weight | 1×                   | 60 weeks                   | 0% <sup>b</sup>              | 4/14<br>(29%) <sup>b</sup>  | Tumor incidence for control rats was based on previous experiments (Della Porta et al., 1968) and was not specifically reported in this paper. | Terracini and Testa (1970) |
|                          |                              |                      | 5 weeks              |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 0% <sup>b</sup>              | 3/5<br>(60%) <sup>b</sup>   |  |                            |
|                          |                              | lympho-sarcoma       | Day 1                |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 1/10<br>(10%) <sup>b</sup>   | 0% <sup>b</sup>             |  |                            |
|                          |                              |                      | 5 weeks              |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 2/8<br>(25%) <sup>b</sup>    | 1/11<br>(9%) <sup>b</sup>   |  |                            |
|                          |                              | kidney (ana-plastic) | Day 1                |                     | 50 µg/g body weight | 1×                   | 60 weeks                   | 14/18<br>(78%) <sup>b</sup>  | 9/13<br>(69%) <sup>b</sup>  |  |                            |
| 5 weeks                  |                              |                      | 50 µg/g body weight  |                     | 1×                  | 60 weeks             | 2/5<br>(40%) <sup>b</sup>  | 5/12<br>(42%) <sup>b</sup>   |                             |  |                            |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                | Species (strain)  | Target site      | Age when first dosed | Dose route, # doses | Dose                    | Duration of exposure | Age at death                              | Tumor incidence <sup>a</sup> |                             | Comments  | Reference               |
|---|-------------------|------------------|----------------------|---------------------|-------------------------|----------------------|---|------------------------------|-----------------------------|---|-------------------------|
|   |                   |                  |                      |                     |                         |                      |   | M                            | F                           |   |                         |
| NMU<br>Methylnitrosourea<br>(continued) |                   | kidney (adenoma) | Day 1                |                     | 50 µg/g body weight     | 1×                   | 60 weeks                                  | 3/14<br>(21%) <sup>b</sup>   | 2/6<br>(33%) <sup>b</sup>   |   |                         |
|   |                   |                  | 5 weeks              |                     | 50 µg/g body weight     | 1×                   | 60 weeks                                  | 1/4<br>(25%) <sup>b</sup>    | 0% <sup>b</sup>             |   |                         |
|   |                   | forestomach      | Day 1                |                     | 50 µg/g body weight     | 1×                   | 60 weeks                                  | 4/14<br>(29%) <sup>b</sup>   | 3/6<br>(50%) <sup>b</sup>   |   |                         |
|   |                   |                  | 5 weeks              |                     | 50 µg/g body weight     | 1×                   | 60 weeks                                  | 0% <sup>c</sup>              | 0% <sup>b</sup>             |   |                         |
|   |                   | intestine        | Day 1                |                     | 50 µg/g body weight     | 1×                   | 60 weeks                                  | 3/10<br>(30%) <sup>b</sup>   | 2/2<br>(100%) <sup>b</sup>  |   |                         |
|   |                   |                  | 5 weeks              |                     | 50 µg/g body weight     | 1×                   | 60 weeks                                  | 2/4<br>(50%) <sup>b</sup>    | 0% <sup>b</sup>             |   |                         |
|   | Mice<br>(C3Hf/Dp) | thymus           | control              | i.p.                | NA                      | NA                   | 120 wks <sup>**</sup>                     | 0/34<br>(0%)                 | 0/25<br>(0%)                | *Age at death from thymic lymphoma reported specifically for some, but not all, dose groups.<br><br>** Control mice were sacrificed at 120 wks.<br><br>*** Age of death for all mice in this dose group, regardless of cancer type. | Terracini et al. (1976) |
|   |                   |                  | Day 1                |                     | 25 µg NMU/g body weight | 1×                   | 29 ± 8.4 wks                              | 2/16<br>(13%) <sup>b</sup>   | 5/25<br>(20%) <sup>b</sup>  |   |                         |
|   |                   |                  | Day 70               |                     | 25 µg NMU/g body weight | 1×                   | 120 wks (M) <sup>***</sup><br>100 wks (F) | 0/20<br>(0%) <sup>c</sup>    | 1/20<br>(5%) <sup>b</sup>   |   |                         |
|   |                   |                  | Day 1                |                     | 50 µg NMU/g body weight | 1×                   | 16.5 ± 0.7 wks                            | 16/24<br>(67%) <sup>b</sup>  | 30/44<br>(68%) <sup>b</sup> |   |                         |
|   |                   |                  | Day 21               |                     | 50 µg NMU/g body weight | 1×                   | 24.5 ± 2.5 wks                            | 14/44<br>(32%) <sup>b</sup>  | 18/38<br>(47%) <sup>b</sup> |   |                         |
|   |                   |                  | Day 70               |                     | 50 µg NMU/g body weight | 1×                   | 31.4 ± 4.4 wks                            | 9/30<br>(30%) <sup>b</sup>   | 6/41<br>(15%) <sup>b</sup>  |   |                         |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                | Species (strain)  | Target site           | Age when first dosed | Dose route, # doses | Dose                    | Duration of exposure | Age at death |             | Tumor incidence          |                          | Reference                |
|---|-------------------|-----------------------|----------------------|---------------------|-------------------------|----------------------|--------------|-------------|--------------------------|--------------------------|--------------------------|
|   |                   |                       |                      |                     |                         |                      | M            | F           | M                        | F                        |                          |
| NMU<br>Methylnitrosourea<br>(continued) | Mice<br>(C3Hf/Dp) | extra-thymic lymphoma | control              | i.p.                | NA                      | NA                   | 120 weeks    | 120 weeks   | 1/34 (3%)                | 2/25 (8%)                | Terracini et al. (1976)  |
|   |                   |                       | Day 1                |                     | 25 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks    | 2/16 (13%) <sup>b</sup>  | 1/25 (4%) <sup>b</sup>   |                          |
|   |                   |                       | Day 70               |                     | 25 µg NMU/g body weight | 1×                   | 120 weeks    | 100 weeks   | 0/20 (0%) <sup>b</sup>   | 0/20 (0%) <sup>b</sup>   |                          |
|   |                   |                       | Day 1                |                     | 50 µg NMU/g body weight | 1×                   | 70 weeks     | 80 weeks    | 0/24 (0%) <sup>b</sup>   | 0/44 (0%) <sup>b</sup>   |                          |
|   |                   |                       | Day 21               |                     | 50 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks    | 1/44 (2%) <sup>b</sup>   | 0/38 (0%) <sup>b</sup>   |                          |
|   |                   |                       | Day 70               |                     | 50 µg NMU/g body weight | 1×                   | 110 weeks    | 90 weeks    | 1/30 (3%) <sup>b</sup>   | 0/41 (0%) <sup>b</sup>   |                          |
|   |                   | lung                  | control              | i.p.                | NA                      | NA                   | 120 weeks    | 120 weeks   | 4/34 (12%)               | 6/25 (24%)               |                          |
|   |                   |                       | Day 1                |                     | 25 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks    | 7/16 (44%) <sup>b</sup>  | 13/25 (52%) <sup>b</sup> |                          |
|   |                   |                       | Day 70               |                     | 25 µg NMU/g body weight | 1×                   | 120 weeks    | 100 weeks   | 12/20 (60%) <sup>b</sup> | 8/20 (40%) <sup>b</sup>  |                          |
|   |                   |                       | Day 1                |                     | 50 µg NMU/g body weight | 1×                   | 70 weeks     | 80 weeks    | 5/24 (21%) <sup>b</sup>  | 11/44 (25%) <sup>b</sup> |                          |
|   |                   |                       | Day 21               |                     | 50 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks    | 23/44 (52%) <sup>b</sup> | 15/38 (39%) <sup>b</sup> |                          |
|   |                   |                       | Day 70               |                     | 50 µg NMU/g body weight | 1×                   | 110 weeks    | 90 weeks    | 18/30 (60%) <sup>b</sup> | 24/41 (59%) <sup>b</sup> |                          |
|   | liver             | control               | i.p.                 | NA                  | NA                      | 120 weeks            | 120 weeks    | 13/34 (38%) | 1/25 (4%)                | Terracini et al. (1976)  |                          |
|   |                   |                       |                      | Day 1               | 25 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks    | 9/16 (56%) <sup>g</sup>  |                          | 2/25 (8%) <sup>b</sup>   |
|   |                   |                       |                      | Day 70              | 25 µg NMU/g body weight | 1×                   | 120 weeks    | 100 weeks   | 12/20 (60%) <sup>g</sup> |                          | 2/20 (10%) <sup>b</sup>  |
|   |                   |                       |                      | Day 1               | 50 µg NMU/g body weight | 1×                   | 70 weeks     | 80 weeks    | 4/24 (17%) <sup>g</sup>  |                          | 3/44 (7%) <sup>b</sup>   |
|   |                   |                       |                      | Day 21              | 50 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks    | 21/44 (48%) <sup>g</sup> |                          | 1/38 (2.6%) <sup>b</sup> |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                | Species (strain)  | Target site | Age when first dosed | Dose route, # doses | Dose                       | Duration of exposure | Age at death |              | Tumor incidence             |                             | Reference               |
|---|-------------------|-------------|----------------------|---------------------|----------------------------|----------------------|--------------|--------------|-----------------------------|-----------------------------|-------------------------|
|   |                   |             |                      |                     |                            |                      | M            | F            | M                           | F                           |                         |
| NMU<br>Methylnitrosourea<br>(continued) | Mice<br>(C3Hf/Dp) |             | Day 70               |                     | 50 µg NMU/g<br>body weight | 1×                   | 110<br>weeks | 90<br>weeks  | 8/30<br>(27%) <sup>g</sup>  | 2/41<br>(5%) <sup>b</sup>   | Terracini et al. (1976) |
|   |                   | stomach     | control              | i.p.                | NA                         | NA                   | 120<br>weeks | 120<br>weeks | 0/34<br>(0%)                | 5/25<br>(20%)               |                         |
|   |                   |             | Day 1                |                     | 25 µg NMU/g<br>body weight | 1×                   | 100<br>weeks | 90<br>weeks  | 2/16<br>(13%) <sup>b</sup>  | 10/25<br>(40%) <sup>b</sup> |                         |
|   |                   |             | Day 70               |                     | 25 µg NMU/g<br>body weight | 1×                   | 120<br>weeks | 100<br>weeks | 3/20<br>(15%) <sup>b</sup>  | 7/20<br>(35%) <sup>b</sup>  |                         |
|   |                   |             | Day 1                |                     | 50 µg NMU/g<br>body weight | 1×                   | 70<br>weeks  | 80<br>weeks  | 2/24<br>(8%) <sup>b</sup>   | 1/44<br>(2%) <sup>b</sup>   |                         |
|   |                   |             | Day 21               |                     | 50 µg NMU/g<br>body weight | 1×                   | 100<br>weeks | 90<br>weeks  | 19/44<br>(43%) <sup>b</sup> | 9/38<br>(24%) <sup>b</sup>  |                         |
|   |                   |             | Day 70               |                     | 50 µg NMU/g<br>body weight | 1×                   | 110<br>weeks | 90<br>weeks  | 8/30<br>(27%) <sup>b</sup>  | 21/41<br>(51%) <sup>b</sup> |                         |
|   |                   | kidney      | control              | i.p.                | NA                         | NA                   | 120<br>weeks | 120<br>weeks | 0/34<br>(0%)                | 0/25<br>(0%)                |                         |
|   |                   |             | Day 1                |                     | 25 µg NMU/g<br>body weight | 1×                   | 100<br>weeks | 90<br>weeks  | 0/16<br>(0%) <sup>b</sup>   | 0/25<br>(0%) <sup>b</sup>   |                         |
|   |                   |             | Day 70               |                     | 25 µg NMU/g<br>body weight | 1×                   | 120<br>weeks | 100<br>weeks | 0/20<br>(0%) <sup>b</sup>   | 0/20<br>(0%) <sup>b</sup>   |                         |
|   |                   |             | Day 1                |                     | 50 µg NMU/g<br>body weight | 1×                   | 70<br>weeks  | 80<br>weeks  | 0/24<br>(0%) <sup>b</sup>   | 4/44<br>(9%) <sup>b</sup>   |                         |
|   |                   |             | Day 21               |                     | 50 µg NMU/g<br>body weight | 1×                   | 100<br>weeks | 90<br>weeks  | 1/44<br>(2%) <sup>b</sup>   | 4/38<br>(11%) <sup>b</sup>  |                         |
|   |                   |             | Day 70               |                     | 50 µg NMU/g<br>body weight | 1×                   | 110<br>weeks | 90<br>weeks  | 5/30<br>(17%) <sup>b</sup>  | 7/41<br>(17%) <sup>b</sup>  |                         |



**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical                                | Species (strain)  | Target site      | Age when first dosed | Dose route, # doses | Dose                    | Duration of exposure | Age at death |           | Tumor incidence        |                          | Reference               |
|---|-------------------|------------------|----------------------|---------------------|-------------------------|----------------------|--------------|-----------|------------------------|--------------------------|-------------------------|
|   |                   |                  |                      |                     |                         |                      | M            | F         | M                      | F                        |                         |
| NMU<br>Methylnitrosourea<br>(continued) | Mice<br>(C3Hf/Dp) | ovary            | control              | i.p.                | NA                      | NA                   | 120 weeks    | 120 weeks | NA                     | 3/25 (12%)               | Terracini et al. (1976) |
|   |                   |                  | Day 1                |                     | 25 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks  | NA                     | 2/25 (8%) <sup>b</sup>   |                         |
|   |                   |                  | Day 70               |                     | 25 µg NMU/g body weight | 1×                   | 120 weeks    | 100 weeks | NA                     | 4/20 (20%) <sup>b</sup>  |                         |
|   |                   |                  | Day 1                |                     | 50 µg NMU/g body weight | 1×                   | 70 weeks     | 80 weeks  | NA                     | 0/44 (0%) <sup>b</sup>   |                         |
|   |                   |                  | Day 21               |                     | 50 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks  | NA                     | 9/38 (24%) <sup>b</sup>  |                         |
|   |                   |                  | Day 70               |                     | 50 µg NMU/g body weight | 1×                   | 110 weeks    | 90 weeks  | NA                     | 16/41 (39%) <sup>b</sup> |                         |
|   |                   | mammary          | control              | i.p.                | NA                      | NA                   | 120 weeks    | 120 weeks | NA                     | 2/25 (8%)                |                         |
|   |                   |                  | Day 1                |                     | 25 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks  | NA                     | 1/25 (4%) <sup>b</sup>   |                         |
|   |                   |                  | Day 70               |                     | 25 µg NMU/g body weight | 1×                   | 120 weeks    | 100 weeks | NA                     | 0/20 (0%) <sup>b</sup>   |                         |
|   |                   |                  | Day 1                |                     | 50 µg NMU/g body weight | 1×                   | 70 weeks     | 80 weeks  | NA                     | 0/44 (0%) <sup>b</sup>   |                         |
|   |                   |                  | Day 21               |                     | 50 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks  | 1/44 (2%) <sup>b</sup> | 0/38 (0%) <sup>b</sup>   |                         |
|   |                   |                  | Day 70               |                     | 50 µg NMU/g body weight |                      | 110 weeks    | 90 weeks  | NA                     | 4/41 (9.8%) <sup>b</sup> |                         |
|   |                   | uterus or vagina | control              | i.p.                | NA                      | NA                   | 120 weeks    | 120 weeks | NA                     | 1/25 (4%)                |                         |
|   |                   |                  | Day 1                |                     | 25 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks  | NA                     | 1/25 (4%) <sup>b</sup>   |                         |
|   |                   |                  | Day 70               |                     | 25 µg NMU/g body weight | 1×                   | 120 weeks    | 100 weeks | NA                     | 6/20 (30%) <sup>b</sup>  |                         |
|   |                   |                  | Day 1                |                     | 50 µg NMU/g body weight | 1×                   | 70 weeks     | 80 weeks  | NA                     | 0/44 (0%) <sup>b</sup>   |                         |
|   |                   |                  | Day 21               |                     | 50 µg NMU/g body weight | 1×                   | 100 weeks    | 90 weeks  | NA                     | 1/38 (3%) <sup>b</sup>   |                         |
|   |                   |                  | Day 70               |                     | 50 µg NMU/g body weight |                      | 110 weeks    | 90 weeks  |                        | 7/41 (17%) <sup>b</sup>  |                         |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical | Species (strain) | Target site      | Age when first dosed | Dose route, # doses | Dose                  | Duration of exposure | Age at death                 | Tumors <sup>a</sup>      |                          | Comments   | Reference               |
|----------|------------------|------------------|----------------------|---------------------|-----------------------|----------------------|------------------------------|--------------------------|--------------------------|--|-------------------------|
|          |                  |                  |                      |                     |                       |                      |                              | M                        | F                        |  |                         |
| Urethane | Mice (SWR)       | lung adenoma     | Newborn              | s.c.                | 0.18 mg/g body weight | 1×                   | 10 weeks                     | 100% <sup>b</sup>        |                          | The average number of tumors per mouse increased linearly with dose. | Kaye and Trainin (1966) |
|          |                  |                  | 11–22 weeks          | s.c.                | 0.25 mg/g body weight | 1×                   | 23–34 weeks                  | 0% <sup>b</sup>          |                          |  |                         |
|          | Mice (C3H/f)     | liver            | Control              | Control             | None                  | N/A                  | 493 days (m)<br>553 days (f) | 14/97 (14%)              | 1/77 (1%)                | The number of lung tumors among the controls was not provided.       | Liebelt et al. (1964)   |
|          |                  |                  | Day 1                | i.p.                | 0.8 mg/g body weight  | 1×                   | 481 days (m)<br>434 days (f) | 27/30 (90%) <sup>g</sup> | 18/39 (46%) <sup>g</sup> |  |                         |
|          |                  |                  | 8–10 weeks           | i.p.                | 1 mg/g body weight    | 1×                   | 321 days (m)<br>-            | 6/25 (24%) <sup>c</sup>  | 0/32 (0%) <sup>c</sup>   |  |                         |
|          |                  | lung             | Control              | Control             | None                  | N/A                  | 493 days (m)<br>553 days (f) | 0/97 (0%)                | 0/77 (0%)                |  |                         |
|          |                  |                  | Day 1                | i.p.                | 0.8 mg/g body weight  | 1×                   | 401 days (m)<br>408 days (f) | 14/30 (46%) <sup>g</sup> | 19/39 (48%) <sup>g</sup> |  |                         |
|          |                  |                  | 8–10 weeks           | i.p.                | 1 mg/g body weight    | 1×                   | 506 days (m)<br>-            | 2/25 (8%) <sup>c</sup>   | 0/32 (0%) <sup>c</sup>   |  |                         |
|          |                  | reticular tissue | Control              | Control             | None                  | N/A                  | 493 days (m)<br>553 days (f) | 2/97 (2%)                | 6/77 (8%)                |  |                         |
|          |                  |                  | Day 1                | i.p.                | 0.8 mg/g body weight  | 1×                   | 285 days (m)<br>343 days (f) | 4/30 (13%) <sup>c</sup>  | 22/39 (56%) <sup>g</sup> |  |                         |
|          |                  |                  | 8–10 weeks           | i.p.                | 1 mg/g body weight    | 1×                   | -<br>453 days (f)            | 0/25 (25%) <sup>c</sup>  | 4/32 (13%) <sup>c</sup>  |  |                         |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical             | Species (strain) | Target site        | Age when first dosed | Dose route, # doses | Dose                             | Duration of exposure | Age at death | Tumors <sup>a</sup>       |   | Comments   | Reference                  |
|----------------------|------------------|--------------------|----------------------|---------------------|----------------------------------|----------------------|--------------|---------------------------|---|--|----------------------------|
|                      |                  |                    |                      |                     |                                  |                      |              | M                         | F |  |                            |
| Urethane (continued) | Mice (Swiss)     | leukemia           | Control              | Control             | None                             | N/A                  | 8–10 months  | 1%                        |   | Highest tumor rates when dosed at birth. Exposure to newborns was followed by 21.6% leukemia, occurring at a mean age of 105 days. | Fiore-Donati et al. (1962) |
|                      |                  |                    | Day 1                | s.c.                | 2 mg in 0.05 mL aqueous solution | 1×                   |              | 13/60 (22%) <sup>b</sup>  |   |  |                            |
|                      |                  |                    | Day 5                |                     | 4 mg in 0.05 mL aqueous solution | 1×                   |              | 7/39 (18%) <sup>b</sup>   |   |  |                            |
|                      |                  |                    | Day 40               |                     | 20 mg in 0.1 mL aqueous solution | 1×                   |              | 2/63 (3%) <sup>b</sup>    |   |  |                            |
|                      | Mice (Swiss)     | lung adenoma       | Control 2 weeks      | Control             | None                             | N/A                  | 9 weeks      | 0/15 (0%)                 | — | The proportion of animals with adenomas decreased steadily with age of exposure.   | Rogers (1951)              |
|                      |                  |                    | Control 4 weeks      | Control             | None                             | N/A                  | 11 weeks     | 0/14 (0%)                 | — |  |                            |
|                      |                  |                    | Control 6 weeks      | Control             | None                             | N/A                  | 13 weeks     | 1/15 (7%)                 | — |  |                            |
|                      |                  |                    | Control 8 weeks      | Control             | None                             | N/A                  | 15 weeks     | 2/15 (13%)                | — |  |                            |
|                      |                  |                    | Control 10 weeks     | Control             | None                             | N/A                  | 17 weeks     | 0/15 (0%)                 | — |  |                            |
|                      |                  |                    | 2 weeks              | i.p.                | 1 mg/g body weight               | 1×                   | 9 weeks      | 24/24 (100%) <sup>b</sup> | — |  |                            |
| 4 weeks              | i.p.             | 1 mg/g body weight | 1×                   | 11 weeks            | 23/25 (92%) <sup>b</sup>         | —                    |              |                           |   |  |                            |
| 6 weeks              | i.p.             | 1 mg/g body weight | 1×                   | 13 weeks            | 22/25 (88%) <sup>b</sup>         | —                    |              |                           |   |  |                            |
| 8 weeks              | i.p.             | 1 mg/g body weight | 1×                   | 15 weeks            | 21/25 (84%) <sup>b</sup>         | —                    |              |                           |   |  |                            |
| 10 weeks             | i.p.             | 1 mg/g body weight | 1×                   | 17 weeks            | 19/25 (76%) <sup>b</sup>         | —                    |              |                           |   |  |                            |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical             | Species (strain) | Target site  | Age when first dosed | Dose route, # doses | Dose                  | Duration of exposure | Age at death | Tumors <sup>a</sup>       |   | Comments | Reference |
|----------------------|------------------|--------------|----------------------|---------------------|-----------------------|----------------------|--------------|---------------------------|---|----------|-----------|
|                      |                  |              |                      |                     |                       |                      |              | M                         | F |          |           |
| Urethane (continued) | Mice (Swiss)     | lung adenoma | 3 weeks              | i.p.                | 0.25 mg/g body weight | 1×                   | 12 weeks     | 16/19 (84%) <sup>b</sup>  | — |          |           |
|                      |                  |              |                      |                     | 0.5 mg/g body weight  | 1×                   | 12 weeks     | 16/20 (80%) <sup>b</sup>  | — |          |           |
|                      |                  |              |                      |                     | 1 mg/g body weight    | 1×                   | 12 weeks     | 18/20 (90%) <sup>b</sup>  | — |          |           |
|                      |                  |              | 8 weeks              | i.p.                | 0.25 mg/g body weight | 1×                   | 17 weeks     | 4/17 (24%) <sup>b</sup>   | — |          |           |
|                      |                  |              |                      |                     | 0.5 mg/g body weight  | 1×                   | 17 weeks     | 15/16 (94%) <sup>b</sup>  | — |          |           |
|                      |                  |              |                      |                     | 1 mg/g body weight    | 1×                   | 17 weeks     | 18/18 (100%) <sup>b</sup> | — |          |           |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical             | Species (strain) | Target site  | Age when first dosed | Dose route, # doses | Dose                                       | Duration of exposure  | Age at death | Tumor incidence <sup>a</sup> |                           | Comments | Reference                    |
|----------------------|------------------|--------------|----------------------|---------------------|--|---|--------------|------------------------------|---------------------------|----------|------------------------------|
|                      |                  |              |                      |                     |  |   |              | M                            | F                         |          |                              |
| Urethane (continued) | Mice (Swiss)     | liver        | Control              | Control             | N/A  | N/A   | 360–720 days | 10/227 (4.4%)                | 4/222 (8.22%)             |          | Chieco-Bianchi et al. (1963) |
|                      |                  |              | Day 1                | s.c.                | 1 mg/g body weight                         | 1×  | 180 days     | 1/20 (5%) <sup>g</sup>       | 0/20 (0%) <sup>c</sup>    |          |                              |
|                      |                  |              | Day 1                | s.c.                | 1 mg/g body weight                         | 1×  | 240 days     | 2/17 (12%) <sup>g</sup>      | 0/12 (0%) <sup>c</sup>    |          |                              |
|                      |                  |              | Day 1                | s.c.                | 1 mg/g body weight                         | 1×  | 300 days     | 5/18 (28%) <sup>g</sup>      | 0/16 (0%) <sup>c</sup>    |          |                              |
|                      |                  |              | Day 1                | s.c.                | 1 mg/g body weight                         | 1×  | 360 days     | 11/20 (55%) <sup>g</sup>     | 0/23 (0%) <sup>c</sup>    |          |                              |
|                      |                  |              | Day 1                | s.c.                | 1 mg/g body weight                         | 1×  | 420 days     | 13/15 (87%) <sup>g</sup>     | 2/22 (9%) <sup>g</sup>    |          |                              |
|                      |                  |              | Day 1                | s.c.                | 1 mg/g body weight                         | 1×  | 480 days     | 17/23 (74%) <sup>c</sup>     | 2/25 (8%) <sup>c</sup>    |          |                              |
|                      |                  |              | Day 5                | s.c.                | 1 mg/g body weight                         | 1×  | 420 days     | 9/13 (69.2%) <sup>b</sup>    | 2/11 (18.2%) <sup>b</sup> |          |                              |
|                      |                  |              | Day 20               | s.c.                | 1 mg/g body weight                         | 1×  | 420 days     | 1/13 (8%) <sup>b</sup>       | 0/16 (0%) <sup>b</sup>    |          |                              |
|                      |                  |              | Day 40               | s.c.                | 1 mg/g body weight                         | 1×  | 420 days     | 0/11 (0%) <sup>b</sup>       | 0/9 (0%) <sup>b</sup>     |          |                              |
|                      |                  | Mice (Swiss) | skin                 | Control             | Control                                    | N/A   | N/A          | 180–550 days                 | 30/712 (4.21%)            |          |                              |
|                      |                  |              | Day 1                | s.c.                | 1 mg urethane/g body weight; 5% croton oil | single dose urethane, croton oil applied 2×/week for 10 mos | 660 days     | 26/59 (44.1%) <sup>g</sup>   |                           |          |                              |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical             | Species (strain)            | Target site     | Age when first dosed | Dose route, # doses | Dose                                       | Duration of exposure  | Age at death | Tumor incidence <sup>a</sup> |                           | Comments | Reference    |
|----------------------|-----------------------------|-----------------|----------------------|---------------------|--|---|--------------|------------------------------|---------------------------|----------|--------------|
|                      |                             |                 |                      |                     |  |   |              | M                            | F                         |          |              |
| Urethane (continued) |                             |                 | Day 40               | s.c.                | 1 mg urethane/g body weight; 5% croton oil | single dose urethane, croton oil applied 2x/week for 10 mos | 700 days     | 8/41 (19.5%) <sup>b</sup>    |                           |          |              |
|                      | Mice (B6AF <sub>1</sub> /J) | liver           | Control              | gavage              | N/A  | N/A   | 71 weeks     | 1/25 (4%)                    | 0/25 (0%)                 |          | Klein (1966) |
|                      |                             |                 | Day 1                |                     | 1 mg/g body weight                         | 1x  | 66 weeks     | 9/20 (45%) <sup>g</sup>      | 9/26 (35%) <sup>g</sup>   |          |              |
|                      |                             |                 | Day 7                |                     | 1 mg/g body weight                         | 1x  | 67 weeks     | 20/22 (91%) <sup>g</sup>     | 20/26 (77%) <sup>g</sup>  |          |              |
|                      |                             |                 | Day 14               |                     | 1 mg/g body weight                         | 1x  | 68 weeks     | 16/20 (80%) <sup>g</sup>     | 10/23 (43%) <sup>g</sup>  |          |              |
|                      |                             |                 | Day 21               |                     | 1 mg/g body weight                         | 1x  | 69 weeks     | 13/23 (57%) <sup>g</sup>     | 1/20 (5%) <sup>g</sup>    |          |              |
|                      |                             |                 | Day 28               |                     | 1 mg/g body weight                         | 1x  | 70 weeks     | 4/24 (17%) <sup>g</sup>      | 1/20 (5%) <sup>g</sup>    |          |              |
|                      |                             | lung            | Control              | gavage              | 1 mg/g body weight                         | 1x  | 71 weeks     | 9/25 (36%)                   | 6/25 (24%)                |          |              |
|                      |                             |                 | Day 1                |                     | 1 mg/g body weight                         | 1x  | 66 weeks     | 20/20 (100%) <sup>b</sup>    | 25/26 (96%) <sup>b</sup>  |          |              |
|                      |                             |                 | Day 7                |                     | 1 mg/g body weight                         | 1x  | 67 weeks     | 22/22 (100%) <sup>b</sup>    | 26/26 (100%) <sup>b</sup> |          |              |
|                      |                             |                 | Day 14               |                     | 1 mg/g body weight                         | 1x  | 68 weeks     | 19/20 (95%) <sup>b</sup>     | 19/23 (83%) <sup>b</sup>  |          |              |
|                      |                             |                 | Day 21               |                     | 1 mg/g body weight                         | 1x  | 69 weeks     | 23/23 (100%) <sup>b</sup>    | 19/20 (95%) <sup>b</sup>  |          |              |
|                      |                             |                 | Day 28               |                     | 1 mg/g body weight                         | 1x  | 70 weeks     | 24/24 (100%) <sup>b</sup>    | 20/20 (100%) <sup>b</sup> |          |              |
|                      | Mice (B6AF <sub>1</sub> /J) | Harderian gland | Control              | gavage              | 1 mg/g body weight                         | 1x  | 71 weeks     | 0/25 (0%)                    | 0/25 (0%)                 |          | Klein (1966) |
|                      |                             |                 | Day 1                |                     | 1 mg/g body weight                         | 1x  | 66 weeks     | 0/20 (0%) <sup>c</sup>       | 1/26 (4%) <sup>b</sup>    |          |              |

**Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)**

| Chemical             | Species (strain) | Target site | Age when first dosed | Dose route, # doses | Dose               | Duration of exposure | Age at death | Tumor incidence <sup>a</sup> |                         | Comments | Reference |           |
|----------------------|------------------|-------------|----------------------|---------------------|--------------------|----------------------|--------------|------------------------------|-------------------------|----------|-----------|-----------|
|                      |                  |             |                      |                     |                    |                      |              | M                            | F                       |          |           |           |
| Urethane (continued) |                  |             | Day 7                |                     | 1 mg/g body weight | 1×                   | 67 weeks     | 0/22 (0%) <sup>c</sup>       | 1/26 (4%) <sup>b</sup>  |          |           |           |
|                      |                  |             | Day 14               |                     | 1 mg/g body weight | 1×                   | 68 weeks     | 0/20 (0%) <sup>c</sup>       | 2/23 (9%) <sup>b</sup>  |          |           |           |
|                      |                  |             | Day 21               |                     | 1 mg/g body weight | 1×                   | 69 weeks     | 1/23 (4%) <sup>b</sup>       | 0/20 (0%) <sup>f</sup>  |          |           |           |
|                      |                  |             | Day 28               |                     | 1 mg/g body weight | 1×                   | 70 weeks     | 0/24 (0%) <sup>c</sup>       | 0/20 (0%) <sup>f</sup>  |          |           |           |
|                      |                  | forestomach | Control              | gavage              |                    | 1 mg/g body weight   | 1×           | 71 weeks                     | 0/25 (0%)               |          |           | 1/25 (4%) |
|                      |                  |             | Day 1                |                     | 1 mg/g body weight | 1×                   | 66 weeks     | 0/20 (0%) <sup>c</sup>       | 3/26 (12%) <sup>b</sup> |          |           |           |
|                      |                  |             | Day 7                |                     | 1 mg/g body weight | 1×                   | 67 weeks     | 1/22 (5%) <sup>b</sup>       | 1/26 (4%) <sup>b</sup>  |          |           |           |
|                      |                  |             | Day 14               |                     | 1 mg/g body weight | 1×                   | 68 weeks     | 1/20 (5%) <sup>b</sup>       | 4/23 (17%) <sup>b</sup> |          |           |           |
|                      |                  |             | Day 21               |                     | 1 mg/g body weight | 1×                   | 69 weeks     | 0/23 (0%) <sup>c</sup>       | 1/20 (5%) <sup>b</sup>  |          |           |           |
|                      |                  |             | Day 28               |                     | 1 mg/g body weight | 1×                   | 70 weeks     | 2/24 (8%) <sup>b</sup>       | 1/20 (5%) <sup>b</sup>  |          |           |           |

<sup>a</sup> Where not delineated by gender, data combined by study authors or gender not specified. Where percentages only are given, number of subjects not specified.

<sup>b</sup> Not evaluated by authors.

<sup>c</sup> Evaluated but not significant compared with controls.

<sup>d</sup> Study also included mammary fibroadenomas and fibromas as well as other types of cancers.

<sup>e</sup> 8–9 weeks old.

<sup>f</sup> Includes survivors up to 40 weeks only.

<sup>g</sup> Significant compared with controls.

i.p. = intraperitoneal injection; s.c. = subcutaneous injection

**Table 4. Ratio of early-life to adult cancer potencies for studies with repeated exposures of juvenile and adult animals to carcinogens with a mutagenic mode of action\***

| Compound  | Species (strain)           | Sex                           | Dose       | Tumor              | Unweighted geometric mean | 2.5%   | Median      | 97.5% | Reference                     |
|---|----------------------------|-------------------------------|------------|--------------------|---------------------------|--------|-------------|-------|-------------------------------|
| Benzidine   | Mice (B6C3F <sub>1</sub> ) | male                          |            | liver              | 111                       | 64     | <b>110</b>  | 198   | Vesselinovitch et al. (1975b) |
|   |                            | female                        |            | liver              | 0.16                      | 0.004  | <b>0.22</b> | 1.1   |                               |
| 3-MU<br>3-Methylcholanthrene<br>(formerly known as 20-methylcholanthrene) | Mice (Albino)              | male                          | 0.25 mg/g  | hepatoma           | 33                        | 7.4    | <b>30</b>   | 268   | Klein (1959)                  |
|   |                            | female                        | 0.25 mg/g  | hepatoma           | 7.7                       | 1.1    | <b>7.1</b>  | 85    |                               |
|   |                            | male                          | 0.25 mg/g  | forestomach        | 0.91                      | 0.39   | <b>0.91</b> | 2.1   |                               |
|   |                            | female                        | 0.25 mg/g  | forestomach        | 1.5                       | 0.58   | <b>1.5</b>  | 4.2   |                               |
|   |                            | male                          | 0.25 mg/g  | skin               | 1.8                       | 0.048  | <b>2.1</b>  | 22    |                               |
|   |                            | female                        | 0.25 mg/g  | skin               | 1.5                       | 0.023  | <b>1.8</b>  | 21    |                               |
| Safrole   | Mice (B6C3F <sub>1</sub> ) | male                          |            | liver              | 47                        | 16     | <b>44</b>   | 198   | Vesselinovitch et al. (1979b) |
|   |                            | female                        |            | liver              | 0.12                      | 0.002  | <b>0.18</b> | 1.1   |                               |
| VC<br>Vinyl chloride  | Rats (Sprague-Dawley)      | male                          | 6,000 ppm  | liver-angiosarcoma | 6.7                       | 0.035  | <b>9.8</b>  | 57    | Maltoni et al. (1984)         |
|   |                            | male                          | 10,000 ppm | liver-angiosarcoma | 7.4                       | 0.035  | <b>11</b>   | 62    |                               |
|   |                            | female                        | 6,000 ppm  | liver-angiosarcoma | 13                        | 4.9    | <b>13</b>   | 33    |                               |
|   |                            | female                        | 10,000 ppm | liver-angiosarcoma | 30                        | 8.7    | <b>29</b>   | 121   |                               |
|   |                            | male                          | 6,000 ppm  | zymbal gland       | 0.73                      | 0.0032 | <b>1.1</b>  | 30    |                               |
|   |                            | male                          | 10,000 ppm | zymbal gland       | 0.27                      | 0.0022 | <b>0.4</b>  | 5.4   |                               |
|   |                            | female                        | 6,000 ppm  | zymbal gland       | 0.48                      | 0.0027 | <b>0.7</b>  | 16    |                               |
|   |                            | female                        | 10,000 ppm | zymbal gland       | 0.15                      | 0.0014 | <b>0.19</b> | 4.5   |                               |
|   |                            | male                          | 10,000 ppm | leukemia           | 21                        | 0.026  | <b>37</b>   | 514   |                               |
|   |                            | female                        | 6,000 ppm  | leukemia           | 1.3                       | 0.0035 | <b>1.7</b>  | 153   |                               |
|   |                            | female                        | 10,000 ppm | leukemia           | 0.29                      | 0.0019 | <b>0.35</b> | 17    |                               |
|   |                            | male                          | 6,000 ppm  | nephroblastomas    | 0.15                      | 0.0014 | <b>0.19</b> | 4.8   |                               |
|   |                            | male                          | 10,000 ppm | nephroblastomas    | 0.17                      | 0.0015 | <b>0.21</b> | 6.2   |                               |
|   |                            | female                        | 6,000 ppm  | nephroblastomas    | 0.28                      | 0.0018 | <b>0.33</b> | 16    |                               |
|   |                            | female                        | 10,000 ppm | nephroblastomas    | 0.24                      | 0.0017 | <b>0.29</b> | 11    |                               |
| male  | 6,000 ppm                  | angiosarcomas-<br>other sites | 0.9        | 0.0033             | <b>1.26</b>               | 53     |             |       |                               |
| male  | 10,000 ppm                 | angiosarcomas-                | 0.25       | 0.0017             | <b>0.30</b>               | 12     |             |       |                               |



**Table 4. Ratio of early-life to adult cancer potencies for studies with repeated exposures of juvenile and adult animals to mutagenic chemicals (continued)**

| Compound                            | Species (strain) | Sex           | Dose       | Tumor                                 | Unweighted geometric mean | 2.5%   | Median      | 97.5% | Reference |
|-------------------------------------|------------------|---------------|------------|---------------------------------------|---------------------------|--------|-------------|-------|-----------|
|                                     |                  |               |            | other sites                           |                           |        |             |       |           |
| VC<br>Vinyl chloride<br>(continued) |                  | female        | 6,000 ppm  | angiosarcomas-<br>other sites         | 0.24                      | 0.0017 | <b>0.29</b> | 11    |           |
|                                     |                  | female        | 10,000 ppm | angiosarcomas-<br>other sites         | 0.32                      | 0.0019 | <b>0.38</b> | 20    |           |
|                                     |                  | male          | 6,000 ppm  | angiomas &<br>fibromas-other<br>sites | 0.72                      | 0.0031 | <b>1.0</b>  | 33    |           |
|                                     |                  | male          | 10,000 ppm | angiomas &<br>fibromas-other<br>sites | 1.4                       | 0.0045 | <b>2.36</b> | 47    |           |
|                                     |                  | female        | 6,000 ppm  | angiomas &<br>fibromas-other<br>sites | 0.27                      | 0.0018 | <b>0.33</b> | 16    |           |
|                                     |                  | female        | 10,000 ppm | angiomas &<br>fibromas-other<br>sites | 0.52                      | 0.0024 | <b>0.63</b> | 41    |           |
|                                     |                  | male          | 6,000 ppm  | hepatoma                              | 62                        | 11     | <b>58</b>   | 543   |           |
|                                     |                  | male          | 10,000 ppm | hepatoma                              | 34                        | 8.2    | <b>32</b>   | 218   |           |
|                                     |                  | female        | 6,000 ppm  | hepatoma                              | 55                        | 13     | <b>51</b>   | 352   |           |
|                                     |                  | female        | 10,000 ppm | hepatoma                              | 55                        | 8.4    | <b>53</b>   | 513   |           |
|                                     |                  | male          | 6,000 ppm  | skin carcinomas                       | 1.1                       | 0.0035 | <b>1.5</b>  | 82    |           |
|                                     |                  | male          | 10,000 ppm | skin carcinomas                       | 0.41                      | 0.0024 | <b>0.56</b> | 15    |           |
|                                     |                  | female        | 6,000 ppm  | skin carcinomas                       | 0.46                      | 0.0024 | <b>0.59</b> | 24    |           |
|                                     |                  | female        | 10,000 ppm | skin carcinomas                       | 0.31                      | 0.0019 | <b>0.37</b> | 19    |           |
|                                     |                  | male          | 6,000 ppm  | neuroblastoma                         | 0.21                      | 0.0016 | <b>0.26</b> | 9.5   |           |
|                                     |                  | male          | 10,000 ppm | neuroblastoma                         | 0.20                      | 0.0016 | <b>0.24</b> | 8.5   |           |
|                                     |                  | female        | 6,000 ppm  | neuroblastoma                         | 0.27                      | 0.0018 | <b>0.32</b> | 15    |           |
| female                              | 10,000 ppm       | neuroblastoma | 0.14       | 0.0014                                | <b>0.18</b>               | 4.4    |             |       |           |

\* The 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses.

**Table 5. Ratio of early-life to adult cancer potencies for studies with repeated exposures of juvenile and adult animals to chemicals with a nonmutagenic mode of action\***

| Compound | Species (strain)           | Sex    | Dose | Tumor                     | Ratio of juvenile to adult potency |        |              |       | Reference                     |
|----------|----------------------------|--------|------|---------------------------|------------------------------------|--------|--------------|-------|-------------------------------|
|          |                            |        |      |                           | Unweighted geometric mean          | 2.5%   | Median       | 97.5% |                               |
| Amitrole | Mice (B6C3F <sub>1</sub> ) | male   | NA   | liver                     | 13                                 | 5.1    | <b>14</b>    | 30    | Vesselinovitch (1983)         |
|          |                            | female | NA   | liver                     | 0.14                               | 0.0013 | <b>0.18</b>  | 3.9   |                               |
| DDT      | Mice (B6C3F <sub>1</sub> ) | male   | NA   | liver                     | 1.3                                | 0.0044 | <b>2.5</b>   | 25    | Vesselinovitch et al. (1979a) |
| Dieldrin | Mice (B6C3F <sub>1</sub> ) | male   | NA   | liver                     | 0.75                               | 0.0031 | <b>1.2</b>   | 27    | Vesselinovitch et al. (1979a) |
| DPH      | Rats (F344/N)              | male   | 630  | liver                     | 0.4                                | 0.0024 | <b>0.54</b>  | 16    | Chhabra et al. (1993b)        |
|          |                            | female | 630  | liver                     | 0.24                               | 0.0017 | <b>0.29</b>  | 12    |                               |
|          | Mice (B6C3F <sub>1</sub> ) | male   | 210  | liver                     | 1.5                                | 0.0040 | <b>2.4</b>   | 71    |                               |
|          |                            | female | 210  | liver                     | 1.3                                | 0.0056 | <b>2.6</b>   | 15    |                               |
| ETU      | Rats (F344/N)              | male   | 90   | thyroid                   | 0.37                               | 0.0029 | <b>0.61</b>  | 5.4   | Chhabra et al. (1992)         |
|          |                            | female | 90   | thyroid                   | 0.23                               | 0.0018 | <b>0.3</b>   | 7.0   |                               |
|          | Mice (B6C3F <sub>1</sub> ) | male   | 330  | liver                     | 0.091                              | 0.0011 | <b>0.12</b>  | 1.9   |                               |
|          |                            | female | 330  | liver                     | 0.057                              | 0.0010 | <b>0.081</b> | 0.65  |                               |
|          |                            | male   | 330  | thyroid                   | 0.41                               | 0.0022 | <b>0.52</b>  | 25    |                               |
|          |                            | female | 330  | thyroid                   | 0.4                                | 0.0024 | <b>0.55</b>  | 16    |                               |
|          |                            | male   | 330  | pituitary                 | 0.32                               | 0.0019 | <b>0.38</b>  | 22    |                               |
|          |                            | female | 330  | pituitary                 | 0.24                               | 0.0018 | <b>0.32</b>  | 6.9   |                               |
| PBB      | Rats (F344/N)              | male   | 10   | liver                     | 0.59                               | 0.0041 | <b>1.1</b>   | 6.6   | Chhabra et al. (1993a)        |
|          |                            | female | 10   | liver                     | 0.063                              | 0.0009 | <b>0.079</b> | 1.2   |                               |
|          |                            | male   | 10   | mononuclear cell leukemia | 0.79                               | 0.0035 | <b>1.4</b>   | 18    |                               |
|          |                            | female | 10   | mononuclear cell leukemia | 0.21                               | 0.0017 | <b>0.28</b>  | 6.0   |                               |
|          | Mice (B6C3F <sub>1</sub> ) | male   | 30   | liver                     | 3.9                                | 1.9    | <b>3.9</b>   | 7.5   |                               |
|          |                            | female | 30   | liver                     | 1.0                                | 0.37   | <b>1.05</b>  | 2.1   |                               |

\* The 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses.

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action\***

| Compound                  | Species (strain)           | Sex       | Dose      | Tumor   | Day     | Ratio of juvenile to adult potency |             |             |        | Reference                     |
|---------------------------|----------------------------|-----------|-----------|---------|---------|------------------------------------|-------------|-------------|--------|-------------------------------|
|                           |                            |           |           |         |         | Unweighted geometric mean          | 2.5%        | Median      | 97.5 % |                               |
| BaP*                      | Mice (B6C3F <sub>1</sub> ) | male      | 75 µg/kg  | liver   | 1 day   | 9.3                                | 2.9         | <b>8.4</b>  | 55     | Vesselinovitch et al. (1975a) |
|                           |                            |           |           |         | 15 days | 11                                 | 3.5         | <b>9.6</b>  | 61     |                               |
|                           |                            | female    | 75 µg/kg  |         | 1 day   | 1.2                                | 0.0083      | <b>1.6</b>  | 31     |                               |
|                           |                            |           |           |         | 15 days | 1.7                                | 0.015       | <b>2.1</b>  | 36     |                               |
|                           |                            | male      | 150 µg/kg |         | 1 day   | 29                                 | 8.2         | <b>26</b>   | 194    |                               |
|                           |                            |           |           |         | 15 days | 15                                 | 4.1         | <b>13</b>   | 109    |                               |
|                           | female                     | 150 µg/kg |           | 1 day   | 8.8     | 1.4                                | <b>8.1</b>  | 94          |        |                               |
|                           |                            |           |           | 15 days | 1.2     | 0.0082                             | <b>1.6</b>  | 30          |        |                               |
|                           | Mice (C3AF <sub>1</sub> )  | male      | 75 µg/kg  | liver   | 1 day   | 11                                 | 2.1         | <b>10</b>   | 112    |                               |
|                           |                            |           |           |         | 15 days | 7.5                                | 1.1         | <b>7.0</b>  | 83     |                               |
|                           |                            | female    | 75 µg/kg  |         | 1 day   | 0.2                                | 0.0018      | <b>0.26</b> | 9.1    |                               |
|                           |                            |           |           |         | 15 days | 0.2                                | 0.0017      | <b>0.24</b> | 8.5    |                               |
|                           |                            | male      | 150 µg/kg |         | 1 day   | 14                                 | 3.0         | <b>12.8</b> | 130    |                               |
|                           |                            |           |           |         | 15 days | 3.6                                | 0.11        | <b>3.8</b>  | 49     |                               |
|                           | female                     | 150 µg/kg |           | 1 day   | 0.2     | 0.0017                             | <b>0.24</b> | 8.8         |        |                               |
|                           |                            |           |           | 15 days | 0.2     | 0.0017                             | <b>0.24</b> | 8.7         |        |                               |
|                           | Mice (B6C3F <sub>1</sub> ) | Male      | 75 µg/kg  | lung    | 1 day   | 1.2                                | 0.45        | <b>1.2</b>  | 3.4    |                               |
|                           |                            |           |           |         | 15 days | 0.2                                | 0.0046      | <b>0.31</b> | 1.4    |                               |
|                           |                            | female    | 75 µg/kg  | lung    | 1 day   | 2.8                                | 1.096       | <b>2.7</b>  | 9.5    |                               |
|                           |                            |           |           |         | 15 days | 1.4                                | 0.41        | <b>1.4</b>  | 5.1    |                               |
|                           |                            | Male      | 150 µg/kg | lung    | 1 day   | 2.2                                | 1.0         | <b>2.1</b>  | 5.4    |                               |
|                           |                            |           |           |         | 15 days | 0.8                                | 0.2         | <b>0.82</b> | 2.3    |                               |
|                           | female                     | 150 µg/kg | lung      | 1 day   | 7.9     | 2.6                                | <b>7.2</b>  | 43          |        |                               |
|                           |                            |           |           | 15 days | 3.7     | 1.1                                | <b>3.4</b>  | 22          |        |                               |
| Mice (C3AF <sub>1</sub> ) | male                       | 75 µg/kg  | lung      | 1 day   | 1.2     | 0.47                               | <b>1.2</b>  | 3.2         |        |                               |
|                           |                            |           |           | 15 days | 1.1     | 0.43                               | <b>1.08</b> | 3.1         |        |                               |

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound            | Species (strain)           | Sex                       | Dose      | Tumor   | Day     | Ratio of juvenile to adult potency |             |             |            | Reference                       |     |
|---------------------|----------------------------|---------------------------|-----------|---------|---------|------------------------------------|-------------|-------------|------------|---------------------------------|-----|
|                     |                            |                           |           |         |         | Unweighted geometric mean          | 2.5%        | Median      | 97.5 %     |                                 |     |
| BaP*<br>(continued) |                            | female                    | 75 µg/kg  | lung    | 1 day   | 1.6                                | 0.66        | <b>1.55</b> | 4.0        |                                 |     |
|                     |                            |                           |           |         | 15 days | 1.6                                | 0.71        | <b>1.63</b> | 4.2        |                                 |     |
|                     |                            | male                      | 150 µg/kg | lung    | 1 day   | 1.5                                | 0.57        | <b>1.5</b>  | 5.0        |                                 |     |
|                     |                            |                           |           |         | 15 days | 1.9                                | 0.71        | <b>1.8</b>  | 6.0        |                                 |     |
|                     |                            | female                    | 150 µg/kg | lung    | 1 day   | 1.3                                | 0.61        | <b>1.3</b>  | 2.9        |                                 |     |
|                     |                            |                           |           |         | 15 days | 1.2                                | 0.54        | <b>1.1</b>  | 2.6        |                                 |     |
| DBA                 | Mice                       |                           |           | lung    |         | 178                                | 20          | <b>143</b>  | 5100       | Law (1940)                      |     |
| DEN**               | Mice (B6C3F <sub>1</sub> ) | male                      | 6 µg/kg   | liver   | 1 day   | 9.0                                | 3.5         | <b>8.3</b>  | 37         | Vesselinovitch et al.<br>(1984) |     |
|                     |                            |                           |           |         | 15 days | 8.9                                | 3.5         | <b>8.2</b>  | 36         |                                 |     |
|                     |                            | female                    | 6 µg/kg   | liver   | 1 day   | 35                                 | 9.1         | <b>31</b>   | 239        |                                 |     |
|                     |                            |                           |           |         | 15 days | 25                                 | 6.3         | <b>226</b>  | 175        |                                 |     |
|                     |                            | male                      | 12 µg/kg  | liver   | 1 day   | 9.6                                | 3.3         | <b>8.8</b>  | 50         |                                 |     |
|                     |                            |                           |           |         | 15 days | 9.8                                | 3.4         | <b>8.9</b>  | 51         |                                 |     |
|                     |                            | female                    | 12 µg/kg  | liver   | 1 day   | 16                                 | 5.9         | <b>15</b>   | 67         |                                 |     |
|                     |                            |                           |           |         | 15 days | 19                                 | 7.1         | <b>18</b>   | 79         |                                 |     |
|                     |                            | Mice (C3AF <sub>1</sub> ) | male      | 6 µg/kg | liver   | 1 day                              | 7.3         | 2.9         | <b>6.9</b> |                                 | 26  |
|                     |                            |                           |           |         |         | 15 days                            | 3.5         | 1.4         | <b>3.3</b> |                                 | 13  |
|                     |                            |                           | female    | 6 µg/kg | liver   | 1 day                              | 17          | 3.2         | <b>16</b>  |                                 | 166 |
|                     |                            |                           |           |         |         | 15 days                            | 6.4         | 0.86        | <b>6.0</b> |                                 | 73  |
|                     | male                       |                           | 12 µg/kg  | liver   | 1 day   | 11                                 | 3.7         | <b>9.5</b>  | 53         |                                 |     |
|                     |                            |                           |           |         | 15 days | 9.8                                | 3.4         | <b>8.9</b>  | 50         |                                 |     |
|                     | female                     | 12 µg/kg                  | liver     | 1 day   | 40      | 8.5                                | <b>36</b>   | 340         |            |                                 |     |
|                     |                            |                           |           | 15 days | 25      | 5.0                                | <b>22</b>   | 221         |            |                                 |     |
|                     | Mice (B6C3F <sub>1</sub> ) | male                      | 6 µg/kg   | lung    | 1 day   | 0.5                                | 0.27        | <b>0.52</b> | 0.93       |                                 |     |
|                     |                            |                           |           |         | 15 days | 1.6                                | 0.95        | <b>1.6</b>  | 2.7        |                                 |     |
| female              |                            | 6 µg/kg                   | lung      | 1 day   | 0.9     | 0.54                               | <b>0.89</b> | 1.5         |            |                                 |     |
|                     |                            |                           |           | 15 days | 1.2     | 0.76                               | <b>1.2</b>  | 2.0         |            |                                 |     |

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound             | Species (strain)          | Sex        | Dose     | Tumor      | Day          | Ratio of juvenile to adult potency |            |              |                      | Reference             |
|----------------------|---------------------------|------------|----------|------------|--------------|------------------------------------|------------|--------------|----------------------|-----------------------|
|                      |                           |            |          |            |              | Unweighted geometric mean          | 2.5%       | Median       | 97.5 %               |                       |
| DEN**<br>(continued) |                           | male       | 12 µg/kg | lung       | 1 day        | 0.4                                | 0.21       | <b>0.40</b>  | 0.73                 |                       |
|                      |                           |            |          |            | 15 days      | 0.7                                | 0.39       | <b>0.66</b>  | 1.1                  |                       |
|                      |                           | female     | 12 µg/kg | lung       | 1 day        | 0.7                                | 0.44       | <b>0.73</b>  | 1.2                  |                       |
|                      |                           |            |          |            | 15 days      | 1.4                                | 0.88       | <b>1.4</b>   | 2.3                  |                       |
|                      | Mice (C3AF <sub>1</sub> ) | male       | 6 µg/kg  | lung       | 1 day        | 0.7                                | 0.22       | <b>0.67</b>  | 1.7                  |                       |
|                      |                           |            |          |            | 15 days      | 0.5                                | 0.21       | <b>0.56</b>  | 1.3                  |                       |
|                      |                           | female     | 6 µg/kg  | lung       | 1 day        | 1.1                                | 0.45       | <b>1.1</b>   | 2.5                  |                       |
|                      |                           |            |          |            | 15 days      | 0.7                                | 0.36       | <b>0.74</b>  | 1.5                  |                       |
|                      |                           | male       | 12 µg/kg | lung       | 1 day        | 0.3                                | 0.084      | <b>0.33</b>  | 0.76                 |                       |
|                      |                           |            |          |            | 15 days      | 0.6                                | 0.26       | <b>0.62</b>  | 1.4                  |                       |
| female               | 12 µg/kg                  | lung       | 1 day    | 0.7        | 0.35         | <b>0.75</b>                        | 1.6        |              |                      |                       |
|                      |                           |            | 15 days  | 0.7        | 0.37         | <b>0.75</b>                        | 1.5        |              |                      |                       |
| DMBA <sup>#</sup>    | Rats (Wistar)             | male       |          | total      | 2 vs 5–8 wks | 3.3                                | 1.3        | <b>3.2</b>   | 10                   | Meranze et al. (1969) |
|                      |                           |            |          |            | 2 vs 26 wks  | 3.2                                | 1.3        | <b>3.1</b>   | 9.7                  |                       |
|                      |                           | female     |          | total      | 2 vs 5–8 wks | 1.3                                | 0.68       | <b>1.3</b>   | 2.5                  |                       |
|                      |                           |            |          |            | 2 vs 26 wks  | 3.3                                | 1.2        | <b>3.0</b>   | 16                   |                       |
|                      |                           |            |          | mammary    | 2 vs 5–8 wks | 0.0                                | 0.0012     | <b>0.056</b> | 0.26                 |                       |
|                      |                           |            |          |            | 2 vs 26 wks  | 0.2                                | 0.0023     | <b>0.29</b>  | 5.3                  |                       |
|                      | 5 vs 26 wks               | 7.1        | 1.8      | <b>6.4</b> | 55           |                                    |            |              |                      |                       |
|                      | Mice (Balb/c)             | male       | 15 µg    | lung       | 1 day        | 30                                 | 2.8        | <b>22</b>    | 1482                 | Walters (1966)        |
|                      |                           |            |          |            | 15–19 days   | 1.0                                | 0.28       | <b>1.0</b>   | 3.5                  |                       |
|                      |                           | male       | 30 µgx2  | lung       | 15–19 days   | 14                                 | 1.056      | <b>10</b>    | 978                  |                       |
| female               |                           |            |          |            | 15 µg        | lung                               | 1 day      | 60           | 6.0                  |                       |
|                      |                           | 15–19 days | 3.1      | 0.51       |              |                                    | <b>3.0</b> | 22           |                      |                       |
| female               |                           | 30 µgx2    | lung     | 15–19 days | 15           | 1.2                                | <b>11</b>  | 1004         |                      |                       |
| Mice (Swiss)         |                           |            | lymphoma |            | 2.7          | 0.60                               | <b>2.5</b> | 19           | Pietra et al. (1961) |                       |
|                      |                           |            | lung     |            | 9.1          | 2.9                                | <b>8.7</b> | 40           |                      |                       |

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound | Species (strain)           | Sex    | Dose    | Tumor | Day          | Ratio of juvenile to adult potency |            |             |             | Reference             |                              |      |
|----------|----------------------------|--------|---------|-------|--------------|------------------------------------|------------|-------------|-------------|-----------------------|------------------------------|------|
|          |                            |        |         |       |              | Unweighted geometric mean          | 2.5%       | Median      | 97.5 %      |                       |                              |      |
| DMN***   | Rats (Wistar)              |        | 3 wks   | total | 1 month      | 0.7                                | 0.41       | <b>0.73</b> | 1.3         | Hard (1979)           |                              |      |
|          |                            |        |         |       | 1.5 months   | 1.1                                | 0.58       | <b>1.1</b>  | 2.1         |                       |                              |      |
|          |                            |        |         |       | 2 months     | 1.5                                | 0.75       | <b>1.5</b>  | 3.0         |                       |                              |      |
|          |                            |        |         |       | 3 months     | 0.9                                | 0.50       | <b>0.94</b> | 1.8         |                       |                              |      |
|          |                            |        | 24 hr   |       | 1 month      | 0.3                                | 0.13       | <b>0.28</b> | 0.6         |                       |                              |      |
|          |                            |        |         |       | 1.5 months   | 0.4                                | 0.18       | <b>0.42</b> | 0.9         |                       |                              |      |
|          |                            |        |         |       | 2 months     | 0.6                                | 0.24       | <b>0.56</b> | 1.3         |                       |                              |      |
|          |                            |        |         |       | 3 months     | 0.4                                | 0.16       | <b>0.36</b> | 0.78        |                       |                              |      |
|          |                            |        | 1 month |       | 1.5 months   | 1.5                                | 0.80       | <b>1.52</b> | 3.0         |                       |                              |      |
|          |                            |        |         |       | 2 months     | 2.0                                | 1.0        | <b>2.0</b>  | 4.2         |                       |                              |      |
| 3 months | 1.3                        | 0.69   |         |       | <b>1.3</b>   | 2.5                                |            |             |             |                       |                              |      |
| ENU      | Mice (B6C3F <sub>1</sub> ) | male   |         | liver |              | 7.8                                | 3.9        | <b>7.7</b>  | 18          | Vesselinovitch (1983) |                              |      |
|          |                            | female |         |       |              | 7.1                                | 2.9        | <b>6.9</b>  | 21          |                       |                              |      |
|          | Rats (Wistar)              | male   |         |       | nerve tissue | 1 day                              | 27         | 2.5         | <b>20</b>   | 1374                  | Naito et al. (1981)          |      |
|          |                            |        |         |       |              | 1 week                             | 1.6        | 0.61        | <b>1.6</b>  | 4.6                   |                              |      |
|          |                            |        |         |       |              | 2 weeks                            | 1.6        | 0.58        | <b>1.6</b>  | 4.8                   |                              |      |
|          |                            |        |         |       |              | 3 weeks                            | 0.7        | 0.12        | <b>0.72</b> | 2.3                   |                              |      |
|          |                            |        |         |       |              | female                             | 1 day      | 64          | 6.0         | <b>50</b>             |                              | 2488 |
|          |                            |        |         |       |              |                                    | 1 weeks    | 9.6         | 2.6         | <b>8.9</b>            |                              | 59   |
|          |                            |        |         |       |              |                                    | 2 weeks    | 6.2         | 1.6         | <b>5.7</b>            |                              | 40   |
|          | Mice (B6C3F <sub>1</sub> ) | male   | 60 µg/g |       | lung         | 1                                  | 1.0        | 0.60        | <b>1.0</b>  | 1.7                   | Vesselinovitch et al. (1974) |      |
|          |                            |        |         |       |              | 15                                 | 1.1        | 0.66        | <b>1.1</b>  | 1.8                   |                              |      |
|          |                            | female |         |       |              | 1                                  | 2.1        | 1.17        | <b>2.1</b>  | 4.1                   |                              |      |
|          |                            |        |         |       |              | 15                                 | 1.0        | 0.60        | <b>1.0</b>  | 1.7                   |                              |      |
| male     | 120 µg/g                   |        | lung    | 1     | 1.0          | 0.60                               | <b>1.0</b> | 1.7         |             |                       |                              |      |

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound           | Species (strain)           | Sex      | Dose     | Tumor     | Day                       | Ratio of juvenile to adult potency |             |             |        | Reference |
|--------------------|----------------------------|----------|----------|-----------|---------------------------|------------------------------------|-------------|-------------|--------|-----------|
|                    |                            |          |          |           |                           | Unweighted geometric mean          | 2.5%        | Median      | 97.5 % |           |
|                    |                            |          |          |           | 15                        | 1.1                                | 0.66        | <b>1.0</b>  | 1.8    |           |
| ENU<br>(continued) |                            | female   | 120 µg/g | lung      | 1                         | 2.1                                | 1.2         | <b>2.1</b>  | 4.1    |           |
|                    |                            |          |          |           | 15                        | 1.0                                | 0.60        | <b>1.0</b>  | 1.7    |           |
|                    |                            |          |          |           | Mice (C3AF <sub>1</sub> ) | male                               | 60 µg/g     | lung        | 1      |           |
|                    | 15                         | 52       | 5.2      | <b>39</b> |                           |                                    |             |             | 2141   |           |
|                    | female                     | 60 µg/g  | lung     | 15        |                           | 0.7                                | 0.32        | <b>0.72</b> | 1.6    |           |
|                    |                            |          |          | male      |                           | 120 µg/g                           | lung        | 1           | 0.9    |           |
|                    | 15                         | 0.7      | 0.28     |           |                           |                                    |             | <b>0.67</b> | 1.6    |           |
|                    | female                     | 120 µg/g | lung     | 1         |                           | 0.5                                | 0.24        | <b>0.54</b> | 1.2    |           |
|                    |                            |          |          | 15        | 0.4                       | 0.18                               | <b>0.42</b> | 0.92        |        |           |
|                    | Mice (B6C3F <sub>1</sub> ) | male     | 60 µg/g  | liver     | 1                         | 8.8                                | 4.2         | <b>8.5</b>  | 22     |           |
|                    |                            |          |          |           | 15                        | 14                                 | 6.2         | <b>14</b>   | 37     |           |
|                    |                            | female   | 60 µg/g  | liver     | 1                         | 6.3                                | 2.6         | <b>6.1</b>  | 18     |           |
|                    |                            |          |          |           | 15                        | 5.6                                | 2.4         | <b>5.4</b>  | 16     |           |
|                    |                            | male     | 120 µg/g | liver     | 1                         | 5.2                                | 2.5         | <b>5.1</b>  | 11     |           |
|                    |                            |          |          |           | 15                        | 7.6                                | 3.9         | <b>7.5</b>  | 17     |           |
|                    |                            | female   | 120 µg/g | liver     | 1                         | 11                                 | 4.1         | <b>11</b>   | 46     |           |
|                    |                            |          |          |           | 15                        | 14                                 | 4.9         | <b>13</b>   | 55     |           |
|                    | Mice (C3AF <sub>1</sub> )  | male     | 60 µg/g  | liver     | 1                         | 12                                 | 4.7         | <b>11</b>   | 43     |           |
|                    |                            |          |          |           | 15                        | 8.1                                | 3.2         | <b>7.6</b>  | 29     |           |
|                    |                            | female   | 60 µg/g  | liver     | 1                         | 7.5                                | 2.6         | <b>7.0</b>  | 32     |           |
|                    |                            |          |          |           | 15                        | 4.8                                | 1.8         | <b>4.6</b>  | 18     |           |
|                    |                            | male     | 120 µg/g | liver     | 1                         | 9.8                                | 4.1         | <b>9.3</b>  | 32     |           |
|                    |                            |          |          |           | 15                        | 6.6                                | 2.7         | <b>6.3</b>  | 23     |           |
|                    |                            | female   | 120 µg/g | liver     | 1                         | 5.4                                | 1.7         | <b>5.0</b>  | 25     |           |
|                    |                            |          |          |           | 15                        | 5.4                                | 1.7         | <b>5.1</b>  | 25     |           |
|                    | Mice (B6C3F <sub>1</sub> ) | male     | 60 µg/g  | kidney    | 1                         | 2.2                                | 0.73        | <b>2.1</b>  | 8.0    |           |
|                    |                            |          |          |           | 15                        | 1.2                                | 0.29        | <b>1.2</b>  | 5.1    |           |

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound           | Species (strain)           | Sex    | Dose     | Tumor     | Day | Ratio of juvenile to adult potency |        |              |        | Reference |
|--------------------|----------------------------|--------|----------|-----------|-----|------------------------------------|--------|--------------|--------|-----------|
|                    |                            |        |          |           |     | Unweighted geometric mean          | 2.5%   | Median       | 97.5 % |           |
| ENU<br>(continued) |                            | female | 60 µg/g  | kidney    | 1   | 0.7                                | 0.024  | <b>0.85</b>  | 5.9    |           |
|                    |                            |        |          |           | 15  | 2.6                                | 0.61   | <b>2.5</b>   | 15     |           |
|                    |                            | male   | 120 µg/g | kidney    | 1   | 1.7                                | 0.65   | <b>1.7</b>   | 4.4    |           |
|                    |                            |        |          |           | 15  | 2.6                                | 1.14   | <b>2.6</b>   | 6.4    |           |
|                    |                            | female | 120 µg/g | kidney    | 1   | 0.9                                | 0.37   | <b>0.87</b>  | 2.0    |           |
|                    |                            |        |          |           | 15  | 1.4                                | 0.67   | <b>1.4</b>   | 3.2    |           |
|                    | Mice (C3AF <sub>1</sub> )  | male   | 60 µg/g  | kidney    | 1   | 1.8                                | 0.17   | <b>1.9</b>   | 15     |           |
|                    |                            |        |          |           | 15  | 2.0                                | 0.25   | <b>2.0</b>   | 16     |           |
|                    |                            | female | 60 µg/g  | kidney    | 1   | 1.0                                | 0.016  | <b>1.3</b>   | 13     |           |
|                    |                            |        |          |           | 15  | 2.1                                | 0.16   | <b>2.2</b>   | 20     |           |
|                    |                            | male   | 120 µg/g | kidney    | 1   | 0.2                                | 0.0029 | <b>0.24</b>  | 1.5    |           |
|                    |                            |        |          |           | 15  | 1.5                                | 0.38   | <b>1.5</b>   | 5.9    |           |
|                    |                            | female | 120 µg/g | kidney    | 1   | 2.3                                | 0.17   | <b>2.4</b>   | 20     |           |
|                    |                            |        |          |           | 15  | 7.1                                | 1.8    | <b>6.5</b>   | 47     |           |
|                    | Mice (B6C3F <sub>1</sub> ) | male   | 60 µg/g  | Harderian | 1   | 0.3                                | 0.018  | <b>0.41</b>  | 1.4    |           |
|                    |                            |        |          |           | 15  | 0.5                                | 0.075  | <b>0.52</b>  | 1.4    |           |
|                    |                            | female | 60 µg/g  | Harderian | 1   | 0.1                                | 0.0025 | <b>0.16</b>  | 0.74   |           |
|                    |                            |        |          |           | 15  | 0.8                                | 0.35   | <b>0.84</b>  | 2.0    |           |
|                    |                            | male   | 120 µg/g | Harderian | 1   | 0.4                                | 0.13   | <b>0.42</b>  | 0.96   |           |
|                    |                            |        |          |           | 15  | 0.6                                | 0.26   | <b>0.57</b>  | 1.2    |           |
|                    |                            | female | 120 µg/g | Harderian | 1   | 0.1                                | 0.0030 | <b>0.18</b>  | 0.85   |           |
|                    |                            |        |          |           | 15  | 0.7                                | 0.17   | <b>0.77</b>  | 2.1    |           |
|                    | Mice (C3AF <sub>1</sub> )  | male   | 60 µg/g  | Harderian | 1   | 0.1                                | 0.0023 | <b>0.20</b>  | 1.3    |           |
|                    |                            |        |          |           | 15  | 0.1                                | 0.0016 | <b>0.18</b>  | 1.8    |           |
|                    |                            | female | 60 µg/g  | Harderian | 1   | 0.4                                | 0.019  | <b>0.52</b>  | 2.5    |           |
|                    |                            |        |          |           | 15  | 0.8                                | 0.15   | <b>0.85</b>  | 3.4    |           |
|                    |                            | male   | 120 µg/g | Harderian | 1   | 0.1                                | 0.0010 | <b>0.086</b> | 1.0    |           |
|                    |                            |        |          |           | 15  | 0.3                                | 0.0050 | <b>0.40</b>  | 2.8    |           |



**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound           | Species (strain)           | Sex                       | Dose     | Tumor         | Day     | Ratio of juvenile to adult potency |        |              |              | Reference                  |      |
|--------------------|----------------------------|---------------------------|----------|---------------|---------|------------------------------------|--------|--------------|--------------|----------------------------|------|
|                    |                            |                           |          |               |         | Unweighted geometric mean          | 2.5%   | Median       | 97.5 %       |                            |      |
| ENU<br>(continued) |                            | female                    | 120 µg/g | Harderian     | 1       | 0.1                                | 0.0012 | <b>0.094</b> | 1.2          |                            |      |
|                    |                            |                           |          |               | 15      | 0.1                                | 0.0012 | <b>0.081</b> | 0.90         |                            |      |
|                    | Mice (B6C3F <sub>1</sub> ) | male                      | 60 µg/g  | stomach       | 1       | 0.3                                | 0.0091 | <b>0.34</b>  | 2.4          |                            |      |
|                    |                            |                           |          |               | 15      | 1.9                                | 0.61   | <b>1.82</b>  | 8.7          |                            |      |
|                    |                            | female                    | 60 µg/g  | stomach       | 1       | 0.2                                | 0.0083 | <b>0.26</b>  | 1.1          |                            |      |
|                    |                            |                           |          |               | 15      | 0.2                                | 0.0072 | <b>0.24</b>  | 1.0          |                            |      |
|                    |                            | male                      | 120 µg/g | stomach       | 1       | 0.2                                | 0.0059 | <b>0.20</b>  | 0.90         |                            |      |
|                    |                            |                           |          |               | 15      | 1.2                                | 0.50   | <b>1.2</b>   | 2.9          |                            |      |
|                    |                            | female                    | 120 µg/g | stomach       | 1       | 0.6                                | 0.19   | <b>0.60</b>  | 1.5          |                            |      |
|                    |                            |                           |          |               | 15      | 1.6                                | 0.67   | <b>1.6</b>   | 3.7          |                            |      |
|                    |                            | Mice (C3AF <sub>1</sub> ) | male     | 60 µg/g       | stomach | 1                                  | 0.0    | 0.0009       | <b>0.063</b> |                            | 0.51 |
|                    |                            |                           |          |               |         | 15                                 | 0.3    | 0.023        | <b>0.41</b>  |                            | 1.3  |
|                    |                            |                           | female   | 60 µg/g       | stomach | 1                                  | 0.8    | 0.085        | <b>0.89</b>  |                            | 3.5  |
|                    |                            |                           |          |               |         | 15                                 | 1.1    | 0.19         | <b>1.1</b>   |                            | 4.5  |
|                    | male                       |                           | 120 µg/g | stomach       | 1       | 0.2                                | 0.010  | <b>0.19</b>  | 0.56         |                            |      |
|                    |                            |                           |          |               | 15      | 0.7                                | 0.32   | <b>0.70</b>  | 1.5          |                            |      |
|                    | female                     |                           | 120 µg/g | stomach       | 1       | 0.4                                | 0.14   | <b>0.46</b>  | 1.2          |                            |      |
|                    |                            |                           |          |               | 15      | 0.6                                | 0.24   | <b>0.64</b>  | 1.5          |                            |      |
| NMU                | Mice (BC3F <sub>1</sub> )  | male                      | 50 µg/g  | lung adenomas | 1       | 3.4                                | 1.3    | <b>3.3</b>   | 9.3          | Terracini and Testa (1970) |      |
|                    |                            | female                    | 50 µg/g  | lung adenomas | 1       | 6.3                                | 2.4    | <b>6.0</b>   | 23           |                            |      |
|                    |                            | male                      | 50 µg/g  | lymphosarcoma | 1       | 2.5                                | 1.1    | <b>2.4</b>   | 6.4          |                            |      |
|                    |                            | female                    | 50 µg/g  | lymphosarcoma | 1       | 1.1                                | 0.49   | <b>1.1</b>   | 2.4          |                            |      |
|                    |                            | male                      | 50 µg/g  | hepatoma      | 1       | 35                                 | 6.5    | <b>32</b>    | 324          |                            |      |
|                    |                            | female                    | 50 µg/g  | hepatoma      | 1       | 0.3                                | 0.0023 | <b>0.39</b>  | 13           |                            |      |
|                    |                            | male                      | 50 µg/g  | renal adenoma | 1       | 0.9                                | 0.0093 | <b>1.2</b>   | 13           |                            |      |
|                    |                            | female                    | 50 µg/g  | renal adenoma | 1       | 1.3                                | 0.0081 | <b>1.7</b>   | 33           |                            |      |
|                    |                            | male                      | 50 µg/g  | forestomach   | 1       | 0.0                                | 0.0006 | <b>0.039</b> | 0.52         |                            |      |
|                    |                            | female                    | 50 µg/g  | forestomach   | 1       | 0.1                                | 0.0027 | <b>0.15</b>  | 0.69         |                            |      |

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound        | Species (strain) | Sex           | Dose    | Tumor           | Day    | Ratio of juvenile to adult potency |        |              |        | Reference |
|-----------------|------------------|---------------|---------|-----------------|--------|------------------------------------|--------|--------------|--------|-----------|
|                 |                  |               |         |                 |        | Unweighted geometric mean          | 2.5%   | Median       | 97.5 % |           |
|                 | Mice (C3Hf/Dp)   | male          | 25 µg/g | thymic lymphoma | 1      | 1.9                                | 0.048  | <b>2.1</b>   | 23     |           |
| NMU (continued) |                  | female        | 25 µg/g | thymic lymphoma | 1      | 1.2                                | 0.0089 | <b>1.5</b>   | 30     |           |
|                 |                  | male          | 25 µg/g | lung adenomas   | 1      | 1.0                                | 0.013  | <b>1.2</b>   | 11     |           |
|                 |                  | female        | 25 µg/g | lung adenomas   | 1      | 0.4                                | 0.018  | <b>0.46</b>  | 1.7    |           |
|                 |                  | male          | 25 µg/g | liver tumor     | 1      | 0.2                                | 0.0016 | <b>0.21</b>  | 4.6    |           |
|                 |                  | female        | 25 µg/g | liver tumor     | 1      | 0.3                                | 0.0026 | <b>0.39</b>  | 4.4    |           |
|                 |                  | male          | 25 µg/g | Stomach         | 1      | 0.5                                | 0.0045 | <b>0.67</b>  | 6.8    |           |
|                 |                  | female        | 25 µg/g | Stomach         | 1      | 0.3                                | 0.0046 | <b>0.43</b>  | 3.8    |           |
|                 |                  |               |         | ovarian         | 1      | 0.1                                | 0.0014 | <b>0.17</b>  | 3.5    |           |
|                 |                  |               |         | uterine/vaginal | 1      | 8.6                                | 1.1    | <b>8.1</b>   | 97     |           |
|                 |                  | male          | 50 µg/g | thymic lymphoma | 1      | 7.9                                | 3.1    | <b>7.4</b>   | 30     |           |
|                 |                  | female        | 50 µg/g | thymic lymphoma | 1      | 3.1                                | 1.3    | <b>3.0</b>   | 7.8    |           |
|                 |                  | male          | 50 µg/g | lung adenomas   | 1      | 0.04                               | 0.0008 | <b>0.058</b> | 0.45   |           |
|                 |                  | female        | 50 µg/g | lung adenomas   | 1      | 0.1                                | 0.0012 | <b>0.084</b> | 0.53   |           |
|                 |                  | male          | 50 µg/g | liver tumor     | 1      | 0.2                                | 0.0021 | <b>0.33</b>  | 7.8    |           |
|                 |                  | female        | 50 µg/g | liver tumor     | 1      | 0.1                                | 0.0011 | <b>0.13</b>  | 4.5    |           |
|                 |                  | male          | 50 µg/g | Stomach         | 1      | 0.01                               | 0.0003 | <b>0.013</b> | 0.12   |           |
|                 |                  | female        | 50 µg/g | Stomach         | 1      | 0.1                                | 0.0022 | <b>0.15</b>  | 0.96   |           |
|                 |                  |               |         | ovarian         | 1      | 0.0                                | 0.0003 | <b>0.014</b> | 0.14   |           |
|                 |                  |               |         | uterine/vaginal | 1      | 0.0                                | 0.0005 | <b>0.034</b> | 0.46   |           |
|                 |                  | male          | 50 µg/g | thymic lymphoma | 21     | 4.3                                | 1.6    | <b>4.1</b>   | 17     |           |
|                 |                  | female        | 50 µg/g | thymic lymphoma | 21     | 1.0                                | 0.39   | <b>1.0</b>   | 2.6    |           |
| male            | 50 µg/g          | lung adenomas | 21      | 0.1             | 0.0022 | <b>0.22</b>                        | 1.1    |              |        |           |
| female          | 50 µg/g          | lung adenomas | 21      | 0.7             | 0.30   | <b>0.75</b>                        | 1.7    |              |        |           |

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound              | Species (strain)          | Sex             | Dose     | Tumor           | Day | Ratio of juvenile to adult potency |            |              |                     | Reference                        |
|-----------------------|---------------------------|-----------------|----------|-----------------|-----|------------------------------------|------------|--------------|---------------------|----------------------------------|
|                       |                           |                 |          |                 |     | Unweighted geometric mean          | 2.5%       | Median       | 97.5 %              |                                  |
| NMU (continued)       |                           | male            | 50 µg/g  | liver tumor     | 21  | 0.1                                | 0.0013     | <b>0.15</b>  | 4.3                 |                                  |
|                       |                           | female          | 50 µg/g  | liver tumor     | 21  | 0.9                                | 0.0051     | <b>1.4</b>   | 23                  |                                  |
|                       |                           | male            | 50 µg/g  | stomach         | 21  | 0.1                                | 0.001      | <b>0.08</b>  | 0.64                |                                  |
|                       |                           | female          | 50 µg/g  | stomach         | 21  | 1.8                                | 0.77       | <b>1.8</b>   | 4.7                 |                                  |
|                       |                           |                 |          | ovarian         | 21  | 0.0                                | 0.0007     | <b>0.055</b> | 0.97                |                                  |
|                       |                           |                 |          | uterine/vaginal | 21  | 1.7                                | 0.59       | <b>1.7</b>   | 6.4                 |                                  |
| Urethane              | Mice (Swiss)              | male            | 1 mg/g   | liver           | 1   | 24                                 | 4.4        | <b>21</b>    | 220                 | Chieco-Bianchi et al. (1963)     |
|                       |                           | female          | 1 mg/g   | liver           | 1   | 0.4                                | 0.0044     | <b>0.54</b>  | 13                  |                                  |
|                       |                           | male            | 1 mg/g   | liver           | 5   | 14                                 | 2.4        | <b>13</b>    | 137                 |                                  |
|                       |                           | female          | 1 mg/g   | liver           | 5   | 1.2                                | 0.017      | <b>1.4</b>   | 26                  |                                  |
|                       |                           | male            | 1 mg/g   | liver           | 20  | 0.2                                | 0.0018     | <b>0.28</b>  | 10                  |                                  |
|                       |                           | female          | 1 mg/g   | liver           | 20  | 0.1                                | 0.0011     | <b>0.12</b>  | 4.8                 |                                  |
|                       |                           | both            | 1 mg/g   | skin            | 1   | 0.2                                | 0.0027     | <b>0.32</b>  | 5.4                 |                                  |
| Urethane + croton oil | Mice (Swiss)              | both            | 1 mg/g   | skin            | 1   | 2.9                                | 1.2        | <b>2.8</b>   | 8.2                 |                                  |
| Urethane              | Rats (MRC Wistar-derived) | male/<br>female | 16%×6    | neurilemmomas   | 1   | 0.2                                | 0.0028     | <b>0.33</b>  | 4.5                 | Choudari Kommineni et al. (1970) |
|                       |                           | male/<br>female | 16%×6    | neurilemmomas   | 28  | 0.4                                | 0.0045     | <b>0.51</b>  | 6.3                 |                                  |
|                       |                           | male/<br>female | 16%×6    | liver           | 1   | 7.9                                | 1.4        | <b>7.1</b>   | 82                  |                                  |
|                       |                           | male/<br>female | 16%×6    | liver           | 28  | 0.2                                | 0.0026     | <b>0.4</b>   | 11.7                |                                  |
|                       |                           | male/<br>female | 16%×6    | thyroid         | 1   | 0.0                                | 0.0006     | <b>0.039</b> | 0.67                |                                  |
|                       |                           | male/<br>female | 16%×6    | thyroid         | 28  | 0.1                                | 0.0011     | <b>0.1</b>   | 1.5                 |                                  |
|                       | Mice (Swiss)              | male/<br>female | 1 mg/g   | lung            | 1   | 15                                 | 1.2        | <b>11</b>    | 997                 | De Benedictis et al. (1962)      |
| Mice (Swiss)          |                           |                 | leukemia |                 | 6.7 | 1.7                                | <b>6.1</b> | 45           | Fiore-Donati et al. |                                  |

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound             | Species (strain)            | Sex    | Dose   | Tumor              | Day          | Ratio of juvenile to adult potency |        |              |        | Reference             |
|----------------------|-----------------------------|--------|--------|--------------------|--------------|------------------------------------|--------|--------------|--------|-----------------------|
|                      |                             |        |        |                    |              | Unweighted geometric mean          | 2.5%   | Median       | 97.5 % |                       |
|                      |                             |        |        |                    |              | 5.1                                | 1.1    | <b>4.7</b>   | 38     | (1962)                |
| Urethane (continued) | Mice (B6AF <sub>1</sub> /J) | male   | 1 mg/g | liver              | 21           | 5.1                                | 1.4    | <b>4.7</b>   | 30     | Klein (1966)          |
|                      |                             | female | 1 mg/g | liver              | 21           | 0.2                                | 0.0019 | <b>0.26</b>  | 6.0    |                       |
|                      |                             |        |        | Harderian gland    | 1            | 0.3                                | 0.0021 | <b>0.33</b>  | 11     |                       |
|                      |                             |        |        |                    | 7            | 0.3                                | 0.0021 | <b>0.33</b>  | 11     |                       |
|                      |                             |        |        |                    | 14           | 0.6                                | 0.0044 | <b>0.85</b>  | 20     |                       |
|                      |                             | male   | 1 mg/g | Harderian gland    | 21           | 0.3                                | 0.0024 | <b>0.41</b>  | 13     |                       |
|                      |                             | male   | 1 mg/g | forestomach        | 1            | 0.1                                | 0.0009 | <b>0.079</b> | 1.9    |                       |
|                      |                             | female | 1 mg/g | forestomach        | 1            | 0.4                                | 0.0028 | <b>0.49</b>  | 11     |                       |
|                      |                             | male   | 1 mg/g | forestomach        | 7            | 0.1                                | 0.0017 | <b>0.19</b>  | 3.5    |                       |
|                      |                             | female | 1 mg/g | forestomach        | 7            | 0.1                                | 0.0013 | <b>0.16</b>  | 5.0    |                       |
|                      |                             | male   | 1 mg/g | forestomach        | 14           | 0.2                                | 0.0018 | <b>0.21</b>  | 3.9    |                       |
|                      |                             | female | 1 mg/g | forestomach        | 14           | 0.8                                | 0.0056 | <b>1.1</b>   | 18     |                       |
|                      |                             | male   | 1 mg/g | forestomach        | 21           | 0.1                                | 0.0008 | <b>0.072</b> | 1.7    |                       |
|                      |                             | female | 1 mg/g | forestomach        | 21           | 0.2                                | 0.0015 | <b>0.2</b>   | 6.3    |                       |
|                      |                             |        |        | lung               | 1            | 1.0                                | 0.36   | <b>0.95</b>  | 2.5    |                       |
|                      |                             | male   | 1 mg/g | lung               | 14           | 0.8                                | 0.26   | <b>0.8</b>   | 2.3    |                       |
| female               | 1 mg/g                      | lung   | 14     | 0.4                | 0.16         | <b>0.45</b>                        | 1.1    |              |        |                       |
|                      |                             |        | 21     | 0.9                | 0.31         | <b>0.86</b>                        | 2.4    |              |        |                       |
| Mice (C3H/f)         | Mice (C3H/f)                | male   | 1 mg/g | liver              | 1            | 14                                 | 4.0    | <b>12</b>    | 81     | Liebelt et al. (1964) |
|                      |                             | female | 1 mg/g | liver              | 1            | 16                                 | 3.2    | <b>15</b>    | 155    |                       |
|                      |                             | male   | 1 mg/g | lung               | 1            | 5.9                                | 1.7    | <b>5.6</b>   | 28     |                       |
|                      |                             | female | 1 mg/g | lung               | 1            | 22                                 | 4.5    | <b>20</b>    | 203    |                       |
|                      |                             | male   | 1 mg/g | reticular tissue   | 1            | 2.0                                | 0.023  | <b>2.3</b>   | 38     |                       |
|                      |                             | female | 1 mg/g | reticular tissue   | 1            | 8.6                                | 2.3    | <b>7.7</b>   | 60     |                       |
| Mice (Swiss)         |                             |        | 1 mg/g | pulmonary adenomas | 2 vs 4 weeks | 14                                 | 1.1    | <b>10.1</b>  | 965    | Rogers (1951)         |

**Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)**

| Compound             | Species (strain) | Sex | Dose      | Tumor              | Day           | Ratio of juvenile to adult potency |      |             |        | Reference |
|----------------------|------------------|-----|-----------|--------------------|---------------|------------------------------------|------|-------------|--------|-----------|
|                      |                  |     |           |                    |               | Unweighted geometric mean          | 2.5% | Median      | 97.5 % |           |
|                      |                  |     | 1 mg/g    | pulmonary adenomas | 2 vs 6 weeks  | 16                                 | 1.3  | <b>11.3</b> | 1025   |           |
| Urethane (continued) |                  |     | 1 mg/g    | pulmonary adenomas | 2 vs 8 weeks  | 19                                 | 1.6  | <b>13.3</b> | 1126   |           |
|                      |                  |     | 1 mg/g    | pulmonary adenomas | 2 vs 10 weeks | 21                                 | 1.9  | <b>14.5</b> | 1168   |           |
|                      |                  |     | 0.25 mg/g | adenomas           | 3 vs 8 weeks  | 7.1                                | 2.3  | <b>6.7</b>  | 29     |           |
|                      |                  |     | 0.5 mg/g  | adenomas           | 3 vs 8 weeks  | 0.7                                | 0.29 | <b>0.67</b> | 1.6    |           |
|                      |                  |     | 1.0 mg/g  | adenomas           | 3 vs 8 weeks  | 0.7                                | 0.28 | <b>0.68</b> | 1.6    |           |

\* The 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses.

**Table 7. Ratio of early-life to adult cancer potencies for studies with lifetime exposures starting with juvenile and adult animals to carcinogens with mutagenic or nonmutagenic modes of action\***

| Compound                      | Species (strain)            | Sex    | Dose       | Tumor     | Unweighted geometric mean | 2.5%   | Median      | 97.5% | Reference                     |
|-------------------------------|-----------------------------|--------|------------|-----------|---------------------------|--------|-------------|-------|-------------------------------|
| <b>Mutagenic compounds</b>    |                             |        |            |           |                           |        |             |       |                               |
| DEN                           | Rats (Colworth)             |        | multiple   | liver     | 2.8                       | 0.0093 | <b>5.6</b>  | 23    | Peto et al. (1984)            |
|                               |                             |        |            | esophagus | 0.18                      | 0.0015 | <b>0.23</b> | 4.8   |                               |
| Safrole                       | Mice (B6C3F <sub>1</sub> )  | male   |            | liver     | 50                        | 3.7    | <b>50</b>   | 253   | Vesselinovitch et al. (1979b) |
|                               |                             | female |            | liver     | 4.0                       | 0.007  | <b>4.0</b>  | 23    |                               |
| Urethane                      | Mice (B6AF <sub>1</sub> /J) | male   | 2.5 mg/pup | liver     | 79                        | 0.36   | <b>102</b>  | 1,064 | Klein (1966)                  |
|                               |                             | female | 2.5 mg/pup | liver     | 0.47                      | 0.0022 | <b>0.55</b> | 42    |                               |
| <b>Nonmutagenic compounds</b> |                             |        |            |           |                           |        |             |       |                               |
| DDT                           | Mice (B6C3F <sub>1</sub> )  |        |            | liver     | 23                        | 0.0023 | <b>0.58</b> | 23    | Vesselinovitch et al. (1979a) |
| Dieldrin                      | Mice (B6C3F <sub>1</sub> )  |        |            | liver     | 91                        | 0.014  | <b>14</b>   | 91    | Vesselinovitch et al. (1979a) |
| DPH                           | Rats (F344/N)               | male   | 630:800    | liver     | 0.31                      | 0.0019 | <b>0.37</b> | 18    | Chhabra et al. (1993b)        |
|                               |                             |        | 630:2,400  | liver     | 0.36                      | 0.0021 | <b>0.45</b> | 17    |                               |
|                               |                             | female | 630:800    | liver     | 0.33                      | 0.0019 | <b>0.39</b> | 21    |                               |
|                               |                             |        | 630:2,400  | liver     | 0.33                      | 0.0019 | <b>0.39</b> | 21    |                               |
|                               | Mice (B6C3F <sub>1</sub> )  | male   | 210:100    | liver     | 0.71                      | 0.0028 | <b>0.93</b> | 49    |                               |
|                               |                             |        | 210:300    | liver     | 14                        | 0.03   | <b>23</b>   | 214   |                               |
|                               |                             | female | 210:200    | liver     | 0.32                      | 0.002  | <b>0.42</b> | 13    |                               |
|                               |                             |        | 210:600    | liver     | 0.35                      | 0.0023 | <b>0.53</b> | 8.8   |                               |
| ETU                           | Rats (F344/N)               | male   | 90:83      | thyroid   | 0.23                      | 0.0017 | <b>0.3</b>  | 7.3   | Chhabra et al. (1992)         |
|                               |                             |        | 90:250     | thyroid   | 9.1                       | 1.1    | <b>10.5</b> | 27    |                               |
|                               |                             | female | 90:83      | thyroid   | 0.37                      | 0.0021 | <b>0.46</b> | 19    |                               |
|                               |                             |        | 90:250     | thyroid   | 0.61                      | 0.0034 | <b>1.1</b>  | 10    |                               |

**Table 7. Ratio of early-life to adult cancer potencies for studies with lifetime exposures starting with juvenile and adult animals to carcinogens with mutagenic or nonmutagenic modes of action (continued)**

| Compound           | Species (strain)           | Sex       | Dose      | Tumor                     | Unweighted geometric mean | 2.5%       | Median      | 97.5% | Reference              |
|--------------------|----------------------------|-----------|-----------|---------------------------|---------------------------|------------|-------------|-------|------------------------|
| ETU<br>(continued) | Mice (B6C3F <sub>1</sub> ) | male      | 330:330   | liver                     | 0.37                      | 0.0022     | <b>0.5</b>  | 14    |                        |
|                    |                            |           | 330:1,000 | liver                     | 0.48                      | 0.0027     | <b>0.75</b> | 12    |                        |
|                    |                            | female    | 330:330   | liver                     | 0.33                      | 0.0023     | <b>0.5</b>  | 7.8   |                        |
|                    |                            |           | 330:1,000 | liver                     | 0.42                      | 0.0025     | <b>0.65</b> | 11    |                        |
|                    |                            | male      | 330:330   | thyroid                   | 0.44                      | 0.0022     | <b>0.52</b> | 34    |                        |
|                    |                            |           | 330:1,000 | thyroid                   | 0.63                      | 0.0035     | <b>1.12</b> | 10    |                        |
|                    |                            | female    | 330:330   | thyroid                   | 5.2                       | 0.011      | <b>10</b>   | 108   |                        |
|                    |                            |           | 330:1,000 | thyroid                   | 0.18                      | 0.0016     | <b>0.24</b> | 4.2   |                        |
|                    |                            | male      | 330:330   | pituitary                 | 0.40                      | 0.0021     | <b>0.47</b> | 32    |                        |
|                    |                            |           | 330:1,000 | pituitary                 | 0.18                      | 0.0015     | <b>0.22</b> | 5.7   |                        |
| female             | 330:330                    | pituitary | 0.21      | 0.0016                    | <b>0.26</b>               | 10         |             |       |                        |
|                    | 330:1,000                  | pituitary | 0.27      | 0.0019                    | <b>0.36</b>               | 9.0        |             |       |                        |
| PBB                | Rats (F344/N)              | male      | 10:10     | liver                     | 0.39                      | 0.0023     | <b>0.56</b> | 13    | Chhabra et al. (1993a) |
|                    |                            |           | 10:30     | liver                     | 0.18                      | 0.0016     | <b>0.25</b> | 4.3   |                        |
|                    |                            | female    | 10:10     | liver                     | 36                        | 15         | <b>36</b>   | 86    |                        |
|                    |                            |           | 10:30     | liver                     | 3.1                       | 0.023      | <b>4.6</b>  | 22    |                        |
|                    |                            | male      | 10:10     | mononuclear cell leukemia | 0.51                      | 0.0025     | <b>0.69</b> | 23    |                        |
|                    |                            | male      | 10:30     | mononuclear cell leukemia | 0.77                      | 0.0031     | <b>1.1</b>  | 35    |                        |
|                    |                            | female    | 10:10     | mononuclear cell leukemia | 0.54                      | 0.0026     | <b>0.74</b> | 24    |                        |
|                    |                            | female    | 10:30     | mononuclear cell leukemia | 0.34                      | 0.0021     | <b>0.45</b> | 15    |                        |
|                    | Mice (B6C3F <sub>1</sub> ) | male      | 30:30     | liver                     | 8.9                       | 0.015      | <b>12.2</b> | 1,076 |                        |
|                    |                            | female    | 30:30     | liver                     | 4.4                       | 0.0075     | <b>6.2</b>  | 786   |                        |
| male               |                            | 10:10     | liver     | 0.15                      | 0.0014                    | <b>0.2</b> | 3.9         |       |                        |

**Table 7. Ratio of early-life to adult cancer potencies for studies with lifetime exposures starting with juvenile and adult animals to carcinogens with mutagenic or nonmutagenic modes of action (continued)**

| Compound | Species (strain) | Sex    | Dose  | Tumor | Unweighted geometric mean | 2.5%   | Median      | 97.5% | Reference |
|----------|------------------|--------|-------|-------|---------------------------|--------|-------------|-------|-----------|
|          |                  | female | 10:10 | liver | 0.29                      | 0.0021 | <b>0.43</b> | 7.0   |           |

\* The 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses.



**Table 8. Summary of quantitative estimates of ratio of early-life to adult cancer potencies**

| Dose  | Tissue                                | Number of chemicals | Inverse-weighted geometric mean ratio | Unweighted Minimum | Unweighted Maximum | Number of ratios | Percentage >1 |
|---|---------------------------------------|---------------------|---------------------------------------|--------------------|--------------------|------------------|---------------|
| <b>Chemicals with mutagenic mode of action</b>    |                                       |                     |                                       |                    |                    |                  |               |
| Repeated  |                                       | 4                   | 10.5                                  | 0.12               | 111                | 45               | 42            |
| Lifetime  |                                       | 3                   | 8.7                                   | 0.18               | 79                 | 6                | 67            |
|   | <b>Combined repeated and lifetime</b> | <b>6</b>            | <b>10.4</b>                           | <b>0.12</b>        | <b>111</b>         | <b>51</b>        | <b>45</b>     |
| Acute   | <b>Combined</b>                       | 11                  | 1.5                                   | 0.01               | 178                | 268              | 55            |
|   | Forestomach                           | 3                   | 0.076                                 | 0.01               | 1.9                | 32               | 16            |
|   | Harderian                             | 2                   | 0.48                                  | 0.06               | 0.8                | 20               | 0.0           |
|   | Kidney                                | 2                   | 1.6                                   | 0.17               | 7.1                | 18               | 78            |
|   | Leukemia                              | 1                   | 5.9                                   | 5.1                | 6.7                | 2                | 100           |
|   | Liver                                 | 5                   | 8.1                                   | 0.10               | 40                 | 70               | 77            |
|   | Lung                                  | 7                   | 1.1                                   | 0.04               | 178                | 77               | 56            |
|   | Lymph                                 | 2                   | 1.8                                   | 1.1                | 2.7                | 3                | 100           |
|   | Mammary (wk 5 vs wk 26)               | 1                   | 7.1                                   | NA                 | NA                 | 1                | 100           |
|   | Mammary (wk 2 vs wk 5–8 or 26)        | 1                   | 0.071                                 | NA                 | NA                 | 2                | 0             |
|   | Nerve                                 | 2                   | 2.3                                   | 0.24               | 64                 | 8                | 75            |
|   | Nerve (Day 1 comparison)              | 2                   | 10                                    | 0.24               | 64                 | 3                | 67            |
|   | Ovarian                               | 1                   | 0.033                                 | 0.01               | 0.13               | 3                | 0             |
|   | Reticular tissue                      | 1                   | 6.5                                   | 1.96               | 8.6                | 2                | 100           |
|   | Thymic lymphoma                       | 1                   | 2.8                                   | 1.01               | 7.9                | 6                | 100           |
|   | Thyroid                               | 1                   | 0.05                                  | 0.03               | 0.08               | 2                | 0             |
|   | Uterine/vaginal                       | 1                   | 1.6                                   | 0.03               | 8.6                | 3                | 67            |
| Day 1   | 7                                     | 1.7                 | 0.01                                  | 178                | 127                | 55               |               |
| Day 15  | 3                                     | 1.5                 | 0.06                                  | 52                 | 74                 | 65               |               |
| <b>Chemicals with nonmutagenic mode of action</b> |                                       |                     |                                       |                    |                    |                  |               |
| Repeated  |                                       | 6                   | 2.2                                   | 0.06               | 13                 | 22               | 27            |
| Lifetime  |                                       | 5                   | 3.4                                   | 0.15               | 36                 | 38               | 21            |

**Table 9. Excess Relative Risk (ERR) estimates for cancer incidence from Life Span Study (Japanese survivors)<sup>a</sup>**

| Site                       | Average ERR at 1 Sv |                  |
|----------------------------|---------------------|------------------|
|                            | <20 <sup>b</sup>    | >20 <sup>b</sup> |
| Stomach                    | 0.74                | 0.24             |
| Colon                      | 0.62                | 0.7              |
| Liver                      | 1.3                 | 0.31             |
| Lung                       | 0.57                | 1.1              |
| Bone and connective tissue | 11                  | 0.42             |
| Skin                       | 5.4                 | 0.39             |
| Breast                     | 3.3                 | 0.98             |
| Urinary bladder            | 0.71                | 0.79             |
| Leukemia                   | 6.1                 | 3.7              |

<sup>a</sup> Information extracted from tables in UNSCEAR, Annex I (2000).

<sup>b</sup> Age at exposure.

**Table 10. Excess Relative Risk (ERR) estimates for incidence of thyroid cancer from Life Span Study<sup>a</sup>**

| <b>Age at exposure</b> | <b>Average ERR at 1 Sv<br/>(No. cases)</b> |
|------------------------|--|
| 0–9 yr                 | 10.25 (24)                                 |
| 10–19 yr               | 4.5 (35)                                   |
| 20–29 yr               | 0.10 (18)                                  |
| >30 yr                 | 0.04 (55)                                  |

<sup>a</sup>Information extracted from tables in UNSCEAR, Annex I (2000).

**Table 11. Coefficients for the Revised Methodology mortality risk model (from U.S. EPA, 1999)<sup>a</sup>**

| Cancer type    | Risk model type <sup>b</sup> | Age group |         |         |         |         |
|----------------|------------------------------|-----------|---------|---------|---------|---------|
|                |                              | 0-9       | 10-19   | 20-29   | 30-39   | 40+     |
| <b>Male:</b>   |                              |           |         |         |         |         |
| Stomach        | R                            | 1.223     | 1.972   | 2.044   | 0.3024  | 0.2745  |
| Colon          | R                            | 2.290     | 2.290   | 0.2787  | 0.4395  | 0.08881 |
| Liver          | R                            | 0.9877    | 0.9877  | 0.9877  | 0.9877  | 0.9877  |
| Lung           | R                            | 0.4480    | 0.4480  | 0.0435  | 0.1315  | 0.1680  |
| Bone           | A                            | 0.09387   | 0.09387 | 0.09387 | 0.09387 | 0.09387 |
| Skin           | A                            | 0.06597   | 0.06597 | 0.06597 | 0.06597 | 0.06597 |
| Breast         | R                            | 0.0       | 0.0     | 0.0     | 0.0     | 0.0     |
| Ovary          | R                            | 0.0       | 0.0     | 0.0     | 0.0     | 0.0     |
| Bladder        | R                            | 1.037     | 1.037   | 1.037   | 1.037   | 1.037   |
| Kidney         | R                            | 0.2938    | 0.2938  | 0.2938  | 0.2938  | 0.2938  |
| Thyroid        | A                            | 0.1667    | 0.1667  | 0.1667  | 0.1667  | 0.1667  |
| Leukemia       | R                            | 982.3     | 311.3   | 416.6   | 264.4   | 143.6   |
| <b>Female:</b> |                              |           |         |         |         |         |
| Stomach        | R                            | 3.581     | 4.585   | 4.552   | 0.6309  | 0.5424  |
| Colon          | R                            | 3.265     | 3.265   | 0.6183  | 0.8921  | 0.1921  |
| Liver          | R                            | 0.9877    | 0.9877  | 0.9877  | 0.9877  | 0.9877  |
| Lung           | R                            | 1.359     | 1.359   | 0.1620  | 0.4396  | 0.6047  |
| Bone           | A                            | 0.09387   | 0.09387 | 0.09387 | 0.09387 | 0.09387 |
| Skin           | A                            | 0.06597   | 0.06597 | 0.06597 | 0.06597 | 0.06597 |
| Breast         | R                            | 0.7000    | 0.7000  | 0.3000  | 0.3000  | 0.1000  |
| Ovary          | R                            | 0.7185    | 0.7185  | 0.7185  | 0.7185  | 0.7185  |
| Bladder        | R                            | 1.049     | 1.049   | 1.049   | 1.049   | 1.049   |
| Kidney         | R                            | 0.2938    | 0.2938  | 0.2938  | 0.2938  | 0.2938  |
| Thyroid        | A                            | 0.3333    | 0.3333  | 0.1667  | 0.1667  | 0.1667  |
| Leukemia       | R                            | 1,176     | 284.9   | 370.06  | 178.8   | 157.1   |

<sup>a</sup> The coefficients were derived using several models applied to data from A-bomb survivors and selected medical exposures.

<sup>b</sup> A = absolute risk with coefficient units of  $10^{-4} (\text{Gy y})^{-1}$ ; R= relative risk with coefficient units of  $\text{Gy}^{-1}$ .

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