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

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PREFACE

[Once finalized, this Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens will be intended as guidance only.] EPA cancer risk assessments may be conducted differently than envisioned in this draft Supplemental Guidance for many reasons, including (but not limited to) new information, new scientific understanding, or new science policy judgment. The science of risk assessment (especially with respect to accounting for early-life exposures to toxicants) continues to develop rapidly, and specific components of this Supplemental Guidance may become outdated or may otherwise require modification in individual settings.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 whatsoever to achieving that goal. Therefore, the Supplemental Guidance will have no binding effect on EPA or on any regulated entity. Where EPA does use the approaches in the Supplemental Guidance in developing a future risk assessment, it will be because EPA has decided in the context of that risk assessment that the approaches from the Supplemental Guidance that were employed 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. Thus, EPA is not establishing any substantive, binding "rules" under the Administrative Procedure Act or any other law in publishing this Supplemental Guidance, but is instead issuing the Supplemental Guidance as a non-binding statement of policy.

1. INTRODUCTION

Cancer risk to children in the context of the U.S. Environmental Protection Agency's Cancer Guidelines (U.S. EPA, 2003) 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 exposures occurring later in life. Evaluating childhood cancer and childhood exposures resulting in cancer later in life are related, but separable, issues; the focus here will be on childhood exposures resulting in cancer later in life.

Historically, the focus on cancer has been as a disease associated with aging, resulting from extended exposure periods with prolonged latency periods before the cancers appear. Because much of cancer epidemiology addresses occupational exposures, and rodent cancer studies were designed to last approximately a lifetime (two years) beginning after sexual maturity, the cancer database used by U.S. EPA and other agencies for risk assessment focuses on adults. Thus, one need 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, 1997), diet, lifestyle, associations with congenital malformations (Bosland, 1996; Cortes, 1998), and exposure to biological and physical agents and chemicals in the environment. In some cases, tumors in adults and children have been compared. 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 sensitive for a number of tumor types (NAS, 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. The relative rarity in the incidence of childhood cancers and a lack of animal testing guidelines with perinatal[1] exposure impede a full assessment of children's cancer risks from exposure to chemicals in the environment.

Although there are similarities between childhood and adult tumors, significant differences also are 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 (U.S. Cancer Statistics Working Group, 2002, Reis et al., 1999). 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) (Israel, 1995; Anderson et al., 2000). Unequivocal evidence of childhood cancer in humans occurring from chemical exposures is limited (Reis et al., 1999). Pharmacological use of diethylstilbesterol (DES) during pregnancy to prevent spontaneous abortion resulted in no observable adult tumors, but induced clear cell adenocarcinoma of the vagina in the daughters exposed *in utero* (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., 2002; Waalkes et al., 2003), as well as studies suggesting that altered development can affect later susceptibility[2] to cancer induced by exposure to other chemicals (Anderson et al., 2002; Birnbaum and Fenton, 2003). Infrequently, perinatal exposure in animals has been shown

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

2 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.

to induce different tumor profiles than those observed with adult exposures. Studies with saccharin (Cohen et al., 1995; Whysner and Williams, 1996) and ascorbate (Cohen et al., 1995, 1998; NTP, 1983) found cancer only when exposures were initiated in the perinatal period; by 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). These 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., 2002). The effects of maternal exposures and transplacental carcinogens require separate evaluation and are not directly addressed 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 relatively mature, though substantial growth in body size continues thereafter. Data are limited to ascertain the relative contributions of the effects of carcinogens at early lifestages and the longer period for tumor expression that early-life exposure affords to possible increased susceptibility. 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 (Peto et al., 1984), benzidine (Vesselinovitch et al., 1979), DDT (Vesselinovitch et al., 1979), and polybrominated biphenyls (Chhabra et al., 1993b). Reviews comparing perinatal 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 tumors 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 et al., 1998). There is, however, reason to surmise that mutagenic chemicals, which would be expected to cause irreversible changes to DNA, would exhibit an increased effect from early-life exposure. Several studies have shown increased susceptibility of weanling animals to the formation of DNA adducts following exposure to vinyl chloride (Morinello et al., 2002a, b; Laib et al., 1989). Additionally, 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). The neonatal mouse model for carcinogenesis, which uses two doses prior to weaning followed by observation of tumors at one year, shows carcinogenic responses only for mutagenic carcinogens, but not carcinogens acting through other modes of action (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 (Ginsberg, 2003; Miller et al., 2002; Scheuplein et al., 2002; Anderson et al., 2000; Birnbaum and Fenton, 2003). Some aspects potentially leading to childhood susceptibility include:

- 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.
- Some embryonic cells, such as brain cells, lack key DNA repair enzymes.
- Some components of the immune system are not fully functional during development.
- Hormonal systems operate at different levels during different lifestages.
- Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life.

The standard methodology to calculate cancer risk uses the lifetime average daily dose, which accounts 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[3] are based upon effects observed following adult exposures. Since a much larger database exists for chemicals inducing cancer in adult humans or animals, it is necessary to determine whether adjustment of adult-based cancer slope factors would be appropriate when assessing cancer risks from exposures early in life. The analysis undertaken here addresses this issue, focusing upon studies that define the potential duration and degree of increased susceptibility arising from childhood (or perinatal and juvenile animal) exposures. This analysis forms the basis for developing supplemental guidance to risk assessors for evaluating cancer risks of childhood exposures.

3 Cancer slope factor - An 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, is generally reserved for use in the low-dose region of the dose-response relationship. It is often an upper bound, approximating a 95% confidence limit.

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 available literature was reviewed to identify animal studies that compared tumor incidence between early-life and adult 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 exposures as separate experimental groups. These studies were identified through existing review articles and searches of the literature. Reviews of increased cancer susceptibility from early-life exposure in animals were provided by McConnell (1992), Ginsberg (2003), Anderson et al. (2000), Miller et al. (2002), and U.S. EPA (1996). Additional literature was identified based on further literature searches, studies conducted by the National Toxicology Program, and other suggestions. The chemicals reviewed and evaluated quantitatively, and their references, are shown in Table 1.

Tables 2 and 3 include information on the methods and results from the animal studies identified in Table 1. Pertinent information on species, sex, dosing regimen, and tumor incidence is given. Additionally, a 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 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. The literature can be divided roughly into two types of exposure scenarios: those that include repeated exposures for the early postnatal to juvenile period, 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 both early postnatal to juvenile exposures and adult chronic exposures. Table 3 includes studies with acute exposures. A discussion of the implications of the different exposure scenarios is included in the results.

Studies also were identified for several other chemicals not included in Tables 1, 2, and 3. Unlike the chemicals and studies in the tables, these other studies did not include juvenile and adult animals in the same experiment and/or were not conducted in the same laboratory setting. Additionally, the studies typically 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_1 mice) or the doses provided to the juveniles and adults were vastly different (e.g., for tamoxifen studies, 1 mg/kg-day was given to pups in Carthew et al., 2000 while approximately 42 mg/kg-day was given to adults in Carthew et al., 1995, 1996). Due to these factors, the chemicals that belong to this group were not evaluated quantitatively. These chemicals include tamoxifen (Carthew et al., 1995, 1996, 2000; Newbold et al., 1997), azidothymidine (Diwan et al., 1999; NTP, 1999), DES (Newbold et al., 1998, 1990; Gass et al., 1964; Greenman et al., 1990), saccharin (Cohen et al., 1995; Whysner and Williams, 1996), and ascorbate (Cohen et al., 1995, 1998; NTP, 1983). In addition, there were several studies available assessing radiation in animal studies (Sasaki et al., 1978; Covelli et al, 1984; Di et al., 1990). However, 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 is 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, 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 (U.S. EPA, 1986; Dearfield et al., 1991; U.S. EPA, 1991; Waters et al., 1999), as has been done for several chemicals (e.g., Dearfield et al., 1999; U.S. EPA, 2000; McCarroll et al., 2002). 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, mutagenic 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 carcinogens.

2.3 QUANTITATIVE METHODS

2.3.1 Repeated Exposures

The primary analysis examined studies with repeated exposures during the early postnatal period to juvenile period and comparable chronic adult exposures. These early-life exposures lasted only a few weeks in most studies, but in a few cases continued through the end of the study, approximating full lifetime exposure. The objective was to estimate the increased incidence (relative to controls) attributable to early-life exposure. Because the early-life exposure durations differed across studies, each increased incidence was divided by the number of weeks of early-life exposure. This calculation normalizes the incidence per time for early-life vs. later-life exposures.

When the early-life exposure lasted only a few weeks, the increased incidence per week of early-life exposure ($IIPW_E$) was estimated as:

$$IIPW_E = \frac{\text{Incidence from “early-life” exposure – Control incidence}}{\text{Weeks exposed in “early-life” study}}$$

When the early-life exposure continued through the end of the study, the increased incidence attributable to early-life exposure was estimated as the difference between the increase in this “full-life” study and the increase in a conventional chronic study, where exposure begins later, after the animals are a few months old. The extra duration of early-life exposure was estimated as the difference between exposure durations in the "full-life" and “later-exposure-only” studies to estimate the increase in risk over the incremental exposure period. Thus, the increased incidence per week of early-life exposure was estimated in these cases as:

$$IIPW_E = \frac{\text{Incidence from "full-life" exposure - Incidence from “later-only” exposure}}{\text{Weeks exposed in "full-life" study – Weeks exposed in “later-only” study}}$$

In either case, the increased incidence per week of early-life exposure was compared with the analogous increase from the parallel “later-exposure-only” study to estimate the susceptibility of early-life exposure:

$$IIPW_L = \frac{\text{Incidence from “later-only” exposure – Control incidence}}{\text{Weeks exposed in “later-only” study}}$$

$$\text{Ratio} = IIPW_E / IIPW_L$$

For a few chemicals, tumors were observed only from early-life exposure, or the tumors induced by early-life exposure were different from those induced by later exposure. No ratios were calculated in these cases. These chemicals were listed as providing qualitative evidence for a period of unique or differential susceptibility, respectively, early in life.

Two uncertainties in this analysis are worth noting:

- The normalization by weeks of exposure would not be appropriate if the period of susceptibility is very short. It is, however, consistent with U.S. EPA's prior assumption that cancer risks are proportional to exposure duration. Increased-incidence-per-week-of-exposure is used in this analysis because the objective is to investigate whether this assumption is appropriate for all ages.

- Relative to body weight, food and water consumption generally are higher earlier in life, making it difficult to estimate doses that are expressed as concentrations in food or water. Weekly consumption rates and body weights generally were not available to allow more precise expression of these doses in terms of mg/kg-day. Whether the potential differences observed between early-life and later-life exposure can be attributed to this imprecision in dose is discussed below.

2.3.2 Acute Exposures

A second analysis examined studies with acute exposure during the early postnatal, juvenile, and adult periods. Typically these studies used a single dose, but in a few cases a small number of doses were administered within a period of a few days rather than repeated exposure. This analysis compared increased incidence (relative to controls) following early-life or later-life exposure. In this analysis, there was no need to normalize by the number of weeks of exposure because the exposure durations were identical at each age. The results were examined to determine whether the single-dose studies collectively show a similar pattern to the multiple-dose studies.

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 mutagenic chemicals, 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 United Nations Scientific Committee on the Effects of Atomic Radiation report (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, U.S. 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) are 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 assessed radiation in animal studies (Sasaki et al., 1978; Covelli et al, 1984; Di et al., 1990). 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 being addressed in this analysis was whether and how available quantitative

scientific data would 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 required 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 8-10), 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 23 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. These studies used 16 chemicals, listed in Table 1. Of the identified studies, there were 14 experiments involving repeated exposures during early postnatal and adult lifestages (Table 1) and 16 experiments using acute exposures (typically single doses) at different ages (Table 1). Some of the experiments 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, although for vinyl chloride there also were studies with hamsters. These studies serve as the basis for the quantitative analyses presented later in the results.

In addition to the studies identified in Table 1, studies were identified for five other chemicals (saccharin, ascorbate, DES, tamoxifen, and azidothymidine) with early postnatal exposure that were not evaluated quantitatively, as indicated in the Methods section. Unlike the studies used for quantitative comparisons, different lifestages were not evaluated in a single study for these chemicals. These studies do report that different tumors arose following early-life exposure than from adult exposure, although limitations of study design may contribute to this observation. Azidothymidine, for example, was studied in different strains of mice using different dose routes, so it is unclear if the differential tumor sites (i.e., lung tumors in perinatally

exposed, but not adult-exposed, mice) reflect age-dependent effects, strain-dependent effects, dose-dependent effects, or some combination (Diwan et al., 1999; NTP, 1999). It generally is believed for DES that the uterine tumors observed with early postnatal exposures of mice reflect a developmental susceptibility of that organ compared with adult exposures; however there appear to be strain-dependent differences in the tumor sites in adult mice so the impact of strain in the studies with mice of different ages is again unclear (Gass et al., 1964; Greenman et al., 1990; Newbold et al., 1990). In mice of different strains, uterine tumors also were observed in young animals, but not adults, with tamoxifen (Carthew et al., 1996; Newbold et al., 1997). Young Wistar rats appeared more sensitive than adult Wistar rats to uterine tumors following tamoxifen exposure (Carthew et al., 1996; Carthew et al., 2000). The data for tamoxifen-induced effects in rats also were not used quantitatively due to the differences in doses (i.e., 1 mg/kg-day in young rats and approximately 42 mg/kg-day in adult rats), which would result in an underestimate of the early susceptibility. Furthermore, the adult dosing period of only three months in the tamoxifen study potentially results in an overestimate of the early susceptibility compared with the other adult studies with chronic dosing. Developmental susceptibilities are believed to play a key role in effects observed with saccharin (Whysner and Williams, 1996; Cohen et al., 1995) and ascorbate (NTP, 1993; Cohen et al., 1998), with bladder tumors arising only when early-life exposures occurred.

There does not appear to be an appropriate way to predict the effects of early exposures to these five chemicals from the effects observed following chronic adult exposures. When perinatal data are available for a chemical, they may be adequate for direct use in developing age-specific cancer risk estimates. However, it does not appear appropriate to use data from these five chemicals for general considerations. In the extreme case where adult tumors were absent (e.g., ascorbate), only perinatal studies would indicate whether a cancer risk exists. To date, such examples are rare (McConnell, 1992; U.S. EPA, 1996).

Analyses of the difference in cancer risk from exposures during different lifetime periods ideally need to address both the period of potential susceptibility and the magnitude of the susceptibility. Available studies used a variety of different study designs (see Tables 2 and 3),

which can be valuable because they provide different information. 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 clearly defined doses and time periods addressing both period and magnitude of susceptibility.

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. Finally, comparisons within a single study 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 polybrominated biphenyl study (Chhabra et al., 1993b), in which mobilization of such lipid-soluble chemicals into mother's milk would be expected to result in infants getting 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 (Chhabra et al., 1993a) 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. When risk assessments for humans explicitly account for childhood exposures, ascribing effects in animal studies solely to lifestage susceptibility when there also are

differences in the exposures will lead to estimates that are somewhat inaccurate. However, there are substantial and clear benefits 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 database. 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 proposed U.S. EPA Cancer Guidelines (U.S. EPA, 2003), 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 (Murdoch et al., 1992; Goddard et al., 1995).

3.2 QUANTITATIVE EVALUATION OF THE DATABASE

As described in the Methods section, the increased incidence of cancer from exposures during different lifetime periods was calculated as a ratio of (increased tumor incidence/dosing time) in juveniles over (increased tumor incidence/dosing time) in adults. Tables 4-6 present those studies from Tables 2 and 3 that were determined qualitatively to contain the most complete information from the available database and were used for further analysis. Based on the studies available, the calculations were organized into three 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 mutagenic mode of action, where the compounds were administered by an acute dosing regimen (Table 5); and 3) compounds acting primarily through a mode of action other than mutagenicity with chronic adult dosing and repeated early postnatal dosing (Table 6). These 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 perinatal and/or chronic exposure. These studies help define the periods of increased vulnerability and the magnitude of the susceptibility.

3.2.1.1 Early postnatal, juvenile, and chronic adult studies of mutagenic chemicals

Studies comparing early postnatal, juvenile, and chronic adult exposures exist for five mutagens [benzo[a]pyrene (BaP), benzidine, diethylnitrosamine (DEN), safrole, and vinyl chloride], two of which also had acute dosing studies. 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 were more effective than adult exposures were at inducing tumors (Table 4 and Figures 1-2). 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.

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 for the repeated dosing studies (0.3 - 65, median 10, 82% of ratios greater than 1, Tables 5 and 7) and acute dosing studies (0.1 - 58, median 1.8, about 75% of ratios greater than 1, Tables 5 and 7), suggesting that these differences in dosing are not the sole determinant of the increased incidence of early tumors. 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 mutagenic chemicals

Acute dosing studies are available for seven mutagenic chemicals that were administered to mice or rats [BaP, dibenzanthracene (DBA), DEN, dimethylbenzanthracene (DMBA), dimethylnitrosamine (DMN), ethylnitrosourea (ENU), and urethane (also known as ethyl carbamate)] (Table 1). Except for ethylnitrosourea, 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 5). 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 are by subcutaneous or IP injection, which historically have not been considered quantitatively relevant routes of environmental exposure for human cancer risk assessment by U.S. EPA. For purposes of comparing age-dependent susceptibilities to tumor development these data clearly 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 compared with oral exposure.

The early exposures often resulted in higher incidence of tumors than later exposures, with increased early susceptibilities up to 60-fold (ratios in Table 5 range from 0.5 to 58, with a median of 1.7, and 74% of ratios greater than 1, Figures 1-2, Table 7). When no adult tumors occurred, the increased early susceptibility could not be calculated, because it becomes infinite (e.g., urethane-induced lung adenomas in Kaye et al., 1966). 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 liver and kidney tumors).

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 6-8 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 6.2 is obtained when comparing susceptibilities of 5-8 week and 26 week old rats (Table 5). 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 sensitive 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. Other examples of deviations from the general trend towards an age-dependent decline include lung tumors in C3AF1 mice observed following BaP exposure on days 1, 15, and 42, which were similar in incidence throughout, while a decline in incidence with age was seen in B6C3F1 mice. DEN-induced lung tumors were somewhat lower in incidence following exposure on day 1 than observed with the day 15 or day 42 exposures (Vesselinovitch et al., 1975) (Tables 3 and 5).

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.

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 6). 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 dosing studies were identified for these agents.

These chemicals demonstrated a range of behaviors for early-lifestage exposure and the development of cancer. The magnitude of the apparent early-lifestage susceptibility when similar tumors were observed varied and, unlike for the mutagens, tended to be dependent upon analyses of tumor incidence that were not statistically significantly different from incidence in controls (though the combined perinatal and adult exposures were generally statistically significant even when the separate lifestage exposures were not). With ETU, no tumors in mice or rats were observed following perinatal exposure alone (except a small, non-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.

For the other five chemicals (amitrole, DDT, dieldrin, PBB, DPH), the same tumors were observed from early and/or adult exposures. Analysis of the incidence of tumors per time of

exposure shows substantial early-lifestage susceptibilities, particularly for liver tumors. Amitrole, which also is a thyroid hormone disrupting agent, was evaluated only for mouse liver tumors. Amitrole increased mouse liver tumors in males (ratio of 17.5), but caused no liver tumors in juvenile females, following exposure during the early postnatal period. Adult exposures increased liver tumors in males and females. The studies of mouse liver tumors following DDT and dieldrin dosing showed early-lifestage susceptibility (ratios of 10 and 13, respectively).

The major factor which complicates the interpretation of these studies 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 sensitive to exposures to chemical causing cancer through a variety of modes of action other than mutagenicity. However, the studies with ethylene thiourea indicate that this is not necessarily the case for all modes of action.

3.2.3 IONIZING RADIATION

As mentioned earlier, 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 8 and 9 are extracted from the tables in Annex I. The excess relative risk (ERR) is simply 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 9. Most sites show greater risks in the younger than 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. Table 10 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 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 to use the existing scientific database on early postnatal and juvenile exposures to carcinogens to evaluate the availability of information that would inform a science policy decision on whether and how to assess the risk from childhood exposures to chemicals for which we have evidence of carcinogenicity only in adult humans or laboratory animals. The database overall is of modest size (particularly compared with the number of chemicals that have been studied in adult occupational epidemiological studies or chronic bioassays, often for regulatory purposes or by the National Toxicology Program). The majority of the human data involves exposures to ionizing radiation or DES (Anderson et al., 2000). The experimental studies used sixteen chemicals, ten of which had mutagenic modes of action.

Previously published or internal U.S. EPA analyses have concluded that the standard animal bioassay protocol was rarely missing 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 undertaken. 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 studies with perinatal exposures without a directly comparative adult study.

Two other kinds of information can contribute to decision-making to develop a scientifically informed policy: theoretical analyses and analyses of stop studies.[4] Theoretical analyses suggest that the differential sensitivity would depend in part on the mode of action (i.e., at what step in the cancer process the chemical was acting) and that the lifetime average daily dose may underestimate or overestimate the cancer risk when exposures are time-dependent (Murdoch et al., 1992; Goddard et al., 1995). 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 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., 1981). Analysis by Halmes and coworkers (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 equal was incorrect, and usually underestimated risk. This unequal distribution of risk 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 look at later periods of life; e.g., Drew et al., 1981), 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 impact for two chemicals, causing tumors not observed at lower doses, indicating 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 do provide perspective on the standard cancer risk assessment averaging practice and its application in earlier periods, and they contribute to concerns that alternatives approaches for estimating risks from early childhood exposure 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 chemical mutagens are not identical processes, both involve direct damage to DNA as critical causative steps in the process. In both cases, the impacts of early exposure appear 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 8 and 10, A-bomb survivors exhibit different lifestage dependencies at different tumor sites, though the

4 Stop studies are studies in which exposure is halted after a predetermined period.

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 8 are based on Japanese baselines while the coefficients in Table 10 reflect transporting the risks from the Japanese population to the United States. However, it is clear that the total radiation-related tumor incidence showed a general slow decline with age at exposure.

The chemical mutagen studies in rodents 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 the most sensitive, though some degree of increased susceptibility through puberty in rats (beginning around 5-7 weeks) and mice (beginning around 4-6 weeks) exists.

All the acute dosing studies with animals of different ages used mutagenic chemicals (Tables 3 and 5). These studies provide the clearest indications 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 and coworkers uses a unique chronic study design in which rats were exposed starting at 3, 6, or 20 weeks of life. This design provides information on the sensitivity of early exposure periods within a nearly lifetime exposure (Peto et al., 1984).

Another strength of evaluating lifestage susceptibility to chemicals with a mutagenic mode of action is that there are biological rationales to explain why these kinds of 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 cells per initiated dose. These periods of cell replication can vary for different tissues. For example, DMBA appears 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. In addition, it is proposed that early exposure shortens the latency period. While these factors may apply to other modes of action as well, it clearly could increase the effects of early exposures to mutagens (Halmes et al, 2000).

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 tumors from perinatal exposure (e.g., polybrominated biphenyls), 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. There are no studies directly comparable to the single-dose studies with mutagens, which clearly show significant differences in tumor responses after identical doses at different lifestages.

Evidence for the impact of early-lifestage exposures on tumor incidence was observed clearly in the study with polybrominated biphenyls and is indicated by the studies with DDT, dieldrin, diphenylhydantoin. These studies show increased incidence in mice from perinatal exposure, though only those for polybrominated biphenyls were statistically significant (and 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 diphylhydantoin

and polybrominated biphenyl studies.

There are indications of chemicals causing different tumor types with early-lifestage exposures compared with those for adults (i.e., azidothymidine, tamoxifen, DES, saccharin, and ascorbate). In addition, studies with *in utero* exposure to atrazine (Fenton et al., 2002), DES, arsenic (Waalkes et al., 2003) indicate that early-life exposures to compounds can alter susceptibility of endocrine and reproductive organs. Two of these compounds (i.e., DES 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 (Newbold et al., 2001; Laurenzana et al., 2002). These studies will evaluate cancer incidence in offspring exposed *in utero*, during lactation, and through adulthood via diet. A recent study with genistein found uterine tumor development to be dependent upon early-lifestage exposures (Newbold et al., 2001). 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. This information likely needs to be extended further.

Further research needs that address potential increased risk of cancer among children, or from *in utero* or childhood exposures, include a combination of epidemiological studies, experimental studies, and analyses of the existing database. One focus for additional experimental research is a broader evaluation of the ability of compounds that affect endocrine function or the development of endocrine-sensitive tissues to alter susceptibility to cancer with perinatal exposures. This is a particular concern because the tumors appear to involve different sites than those from adult exposures, an effect that has been observed relatively infrequently. While the National Toxicology Program lifespan studies will be very useful, they will not have comparable adult-only 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, not just mothers, in all the experimental studies is essential for evaluating whether there is great childhood susceptibility or simply higher exposure. Pharmacokinetic modeling would better

define the internal doses to improve determination of the magnitude of increased susceptibility. Additional analyses of the existing database could focus on the *in utero* period, which was included here only when there was also early postnatal exposure, or on age-dependency of early events in the cancer process.

In summary, the existing animal database supports the conclusion that there is greater susceptibility for the development of tumors as a result of exposures to chemicals acting through a mutagenic mode of action, when the exposure occur in early lifestages as compared with later life stages. Thus, a risk assessment approach using estimates from chronic studies (i.e., cancer slope factors) with appropriate modifications to address the impact of early-lifestage exposure appears feasible. For chemicals acting through a non-mutagenic mode of action, the available data suggest that a range of approaches needs to be developed over time for addressing cancer risk estimates from childhood exposures. Development of such approaches requires additional research to provide an expanded scientific basis for their support.

[Having considered the analysis above, the following discussion presents, at this time, a possible approach for assessing cancer susceptibility from early-life exposure to carcinogens. A final decision by the Agency on the use of this or any alternative approach will reflect public comments and recommendations from the Science Advisory Board's review of this document.]

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

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. Consistent with the approach and recommendations of the U.S. EPA cancer risk assessment guidelines, any assessment of cancer susceptibility should begin with a critical analysis of the available information. Figure 3 shows the proposed steps in the process.

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 exposures different than adults (either higher or lower), due to differences in size, physiology and behavior. For example, children generally eat more food, drink more water, and breathe more air relative to their body weight than adults. Children's normal activities, such as putting their hands in their mouths, playing on the ground or breastfeeding, 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 internal doses due to differences in intake or absorption rates. On the other hand, children are less likely than adults to be exposed to products typically used in industrial settings and often have more limited diets than adults. EPA continues to develop better tools for assessing childhood exposure differences, such as the Child-Specific Exposure Factors Handbook (U.S. EPA, 2002), and models, such as Stochastic Human Exposure and Dose Simulation (SHEDS) and Consolidated Human Activity Database (CHAD) (McCurdy, T., 2000; Zartarian, V.G., 2000).

When assessing risks, if the data are available and appropriate, it is important to include exposure that is measured or modeled for all lifestages including those during childhood and during adulthood.

1. If the available information includes an epidemiologic study of the effects of childhood exposure or an animal bioassay involving early-life exposure, then these studies should be analyzed to develop risk estimates that include childhood exposure. An example is the IRIS assessment of vinyl chloride (U.S. EPA, 2000a; U.S. EPA, 2000b).

2. If there are no early-life studies, but the available information is sufficient to establish the agent's mode of action, then the implications of that mode of action for children should be used to develop separate risk estimates for childhood exposure. Mode-of-action studies can be a source of data on quantitative differences between children and adults. 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 separate risk estimates for childhood exposure. Some examples include the potential for children to have a higher internal dose of the active agent or an increased occurrence of a key precursor event (see section 2.5.3.4 of the cancer guidelines).

2a. When the data indicate a mutagenic mode of action[5], the available science (discussed above) indicates that higher cancer risks typically result from a given exposure occurring early in life when compared with the same amount of exposure during adulthood. Consequently, in the absence of early-life studies on a specific agent under consideration, U.S. EPA generally should:

Use linear extrapolation to lower doses (see section 3.3.1 of the U.S. EPA 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.

Adjust risk estimates that pertain to childhood exposure. This choice is proposed because risk estimates based on a lifetime-average daily dose do not consider the potential for higher cancer risks from early-life exposure. The following adjustments represent a practical approach that reflects the results of the preceding analysis, which found that cancer risks generally were higher from early-life exposure than from similar exposure durations later in life:

- For exposures before 2 years of age, a 10-fold adjustment.

5 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 (OECD, 1998; Cimino, 2001; 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. Mutagenic carcinogens 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 section 2.3.5.1. of the proposed EPA cancer guidelines (U.S. EPA, 2003).

- For exposures between 2 and 15 years of age, a 3-fold adjustment.
- For exposures after 15 years of age, no adjustment.

These adjustments reflect the potential for early-life exposure to make a greater contribution to cancers appearing later in life; any exposure differences in early life also should be accounted for. The 10-fold adjustment represents an approximation of the median tumor incidence ratio from juvenile or adult exposures in the repeated dosing studies (see Table 7). This adjustment is applied for the first 2 years of life, when pharmacokinetic and pharmacodynamic differences between children and adults are greatest (Ginsberg et al., 2002; Renwick, 1998). The 3-fold adjustment represents an intermediate level of adjustment that is applied after 2 years of age, when pharmacokinetic processes mostly resemble those of adults (Ginsberg et al., 2002; Renwick, 1998), through 15 years of age, representing middle adolescence approximately following the period of rapid developmental changes in puberty. Data are not available to calculate a specific dose-response adjustment factor for the 2-15 year age range, so EPA selected the 3-fold adjustment because it reflects a midpoint between the 10-fold adjustment for the first two years of life and a unity adjustment 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.

The 10-fold and 3-fold adjustments in slope factor are to be integrated 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 should be integrated with corresponding age-specific estimates of exposure to assess cancer risk. For example: 1) 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); 2) where there are data (measured or modeled) for childhood exposures, use the age-group specific exposure values along with the corresponding adjustments to the slope factor; and 3) where there are no relevant data or models for childhood exposures and only life-time average exposure is available, use the life-time exposure data 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 will be small relative to the overall uncertainty of such estimates. Regardless, these adjustments should be applied by U.S. EPA when estimating the cancer risk resulting from childhood exposure.

These adjustments should be applied when developing risk estimates from conventional animal bioassays or epidemiologic studies of effects of adult exposure. Accordingly, they do not address childhood cancers. Some examples follow at the end of this section.

2b. When a mode of action other than mutagenicity is established, although the available science (discussed earlier) indicates that higher cancer risks sometimes result from early-life exposure, there is insufficient information currently available to determine a general adjustment, consequently, no general adjustment is recommended at this time. U.S. EPA expects that as other modes of action become better understood, this information will include data on quantitative differences between children and adults, and these differences will be reflected in risk estimates for childhood exposure. U.S. EPA expects to expand this supplemental guidance to include other modes of action as they are understood and used in risk assessments.

3. When the mode of action cannot be established, the policy choice would be to use linear

extrapolation to lower doses such that risk estimates are based on a lifetime-average daily dose without further adjustment. Consequently, 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 risk estimates that generally are protective, based on the use of linear extrapolation as a default in the absence of information on the likely shape of the dose-response curve.

6. SOME EXAMPLES OF ADJUSTMENTS UNDER STEP 2A (MUTAGENIC AGENTS)

Consider a scenario of exposure to a mutagenic agent. Suppose the slope factor is 2 per mg/kg-d, and the exposure rate is 0.0001 mg/kg-d. The risk from lifetime exposure is calculated by multiplying the slope factor and the exposure rate:

$$\text{Risk} = (2 \text{ per mg/kg-d}) \times (0.0001 \text{ mg/kg-d}) = 2 \times 10^{-4}$$

If the scenario is altered so that exposure will occur for only 5 years, use of a lifetime-average daily dose would reduce the calculated risk, regardless of the age when exposure occurs:

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

If this less-than-lifetime exposure occurs during childhood, the risk calculations are adjusted to consider the potential for higher cancer risks from early-life exposure, as described in step 2a above:

a. For a child exposed between ages 5 and 10, a 3-fold risk adjustment is made because the exposure occurs entirely between ages 2 and 15:

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

b. For a child exposed between ages 12 and 17, the risk adjustment is applied to only the 3-year portion occurring before age 15:

Risk = 3 x (2 per mg/kg-d) x (0.0001 mg/kg-d) x (3 yr/70 yr)
+ (2 per mg/kg-d) x (0.0001 mg/kg-d) x (2 yr/70 yr)
= $2.6 \times 10^{-5} + 0.6 \times 10^{-5}$
= 3.2×10^{-5}

c. For a child exposed from birth through age 5, separate risk adjustments are applied to the periods before and after age 2:

Risk = 10 x (2 per mg/kg-d) x (0.0001 mg/kg-d) x (2 yr/70 yr)
+ 3 x (2 per mg/kg-d) x (0.0001 mg/kg-d) x (3 yr/70 yr)
= $5.7 \times 10^{-5} + 2.6 \times 10^{-5}$
= 8.3×10^{-5}

These calculations also can consider changes in the exposure level or differences in intake between children and adults. For example, consider a scenario of 5 years of exposure to the same mutagenic agent, but suppose the exposure rate is 0.0002 mg/kg-d during first 2 years and 0.0001 during the last 3 years:

a. For a child exposed between birth and ages 5, consideration of the different exposure periods yields:

Risk = 10 x (2 per mg/kg-d) x (0.0002 mg/kg-d) x (2 yr/70 yr)
+ 3 x (2 per mg/kg-d) x (0.0001 mg/kg-d) x (3 yr/70 yr)
= $11.4 \times 10^{-5} + 2.6 \times 10^{-5}$
= 1.4×10^{-4}

b. For comparison, the same risk calculation for exposure later in life (after age 15) would be carried out without adjustment:

Risk = (2 per mg/kg-d) x (0.0002 mg/kg-d) x (2 yr/70 yr)
+ (2 per mg/kg-d) x (0.0001 mg/kg-d) x (3 yr/70 yr)
= 1.1 x 10-5 + 0.9 x 10-5
= 2 x 10-5

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

Chemical	References	Study Type
Amitrole	Vesselinovitch et al., 1983	Repeat dosing
Benzo(a)pyrene (BaP)	Vesselinovitch et al., 1975 Neal and Rigdon, 1967	Acute exposure Repeat dosing
Benzidine	Vesselinovitch et al., 1983 Vesselinovitch et al., 1979	Repeat dosing Repeat dosing
Dibenzanthracene (DBA)	Law, 1940	Acute exposure
Dichlorodiphenyltrichloroethane (DDT)	Vesselinovitch et al., 1979	Repeat dosing
Dieldrin	Vesselinovitch et al., 1979	Repeat dosing
Diethylnitrosamine (DEN)	Peto et al., 1984 Vesselinovitch et al., 1984 Vesselinovitch et al., 1983 Vesselinovitch et al., 1979	Repeat dosing Acute exposure Acute exposure Acute exposure - *data not used in analysis*
Dimethylbenz(a)anthracene (DMBA)	Russo et al., 1979 Meranze et al., 1969 Walters, 1966 Pietra et al., 1961	Acute exposure – *data not used in analysis* Acute exposure Acute exposure Acute exposure
Dimethylnitrosamine (DMN)	Hard, 1979	Acute exposure
Diphenylhydantoin, 5,5- (DPH)	Chhabra et al., 1993a	Repeat dosing
Ethylnitrosourea (ENU)	Maekawa et al., 1990 Vesselinovitch et al., 1983 Naito et al., 1981 Vesselinovitch et al., 1979	Acute exposure Acute exposure Acute exposure Acute exposure
Ethylene thiourea (ETU)	Chhabra et al., 1992	Repeat dosing
Polybrominated biphenyls (PBBs)	Chhabra et al., 1993b	Repeat dosing
Safrole	Vesselinovitch et al., 1983 Vesselinovitch et al., 1979	Repeat dosing Repeat dosing
Urethane	Kaye et al., 1966 Liebelt et al., 1964 Fiore-Donati et al., 1962 Rogers, 1950	Acute exposure Acute exposure Acute exposure Acute exposure
Vinyl chloride (VC)	Drew et al., 1983 Maltoni et al., 1981	Repeat dosing – *data not used in analysis* Repeat dosing

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult chronic exposure.

Chemical	Species	Target site	Age when first dosed	Dose Route, # doses	Dose	Duration of exposure	Age at death	Tumors[i]		Comments	Reference
								M	F		
Amitrole	Mice ($B6C3F_1$)	Liver	Control	None	Control: 0 ppm	N/A	90 weeks	1/98 (1%)	0/96 (0%)	Duration of exposure was longest among adults (from weaning to 90 weeks).	Vesselinovitch et al., 1983
			Gestation day 12	Diet, to mothers	500 ppm	Gestation day 12 to delivery		6/74 (8%)[c]	0/83 (0%)[c]		
			Newborn	Diet, to mothers	500 ppm	Birth until weaning		10/45 (22%)[c]	0/55 (0%)[c]		
			At weaning	Diet, to offspring	500 ppm	From weaning to 90 weeks		20/55 (36%)[c]	9/49 (18%)[c]		
Benzo(a)pyrene (B(a)P)	Mice (CFW)	Stomach	Control Day 30	Control Diet, daily	0 mg/g food	110 days	140 days	0/171 (0%)	0/118 (0%)	Doses from 0.001 to 0.25 mg/g food.	Neal and Rigdon, 1967
			Days 17-22	Diet, daily	0.05 mg/g food	107 – 197 days	124-219 days	24/34 (70%)[c]			
			Days 31-71	Diet, daily	0.045 mg/g food	110 days	141-181 days	4/40 (10%)[c]			
Benzidine	Mice ($B6C3F_1$)	Liver	Control	None	Control: 0 ppm	N/A	90 weeks	1/98 (1%)	0/96 (0%)	Duration of exposure was longest among adults (from weaning to 90 weeks).	Vesselinovitch et al., 1983
			Gestation day 12	Diet, to mothers	150 ppm	Gestation day 12 to delivery		8/36 (22%)[c]	2/56 (4%)[c]		
			Newborn	Diet, to mothers	150 ppm	Birth until weaning		35/52 (67%)[c]	9/43 (21%)[c]		
			At weaning	Diet, to offspring	150 ppm	From weaning to 90 weeks		22/26 (85%)[c]	16/25 (64%)[c]		
Benzidine	Mice ($B6C3F_1$)	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., 1979
			Gestation day 12	Diet, to mothers	150 ppm	Gestation day 12 to delivery		17/55 (31%)[a]	2/62 (3%)[b]		
			Newborn	Diet, to mothers	150 ppm	Birth until weaning		62/65 (95%)[a]	2/43 (5%)[b]		
			At weaning	Diet, to offspring	150 ppm	From weaning to 90 weeks		25/44 (57%)[a]	48/50 (96%)[a]		
			Gestation day 12	Diet, to mothers	150 ppm	Gestation day 12 until weaning		49/49 (100%)[a]	12/48 (25%)[a]		
			Gestation day 12	Diet, to mothers	150 ppm	Gestation day 12 until 90 weeks		50/50 (100%)[a]	47/50 (94%)[a]		

a) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

[i] Where not delineated by gender, data combined by study authors or gender not specified. Where percentages only are given, number of subjects not specified.

Chemical	Species	Target site	Age when first dosed	Dose Route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
DDT Dichlorodiphenyltrichloroethane	Mice (B6C3F1)	Liver	Control	None	Control: 0 ppm	N/A	90 weeks	1/50 (2%)	-		Vesselinovitch et al., 1979
			Week 1	Gavage, daily	230 ug	Weeks 1-4		5/49 (10%)[b]	-		
			Week 5	Diet, daily	150 ppm	Weeks 5-90		8/49 (16%)[b]	-		
			Weeks 1	Gavage, daily until 4 weeks, then in diet	230 ug 150 ppm (diet)	Weeks 1-90		10/50 (20%)[a]	-		
Dieldrin	Mice (B6C3F1)	Liver	Control	None	Control: 0 ppm	N/A	90 weeks	1/58 (2%)	-		Vesselinovitch et al., 1979
			Week 1	Gavage, daily	12.5 ug	Week 1-4		3/46 (7%)[b]	-		
			Week 5	Diet, daily	10 ppm	Weeks 5-90		7/60 (12%)[b]	-		
			Week 1	Gavage, daily until 4 weeks, then in diet	12.5 ug 10 ppm	Weeks 1-90		21/70 (30%)[a]	-		
DEN Diethylnitrosamin[ii]	Rat (Colworth)	Liver	Week 3	Diet (in drinking water), daily	16 different doses combined[iii]	From week 3 until death	6 months-3 years	105/180 (58%)[c]		Highest tumor rate when dosed at earlier ages. No control group.	Peto et al., 1984
			Week 6			From week 6 until death		714/1440 (50%)[c]			
			Week 20			From week 20 until death		76/180 (42%)[c]			
DEN Diethylnitrosamin[iv]	Rat (Colworth)	Esophagus	Week 3	Diet (in drinking water), daily	16 different doses combined[v]	From week 3 until death		77/180 (43%)[c]			Peto et al., 1984
			Week 6			From week 6 until death		663/1440 (46%)[c]			
			Week 20			From week 20 until death		88/180 (49%)[c]			

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Reported as NDEA (N-nitrosodiethylamine) in the original document.
[i] Results from each dose are not available.
[v] Reported as NDEA (N-nitrosodiethylamine) in the original document.
Results from each dose are not available.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
DPH Diphenylhydantoin, 5,5-	Rats (F344/N)	Liver	Control	Control	0 ppm	N/A	2 years	0/50 (0%)	0/50 (0%)	In rats, perinatal exposure ranged from 63-630 ppm, and adult rat exposures ranged from 240-2400 ppm. In mice, perinatal exposure ranged from 21 to 210 ppm. Adult exposure ranged from 30-300 ppm in males and 60-600 ppm in females. Tumor incidences are combined adenomas and carcinomas.	Chhabra et al., 1993a
			Perinatal	Diet, daily	630 ppm	Perinatal through 8 weeks		1/50 (2%)[b]	0/49 (0%)[b]		
			8 weeks		800 ppm	8 weeks – 2 years		2/50 (4%)[b]	1/50 (2%)[b]		
			8 weeks		2400 ppm	8 weeks – 2 years		4/50 (8%)[b]	1/50 (2%)[b]		
			Perinatal		630-800	Perinatal through 2 years		1/49 (2%)[b]	0/50 (0%)[b]		
			Perinatal		630-2400 ppm	Perinatal through 2 years		5/49 (10%)[a]	0/50 (0%)[b]		
	Mice ($B6C3F_1$)	Liver	Control	Control male	0 ppm	N/A	2 years	29/50 (58%)			
			Perinatal	Diet, male	210 ppm	Perinatal through 8 weeks		33/50 (66%)[b]			
			8 weeks		100 ppm	8 weeks – 2 years		29/49 (59%)[b]			
			8 weeks		300 ppm	8 weeks – 2 years		26/49 (53%)[b]			
			Perinatal		210-100 ppm	Perinatal through 2 years		35/49 (71%)[b]			
			Perinatal		210-300 ppm	Perinatal through 2 years		41/50 (82%)[a]			
			Control	Control female	0 ppm	N/A	2 years		5/48 (10.4%)[b]		
			Perinatal	Diet, female	210 ppm	Perinatal through 8 weeks			12/49 (24.5%)[b]		
			8 weeks		200 ppm	8 weeks – 2 years			14/49 (28%)[a]		
			8 weeks		600 ppm	8 weeks – 2 years			30/50 (60%)[a]		
			Perinatal		210-200 ppm	Perinatal through 2 years			16/50 (32%)[a]		
			Perinatal		210-600 ppm	Perinatal through 2 years			34/50 (68%)[a]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
TU thylene hiourea	Rat (F344/N)	Thyroid	Control	Control	0 ppm	N/A	2 years	1/49 (2%)	3/50 (6%)	Target site tumors were adenomas or carcinomas.	Chhabra et al., 1992
			Perinatal	Diet, daily	90 ppm	Perinatal through 8 weeks		4/49 (8%)[b]	3/50 (6%)[b]		
			8 weeks		83 ppm	8 weeks – 2 years		12/46 (26%)[a]	7/44 (16%)[b]		
			8 weeks		250 ppm	8 weeks – 2 years		37/50 (74%)[a]	30/49 (61%)[a]		
			Perinatal		90-83 ppm	Perinatal through 2 years		13/50 (26%)[a]	9/47 (19%)[b]		
	Mice ($B6C3F_1$)	Liver	Control	Control	0 ppm	N/A	2 years	20/49 (41%)	4/50 (8%)		
			Perinatal	Diet, daily	330 ppm	Perinatal through 8 weeks		13/49 (26.5%)[b]	5/49 (10%)[b]		
			8 weeks		330 ppm	8 weeks – 2 years		32/50 (64%)[a]	44/50 (88%)[a]		
			8 weeks		1000 ppm	8 weeks – 2 years		46/50 (92%)[a]	48/50 (96%)[a]		
			Perinatal		330-330 ppm	Perinatal through 2 years		34/49 (69%)[a]	46/50 (92%)[a]		
		Thyroid	Control	Control	0 ppm	N/A		1/50 (2%)	0/50 (0%)		
			Perinatal	Diet, daily	330 ppm	Perinatal through 8 weeks		1/46 (2%)[b]	1/49 (2%)[b]		
			8 weeks		330 ppm	8 weeks – 2 years		1/49 (2%)[b]	2/50 (4%)[b]		
			8 weeks		1000 ppm	8 weeks – 2 years		29/50 (58%)[a]	38/50 (76%)[a]		
			Perinatal		330-330 ppm	Perinatal through 2 years		2/48 (4%)[b]	10/49 (20%)[a]		
		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%)[b]	11/48 (23%)[b]		
			8 weeks		330 ppm	8 weeks – 2 years		0/42 (0%)[b]	19/49 (39%)[b]		
			8 weeks		1000 ppm	8 weeks – 2 years		8/41 (19.5%)[a]	26/49 (53%)[a]		
			Perinatal		330-330 ppm	Perinatal through 2 years		0/45 (0%)[b]	26/47 (55%)[a]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
PBBs Polybrominated biphenyls	Rats (F344/N)	Liver[vi]	Control	Control	0 ppm	N/A	2 years	1/50 (2%)	0/50 (0%)	Findings suggest that combined perinatal and adult exposure increases PBB-related hepatocellular carcinogenicity relative to adult-only exposure in mice and female rats. Apparent association between increasing incidences of MCL and exposure to PBB in male and female rats.	Chhabra et al., 1993b
			Perinatal	Diet	10 ppm	Perinatal – 8 weeks		5/50 (10%)[b]	0/50 (0%)[b]		
			8 weeks		10 ppm	8 weeks – 2 years		12/49 (24%)[a]	12/50 (24%)[a]		
			8 weeks		30 ppm	8 weeks – 2 years		41/50 (82%)[a]	39/50 (78%)[a]		
			Perinatal		10-10 ppm	Perinatal – 2 years		16/50 (32%)[a]	39/50 (78%)[a]		
			Perinatal		10-30 ppm	Perinatal – 2 years		41/50 (82%)[a]	47/50 (94%)[a]		
		Mononuclear cell leukemia (MCL)	Control	Control	0 ppm	N/A	2 years	25/50 (50%)	14/50 (28%)		
			Perinatal	Diet	10 ppm	Perinatal – 8 weeks		31/50 (62%)[b]	13/50 (26%)[b]		
			8 weeks		10 ppm	8 weeks – 2 years		33/50 (66%)[a]	22/50 (44%)[b]		
			8 weeks		30 ppm	8 weeks – 2 years		31/50 (62%)[b]	23/50 (46%)[a]		
			Perinatal		10-10 ppm	Perinatal – 2 years		37/50 (74%)[a]	27/50 (54%)[a]		
			Perinatal		10-30 ppm	Perinatal – 2 years		37/50 (74%)[a]	25/50 (50%)[a]		
	Mice ($B6C3F_1$)	Liver[vii]	Control	Control	0 ppm	N/A	2 years	16/50 (32%)	5/50 (10%)		
			Perinatal	Diet	30 ppm	Perinatal – 8 weeks		40/50 (80%)[a]	21/50 (42%)[a]		
			8 weeks		10 ppm	8 weeks – 2 years		48/49 (98%)[a]	42/50 (84%)[a]		
			8 weeks		30 ppm	8 weeks – 2 years		48/50 (96%)[a]	47/48 (98%)[a]		
			Perinatal		10-30 ppm	Perinatal – 2 years		48/50 (96%)[a]	50/50 (100%)[a]		
			Perinatal		30-30 ppm	Perinatal – 2 years		50/50 (100%)[a]	47/47 (100%)[a]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

[vi] Tumors were adenomas or carcinomas.
[vii] Tumors were adenomas or carcinomas.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
Safrole	Mice ($B6C3F_1$)	Liver	Control	Control	None	N/A	90 weeks	1/98 (1%)	0/96 (0%)		Vesselinovitch et al., 1983
			Gestation day 12, 14, 16 or 18	IP	120 ug/g body weight	1x		2/62 (3%)[c]	0/65 (0%)[c]		
			Delivery		120 ug/g body weight	Alternate days from delivery to weaning		28/83 (34%)[c]	2/80 (2.5%)[c]		
			Weaning		120 ug/g body weight	Twice weekly from weaning through 90 weeks		4/35 (11%)[c]	22/36 (61%)[c]		
Safrole	Mice ($B6C3F_1$)	Liver	Control	None	None	N/A	90 weeks	1/98 (1%)	0/100 (0%)	Highest tumor rate in males due to preweaning treatment. Highest tumor rate in females due to susceptibility in adulthood.	Vesselinovitch et al., 1979
			Day 12, 14, 16, or 18 of gestation	Diet, to mothers	120 ug/g body weight	Single day		4/60 (7%)[b]	0/65 (0%)[b]		
			Newborn	Diet, to mothers, on alternate days	120 ug/g body weight	From birth until weaning		27/83 (32%)[a]	1/79 (1%)[b]		
			At weaning	Diet, to offspring, 2x weekly	120 ug/g body weight	From weaning until 90 weeks		4/50 (8%)[b]	28/50 (56%)[a]		
			Day 12, 14, 16, or 18 of gestation	Diet, to mothers, alternate days	120 ug/g body weight	From gestation until weaning		25/67 (37%)[c]	0/71 (0%)[c]		
			12, 14, 16, or 18 day of gestation	Diet, to mothers, alternate days until weaning; Diet, to offspring, 2x weekly	120 ug/g body weight	From gestation until 90 weeks		25/50 (50%)[c]	41/64 (64%)[c]		
VC Vinyl Chloride	Rats (Fischer-344)	Hemangio-sarcoma (all sites including liver)	Control	None	None	N/A	703 days ±15	-	2/112 (2%)	Highest tumor rate when exposed starting at birth.	Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	100 ppm	6 months	682 days ±14	-	4/76 (5%)[b]		
			Month 0			12 months	634 days ±20	-	12/56 (21%)[a]		
			Month 0			18 months	575 days ±15	-	15/55 (27%)[a]		
			Month 0			24 months	622 days ±11	-	24/55 (44%)[a]		
			Month 6			6 months	703 days ±24	-	2/53 (4%)[b]		
			Month 12			6 months	688 days ±25	-	0/53 (0%)[b]		
			Month 18			6 months	708 days ±21	-	0/53 (0%)[b]		
			Month 6			12 months	659 days ±17	-	5/55 (9%)[b]		
			Month 12			12 months	717 days ±17	-	2/50 (4%)[b]		

a) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
VC Vinyl Chloride	Rats (Fischer-344)	Mammary gland (fibro-adenoma + adeno-carcinoma)	Control	None	None	N/A	703 days ±15	-	29/112 (26%)	Rates for fibroadenoma were consistently higher than for adenocarcinoma. Highest tumor rate when exposed starting at birth.	Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	100 ppm	6 months	682 days ±14	-	34/76 (45%)[c]		
			Month 0			12 months	634 days ±20	-	39/56 (70%)[c]		
			Month 0			18 months	575 days ±15	-	33/55 (60%)[c]		
			Month 0			24 months	622 days ±11	-	31/55 (56%)[c]		
			Month 6			6 months	703 days ±24	-	25/53 (47%)[c]		
			Month 12			6 months	688 days ±25	-	20/53 (38%)[c]		
			Month 18			6 months	708 days ±21	-	22/53 (42%)[c]		
			Month 6			12 months	659 days ±17	-	20/55 (36%)[c]		
			Month 12			12 months	717 days ±17	-	15/50 (30%)[c]		
VC	Rats (Fischer-344)	Liver (neoplastic nodules + hepato-cellular carcinoma)	Control	None	None	N/A	703 days ±15	-	5/112 (4%)	Rates for neoplastic nodules were mostly higher than for hepatocellular carcinoma. Highest tumor rate when exposed starting at birth.	Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	100 ppm	6 months	682 days ±14	-	18/75 (24%)[c]		
			Month 0			12 months	634 days ±20	-	24/56 (43%)[c]		
			Month 0			18 months	575 days ±15	-	15/54 (28%)[c]		
			Month 0			24 months	622 days ±11	-	15/55 (27%)[c]		
			Month 6			6 months	703 days ±24	-	16/52 (31%)[c]		
			Month 12			6 months	688 days ±25	-	2/51 (4%)[c]		
			Month 18			6 months	708 days ±21	-	5/53 (9%)[c]		
			Month 6			12 months	659 days ±17	-	5/54 (9%)[c]		
			Month 12			12 months	717 days ±17	-	4/49 (8%)[c]		
VC	Hamsters (golden Syrian)	Hemangio-sarcoma	Control	None	None	N/A	463 days ±11	-	0/143 (0%)	Highest tumor rate when exposed starting at birth.	Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	200 ppm	6 months	390 days ±12	-	13/88 (15%)[a]		
			Month 0			12 months	355 days ±10	-	4/52 (8%)[a]		
			Month 0			18 months	342 days ±8	-	2/103 (2%)[b]		
			Month 6			6 months	468 days ±16	-	3/53 (6%)[a]		
			Month 12			6 months	456 days ±17	-	0/50 (0%)[b]		
			Month 18			6 months	499 days ±14	-	0/52 (0%)[b]		
			Month 6			12 months	455 days ±13	-	1/44 (2%)[b]		
			Month 12			12 months	424 days ±15	-	0/43 (0%)[b]		
VC	Hamsters (golden Syrian)	Mammary gland	Control	None	None	N/A	463 days ±11	-	0/143 (0%)	Highest tumor rate when exposed starting at birth.	Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	200 ppm	6 months	390 days ±12	-	28/87 (32%)[a]		
			Month 0			12 months	355 days ±10	-	31/52 (60%)[a]		
			Month 0			18 months	342 days ±8	-	47/102 (46%)[a]		
			Month 6			6 months	468 days ±16	-	2/52 (4%)[a]		
			Month 12			6 months	456 days ±17	-	0/50 (0%)[b]		
			Month 18			6 months	499 days ±14	-	1/52 (2%)[b]		
			Month 6			12 months	455 days ±13	-	6/44 (14%)[a]		
			Month 12			12 months	424 days ±15	-	0/42 (0%)[b]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
VC Vinyl Chloride	Hamsters (golden Syrian)	Stomach	Control	None	None	N/A	463 days ±11	-	5/138 (4%)		Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	200 ppm	6 months	390 days ±12	-	23/88 (26%)[a]		
			Month 0			12 months	355 days ±10	-	3/50 (6%)[a]		
			Month 0			18 months	342 days ±8	-	20/101 (20%)[a]		
			Month 6			6 months	468 days ±16	-	15/53 (28%)[a]		
			Month 12			6 months	456 days ±17	-	6/49 (12%)[a]		
			Month 18			6 months	499 days ±14	-	0/52 (0%)[b]		
			Month 6			12 months	455 days ±13	-	10/44 (23%)[a]		
			Month 12			12 months	424 days ±15	-	3/41 (7%)[b]		
VC	Hamsters (golden Syrian)	Skin	Control	None	None	N/A	463 days ±11	-	0/133 (0%)	Highest tumor rate when exposed starting at birth. No tumors found for those exposed starting at 6 m. or older.	Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	200 ppm	6 months	390 days ±12	-	2/80 (3%)[b]		
			Month 0			12 months	355 days ±10	-	9/48 (19%)[a]		
			Month 0			18 months	342 days ±8	-	3/90 (3%)[b]		
			Month 6			6 months	468 days ±16	-	0/49 (0%)[b]		
			Month 12			6 months	456 days ±17	-	0/46 (0%)[b]		
			Month 18			6 months	499 days ±14	-	0/50 (0%)[b]		
			Month 6			12 months	455 days ±13	-	0/38 (0%)[b]		
			Month 12			12 months	424 days ±15	-	0/30 (0%)[b]		
VC	Mice ($B6C3F_1$)	Hemangio-sarcoma	Control	None	None	N/A	780 days ±21	-	4/69 (6%)		Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	50 ppm	6 months	316 days ±8	-	46/67 (69%)[a]		
			Month 0			12 months	301 days ±5	-	69/90 (77%)[a]		
			Month 6			6 months	480 days ±13	-	27/42 (64%)[a]		
			Month 12			6 months	695 days ±12	-	30/51 (59%)[a]		
			Month 6			12 months	479 days ±9	-	30/48 (63%)[a]		
			Month 12			12 months	632 days ±12	-	29/48 (60%)[a]		
VC	Mice ($B6C3F_1$)	Mammary gland	Control	None	None	N/A	780 days ±21	-	3/69 (4%)	Lowest tumor rates when dosed after 12 months.	Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	50 ppm	6 months	316 days ±8	-	29/67 (43%)[a]		
			Month 0			12 months	301 days ±5	-	37/90 (41%)[a]		
			Month 6			6 months	480 days ±13	-	13/42 (31%)[a]		
			Month 12			6 months	695 days ±12	-	4/51 (8%)[a]		
			Month 6			12 months	479 days ±9	-	9/48 (19%)[a]		
			Month 12			12 months	632 days ±12	-	4/48 (8%)[a]		
VC	Mice (CD-1 Swiss)	Hemangio-sarcoma	Control	None	None	N/A	474 days ±14	-	1/71 (1%)	Lowest tumor rates when dosed after 12 months.	Drew et al., 1983)
			Month 0	Inhalation, 6 hours/day, 5 days/week	50 ppm	6 months	340 days ±10	-	29/67 (43%)[a]		
			Month 0			12 months	347 days ±9	-	30/47 (64%)[a]		
			Month 0			18 months	321 days ±7	-	20/45 (44%)[a]		
			Month 6			6 months	472 days ±15	-	11/49 (22%)[a]		
			Month 12			6 months	521 days ±15	-	5/53 (9%)[b]		
			Month 6			12 months	443 days ±16	-	17/46 (37%)[a]		
			Month 12			12 months	472 days ±20	-	3/50 (6%)[b]		

a) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
VC Vinyl Chloride	Mice (CD-1 Swiss)	Mammary gland	Control	None	None	N/A	474 days ± 14	-	3/69 (4%)	Lowest tumor rates when dosed after 12 months.	Drew et al., 1983)
			Month 0	Inhalation, 6 hours/day, 5 days/week	50 ppm	6 months	340 days ± 10	-	33/67 (49%)[a]		
			Month 0			12 months	347 days ± 9	-	22/47 (47%)[a]		
			Month 0			18 months	321 days ± 7	-	22/45 (49%)[a]		
			Month 6			6 months	472 days ± 15	-	13/49 (27%)[a]		
			Month 12			6 months	521 days ± 15	-	2/53 (4%)[b]		
			Month 6			12 months	443 days ± 16	-	8/45 (18%)[a]		
			Month 12			12 months	472 days ± 20	-	0/50 (0%)[b]		
VC	Mice (CD-1 Swiss)	Lung	Control	None	None	N/A	474 days ± 14	-	9/71 (13%)	Lowest tumor rates when dosed after 12 months.	Drew et al., 1983
			Month 0	Inhalation, 6 hours/day, 5 days/week	50 ppm	6 months	340 days ± 10	-	18/65 (28%)[a]		
			Month 0			12 months	347 days ± 9	-	15/47 (32%)[a]		
			Month 0			18 months	321 days ± 7	-	11/45 (24%)[a]		
			Month 6			6 months	472 days ± 15	-	13/49 (27%)[a]		
			Month 12			6 months	521 days ± 15	-	7/53 (13%)[b]		
			Month 6			12 months	443 days ± 16	-	9/46 (20%)[a]		
			Month 12			12 months	472 days ± 20	-	3/50 (6%)[b]		
VC[viii] Vinyl Chloride	Rats (Sprague-Dawley)	Liver angio-sarcoma	Control	Control	0 ppm	N/A	154 weeks	0%	-	Higher tumor risk when exposed at birth, higher for females.	Maltoni et al., 1981
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks		27.8%[c]	50%[c]		
					10,000 ppm			25%[c]	45%[c]		
			Week 11		6,000 ppm			0%[c]	0%[c]		
					10,000 ppm			1.7%[c]	0%[c]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

[iii] This study contained a number of species, dosages, and types of tumors.

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

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[i]		Comments	Reference
								M	F		
Benzo(a)pyrene	Mice ($B6C3F_1$)	Liver	Control	Control	None	N/A	142 weeks	7/100 (7%)	1/98 (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. + higher for males	Vesselinovitch et al., 1975
			Day 1	IP[ii]	75 ug/g body weight	1x	86 weeks (m) 129 weeks (f)	26/47 (55%)[c]	3/45 (7%)[c]		
					150 ug/g body weight	1x	81 weeks (m) 121 weeks (f)	51/63 (81%)[c]	8/45 (18%)[c]		
			Day 15	IP	75 ug/g body weight	1x	93 weeks (m) 116 weeks (f)	36/60 (60%)[c]	4/55 (7%)[c]		
					150 ug/g body weight	1x	81 weeks (m) 90 weeks (f)	32/55 (58%)[c]	3/45 (7%)[c]		
			Day 42	IP	75 ug/g body weight	1x	108 weeks(m)	7/55 (13%)[c]	0/47 (0%)[c]		
					150 ug/g body weight	1x	87 weeks (m)	4/47 (9%)[c]	0/46 (0%)[c]		
Benzo(a)pyrene	Mice ($C3A\ F_1$)	Liver	Control	Control	None	N/A	142 weeks	8/100 (8%)	1/100 (1%)	+ higher for males "Age at death" is the average age at which tumors were observed.	Vesselinovitch et al., 1975
			Day 1	IP	75 ug/g body weight	1x	80 weeks (m) 91 weeks (f)	21/62 (34%)[c]	1/45 (2%)[c]		
					150 ug/g body weight	1x	69 weeks (m) 701 weeks (f)	24/52 (46%)[c]	1/56 (2%)[c]		
			Day 15	IP	75 ug/g body weight	1x	90 weeks (m) 102 weeks (f)	15/56 (27%)[c]	1/49 (2%)[c]		
					150 ug/g body weight	1x	77 weeks (m) 62 weeks (f)	12/53 (23%)[c]	1/57 (2%)[c]		
			Day 42	IP	75 ug/g body weight	1x		0/30 (0%)[c]	0/32 (0%)[c]		
					150 ug/g body weight	1x	79 weeks (m)	1/32 (3%)[b]	0/40 (0%)[c]		
Benzo(a)pyrene	Mice ($B6C3F_1$)	Lung	Control	Control	Control	N/A	142 weeks	13/100 (13%)	9/100 (9%)	Both sexes developed lung tumors with higher incidence when treated with B(a)P at birth than at 15 or 42 days of age ($p<0.05$).	Vesselinovitch et al., 1975
			Day 1	IP	75 ug/g body weight	1x	103 weeks(m) 126 weeks (f)	20/47 (43%)[c]	22/45 (49%)[c]		
					150 ug/g body weight	1x	84 weeks(m) 112 weeks (f)	37/63 (59%)[c]	28/45 (62%)[c]		
			Day 15	IP	75 ug/g body weight	1x	103 weeks(m) 122 weeks (f)	15/60 (25%)[c]	18/55 (33%)[c]		
					150 ug/g body weight	1x	82 weeks(m) 101 weeks (f)	20/55 (36%)[c]	18/45 (40%)[c]		
			Day 42	IP	75 ug/g body weight	1x	119 weeks(m) 131 weeks (f)	20/55 (36%)[c]	12/47 (26%)[c]		
					150 ug/g body weight	1x	95 weeks(m) 118 weeks (f)	18/47 (38%)[c]	8/46 (17%)[c]		

a) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

[i] Where not delineated by gender, data combined by study authors or gender not specified. Where percentages only are given, number of subjects not specified.
[ii] Intraperitoneal injection (IP)

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
Benzo(a)pyrene	Mice (C3A F_1)	Lung	Control	Control	None	N/A	142 weeks	60/100 (60%)	50/100 (50%)	Of the 2 mouse strains tested, C3AF1 mice developed significantly more tumors than did the B6C3F1 mice ($p<0.001$)	Vesselinovitch et al., 1975
			Day 1	IP	75 ug/g body weight	1x	78 weeks(m) 82 weeks (f)	58/62 (93%)[c]	42/45 (93%)[c]		
					150 ug/g body weight	1x	70 weeks(m) 73 weeks (f)	48/52 (92%)[c]	52/56 (93%)[c]		
			Day 15	IP	75 ug/g body weight	1x	87 weeks(m) 98 weeks (f)	52/56 (93%)[c]	46/49 (94%)[c]		
					150 ug/g body weight	1x	75 weeks(m) 79 weeks (f)	50/53 (94%)[c]	52/57 (91%)[c]		
			Day 42	IP	75 ug/g body weight	1x	91 weeks(m) 93 weeks (f)	28/30 (93%)[c]	28/32 (87%)[c]		
					150 ug/g body weight	1x	85 weeks(m) 83 weeks (f)	28/32 (87%)[c]	36/40 (90%)[c]		
DBA Dibenzanthracene	Mice (Caracul x P stock)	Lung	Control	Control	None	N/A	228 days	1/31 (3.2%)			Law, 1940
			Day 1	IP	4 mg per cm^3 vehicle	1x	181 days	24/24 (100%)[c]			
			2 months	SC[m]	4 mg per cm^3 vehicle	1x	189 days	2/29 (6.9%)[c]			
DEN Diethylnitrosamine	Mice ($B6C3F_1$)	Liver	Control	Control	Vehicle (0.1 trioctanoin/g body weight)	4x	142 weeks(m) 137 weeks (f)	7/98 (7%)	1/100 (1%)	Animals treated as newborns and infants developed significantly more liver tumors than animals that were treated as young adults. Newborns and infant females developed liver tumors at a later age than similarly treated males.	Vesselinovitch et al., 1984
			Day 1	IP (3-, 6-and 6-day intervals)	1.5 ug/g body weight	4x	67 weeks (m) 90 weeks (f)	37/51 (73%)[c]	45/64 (70%)[c]		
					3 ug/g body weight	4x	65 weeks (m) 80 weeks (f)	40/58 (69%)[c]	44/65 (68%)[c]		
			Day 15		1.5 ug/g body weight	4x	86 weeks (m) 117 weeks (f)	41/57 (72%)[c]	40/71 (56%)[c]		
					3 ug/g body weight	4x	76 weeks (m) 96 weeks (f)	48/69 (70%)[c]	46/62 (74%)[c]		
			Day 42		1.5 ug/g body weight	4x	117 weeks(m) 135 weeks (f)	9/49 (18%)[c]	1/47 (2%)[c]		
					3 ug/g body weight	4x	123 weeks(m) 133 weeks (f)	6/38 (16%)[c]	4/57 (7%)[c]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

[i] Subcutaneous injection (SC)

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
DEN Diethylnitrosamine	Mice ($C3AF_1$)	Liver	Control	Control	Vehicle (0.1 trioctanoin/g body weight)	4x	123 weeks(m) 131weeks (f)	8/99 (8%)	1/97 (1%)	Highest tumor rate when dosed at early ages. Newborns and infant females developed liver tumors at a lower incidence than similarly treated males. + higher for males	Vesselinovitch et al., 1984
			Day 1	IP (3-, 6-and 6-day intervals)	1.5 ug/g body weight	4x	64 weeks (m) 84 weeks (f)	23/32 (72%)[c]	11/39 (28%)[c]		
					3 ug/g body weight	4x	59 weeks (m) 76 weeks (f)	39/58 (67%)[c]	26/50 (52%)[c]		
			Day 15		1.5 ug/g body weight	4x	82 weeks (m) 102 weeks (f)	22/46 (48%)[c]	8/65 (12%)[c]		
					3 ug/g body weight	4x	74 weeks (m) 94 weeks (f)	35/54 (65%)[c]	22/62 (35%)[c]		
			Day 42		1.5 ug/g body weight	4x	105 weeks(m) 106 weeks (f)	12/56 (22%)[c]	0/53 (0%)[c]		
					3 ug/g body weight	4x	105 weeks(m) 103 weeks (f)	9/57 (16%)[c]	0/56 (0%)[c]		
DEN Diethylnitrosamine	Mice ($B6C3F_1$)	Lung	Control	Control	Vehicle (0.1 trioctanoin/g body weight)	4x	142 weeks(m) 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 to their earlier detection caused by shorter survival.	Vesselinovitch et al., 1984
			Day 1	IP (3-, 6-and 6-day intervals)	1.5 ug/g body weight	4x	70 weeks (m) 91 weeks (f)	29/51 (57%)[c]	49/64 (77%)[c]		
					3 ug/g body weight	4x	68 weeks (m) 81 weeks (f)	34/58 (59%)[c]	42/65 (65%)[c]		
			Day 15		1.5 ug/g body weight	4x	87 weeks (m) 115 weeks (f)	51/57 (89%)[c]	61/71 (86%)[c]		
					3 ug/g body weight	4x	77 weeks (m) 97 weeks (f)	51/69 (74%)[c]	53/62 (85%)[c]		
			Day 42		1.5 ug/g body weight	4x	123 weeks(m) 129 weeks (f)	38/49 (78%)[c]	38/47 (81%)[c]		
					3 ug/g body weight	4x	121 weeks(m) 127 weeks (f)	33/38 (87%)[c]	43/57 (75%)[c]		
DEN Diethylnitrosamine	Mice ($C3AF_1$)	Lung	Control	Control	Vehicle (0.1 trioctanoin/g body weight)	4x	142 weeks(m) 137weeks (f)	60/99 (61%)	50/97 (52%)	Of the two strains, C3AF1 mice developed lung tumors with a higher incidence and multiplicity than B6C3F1 hybrids.	Vesselinovitch et al., 1984
			Day 1	IP (3-, 6-and 6-day intervals)	1.5 ug/g body weight	4x	65 weeks (m) 84 weeks (f)	30/32 (94%)[c]	38/39 (97%)[c]		
					3 ug/g body weight	4x	59 weeks (m) 76 weeks (f)	49/58 (84%)[c]	46/50 (92%)[c]		
			Day 15		1.5 ug/g body weight	4x	80 weeks (m) 101 weeks (f)	42/46 (91%)[c]	61/65 (94%)[c]		
					3 ug/g body weight	4x	74 weeks (m) 92 weeks (f)	50/54 (93%)[c]	57/62 (92%)[c]		
			Day 42		1.5 ug/g body weight	4x	104 weeks(m) 110 weeks (f)	55/56 (98%)[c]	52/53 (98%)[c]		
					3 ug/g body weight	4x	101 weeks(m) 102 weeks (f)	56/57 (98%)[c]	54/56 (96%)[c]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
DEN Diethylnitrosamin	Mice ($B6C3F_1$)	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 et al., 1983
			Gestation day 18	IP	1.5 ug/g body weight	1x		2/50 (4%)[c]	1/51 (2%)[c]		
			Day 15	IP (3-, 6- and 6-day intervals)	1.5 ug/g body weight	4x		47/51 (92%)[c]	60/64 (94%)[c]		
			Day 42		1.5 ug/g body weight	4x		13/49 (26%)[c]	3/47 (6%)[c]		
DEN Diethylnitrosamin	Mice ($B6C3F_1$)	Liver	Day 1	IP	1.5 ug/g body weight	1x	73 weeks	15/59 (25%)[c]	-	At the 1.5 ug dose level, 1-day-old mice developed significantly fewer liver tumors than similarly treated infants (Day 15) ($p<0.025$). Tumor incidence in treated groups versus controls was not evaluated.	Vesselinovitch et al., 1979
					5 ug/g body weight	1x		29/45 (64%)[c]	-		
					10 ug/g body weight	1x		24/25 (96%)[c]	-		
			Day 15	IP	1.5 ug/g body weight	1x		13/24 (54%)[c]	-		
					5 ug/g body weight	1x		40/54 (74%)[c]	-		
					10 ug/g body weight	1x		25/25 (100%)[c]	-		
DMBA Dimethyl-benz(a)anthracene	Rats (Sprague-Dawley)	Mammary adeno-sarcoma	Day 20	Gavage	10 mg/100 g body weight	1x	Week 25	-	3/6 (50%)[c]	36 of 42 (86%) animals dosed at age 20 days died soon after. Highest number of tumors per animal was in the 46-day group, with decreasing numbers in the older animals. Animals were sacrificed 22 weeks after treatment.	Russo et al., 1979
			Day 30		10 mg/100 g body weight	1x	Week 26	-	14/15 (93%)[c]		
			Day 40		10 mg/100 g body weight	1x	Week 27	-	8/9 (89%)[c]		
			Day 46		10 mg/100 g body weight	1x	Week 28	-	8/8 (100%)[c]		
			Day 55		10 mg/100 g body weight	1x	Week 29	-	33/34 (97%)[c]		
			Day 70		10 mg/100 g body weight	1x	Week 32	-	5/8 (63%)[c]		
			Day 140		10 mg/100 g body weight	1x	Week 42	-	10/15 (67%)[c]		
			Day 180		10 mg/100 g body weight	1x	Week 47	-	14/26 (54%)[c]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
DMBA Dimethyl-benz(a)anthracene	Rats (Wistar)	Mammary carcinoma[iv]	Control 5-8 weeks	Control	None	N/A	17 months	0/22 (0%)	0%	Highest tumor rate in females exposed at 5-8 weeks. Animals were observed for 16 months following treatment.	Meranze et al., 1969
			Control 26 weeks	Control	None	N/A	20 months	0/31 (0%)	2/45 (4%)		
			< Week 2	Gavage	0.5-1.0 mg	1x	Week 40-56	0/23 (0%)[c]	4/50 (8%)[c]		
			Week 5-8		15 mg	1x	Week 14-55	0/23 (0%)[c]	14/25 (56%)[c]		
			Week 26		15 mg	1x	Week 32-73	0/34 (0%)[c]	4/26 (15%)[c]		
	Rats (Wistar, castrated)	Mammary carcinoma	Week 5-8	Gavage	15 mg	1x	Week 14-55	0/21 (0%)[c]	0/22 (0%)[c]		
			Week 26		15 mg	1x	Week 32-73	0/33 (0%)[c]	0/26 (0%)[c]		
	Rats (Wistar)	Total tumors	Control 5-8 weeks	Control	None	N/A	17 months	0/22 (0%)	0%	Total tumors includes leukemia.	
			Control 26 weeks	Control	None	N/A	20 months	2/31 (6%)	5/45 (11%)		
			< Week 2	Gavage	0.5-1.0 mg	1x	Week 40-56	16/23 (70%)[c]	36/50 (72%)[c]		
			Week 5-8		15 mg	1x	Week 14-55	7/23 (30%)[c]	16/25 (64%)[c]		
			Week 26		15 mg	1x	Week 32-73	12/34 (35%)[c]	13/26 (50%)[c]		
DMBA Dimethyl-benz(a)anthracene	Mice (BALB/c)	Lung	Control: Day 1	Control SC	Aqueous gelatine	1x	40 weeks	0/12 (0%)	7/23 (30%)	15 ug DMBA gave rise to a significantly greater incidence of lung tumors when administered to newborn mice than to suckling or young adults.	Walters, 1966
			Day 1	SC	15 ug	1x	40 weeks[v]	14/14 (100%)[c]	24/24 (100%)[c]		
			Week 2-3 (suckling)	SC	15 ug	1x	42-43 weeks	12/23 (52%)[c]	16/22 (73%)[c]		
				SC	30 ug (60 ug total)	2x	42-43 weeks	14/14 (100%)[c]	24/24 (100%)[c]		
			Adult[vi]	SC	15 ug	1x	48-49 weeks	6/12 (50%)[c]	15/33 (45%)[c]		
				SC	30 ug (60 ug total)	2x	48-49 weeks	9/10 (90%)[c]	21/23 (91%)[c]		
				SC	30 ug (180 ug total)	6x	48-49 weeks	12/12 (100%)[c]	13/13 (100%)[c]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

[v] Study also included mammary fibroadenomas and fibromas, as well as other types of cancers.
[vi] Includes survivors up to 40 weeks only.
[i] Exact age not noted.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
DMBA Dimethyl-benz(a)anthracene	Mice (Swiss)	Lymphoma	Control	Control	None	N/A	31-52 weeks	3/408 (0.7%)		Higher tumor rates at younger age of exposure. Only one treatment group was exposed IP; others were exposed by subcutaneous injection.	Pietra et al., 1961
			Day 1	IP	30-40 ug	1x	13-33 weeks	6/31 (19%)[c]			
			Day 1	SC	30-40 ug	1x	12-27 weeks	8/27 (30%)[c]			
			Week 8	SC	900 ug	1x	30 weeks	1/13 (8%)[c]			
DMBA Dimethyl-benz(a)anthracene	Mice (Swiss)	Lung	Control	Control	None	N/A	31-52 weeks	4/408 (0.9%)			Pietra et al., 1961
			Day 1	IP	30-40 ug	1x	13-33 weeks	24/31 (77%)[c]			
			Day 1	SC	30-40 ug	1x	12-27 weeks	23/27 (85%)[c]			
			Week 8	SC	900 ug	1x	30 weeks	2/13 (15%)[c]			
DMN Dimethyl-nitrosamine	Rats (Wistar)	Kidney carcinoma	Day 1	IP	20 mg/kg	1x	≥ 5 months	1/33 (3)[c]		In the neonatal group, the dose was reduced to 20 mg/kg in order to achieve approximately equivalent numbers of survivors. No control group.	Hard, 1979
			Day 21		30 mg/kg	1x		5/39 (13)[c]			
			Month 1		30 mg/kg	1x		2/33 (6)[c]			
			Month 1.5		30 mg/kg	1x		1/28 (4)[c]			
			Month 2		30 mg/kg	1x		1/26 (4)[c]			
			Month 3		30 mg/kg	1x		10/27 (37)[c]			
			Month 4		30 mg/kg	1x		7/32 (22)[c]			
			Month 5		30 mg/kg	1x		0/14 (0)[c]			
DMN Dimethyl-nitrosamine	Rats (Wistar)	Kidney adenoma	Day 1	IP	20 mg/kg	1x	≥ 5 months	1/33 (3)[c]			Hard, 1979
			Day 21		30 mg/kg	1x		13/39 (33)[c]			
			Month 1		30 mg/kg	1x		11/33 (33)[c]			
			Month 1.5		30 mg/kg	1x		13/28 (48)[c]			
			Month 2		30 mg/kg	1x		11/26 (42)[c]			
			Month 3		30 mg/kg	1x		18/27 (67)[c]			
			Month 4		30 mg/kg	1x		17/32 (53)[c]			
			Month 5		30 mg/kg	1x		6/14 (43)[c]			
DMN Dimethyl-nitrosamine	Rats (Wistar)	Kidney mesenchymal tumors	Day 1	IP	20 mg/kg	1x	≥ 5 months	8/33 (24)[c]		Mesenchymal tumors were most frequent in the 3 youngest age groups (z test, $p < 0.001$).	Hard, 1979
			Day 21		30 mg/kg	1x		18/39 (46)[c]			
			Month 1		30 mg/kg	1x		23/33 (70)[c]			
			Month 1.5		30 mg/kg	1x		5/28 (19)[c]			
			Month 2		30 mg/kg	1x		2/26 (8)[c]			
			Month 3		30 mg/kg	1x		3/27 (11)[c]			
			Month 4		30 mg/kg	1x		7/32 (22)[c]			
			Month 5		30 mg/kg	1x		0/14 (0)[c]			

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
DMN Dimethyl-nitrosamine	Rats (Wistar)	Kidney cortical epithelial tumors	Day 1	IP	20 mg/kg	1x	≥ 5 months	2/33 (6)[c]			Hard, 1979
			Day 21		30 mg/kg	1x		16/39 (41)[c]			
			Month 1		30 mg/kg	1x		12/33 (36)[c]			
			Month 1.5		30 mg/kg	1x		14/28 (52)[c]			
			Month 2		30 mg/kg	1x		11/26 (42)[c]			
			Month 3		30 mg/kg	1x		18/27 (67)[c]			
			Month 4		30 mg/kg	1x		21/32 (66)[c]			
			Month 5		30 mg/kg	1x		6/14 (43)[c]			
DMN Dimethyl-nitrosamine	Rats (Wistar)	Total tumors	Day 1	IP	20 mg/kg	1x	≥ 5 months	11/33 (33)[c]			Hard, 1979
			Day 21		30 mg/kg	1x		25/39 (64)[c]			
			Month 1		30 mg/kg	1x		25/33 (76)[c]			
			Month 1.5		30 mg/kg	1x		17/28 (63)[c]			
			Month 2		30 mg/kg	1x		13/26 (50)[c]			
			Month 3		30 mg/kg	1x		18/27 (67)[c]			
			Month 4		30 mg/kg	1x		22/32 (69)[c]			
			Month 5		30 mg/kg	1x		7/14 (50)[c]			
ENU Ethylnitrosourea	Rats	Nervous system	Day 1	Injection	20 mg/kg	1x		100%[c]		Susceptibility to neuro-oncogenic effect declined with increasing age.	Maekawa et al., 1990
			Day 30	Injection	20 mg/kg	1x		61%[c]			
ENU Ethylnitrosourea	Mice ($B6C3F_1$)	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 et al., 1983
			Gestation day 18	IP	60 ug/g body weight	1x		28/52 (54%)[c]	18/49 (37%)[c]		
			Day 15		60 ug/g body weight	1x		41/50 (82%)[c]	28/51 (55%)[c]		
			Day 42		60 ug/g body weight	1x		10/50 (20%)[c]	5/50 (10%)[c]		
ENU Ethylnitrosourea	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. Statistically significant decrease in tumor incidence with increasing age of exposure.	Naito et al., 1981
			Gestation day 16	IP	40 mg/kg	1x		26/26 (100%)[c]	18/18 (100%)[c]		
			Day 1	SC	40 mg/kg	1x		12/12 (100%)[a]	16/16 (100%)[a]		
			Week 1		40 mg/kg	1x		12/17 (71%)[c]	18/20 (90%)[c]		
			Week 2		40 mg/kg	1x		10/14 (71%)[c]	14/18 (78%)[c]		
			Week 3		40 mg/kg	1x		6/13 (46%)[c]	5/17 (29%)[c]		
			Week 4		40 mg/kg	1x		8/15 (53%)[c]	2/10 (20%)[c]		

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
ENU Ethylnitrosourea	Mice ($B6C3F_1$)	Lung	Day 12 gestation	IP	60 ug/g body weight	1x		47%[c]		The lowest incidence (47%) of lung tumors was observed in the offspring exposed on gestation day 12. No control group.	Vesselinovitch et al., 1979
			Day 14 gestation			1x		87%[c]			
			Day 16 gestation			1x		96%[c]			
			Day 18 gestation			1x		93%[c]			
			Day 1			1x		93%[c]			
			Day 15			1x		93%[c]			
			Day 42			1x		88%[c]			
ENU Ethylnitrosourea	Mice ($B6C3F_1$)	Liver	Day 12 gestation	IP	60 ug/g body weight	1x		48%[c]	40%[c]	Exposure in adulthood showed significant reductions in tumors. Highest tumor rate seen in early postnatal ages. + higher for males No control group.	Vesselinovitch et al., 1979
			Day 14 gestation			1x		57%[c]	28%[c]		
			Day 16 gestation			1x		67%[c]	32%[c]		
			Day 18 gestation			1x		67%[c]	33%[c]		
			Day 1			1x		83%[c]	55%[c]		
			Day 15			1x		88%[c]	51%[c]		
			Day 42			1x		20%[c]	10%[c]		
ENU Ethylnitrosourea	Mice ($B6C3F_1$)	Kidney	Day 12 gestation	IP	60 ug/g body weight	1x		6%[c]		Highest tumor rate seen in early postnatal ages. No control group.	Vesselinovitch et al., 1979
			Day 14 gestation			1x		13%[c]			
			Day 16 gestation			1x		12%[c]			
			Day 18 gestation			1x		8%[c]			
			Day 1			1x		16%[c]			
			Day 15			1x		19%[c]			
			Day 42			1x		9%[c]			

) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
Urethane	Mice (SWR)	Lung adenoma	Newborn	SC	0.18 mg/g body weight	1x	10 weeks	100%[c]		The average number of tumors per mouse increased linearly with dose.	Kaye et al., 1966
			11-22 weeks	SC	0.25 mg/g body weight	1x	23-34 weeks	0%[c]			
Urethane	Mice (C3H/f)	Liver	Control	Control	None	N/A	493 days (m) 553 days (f)	14/97 (14%)	1/77 (1%)		Liebelt et al., 1964
			Day 1	IP	0.8 mg/g body weight	1x	481 days (m) 434 days (f)	27/30 (90%)[a]	18/39 (46%)[a]		
			8-10 weeks	IP	1 mg/g body weight	1x	321 days (m) -	6/25 (24%)[b]	0/32 (0%)[b]		
Urethane	Mice (C3H/f)	Lung	Control	Control	None	N/A	493 days (m) 553 days (f)	-	-	The number of lung tumors among the controls was not provided.	Liebelt et al., 1964
			Day 1	IP	0.8 mg/g body weight	1x	401 days (m) 408 days (f)	14/30 (46%)[a]	19/39 (48%)[a]		
			8-10 weeks	IP	1 mg/g body weight	1x	506 days (m) -	2/25 (8%)[b]	0/32 (0%)[b]		
Urethane	Mice (C3H/f)	Reticular tissue	Control	Control	None	N/A	493 days (m) 553 days (f)	2/97 (2%)	6/77 (8%)		Liebelt et al., 1964
			Day 1	IP	0.8 mg/g body weight	1x	285 days (m) 343 days (f)	4/30 (13%)[b]	22/39 (56%)[a]		
			8-10 weeks	IP	1 mg/g body weight	1x	- 453 days (f)	0/25 (25%)[b]	4/32 (13%)[b]		
Urethane	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	SC	2 mg in 0.05 ml aqueous solution	1x		13/60 (22%)[c]			
			Day 5		4 mg in 0.05 ml aqueous solution	1x		7/39 (18%)[c]			
			Day 40		20 mg in 0.1 ml aqueous solution	1x		2/63 (3%)[c]			

a) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Chemical	Species	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors		Comments	Reference
								M	F		
Urethane	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, 1950
			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	3/15 (20%)	-		
			Control 10 weeks	Control	None	N/A	17 weeks	0/15 (0%)	-		
			2 weeks	IP	1 mg/g body weight	1x	9 weeks	24/24 (100%)[c]	-		
			4 weeks	IP	1 mg/g body weight	1x	11 weeks	23/25 (92%)[c]	-		
			6 weeks	IP	1 mg/g body weight	1x	13 weeks	22/25 (88%)[c]	-		
			8 weeks	IP	1 mg/g body weight	1x	15 weeks	21/25 (84%)[c]	-		
			10 weeks	IP	1 mg/g body weight	1x	17 weeks	19/25 (76%)[c]	-		
Urethane	Mice (Swiss)	Lung adenoma	3 weeks	IP	0.25 mg/g body weight	1x	12 weeks	16/19 (84%)[c]	-		Rogers, 1950
					0.5 mg/g body weight	1x	12 weeks	16/20 (80%)[c]	-		
					1 mg/g body weight	1x	12 weeks	18/20 (90%)[c]	-		
			8 weeks	IP	0.25 mg/g body weight	1x	17 weeks	4/17 (24%)[c]	-		
					0.5 mg/g body weight	1x	17 weeks	15/16 (94%)[c]	-		
					1 mg/g body weight	1x	17 weeks	18/18 (100%)[c]	-		

a) significant compared to controls; b) evaluated but not significant compared to controls; c) not evaluated by authors.

Table 4. Quantitative estimates of early-life cancer susceptibility for studies with multiple exposures of juvenile and adult animals to mutagenic chemicals.

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Refs.
	Control	Juvenile	Adult	Juvenile	Adult		
B(a)P	0%	70%	10%	70/107=0.65	10/110=0.1	0.65/0.1=6.5	Neal and Rigdon, 1967
Benzidine ***Liver***							Vesselinovitch et al., 1983
Male	1% (1/98)	67% (35/52)	85% (22/26)	(67-1)/3=22	(85-1)/87=1.0	22/1=22	
Female	0% (0/96)	21% (9/43)	64% (16/25)	(21-0)/3=7	(64-0)/87=0.7	7/0.7=10	
Benzidine ***Liver***							Vesselnovitch et al., 1979
Male	1% (1/98)	95% (62/65)	57% (25/44)	(95-1)/ 3=31.3	(57-1)/87=0.6	31.3/0.6=52.2	
Female	0% (0/100)	5% (2/43)	96% (48/50)	5/3=1.7	96/87=1.1	1.7/1.1=1.5	
DEN ***Liver***	NA[i]	58% (105/180)	6 Weeks: 50% (714/1440) 20 Weeks: 42% (76/180)	58-50/3=2.7	50/124=0.4	2.7/0.4=6.8	Peto, 1984
Safrole ***Liver***							Vesselinovitch et al., 1983
Male	1% (1/98)	34% (28/83)	11% (4/35)	(34-1)/12 =2.8	(11-1)/172=0.06	2.8/0.06=46.7	
Female	0% (0/96)	2% (2/80)	61% (22/36)	(2-0)/12=0.2	(61-0)/172=0.4	0.2/0.4=0.5	
Safrole ***Liver***							Vesselnovitch et al., 1979
Male	1% (1/98)	32% (27/83)	8% (4/50)	(32-1)/12[ii]=2.6	(8-1) /172[iii]=0.04	2.6/0.04=65	
Female	0% (0/98)	1% (1/79)	56% (28/56)	1/12=0.1	56/172=0.3	0.1/0.3=0.3	
Vinyl Chloride ***Liver Angiosarcoma***							Maltoni et al., 1981
Male	0%	25%	1.7%	(25-0)/52=0.5	(1.7-0)/52=0.03	0.5/0.03=16.7	
Female	0%	45%	0%	(45-0)/52=22.5	(0-0)/52=0	NC[iv]	

[i] NA: Not available
[ii] Estimated 3 doses for 4 weeks (12 exposures)
[iii] Estimated 2 doses for 86 weeks (172 exposures)
[iv] NC: Not calculated due to lack of tumor development in adult and/or juvenile animals

Table 5. Quantitative estimates of early-life cancer susceptibility for studies with acute exposures of juveniles and adult animals to mutagenic chemicals.

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Ref.
	Control	Juvenile	Adult	Juvenile	Adult		
B(a)P ***Liver***	Male: 7% (7/100) Female: 1% (1/98)						Vesselnovitch et al., 1975
Male $B6C3F_1$ 75 ug/kg		Day 1: 55% (26/47)	13% (7/55)	55-7=48	13-7=6	48/6=8	
		Day 15: 60% (36/60)		60-7=53		53/6=8.8	
Female $B6C3F_1$ 75 ug/kg		Day 1: 7% (3/45)	0%	7-1=6	0-1=-1	NC[v]	
		Day 15: 7% (3/45)		7-1=6		NC	
Male $B6C3F_1$ 150 ug/kg		Day 1: 81% (51/63)	9% (4/47)	81-7=74	9-7=2	74/2=37	
		Day 15: 58% (32/55)		58-7=51		51/2=25.5	
Female $B6C3F_1$ 150 ug/kg		Day 1: 18% (8/45)	0%	18-1=17	0-1=-1	NC	
		Day 15: 7% (3/45)		7-1=6		NC	
B(a)P ***Liver***	Male: 8% (8/100) Female: 1% (1/100)						Vesselnovitch et al., 1975
Male $C3AF_1$ 75 ug/kg		Day 1: 34% (21/62)	0%	34-8=26	0-8=-8	NC	
		Day 15: 27% (15/56)		27-8=19		NC	
Female $C3AF_1$ 75 ug/kg		Day 1: 2% (1/45)	0%	2-1=1	0-1=-1	NC	
		Day 15: 2% (1/49)		2-1=1		NC	
Male $C3AF_1$		Day 1: 46% (24/52)	3% (1/32)	46-8=38	3-8=-5	NC	

[v] Not calculated due to lack of tumor development in adult and/or juvenile animals

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Ref.
	Control	Juvenile	Adult	Juvenile	Adult		
150 ug/kg		Day 15: 23% (12/53)		23-8=15		NC	
Female $C3AF_1$ 150 ug/kg		Day 1: 2% (1/56) Day 15: 2% (1/57)	0%	2-1=1 2-1=1	0-1=-1	NC NC	
B(a)P ***Lung***	Male: 13% (13/100) Female: 9% (9/100)						Vesselnovitch et al., 1975
Male $B6C3F_1$ 75 ug/kg		Day 1: 43% (20/47) Day 15: 25% (15/60)	36% (20/55)	43-13= 30 25-13=12	36-13=23	30/23=1.3 12/23=0.5	
Female $B6C3F_1$ 75 ug/kg		Day 1: 49% (12/45) Day 15: 33% (18/55)	26% (12/47)	49-9=40 33-9=24	26-9=17	40/17=2.4 24/17=1.4	
Male $B6C3F_1$ 150 ug/kg		Day 1: 59% (37/63) Day 15: 36% (20/55)	38% (18/47)	59-13=46 36-13=23	38-13=25	46/25=1.8 23/25=0.9	
Female $B6C3F_1$ 150 ug/kg		Day 1: 62% (28/46) Day 15: 40% (18/45)	17% (8/46)	62-9=53 40-9=31	17-9=8	53/8=6.6 31/8=3.9	
B(a)P ***Lung***	Male: 60% (60/100) Female: 50% (50/100)						Vesselnovitch et al., 1975
Male $C3AF_1$ 75 ug/kg		Day 1: 93% (58/62) Day 15: 93% (52/56)	93% (28/30)	93-60=33 93-60=33	93-60=33	33/33=1 33/33=1	
Female $C3AF_1$ 75 ug/kg		Day 1: 93% (42/45) Day 15: 94% (46/49)	87% (28/32)	93-50=43 94-50=44	87-50=37	43/37=1.1 44/37=1.2	

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Ref.
	Control	Juvenile	Adult	Juvenile	Adult		
Male $C3AF_1$ 150 ug/kg		Day 1: 92% (48/52) Day 15: 94% (50/53)	87% (28/32)	92-60=32 94-60=34	87-60=27	32/27=1.2 34/27=1.3	
Female $C3AF_1$ 150 ug/kg		Day 1: 93% (52/56) Day 15: 91% (52/57)	90% (36/40)	93-50=43 91-50=41	90-50=40	43/40=1.1 41/40=1.0	
DBA ***Lung***	3.2%	100%	6.9%	100-3.2=96.8	6.9-3.2=3.7	96.8/3.2=30.3	Law, 1940
DEN ***Liver*** Male $B6C3F_1$ 6 ug/kg	Male: 7% (7/98) Female: 1% (1/100)	Day 1: 73% (37/51) Day 15: 72% (41/57)	18% (9/49)	(73-7)/4=16.5 (72-7)/4=16.3	(18-7)/4=2.8	16.5/2.8=5.9 16.3/2.8=5.8	Vesselnovitch et al., 1984
Female $B6C3F_1$ 6 ug/kg		Day 1: 70% (48/69) Day 15: 56% (40/71)	2% (1/47)	(70-1)/4=17.3 (56-1)/4=13.8	(2-1)/4=0.3	17.3/0.3=57.7 13.8/0.3=46	
Male $B6C3F_1$ 12 ug/kg		Day 1: 69% (40/58) Day 15: 70% (48/69)	16% (6/38)	(69-7)/4=15.5 (70-7)/4=15.8	(16-7)/4=2.3	15.5/2.3=2.4 15.8/2.3=6.9	
Female $B6C3F_1$ 12 ug/kg		Day 1: 68% (44/65) Day 15: 74% (46/62)	7% (4/57)	(68-1)/4=16.8 (74-1)/4=18.3	(7-1)/4=1.5	16.8/1.5=11 18.3/1.5=12.2	
DEN ***Liver***	Male: 8.1% (8/99) Female: 1% (1/97)						Vesselnovitch et al., 1984

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Ref.
	Control	Juvenile	Adult	Juvenile	Adult		
Male $C3AF_1$ 6 ug/kg		Day 1: 72% (23/32) Day 15: 48% (22/46)	22% (12/56)	(72-8.1)/4=16 (48-8.1)/4=10	(22-8.1)/4=3.5	16/3.5=1.8 10/3.5=2.9	
Female $C3AF_1$ 6 ug/kg		Day 1: 28% (11/39) Day 15: 12% (8/65)	0% (0/53)	(28-1)/4=6.8 (12-1)/4=2.8	(0-1)/4=-0.25	NC NC	
Male $C3AF_1$ 12 ug/kg		Day 1: 67% (39/58) Day 15: 65% (35/54)	16% (9/57)	(67-8.1)/4=14.8 (52-8.1)/4=11	(16-8.1)/4=2	14.8/2=7.4 11/2=5.5	
Female $C3AF_1$ 12 ug/kg		Day 1: 52% (26/50) Day 15: 35% (22/62)	0% (0/56)	(65-1)/4=16 (35-1)/4=8.5	(0-1)/4=-0.25	NC NC	
DEN ***Lung*** Male $B6C3F_1$ 6 ug/kg	Male: 13% (13/98) Female: 9% (9/100)	Day 1: 57% (29/51) Day 15: 89% (51/57)	78% (38/49)	(57-13)/4=11 (89-13)/4=19	(78-13)/4=16.3	11/16.3=0.7 19/16.3=1.2	Vesselnovitch et al., 1984
Female $B6C3F_1$ 6 ug/kg		Day 1: 77% (49/64) Day 15: 86% (61/71)	81% (38/47)	(77-9)/4=17 (86-9)/4=19.3	(81-9)/4=18	17/18=0.9 19.3/18=1.1	
Male $B6C3F_1$ 12 ug/kg		Day 1: 59% Day 15: 74%	87%	(59-13)/4=11.5 (74-13)/4=15.3	(87-13)/4=18.5	11.5/18.5=0.6 15.3/18.5=0.8	
Female $B6C3F_1$ 12 ug/kg		Day 1: 65% Day 15: 85%	75%	(65-9)/4=14 (85-9)/4=19	(75-9)/4=17.3	14/17.3=0.8 19/17.3=1.1	

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Ref.
	Control	Juvenile	Adult	Juvenile	Adult		
DEN ***Lung***	Male: 60.6% (60/99) Female: 51.5% (50/97)						Vesselnovitch et al., 1984
Male $C3AF_1$ 6 ug/kg		Day 1: 94% (30/32) Day 15: 91% (42/46)	98% (55/56)	(94-60.6)/4=8.4 (91-60.6)/4=7.6	(98-60.6)/4=9.4	8.4/9.4=0.9 7.6/9.4=0.8	
Female $C3AF_1$ 6 ug/kg		Day 1: 97% (38/39) Day 15: 94% (61/65)	98% (52/53)	(97-51.5)/4=11.4 (94-51.5)/4=10.7	(98-51.5)/4=11.6	11.4/11.6=1 10.7/11.6=0.9	
Male $C3AF_1$ 12 ug/kg		Day 1: 84% (49/58) Day 15: 93% (50/54)	98% (56/57)	(84-60.6)/4 =5.9 (93-60.6)/4=8.1	(98-60.6)/4=9.4	5.9/9.4=0.6 8.1/9.4=0.9	
Female $C3AF_1$ 12 ug/kg		Day 1: 92% (46/50) Day 15: 92% (57/62)	96% (54/56)	(92-51.5)/4=10.1 (92-51.5)/4=10.1	(96-51.5)/4=11.1	10.1/11.1=0.9 10.1/11.1=0.9	
DEN ***Liver***							Vesselinovitch et al., 1983
Male	1% (1/98)	92% (47/51)	26% (13/49)	(92-1)/4=22.8	(26-1)/4= 6.3	22.8/6.3=3.6	
Female	0% (0/96)	94% (60/64)	6% (3/47)	(94-0)/4=23.5	(6-0)/4=1.3	23.5/1.3=18.1	
DMBA Total tumors Male	5-8 Weeks: 0% (0/22) 26 Weeks: 6% (2/31)	70% (16/23)	30% (7/23) 35% (12/34)	70-0=70	30-0=30 35-6=29	70/30=2.3 70/29=2.4	Meranze et al., 1969
Total tumors Female	5-8 Weeks: 0% 26 Weeks: 11% (5/45)	72% (36/50)	64% (16/25) 50% (13/26)	72-0=72	64-0=64 50-11=39	72/64=1.1 72/39=1.9	

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Ref.
	Control	Juvenile	Adult	Juvenile	Adult		
Mammary Carcinoma Female	5-8 Weeks: 0% 26 Weeks: 4% (2/45)	8% (4/50)	56% (14/25) 15% (4/26)	8-0=8	56-0=56 15-4=9	8/56=0.1 8/9=0.9 5-8 Weeks/26 Weeks: 56/9=6.2	
DMBA ***Lung***	<24 Hours Male: 0% (0/12)						Walters, 1966
Male		<24 Hours: 100% (14/14) 15-19 Days: 52% (12/23)	50% (6/12)	100-0=100 52-0=52	50-0=50	100/50=2 52/50=1.0	
Female	<24 Hours Female: 30% (7/23)	<24 Hours: 100% (24/24) 15-19 Days: 73% (16/22)	45% (15/33)	100-30=70 73-0=73	45-0=45	70/45=1.6 73/45=1.6	
DMBA ***Lymphoma***	0.7% (3/408)	30% (8/27)	8% (1/13)	30-0.7=29.3	8-0.7=7.3	29.3/7.3=4.0	Pietra et al., 1961
Lung	0.9% (4/408)	85% (23/27)	15.3% (2/13)	85-0.9=84.1	15.3-0.9=14.4	84.1/14.4=5.8	
DMN ***Total***	NA[vi]	3 Weeks: 64% (25/39)	1 Month: 76% (25/33) 1.5 Month: 63% (17/28) 2 Month: 50% (13/26) 3 Month: 67% (18/27)	64-0=64	76-0=76 63-0=63 50-0=50 67-0=67	64/76=0.9 64/63=1 64/50=1.3 64/67=1	Hard, 1979
ENU ***Neuronal***	NA	100%	61%	100-0=100	61-0=61	100/61=1.6	Maekawa et al., 1990

[vi] Not Available

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Ref.
	Control	Juvenile	Adult	Juvenile	Adult		
ENU ***Liver*** Male	1% (1/98)	82% (41/50)	20% (10/50)	82-1=81	20-1=19	81/19=4.3	Vesselinovitch et al., 1983
Female	0% (0/96)	55% (28/51)	10% (5/50)	55-0=55	10-0=10	55/10=5.5	
ENU ***Nerve Tissue*** Male	0% (0/16)	Day1: 100% (12/12) Week 1: 71% (12/17) Week 2: 71% (10/14) Week 3: 46% (6/13)	53% (8/15)	100-0=100 71-0=71 71-0=71 46-0=46	53-0=53	100/53=1.9 71/53=1.3 71/53=1.3 46/53=0.9	Naito et al., 1981
Female	0% (0/10)	Day 1: 100% (16/16) Week 1: 90% (18/20) Week 2: 78% (14/18) Week 3: 29% (5/17)	20% (2/10)	100-0=100 90-0=90 78-0=78 29-0=29	20-0=20	100/20=5 90/20=4.5 78/20=3.9 29/20=1.5	
ENU ***Lung***	NA	Day 1: 93% Day 15: 93%	88%	93-0=93 93-0=93	88-0=88	93/88=1.1 93/88=1.1	Vesselinovitch, 1979
ENU ***Liver*** Male	NA	Day 1: 83% Day 15: 88%	20%	83-0=83 88-0=88	20-0=20	83/20=4.2 81/20=4.4	Vesselnovitch et al., 1979
Female		Day 1: 55% Day 15: 51%	10%	55-0=55 51-0=51	10-0=10	55/10=5.5 51/10=5.1	
ENU ***Kidney***	NA	Day 1: 16%	9%	16-0=16	9-0=9	16/9=1.8	Vesselnovitch et al., 1979

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Ref.
	Control	Juvenile	Adult	Juvenile	Adult		
		Day 15: 19%		19-0=19		19/9=2.1	
Urethane ***Lung adenoma***	NA	100%	0%	100-0=100	0-0=0	NC	Kaye et al., 1966
Urethane ***Liver***							Liebelt et al., 1964
Male	14% (14/97)	90% (27/30)	24% (6/25)	90-0=90	24-0=24	90/24=3.8	
Female	1% (1/77)	46% (18/39)	0% (0/25)	46-0=46	0-0=0	NC	
Urethane ***Lung***							Liebelt et al., 1964
Male	NA	46% (14/30)	8% (2/25)	46-0=46	8-0=8	46/8=5.8	
Female		48% (19/39)	0% (0/32)	48-0=48	0-0=0	NC	
Urethane ***Reticular tissue***							Liebelt et al., 1964
Male	2% (2/97)	13% (4/30)	0% (0/25)	13-2=11	0-2=-2	NC	
Female	8% (6/77)	56% (22/39)	13% (4/32)	56-8=48	13-8=5	48/5=9.6	
Urethane ***Leukemia***	1%	Day 1: 21% Day 5: 17%	3%	21-1=20 17-1=16	3-1=2	20/2=10 16/2=8	Fiore-Donati et al., 1962
Urethane ***Pulmonary Adenomas***	2 Weeks: 0% (0/15)	2 Weeks: 100% (24/24)		100-0=100			Rogers, 1950
	4 Weeks: 0% (0/14)		4 Weeks: 92% (23/25)		92-0=92	100/92=1.1	
	6 Weeks: 7% (1/15)		6 Weeks: 88% (22/25)		88-7=81	100/81=1.2	
	8 Weeks: 20% (3/15)		8 Weeks: 84% (21/25)		84-20=64	100/64=1.6	
	10 Weeks: 0% (0/15)		10 Weeks: 76% (19/25)		76-0=76	100/76=1.3	

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Ref.
	Control	Juvenile	Adult	Juvenile	Adult		
Urethane ***Adenomas***	NA						Rogers, 1950
0.25 mg/g		84% (16/19)	24% (4/17)	84-0=84	24-0=24	84/24=3.5	
0.5 mg/g		80% (16/20)	94% (15/16)	80-0=80	94-0=94	80/94=0.9	
1.0 mg/g		90% (18/20)	100% (18/18)	90-0=90	100-0=100	90/100=0.9	

Table 6. Quantitative estimates of early-life cancer susceptibility for studies with multiple exposures of juvenile and adult animals to non-mutagenic chemicals.

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Refs.
	Control	Juvenile	Adult	Juvenile	Adult		
Amitrole ***Liver***							Vesselinovitch et al., 1983
Male Mice	1% (1/98)	22% (10/45)	36% (20/50)	(22-1)/3=7	(36-1)/87=0.4	7/0.4=17.5	
Female Mice	0% (0/96)	0% (0/55)	18% (9/49)	(0-0)/3=0	(18-0)/87=0.2	0/0.2=0	
DDT ***Liver***	2% (1/50)	10% (5/49)	16% (8/49)	(10-2)/4=2	(16-2)/85=0.2	2/0.2=10	Vesselnovitch et al., 1979
Dieldrin ***Liver***	2% (1/58)	7% (3/46)	12% (7/60)	(7-2)/4=1.3	(12-2)/85=0.1	1.3/0.1=13	Vesselnovitch et al., 1979
DPH ***Liver***							Chhabra et al., 1993a
Male Rats	0% (0/50)	2% (1/50)	4% (2/50)	2/11=0.2	4/96=0.04	0.2/0.04=5	
Female Rats	0% (0/50)	0% (0/49)	2% (1/50)	0/11=0	2/96=0.02	0/0.02=0	
Male Mice	58% (29/50)	66% (33/50)	53% (26/49)	(66-58)/11=0.7	(53-58)/96=0	NC[vii]	
Female Mice	10.4% (5/48)	24.5% (12/49)	28% (14/49)	(24.5-10.4)/11=1.3	(28-10.4)/96=0.2	1.3/0.2=6.5	
ETU ***Thyroid***							Chhabra et al., 1992
Male Rats	2% (1/49)	8% (4/49)	26% (12/46)	(8-2)/ 11=0.5	(26-2)/ 96=0.3	0.5/0.3=1.7	
Female Rats	6% (3/50)	6% (3/50)	16% (7/44)	(6-6)/11=0	(16-6)/ 96=0.1	0/0.1=0	

[ii] Not calculated due to lack of tumor development in adult and/or juvenile animals

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Refs.
	Control	Juvenile	Adult	Juvenile	Adult		
ETU							
Liver							
Male Mice	41% (20/49)	26.5% (13/49)	64% (32/50)	(26.5-41)/ 11=0	(64-41)/ 96=0.2	0/0.2=0	
Female Mice	8% (4/50)	10% (5/49)	88% (44/50)	(10-8)/ 11=0.2	(88-8)/ 96=0.8	0.2/0.8=0.25	
Thyroid							
Male Mice	2% (1/50)	2% (1/46)	2% (1/49)	(2-2)/ 11=0	(2-2)/ 96=0	NT[viii]	
Female Mice	0% (0/50)	2% (1/49)	4% (2/50)	(2-0)/ 11=0.2	(4-2)/ 96=0.02	0.2/0.02=10	
Pituitary							
Male Mice	0% (0/44)	0% (0/42)	0% (0/42)	0/11=0	0/96=0	NT	
Female Mice	23% (11/47)	23% (11/48)	39% (19/49)	(23-23)/ 11=0	(39-23)/ 96=0.2	0/0.2=0	
PBB							Chhabra et al., 1993b
Liver							
Male Rats	2% (1/50)	10% (5/50)	24% (12/49)	(10-2)/ 11=0.7	(24-2) /96=0.2	0.7/0.2=3.5	
Female Rats	0% (0/50)	0% (0/50)	24% (12/50)	(0-0)/11=0	(24-2)/ 96=0.2	0/0.2=0	
Mononuclear cell leukemia							
Male Rats	50% (25/50)	62% (31/50)	66% (33/50)	(62-50)/ 11=1.1	(66-50)/ 96=0.2	1.1/0.2=5.5	
Female Rats	28% (14/50)	26% (13/50)	44% (22/50)	(26-28)/ 11=0	(44-28) /96=0.2	0/0.2=0	
Liver							
Male Mice	32% (16/50)	80% (40/50)	94% (48/49)	(80-32)/ 11=4.4	(94-32)/96=0.6	4.4/0.6=7.3	

[viii] No tumor formation observed

Compound and tumor type	Tumor incidence			Tumor incidence/time calculation		(Juvenile tumor incidence/time)/ (Adult tumor incidence/time)	Refs.
	Control	Juvenile	Adult	Juvenile	Adult		
Female Mice	10% (5/50)	42% (21/50)	84% (42/50)	(42-10)/ 11=2.9	(84-10)/96=0.8	2.9/0.8=3.6	

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Table 7. Summary of ratios of juvenile to adult tumor incidence over time for carcinogens acting through a mutagenic mode of action. Acute exposures include both single and four time injection exposures.

Study Type	Minimum	Maximum	Median	Percent of ratios >1
Multiple Exposure	0.3	65	10	82% (9/11)
Acute Exposure, IP on Day 1	0.6	58	1.8	75% (27/36)
Acute Exposure, IP on Day 15	0.5	46	1.7	72% (23/32)
Acute Exposure, Day 1&15	0.5	58	1.8	73% (50/68)
Other Acute Exposures[a]	0.1	8	1.6	77% (20/26)

[a] This includes the analysis for DMBA for mammary tumors assuming that exposure in week 5-8 is adult exposure. If exposure in week 5-8 is assumed juvenile, then the ratio of juvenile to adult tumor incidence over time is 6.2.

Table 8. Excess Relative Risk (ERR) estimates for cancer incidence from Life Span Study (Japanese survivors)[i]

Site	Average ERR at 1 Sv	
	<20[ii]	>20[ii]
Stomach	0.74	0.24
Colon	0.62	0.70
Liver	1.27	0.31
Lung	0.57	1.06
Bone & connective tissue	11.0	0.42
Skin	5.37	0.39
Breast	3.32	0.98
Urinary bladder	0.71	0.79
Leukemia	6.11	3.70

[i] Information extracted from Tables in Annex I of UNSCEAR 2000
[ii] Age at exposure

Table 9. Excess Relative Risk estimates for incidence of thyroid cancer from Life Span Study[i]

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

[i] Information extracted from Tables in Annex I of UNSCEAR 2000

Table 10. Coefficients for the Revised Methodology mortality risk model (from U.S. EPA, 1999)
[The coefficients were derived using several models applied to data from A-bomb survivors and selected medical exposures.]

Cancer type	Risk model type[i]	Age Group				
		0-9	10-19	20-29	30-39	40+
Male:						
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
Female:						
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	1176	284.9	370.06	178.8	157.1

[i] A= absolute risk with coefficient units of 10^{-4} $(Gy\ y)^{-1}$; R= relative risk with coefficient units of Gy^{-1}

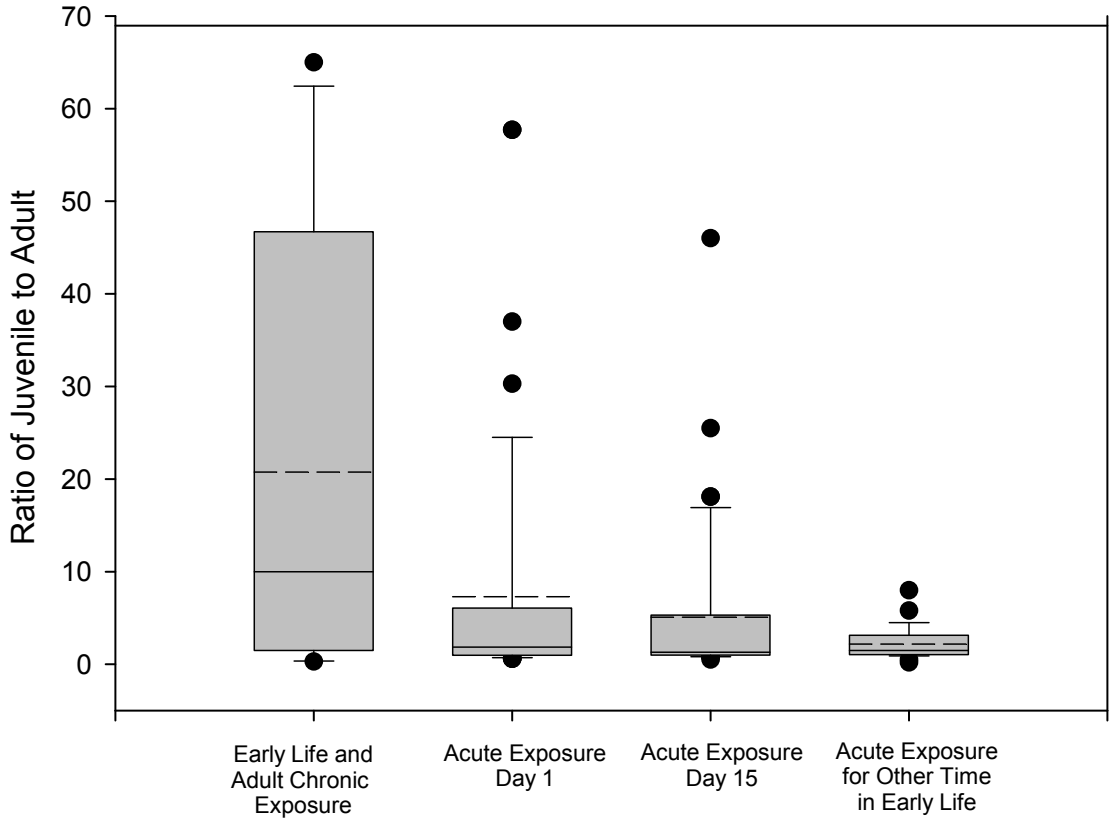

Figure 1: Ratio of juvenile to adult tumor incidence over time for carcinogens primarily acting through a mutagenic mode of action. The box represents the 25th to 75th percentile. The solid line is the median, the dashed line is the mean.

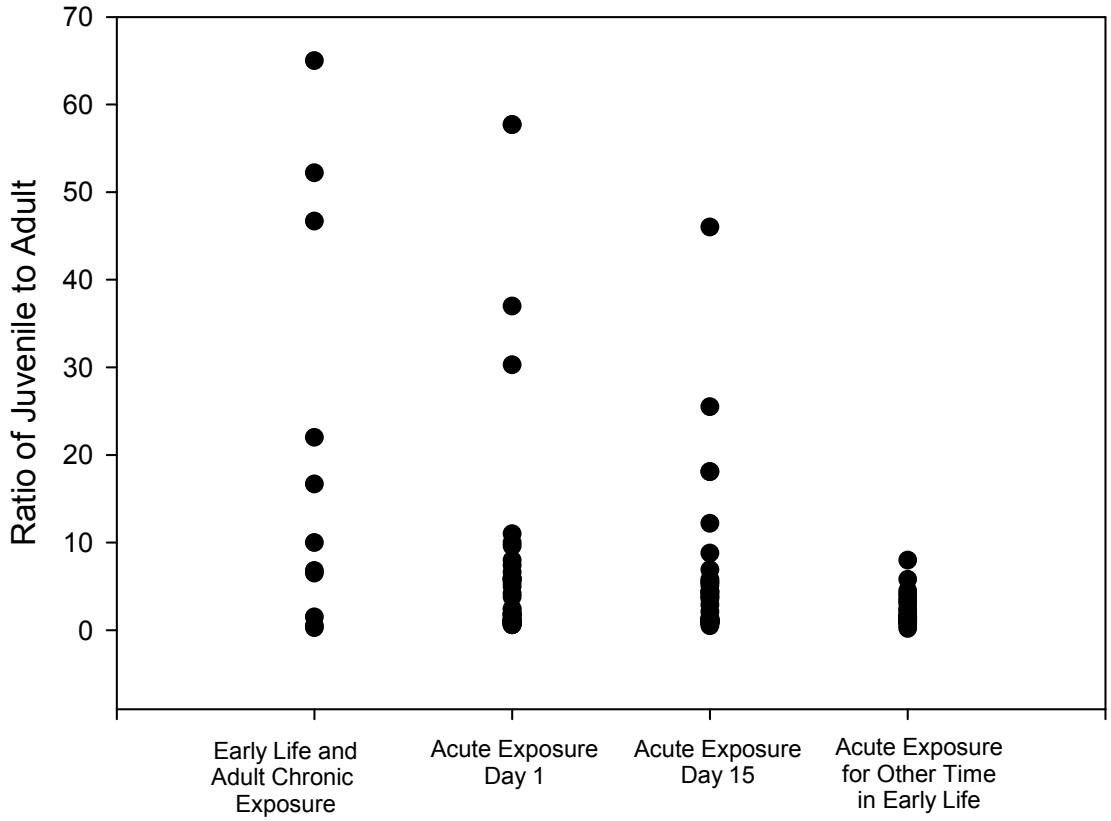

Figure 2: Individual ratios of juvenile to adult tumor incidence over time for carcinogens acting primarily through a mutagenic mode of action.

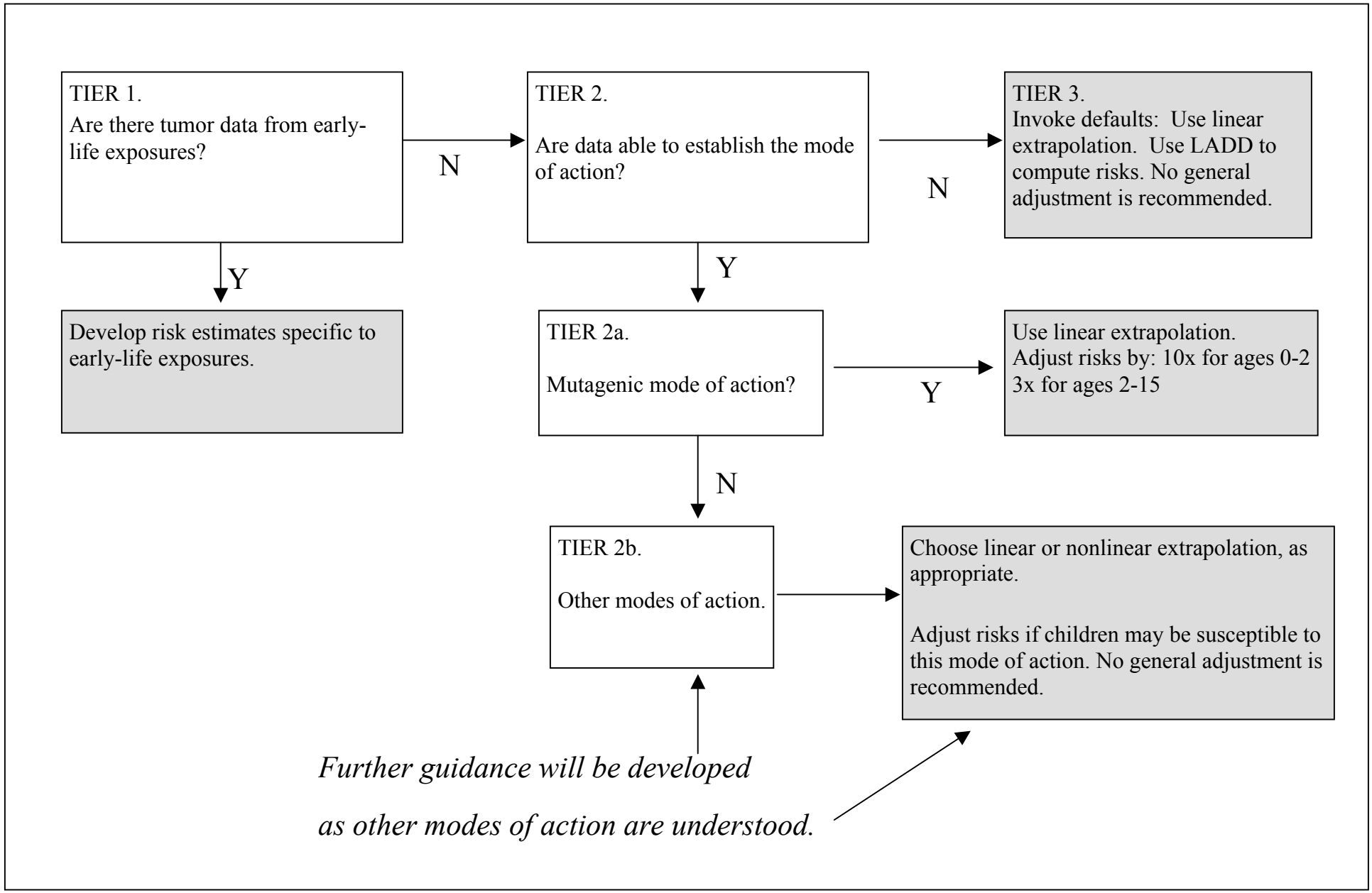

Figure 3: Risk assessment of early-life exposure.