# Age-Related Differences in Susceptibility to Carcinogenesis—A Quantitative Analysis of Empirical Animal Bioassay Data

Dale Hattis,[1] Robert Goble,[1] Abel Russ,[1] Margaret Chu,[2] and Jen Ericson,[1]

[1]George Perkins Marsh Institute, Clark University,950 Main Street,Worcester, Massachusetts 01610

[2]Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. 20460.

**Express mail address for page proofs:**

**Dale Hattis**

**20 Wellington Street**

**Arlington, MA 02476**

**781-641-0305 (phone)**

**508-751-4600 (fax)**

**dhattis@aol.com (email)**

Running Title: Age-Related Differences in Carcinogenesis

Key words: Susceptibility, Carcinogenesis, Fetal, Mutagenic Chemicals, Risk Assessment, Statistical Analysis, Ionizing Radiation

Acknowledgment: This research is supported by a cooperative agreement with the US Environmental Protection Agency--CR 829746-01. However, the conclusions are those of the authors and do not necessarily reflect the views of the US Environmental Protection Agency. We also gratefully acknowledge the assistance of Hugh Barton of USEPA in suggesting some additions and modifications to the data originally presented in USEPA (2003), and the helpful review of technical statistical issues by Woodrow Setzer and Paul White of USEPA.

Abbreviations:

UCL—Upper Confidence Limit

LCL— Lower Confidence Limit

Section headers:

## Abstract

In revising cancer risk assessment guidelines, the U. S. Environmental Protection Agency analyzed animal cancer bioassay data over different periods of life. This paper reports an improved analysis of these data, supplemented with some chemical carcinogenesis observations not included in the original analysis, and animal bioassay studies of ionizing radiation. We use likelihood methods to avoid excluding cases where no tumors were observed specific groups. We express dosage for animals of different weights on a metabolically consistent basis (concentration in air or food, or per unit body weight to the three quarters power). Finally we use a system of dummy variables to represent exposures during fetal, pre-weaning, and weaning-60 day postnatal periods—yielding separate estimates of relative sensitivity per day of dosing in these intervals.

Central estimate results indicate a 5-60 fold increased carcinogenic sensitivity in the birth-weaning period per dose/(body weight$^{3/4}$-day) for mutagenic carcinogens, and a somewhat smaller increase—centered about 5 fold—for radiation carcinogenesis per Gray. Effects were greater in males than in females. There was a similar increased sensitivity in the fetal period for direct-acting nitrosoureas, but no such increased fetal sensitivity was detected for carcinogens requiring metabolic activation. For the birth-weaning period we found similar increased sensitivity for direct administration to the pups as for indirect exposure via lactation. Radiation experiments indicated that carcinogenic sensitivity is not constant through the "adult" period, but dosage delivered in 12-21 month animals appears a few fold less effective than comparable dosage delivered in young adults (90-105 days).

## Introduction

Standard animal cancer bioassays were designed as a qualitative screen for carcinogenic activity. In this context, it is easy to see how the additional difficulties of dosing at early life stages might have been considered to provide a modest incremental return of qualitative hazard identification information compared to the extra effort and complexity of assuring adequate and comparable delivery of test substances over a full lifetime of exposure from conception through adulthood. Therefore conventional animal cancer bioassay studies conducted by the U.S. National Toxicology Program and elsewhere have been designed to start dosing in early adulthood (usually 6-8 weeks in mice and rats—National Toxicology Program 1993; 1999).

Over the last couple of decades, however, animal bioassay results have been routinely used as a basis for quantitative projections of potential cancer risks for populations exposed over a full lifetime, from conception through death. Moreover the results of such risk projections are routinely used to arrive at a variety of types of determinations needed for practical decisions, including:

- How extensive is the cleanup that is needed at hazardous waste sites to achieve risks that are below X incidence of harm with Z confidence? (Hattis and Anderson 1999; USEPA, 2001)

- What health prevention benefits should be expected from reducing exposures by various amounts for toxicants in ambient air, drinking water, and foods subjected to the chemical transformations from different methods of cooking? Do the incremental benefits of specific intervention measures justify their costs, when compared with available alternatives? (NRC 2002; OMB 2000)

In the current revision of cancer risk assessment guidelines by the U. S. Environmental Protection Agency, a question has arisen about whether human exposures during early life stages—during adolescence and before—should be attached any greater weight in risk projections than exposures during adulthood which are analogous to exposures represented in conventional animal bioassay testing. After reviewing an extensive set of non-conventional animal bioassay testing results, EPA (2003) concluded that there was appreciable evidence that juvenile exposures to mutagenic carcinogens conferred greater risks per day of dosing than exposures during adulthood. EPA proposed that for mutagenic chemicals, exposures in the first two years of life should be assumed to be 10 times as potent as exposures in adulthood. A similar 3-fold increase in expected risk was proposed for assessments of the effects of exposures between age 2 and age 15.

Both the age cutoffs used in this proposal, and the extent of the assumed increase in sensitivity relative to adults, were the products of relatively informal analyses of the assembled data base. There was no analysis of data for carcinogenesis following transplacental exposure in the fetal period, and there was no distinction between pre-adult exposures before vs after weaning. Moreover, comparisons were done based on juvenile/adult ratios of raw cancer incidence (the fraction of animals observed to develop tumors) for comparably dosed animals. This potentially introduced distortions of two types: first there was no allowance for tumor multiplicity (more than one effective tumor generation event per animal) in animal groups where a large fraction of the animals developed tumors, and data sets where there were no tumors in adult animals were excluded. In this paper we somewhat expand the data base assembled by EPA, and we do a more formal statistically-weighted analysis of relative cancer potency in terms of cancer transformations per animal per unit dose for animals in different age groups, scaled to the highest

experimental dose used either in adult animals or (if no fully adult animals were tested) the oldest age group of animals included in the experiment. We also derive separate summary relative potency estimates for the fetal, birth-weaning (approximately 21 days in rodents), and weaning-60 day periods. Where dosage spans multiple age groups, we use dummy variables to represent the observed tumor risk as the sum of cancer contributions from dosing in different periods. The data are analyzed in a series of subsets (mutagenic vs non-mutagenic chemicals vs radiation; male vs female; liver vs. non-liver) to show how the results depend on various factors.

## Description of the Data Bases

Table 1 provides an overview of the data. Experimental results described in detail by EPA were corrected in a few cases and supplemented as follows:

- We added esophageal tumors for diethylnitrosamine (DEN) from Peto et al. 1984 (liver, but not esophageal tumors from this paper were included in the EPA analysis),. Additionally control observations were added from Peto et al. 1991.

- The exposure time was corrected for some vinyl chloride groups; we also additional control and comparison group information for 52 week exposures from data of Maltoni et al. 1984,

- We consolidated 6000 and 10000 ppm exposure groups for vinyl chloride--both of these are well over saturating levels for the metabolic activation of this chemical. Results for control (zero-dose) groups were also consolidated in several cases.

- We added the results of major single-dose study of N-nitroso-methylurea by Terracini et al. 1976, as well as several papers on carcinogenesis from ionizing radiation in rats and mice (Sasaki 1991, Di Majo et al. 1990, Knowles 1985, Castanera et al. 1971, Cahill et al. 1975).

- We deleted groups without defined observations for controls (numbers of animals tested and numbers with tumors).

Data for two non-mutagenic chemicals (DDT and dieldrin) were eliminated from the analysis because of the complexity of the dosing protocol used. In these experiments some groups were given gavage exposures, some direct dietary exposures and some both in sequence. This rendered unambiguous calculations of comparable dosages for the different groups difficult.

The principal analyses below maintain the subdivisions between continuous-dosing protocols (in which dosing was maintained at a given rate for a defined period) vs discrete-dosing experiments (in which only a single dose, or up to 4 single doses were given to the animals at defined ages).

The full data bases as well as models used for the statistical analyses of continuous, discrete and radiation dosing data are provided on our website (Hattis 2004): http://www2.clarku.edu/faculty/dhattis.

## Modeling Methods

### Dosimetric Conversions

The assessment of comparable dosimetry for animals in different life stages has been a substantial issue in discussions of the analysis of these data. For various experiments in the original EPA listing, doses are quoted in terms of a concentration in an environmental medium (ppm in diet or water or air to the individual for exposures after weaning, and to the mother in the case of fetal and birth-weaning exposures) and in other cases doses that were directly

administered to animals via intraperitoneal or other injections were originally expressed in terms of $\mu$g/kg of body weight or similar units. For entry into our analysis, we leave the doses expressed in terms of environmental media concentrations unchanged, but we transform the doses expressed as $\mu$g/kg body weight into $\mu$g/(kg body weight)$^{.75}$ by multiplying by estimated individual body weights to the one quarter power. (Body weights for this purpose were taken from Nomura 1976 for mice; NTP 1999 and Zhang et al. 2001 for rats.) The aim of this transformation is to use a dose metric that (to the extent possible with available information short of PBTK modeling) is expected to be approximately proportional to internal daily average systemic concentrations of the parent compounds or putative active metabolites for continuous dosing, or area under the concentration-time curve (AUC) for discrete dosing.

The basis for this approach is similar to the principal current basis for dosimetric conversions for interspecies projections of cancer risks--that risks are assumed to be similar across species if the internal time-integrated concentrations of active metabolites are similar across species. Similarity of internal time-integrated concentrations is assessed with the aid of observations that both bulk uptake and elimination processes tend to scale across species with metabolic rates—approximately in proportion to body weight to the three quarters power (Boxenbaum, 1982; FCCSET 1992; Travis and White 1988; Travis et al. 1990). We have recently found that a similar transformation reconciles clearance rates of drugs across age groups in humans—at least after a period of severely deficient clearance in the first few months of infancy. Table 2, documenting this result, is based on a new regression analysis of human data for pharmaceuticals and methods that have been previously described (Ginsberg et al. 2002; Hattis et al. 2003). We have not located a comparable set of in vivo clearance observations in rats or mice. The literature does contain several reports that indicate depressed liver metabolizing activity in the

neonatal period based on in vitro measurements of the activity of some liver enzymes (Basu et al., 1971; Macleod et al. 1972) and differences between the sexes in the maturation of metabolizing capabilities (with generally greater activity observed in males). To assess the possible influence of a neonatal deficit of either activating or detoxifying activity on our results, the results section includes comparative analyses of the single-dose data for apparent relative sensitivity at narrowly defined time-windows—contrasting day 1 after birth with later periods before and after weaning. These comparisons are done for both carcinogens that are thought to be direct-acting (not requiring metabolic activation, and those that putatively need metabolic activation before directly DNA-reactive substances are generated (see below) . We also assess differences in apparent life stage related sensitivity between the sexes.

For ionizing radiation exposures we have chosen to leave the doses in units of absorbed energy—rads or Gray. If the oxidative products generated by radiation are the actual carcinogenic agents, and if these are predominantly destroyed by metabolism-dependent processes that operate at rates that scale with metabolic rates, it is possible that achieving comparable integrated dose X time levels of the active agents might require similar (body weight)$^{.75}$ conversions as were used for chemicals. Making such a transformation would tend to decrease the time-integrated dosage for the younger postnatal animals, and therefore would tend to increase the assessed sensitivity per dose relative to adult exposures. As it happens, such a transformation would have brought the radiation results more closely into alignment with the results for mutagenic chemicals.

**Equation Fit and Statistical Optimization**

One basic difference between our methodology and that used for these data by EPA is a transformation of the raw observations of tumor incidence in different groups into the estimated number of tumor transformations per animal. This corrects for the fact that experimenters cannot usually distinguish between cases where one or more than one tumor was induced at in a particular organ within a specific animal (or where more than one tumor would have been induced at the site studied had the animal lived to the end of the observation period). To accomplish this we use the same Poisson transformation that has been traditionally used for the multistage and related statistical models of carcinogenesis. [The Poisson distribution is appropriate for processes that occur as the result of independent events where the number of possible events occurring in a particular unit of observation is unlimited. Our use of the Poisson distribution in this case derives from the basic fact that tumors start in individual cells (Fialkow 1997; Knudson, 1973; 1977). Each tumor is conceived to be an independent event arising as the result of the completion of the last stage mutation in one stem cell out of many other susceptible stem cells in a particular organ. It should be noted that this last stage event will not generally have occurred during the pre-adult life stages that are the focus of our analysis, but the effects of these early life exposures will be manifested as incremental tumors that occur during the life-long period of observation of the animals.]:

Fraction of animals with tumors = $P_{tumor} = 1 - P_{no\ tumor}$ (1)

$P_{no\ tumor} = e^{-m} = \exp(-m)$ where m = tumor transformations/animal at the studied site (2)

Solving for m:

$$M = -\ln(P_{\text{no tumor}}) = -\ln(1 - \text{Fraction of animals with tumors}) \quad (3)$$

Because most of the experiments utilize only a single dose of carcinogen for each age group, no more sophisticated multistage treatment of tumor dose response is possible with these data. Given this, relative cancer transformation rates in different age groups in comparison with adult animals were estimated by fitting the continuous data to:

$$\text{Fraction with tumors} = 1 - e^{-[B + A(a + fF + cC + wW)]} \quad (4)$$

Where:

B = group background transformations per animal

A = group adult transformations per animal at the highest adult dose rate

a = fraction of the adult period with dosing at the maximum adult rate (this term reflects an adjustment where a group received less than the full adult dosing rate)

f = fraction of the fetal period with dosing at the maximum adult rate (also adjusted for dose rate as needed

F = fetal/adult sensitivity ratio

c = fraction of the birth-weaning period with dosing at the maximum adult rate (also adjusted for dose rate as needed)

C = birth-weaning/adult sensitivity ratio

w = fraction of the weaning-60 day period with dosing at the maximum adult rate (also adjusted for dose rate as needed)

W = weaning-60 day/adult sensitivity ratio.

In this equation the terms designated with lower case letters represent the input dosing and tumor response data for each group of dosed animals or controls. Where continuous daily dosing occurred over only part of a lifestage, the fraction of the lifestage where dosing occurred was entered. Similarly where dosing for a particular group occurred at a fraction of the maximal rate given to adults, that fraction was entered as input data. This model form treats contributions to ultimate cancer transformation events from different life stages as additive.

The equation has two types of estimated parameters (designated with upper case letters). First, "A" and "B" are used only within specific experiments (a particular tumor type associated with exposure to a particular chemical in a particular animal group). By contrast, the three remaining "generic" parameters ("F", "C", and "W") are estimated based on the results of all the dose groups for all chemicals and animals included in a particular run that contained some dosing within each life stage, compared to controls. Thus for these generic parameters the results represent summary central estimates (and confidence limits) for all chemicals, tumor types, species (rats and mice) and other characteristics of the included experimental data. In the light of this, the results section below presents alternative sets of estimates designed to explore the influence of gender, mutagenic character, tumor site, and other characteristics on the assessments of differences in susceptibility among life stages. Finally, because the doses used in the model

fitting were expressed in terms of dose/(body weight)$^{.75}$ the units of the relative sensitivity parameters should similarly be understood to be

$$\frac{\text{life - stage - specific cancer transformations per dose/body weight}^{3/4}\text{ - day}}{\text{adult cancer transformations per dose/body weight}^{3/4}\text{ - day}} \quad (5)$$

Estimates of the upper-case terms were derived by minimizing the "deviance" between observed and model predicted data points, as described by Haas (1994) and McCullagh and Nelder (1989):

For non-zero numbers of tumors in a particular group the "deviance" is

$$-2\sum_{i=1}^{k}\left[N_i \ln\left(\frac{\pi_i}{\pi_i^0}\right) + (T_i - N_i)\ln\left(\frac{1-\pi_i}{1-\pi_i^0}\right)\right] \quad (6)$$

Where:

k is the number of dose groups

$N_i$ is the number of animals with tumors in group *I*

$T_i$ is the total number of animals in group *I*

$\pi_i$ is the model-predicted proportion of animals with tumors in group *I*

$\pi_i^0$ is $N_i / T_i$

This deviance-minimization optimization was accomplished in Microsoft Excel spreadsheets using the "solver" facility. Haas 1994 also provided procedures for deriving profile-likelihood-based confidence intervals (Venzon and Moolgavkar 1988) for these fitted parameters based on the chi-squared statistic. For each confidence interval estimate, all parameters other than the one being assessed were allowed to vary. Thus the upper and lower 95% confidence limits for the birth-weaning/adult sensitivity estimates reflect possible uncertainties in all the group background transformations per animal, group adult transformations per animal, and the sensitivities of fetal and weaning-60 day life stages relative to adults. A similar approach was used for the discrete dosing data and for the combined continuous and discrete data by dividing the doses by the estimated numbers of days in each dosing period (8 days for the fetal dosing period, 21 days for the birth-weaning life stage, and 39 days for the weaning-60 day life stage, and 663 days for the adult period.

## Results and Discussion--Relative Sensitivity of Different Life Stages in Animals

Before considering the age-related differential sensitivity results for continuous vs discrete dosing in detail, it is worth noting that they may be reflecting somewhat different factors. The continuous dosing results:

- Include enzyme induction effects, if any
- Inherently reflect a dilution of any fluctuations in short-term sensitivity caused by, for

example, waves of cell proliferation in specific organs in narrow time windows

- Possibly present fewer complications from high dose kinetic and dynamic nonlinearities, and
- Have somewhat more straightforward implications for adaptation of traditional chronic dosing assessments.

On the other hand, the results from experiments where dosing was administered at discrete times:

- Almost always exclude direct enzyme induction effects
- Are capable of revealing short term sensitivity fluctuations, to the extent that these occur
- Are likely to be done at somewhat higher dose rates, with some increase in potential complications from high-dose nonlinearities
- Have more straightforward implications for assessment of risks from acute exposure events.

**Results for Overall Continuous Chemical, Discrete Chemical, and Radiation Dosing Data Sets**

Table 3 shows the results of fitting the continuous and discrete dosing data as a whole, together with similar results for radiation exposures. In all three sets of data, the birth-weaning period is suggested to be the most sensitive per day of dosing, followed by the fetal period and the weaning-60 day period. Each independent data set yields a central estimate of the birth-weaning sensitivity that is about 5-10 fold greater than the sensitivity per day of dosing in aduthood, with doses expressed per body weight$^{.75}$.

**Mutagenic vs Non-Mutagenic Chemicals**

In the case of the continuous dosing data, some of the chemicals were classified by EPA as mutagenic, and some not. (All the chemicals with discrete dosing data, and ionizing radiation, are mutagenic.) Table 4 shows the continuous dosing results broken out for mutagens vs non-mutagens. In contrast with the mutagens, for non-mutagenic carcinogens none of the age groups manifest significantly greater sensitivity than is seen for adults (defined as 1 in these tables). It should also be noted that separating out the non-mutagens leaves the mutagenic compounds showing significantly more birth-weaning period sensitivity than is seen for either the discrete-dosing chemical data or the radiation observations.

**Male vs Female Animals**

Tables 5-7 show the contrast between results in male vs female animals for continuously-dosed mutagens, mutagenic chemicals delivered in discrete doses, and radiation experiments, respectively. The differences appear most prominent for the continuous dosing data (Table 5)—where males seem to have much larger increases in sensitivity relative to adults for the fetal and birth-weaning life stages, and by contrast, females show a large increase in sensitivity for the weaning-60 day period. Considerable reserve is in order in interpreting the latter result, however, in the light of the slender database available for the continuous dosing analysis (only 3 chemicals and 16 dose groups in each sex), and the fact that neither the larger set of discrete-dosing data (Table 6) nor the radiation-dosing data (Table 7, based on fetal and weaning-60 day stages only) exhibits a similar enhanced female relative sensitivity for the weaning-60 period, compared to males.

One way of weighing the different observations from continuous vs discrete chemical dosing experiments is to combine the two sets of results into a single model for analysis. The results of such a combination for male and female life-stage relative sensitivity ratios are shown in Table 8. The combined data tend to reinforce the suggestion that there are male-female differences in age-related sensitivity patterns, but fails to sustain the initial suggestion from the continuous dosing data of an increase in the sensitivity for females in the weaning-60 day period relative to adults. On the other hand, the combined data do indicate an increased sensitivity for this period in males. The combined data for the fetal and birth-weaning periods indicate much more prominent excess sensitivity relative to adults in males than in females.

**Distributional Form for the Statistical Uncertainties in Estimated Life Stage/Adult Sensitivities**

Figures 1 and 2 show lognormal probability plots (Hattis and Burmaster 1994) of the statistical uncertainty distributions for the life stage/adult sensitivity ratios for the male and female combined discrete and continuous dosing data for mutagenic carcinogens. In this type of plot, correspondence of the points to the fitted line is an indicator of the fit of a lognormal distribution to the statistical uncertainties in central estimate life stage/adult sensitivity ratios. (The Z-Score that makes up the X-axis is the number of standard errors above or below the median of the normal distribution $\log_{10}$ transformed values). It can be seen that the uncertainty distributions are well described by the lognormal fits. We stress that these plots are of confidence limits on the aggregate central tendency results for all chemicals in the covered groups. The uncertainties in estimates for individual chemicals are analyzed separately in a companion paper; together with implications for human risk for a particular mutagenic chemical.

**Rats vs Mice**

Table 9 shows comparative results in for life-stage specific relative tumor sensitivities in rats vs mice for the combined discrete and continuous dosing experiments. There is a suggestion that the rat data may indicate somewhat larger effects relative to adults for the fetal and weaning-60 day life stages; however the 95% confidence limits overlap. In the light of the very limited numbers of chemicals with relevant observations for rats, there should be no strong inference that the suggested rat/mouse differences are real.

**Direct Acting Carcinogens vs Agents Requiring Metabolic Activation**

All but two of the mutagenic carcinogens covered in the data base are thought to require metabolic activation to produce DNA reactive agents (U.S. EPA 2003). The two exceptions are the nitrosoureas—methyl- and ethylnitrosoura. Comparing life stage/adult sensitivity results for the metabolically activated vs direct-acting compounds can shed light on whether the previous results, including the relevant dosimetry, are likely to have been appreciably distorted by immaturity of metabolic activating systems in the neonatal period.

Table 10 shows the relevant comparison utilizing our standard breakdown of life stages, based on the single-dose data. The results indicate a clear difference in fetal sensitivity for direct-acting vs metabolically-activated compounds. As might have been expected, there is, if anything, less carcinogenic susceptibility in the fetal period for metabolically-activated compounds, while the fetal life stage shows 5-25 fold greater sensitivity than adults for the direct-acting nitrosoureas.

Table 11 shows the results of using a finer breakdown of time periods—made possible by the focus on data resulting from direct dosing at discrete times. Beyond the fetal period there is no apparent difference in the pattern of relative sensitivity with age between the nitrosoureas and the metabolically activated carcinogens. In both cases relative sensitivity peaks near birth, and declines progressively thereafter until it reaches about double the adult sensitivity at day 21. Beyond the fetal period, there is thus no indication of a perinatal deficit in metabolic activating activity for this set of carcinogens.

**Direct Dosing in the Birth-Weaning Period vs Dosing via Lactation**

Another important dosimetric issue is whether the lactational exposures resulting from primary dietary exposure to maternal animals are in fact equivalent to doses directly administered to pups during the birth-weaning period. Table 12 shows the results of separate estimations of the relative tumor susceptibility for direct vs lactational exposure for the combined set of continuous and discrete dosing experiments. It can be seen that no diminution in birth-weaning sensitivity is indicated for lactational exposures in comparison to direct administration of known doses. If anything, the lactational exposures appear somewhat more potent than direct administration per unit of estimated external exposure, although the 95% confidence limits overlap. One possible interpretation of this, if repeated, is that some of the bolus doses given in the direct administration experiments may have partially saturated metabolic activation pathways, leading to less effective dose of DNA-reactive metabolites per unit exposure than when similar materials are administered more slowly via milk.

**Radiation Results for a Different Times During the "Adult" Period**

The "adult" comparison groups for the discrete chemical dosing experiments generally were exposed in early adulthood—within 4-6 months of age. By contrast the radiation experiments include groups extending to much older ages—up to 16-18 months. It can be seen in Table 13 that these data indicate a considerable reduction in sensitivity for radiogenic cancer induction with advancing age.

**Liver Tumors vs Tumors in Other Organs**

As indicated in Table 1, many of the tumors studied in these rodent experiments come from the liver, particularly for the continuous dosing studies. In analyses not presented here because of space limitations (see website for results) it is found that in general life-stage specific enhancements of sensitivity seem to be greater for the liver than lung but life-stage specific excesses in sensitivity are still apparent for the aggregate of non-liver non-lung organs.

**Toward Quantitative Applications in Human Health Risk Assessment**

On a qualitative level, this analysis provides more detailed understanding and confidence in the fact that there is an increased early-life sensitivity for mutagenic carcinogens—reinforcing the conclusions drawn by EPA (2003). The next step toward applying these data for quantitative human risk assessment is to develop a time/age mapping between rodents and people. What ages in people approximately correspond to the rodent fetal, birth-weaning, and weaning-60 day periods studied in this analysis? A companion paper develops a preliminary mapping based on the times at which rodents and people attain various fractions of the average body weights they have at sexual maturity. In this second paper we also do a Monte-Carlo model-based

distributional analysis of the combined uncertainties in (1) the central estimates of life-stage-related differences in carcinogenesis susceptibility, as derived in this paper, (2) the chemical-to-chemical variation in the life-stage related susceptibility estimates, and (3) the rodent/human time mapping uncertainty. Quantitative assessment of these three uncertainties together is needed for full distributional analyses of cancer risks for exposures in early life stages.

# References

Basu TK, Dickerson JWT, Parke DVW. 1971. Effect of development on the activity of microsomal drug-metabolizing enzymes in rat liver. Biochem J 124:19-24.

Boxenbaum H. 1982. Interspecies scaling, allometry, physiological time, and the ground plan of pharmacokinetics. J Pharmacokinet Biopharm 10:201-227.

Cahill DF, Wright JF, Godbold JH, Ward JM, Laskey JW, Tompkins EA. 1975. Neoplastic and life-span effects of chronic exposure to tritium. II Rats exposed in utero. J Natl Cancer Inst 55:1165-1169.

Castanera TJ, Jones DC, Kimeldorf DJ, Rosen VJ. 1971. The effect of age at exposure to a sublethal dose of fast neutrons on tumorigenesis in the male rat. Cancer Res 31:1543-1549.

Di Majo V, Coppola M, Rebessi S, Covelli V. 1990. Age-related susceptibility of mouse liver to induction of tumors by neutrons. Radiat Res 124:227-234.

FCCSET. 1992. Draft Report: A Cross-Species Scaling Factor for Carcinogen Risk Assessment Based on Equivalence of mg/kg$^{3/4}$/Day. Ad Hoc Working Group on Risk Assessment, Federal Coordinating Council for Science, Engineering and Technology, Federal Register 57: 24152-24173,.

Fialkow PJ. 1977. Clonal origin and stem cell evolution of human tumors. In: Genetics of Human Cancer (Mulvihill JJ, Miller RW, Fraumeni JF, eds) New York: Raven Press, 439-452.

Ginsberg G, Hattis D, Sonawane B, Russ A, Banati P, Kozlak M, Smolenski S, Goble R. 2002. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 66:185-200.

Haas, C. N. 1994. Dose response analysis using spreadsheets. Risk Anal 14:1097-1100.

Hattis, D. 2004. Human Interindividual Variability in Parameters Related to Susceptibility for Toxic Effects. Available: http://www2.clarku.edu/faculty/dhattis [accessed 11 May 2004].

Hattis D, Anderson E. 1999. What should be the implications of uncertainty, variability, and inherent 'biases'/'conservatism' for risk management decision making? Risk Anal 19:95-107.

Hattis D, Burmaster DE. 1994. Assessment of variability and uncertainty distributions for practical risk analyses. Risk Anal 14: 713-730.

Hattis D, Ginsberg G, Sonawane B, Smolenski S, Russ A, Kozlak M, Goble R. 2003. Differences in pharmacokinetics between children and adults—II. Children's variability in drug elimination half-lives and in some parameters needed for physiologically-based pharmacokinetic modeling. Risk Anal 23: 117-142.

Knowles JF. 1985. Changing sensitivity of neonatal rats to tumorigenic effects of N-Nitroso-N-ethylurea and X-radiation, given singly or combined. J Natl Cancer Inst 74:853-857.

Knudson A.G. 1973. Mutation and human cancer. Adv Cancer Res 17:317-352.

Knudson, A.G. 1977. Genetics and etiology of human cancer. Adv Hum Genet 8:1-66.

Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D 1984. Experimental research on vinyl chloride carcinogenesis. Vol II of Archives of Research on Industrial Carcinogenesis. Maltoni C, Mehlman MA, eds) Princeton NJ: Princeton Scientific Publishers Inc.

MacLeod SM, Renton KW, Eade NR. 1972. Development of hepatic microsomal drug-oxidizing enzymes in immature male and female rats. J Pharmacol Exp Ther 183:489-498.

McCullagh P, Nelder JA. 1989. General Linear Models. 2nd ed. London:Chapman and Hall, p. 34.

National Research Council. 2002. Estimating the Public Health Benefits of Proposed Air Pollution Regulations, Washington, DC:National Academy Press.

NTP. 1993. Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 77-47-4) in B6C3F1 Mice (Inhalation Studies). Research Triangle Park, North Carolina:National Toxicology Program TR-434.

NTP. 1999. Toxicology and Carcinogenesis Studies of Pentachlorophenol (CAS No. 87-86-5) in F344/N Rats (Feed Studies). Research Triangle Park, North Carolina:National Toxicology Program TR-483.

Nomura T. 1976. Comparison of tumour susceptibility among various organs of foetal, young and adult ICR/Jcl mice. Br J Cancer 33:521-533.

OMB. 2000. Guidelines to Standardize Measures of Costs and Benefits and the Format of Accounting Statements. Memorandum from Jacob J. Lew. March 22, 2000. Washington,

DC: Office of Management and Budget Available: http://www.whitehouse.gov/omb/memoranda/m00-08.pdf [accessed 11 May 2004].

Peto R, Gray R, Brantom P, Grasso P. 1991. Effects on 4080 rats of chronic ingestion of N-Nitrosodiethylamine or N-Nitrosodimethylamine: A detailed dose-response study" Cancer Res 51:6415–6451.

Peto R, Gray R, Brantom P, Grasso P. 1984. Nitrosamine carcinogenesis in 5120 rodents: chronic administration of sixteen different concentrations of NDEA, NDMA, NPYR and NPIP in the water of 4440 inbred rats, with parallel studies on NDEA alone of the effect of age of starting (3,6 or 20 weeks) and of species (rats, mice, or hamsters). IARC Sci Publ 57:627-665.

Sasaki S. 1991. Influence of the age of mice at exposure to radiation on life-shortening and carcinogenesis. J Radiat Res (Tokyo) 32 Supplement 2:73-85.

Terracini B, Testa MC, Cabral JB, Rossi L. 1976. The roles of age at treatment and dose in carcinogenesis in C3HfDp mice with a single administration of N-nitroso-N-methylurea Br J Cancer 33:427-439.

Travis CC, White RK. 1988. Interspecific scaling of toxicity data. Risk Anal 8:119-125.

Travis DC, White RK, Ward RC. 1990. Interspecies extrapolation of pharmacokinetics. J Theor Biol 142: 285-304.

U. S. EPA. 2001. Risk Assessment Guidance for Superfund: Volume III – Part A, Process for Conducting Probabilistic Risk Assessment. Washington, DC, U. S. Environmental

Protection Agency No. EPA/540-R-02-002, National Technical Information Service No. PB2002 963302.

U.S. EPA. 2003. Supplemental Guidance For Assessing Cancer Susceptibility From Early-Life Exposure To Carcinogens (External Review Draft). Washington, DC:Risk Assessment Forum, Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55446 [accessed 11 May 2004].

Venzon DJ, Moolgavkar SH. 1988. A method for computing profile-likelihood-based confidence intervals. Appl Statistics 37:87-94.

Zhang S, Leske DA, Lanier WL, Holmes JM. 2001. Postnatal growth retardation exacerbates acidosis-induced retinopathy in the neonatal rat. Curr Eye Res 22:133-139.

**Table 1.** Overall Description of the Data Bases

| | | | Dose Groups With Exposures in Specific Life Stages (and numbers of animals*tumor-site observations[f] in parentheses) | | | | |
|---|---|---|---|---|---|---|---|
| Dosing Protocol | Number of Chemicals or Radiation Types | Total Dose Groups | Control Groups | Fetal | Birth-Weaning | Weaning-60 Days | Adult (60+ Days |
| Continuous | 9 (5 mutagenic) [b] | 151[a] (103 liver) | 29(2562) | 14 (820) | 62 (3071) | 62 (6128) | 85 (7544) |
| Discrete (1-4X) | 6 (all mutagenic) [c] | 274[a] (90 liver) | 45 (2926) | 8 (290) | 117[d] (4681) | 85[d] (3596) | 37 (979) |
| Radiation | 4[e] | 138 (42 liver) | 21 (4283) | 18 (1323) | 18 (1744) | 18 (1529) | 63 (3668) |

[a] The numbers of groups do not add to the total because some groups had dosing in more than one life stage.

[b] The chemicals classified as mutagenic were benzidine, benzo(a)pyrene, diethylnitrosamine, safrole, and vinyl chloride. The chemicals classified as not mutagenic were amitrole, diphenylhydantoin, ethylene thiourea, and polybrominated biphenyls.

[c] Benzo(a)pyrene, diethylnitrosamine, dimethylbenzanthracene, ethylnitrosourea, methylnitrosourea, and urethane.

[d] 66 groups were dosed on the first day after birth; 69 groups received exposures between day 1 and day 21; 19 groups were dosed on day 21; and 68 groups were dosed between day 22 and day 60. This finer breakdown will be used in the expanded-time analysis of the single dose data below. The sum of these numbers exceeds the total because some groups received dosing in more than one of these more finely divided time categories.

[e] The ionizing radiation exposures were from Cs-137 gamma rays, x-rays, neutrons, and internal beta rays resulting from the injection of tritiated water.

[f] In some experiments tumor observations were reported separately for two or more anatomical sites (e.g. liver and stomach). In these cases the numbers reported here count the same individual animals more than once.

**Table 2.** Geometric Mean Ratios[a] of Child/Adult Clearance/Body Weight and (Clearance/Body Weight$^{3/4}$). Data Represent Regression Results from 104 Data Groups for 27 Drugs for Humans in Various Age Ranges

| Form for Expressing Total Body Clearance | Premature neonates | Full term neonates | 1 wk – 2 mo | 2 – 6 mo | 6 mo – 2 yr | 2 – 12 yr | 12 – 18 yr |
|---|---|---|---|---|---|---|---|
| Mg/Kg Body Weight | 0.52[a] | 0.66 | 0.77 | 1.21 | 1.71 | 1.42 | 0.97 |
| | (0.43-0.63)[b] | (0.61-0.73) | (0.71-0.84) | (1.06-1.39) | (1.52-1.92) | (1.31-1.53) | (0.78-1.2) |
| Mg/(Kg Body Weight)$^{3/4}$ [c] | 0.23 | 0.31 | 0.38 | 0.68 | 1.03 | 1.08 | 0.93 |
| | (0.19-0.28)[b] | (0.28-0.34) | (0.35-0.42) | (0.59-0.78) | (0.91-1.17) | (1.00-1.17) | (0.74-1.17) |

[a]These data are the antilogs of the "B" coefficients that result from fitting the equation:
Log(Mean Clearance) = $B_0$ (intercept) + $B_1$*(1 or 0 for chemical 1) + $B_2$*(1 or 0 for chemical 2) + …
+ $B_a$*(1 or 0 for age group 1) + $B_b$*(1 or 0 for age group 2) + …

For a fuller description of the underlying data and methodology see Ginsberg et al (2002), Hattis et al (2003), and our web site (Hattis, 2004)--http://www2.clarku.edu/faculty/dhattis.

[b]Parentheses show the ± 1 standard error range.

[c]Input Clearance/(Kg Body Weight)$^{3/4}$ data for the regression results reported in this line were calculated from Clearance/Body Weight data by multiplying by group mean estimated body weights$^{1/4}$. For children age 2 and above, body weights for this transformation were estimated using the formulae in Hattis et al. (2003), averaged for both sexes. Body weights of 2.5 and 3.5 kg were assumed for premature and full term neonates under one week of age respectively, and a log-linear interpolation was made between 3.5 kg at age 1 week and 6.3 kg at 2 months for groups with mean ages in that interval.

**Table 3.** Summary of Results from Fitting Cancer Bioassay Data--Relative Susceptibility of Different Life Stages Per Day of Dosing

All Continuous Chemical Dosing Experiments (based on a total of 151 group tumor incidence observations for 9 chemicals).

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period (8 days beginning GD 12) | 4.9 | 0.5 | 9.3 |
| Birth-Weaning (21 days) | 8.7 | 6.5 | 10.8 |
| Weaning-60 days (39 days) | 0.000 | 0.000 | 0.24 |

All Discrete Chemical Dosing Experiments (based on a total of 274 group tumor incidence observations for 6 chemicals).

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period (8 days beginning GD 12) | 5.1 | 3.6 | 8.5 |
| Birth-Weaning (21 days) | 10.5 | 7.2 | 16.2 |
| Weaning-60 days (39 days) | 1.51 | 1.03 | 2.31 |

All Ionizing Radiation Dosing Experiments (based on a total of 138 group tumor incidence observations for 4 radiation types).

| | **Maximum likelihood estimate of cancer inductions per dose in rads or Gray relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period (8 days beginning GD 12) | 3.5 | 2.2 | 5.7 |
| Birth-Weaning (21 days) | 5.3 | 3.9 | 8.3 |
| Weaning-60 days (39 days) | 2.4 | 1.8 | 3.4 |

**Table 4.** Comparative Results for Continuous Dosing of Chemicals Classified as Mutagenic vs those Classified as Not Mutagenic--Relative Susceptibility of Different Life Stages Per Day of Dosing

Chemicals Classified by EPA as Mutagenic (5 compounds, 43 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 8.4 | 3.5 | 15.5 |
| Birth-Weaning | 24 | 17.1 | 34 |
| Weaning-60 days | 3.7 | 0.0 | 9.1 |

Chemicals Classified by EPA as Not Mutagenic (4 compounds, 108 tumor incidence observations in animal groups):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 0.0 | 0.0 | 17.4 |
| Birth-Weaning | 3.0 | 0.0 | 4.7 |
| Weaning-60 days | 0.0 | 0.0 | 2.0 |

**Table 5.** Comparative Results for Male vs Female Animals for Mutagenic Chemicals Given in Continuous Dosing Experiments

Male Animals—Continuous Dosing for Chemicals Classified by EPA as Mutagenic (3 compounds, 16 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 35 | 16.5 | 72 |
| Birth-Weaning | 133 | 80 | 245 |
| Weaning-60 days | 0.0 | 0.0 | 9.7 |

Female Animals—Continuous Dosing for Chemicals Classified by EPA as Mutagenic (3 compounds, 16 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 2.3 | 0.24 | 9.7 |
| Birth-Weaning | 3.4 | 1.1 | 8.4 |
| Weaning-60 days | 41 | 18 | 98 |

**Table 6.** Comparative Results for Male vs Female Animals for Mutagenic Chemicals Given in Discrete Dosing Experiments

Male Animals—Discrete Dosing for Chemicals Classified by EPA as Mutagenic (6 compounds, 137 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 5.7 | 3.5 | 11.1 |
| Birth-Weaning | 11.1 | 6.6 | 19.5 |
| Weaning-60 days | 1.58 | 0.99 | 2.6 |

Female Animals—Discrete Dosing for Chemicals Classified by EPA as Mutagenic (6 compounds, 137 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 4.4 | 2.1 | 10.2 |
| Birth-Weaning | 9.7 | 5.6 | 20 |
| Weaning-60 days | 1.45 | 0.75 | 3.2 |

**Table 7.** Comparative Results for Male vs Female Animals for Radiation Dosing Experiments

Male Animals—66 tumor incidence observations for two forms of radiation (x-rays and neutrons):

| | **Maximum likelihood estimate of cancer inductions per dose in rads or Gray relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 7.4 | 3.2 | 43 |
| Birth-Weaning | no data | no data | no data |
| Weaning-60 days | 2.3 | 1.6 | 3.3 |

Female Animals—69 tumor incidence observations for three forms of radiation (gamma rays, neutrons, and internal exposure to beta rays from tritiated water)

| | **Maximum likelihood estimate of cancer inductions per dose in rads or Gray relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 2.7 | 1.5 | 5.4 |
| Birth-Weaning | 4.7 | 3.4 | 8.7 |
| Weaning-60 days | 2.4 | 1.4 | 4.6 |

**Table 8.** Comparative Results for Male vs Female Animals for Mutagenic Chemicals—Analysis of Combined Data from Continuous and Discrete Dosing Experiments

Male Animals (9 compounds, 153 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ -day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** | **Arithmetic Mean .** |
|---|---|---|---|---|
| Fetal Period | 25 | 15.6 | 42 | 27 |
| Birth-Weaning | 57 | 38 | 90 | 59 |
| Weaning-60 days | 5.0 | 3.1 | 8.6 | 5.3 |

Female Animals (9 compounds, 153 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ -day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** | **Arithmetic Mean .** |
|---|---|---|---|---|
| Fetal Period | 1.77 | 1.05 | 2.9 | 1.83 |
| Birth-Weaning | 4.4 | 3.3 | 6.0 | 4.5 |
| Weaning-60 days | 0.82 | 0.50 | 1.29 | 0.85 |

**Table 9.** Comparative Results for Mice Vs Rats in Combined Discrete + Continuous Dosing Experiments

Mice—Discrete + Continuous Dosing for Chemicals Classified by EPA as Mutagenic (8 compounds, 265 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 6.5 | 4.2 | 9.9 |
| Birth-Weaning | 17.7 | 13.2 | 24 |
| Weaning-60 days | 2.3 | 1.53 | 3.3 |

Rats—Discrete + Continuous Dosing for Chemicals Classified by EPA as Mutagenic (4 compounds, 44 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 18.9 | 8.3 | 45 |
| Birth-Weaning | 21 | 11.7 | 38 |
| Weaning-60 days | 3.9 | 1.94 | 7.3 |

**Table 10.** Comparative Results for Discrete Dosing of Chemicals for Direct-Acting Nitrosoureas vs Other Mutagenic Carcinogens Thought to Require Metabolic Activation to DNA Reactive Compounds—Standard Breakdown of Life Stages

Direct-Acting--Ethylnitrosourea and Methylnitrosourea (108 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 11.6 | 5.4 | 25 |
| Birth-Weaning | 10.2 | 5.1 | 21 |
| Weaning-60 days | 2.7 | 1.37 | 5.6 |

Metabolically-Activated Mutagenic Carcinogens (Benzo(a)pyrene, dethylnitrosamine, dimethylbenzanthracene, and urethane, 166 tumor incidence observations in animal groups):

Direct-Acting--Ethylnitrosourea and Methylnitrosourea (108 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 0.21 | 0.01 | 0.90 |
| Birth-Weaning | 15.0 | 8.4 | 33 |
| Weaning-60 days | 1.24 | 0.76 | 2.3 |

**Table 11.** Comparative Results for Discrete Dosing of Chemicals for Direct-Acting Nitrosoureas vs Other Mutagenic Carcinogens Thought to Require Metabolic Activation to DNA Reactive Compounds—Expanded Breakdown of Ages

Direct-Acting--Ethylnitrosourea and Methylnitrosourea (108 tumor incidence observations):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 4.4 | 2.0 | 12.4 |
| Day 1 | 6.2 | 3.6 | 18.0 |
| Other Birth-Weaning (except 1 or 21 days) | 3.7 | 1.8 | 10.0 |
| Day 21 | 2.2 | 1.44 | 4.9 |
| >21 Weaning-60 days | 0.92 | 0.38 | 2.7 |

Metabolically-Activated Mutagenic Carcinogens (Benzo(a)pyrene, diethylnitrosamine, dimethylbenzanthracene, and urethane, 166 tumor incidence observations in animal groups):

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 0.13 | 0.01 | 0.52 |
| Day 1 | 17.3 | 10.0 | 36 |
| Other Birth-Weaning (except 1 or 21 days) | 10.7 | 6.2 | 22 |
| Day 21 | 1.9 | 1.06 | 3.7 |
| >21 Weaning-60 days | 0.87 | 0.54 | 1.52 |

**Table 12.** Effect of Separate Estimation of Relative Sensitivity in the Birth-Weaning Period for Lactational Exposures vs Direct Administration—Combined Continuous and Discrete Dosing Data for Mutagenic Carcinogens

(9 mutagenic carcinogens, 317 tumor incidence observations:

| | **Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ –day) relative to comparably dosed adults** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 6.0 | 5.5 | 8.8 |
| Birth-Weaning Direct | 11.6 | 8.5 | 16.1 |
| Birth-Weaning Lactational | 21.4 | 15.3 | 30 |
| Weaning-60 days | 1.70 | 0.77 | 2.4 |

**Table 13.** Relative Sensitivity for Radiation-Related Carcinogenesis Indicated by an Expanded Breakdown of Adult Age Groups

All Ionizing Radiation Dosing Experiments (based on a total of 138 group tumor incidence observations for 4 radiation types):

| | **Maximum likelihood estimate of cancer inductions per rad or Gray relative to young adults (90-105 days)** | **95% LCL** | **95% UCL** |
|---|---|---|---|
| Fetal Period | 2.1 | 1.3 | 3.4 |
| Birth-Weaning | 3.1 | 2.2 | 4.8 |
| Weaning-60 days | 1.5 | 1.1 | 2.1 |
| 6-12 months | 0.32 | 0.00 | 0.69 |
| Elderly (19-21 months) | 0.36 | 0.19 | 0.60 |

## Figure Legends

**Figure 1.** Females—Lognormal Plots of Likelihood-Based Uncertainty Distributions for Cancer Transformations Per Daily Dose for Various Life Stages for Mutagenic Chemicals (Relative to Comparable Exposures of Adults) for Combined Discrete and Continuous Dosing Experiments

**Figure 2.** Males—Lognormal Plots of Likelihood-Based Uncertainty Distributions for Cancer Transformations Per Daily Dose for Various Life Stages for Mutagenic Chemicals (Relative to Comparable Exposures of Adults) for Combined Discrete and Continuous Dosing Experiments

**Figure 1**

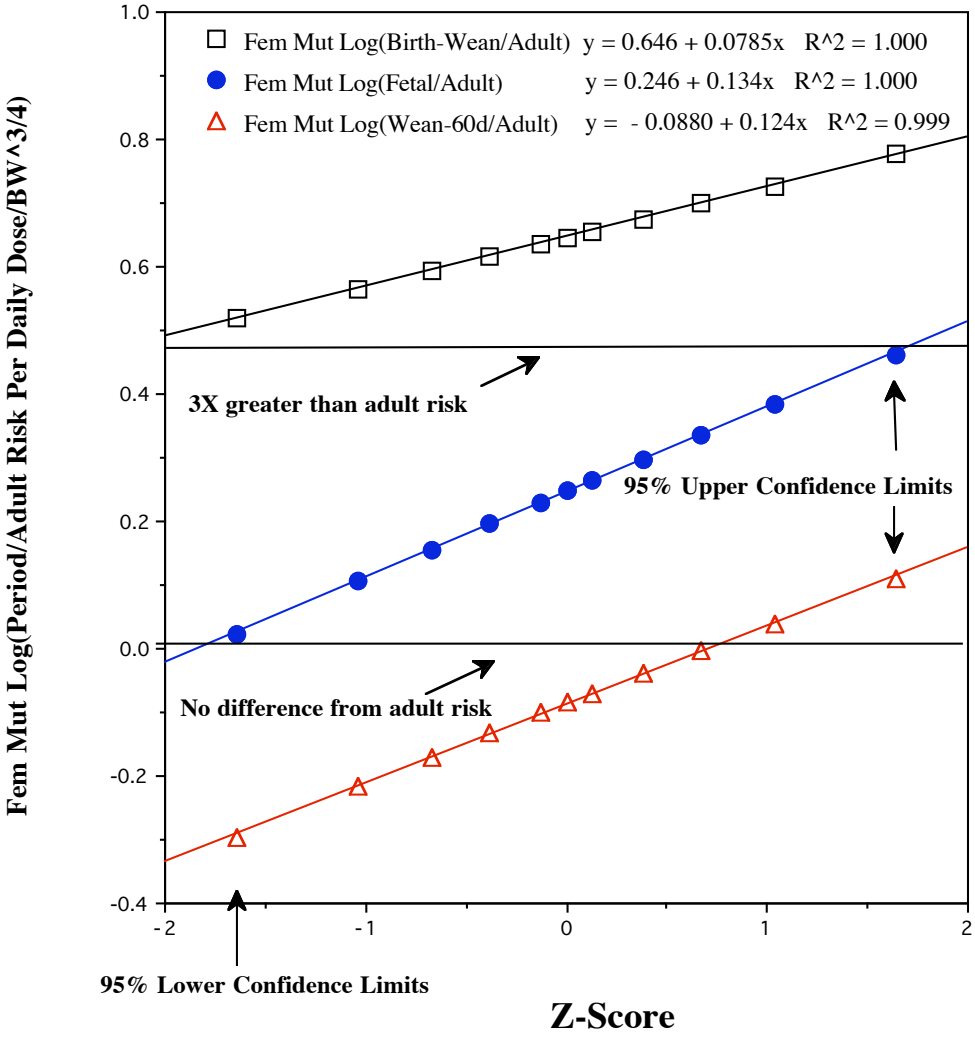
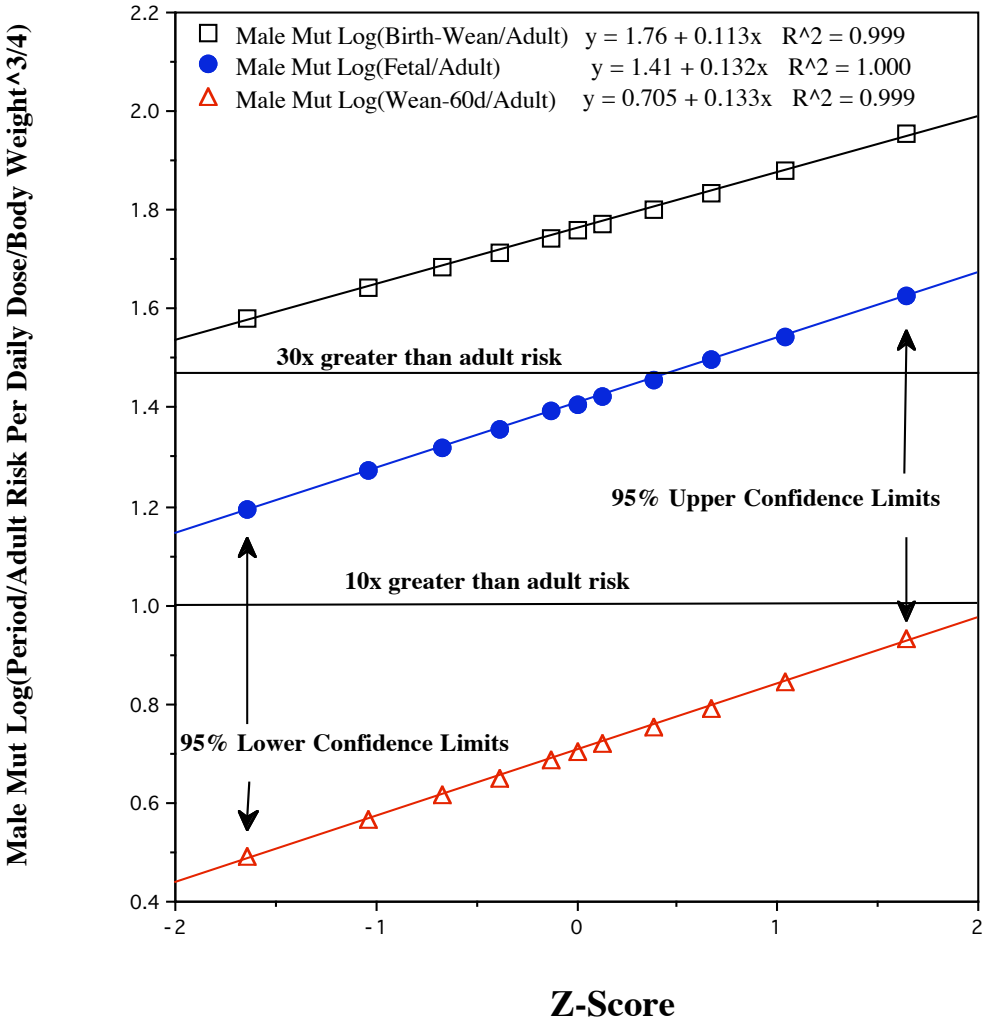

Fem Mut Log(Birth-Wean/Adult) y = 0.646 + 0.0785x R^2 = 1.000
Fem Mut Log(Fetal/Adult) y = 0.246 + 0.134x R^2 = 1.000
Fem Mut Log(Wean-60d/Adult) y = - 0.0880 + 0.124x R^2 = 0.999
3X greater than adult risk
95% Upper Confidence Limits
No difference from adult risk
95% Lower Confidence Limits
Fem Mut Log(Period/Adult Risk Per Daily Dose/BW^3/4)
Z-Score
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-2
-1
0
1
2

**Figure 2**


Male Mut Log(Birth-Wean/Adult) y = 1.76 + 0.113x R^2 = 0.999
Male Mut Log(Fetal/Adult) y = 1.41 + 0.132x R^2 = 1.000
Male Mut Log(Wean-60d/Adult) y = 0.705 + 0.133x R^2 = 0.999
30x greater than adult risk
95% Upper Confidence Limits
10x greater than adult risk
95% Lower Confidence Limits
Male Mut Log(Period/Adult Risk Per Daily Dose/Body Weight^3/4)
Z-Score
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
-2
-1
0
1
2