

Appendix to Barton et al., Assessing Susceptibility from Early-Life Exposure to Carcinogens

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Discussion of potential influence of prior on the log ratio of juvenile to adult cancer potency

The prior for the log ratio of juvenile to adult cancer potency has some influence over the posterior estimates for the ratio of juvenile to adult potency. The magnitude of that influence depends on the amount of support in the data for different values of the log ratio. The prior also effectively downweights extremely large or small values for the juvenile to adult potency ratio. Figure A1 illustrates this with some examples. Figure A1-A shows a situation in which there is strong support in the data for a specific ratio, as indicated by the likelihood function, which is centered around a particular value. For this example, using a broader prior (Figure A1-B) has little effect on the position and shape of the posterior. In both figures, the posterior pretty much overlays the likelihood function, indicating that the data dominate the estimate for the log-ratio in this case.

The second row of figures shows an example in which the maximum likelihood estimate for the log-ratio is infinite – the likelihood function increases indefinitely as the log-ratio increases (this is the case when there are tumors from juvenile exposure and no tumors from adult exposures). In this case, when the standard deviation of the prior is smaller (Figure A1-C), the posterior distribution of the log-ratio is drawn to slightly smaller values than when the standard deviation for the prior distribution is larger (Figure A1-D), as the prior has more influence on the posterior in this case. However, for both priors, the posterior distribution has a single mode at a finite value, because the prior downweights very large values.

Finally, an example is shown in Figures A1-E and A1-F for a repeated exposure study in

which the data are consistent with a juvenile to adult ratio of 0 (or a log-ratio of $-\infty$). This is evident because the likelihood function does not drop all the way to 0 on the left hand side, but levels off at a positive value. In this case, the prior forces the left hand curve of the posterior to drop to 0, but in the prior with the greater standard deviation (Figure A1-F) this happens farther to the left (towards smaller values) than it does with the prior with the smaller standard deviation (Figure A1-E). As a result, the posterior mean for the log-ratio is somewhat smaller when the prior has a larger standard deviation, and the variance is substantially greater. One consequence of this is that weighted geometric means will likely be larger when the prior has a greater standard deviation, because the variance of estimates of low ratios will be greater, and thus their weight relative to the larger ratios will be smaller.

Discussion of influence of experimental design on ability to ascertain juvenile susceptibility

The ability to estimate with any accuracy the juvenile to adult cancer potency ratio depends on the experimental design used. The lifetime design has less ability to distinguish increased susceptibility from early-life exposure than the other types of designs as suggested by the greater influence of the value of the prior distribution selected for λ (natural log of juvenile to adult cancer potency ratio) with this study design as compared to the juvenile versus adult design. Consider two different experimental designs. In the first design, the “lifetime” design, a group of animals are exposed starting as juveniles, and exposure continues through adulthood. A second group is exposed only in adulthood, and the juvenile:adult ratio results from a comparison of tumor incidences

in the two groups. In the second design, the “repeated” design, one group of animals is exposed only during the juvenile period, and is then followed through adulthood to assess tumor incidence, and a second group of animals is exposed only through adulthood. The lifetime design is a particularly insensitive design for estimating the juvenile:adult ratio. The following example demonstrates the magnitude of the problem: Suppose the risk per day of exposure of a chemical is ten fold greater in the juvenile period as in the adult period, and animals exposed through adulthood at a particular dose level have an extra risk of 60% for having at least one tumor, while 1% of control animals have tumors. The adult exposure period is 94 weeks, while the juvenile exposure period is 4 weeks. Thus, in the lifetime design, the group of animals exposed as juveniles will receive a total of 98 weeks of exposure, (4 in juvenile and 94 in adult), while those receiving the adult-only exposure receives 94 weeks of exposure. In the repeated design, animals exposed as juveniles receive only 4 weeks of exposure, while the adults receive 94 weeks (same as in the lifetime design). Each group starts with 50 animals. Under these assumptions, using equations (1) and (2) from Methods, Supplementary Table S8 shows the expected number of animals with tumors in the three treatment groups (control, juvenile-exposed, adult-exposed) in the two designs.

In the “Lifetime” design, only six more juvenile-exposed animals have tumors than in the adult-exposed group, whereas in the “repeated” design, 16 juvenile-exposed animals have tumors. The data in the lifetime design are consistent with the hypothesis of no tumors being induced during the juvenile period (i.e. the ratios 36/50 and 30/50 are not statistically significantly different and would be considered no risk from juvenile

exposure). However, the real response is a 10 times greater risk from early-life exposure. The difference between the results from the two different study designs is due to using the one-hit model: each additional week of a long exposure contributes less than the previous week to the total number of animals with tumors. Even if the one-hit model is not correct, chronic exposure probably results in a non-statistically-significant increase for the lifetime exposure including juveniles as compared with only adult exposure.]

Illustration of equivalency of comparing potencies and doses

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

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

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

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

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

equal:

:

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

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

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

Ionizing Radiation

Although there are recognized differences in toxicokinetics and toxicodynamics between radiation and mutagenic chemicals, the human radiation 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. The most relevant information comes from the A-bomb survivor reports 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). This paper presents relevant results from the UNSCEAR report for the excess relative risk (ERR) for early-life vs. later in life

exposures. The ERR is the increased cancer rate relative to an unexposed population; an ERR of 1 corresponds to a doubling of the cancer rate.

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).

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, with the exception of thyroid tumors, which had greater numbers and allowed more age groups. Excess risk values presented are based on Japanese baselines.

A statistically significant excess cancer mortality associated with radiation has been found among the atomic bomb survivors for the following types of cancer: esophagus, stomach, colon, liver, lung, bone and connective tissue, skin, breast, urinary tract, leukemia., and thyroid tumors (Supplementary Tables 9 and 10). Most sites show greater risks in the younger than the older ages.

Supplementary Table 7 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.

References

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Figure Legends

Figure A1: Three examples illustrating the influence that the prior for the log juvenile to adult ratio has over the posterior for that parameter. In each panel, the gray curve represents the prior: Gaussian with mean 0 and standard deviation 3 for the left three panels (A, C, E), and either 6 [top two right panels (B, D)] or 9 [bottom right panel (F)]. The dotted curve represents the profile likelihood for the log ratio (that is, for each value of the log-ratio, the other model parameters were estimated via maximum likelihood, and the resulting likelihood value plotted). The solid curve is the posterior distribution for the log-ratio. Note that the x-axis is labeled in terms of ratio, not log-ratio. The x-axis value corresponding to the peak of the profile likelihood curve would be the maximum likelihood estimate for log-ratio.

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