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Re: review chromium-6 document draft dated January 2008

REVIEW:

I spent considerable time reviewing the document and the underlying assumptions as well as equations.

Overall, the document is very accurate in regards to scientific presentation and historical data, as well as equations utilized throughout the text.

The salient points of my review will therefore focus on only several areas that directly impact the recommended target value for chromium-6 in drinking water.

The first is that only selected data from the NTP studies is used (reference 2007b) to derive the target value. By selected data, I mean only one subset of data from a single study out of the entire NTP database is deemed relevant. This is the one study describing the combined incidence of adenomas and carcinomas in male B6C3F1 mice. The data from all other rodent studies involving chromium-6 ingestion is not utilized.

The second is the equation on page 97.

This is where the 0.06 ppb threshold is derived, from oral intake and "shower inhalation". Contribution from "shower inhalation" is negligible in comparison to oral (drinking intake), so one needs to focus primarily on the oral intake value and its derivation.

The third is the oral intake value for the LED10 on page 80 of 1.1 mg/kg-day(mouse). It is this value that drives the 0.06 ppb limit.

The questions then are:

Is it reasonable to use rodent data versus human?
Is the use of a limited or selected subset of rodent data valid?
Should an LED10 be used (versus an ED10)?
If so, is the LED10 derived appropriately?

The answer to the first question appears to be yes, based on the paucity and poor quality of human data.

The answer to the next three questions, however, appears to be "no" as their use and derivation appear to conflict directly with guidelines in the EPA publication 630/P-03/001B, Guidelines for Carcinogen Risk Assessment (March 2005).

Note: underlined text is a direct quote from this EPA document (page 3-33).

Depending on the supporting data and modeling approach, a slope factor can have a mix of traits that tend to either estimate, overestimate, or underestimate risk.

Some examples of traits that tend to overestimate risk include the following.
• The slope factor is derived from data on a highly susceptible animal strain.
• Linear extrapolation is used as a default and extends over several orders of magnitude.
• The largest of several slope factors is chosen.

Based on the above, it appears that this review used all three traits.

#1) The mouse is a susceptible strain (vs even another rodent strain such as a rat that was concurrently tested by the NTP). Why was the data for the rat excluded? Furthermore, the results from this one single mouse experiment, used to derive all factors in the text, appears to be have a higher tumor incidence rate than even other mouse studies performed by the NTP. In essence, the data used represents the most sensitive gender of the most sensitive study of the most sensitive strain, and all other NTP results are discarded.

#2) Linear extrapolation was used to derive an LED10 at 95% confidence interval (not an ED10).

#3) The largest of several slope factors was chosen as the sole parameter to derive the slope (rather than the mean of all experiments).

The latter two are critical as #2 vastly overestimates true risk even for the model used. Regarding #3, not only was the largest slope factor, but this factor is vastly higher than other slope factors for other rodent studies done by the NTP (perhaps by over a magnitude).

Overall, it appears that the summation of the events for what has occurred with the analysis is depicted by the FDA in Figure 3.1 (page 3-35). For those without access to the document and figure, a similar graph is attached at the end of this document (on page 5). It appears that the slope may have been vastly overestimated (upper green line in the EPA Figure 3.1). Given the lack of details as to how tables 9 and 10 were generated, it is difficult to determine the absolute variation or magnitude of increase that occurred, but it is probably substantial

Regarding how the data should be handled, and the slope factor derived, can also be found in the EPA publication 630/P-03/001B, Guidelines for Carcinogen Risk Assessment (March 2005).

Some examples of traits that inherently neither overestimate nor underestimate risk include the following.

• Several slope factors for the same tumor are averaged or a slope factor is derived from pooled data from several studies.

Basically, what needs to be done is the slope response curves need to be derived from other published other rodent studies. As earlier publications in the literature were not as rigorous in technical components, the studies can be limited to those reported by the NTP in their 2007 publications (references NTP 2007a & NTP2007b in the review document).

There is no need to review data published many years ago.

However, all the NTP2007 studies need to be analyzed and slope factors derived for each study by an accepted methodology. Then the mean median (preferably) slope factor is to be utilized for subsequent calculations. NOT the 95% confidence interval.

Note that the use of a mean or median ED10 (not a 95% confidence interval) is also described in the EPA document.

Furthermore, the average slope factor (not the upper and lower limits) is to be used to generate the slope factors. Thus, risk assessors should calculate, to the extent practicable, and present the central estimate and the corresponding upper and lower statistical bounds (such as confidence limits) to inform decision makers.

In summary, guidelines in the cited EPA document should be followed when deriving the ED10 data.

The ED10 used to generate a human equivalent dose) should be calculated by using all available rodent data considered reliable (e.g. all data in NTP2007B report). Do not restrict the data to one gender from one experiment from one species that is highly susceptible compared to other rodent species (or even other strains of the species).

The ED10 should be calculated in such a manner that what is depicted in Figure 3-1 is NOT occurring.

Then the mean value for all studies determined and this value is used to derive the human equivalent dose, which is then used to generate the desired standard.

The entire derivation, all calculated ED10 values, should be available for review as an appendix. This means that for each rodent study that is presented in the 2007a & 2007b NTP publications, that a table is generated and presented similar to tables 9 & 10 on pages 79 and 80 of this document. Then a final table generated that summarize all mean ED10 (not the LED10) values and a mean for all these values generated.

This final value (mg/kg-day) should then be used to generate the human equivalent dose and this value then used to generate the slope factor.

Sincerely,

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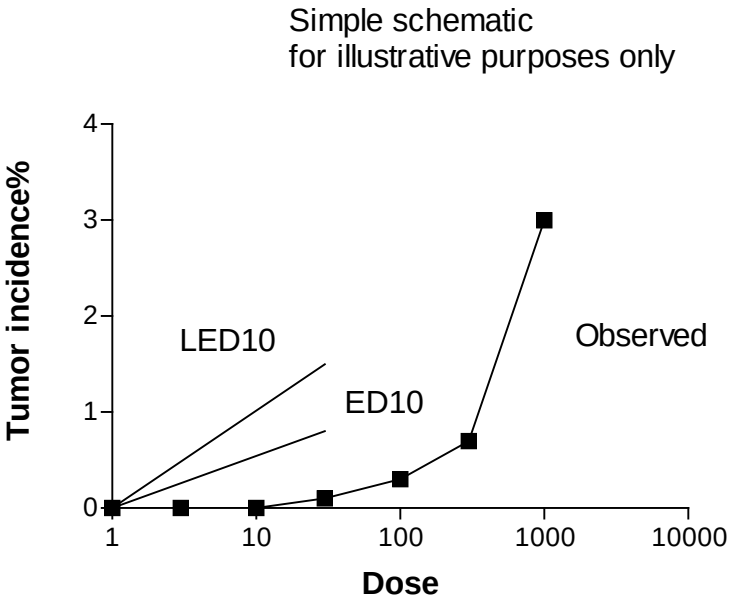
Simple schematic
for illustrative purposes only
Tumor incidence%
4
3
2
1
0
LED10
ED10
Observed
1
10
100
1000
10000
Dose