

Dear Jon

Thanks for giving me the opportunity to comment. I attach a Word file with my thoughts, that you can share with the Committee. In relation to your question in the previous E-Mail

"One question which was previously raised was that TTC was ok for most genotoxic carcinogens, could this be extrapolated to in vivo mutagens for which no carc studies were available?"

The TTC is derived from data on both genotoxic and non-genotoxic carcinogens. Because linear low-dose extrapolation was used, the animal data were treated as if all the compounds acted via a direct genotoxic and mutagenic mode of action. Therefore it really is "designed" to be used in exactly the scenario you question, since if you have chemical-specific carcinogenicity data you should use those data with an MOE approach or whatever.

The analyses in the Kroes et al 2004 paper (which is where the 0.15 value comes from) used data for compounds with structural alerts predictive of mutagenicity and carcinogenicity in this alert analysis. Therefore the 0.15 should not be confused with the 1.5 - it was NOT a case of throwing an extra safety factor at the general TTC from the Gold et al database, but derived from a specific analysis of the data on structural alerts.

With best wishes

Andy  
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-----Original Message-----

From: Jon.Battershill@dh.gsi.gov.uk [mailto:Jon.Battershill@dh.gsi.gov.uk]

Sent: 31 January 2011 14:15

To: Jon.Battershill@dh.gsi.gov.uk

Cc: Renwick A.G.; Karin Burnett

Subject: RE: Draft COM paper on impurities

(See attached file: impuritiesguidance dr2forconsultation.doc)

**Comments by AG Renwick, OBE, Emeritus Professor, Faculty of Medicine ,  
University of Southampton**

My thanks to the Committee for giving me the opportunity to comment on the Guidance Statement and supporting papers

**1. Guidance Statement : Strategy for genotoxicity testing and mutagenic hazard assessment of impurities - MUT/11/01**

I think it would be useful if it was explained that the risk characterisation estimates in the TTC approach are likely to be highly conservative. They assume that there is no threshold in the dose-response relationship and are derived by linear extrapolation from the TD50 in the rodent bioassay – a process that historically the COC has not used because of the model dependence of low-dose extrapolation, with linear extrapolation among the most conservative.

Paragraph 7. “*Kroes derived a decision tree approach for genotoxins for identifying genotoxins where the life-time cancer risk exceeded  $10^{-6}$  at an intake of  $1.5 \mu\text{g}/\text{day}$ . It was noted that this cancer risk was exceeded by 5% of aromatic amines, aromatic nitrates, azo compounds, benzidine derivatives, heavy metal containing compounds, highly chlorinated compounds (excluding dioxins), compounds with miscellaneous Ashby alerts, nitrofuryl-compounds, compounds with strained rings and vinyl containing compounds.*” At  $1.5\mu\text{g}/\text{day}$  a  $10^{-6}$  risk is exceeded by about half of compounds with these structural alerts. The percentage drops to 5-10% of chemicals with these alerts if intake is  $0.15\mu\text{g}/\text{day}$  or less. For any unstudied compound, there would be an approximately 90-95% probability that the cancer risk would be  $10^{-6}$  or less if intake were  $0.15\mu\text{g}/\text{day}$  or less. Therefore the value on line two above should be  $0.15\mu\text{g}/\text{day}$  and not  $1.5\mu\text{g}/\text{day}$ .

Paragraph 8. It could be helpful to summarise the rationale used by Muller et al along the lines of “An exposure of  $1.5\mu\text{g}/\text{day}$  for 12 months or more would give a theoretical risk of  $10^{-5}$ ; this was considered to be acceptable because of the controlled exposure and direct benefit to the exposed individual.”

Paragraphs 14+15. A problem is that this is really the sensitivity for hazard identification and not risk characterisation. It would be useful to point out at this stage that such approaches do not take into account the extent of human exposure, but that the risks arising from the presence of 5% of a genotoxic and carcinogenic impurity would be proportional to human exposure to the compound containing the impurity (see below).

**2. GUIDANCE ON A STRATEGY FOR GENOTOXICITY TESTING AND MUTAGENIC HAZARD ASSESSMENT OF IMPURITIES IN CHEMICAL SUBSTANCES Annex 2 to MUT/11/01**

Paragraph 1. Add the word *assessment* after *hazard*

Paragraph 2. Typo – *using*

Paragraph 3. “...latter situation is the assessment *by regulatory agencies* of the equivalence of a chemical substance sourced from different manufacturers. [Sorry I have slipped back into my old COC/COT habits].

**3. Figure 1: Strategy for the Assessment of impurities in test substances**

Box 1.

*[Impurities giving rise to exposures below TTC are considered to present negligible risk]*

I think that this would be more accurate (but less understandable) if written as

*[There is a high probability of negligible carcinogenic risk for impurities giving rise to exposures below the TTC]*

Box 2.

I am struggling with the logic of points 2 and 3 for compounds where the predicted intake of the impurity is >TTC – but can arise from an exposure to the chemical in the 1µg/day range or >100mg/day. The real cut off where a 5% level of impurity would not be significant would be 3µg/day of the parent chemical. For me it would be more logical if points 2 and 3 were

*2. For impurities present at  $\geq 50$  µg/mg undertake studies with test material using COM guidance Stage 1 (Ames and in vitro micronucleus tests), providing that the exposure to the chemical is 3µg/day or less.*

*3. For impurities present at  $\geq 50$  µg/mg, where the exposure to the chemical is 3µg/day or less, and for impurities present at  $< 50$  µg/mg consider isolating and testing impurities separately or reach pragmatic conclusions based on QSAR.*

It should be explained somewhere in the guidance that this is a risk-based approach, not an analytical methodology limit, and that it would require more work on impurities present at lower concentrations; but that this would only occur when the exposure of the impurity exceeds the TTC value and the exposure to the chemical is relatively high (>3µg/day).

**4. Figure 2: Strategy for the genotoxicity assessment of equivalence between two test substances**

Looks good – no comments.