

Para 4 (page 3)

Line 4, typo 'at that these' times. *Should be 'at those' times?*

Para 6 (page 4)

'... a scientifically valid testing strategy comprising those methods which are believed to be most informative and (when possible) are well validated'

Comment: It would be helpful if COM could be specific here. Does 'most informative' mean (1) most mechanistically informative (2) informs most on genotoxic risk, or (3) informs most on risk of carcinogenicity?

Para 8 (page 5)

'However the detection of such effects does not itself provide direct evidence of inherited mutations'

Comment: It is not clear if this sentence refers to just UDS and SCE in the preceding line, or also to the preceding sentence, starting on line 23.

Para 21 (page 11),

'...overall the available data suggest that mammalian cell assays for mutagenicity including the Mouse Lymphoma Assay do not perform well at discriminating between rodent carcinogens and non-carcinogens'

And

Para 40 (line 19)

'...specificity is considered to be poor for the mammalian cell assays'

Comments.

- a. These sections refer to **Annex 1**, which is scrambled and needs reformatting. A reformatted version of the scrambled section is attached.*
- b. We know from the glossary that COM uses the words 'sensitivity' and 'specificity' with reference to the identification of rodent carcinogens or in vivo genotoxins. There are however inconsistencies between the glossary the headers used in para 1, para 2 and para 3 of Annex 1:
 - i. The SAR table header defines sensitivity, as identification of mutagens or rodent carcinogens;*
 - ii. The Screening test table header defines sensitivity as identification of mutagens (this is the only place it is used in this way);*
 - iii. The genotoxicity test table simply has the header 'sensitivity', with no definition*
 - iv. This inconsistency and scrambling is potentially misleading, because it confounds comparisons between tests in the different tables.**
- c. Unscrambled, the reader would discover that the GADD45a mammalian cell assay, is a significant exception to the statements in Paras 21 and 40, in having a higher specificity compared to the other mammalian cell assay, and comparable sensitivity in the majority of studies*

Para 42 (line 13)

Should read 'Threshold MoGAs can be considered generally...' (extra 'be')

Para 80 (line 1)

*Should read "The *in vivo* Comet assay detects..." (the word 'assay' missing)*

Figure 2, Stage 0

Overall the committee agreed that the GADD45a-GFP genotoxicity assay was suitable for screening (Stage 0). Perhaps such tests should be put in Stage zero in Figure 2?