

**COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**

**DRAFT DISCUSSION PAPER: GENOTOXICITY OF PARA-CHLOROANILINE.**

**Referral**

1. The Advisory Committee on Pesticides have asked for a COM view on the available genotoxicity data on para-chloroaniline (4-chloroaniline, 4-CA).

**Introduction**

2. Information on the background to the referral, introduction to the toxicology of 4 CA, and an overview of retrieved genotoxicity data on 4CA were given in MUT/09/13.

**Additional information retrieved.**

*In vitro*

Studies in mammalian cells

3. Ishidate published brief details of CA assay undertaken in CHL cells. A positive result was reported at 400 µg/ml in the presence of exogenous metabolic activation ( details of inducing agent not provided) using a 3h exposure period and a 21 h recovery period.(Ishidate et al., 1988)
4. In a subsequent publication, the same research group published details of a validation study of 66 chemicals in the *in vitro* micronucleus test in CHL cells using continuous treatment for 24, 48, 72h in the absence of S-9 and 6h exposure (plus 18h, 42h, 66h recovery)in the presence of S-9 (from Phenobarbital/5,6-benzoflavone pretreated male Sprague-Dawley rats. No evidence for a dose related increase in MN induction was reported either in the absence or presence of exogenous metabolic activation was reported. The authors suggest that the original positive result seen for CAs in CHL cell + S-9 needed to be repeated. A copy of this paper has been appended for information as Annex 1. (Matsushima et al., 1999)
5. Do these data alter the COM conclusions with regard to *in vitro* genotoxicity of 4CA?

## *In-vivo*

### Studies in Rodents

6. Para 27 of draft MUT/09/13 refers to a negative BMMN assay in male and female CFLP mice dosed by gavage (gum traganth). The Secretariat obtained a copy of the source reference reported in the IPCS CICAD document on 4 CA. Very few additional details of the study were retrieved as shown in the appended abstract. The secretariat has attempted to source the reference cited in the BUA 1995 report (TLL, 1986/87) but no additional information was available at the time of writing.
7. Abstracts of a further MN assay in NMRI mice dosed by gavage (vehicle not given in abstract) have been identified via the EPA internet site, although very limited data are publicly available. The study report is owned by Hoechst-Celanese. The secretariat have attempted to obtain more information from Celanese USA.  
<http://www.epa.gov/oppt/chemtest/pubs/aniline2.pdf> and  
<http://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearchView/8548709ACC2165E185256930004DEB38>
8. These two negative studies use gavage dosing of 4CA at maximum applied dose of 180 mg/kg or 200 mg/kg bw. Bone marrow cells were harvested at 24h, 48h, 72h. Mortality of one animal was reported at 200 mg/kg bw.
9. A positive result was reported in the study undertaken for the NTP programme at a higher dose of 300 mg/kg for 3 consecutive days dosed orally to B6C3F1 mice with one sampling time of 24h post last dose.
10. All relevant information from these *in-vivo* studies is appended as Annex 2.
11. Do these data alter the COM conclusions with regard to *in vivo* genotoxicity of 4CA?

**Secretariat October 2009**

### **References**

Ishidate M, Harnois M, Sofuni T (A comparative analysis of data on the clastogenicity of 951 chemical substances tested in mammalian cell cultures. Mutation Research 195:151-213.1988).

Matsushima T, Hayashi M, Matsuoka A, Ishidate MJ, Miura K, Shimizu H, Suzuki Y, Morimoto K, Ogura H, Mure K, Koshi K, Sofuni T (Validation study of the *in vitro* micronucleus test in a Chinese hamster lung cell line (CHL/IU). *Mutagenesis* 14:569-580.1999).