Comment on the Draft NTP Technical Report TR-582 on Vinylidene Chloride

Genotoxicity Assessment

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Observation

- Discussion and conclusions, page 121

  "*The results from a variety of genetic toxicology studies, including approaches such as bacterial mutagenicity assays, yeast test systems, mammalian cell lines, and in vivo tests indicate that vinylidene chloride has mutagenic, clastogenic, and aneugenic properties.*"

- ***This statement is not in line with***
  - ***the genotoxicity data in the report***
  - ***the genotoxicity data in the public domain***

Genotoxicity data in the report

- *In vitro*
  - **Negative** bacterial mutagenicity assay in Salmonella *typhimurium (Mortelmans et al. 1986)*
  - **Positive** in vitro mammalian mutagenicity assay in L5178Y (McGregor et al. 1991)
- *In vivo*
  - **Negative** sex-linked recessive lethal mutation assay in Drosophila *melanogaster (Foureman et al. 1994)*
  - **Negative** micronucleus assay in mouse peripheral blood. (MacGregor et al. 1990)
- Supporting information
  - Reitz et al. 1980 reporting on DNA-adduct formation **but**
    - Reitz et al conclude in their publication: *"…the failure to demonstrate significant genetic effects with tumorigenic doses of vinylidene chloride suggested that epigenetic mechanisms might be operating*".
    - DNA-adducts should be primarily interpreted as markers of exposure (Swenberg et al. 2008)

Other assessments

- CICAD report (2003), SCOEL (2007)
  - "*1,1-DCE causes gene mutations in microorganisms in the presence of an exogenous activation system. Although most tests with mammalian cells show no evidence of genetic toxicity, the test battery is incomplete because it lacks a test for chromosomal damage in the mouse lymphoma system*."
  - The positive study by McGregor et al. is cited, but apparently considered not sufficient to impact the overall conclusion.
- REACH dossier (2009)
  - "…*Several in vitro assays with 1,1-dichloroethene showed genotoxic activity, especially in the presence of exogenous metabolic activation. On the other hand, no genotoxicity was observed for 1,1-dichloroethene in in vivo testing systems.* "
  - 3 **negative** in vivo key study results are provided.

Conclusions

- The current report is not aligned with the experimental data;
  - Genotoxicity findings are “equivocal” at best
  - Possibility of « non-genotoxic mode of action » should be represented more prominently.
    - e.g. genomics data on vinylidene chloride induced mesotheliomas, as provided in the draft TR-582 report, suggests involvement of inflammatory pathways
- Further research on the mode of action of vinylidene chloride is required
  - Utility of the studies described in TR-582 will be of limited utility due to absence of a true NOAEL (see also contribution of Nicholas Ball, Dow Chemical Company)

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