Acrylamide: focus on reproductive and developmental effects

Comments by:

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General comments

- The opinion is overall sound and thoughtful, and represents a step forward with regard to the protection of consumers from exposure to process contaminants.
- However, improvements are suggested concerning the assessment of reproductive and developmental effects, since these might be relevant to the risk characterization for specific, potentially vulnerable lifestages (pregnancy, peripubertal).
- Overall the reproductive and developmental sections should focus on the description and discussion of more recent studies (i.e., after the JECFA assessment in 2005) that provide more reliable and accurate information

For older studies, a short, general description might be sufficient; for instance, it is unclear why (Zenick et al., 1986) is currently reported at lines 5240-2 amidst studies published in 2012-13

7.3.5.1. Reproductive toxicity

- Some evidence identifies the immature animals as more sensitive to AA testicular effects but NOT to neurotoxic effects compared to adults (Takahashi et al., 2011, also Koyama et al. 2011a, in the genotoxicity section).
- Lack of a up-to-date extended one-generation or two-generation study to reliably assess effects on pre- and post-natal reproductive development.
- The study by Tyl et al. (2000, reported in 7.3.5.2. “developmental toxicity”) apparently does not meet current standards (only gross, insensitive endpoints, e.g., number of implantations and live pups)
- Glycidamide (GA) study (NTP, 2013, draft report): it is not clear the correspondance between a *GA dose level* and the AA intake. Relevance of this data for the characterization of reproductive hazards?

Reproductive toxicity: dose-response assessment (NOAEL)

Dose-related degeneration of the testicular germinal epithelium: clearly adverse effect, (NTP 2012, 13-week study on diet, 2-year study drinking water)

Such lesion was NOT observed both in old (Johnson et al., 1986; Friedman et al., 1995) and recent (NTP, Takami, 2012, 2013) 2-year studies.

However testicular lesions in chronic studies can easily be obscured by aging-related changes

This does not occur in repeated-dose toxicity studies using young adult *or* immature animals.

Proposal: to derive a NOAEL for *morphological effects on male reproductive organs* and use in hazard characterization

Reproductive toxicity: dose-response assessment (BMD10)

Several recent reproductive studies investigate the same dose range and showed effects: no attempt to calculate a BMD10 has been performed

It is stated that “The data on effects of AA on male reproduction were not suitable for dose-response modelling” but no clear explanation is provided about why deriving a BMD10 is unfeasible.

Could a BMD10 for reproductive effects be considered ?

7.3.5.2. Developmental toxicity

- The study of Ogawa et al. (2012) showed irreversible structural change in a brain region (…sustained increase in hilar mature neurons): this should be considered a relevant and plausible adverse effect (remember that AA is a recognized neurotoxicant in adult animals)
- Structural changes are considere *relevant* for risk assessment of AA: in *7.5.2. Dose-response assessment*, a *structural* change (peripheral axonal degeneration) is used to establish the BMD10 for non-cancer endpoints (current raft)

Proposal: to derive a NOAEL for *effects on morphological development of brain* and use it in hazard characterization

7.3.6.5. Endocrine/reproductive toxicity

- These endpoints are included in the «Mechanisms and Modes of Actions» section since they are related to *mechanims* (endocrine-related but also non-endocrine) of reproductive/developmental effects

BUT

- What is the rationale of the sequence by which studies are presented?
- A more understandable sequence would help the reader to agree with the conclusion of the draft opinion.

Maybe, this section can be included together with «Reproductive and Revelopment toxicity»???

Additional recommendations

- Up-to-date extended one generation or 2-generation studies to assess AA effects on reproductive development and maturation
- Clarification on the relevance of endocrine-related mechanisms for reproductive/developmental effects and for *tumour development* in specific target tissues (e.g. thyroid, ovary)
- Developmental neurotoxicity: clarification on the link between early molecular/structural changes and adverse outcomes in later life

These additional data would support AA risk assessment for ***potentially vulnerable as well as more exposed*** lifestages, like infants, toddlers and children


THANK YOU!
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