European Food Safety Authority

DISCUSSION GROUP 3

Mechanism of carcinogenicity

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1. Review the recent evidence for the mutagenicity and genotoxicity of acrylamide and glycidamide

Recent in vivo evidence includes:

a) GA is formed by CYP2E1 from AA (not in CYP2E1 ko)

Genotox endpoints:
DNA damage (Comet assay), adducts, micronuclei, germ cell mutations, dominant lethality.

b) Mutations in vivo: hprt, cII (AA+GA), $TK^{+/-}$(GA)

c) Cannot identify thresholds for DNA binding:
(lowest dose from control feed ~1 µg/kg*d, corresponding to $1/10^8$ DNA adducts)

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1. Review the recent evidence for the mutagenicity and genotoxicity of acrylamide and glycidamide, continued

GA and DNA adducts are distributed through the whole body.

Genotox alone does not explain the target sites for tumors.

Tumorigenicity of GA in neonates suggests increased sensitivity during early life exposure.

Human infants express CYP2E1 by the time of weaning and presumably form GA.

2. Review the recent evidences for the non-genotoxic mechanism of acrylamide (and glycidamide)

Proposals for the mode of action (MOA):

Mammary tumors
(disruption of hormonal status in aged female rats)

Testes
(related to Leydig cell tumors, prevalent in the male F344 rat)

Question if both are relevant to humans

Thyroid tumors: No plausible explanation.

CNS tumors are disputed
(new data will confirm or discount)

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2. Review the recent evidences for the non-genotoxic mechanism of acrylamide (and glycidamide), continued

Tumor spectrum im mice still incomplete but so far differing from the rat tumor sites.

No theories for the mouse tumors (liver, lung, Harderian gland)

No convincing evidence of non-genotoxic mechanisms (e.g. oxidative stress, cell proliferation, apoptosis) at relevant doses.

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2. Review the recent evidences for the non-genotoxic mechanism of acrylamide (and glycidamide), continued

Overall conclusion to this point.

Need for a systematic review of the MOA and human relevance for each tumor type.

Different mechanisms are possible for different tumor types in experimental animals.

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3. Weight the evidence as to whether AA acts via a non-genotoxic or genotoxic mechanism in contrast to its genotoxic metabolite.

The margin of exposure (MOE) at dietary levels are such that only genotoxic mechanisms are likely to be relevant.

We do not have evidence for non-genotoxic mechanisms at relevant doses.

Only in exceptional circumstances could you discount the relevance of a genotoxic MOA.

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4. Exploration of the consequences of changed conclusions about genotoxic versus non-genotoxic mechanism of carcinogenesis for human risk assessment.

No changes anticipated.

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Revised question:

How do we improve the risk assessment?

New results, e.g. tumor dose-response data and mechanistic data should increase confidence leading to improved Quantitative Risk Assessment (QRA)

Information of species sensitivity, DNA and/or protein adduct levels, other biomarkers, and PBPK modelling should reduce the uncertainty in human extrapolation.

We should not expect concordance in tumor site profiles in different species.