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DISCUSSION GROUP 2

Biomarkers – new insights in exposure and mode of action

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1.New insights into species differences in the kinetics of acrylamide

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Excretion pattern in rat, mice and humans known (Doerge et al; Fennell et al., 2006), Knock out mice (CYP2E1 -/-)
New data on swine relevant to man in excretion pattern of metabolites (Aureli et al., 2007)

Relevance of species at doses relevant to human exposure
PB-PK PD model for Acrylamide and Its Metabolites in Mice, Rats, and Humans (Young et al., 2007).

Research needs

Methods to detect all metabolites in urine (cover whole dose range)
In vitro comparisons between species (isolated hepatocytes)

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2. Acrylamide's biomarkers-effects in relation to exposure some better than others.

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Haemoglobin adducts

-AA Hb adduct peaks at 2, GA at 16 h longer term 120 days
-Inter-laboratory comparison difficult different techniques in different labs

-Low correlation between Dietary intake (FFQ) and adduct formation (AA, GA)
-Basing epidemio studies on internal dose and diet information- more precise approach

Research needs

-Bio-banking material/ repeated sampling for internal dose determination
-For epidemio studies one should include Hb adducts as marker
-Stability of the adduct ?
-Other hepatic adducts (SH groups) ?

2. Acrylamide's biomarkers-effects in relation to exposure some better than others.

DNA adducts

Extrapolated in Young et al., 2007
Reflect the biological active dose

-Not measured in human- why ?
-Small amount–Would it affect cancer rate at such predicted low levels? Low levels of predicted N7 (predominant adduct)

Relationship between adducts and cancer (new NTP study ?) ?

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2.Use of urinary metabolites (acrylamide and glycidamide) as biomarker

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Research needs

-Intake correlation with urinary biomarkers better with more accurate intake estimates but,

1.Specificity of metabolites-confounding factors (other sources of metabolites, medication, age, disease)

2. Short term biomarker only because half life short

Depends on purpose of study, for validation of dietary estimates useful but for cancer not reflecting long-term

Chemical Industry

Explore worker exposure: sample Friday pm- Monday am deduce work exposure from food questionnaire / also more long term monitoring

3. Physiologically-based pharmacokinetic models

3 models

From **Kirman et al., 2003** PB-TK TD Hb adducts- 2 compartment model

Walker et al, 2007 Children only TK multi-compartmental model adjusted in neonates and children for CYP2E1 ontogeny- no effects
Population variability CYP2E1, GSTM1 AND EH
EPA code not released , comments available scientific advisory board website (US)

Young et al al, 2007- PB-TK TD multi-compartmental models

3. Physiologically-based pharmacokinetic models: suggestions for future research

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Inconsistencies ?
Data gap GST, EH ontogeny

Young et al., 2007
Critical data TK GA serum and Hb-adduct formation curve

Data on DNA-adducts in humans needed to test the correctness and accuracy of prediction
Lacking data on population variability
Refinement of the young model would be to include neonate and infants

Ethanol and interaction, ethyl carbamate and solvents (eg)

4. Impact of biomarkers on the risk assessment (both for exposure and the mode of action)

Conclusions and Research needs

-Biomarkers help
estimate intake, extrapolation animal-man, epidemio, metabolic polymorphism population level.
-Acrylonitrile adducts to discriminate origin of AA (diet/smoking)
-Endogenous production of acrylamide ?

-Immunological approaches
-Neo-epitope-based adducts high throughput and cheap
-Serum antibodies to high levels of AA ?
- Monoclonal Anti-bodies against DNA-adducts ?

-Type of biomarker OMICs: gene, proteins, metabolites