Toxicity profiles of heterocyclic aromatic amines

Bettina Seeger and Pablo Steinberg
Institute for Food Toxicology and Analytical Chemistry
Mutagenic compounds present in strongly heated meat

HCAs are formed during the heating of meat, fish and poultry, by condensation of creatinine with amino acids.
The consumption of **HCAs** increases the risk to develop colon, prostate and breast cancer.
## Target organs of carcinogenic heterocyclic aromatic amines in the rat

<table>
<thead>
<tr>
<th>HCA</th>
<th>Target organs/tissues</th>
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<tbody>
<tr>
<td>Trp-P-1</td>
<td>liver</td>
</tr>
<tr>
<td>Trp-P-2</td>
<td>liver, urinary bladder</td>
</tr>
<tr>
<td>Glu-P-1</td>
<td>liver, small and large intestine, Zymbal gland, clitoris</td>
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<tr>
<td>Glu-P-2</td>
<td>liver, small and large intestine, Zymbal gland, clitoris</td>
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<tr>
<td>AαC</td>
<td>liver, blood vessels</td>
</tr>
<tr>
<td>MeAαC</td>
<td>liver</td>
</tr>
<tr>
<td>IQ</td>
<td>liver, small and large intestine, Zymbal gland, clitoris, skin</td>
</tr>
<tr>
<td>MeIQ</td>
<td>large intestine, Zymbal gland, skin, oral cavity, mammary gland</td>
</tr>
<tr>
<td>MeIQx</td>
<td>liver, Zymbal gland, clitoris, skin</td>
</tr>
<tr>
<td>PhIP</td>
<td>large intestine, mammary gland, prostate</td>
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PhIP metabolism

PhIP is activated by the CYP1 family and further esterified by NATs and SULTs into unstable products.
unstable DNA-reactive products of PhilP can lead to mutations by adduct formation.
Heterocyclic aromatic amines: Results (I)
Heterocyclic aromatic amines: Results (II)

Trp-P-1 was the only tested HCA that led to a positive response in the ERα, PPARγ2 and Nrf2 CALUX® assays.
Trp-P-2, MeAαC and AαC induced a clear positive effect in the PAH CALUX® assay. MelQ and PhIP induced luciferase activity to a limited extent and in a concentration-independent way.
Only Trp-P-1 and Trp-P-2 enhanced luciferase expression in the p53 CALUX® assay. When a metabolic activation step was coupled, Trp-P-1, Glu-P-2, MelQ, MelQx and PhIP induced a positive response.
Heterocyclic aromatic amines: Summary of the results obtained

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**Trp-P-1** was the only tested HCA that led to a positive response in the ERα, PPARγ2 and Nrf2 CALUX® assays.

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22.04.2016

University of Veterinary Medicine Hannover, Foundation
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**MelQx elicited no ERα-related activity**
Lauber et al. (2004)

**PhiP elicited ERα-related activity**
Gooderham et al. (2002) and Lauber et al. (2004)
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By means of the PAH CALUX® assay activation of the AhR is quantified.

Activation of the AhR and interaction with xenobiotic response elements could lead to an induction of CYP enzymes.

Trp-P-2 and AαC did not lead to an activation of the AhR to a DNA binding form in a gel retardation assay. Kleman et al. (1992)

Gene expression profiles of PhiP and MelQx in HepaRG™ cells showed responses of downstream targets of the AhR: CYP 1A1, 1A2, 1B1 and dehydrogenase 3A1. Dumont et al. (2010).
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Most HCAs require metabolic activation to form DNA adducts and acting mutagenically in bacterial as well as mammalian cell-based genotoxicity assays.
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The Nrf2 CALUX® assay provides information on the mechanism underlying the genotoxic effect.

Activity in the p53 and Nrf2 CALUX® assays shows that the compound acts via a toxicity pathway involving oxidative stress.
Conclusions

• The results obtained show that the battery of CALUX® assays performed in the present study can successfully be used to screen for molecular cell targets of carcinogenic compounds such as HCAs.

• Due to the particular responsive elements present in the different promoters, the cell lines specifically respond to the pathway of interest, and the interpretation of the results is much easier than when utilizing complex promoters.
Acknowledgements

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Abraham A. Brouwer

