

Toxic and Genotoxic Effects of Azaarenes: Isomers and Metabolites

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Hazard assessment of PAH

- homocyclic compounds
- narcotic effects
- heterocyclic compounds
- metabolites
- different biological endpoints

Azaarenes

- nitrogen containing heterocyclic polyaromatic compounds
- found in air, water, sediments natural and anthropogenic origin
- metabolites observed in the field
- toxicity, mutagenicity, carcinogenicity, teratogenicity

Aims

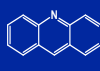
- Gaining insight in the role of metabolism of azaarenes in the type and level of adverse biological effects
- Relating toxicity with molecular descriptors

MATERIALS AND METHODS

azaarenes used in this study



quinoline



acridine



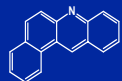
phenanthridine



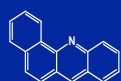
benzo[f]quinoline



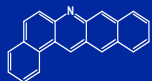
benzo[h]quinoline



benz[a]acridine



benz[c]acridine



dibenz[a,i]acridine

Setup of Toxicity Experiments

- *Chironomus riparius*
- 50 newly hatched first instar larvae
- 100 ml Dutch Standard Water
- 1 ml food (trouvit in DSW)
- 2 controls and 5 concentrations (triplicate)
- survival after 96 hours

Molecular Descriptors

Molecular volume (Vol)

Surface area (SA)

valence indices ($^3\chi_p, ^4\chi_p, ^5\chi_p$)

$\log K_{ow}$

Dipole moment (D)

HOMO, LUMO

Heat of formation (HF)

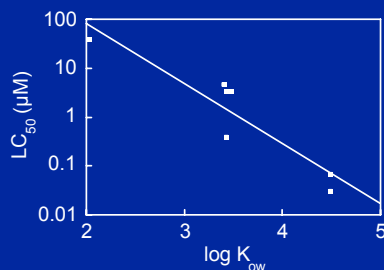
Toxicity of Azaarenes

	kind	LC ₅₀ (95% conf. intervals) (μM)
Qui	2-ring	37.91 (23.85 - 60.27)
BfQ	3-ring	4.64 (2.13 - 10.10)
Phe	3-ring	3.42 (2.89 - 4.05)
BhQ	3-ring	3.38 (2.78 - 4.11)
Acr	3-ring	0.40 (0.34 - 0.46)
BaA	4-ring	0.07 (0.06 - 0.07)
BcA	4-ring	0.03 (0.03 - 0.03)
Aco	meta	> 4.8
Pho	meta	> 3.5

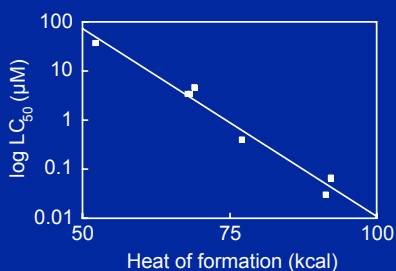
Toxicity of Azaarenes

- Metabolites are less toxic than parent compounds
- Toxicity increases with increasing number of rings
- Exception → acridine

$\log K_{ow}$



Heat of formation



acridine is more toxic than the other isomers, because it is transformed

Setup of Genotoxicity Experiments

- Mutatox™ test
- *Vibrio fischeri*
- bacteria incubated for 45 min at 35°C
- test at 27°C
- light levels measured every hr (10-24h)
- LOEC: light levels 4x control level

Genotoxicity of Azaarenes

	kind	LOEC (μM)
Qui	2-ring	88.025
Pho	meta	4.408
BhQ	3-ring	2.544
Acr	3-ring	1.883
Phe	3-ring	1.234
BaA	4-ring	0.010
Aco	meta	0.005
BcA	4-ring	> 0.19
BfQ	3-ring	> 0.12

Genotoxicity

	LOEC correlation coefficients	
	log K_{ow}	heat of formation
all compounds	0.60	0.06
without acridone	0.96	0.62
without metabolites	0.98	0.99

Conclusions

- Metabolism decreases toxicity, but can increase genotoxicity
- Toxicity and genotoxicity are well described by transport related molecular descriptors (log K_{ow})
- In both cases exceptions

Conclusions

Metabolism causes changes in the level of impact on different biological endpoints, clearly putting severe limitations on environmental standards solely based on narcotic effects of parent PAHs