

Acute Toxicity, Chronic Toxicity and Genotoxicity of Azaarenes

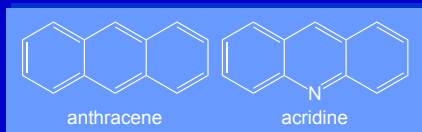
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Introduction

- Hazard assessment of PAH :
Mostly based on narcotic effects of
homocyclic compounds
- Lacking knowledge of:
 - Heterocyclic compounds
 - Metabolites
 - Different biological endpoints

Azaarenes



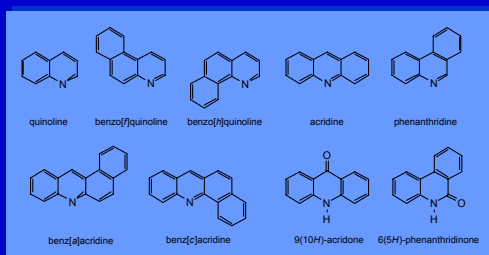
- Found in air, water, sediments
- Natural and anthropogenic origin
- Metabolites observed in the field
- Toxicity, mutagenicity, carcinogenicity, teratogenicity

Aims

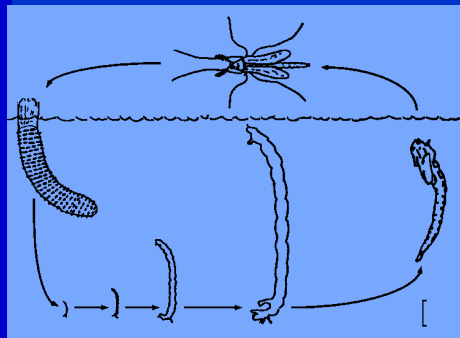
Gaining insight into

- the roles of metabolism and isomerism in the type
and level of adverse biological effects
- the relationship between chemical structure and type
and level of adverse biological effects

Azaarenes tested



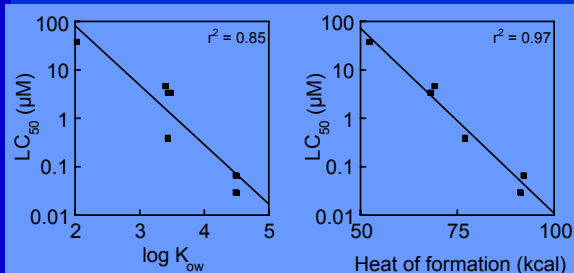
Chironomus riparius



Acute Toxicity of Azaarenes

	Type	LC ₅₀ (95% c.i.) (μM)
Qui	2-ring	37.91 (23.85 - 60.37)
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	3-ring meta	> 4.8
Pho	3-ring meta	> 3.5

Correlation with Molecular Descriptors



Acute Toxicity

- Metabolism decreases toxicity
- Toxicity increases with number of rings, with the exception of ACRIDINE
- LC₅₀ correlates well with transport related descriptors
- Suspected photodegradation of ACRIDINE

Genotoxicity of Azaarenes (Mutatox test)

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

Correlation with Molecular Descriptors

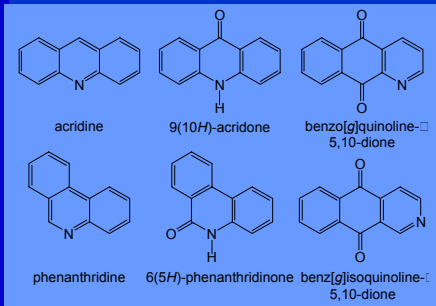
	LOEC corr. coeff.	Log K _{ow}	HF
All compounds	0.60	0.17	
Without acridone	0.96	0.62	
Without metabolites	0.97	0.96	

- large differences in log K_{ow} between tautomers
- correlation of log K_{ow} with genotoxicity strongly increases when keto-form of acridone is used (r = 0.97 vs r = 0.60)

Genotoxicity

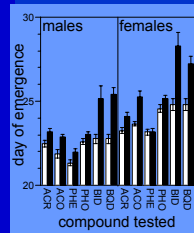
- Metabolism may increase genotoxicity
- Genotoxicity increases with number of rings
- LOEC correlates well with transport related descriptors, but more exceptions than for toxicity
- ACRIDONE is the exception: tautomer differences

Chronic Toxicity of Azaarenes



Chronic Toxicity of Azaarenes

Day of Emergence



Mouthpart Deformity

Fluctuating Asymmetry

	control	exposed
Acr	1.29 ± 0.44	1.02 ± 0.22
Aco	0.82 ± 0.20	0.71 ± 0.19
Phe	n.n.d.	1.38 ± 0.28
Pho	1.14 ± 0.26	1.20 ± 0.21
Bid	1.05 ± 0.24	DA
Bqd	n.n.d.	1.08 ± 0.20

n.n.d.: no normal distribution
DA: directional asymmetry

Chronic Toxicity

- Delay of emergence occurs at concentrations (far) below acute LC₁₀
- Metabolites also provoke this delay
- Azaarenes do not induce mouthpart deformities at these concentrations
- Therefore fluctuating asymmetry does not correlate with either genotoxicity or teratogenicity

Hazard Assessment

- Large differences in toxicity can occur between isomers, and are often hard to describe with molecular descriptors
- Metabolism can either increase or decrease biological effects
- Acute to chronic ratios may exceed the often used factor of 10: chronic toxicity may be underestimated