

IS THERE A RELATIONSHIP BETWEEN DIRECT TOXIC, GENOTOXIC AND TERATOGENIC EFFECTS OF NPAHS ON THE MIDGE *CHIRONOMUS RIPARIUS*?

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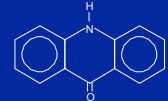
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NPAHs

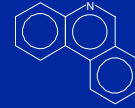
nitrogen substituted polycyclic hetero-aromatic hydrocarbons



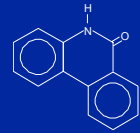
acridine



9(10H)-acridone



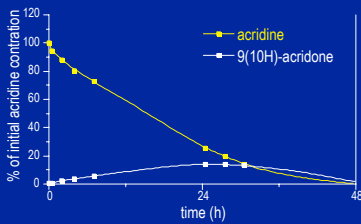
phenanthridine



6(5H)-phenanthridinone

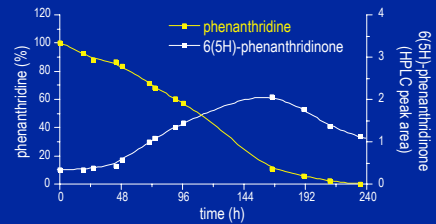
ACRIDINE METABOLISM

by *Dreissena polymorpha*

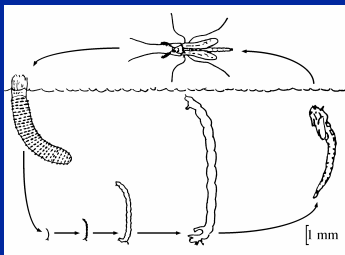


PHENANTHRIDINE METABOLISM

by *Chironomus riparius*



CHIRONOMUS RIPARIUS



ACUTE EXPERIMENTS

- 50 newly hatched first instar larvae
- 100 ml Dutch Standard Water (DSW)
- glass vessel
- 1 ml food (trouvit in DSW)
- 96 hours
- 2 controls and 5 concentrations
- metabolites only at maximum water solubility
- survival

ACUTE TOXICITY

NOEC (μM)	
acridine	0.2
9(10H)-acridone	> 5.9
phenanthridine	2.3
6(5H)-phenanthridinone	> 4.6

GENOTOXICITY

	Mutatox™	
	LOEC (μM)	CMR (μM)
acridine	1.9	16.1
9(10H)-acridone	0.005	0.02
phenanthridine	1.2	12.4
6(5H)-phenanthridinone	4.4	> 23

CONCLUSIONS

- The isomers acridine and phenanthridine show significant differences in acute toxicity.
- Metabolism of acridine and phenanthridine causes a decrease in acute toxicity.
- One of the two metabolites, 9(10H)-acridone, appeared to be highly genotoxic.
- Acute toxicity and genotoxicity differ in underlying mechanism.

QUESTION

Do genotoxic NPAHs induce developmental disturbances (teratogenicity)?

DEVELOPMENTAL DISTURBANCES

- Developmental disturbances can be expressed as deformities in the mouthparts
- Deformity studied: fluctuating asymmetry (FA) in pecten epipharyngis
- Benz[*g*]isoquinoline-5,10-dione teratogenic to cricket *Acheta domesticus* (Walton *et al.*, 1983)



FLUCTUATING ASYMMETRY (FA)

- Random differences which occur between the left and right sides of a normally bilaterally symmetrical organism (Van Valen, 1962)

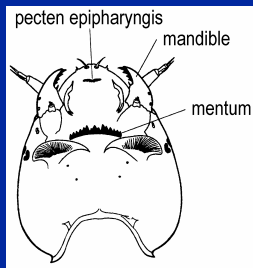
$$FA = \sum \frac{(\text{left-right})^2}{N}$$

FA is used

- as an indicator of the level of developmental stability of populations
- in defining the influence of both environmental and genetic stress on development

HEAD CAPSULE

of *Chironomus riparius*



PECTEN EPIPHARYNGIS

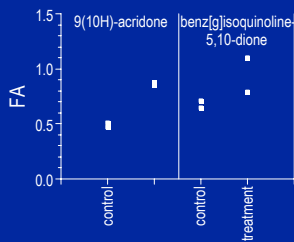
symmetrical pecten
epipharyngis



asymmetrical pecten
epipharyngis



RESULTS TERATOGENICITY



GENOTOXICITY AND TERATOGENICITY

	MutaTox™	FA
acridine	-	?
9(10H)-acridone	+	+
phenanthridine	-	?
6(5H)-phenanthridinone	-	?
benz[ghi]isoquinoline-5,10-dione	+	+

CONCLUSIONS

- Metabolism of acridine and phenanthridine causes a decrease in acute toxicity.
- The metabolite 9(10H)-acridone is highly genotoxic, in contrast to its isomer, the metabolite 5(6H)-phenanthridinone.
- The results of genotoxicity and teratogenicity suggest that teratogenicity is caused by DNA damage.