Occurrence, fate and risks of metabolites

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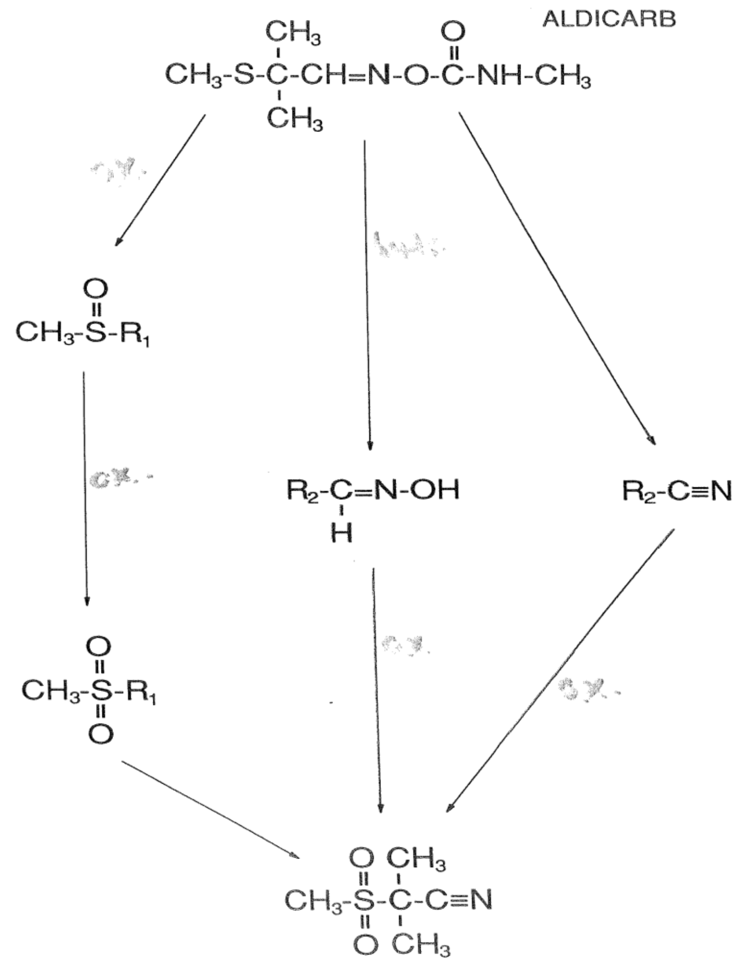
RIVM – Laboratory for Ecological Risk Assessment

Metabolites

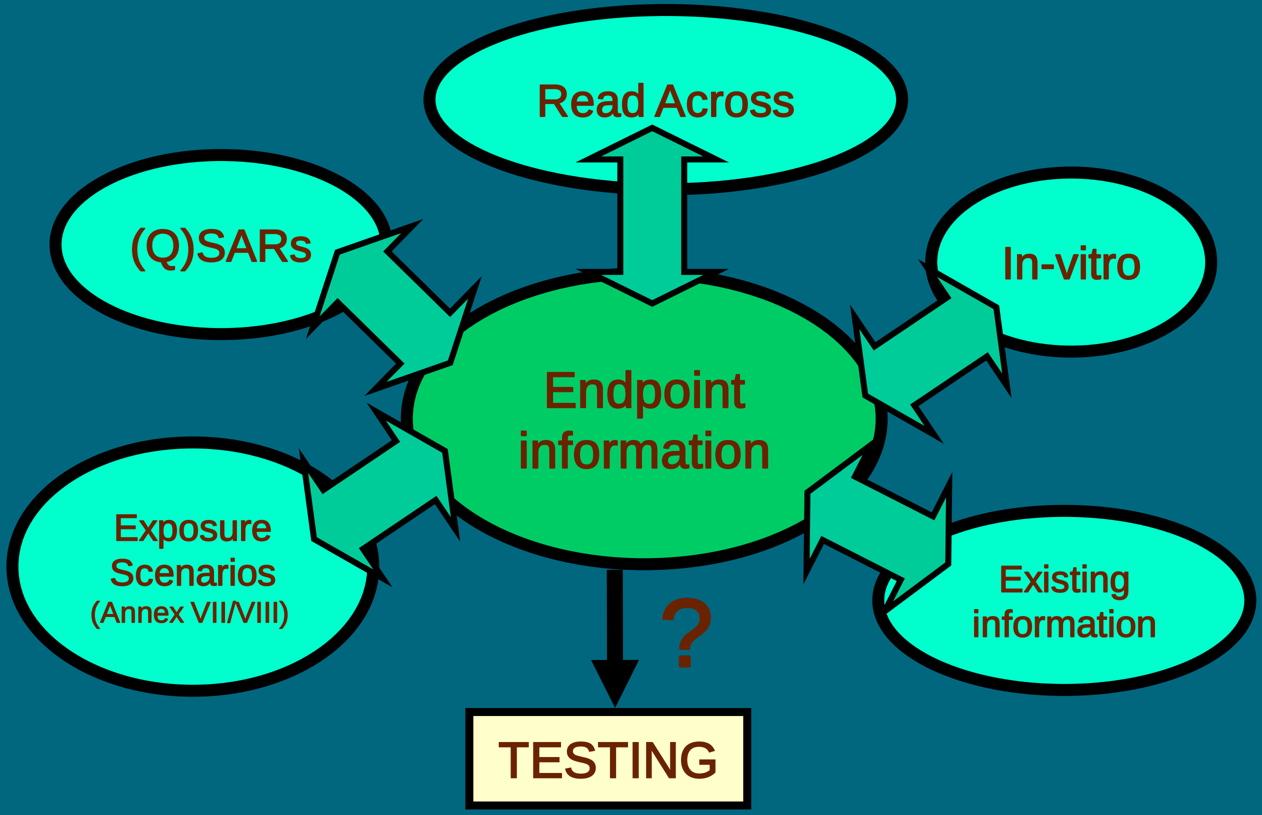
- Incomplete degradation parent compound
  - Cascade of transformations possible: example Aldicarb
  - Complex spectrum of metabolites
  - Communality: more polar chemicals – oxidation

- Unknowns
  - Fate?
  - Distribution?
  - Effects?
  - Risks?

- Legislation
  - WFD
  - REACH
  - Soil Directive?


ALDICARB
CH3-S-C(CH3)2-CH=N-O-C(=O)-NH-CH3
CH3-S(=O)-R1
CH3-S(=O)2-R1
R2-C(H)=N-OH
R2-C≡N
CH3-S(=O)2-C(CH3)2-C≡N

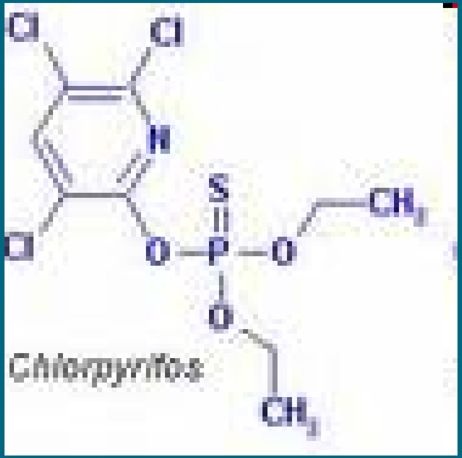
Intelligent Testing Strategies (ITS)



Constituents of an Intelligent (or Integrated) Testing Strategy (ITS)

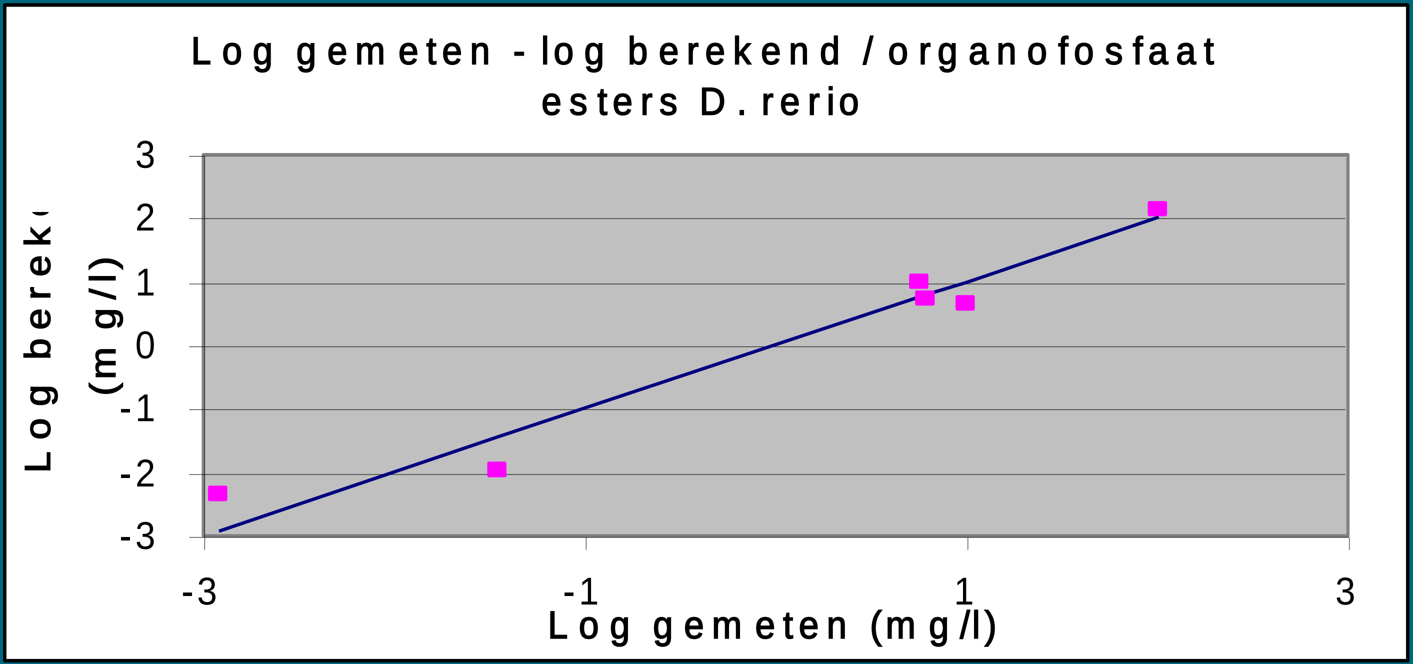
Example: carbamates / organophosphates

- 18 O-P and S-P esters (max. # tox.data 1 organism: carp)
- 16 carbamates (1 organism: tox. data 8 compounds)



- Carbamates: aq.tox. data usually lacking or limited #)
- O-P and S-P esters: aq.tox.data 5-8 chemicals

QSAR: EC_{50}



-Log EC_{50} (mg L^{-1}) = 124.7 + 11.7 * Log E_{homo} – 14.4 * Log (Δ electronic charges at P and O/S-atoms)

$R^2 = 0.95$, p = 0.01, F = 30.9

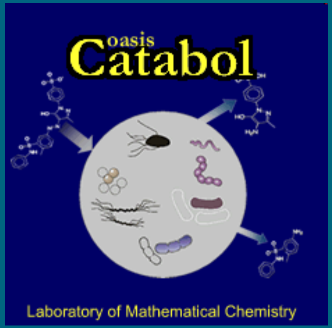
Metabolization

EXPERIMENTAL DATA

- Carbamates: 63 % of chemicals
- O-P/S-P: 33 %

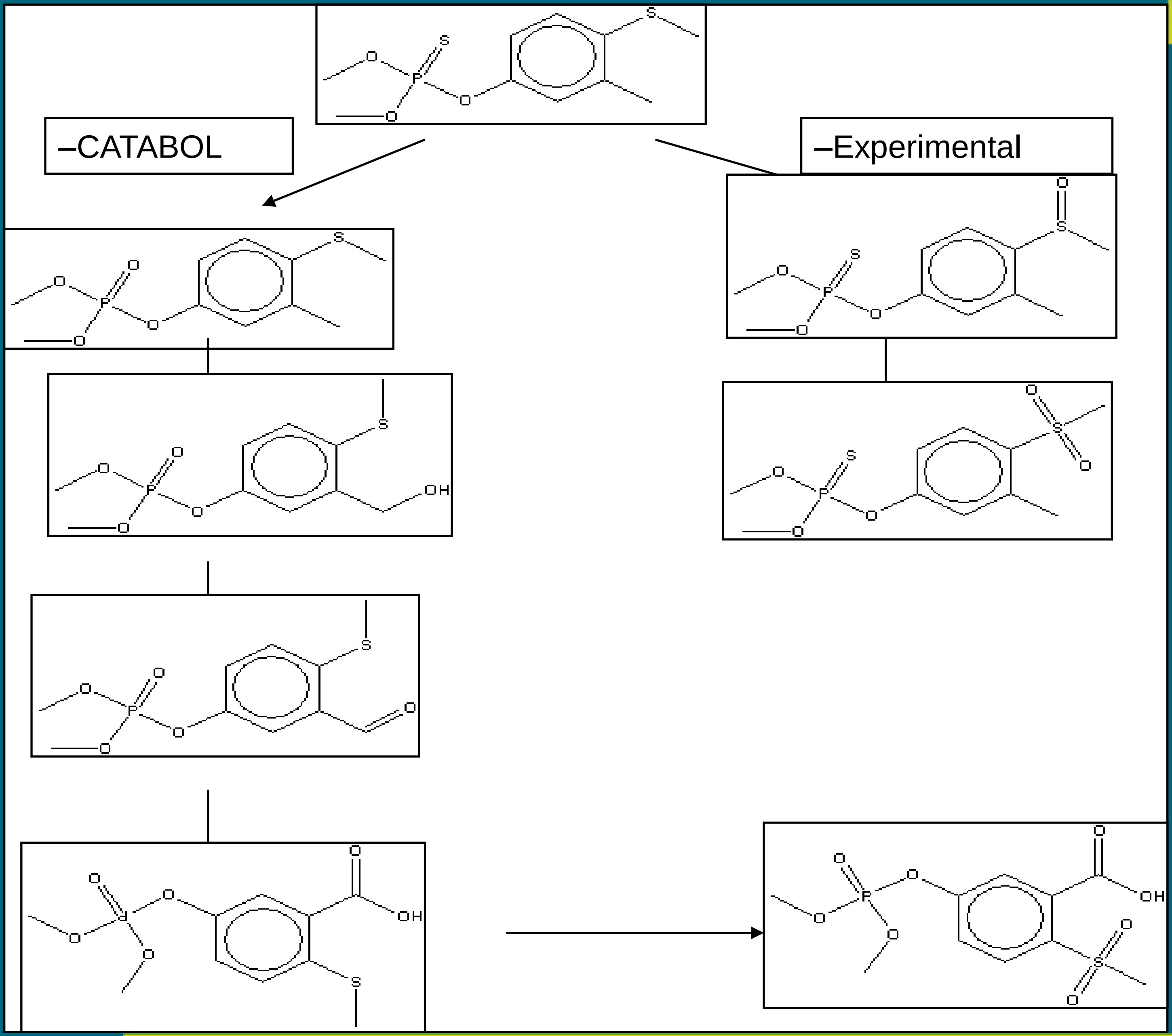
CATABOL (Prof. Mekenyan – Bulgaria)

- Transformation pathways: stable and labile metabolites



COMPARISON:

- May transformation pathways yield the metabolites experimentally observed?


–CATABOL
–Experimental

Metabolization

- CORRECT PREDICTIONS:
- Carbamates: 30 %
- O-P/S-P: 33 %

- Overall: 5 / 16 correct

Aquatic Tox Metabolites Carbamates

Parent compound	EC50 (mg L^{-1})	EC50 (mg L^{-1})
		CATABOL
		metabolite
Propoxur	0.33	8.50
Aldicarb	0.48	0.65
Nabam	**0.03**	**0.02**
Phenol, 2-(1-methylethyl)-methylcarbamate	**0.34**	**0.09**
2,2-Dimethyl-1,3-benzodioxal-4-ol methylcarbamate	**0.31**	**0.03**
Thiodicarb	0.30	0.52
Benfuracarb	**1.65**	**0.05**

Aquatic Tox Metabolites Phosphates

Parent compound	EC50 (mg L^{-1})	EC50 (mg L^{-1}) CATABOL metabolite
O-P-esters		
Dipterex	10.16	19.44
Dichlorvos	14.38	135.05
Chlorfenvinphos	0.42	8.76
Methamidphos	>10000	>10000
Phosphamidon	0.15	4.23
Ethoprophos	>200	1930.83
Profenofos	>25	25.50

Aquatic Tox Metabolites Phosphates

Parent	EC50 (mg L^{-1})	EC50 (mg L^{-1})
Compound	Parent	CATABOL
		metabolite
S-P-esters		
Fenthion	**1.05**	**0.91**
Parathion	1.24	1.56
Dimethoate	9.98	14.32
Methylazinphos	**0.33**	**0.29**
Malathion	0.07	0.09
Fenitrothion	**10.65**	**0.59**
Parathion, methyl	**13.17**	**1.16**
Diazinon	**0.17**	**0.05**
Phosmet	**0.41**	**0.07**
Fonophos	0.11	2.03
Demeton	**4.36**	**0.40**

So…..

Lots of unknowns:

1 – Emergence of metabolites?

2 – Fate/persistence?

3 – Effects: some >, some < toxic than parent?

4 – Risks?

5 – How to deal with metabolites in regulation:
WFD/REACH?

Proposed

Workshop “How to deal with metabolites in regulation?”

1 – Monitoring emerging metabolites

2 – Information needs

3 – Complex mixtures

4 – Adaptation of ecotox testing

5 – Fate assessment

6 – Effect assessment

7 – Data gaps

8 – Risks assessment – REACH/WFD