



Risiken erkennen – Gesundheit schützen

Mehrfachrückstände von
Pflanzenschutzmitteln in
Lebensmitteln

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10.11.2005

**Cumulative Risk
Assessment: Science and
Policy Issues
The Dutch Approach**

10:00 - 10:30

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Cumulative Risk Assessment: Science and Policy issues

The Dutch Approach (with an example of pesticides)

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Cumulative exposure to various compounds is an area receiving increasing attention. In particular the cumulative exposure to residues of pesticides in food is a potential area of concern. This issue is especially relevant for pesticides with a common mechanism of toxicity (e.g. organophosphates). Non-governmental organisations emphasise the need for inclusion of cumulative exposure in the risk assessment procedures for pesticides. Recently also new regulations have been formulated stating that cumulative exposure to pesticides should be included in the risk assessment as soon as adequate methods become available. In 2005, RIVM has evaluated the available information on cumulative exposure to pesticides and in particular what methods are available for an adequate cumulative risk assessment. In this respect both exposure calculations and toxicological (hazard) issues were taken into account.

The basis for each type of cumulative risk assessment is the approach by which various substances can be summed. Two methods can be used at this point: the Hazard Index and the use of Relative Potency Factors (RPFs). The RPF approach is the most relevant approach but conceptually this method is only applicable when there is true dose addition. It is not clear whether the effects of all organophosphate combinations are truly additive and whether the approach with Relative Potency Factors (RPF) is valid. Data exist that support the concept of dose addition for organophosphates but data that contradict the concept of dose addition can also be found in the scientific literature. More information on this issue is required.

In addition, problems may arise on the issue of available residue data of pesticides. In the current approaches for cumulative risk assessment for pesticides monitoring data are being used, providing the most relevant intake of the population. However, within the procedures for authorisation of pesticides, field trial studies are being used. These data in a probabilistic assessment for example, will provide a unrealistic worst case intake assessment. The conceptual problem arises with a new pesticide for which no monitoring data are available: what data should be used then ? A further issue to be solved is the regional differences in intakes throughout Europe. A cumulative risk assessment might result in a problematic outcome in one region but not necessarily in another.

The inclusion of cumulative exposure to pesticides also has an impact on risk management decisions for authorisation and inspection procedures; policy makers will have to make choices in this area. Some examples will be given in the presentation. For example, a new organophosphate pesticide is notified. The risk assessment for the single substance does not provide any health risk. However, adding the new use of the new substance might result in a cumulative intake that exceeds the health based limit values. What to do then? Do not allow the use of the new pesticide? Or ban the active substance that contributes most to the cumulative risk or the one that is most toxic? Do we handle bans on the level of active substances or on the level of products? Do we also take into account other aspects like operator exposure or environmental risks? Such decisions have to be made by risk managers. Without such follow up steps the scientific input of providing cumulative risk assessments is not useful. In general RIVM has the following opinion: the validity of the scientific methods to be used in cumulative risk assessments should match the risk management policies. In other words, the more impact the risk management decisions may have, the more sophisticated should be the methods.

In a recent workshop, RIVM discussed several of these issues with Dutch policy makers. At this moment the Dutch approach is to implement cumulative risk assessments where this is possible. However, there is a need for clear uniform criteria to decide for which groups of substances a cumulative risk assessment is relevant. In general, the approach for organophosphate pesticides based on the RPF approach is supported although further information in this issue appears necessary. There is a need to further explore the possibilities to develop our intake calculations in order to provide the necessary output for a thorough risk evaluation.



Cumulative risk assessment: science and policy issues.
The Dutch approach (with an example of pesticides)

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Contents of this presentation

- How to cumulate ?
 - Toxicological basis
- Some examples from organophosphorus pesticides
- Problems with exposure data and calculations
- Consequences for risk management
- Current view from Dutch policy and inspection

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Cumulative Exposure

- **Cumulation**: total exposure to various substances with a common mechanism of action through a certain route of exposure (e.g. dietary intake)
- **Aggregation**: total exposure to one (or more) substance(s) through several routes of exposure (e.g. food, work place, consumer products).



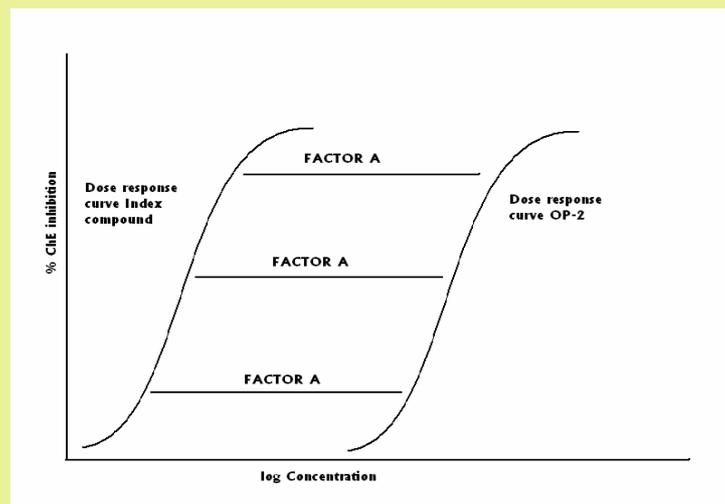
How to sum various substances ?

- **HAZARD INDEX**
 - Based on exposure and a toxicological (limit) value
 - Toxicological limit value is often a health based limit value (e.g. ADI)
 - Relatively simple and fast
 - First screening
- **RELATIVE POTENCY FACTORS**
 - Directly based on toxicological properties
 - Based on dose-addition
 - More difficult to establish
 - Depending on the exposure duration

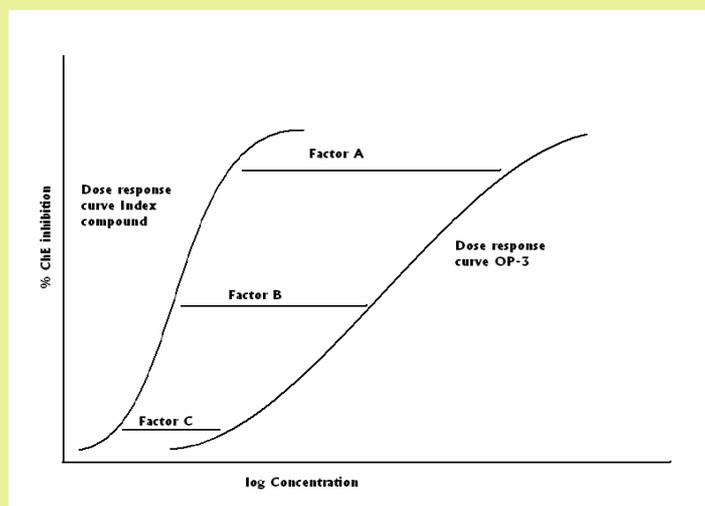
Relative Potency Factors

- RPF approach – principally – is only applicable when the concept of dose addition is valid.
- Dose-addition ?
- Effect-addition ?

Dose Addition = OK



Dose Addition \neq OK



Example

Concentrations of Chlorfyrifos-oxon en Azinophos-Me-oxon on ChE inhibition in brain tissue of the rat – in vitro

Inhibitie %	C=O (nM)	AZM=O (nM)	Factor
10	0.49	4.70	9.6
20	0.92	9.80	10.6
30	1.39	15.99	11.5
40	1.97	23.87	12.1
60	3.70	49.80	13.5
80	7.95	121.22	15.2

Richardson et al. 2001 (Toxicol. Appl. Pharmacol.)

RPFs

- RPF approach – principally – is only applicable when the concept of dose addition is valid.
- Dose-addition ?
- Effect-addition ?
- For OPs, dose addition generally assumed
- However, little evidence for dose addition, primarily indirect
- Data that show ‘addition’ are available for OPs
- Also data available that reject dose addition !

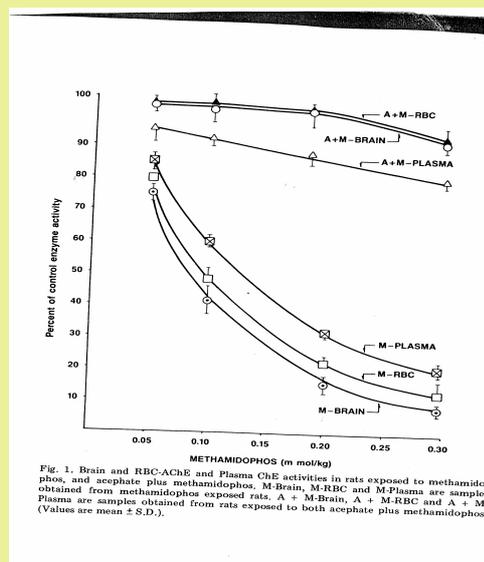
Example 2

Singh, 1986 (Toxicol.)

Methamidophos (M)

Acephate (A)

Combination exposure provides LESS ChE inhibition in vivo



Example 2

Singh, 1986 (Toxicol.)

Methamidophos (I)

Acephate + M (II)

M + A (30s) (III)

M + A (60s)

Result of combination exposure in vitro is time dependent

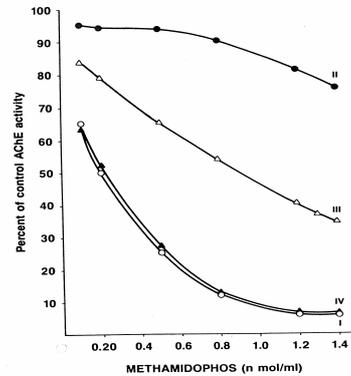


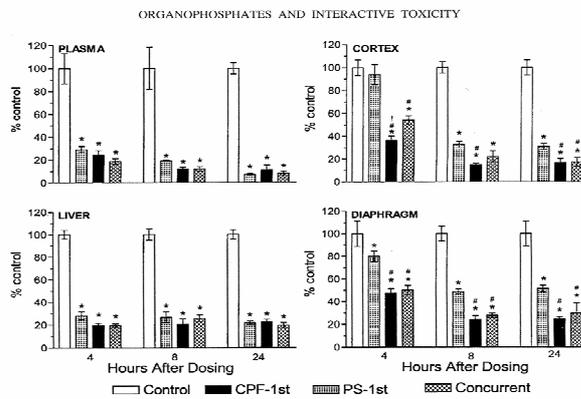
Fig. 3. Residual AChE activity in samples incubated with various doses of phos in presence or absence of acephate. I, —○—, samples exposed to methamidophos; II, —●—, samples exposed to acephate plus methamidophos together; III, —△—, samples exposed to acephate 30 s after methamidophos; and IV, —□—, samples exposed to acephate 60 s after methamidophos.

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Example 3

Order of dosing of 2 OPs determines the outcome of the mixture toxicity



Karanth et al., 2001 (Toxicol. Appl. Pharmacol. 177)

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Cumulative exposure calculations

- The RPF approach is used to express all OPs into a single compound.
- When cumulative exposure calculations are performed using RPFs and dose addition is not valid then.....
- A part of the calculated exposure is 'cooked air'



From a pragmatic point of view:

assumption of dose addition is OK (seems worst case approach)

Fundamental scientific basis:

more data needed

RIVM together with TNO will conduct mechanistic experiments

Chronic and acute exposure

- Chronic exposure: steady state inhibition
- Acute exposure: peak exposure and time to peak on the toxicological target is important (kinetics !)
- RPF chronic \neq RPF acute
- The difference between chronic RPF and acute RPF is substance dependent
- Just as in every risk assessment: the toxicological data should match the exposure duration
 - RPFs, exposure calculations, toxicological endpoint (limit value)

OPs & carbamates ?

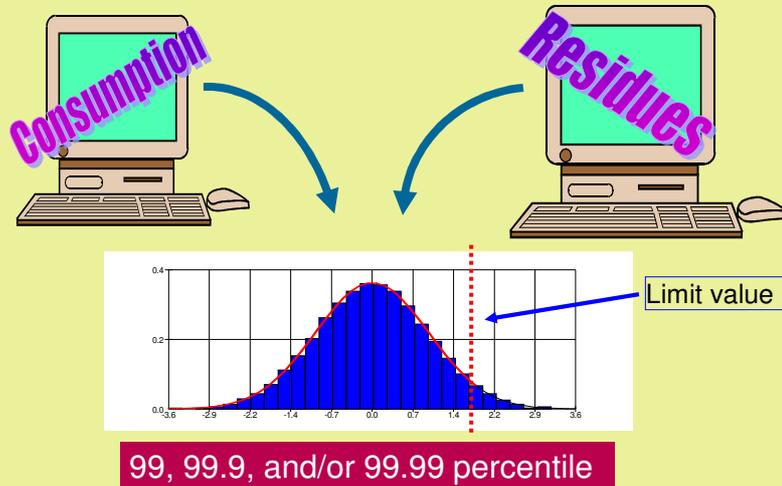
- Do OPs en carbamates have a “common mechanism of toxicity” ? Probably not, although effect addition may occur
- Time scaling:
 - Carbamate exposure (evening) may sum up with a previous OP-induced OP ChE inhibition (morning)
 - OP exposure (evening) does not sum up with a previous carbamate induced ChE inhibition (morning)
- Most international organisations: Not to combine OPs and carbamates.
- Interest of Dutch Food and Non-Food Authority: investigate the possibilities of combining OPs and carbamates

Residue data ?

- In present cumulative exposure calculations in NL, use of monitoring data.
 - Non-random bias
 - What about juices ?
 - What about zero's ?
 - Taken into account the limitations in the conclusions
- What to do in an admission procedure ?
 - What data should we use ?
 - Field trials are not adequate for cumulative exposure calculations
 - If we have a new substance: no monitoring data at all !
 - What about regional differences in the EU ?



Monte Carlo Exposure Calculations



RIKILT approach 2003

- Use Dutch Food Consumption Survey data (about 6200 people – 2 days)
- Use monitoring data VWA for residues
- Use RPFs from EPA (from repeated dose experiments, RBC – AChE inhibition); when not available other endpoints / species / duration were used.
- Estimates for acute RPFs
- Monte Carlo approach for exposure calculations

- About 0.1% of the calculated distribution was > ARfD of the index compound.

Monte Carlo Exposure Calculations

- Monte Carlo Exposure Analysis is an already developed method for probabilistic intake assessment
but.....
- It provides a distribution of person-day combinations
- It does NOT provide the 'fraction of the population above the limit'
- It does NOT provide the 'frequency of exceeding the limit'
- Further development is needed to provide methods that provide such output.

Policy implications(1)

- Method development in the 'risk assessment' area

But also.....

- Arrange procedures for 'risk management' !!!!



What to do in admission procedure ?

- New OP evaluated
- Single OP exposure: no risk
- Cumulative exposure to OPs provides risk

- How to proceed ?
 - New OP cannot be allowed ?
 - Place a ban on the most toxic OP ?
 - Ban the OP with the largest contribution (risk driver) in the cumulative exposure ?
 - Control at active substance or product level ?
 - Similarities / differences in EU member states ?
 - Legal basis ?
 - Also take into account other characteristics (operator exposure, environmental issues) ?



What to do with inspection ?

- Box of oranges: residues of 4 OPs is $0.9 \times \text{MRL}$
- For each substance individually a problem is not encountered.
- Cumulative exposure $> \text{ARfD}$.
- Also if background exposure is responsible ?

- How to proceed ?
 - Is there a health risk, taking into account a composite sample ?
 - Box is destroyed or is a fine given ?
 - Enhance the inspection efforts ?
 - Should we use a group MRL ?



Policy implications (2)

- Is there a health risk from cumulative OP exposure?.....
Possibly
- Should cumulative exposure assessment be an integral part of pesticide policy ?
 - Yes according to consumer organisations, politics, science
- Take into account our gaps of knowledge and methods.....



The Dutch position

- Recent workshop with Dutch Institutes (RIVM, RIKILT, TNO), Ministries (Public Health, Agriculture), and the Food and Non-Food Authority (VWA):
- Propose universal criteria to determine groups of substances for which cumulative risk assessment is relevant
- Start to implement cumulative risk assessment where possible
 - E.g. work on the implementation for OPs
- Cumulative risk assessment should become an issue in both admission as well as inspection procedures
- Look at other groups of substances where cumulation might be relevant (outside pesticide area)
- Also take a closer look at the issue of aggregate exposure



Thanks for your attention !