BfR
Risiken erkennen – Gesundheit schützen

Mehrfachrückstände von Pflanzenschutzmitteln in Lebensmitteln

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Cumulative Risk Assessment in the UK

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Cumulative Risk Assessment in the UK

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The COT report

In 2000, the United Kingdom (UK) Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) established a Working Group to prepare a draft report entitled "Risk Assessment of Mixtures of Pesticides and similar compounds." After the text had been agreed by the full COT, this was published as a COT report and is available on the COT website. The working group comprised COT members with appropriate expertise, co-opted experts (a medical statistician, John Groton from the Netherlands and others) and also assessors from UK government departments, including PSD, the Veterinary Medicines Directorate, Health and Safety Executive, Food Standards Agency and the Department of Health. The working group undertook a detailed study of work on the toxicology of mixtures and made recommendations on research and on possible changes in risk assessment to account for the combined effects of components of mixtures. The working group also identified gaps in data that might need to be filled to enable cumulative risk assessment to be undertaken. This was particularly in relation to residues data.

The recommendations other than those on research

These were that

1) All sources of exposure to pesticides should be considered.
2) A framework should be established to decide when it was appropriate to undertake combined risk assessment.
3) The default assumptions in considering combined exposure should be: compounds with qualitatively the same toxicological action will act additively (dose additivity): pesticides with qualitatively different toxicological action will act independently.
4) The working group suggested that a toxicity equivalence factor (TEF) approach may be appropriate in the case of dose additivity.
5) The working group considered that probabilistic exposure assessment might be needed, but that this would be contingent on changes in residue surveillance.

Evidence considered

The working group considered a large amount of scientific evidence on mixture toxicology eg Jonker et al (1990), Groten et al (1997) and Chaturvedi (1993). Studies of complex mixtures (often used in environmental toxicology) rarely gave any information on the nature of combined actions. To obtain such information, it was considered necessary to study the mixture and components and that to separate out combined actions and interactions, a full dose response was needed for the components and for the mixture. The working group considered that the evidence was consistent with the assumption that no interaction occurs at residue type doses and consistent with the assumption that pesticides with qualitatively different toxicological action will act independently, although studies were difficult to undertake. It was considered that pesticides with qualitatively the same toxicological action would act additively, although in many cases where acute endpoints of toxicity were being sought the effect would be less than additive, for pharmacokinetic reasons. The working group was highly critical of some of the literature on mixtures, because studies were often designed in such a way that the type of combined action could not be determined, frequently because a linear dose-response was assumed (log dose/probit response is often linear), and elementary statistics were ignored

After the COT report

After publication of the report, the Food Standards Agency established a Committee of officials to carry forward the COT's recommendations. This Committee considered three initial problems.

1. How to prioritise groups of pesticides with a common mechanism of action (common mechanism groups – CMGs) for attention.
2. How to define CMGs (what is a common mechanism of action?).
3. How to relate exposure to pesticides with a common mechanism of action but quantitatively different toxicity (ie how to cumulate).

Prioritisation

The Committee considered that CMGs should be prioritised for attention based upon size (ie number of ais), public concern and potential for adverse effect in humans from the group.

Cumulation

There is no consensus in the UK on the best method of cumulation. Five methods were discussed by Wilkinson et al (2000). They are 1) Hazard index (HI) 2) Point of departure index (PODI) 3)Toxicity equivalence factors 4) Combined margin of exposure (MOE_T) 5) Cumulative risk index (CRI). All have advantages and disadvantages thus HIs and CRIs do not well-describe relative toxicity as they are dependant on uncertainty factors (UFs) which may be different with different compounds, as well as dose spacing; on the other hand data with appropriately different UFs (eg NOAELs from human data with a UF of 10 and NOAELs from animal data with a UF of 100) can be incorporated. TEF methods need a reference compound with a good database. All methods need a decision on a group UF or level of acceptability and all the methods give similar results. Much of the argument is seeking the avoidance of estimating a group UF.

Research Recommendations

The COT made a number of research recommendations. They included 1) The development of biomarkers of exposure and 2) biomarkers of effect 3) Characterization of variation in human response to mixtures 4) Work should be undertaken, in suitable experimental systems, to characterise both the nature of, and dose-response relationships for, combined actions of pesticides, veterinary medicines and similar substances. Such studies should be performed at doses that include those potentially ingested by humans in the diet. 5) Groups of pesticides having common targets of toxicological action should be identified. Such work might include the identification of sites of action at a molecular level, to identify those groups of compounds that would be expected to show simple similar action. Studies of protein and/or RNA expression, using modern array technology, in relevant systems might be appropriate in some cases. These might be followed up by more detailed mechanistic studies of gene expression and/or enzyme or hormonal activity as necessary. The first research call was last year and proposals in response to the 2nd Research Call applications just been reviewed. Progress will be reviewed at a research workshop on 24th/25th November 2005.

Other UK activities

UK has done an organophosphate (OP) cumulative risk assessment using two different TEF methods; the first draft has gone through the regulatory system. Dutch dietary data were used, with old residues information. UK has used the HI method in the past. UK plans to redo the TEF cumulative risk assessment with new UK dietary data and more recent residues data.

Conclusions

The optimal method of cumulating is not yet defined, nor is the place of cumulative risk assessment in the overall risk assessment paradigm clear. In the future more sophisticated methods may be used to investigate combined actions of pesticides, including PBPK, proteomics and genomics.

References

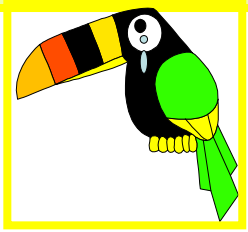
Groten et al. Subacute toxicity of a mixture of nine chemicals in rats: detecting interactive effects with a fractionated two-level factorial design. Fundam Appl Toxicol 1997; 36: 15-29.

Jonker et al. 4-week oral toxicity of a combination of eight chemicals in rats: comparison with the toxicity of the individual compounds. Food Chem Toxicol 1990; 28: 623-63.

Chaturvedi AK. Biochemical and toxicological studies on mixtures of three commonly-sued herbicides in mice. Arch Contam Toxicol 1993; 24: 449-454.

Wilkinson CF et al. Assessing the risks of exposures to multiple chemicals with a common mechanism of toxicity: how to cumulate? Reg Toxicol Pharmacol 2000; 31: 30-43.

CUMULATIVE RISK ASSESSMENT IN THE UK



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WiGRAMP

- report
  - Nomenclature used
  - Recommendations other than research
    - Default assumptions
      - **Evidence base**
  - How the recommendations are being carried forward
    - Identification of common mechanism groups
    - How to cumulate
  - Research recommendations
    - How FSA commissions research
    - Progress so far on research

The future

- New methods of dealing with toxicity and exposure data eg probabilistic, Bayesian
- Role of PBPK
- Role of cumulative risk assessment in the overall risk assessment process

WiGRAMP REPORT 1

- In 2000, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) established a Working Group to prepare a draft report on Risk Assessment of Mixtures of Pesticides and similar compounds.
- This was published as a COT report and is available on the COT website; www.food.gov.uk/science/ouradvisors/toxicity/ .

WiGRAMP REPORT 2

- The COT is a committee of independent experts, whose secretariat is supplied by the Food Standards Agency and the Department of Health
- The Working group comprised COT members with appropriate expertise, co-opted experts (a medical statistician, John Groton from the Netherlands and others)
- Assessors from Government Departments: PSD, the Veterinary Medicines Directorate, Health and Safety Executive, Food Standards Agency, Department of Health

WiGRAMP REPORT 3

- WiGRAMP undertook a detailed study of work on the toxicology of mixtures
- Made recommendations on research and possible changes in risk assessment to account for mixtures
- Identified gaps in data that might need to be filled to enable cumulative risk assessment to be undertaken

WiGRAMP REPORT 4: MIXTURE TOXICOLOGY

Terminology			
Type of combined effect	Subtypes	Synonyms	Effects observed
Non-interactive	Simple similar action	Additivity	Dose addition
	Simple dissimilar action	Independent action	Response addition
Interactive	Potentiation	Synergy	Greater than dose additive effect
	Antagonism		Less than dose additive effects

WiGRAMP recommendations other than research

- - consider all sources of exposure
- - establish a framework to decide when appropriate to undertake combined risk assessment.
- - default assumptions should be: compounds with qualitatively the same toxicological action will act additively (dose additivity): pesticides with qualitatively different toxicological action will act independently: TEF approach may be appropriate
- - probabilistic exposure assessment may be needed; contingent on changes in residue surveillance

DEFAULT ASSUMPTIONS

- No interaction occurs at residue type doses
- Pesticides with qualitatively the same toxicological action will act additively (dose additivity)
- Pesticides with qualitatively different toxicological action will act independently

EVIDENCE BASE? (1)

2 TYPES OF STUDY

- Study the mixture (top-down – widely used with complex mixtures in environmental toxicology)
- Study the mixture and components

To separate out combined actions and interactions you need a full dose response for the components and for the mixture

EVIDENCE BASE? (2)

- Evidence is consistent with the assumption that no interaction occurs at residue type doses.
- Evidence is consistent with the assumption that pesticides with qualitatively different toxicological action will act independently, although studies are difficult to perform and undertake.
- Pesticides with qualitatively the same toxicological action will act additively, although in many cases where acute endpoints of toxicity are sought the effect is less than additive, for pharmacokinetic reasons

Jonker et al,. 4-week oral toxicity of a combination of eight chemicals in rats: comparison with the toxicity of the individual compounds. Food Chem Toxicol 1990; 28: 623-631; Groten et al. Subacute toxicity of a mixture of nine chemicals in rats: detecting interactive effects with a fractionated two-level factorial design. Fundam Appl Toxicol 1997; 36: 15-29; Chaturvedi AK. Biochemical and toxicological studies on mixtures of three commonly-sued herbicides in mice. Arch Contam Toxicol 1993; 24: 449-454.

DIFFICULTIES OF STUDYING MIXTURES

WiGRAMP was highly critical of some of the literature on mixtures:

- Studies designed in such a way that the type of combined action could not be determined
- Linear dose-response assumed (log dose/probit response is often linear)
- Elementary statistics ignored

AFTER WiGRAMP 1

- Agricultural pesticides regulation is a multidepartment process in the UK.
- The regulatory authority (PSD) is part of DEFRA (Agriculture Ministry)
- but the Department of Health (England), the Food Standards Agency, the Health and Safety Executive and Scottish, Welsh and Northern Irish Government Departments have an effective veto on approvals
- The Government is advised by an advisory committee of independent experts, the advisory committee on pesticides (ACP)

AFTER WiGRAMP 2

- The Food Standards Agency established a Committee of officials to carry forward WiGRAMP's recommendations
- Comprised people from the Food Standards Agency, PSD, Veterinary Medicines Directorate and the Department of Health

2 SCIENTIFIC QUESTIONS AND A POLICY ONE

- How to group pesticides with a common mechanism of action (CMGs)
  - what is a common mechanism of action ?
- How to relate exposure to pesticides with a common mechanism of action but quantitively different toxicity (ie how to cumulate)
- Prioritisation of CMGs for attention

What constitutes a common mechanism of action?

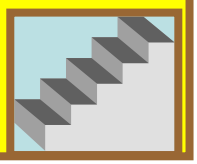
- Cause the same critical effect
- act on the same molecular target at the same target tissue
- act by the same pharmacological mechanisms
- (rare) may share common toxic intermediate

eg the ethylene*bis*dithiocarbamate fungicides

COMMON MECHANISM GROUPS (CMGs)

To do cumulative risk assessment, you need to group pesticides into CMGs

- **Identification** Office of Pesticide Programs (USEPA) 5 step scheme based on
- Proprietary data,
- Literature data
- Mechanistic studies
- SARs
  - (effect in target organisms)



PROBLEMS WITH IDENTIFICATION OF CMGs

- Compounds that have effects on the same organ eg liver, by different/unknown mechanisms ? Assume common mechanism until otherwise proven.
- Carcinogens
- Endocrine disruptors

CMGs

- OP anticholinesterases $\pm$ carbamate anticholinesterases
- Pyrethroids and -ins ? 2 groups (α and non- α cyano)
- Triazines
- 'Conazoles
- Endocrine disruptors ? Several groups

CMGs: PRIORITISATION

- Size of CMG (ie number of ais)
- Public concern (cf OPs)
- Potential for adverse effect in humans from group

How to cumulate 1

(Wilkinson CF et al Reg Toxicol Pharmacol 2000; 31: 30-43).

- Hazard index
- Point of departure index
- Toxicity equivalence factors
- Combined margin of exposure
- Cumulative risk index

How to cumulate 2a Hazard index (HI)

- The hazard index is the sum of the hazard quotients (HQ), where the HQ is exposure/reference dose eg

$$HI = \frac{Exp_1}{RfD_1} + \frac{Exp_2}{RfD_2} \ldots\ldots\ldots \frac{Exp_n}{RfD_n}$$

Should be <1

Disadvantage: RfD depends on uncertainty factor/dose spacing and may not be directly proportional to toxicity
Advantage: can incorporate data with different safety factors eg human data or animal data bases of variable quality.

How to cumulate 2b Adjusted Hazard index (aHI)

- The hazard index is the sum of the hazard quotients (HQ), where the HQ is exposure/reference dose
- but where the reference dose is not based on the group property (cf carbaryl), a reference dose is calculated based upon the group property.

How to cumulate 3 point of departure index (PODI)

- Point of departure (POD) is a variable that reflects toxicity quantitatively eg ED_{10} or NOAEL for the chosen study.

$$PODI = \frac{Exp_1}{POD_1} + \frac{Exp_2}{POD_2} \ldots\ldots \frac{Exp_n}{POD_n}$$

Then to do a risk assessment one needs a group uncertainty factor (often 100).

PODI x UF should be < 1

How to cumulate 4 toxicity equivalence factors (TEFs)

Need an index compound to which the toxicity of each component can be normalized. The TEFs for compounds 1 (Index), 2….n are the ratios

$\frac{POD_I}{POD_I}$, $\frac{POD_I}{POD_I}$, $\frac{POD_I}{POD_I}$ &tc (TEF for index = 1).

$\frac{POD_1}{POD_2} \quad \frac{POD_n}{\quad}$ Then total normalized exposure for index compound and compounds 2 to n are: $Exp_i \times 1 + exp_2 \times TEF_2 \ldots . exp_n \times TEF_n$.

Compare $\sum$ to RfD for index compound (is this appropriate – index compound may be a small component of mixture)

How to cumulate 5 margin of exposure (MOE_T)

- MOE = $\frac{POD}{Exp}$ (?= $\frac{ED10}{Exp}$)

$$MOE_T = \frac{1}{1/MOE_1 + 1/MOE_2 \ldots 1/MOE_N}$$

Need to develop a group uncertainty factor (?100). MOE_T should > UF _

How to cumulate 6 cumulative risk index (CRI)

- RI = $\frac{POD}{Exp \times UF} = \frac{Rfd}{Exp}$

$$CRI = \frac{1}{1/RI_1 + 1/RI_2 + 1/RI_3 \ldots\ldots 1/RI_N} = \frac{1}{HI}$$

Disadvantage: RfD depends on uncertainty factor/dose spacing and may not be directly proportional to toxicity

How to cumulate: pros and cons 1

- TEFs - need a reference compound with a good database:
- HIs and CRIs do not well-describe relative toxicity as are dependant on UFs which may be different with different compounds (aHI avoids this): also allows use of data with different uncertainty factors eg human study X 10 and animals studies X 100.
- PODI - need a “group UF”
- MOE_T needs a decision on level of acceptability

How to cumulate: pros and cons 2

- All the methods give similar results
- Much of the argument is seeking the avoidance of a group uncertainty factor
- The threshold of acceptability of an MOE_T = a group uncertainty factor
- Instead of arguing about pros and cons, should look more critically at calculating the group uncertainty factor…….

How to cumulate: pros and cons 2

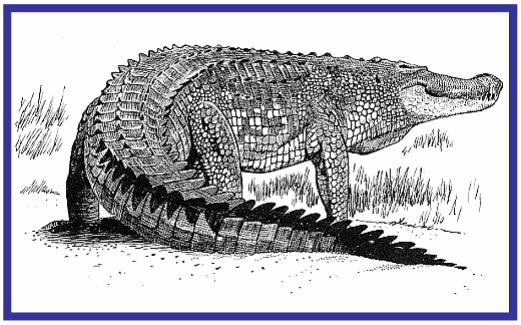
- The threshold of acceptability of an MOE_T = a “reciprocal” of a group uncertainty factor
- Has been said that this exports the decision to the risk manager = administrators

RISK MANAGERS

GROUP UNCERTAINTY FACTOR

- Calculation must be based on a group effect
- UF should be calculated for each component of the mixture (considerations: quality of data base, LOEAL/NOAEL)
- Group UF should be based upon UFs for individual pesticides weighted for content of each pesticide in the mixture

RESEARCH



Research from the WiGRAMP Report Recommendations 1.

1. Development of biomarkers of exposure
2. Development of biomarkers of effect
3. Characterisation of variation in human response to mixtures

Research from the WiGRAMP Report Recommendations 2.

4 a) recommend that further work be undertaken, in suitable experimental systems, to characterise both the nature of, and dose-response relationships for, combined actions of pesticides, veterinary medicines and similar substances. Such studies should be performed at doses that include those potentially ingested by humans in the diet.

b) Groups of pesticides having common targets of toxicological action should be identified. Such work might include the identification of sites of action at a molecular level, to identify those groups of compounds that would be expected to show simple similar action. Studies of protein and/or RNA expression, using modern array technology, in relevant systems may be appropriate in some cases. These may be followed up by more detailed mechanistic studies of gene expression and/or enzyme or hormonal activity as necessary.

Research from the WiGRAMP Report Progess

- 1st Research Call last year
- 2nd Research Call applications just been reviewed
- Research is commissioned by open competition
- External and internal (FSA) reviewers
- Criteria include addressing research requirement, value for money, applicants' track record and skills, clear milestones (kilometerstones), likelihood of achieving goals.
- Research workshop 24th/25th November 2005

Present UK situation

- UK has done an OP cumulative risk assessment using two different TEF methods; first draft has gone through the regulatory system. Dutch dietary data were used, with old residues information. UK has used the HI method in the past
- UK plans to redo it with new UK dietary data and more recent residues data
- Also considering how to group pesticides into CMGs and prioritising CMGs for attention.

Problems

- Identification of CMGs
- Method of cumulating
- Good quality exposure data

Down the road 1

- Probabilistic hazard characterisation
- Bayesian approaches to toxicity and exposure data
- PBPK modeling

Physiologically based pharmacokinetic modelling

Physiological based pharmacokinetic modelling (PBPK) is widely applied to single chemicals, and can be adapted to account for interactions in chemical mixtures

Physiologically based pharmacokinetic modelling

- For a binary mixture, the rate of metabolism of each chemical is calculated using Michaelis-Menten kinetics, along with a modulation factor reflecting the effect of the metabolic interaction. The resulting change in rate of metabolism (RAM) is a function of Michaelis-Menten constants (Vmax and Km), the concentrations at site of metabolism of chemicals 1 and 2 (C_1 and C_2) and the inhibition constant Ki21 which reflects the C_2 at which 50% inhibition occurs.

Physiologically based pharmacokinetic modelling

$$RAM1 = \frac{V\max 1C1}{C1 + Km1\left(1 + \frac{C2}{Ki21}\right)}$$

Down the road 2

- How often do you do it?
- Cumulative risk assessments so far carried out by/on behalf of regulatory authorities
- Companies might be asked to assess the impact of a new product on a cumulative risk assessment – need to predict market share impact on use of other pesticides &tc &tc

Down the road 3

- Probably best to do it after reviewing the ais in the GMG – revoke a few uses/changes patterns of use &tc
- Need toxicology in a similar state for all the ais
  - eg reference doses, NOAELs for critical effects set on same criteria.

CONCLUDING REMARKS

- Developing agreement on defaults for combined actions of pesticides in mixtures
- No clear consensus on how to cumulate - each method presents some problems – advantages and disadvantages more apparent than real
- Initial indications suggest that safety margins are not eroded when cumulative risk assessment is undertaken

THE END