



# CUMULATIVE AND AGGREGATED EXPOSURE TO PESTICIDES (ACROPOLIS PROJECT)

Partners: RIVM, FERA, University of Milan, CRD, IRAS, INRAN,  
NIPH, DLO, NFA, Freshfel Europe and University of Ghent

Associated partners: DTU (Denmark), CSL (Cyprus), ANSES  
(France), FVC (Latvia), NIPH (Slovenia), BPI (Greece)  
AGES (Austria)

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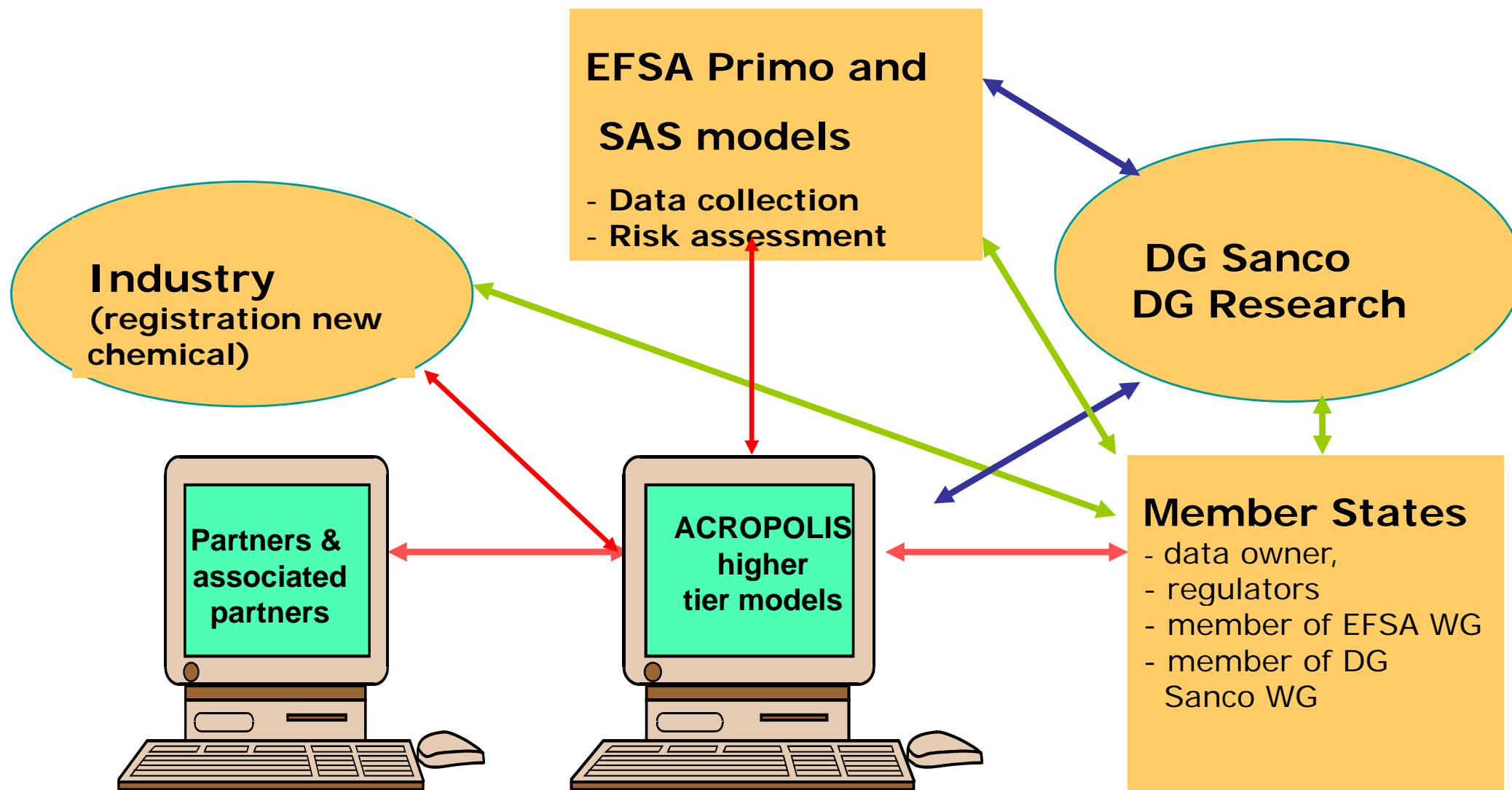


# Aims of EU project ACROPOLIS

- Improved cumulative **exposure** assessment and cumulative hazard assessment;
- To integrate **cumulative and aggregate risk models** in a web-based tool, including accessible data for all stakeholders;
- **Improving the understanding** of cumulative risk assessment methodology of different **stakeholders**.



# Internet exchange of models and results





# Stakeholder involvement

- is concept understandable?
- usefulness?
- attitudes





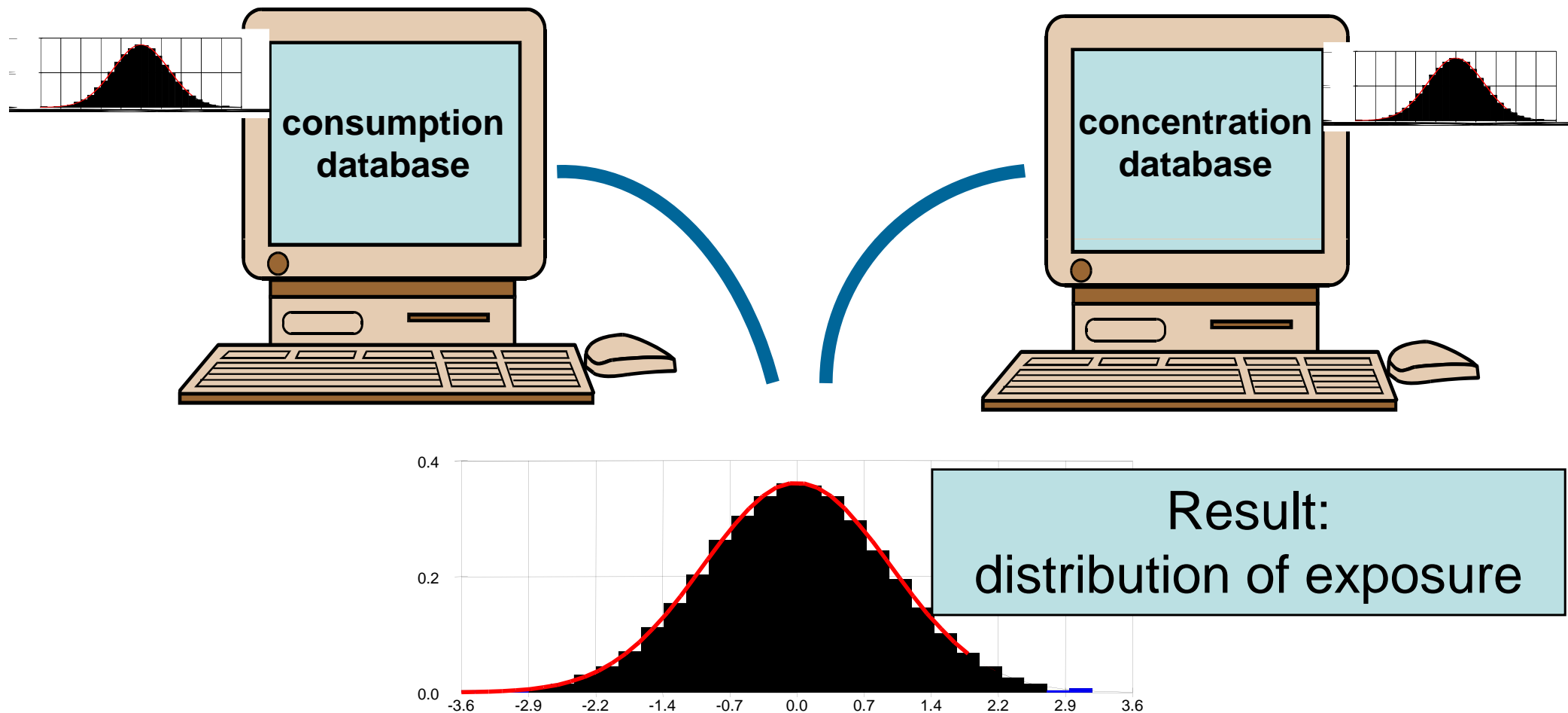


# First stakeholders conference

- DG SANCO expectation from ACROPOLIS
  - call for cooperation EFSA and ACROPOLIS
  - IT tool accessible to all stakeholders
- Carl Schlyter (European Parliament)
  - difficult to explain that it has not been regulated since 2005  
Go for it, and fix the hole!
- Trust in ACROPOLIS from (nearly) all stakeholders



# MCRA: How it works acute

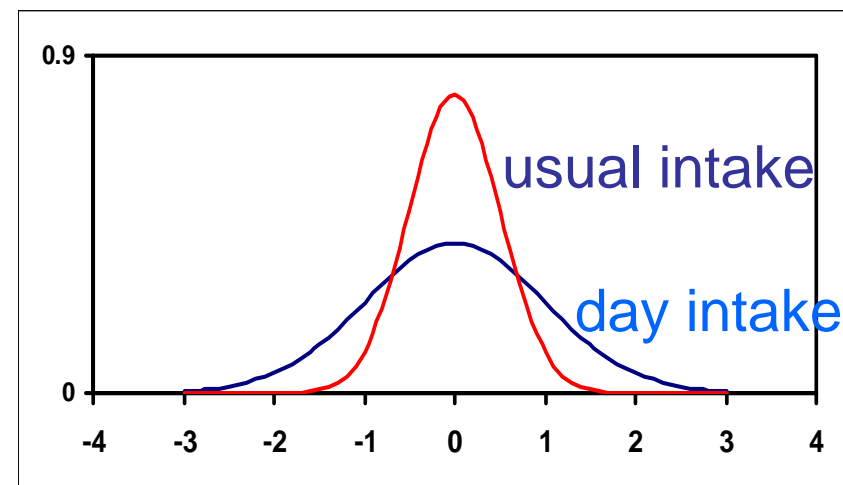


Random sampling from a concentration and a consumption database



# How it works chronic (ETUI project)

- Observed individual Mean  
EFSA Guidance
- variance components model
  - between individuals
  - days within individuals
  - transformation to a log or power (Box-Cox) scale
  - remove within persons variation





# MCRA: Data

summary  
data

## Foods\*

Selected file: No file selected. [Select a file](#)

## Consumptions\*

Selected file: No file selected. [Select a file](#)

## Compounds\*

Selected file: No file selected. [Select a file](#)

## Concentrations\*

Selected file: No file selected. [Select a file](#)

## Effects\*

Selected file: No file selected. [Select a file](#)

[Hide advanced settings](#)

## Processing

Selected file: No file selected. [Select a file](#)

## Unit variability

Selected file: No file selected. [Select a file](#)

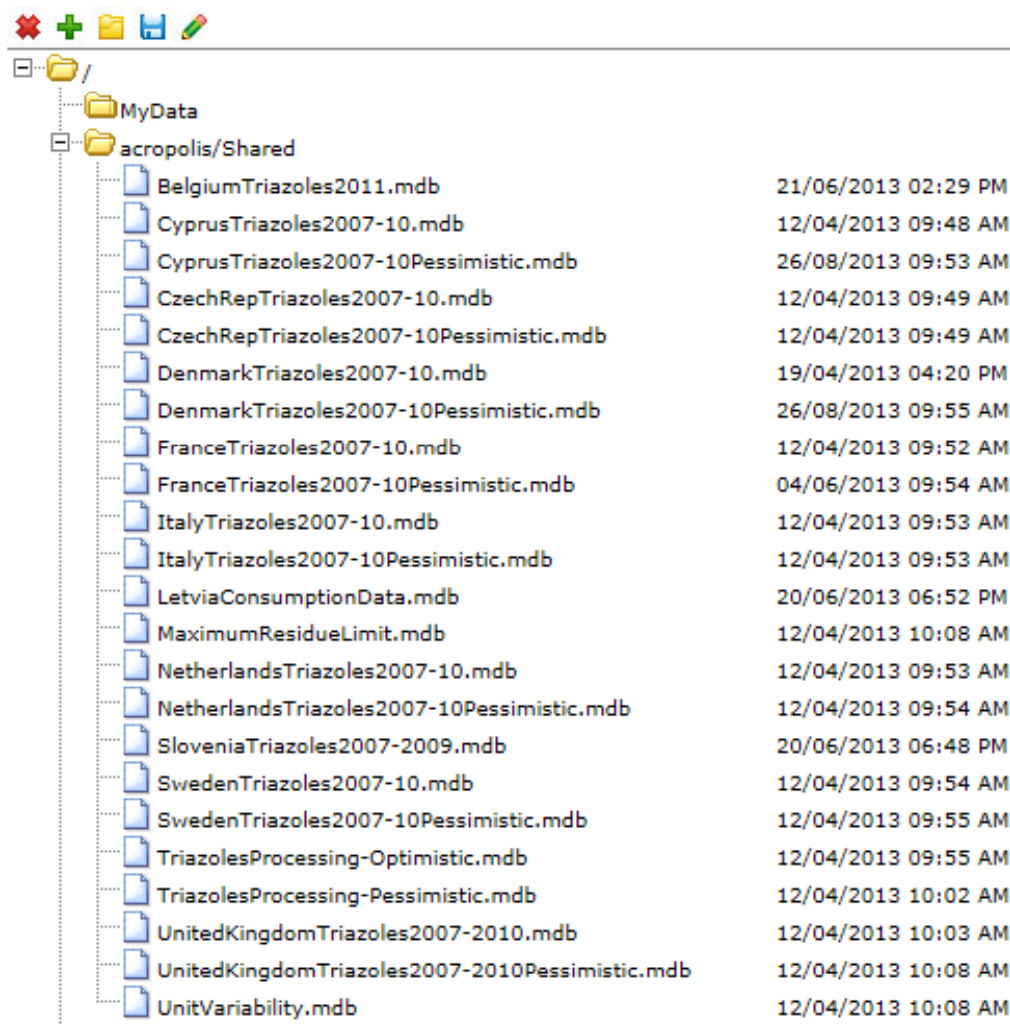
Data

select  
model  
output





# E-Platform and get data connected



File Name	Modification Date
BelgiumTriazoles2011.mdb	21/06/2013 02:29 PM
CyprusTriazoles2007-10.mdb	12/04/2013 09:48 AM
CyprusTriazoles2007-10Pessimistic.mdb	26/08/2013 09:53 AM
CzechRepTriazoles2007-10.mdb	12/04/2013 09:49 AM
CzechRepTriazoles2007-10Pessimistic.mdb	12/04/2013 09:49 AM
DenmarkTriazoles2007-10.mdb	19/04/2013 04:20 PM
DenmarkTriazoles2007-10Pessimistic.mdb	26/08/2013 09:55 AM
FranceTriazoles2007-10.mdb	12/04/2013 09:52 AM
FranceTriazoles2007-10Pessimistic.mdb	04/06/2013 09:54 AM
ItalyTriazoles2007-10.mdb	12/04/2013 09:53 AM
ItalyTriazoles2007-10Pessimistic.mdb	12/04/2013 09:53 AM
LetviaConsumptionData.mdb	20/06/2013 06:52 PM
MaximumResidueLimit.mdb	12/04/2013 10:08 AM
NetherlandsTriazoles2007-10.mdb	12/04/2013 09:53 AM
NetherlandsTriazoles2007-10Pessimistic.mdb	12/04/2013 09:54 AM
SloveniaTriazoles2007-2009.mdb	20/06/2013 06:48 PM
SwedenTriazoles2007-10.mdb	12/04/2013 09:54 AM
SwedenTriazoles2007-10Pessimistic.mdb	12/04/2013 09:55 AM
TriazolesProcessing-Optimistic.mdb	12/04/2013 09:55 AM
TriazolesProcessing-Pessimistic.mdb	12/04/2013 10:02 AM
UnitedKingdomTriazoles2007-2010.mdb	12/04/2013 10:03 AM
UnitedKingdomTriazoles2007-2010Pessimistic.mdb	12/04/2013 10:08 AM
UnitVariability.mdb	12/04/2013 10:08 AM



# New or adjusted information


## Data to add/modify for MCRA 8.0 simulations.

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- ☐ Supervised trial data
- ☐ Adjust toxicological information
- ☐ View and update unit variability information
- ☐ Adjust variability factors
- ☐ Adjust unit variability usage
- ☐ Prepare processing factors
- ☐ Exit

# MCRA: upload focal commodity database

File manager




Select the data source to load.

project

**MCRA**  
Monte Carlo Risk Assessment

**General options**

- [Open an existing project](#)
- [Create a new project](#)
- [Open file manager](#)



MyData		
adminTrainingMCRA8/SharedAnses		
ExampleCumulative.mdb	13/01/2014 02:56 PM	
ExampleCumulativeAnimal1%MRL.mdb	13/01/2014 02:56 PM	
ExampleCumulativeBorrowed.mdb	13/01/2014 02:56 PM	
ExampleCumulativePessimistic.mdb	13/01/2014 02:56 PM	
FocalComCompoundDApple.mdb	13/01/2014 02:57 PM	

Name	Date modified	Type
FocalCommodityCompoundsDApple.mdb	6-5-2013 19:37	Microsoft Access ...

FocalCommodityCompoundsDApple.mdb
All Files
Open
Cancel



# MCRA: common assessment group

data  
select

Select <sup>?</sup>

Food survey   **Compounds**   Conversion   Population Subsets   Food Subsets

Sample Subsets

*A Cumulative Assessment Group (CAG) is defined by linking Compounds to an Effect in table DoseResponseModel (or RelativePotencyFactor). Click on 'Support' and subsequently 'Data Formats Manual' for more information. One compound should be selected as the reference (index) compound (not necessarily a compound with Limit Dose or RPF 1).*

**Cumulative Assessment Group**

(effect) Cranio-facial effect  
(effect) Hepatotoxicity

**Reference compound**

Bitertanol (RPF 2.1)  
Cyproconazole (RPF 2.2)  
Diniconazole (RPF 1)  
Epoxiconazole (RPF 1.5)

Next step >>



# MCRA: consumer only approach

select

Select ?

Compounds Conversion Population Subsets **Food Subsets** Sample Subsets

Specify subsets of foods as eaten (in table FoodConsumption) and foods as measured (in table ConcentrationPerSample or table TabulatedConcentration). The two list will adapt to each other, e.g. selecting only Apple will delete Milk from the other list (no Apple in Milk). Note: the first time execution may take a long time, since a food conversion is performed.

Consumer days only ☐

Use food subsets ☒

Treat food subset as focal food eaters concept ☐

Foods as eaten

☐ Only show selected

Selected: 0 out of 554

Alcoholic mixed drinks  
Alcoholic sauce  
Alfalfa sprouts, fresh (Medicago sativa)  
Animal and vegetable fats and oils  
Apple (Malus domestica)  
Apple strudel  
Asparagus (Asparagus officinalis)  
Aspartam  
Aubergines (egg plants) (Solanum melongena)  
Avocados (Persea americana)  
Bacon  
Baklava  
Bamboo shoots (Bambusa vulgaris)  
Bananas (Musa paradisica)  
Barbecue sauce  
Barley porridge  
Beans (Phaseolus vulgaris)

select

select corresponding foods as measured

Foods as measured

☐ Only show selected

Selected: 0 out of 30

APRICOTS  
AUBERGINE  
BANANAS  
BASIL  
BEANS (WITH PODS)  
BEETROOT  
CARROTS  
CELERIAC  
CELERY LEAVES  
CHERRIES  
CHIVES  
CUCUMBERS  
DATES  
GRAPEFRUIT  
LEEK  
ORANGES  
PARSLEY

select

select corresponding foods as eaten

Show subset statistics

Next step >>





# MCRA: Model (1)

model

Model <sup>?</sup>

Concentrations

Intakes

Monte-Carlo

Uncertainty

Output

Concentration data can be sampled directly from the data (empirical model) or from parametric models. Concentrations < LOR (Limit Of Reporting) (non-detects) can be co-modelled (censored models) or one can specify a non-detects handling method for imputation. Agricultural use data can be used to impose true zeroes for all or part of the non-detects. Effects on concentrations from food processing can be specified in processing factors.

Concentration model

EFSA Guidance Optimistic

EFSA Guidance Pessimistic

Concentration model

Custom

Default concentration model

Non-Detect Spike LogNormal

Non-detects replacement

By  $f \times \text{LOR}$

• Factor  $f$  ( $f \times \text{LOR}$ )

1

Next step >>

# MCRA: Model (2)

**model****Model** <sup>?</sup>

Concentrations   Unit-variability   Intakes   Monte-Carlo   **Uncertainty**   Output

*Repeated analyses are made using resampled data. Results are displayed in the form of approximate confidence intervals. Warning: computation times may be substantially longer.*

Perform uncertainty analysis



Number of iterations per resampled set

Number of resample cycles

Resample concentrations



• Parametric uncertainty



Resample individuals



[Show advanced settings](#)

**Next step >>**



# MCRA: output requirements

model

Model <sup>?</sup>

Concentrations Unit-variability Intakes Monte-Carlo Uncertainty **Output**

Specify details of output that will be generated

Show percentiles for 50 75 90 95 99 99.9

Percentage for drilldown 99.9

Percentage for upper tail 97.5

Show % of population below level(s) Manual

• Exposure levels 1 10 50 100 200 500

• Exposure levels are Percentage

Show advanced settings

Next step >>

← % of ARfD

# MCRA: Output (1)

summary
data
select
model
output

Output ?

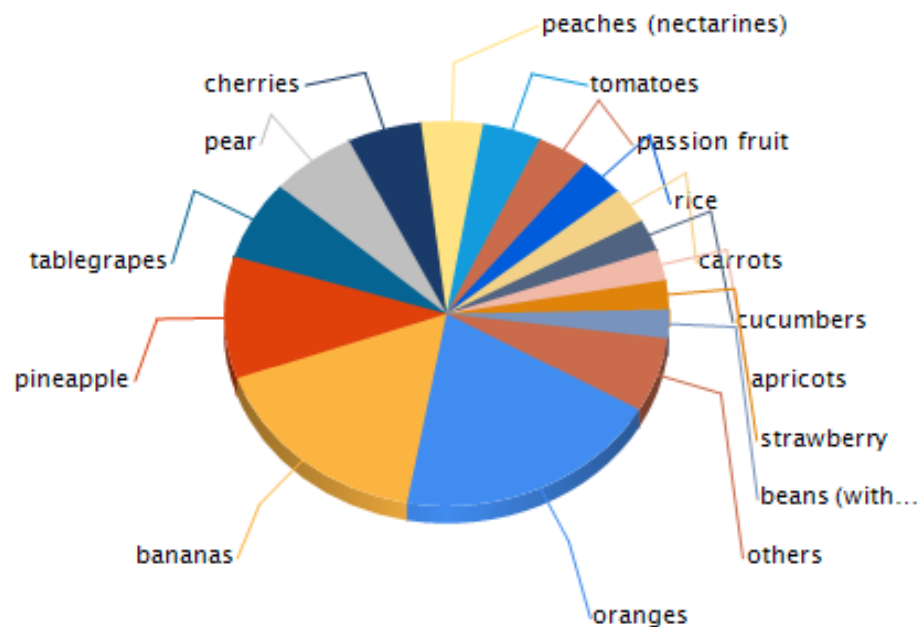
Selection (0): Select an action...

Output	Completed	Description	Select
<a href="#">short</a> <a href="#">detailed</a> <a href="#">conversion</a>	3-10-2013 10:43:9		

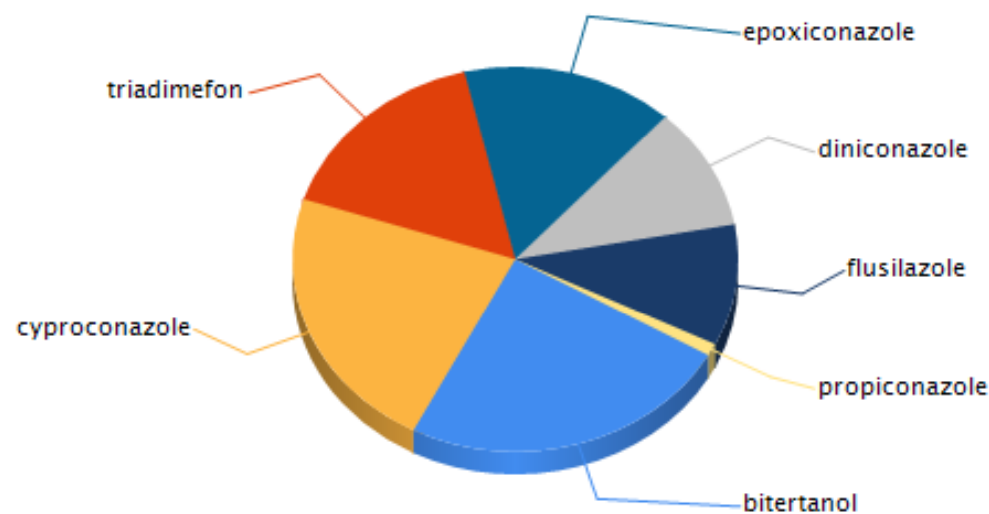


# Output (2): Contribution foods and compounds

Contribution to total exposure distribution for foods as measured



Contribution to the total exposure distribution







# Output (3): Number of person-days per million

## Exposure percentages

Reference: Flusilazole , ARfD = 500 ( $\mu\text{g/kg bw/day}$ ), Safety factor = 100

Exposure ( $\mu\text{g/kg bw/day}$ )	Percentage of reference dose	Margin of Exposure	Percentage	Lower Bound (p2.5)	Upper Bound (p97.5)	Number of people per million exceeding individual days
5	1.00 %	1E+04	79.51 %	77.91 %	80.85 %	204,873
50	10.00 %	1000	99.98 %	99.91 %	100.00 %	199
250	50.00 %	200	100.00 %	100.00 %	100.00 %	0
500	100.00 %	100	100.00 %	100.00 %	100.00 %	0
1000	200.00 %	50	100.00 %	100.00 %	100.00 %	0
2500	500.00 %	20	100.00 %	100.00 %	100.00 %	0



## Output (4): Number of person-days per million (example)

Exposure ( $\mu\text{g/kg}$ bw/day)	Percentage of reference dose	Margin of Exposure	Percentage	Lower Bound (p2.5)	Upper Bound (p97.5)	Number of people per million exceeding individual days
5	1.00 %	1E+04	2.33 %	0.2748	5.321	976,750
50	10.00 %	1000	83.05 %	74.97	91.22	169,460
250	50.00 %	200	99.24 %	98.38	99.79	7,620
500	100.00 %	100	99.96 %	99.86	100	440
1000	200.00 %	50	100.00 %	99.99	100	0
2500	500.00 %	20	100.00 %	100	100	0





# Validation

- DEEM-FCID is standard of US-EPA

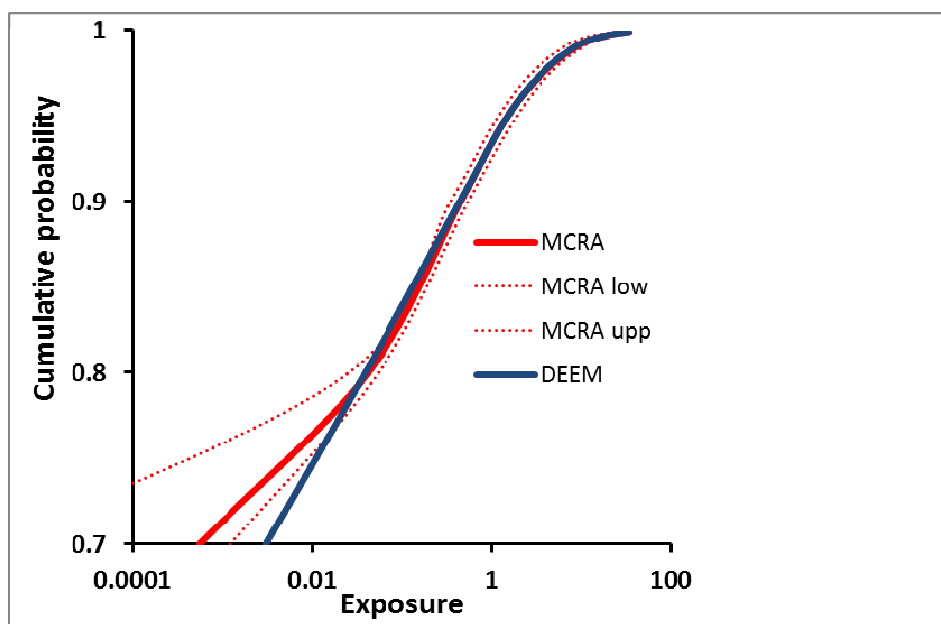
Ver. 3.16, 03-08-d

## DEEM-FCID

Dietary Exposure Evaluation Model

Based on NHANES 2-day food consumption data for 2003-2008

Food translations based on  
EPA/USDA FCID recipe set  
as of February 2012



- Validation result: Good agreement MCRA and DEEM
- DEEM less precise at low exposures due to binning
- Not a problem because upper tail is relevant

# Documentation and help

- In-line documentation of software, using strict protocols for naming classes, methods and properties
- User manual, data format manual, reference manual
- Help function

[Introduction](#)[User Manual](#)[Data Formats Manual](#)[Reference Documents](#)[About](#)[Contact](#)



# ACROPOLIS EXERCISE

- Use of the IT tool and data to calculate **cumulative exposure** to pesticides
  - Triazole pesticides
- **Practicality** of performing a cumulative dietary exposure assessment according to the requirements of the EFSA guidance on probabilistic modelling
- Training and user groups





## Experience 1 ACROPOLIS partners

- Acute and chronic cumulative exposure modelling is possible
- Application of the optimistic model is feasible
- Performance of the pessimistic model run is very laborious:
  1. Determination authorised uses
  2. Supplementation or replacement of RACs with insufficient data
    - Borrowing data from other countries
    - MRLs or field trial data



## Experience 2 ACROPOLIS partners

- Inclusion of MRLs of animal commodities resulted in
  - Unrealistic conclusions regarding the contribution of animal commodities to the dietary exposure.
- Which number of person-days exceeding the ARfD/ADI is associated with an unacceptable health risk is an open issue
  - should be decided by risk managers
  - ACROPOLIS IT tool is open for all stakeholders
  - there is not any decision taken by the tool, it just follows the EFSA guidance



## Experience 3 user group regulators

- More experience is needed with the EFSA guidance and the model with other (larger) CAGs
  - Proof of principle, plan to upscale performance
- Need for 'realistic' scenario that combines the optimistic and pessimistic model run
  - still be argued to be conservative (precautionary principle) but not over-conservative



## Experience 4 user group food authorities

- Pessimistic scenario: replacement LoR
  - Look at historical use
    - If not detected in the past nd (or  $< \text{LoR}$ ) = 0
    - If detected in certain percentage uses insert  $1/2/ \text{LoD}$  or fraction of LoD (or LoR)
- SSD data easy to use
- Animal products are measured and can be made available





## Experience 5 user group industry (a)

- Scenario 1: existing situation → run with monitoring data
- Scenario 2: 100% of use on food A is replaced by new agricultural use
  - Measure 1 or more chemicals in FT of new agricultural use
  - Implication is that monitoring data for food A are no longer relevant
  - ➔ Run with FT data instead of monitoring data for food A  
**Exposure can be higher, equal or lower**  
e.g. high conc. Tebuconazole may still be lower than RPF\*low conc. Flusilazole when RPF=40





## Experience 5 user group industry (b)

- Scenario 3: p% of use on food A is replaced  
→ run where in p% of Monte Carlo draws FT data are sampled, and in (100-p)% the monitoring data
- Scenario 4: the new agricultural use is additional to all existing uses
- Scenario 5: the new agricultural use with compound C is additional to all existing uses without compound C, and replaces existing uses with compound C

(replacement scenarios not in EFSA guidance)



## Second stakeholders conference

- Training was well-received by nearly all stakeholders (NGO did not attend training, although they were invited)
- Pesticide industry was able to connect focal commodity to monitoring and consumption data
- More transparent use of data through the use of the ACROPOLIS IT tool
- Easy-to-use software
- One uniform tool for discussing the level of protection, but no direction or decision has been taken (objective tool)



# DG SANCO and ACROPOLIS

- The European Commission sets the level of protection



- all member states are trained
- European investment should be used
- involvement of stakeholders responsible for pesticide risk assessment
- linking innovation with practical needs of DG SANCO



# Current and future organization

- New concept requires time to digest
- ACROPOLIS follow-up initiative
- Agreement to share data and to use it
- DG SANCO and EFSA cooperation
  - Form 'proof of principle' to a full production server
  - Still a lot of issues to be solved
- Open debate also with NGOs



# Thanks to all the people involved

