Risk assessment chemical contaminants

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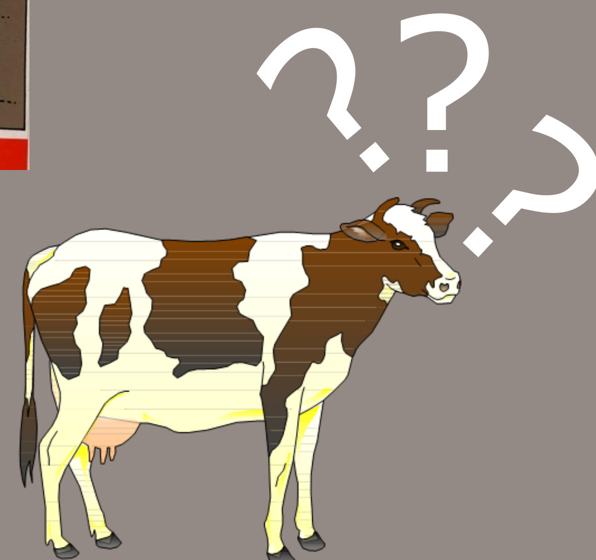
The Belgian dioxin crisis in 1999



General Food Law (EC No. 178/2002)

1.2.2002 EN Official Journal of the European Communities L 31/1

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(Acts whose publication is obligatory)

REGULATION (EC) No 178/2002 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 28 January 2002

laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety

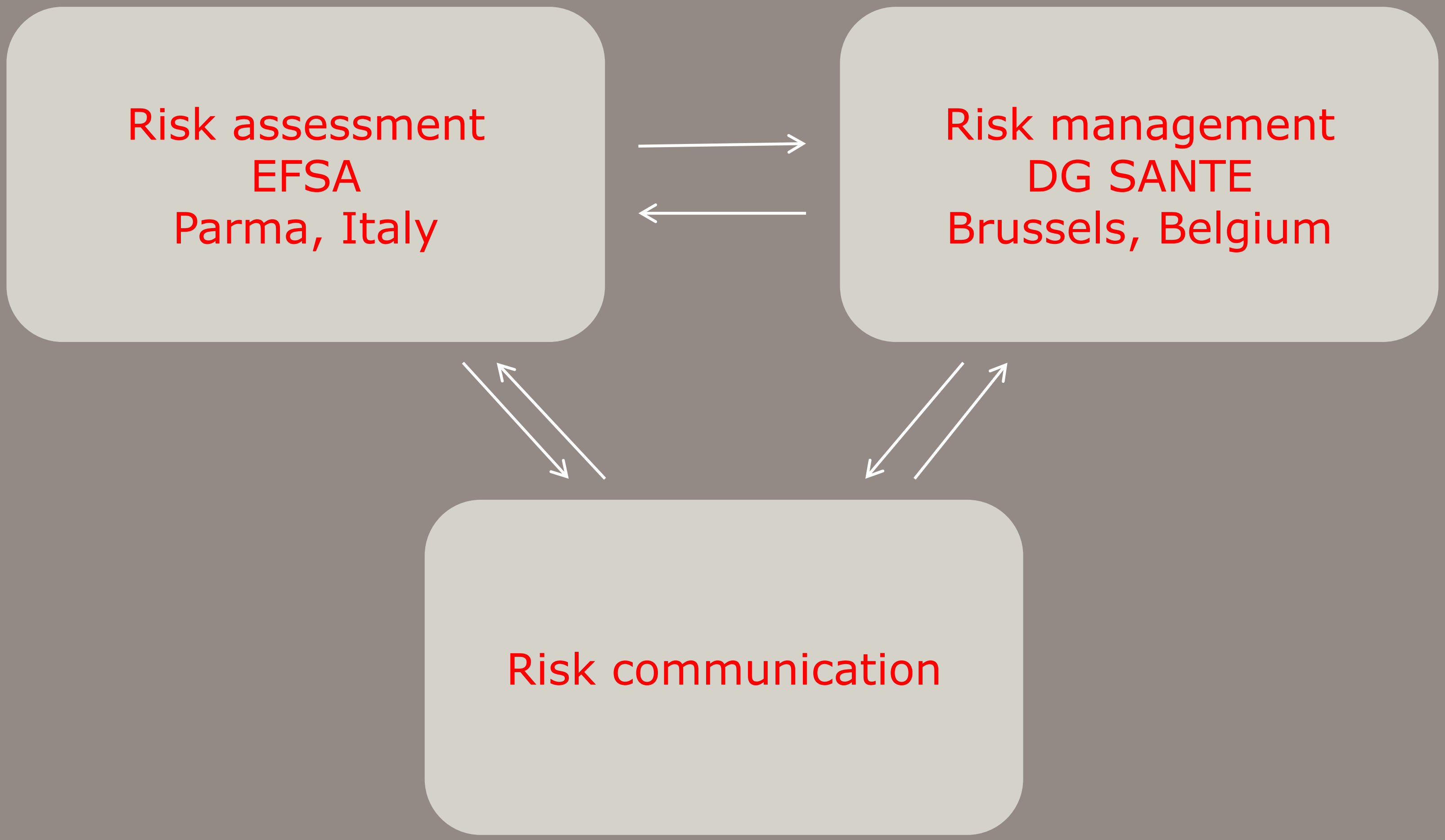
THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Articles 37, 95, 133 and Article 152(4)(b) thereof,

the Member States. When Member States adopt measures governing food, these differences may impede the free movement of food, create unequal conditions of competition, and may thereby directly affect the functioning of the internal market.

- Basis for Food and feed safety management

Risk analysis food chain within the EU



EFSA: responsible for risk assessment

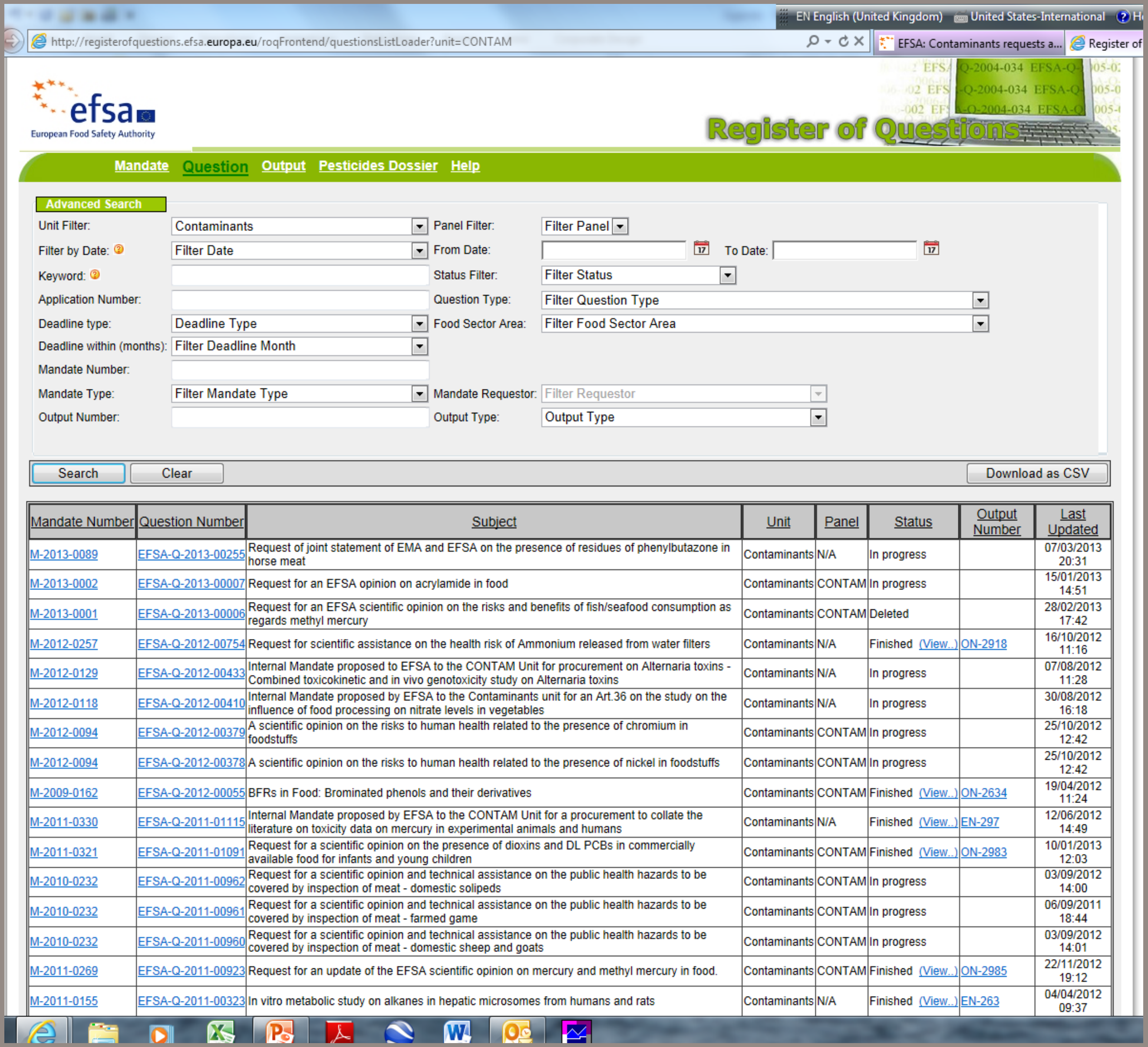
efsa
European Food Safety Authority

- 10 Panels with experts
- Not representation of Member States
- Supported by staff
- Science based risk assessments
- CONTAM Panel: dealing with contaminants

CONTAM Panel

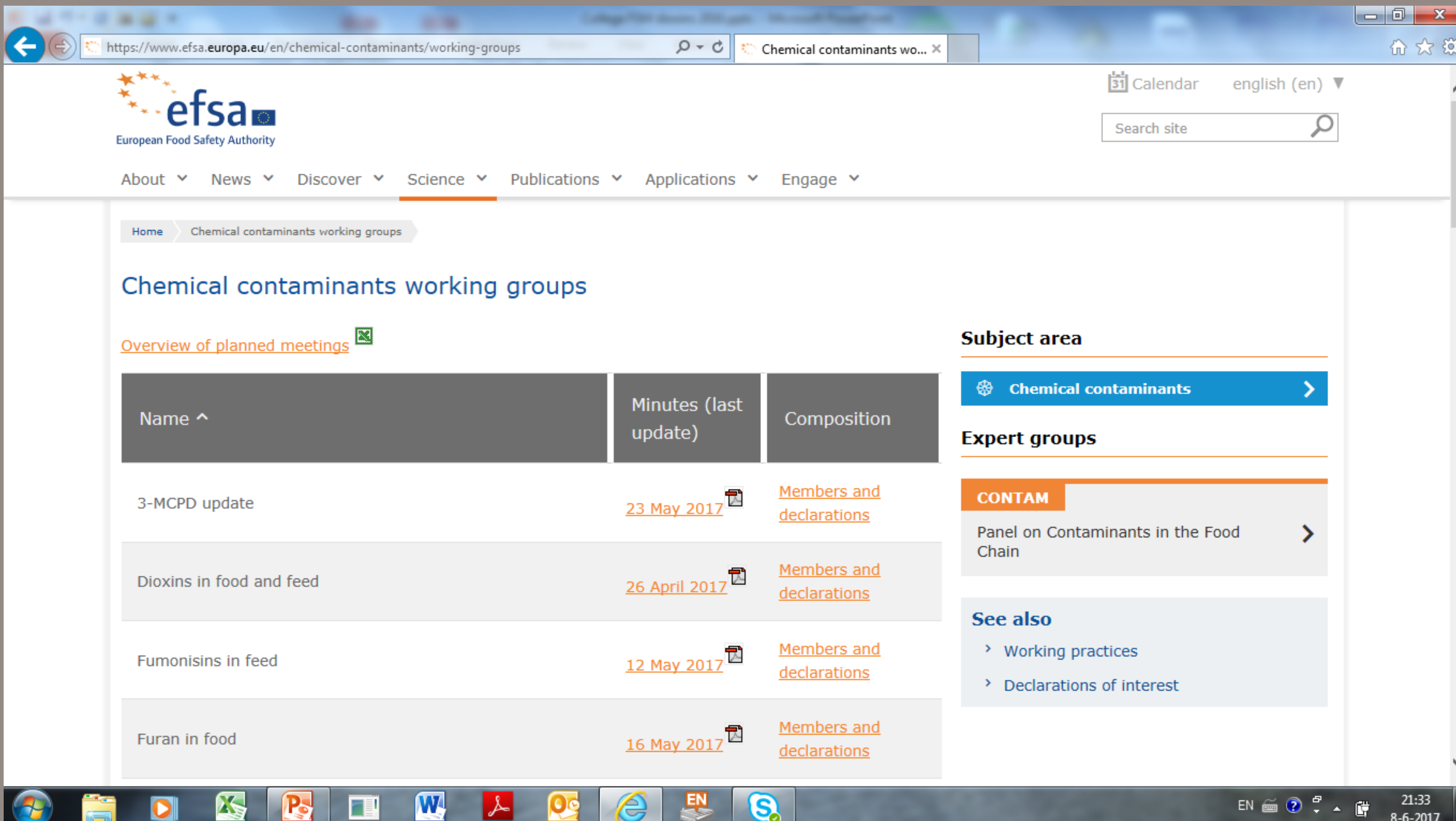
- Dealing with contaminants in the food chain
- Persistent organic pollutants:
    - Dioxins and dl-PCBs, PFASs (PFOS/PFOA), chlorinated parafines
- Metals, Pb, Cd, Hg, As, Cr
- Processing contaminants like furans, acrylamide
- Non-allowed pharmacologically active substances, like chloramphenicol, malachite green and other dyes, nitrofurans
- Mycotoxins, plant toxins, marine biotoxins
    - DON, ZEN, tetrodotoxins

Mandates

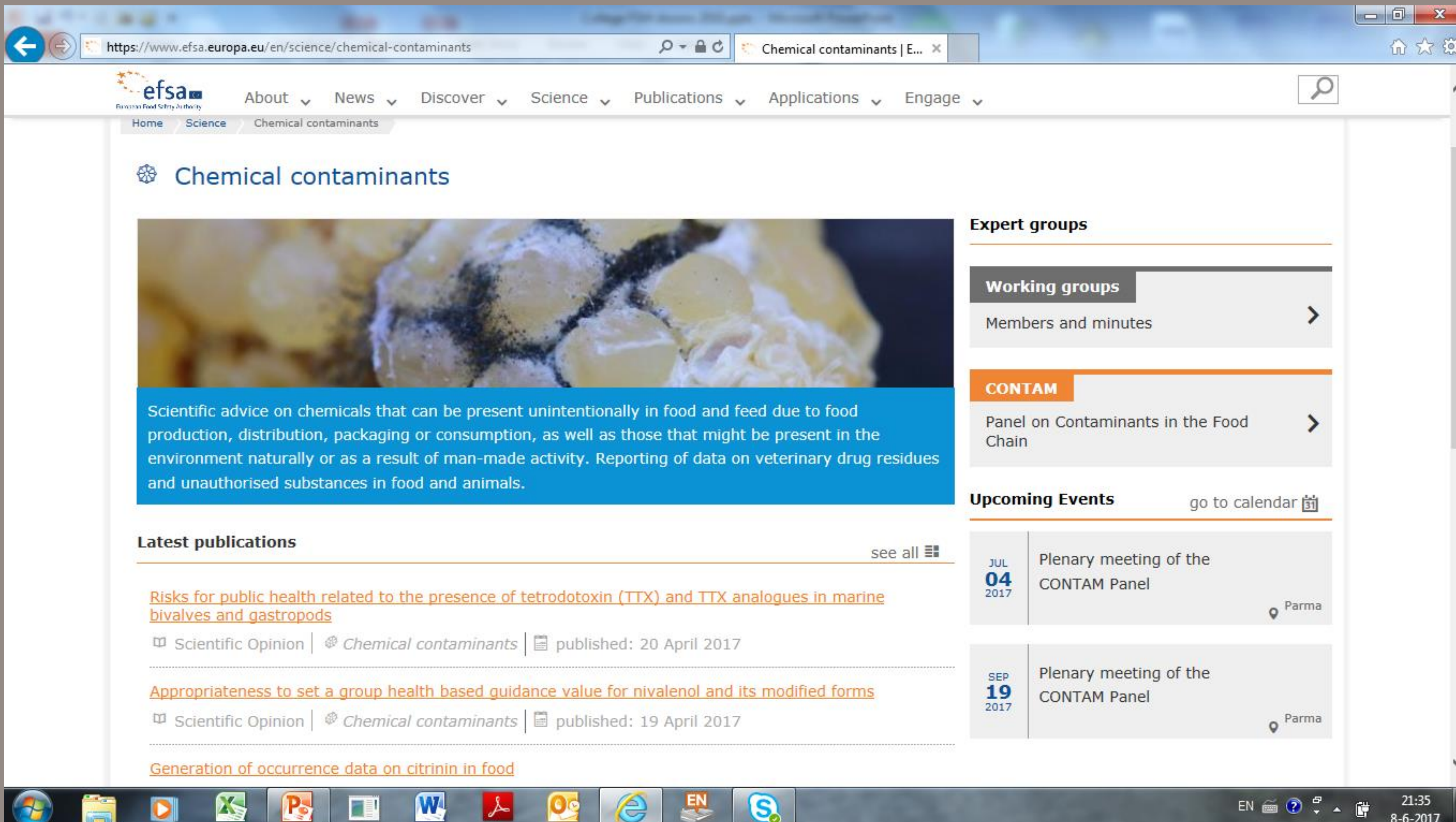


Mandate Number	Question Number	Subject	Unit	Panel	Status	Output Number	Last Updated
M-2013-0089	EFSA-Q-2013-00255	Request of joint statement of EMA and EFSA on the presence of residues of phenylbutazone in horse meat	Contaminants	N/A	In progress		07/03/2013 20:31
M-2013-0002	EFSA-Q-2013-00007	Request for an EFSA opinion on acrylamide in food	Contaminants	CONTAM	In progress		15/01/2013 14:51
M-2013-0001	EFSA-Q-2013-00006	Request for an EFSA scientific opinion on the risks and benefits of fish/seafood consumption as regards methyl mercury	Contaminants	CONTAM	Deleted		28/02/2013 17:42
M-2012-0257	EFSA-Q-2012-00754	Request for scientific assistance on the health risk of Ammonium released from water filters	Contaminants	N/A	Finished (View..)	ON-2918	16/10/2012 11:16
M-2012-0129	EFSA-Q-2012-00433	Internal Mandate proposed to EFSA to the CONTAM Unit for procurement on Alternaria toxins - Combined toxicokinetic and in vivo genotoxicity study on Alternaria toxins	Contaminants	N/A	In progress		07/08/2012 11:28
M-2012-0118	EFSA-Q-2012-00410	Internal Mandate proposed by EFSA to the Contaminants unit for an Art.36 on the study on the influence of food processing on nitrate levels in vegetables	Contaminants	N/A	In progress		30/08/2012 16:18
M-2012-0094	EFSA-Q-2012-00379	A scientific opinion on the risks to human health related to the presence of chromium in foodstuffs	Contaminants	CONTAM	In progress		25/10/2012 12:42
M-2012-0094	EFSA-Q-2012-00378	A scientific opinion on the risks to human health related to the presence of nickel in foodstuffs	Contaminants	CONTAM	In progress		25/10/2012 12:42
M-2009-0162	EFSA-Q-2012-00055	BFRs in Food: Brominated phenols and their derivatives	Contaminants	CONTAM	Finished (View..)	ON-2634	19/04/2012 11:24
M-2011-0330	EFSA-Q-2011-01115	Internal Mandate proposed by EFSA to the CONTAM Unit for a procurement to collate the literature on toxicity data on mercury in experimental animals and humans	Contaminants	N/A	Finished (View..)	EN-297	12/06/2012 14:49
M-2011-0321	EFSA-Q-2011-01091	Request for a scientific opinion on the presence of dioxins and DL PCBs in commercially available food for infants and young children	Contaminants	CONTAM	Finished (View..)	ON-2983	10/01/2013 12:03
M-2010-0232	EFSA-Q-2011-00962	Request for a scientific opinion and technical assistance on the public health hazards to be covered by inspection of meat - domestic solipeds	Contaminants	CONTAM	In progress		03/09/2012 14:00
M-2010-0232	EFSA-Q-2011-00961	Request for a scientific opinion and technical assistance on the public health hazards to be covered by inspection of meat - farmed game	Contaminants	CONTAM	In progress		06/09/2011 18:44
M-2010-0232	EFSA-Q-2011-00960	Request for a scientific opinion and technical assistance on the public health hazards to be covered by inspection of meat - domestic sheep and goats	Contaminants	CONTAM	In progress		03/09/2012 14:01
M-2011-0269	EFSA-Q-2011-00923	Request for an update of the EFSA scientific opinion on mercury and methyl mercury in food.	Contaminants	CONTAM	Finished (View..)	ON-2985	22/11/2012 19:12
M-2011-0155	EFSA-Q-2011-00323	In vitro metabolic study on alkanes in hepatic microsomes from humans and rats	Contaminants	N/A	Finished (View..)	EN-263	04/04/2012 09:37

Working groups



Opinions



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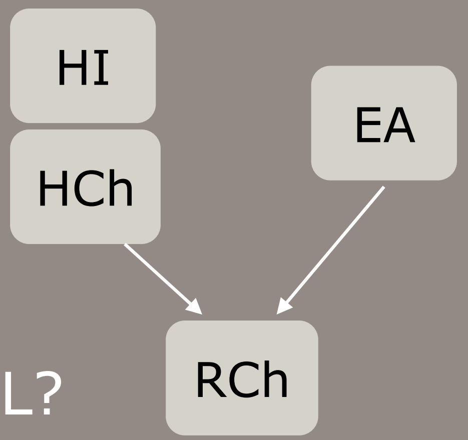
Risk assessment process

- Hazard identification:
  - Which “adverse“ effects?
  - Humans, animals
- Hazard characterization
  - At which dose? LOAEL/NOAEL/BMDL?
- Estimate exposure (different age groups)
  - Data on levels in food/feed
  - Data on food/feed consumption
- Risk characterization:
  - Derive HBGV: ARfD/TDI
  - margin of exposure (MOE); MOE large enough?



Hazard identification

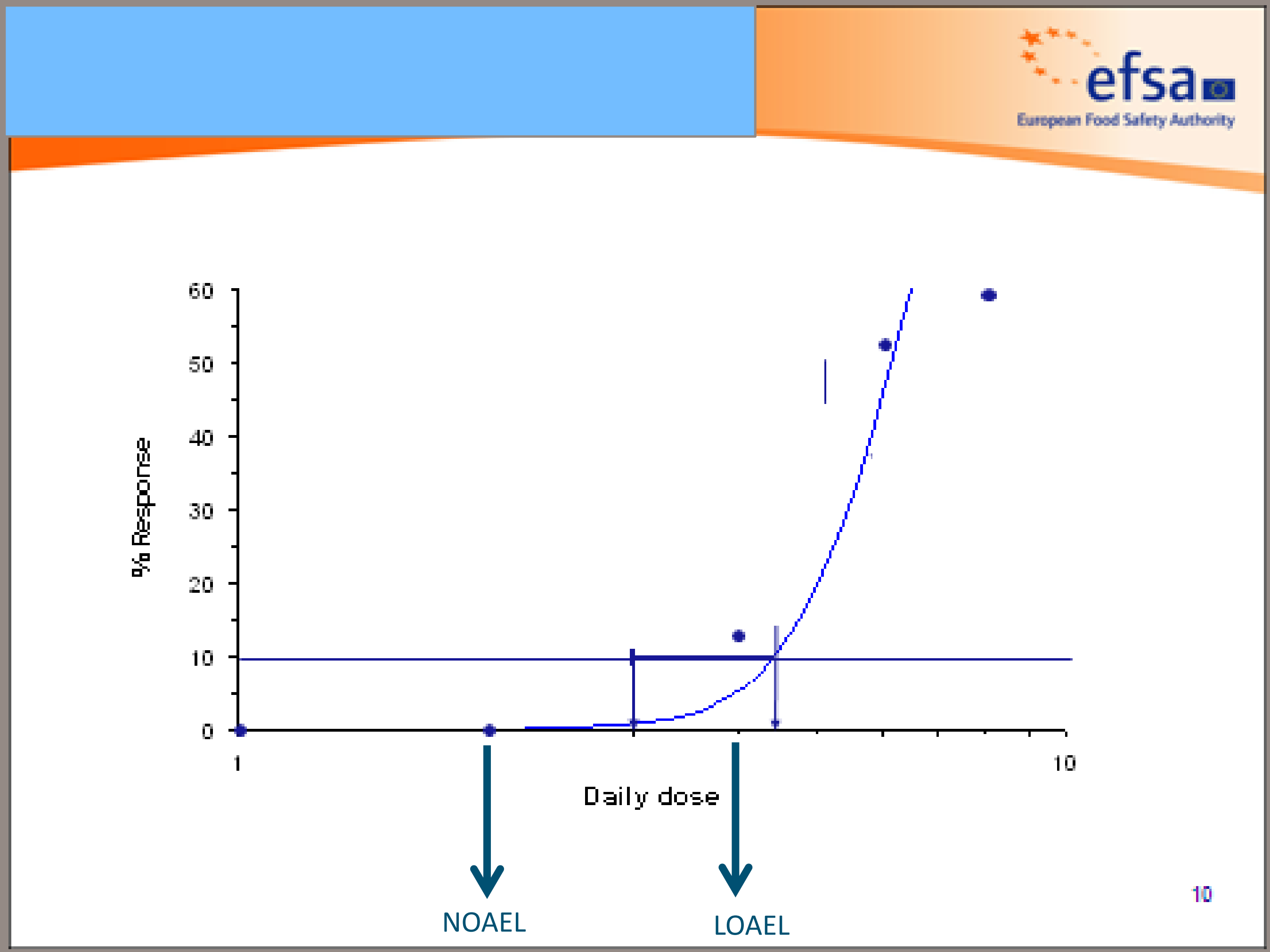
- Which effects to take into account?
- Studies with experimental animals
  - Rats, mice but occasionally also pigs
- Studies with humans,
  - Accidents
  - Background exposure
- In vitro studies (mode of action)
  - E.g. genotoxicity

Hazard characterisation

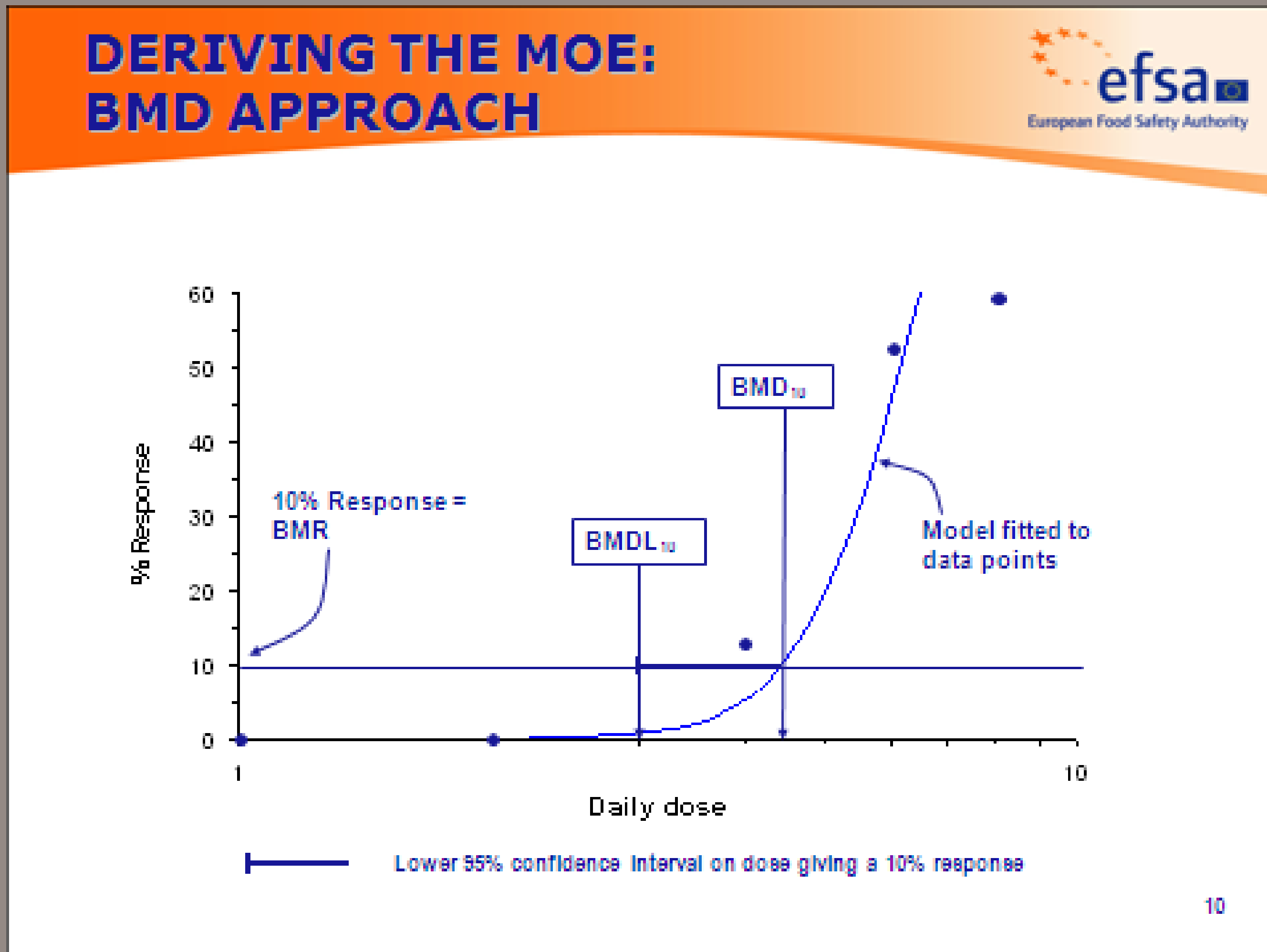
- Which dose is critical?
  - i.e. showing effects
- Classical approach: NOAEL/LOAEL
- New approach: BMD-modelling

"It's the dose that determines the poison"

BMDL-approach



BMDL-approach



Different models for curve fitting

- Previously BMDL based on model with acceptable curve fit and lowest BMDL
  - BMR 10% affected animals for quantal data
  - BMR 5% for continuous data
- Now curve fits evaluated and weighted
  - BMDL-BMDU intervals combined based on weight
  - Model averaging
- Less conservative approach
- Only possible for animal data, not human data
- BMDL used as PoD

Health based guidance values

- Which point of departure (Reference Point)?
- Preference for human data
    - Reduce uncertainty like inter- and intraspecies differences
- If not available, use animal studies (“mildest effect”)
- If not available either: “Threshold of Toxicological Concern (TTC)”

Health based guidance values

- Use of default “Uncertainty Factors (UFs)”
  - interspecies variability in toxicokinetics: 4.0
  - interspecies variability in toxicodynamics: 2.5
  - intraspecies variability in toxicokinetics: 3.16
  - intraspecies variability in toxicodynamics: 3.16
- May be reduced based on information
- Regarded as conservative
  - but not necessarily the case (TTX?)

Hazard characterisation

- Evaluate exposure (example on DON)
- Compare with TDI/ARfD
- Conclude on the risks
- Evaluate the uncertainties in the assessment

- Risk communication

Risks for farm animals

- Relatively few studies, compared to experimental animals
- For some compounds NOAELs/LOAELs determined
- No uncertainty factors applied
- Exposure assessment based on reported levels
    - Use of P50, and P95
- Exposure based on compound feed, or on feed ingredients, if numbers for feed too low
    - No database available, like for humans

In addition

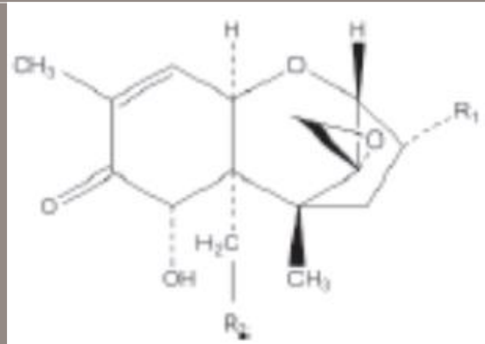
- Transfer feed to food
  - Normally not taken into account for setting MLs
  - Exception is aflatoxin M1
  - For other compounds: ML for feed not necessarily low enough to ensure that food is below ML
- Mode of action
  - Important to understand toxic effects
  - Normally not used in Risk assessment
  - Exception is genotoxicity

Mycotoxins and plant toxins (examples)

Recent work from EFSA on mycotoxins

- Opinions on aflatoxins, OTA, nivalenol, sterigmatocystine, ergot alkaloids, enniatins, T2/HT2, masked forms (ZEN, NIV, T2/HT2, FUMs)
- Recent (2017) opinion on deoxynivalenol (DON)
  - Including ADONs and D3G (modified forms)
- Recent (2016) opinion on zearalenone (ZEN)
  - Including (potential) modified forms
- Opinion on moniliformin (in press)
- Working on DAS, fumonisins

Deoxynivalenol



	R_1	R_2
DON	-OH	-OH
3-Ac-DON	-OAc	-OH
15-Ac-DON	-OH	-OAc
DON-3-glucoside	-Ogluc	-OH

- In particular detected on wheat
    - Co-occurrence with other Fusarium toxins
- Often also 3- and or 15-acetyl-DON and DON-3-glucoside (levels lower than DON)
- Can be transformed into DON in GI-tract
- Typical effects are vomiting at high doses (e.g. mink, pigs)
- and decreased growth in mice and feed intake
- At higher doses immunotoxic

EFSA, 2017

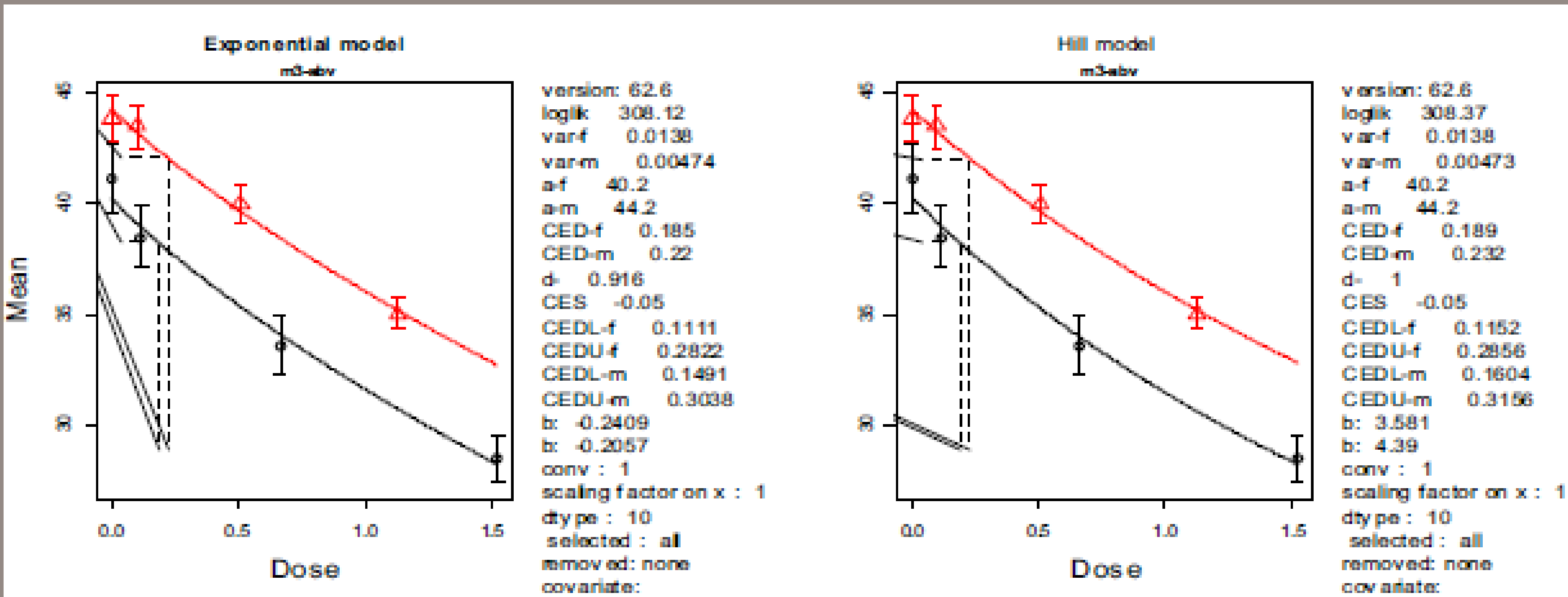
Critical study deoxynivalenol

Iverson et al. (1995) data					
Concentration as reported in the study (mg DON/kg diet)	Average feed consumption (g/day)	Number of animals per group	Average body weight (g)	Number of animals per group	Dose (mg DON/kg bw per day)
Female mice data					
0	4.48	22	41.54	36	0
1	4.44	24	38.71	42	0.115
5	4.46	23	33.76	37	0.661
10	4.34	25	28.55	38	1.520
Male mice data					
0	4.30	24	43.85	37	0
1	4.28	24	43.51	35	0.098
5	4.05	25	40.03	43	0.506
10	3.79	25	35.09	42	1.126

bw: body weight.

- NOAEL female mice: 0.1 mg/kg bw/day

BMD modelling and TDI



- TDI of 1 µg/kg bw/day, based on $BMDL_{05}$ of 0.11 mg/kg bw/day (both sexes combined); UF of 100
  - BMDL05 similar to NOAEL of 0.1 mg/kg bw/day
- ARfD of 8 µg/kg bw/day

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Exposure assessment

- Data collected from member states
- Data set cleaned, a.o. for too high LOQs
- P50 and P95 determined

- In addition MSs provided food consumption data for different age groups

Consumption surveys from MSs

Appendix D – Dietary surveys considered for the acute and chronic human dietary exposure assessment

Table D.1: Dietary surveys used for the estimation of acute and chronic dietary exposure

Country	Survey acronym	Survey period	N of days per subject	N of subjects/N of days						
				Infants	Toddlers	Other children	Adolescents (mean age)	Adults	Elderly	Very elderly
Austria	ASNS – Adults	2010–2012	2	–	–	–	–	308/726	67/181	25/85
	ASNS – Children	2010–2012	3	–	–	128/384	237/706	–	–	–
Belgium	Regional Flanders	2002–2002	3		36/108	625/1875	–	–	–	–
Belgium	Diet National 2004	2004	2		–	–	576/1,187 (16a)	1,292/2,648	511/1,045	704/1,408
Bulgaria	NSFIN	2004	1				–/162	–/691	–/151	–200
Bulgaria	NUTRICHILD	2007	2	861/1,720	428/856	433/867	–	–	–	–
Cyprus	Childhealth	2003	3	–	–	–	303/909 (13a)	–	–	–
CzechRepublic	SISP04	2003–2004	2	–	–	389/778	298/596 (13a)	1666/3,332	–	–
Denmark	DANSDA 2005-08	2005–2008	7	–	–	298/2,085	377/2,622 (13a)	1739/12,127	274/1,916	12/84
Denmark	IAT 2006 07	2006–2007	7	826/5,771	917/6,388	–	–	–	–	–
Estonia	NDS 1997	1997	1					–/1,866	–	–
Finland	DIPP 2001 2009	2001–2009	3	500/1,500	500/1,500	750/2,250	–	–	–	–
Finland	NWSSP07 08	2007–2008	4		–	–	306/1,186 (13a)	–	–	–
Finland	FINDIET2012	2012	2		–	–	–	1,295/2,590	413/826	–
France	INCA2	2007	7		–	482/3,315	973/6,728 (14a)	2,276/15,727	264/1,824	84/571
Germany	VELS	2001–2002	6	159/927	348/1,947	293/1,610	–	–	–	–
Germany	EsKiMo	2006	3		–	835/2,498	393/1,179 (11a)	–	–	–
Germany	National Nutrition Survey II	2007	2		–	–	1,011/2,022 (16a)	10,419/20,838	2,006/4,012	490/980
Greece	Regional Crete	2004–2005	3			838/2,508	–	–	–	–
Greece	DIET LACTATION GR	2005–2007	3		–	–	–	65/350	–	–
Hungary	National Repr Surv	2003	3		–	–	–	1,074/3,222	206/618	80/240
Ireland	NANS 2012	2008–2010	4		–	–	–	1,274/5,096	149/596	77/308
Italy	INRAN SCAI 2005 06	2005–2006	3	16/48	36/108	193/579	247/741 (14a)	2,313/6,939	290/870	228/684
Latvia	EFSA TEST	2008	2			187/377	453/979 (14a)	1,271/2,655	–	–
Latvia	FC PREGNANTWOMEN 2011	2011	2		–	–	–	1,002/2,005	–	–
Netherlands	VCP kids	2006–2007	3		322/644	957/1,914	–	–	–	–

Exposure assessment

- Many data <LOQ, especially for modified forms
- When assuming LOQ levels for non-detects, large overestimation exposure
- Based on detected levels, relative contribution of these forms estimated
  - 10, 15 and 20% for 3-ADON, 15-ADON and D3G
  - Applied to non-detects to determine the sum
- Use of P50 (chronic)/P95 (acute) values
- Combine with consumption data
  - Results in range of mean intake for surveys
  - Both lower- and upperbound

Exposure assessment

- Use of P50 (chronic)/P95 (acute) values
  - Both lower- and upperbound
- Combine with consumption data
  - For each person in each survey
  - Determine mean and P95 for each survey
- Results in range (min-max) of mean and P95 intake for surveys

Chronic exposure assessment DON

Table 33: Summary statistics of probabilistic acute dietary exposure assessment to the sum of DON, 3-Ac-DON, 15-Ac-DON and DON-3-glucoside (at the lower, middle and upper bound) across European dietary surveys (µg/kg bw per day) by age group

Age group[a]	Mean dietary exposure (µg/kg bw per day)			95th percentile dietary exposure (µg/kg bw per day)	
	n	Minimum	Maximum	Minimum	Maximum
		Lower bound			
Infants[b]	6	0.3 (0.1–0.5)	0.5 (0.4–0.9)	1.7 (1.6–1.8)	2.2 (1.9–2.7)
Toddlers	11	0.6 (0.3–1.1)	1.0 (0.9–1.1)	1.8 (1.6–2.0)	3.2 (2.1–4.5)
Other children	20	0.5 (0.5–0.6)	1.0 (0.9–1.1)	1.5 (1.4–1.6)	3.0 (2.7–3.4)
Adolescents	20	0.3 (0.3–0.4)	0.7 (0.6–0.7)	0.8 (0.7–0.9)	2.2 (2.2–2.2)
Adults	24	0.2 (0.2–0.3)	0.4 (0.3–0.5)	0.8 (0.7–1.0)	1.5 (1.3–1.7)
Elderly	16	0.2 (0.2–0.3)	0.4 (0.3–0.5)	0.7 (0.6–0.7)	1.4 (1.1–1.7)
Very elderly	14	0.3 (0.2–0.5)	0.4 (0.3–0.6)	0.7 (0.5–1.0)	1.5 (1.1–2.2)

- Combining P50 occurrence levels with all different consumption surveys (lowerbound: <LOQ equal to zero)

Exposure assessment

Table 33: Summary statistics of probabilistic acute dietary exposure assessment to the sum of DON, 3-Ac-DON, 15-Ac-DON and DON-3-glucoside (at the lower, middle and upper bound) across European dietary surveys (µg/kg bw per day) by age group

Age group[(a)]	Mean dietary exposure (µg/kg bw per day)			95th percentile dietary exposure (µg/kg bw per day)	
	n	Minimum	Maximum	Minimum	Maximum
		Upper bound			
Infants[(b)]	6	1.0 (0.9–1.0)	2.9 (2.8–3.2)	2.7 (2.6–2.8)	6.7 (6.2–7.1)
Toddlers	11	1.5 (1.2–1.9)	2.2 (2.0–2.6)	3.5 (3.3–3.6)	5.4 (4.5–6.5)
Other children	20	1.2 (1.1–1.3)	2.0 (1.9–2.0)	2.6 (2.5–2.7)	4.5 (4.2–4.9)
Adolescents	20	0.6 (0.6–0.6)	1.2 (1.1–1.3)	1.3 (1.3–1.4)	2.9 (2.7–3.2)
Adults	24	0.5 (0.5–0.5)	1.0 (1.0–1.0)	1.5 (1.4–1.6)	2.8 (2.8–2.8)
Elderly	16	0.5 (0.5–0.6)	0.8 (0.8–0.9)	1.3 (1.1–1.6)	2.2 (1.9–2.6)
Very elderly	14	0.5 (0.5–0.6)	0.9 (0.8–1.0)	1.3 (1.2–1.4)	2.2 (1.7–2.9)

- Combining P50 or P95 occurrence levels with all different consumption surveys (upperbound: <LOQ equal to LOQ/LOD) (95% CIs also provided)

Mean exposure (TDI = 1)

Table 33: Summary statistics of probabilistic acute dietary exposure assessment to the sum of DON, 3-Ac-DON, 15-Ac-DON and DON-3-glucoside (at the lower, middle and upper bound) across European dietary surveys (µg/kg bw per day) by age group

Age group[(a)]	Mean dietary exposure (µg/kg bw per day)			Mean dietary exposure (µg/kg bw per day)	
	n	Minimum	Maximum	Minimum	Maximum
		Lower bound		Upper bound	
Infants[(b)]	6	0.3 (0.1–0.5)	0.5 (0.4–0.9)	1.0 (0.9–1.0)	2.9 (2.8–3.2)
Toddlers	11	0.6 (0.3–1.1)	1.0 (0.9–1.1)	1.5 (1.2–1.9)	2.2 (2.0–2.6)
Other children	20	0.5 (0.5–0.6)	1.0 (0.9–1.1)	1.2 (1.1–1.3)	2.0 (1.9–2.0)
Adolescents	20	0.3 (0.3–0.4)	0.7 (0.6–0.7)	0.6 (0.6–0.6)	1.2 (1.1–1.3)
Adults	24	0.2 (0.2–0.3)	0.4 (0.3–0.5)	0.5 (0.5–0.5)	1.0 (1.0–1.0)
Elderly	16	0.2 (0.2–0.3)	0.4 (0.3–0.5)	0.5 (0.5–0.6)	0.8 (0.8–0.9)
Very elderly	14	0.3 (0.2–0.5)	0.4 (0.3–0.6)	0.5 (0.5–0.6)	0.9 (0.8–1.0)

- Combining P50 occurrence levels with all different consumption surveys (95% CIs also provided)

High exposure (P95) (TDI = 1)

Age group[(a)]	n	95th percentile dietary exposure (µg/kg bw per day) Minimum	95th percentile dietary exposure (µg/kg bw per day) Maximum	95th percentile dietary exposure (µg/kg bw per day) Minimum	95th percentile dietary exposure (µg/kg bw per day) Maximum
		Lowerbound		upperbound	
Infants[(b)]	6	1.7 (1.6–1.8)	2.2 (1.9–2.7)	2.7 (2.6–2.8)	6.7 (6.2–7.1)
Toddlers	11	1.8 (1.6–2.0)	3.2 (2.1–4.5)	3.5 (3.3–3.6)	5.4 (4.5–6.5)
Other children	20	1.5 (1.4–1.6)	3.0 (2.7–3.4)	2.6 (2.5–2.7)	4.5 (4.2–4.9)
Adolescents	20	0.8 (0.7–0.9)	2.2 (2.2–2.2)	1.3 (1.3–1.4)	2.9 (2.7–3.2)
Adults	24	0.8 (0.7–1.0)	1.5 (1.3–1.7)	1.5 (1.4–1.6)	2.8 (2.8–2.8)
Elderly	16	0.7 (0.6–0.7)	1.4 (1.1–1.7)	1.3 (1.1–1.6)	2.2 (1.9–2.6)
Very elderly	14	0.7 (0.5–1.0)	1.5 (1.1–2.2)	1.3 (1.2–1.4)	2.2 (1.7–2.9)

- Combining P95 occurrence levels with all different consumption surveys (95% CIs also provided)

LOD/LOQs of (multi)methods

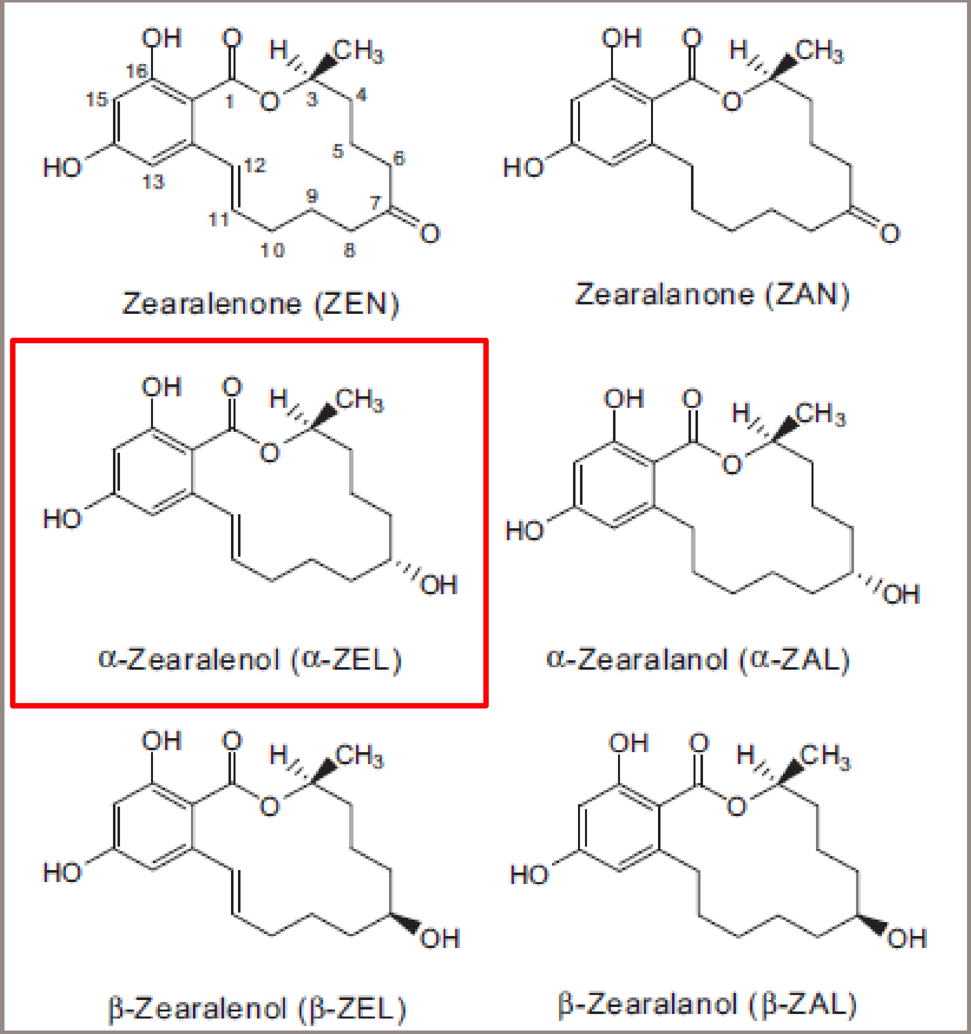
- High number of samples below LOQ causes uncertainty
  - Low LOQs required
- Tendency for rapid analysis and many compounds
  - As a result high LOD/LOQs
- Also problem for trend analysis
- And potentially for deriving maximum levels based on "strict but feasible"

Zearalenone (EFSA, 2016)

- TDI: 0.25 µg/kg bw per day
    - Based on oestrogenic effects in pigs (NOAEL 10.4 µg/kg bw per day; UF of 4x10
- Expressed as ZEN equivalents for ZEN and its modified forms

Metabolites

- Also conjugated forms
- Can be transformed to parents in GI-tract
- α-ZEL most potent animal metabolite, detected in milk by Huang et al., 2014

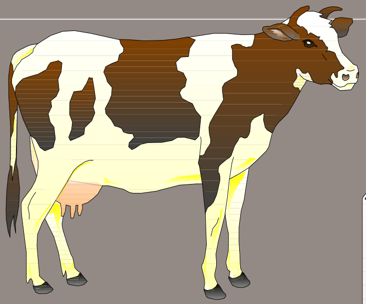


Relative potencies

Table 6: Relative potencies factors (RPFs) given on a molar basis for the phase I and phase II metabolites of ZEN proposed by the EFSA CONTAM Panel

Compound	Relative potency factor (RPF)
ZEN	1.0
ZENGlcs and ZENSulfs	1.0
α-ZEL	60
α-ZELGlcs and α-ZELSulfs	60
β-ZEL	0.2
β-ZELGlcs and β-ZELSulfs	0.2
ZAN	1.5
ZANGlcs and ZANSulfs	1.5
α-ZAL	4.0
α-ZALGlcs, α-ZALSulfs	4.0
β-ZAL	2.0
β-ZALGlcs, β-ZALSulfs	2.0
cis-ZEN	1.0
cis-ZENGlcs and *cis*-ZENSulfs	1.0
cis-α-ZEL	8.0
cis-α-ZELGlcs and *cis*-α-ZELSulfs	8.0
cis-β-ZEL	1.0
cis-β-ZELGlcs and *cis*-β-ZELSulfs	1.0

Potential consequence milk



- Guidance Value for dairy cows: 0.5 mg/kg feed
  - Suppose 2 kg feed means intake of 1 mg ZEN
  - If 1% excreted in milk as α-ZEL: 0.01 mg or 10 μg
  - In 20 litres milk gives level of 0.5 μg/L
- So equivalent to 30 μg ZENeq/L with RPF of 60
- If child of 10 kg drinks 0.5 L: 1.5 μg ZENeq/kg bw/day
- TDI: 0.25 μg/kg bw per day
- So 6-fold exceedance of TDI
- Children(young boys) sensitive to hormones

Consequences

- Based on 0.5 L milk by 10 kg bw child:
- Level should be below 2.5/0.5/60=0.08 µg/L (ppb)

- If 1% transfer is correct:
- Intake cow < 166 µg ZEN
- If 2 kg feed Guidance value dairy cows < 83 µg/kg (6x lower)

- Therefore urgent need for transfer studies and sensitive methods for α-ZEL in milk

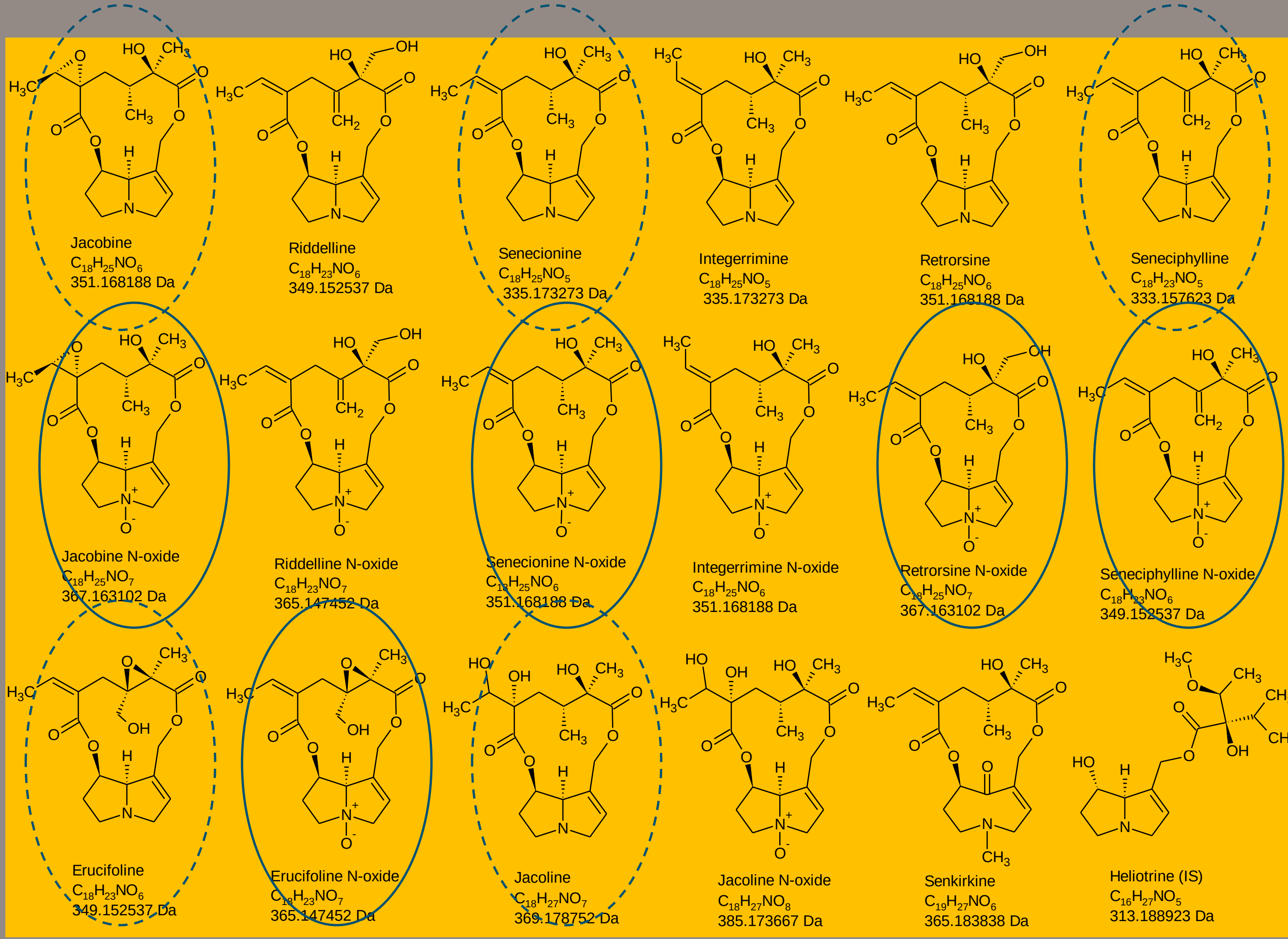
Recent work from EFSA on plant toxins

- Opinion on tropane alkaloids (food)
  - Detected in cereals
  - Lower ARfD established based on human studies
  - Potential risk especially for children
- Opinion on phorbol esters Jatropha (detoxification/feed)
- Opinion on cyanogenic alkaloids
- Opinion on tetrahydrocannabinol
- Report on pyrrolizidine alkaloids (PAs)
  - New $BMDL_{10}$ established for riddelliine
- Working on opium alkaloids

Pyrrolizidine alkaloids (PAs)

- Liver effects like veno-occlusive disease in animals and humans (various incidents)
- Carcinogenic in rats (hepatocellular carcinomas and haemangiosarcomas)
- Genotoxic properties
- Therefore: no threshold so no TDI

Structures of pyrrolizidine alkaloids



Model outcomes

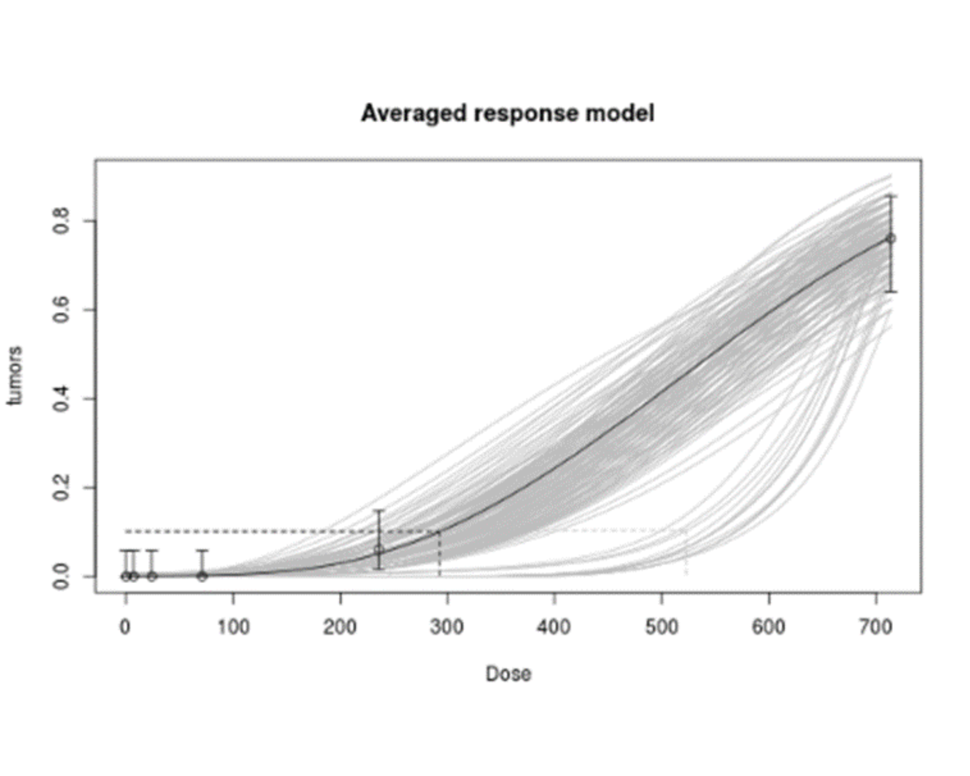
Dose	tumors	N
0	0	50
7	0	50
24	0	50
71	0	50
236	3	50
714	38	50

Table with summary of the fitted models

Model	Number of parameters	Log-likelihood	AIC	BMD	BMDL	BMDU	Converged	Accepted AIC
Null	1	-119.66	241.32	NA	NA	NA	yes	
Full	6	-38.90	89.80	NA	NA	NA	yes	
Logistic	2	-40.32	84.64	363	299	431	yes	yes
Probit	2	-39.63	83.26	328	270	386	yes	yes
Log-logistic	3	-38.95	83.90	278	216	345	yes	yes
Log-probit	3	-38.90	83.80	270	215	323	yes	yes
Weibull	3	-39.00	84.00	290	218	366	yes	yes
Gamma	3	-38.92	83.84	277	216	337	yes	yes
Two-stage	3	-41.12	88.24	208	182	240	no	no

	Logistic	Probit	Log-logistic	Log-probit	Weibull	Gamma
Estimated model weights	0.11	0.23	0.16	0.17	0.16	0.17

BMD modelling Riddelliine



Dose	tumors	N
0	0	50
7	0	50
24	0	50
71	0	50
236	3	50
714	38	50

BMD	BMDL	BMDU
292.53	246.23	522.72

μg/kg bw/day

- MOE > 10,000 so exposure < 25 ng/kg bw/day

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Exposure to PAs from supplements, tea and honey

- Supplements of PA containing plants give highest exposure
- Followed by tea contaminated by weeds
- Third comes honey
- Animal derived products contribute less

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Exposure < 25 ng/kg bw/day

Age class[b]	N	Lower bound[d]			Upper bound[d]		
		Min	Median	Max	Min	Median	Max
Mean dietary exposure (ng/kg bw per day)							
Infants	6	0.0	4.1	30.2	0.0	5.9	42.8
Toddlers	10	0.0	3.2	34.5	0.0	5.2	48.4
Other children	18	0.7	4.2	24.1	1.2	6.4	34.3
Adolescents	17	0.3	3.7	18.4	0.6	5.7	26.1
Adults	17	0.2	6.7	21.3	0.4	10.6	28.8
Elderly	14	3.0	8.1	29.5	4.3	12.4	39.9
Very elderly	12	3.9	9.2	31.1	5.7	13.9	41.8
95th percentile dietary exposure[c] (ng/kg bw per day)							
Infants	5	0.0	–[e]	133.6	0.0	–[e]	185.2
Toddlers	7	0.0	42.8	153.8	0.0	57.1	214.0
Other children	18	3.3	21.2	90.5	6.3	32.5	125.6
Adolescents	17	0.8	14.6	68.4	2.4	24.6	95.1
Adults	17	1.1	30.1	85.7	2.0	42.9	120.0
Elderly	14	15.3	33.8	87.7	21.4	52.7	123.3
Very elderly	9	15.9	30.8	86.7	22.9	42.8	127.2

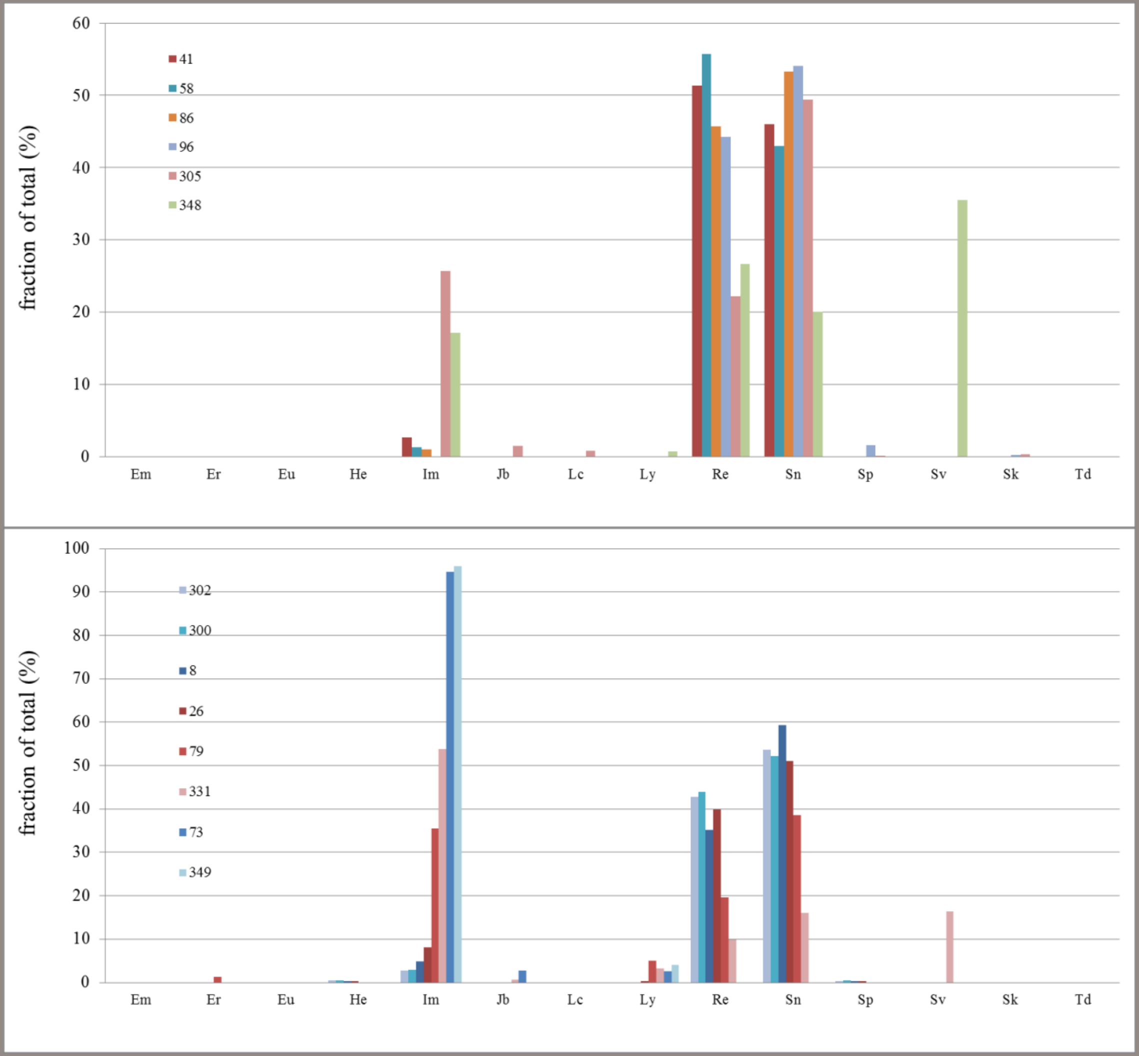
In many cases too high exposure

Which weeds in tea?

Patterns green and black tea (>10 µg/l)

green

black



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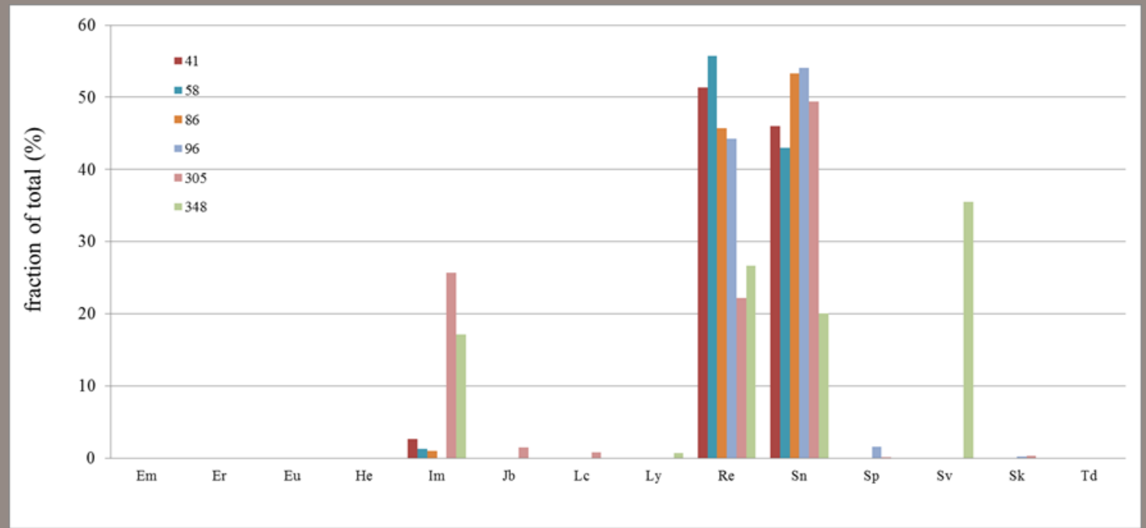
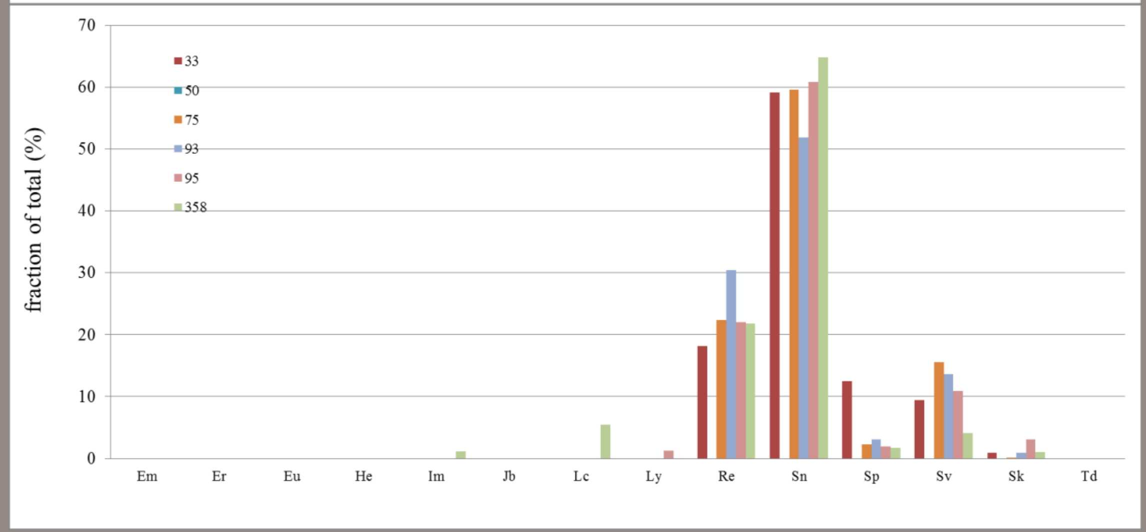
Patterns green and rooibos tea (>10 µg/l)

green

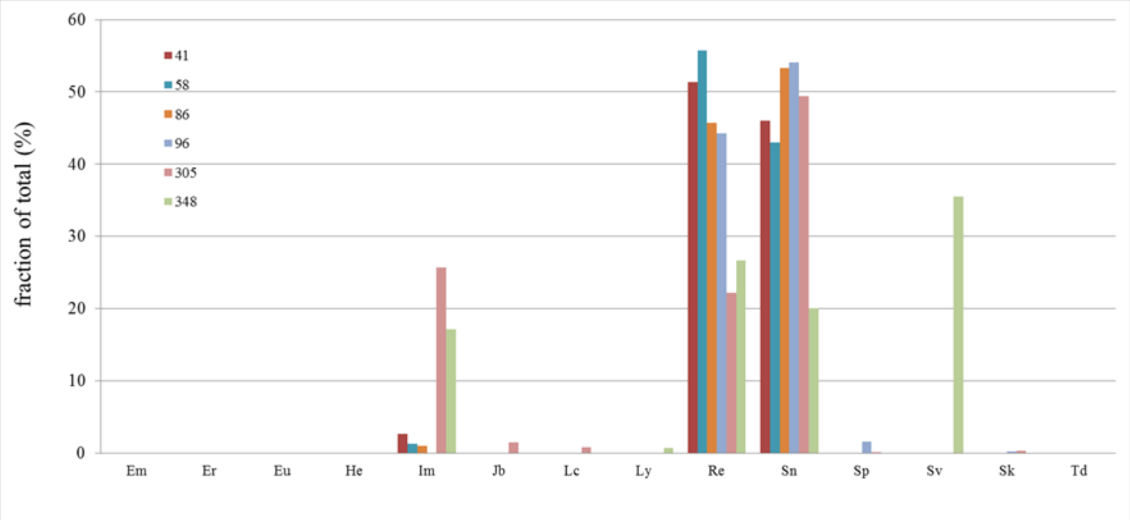


rooibos

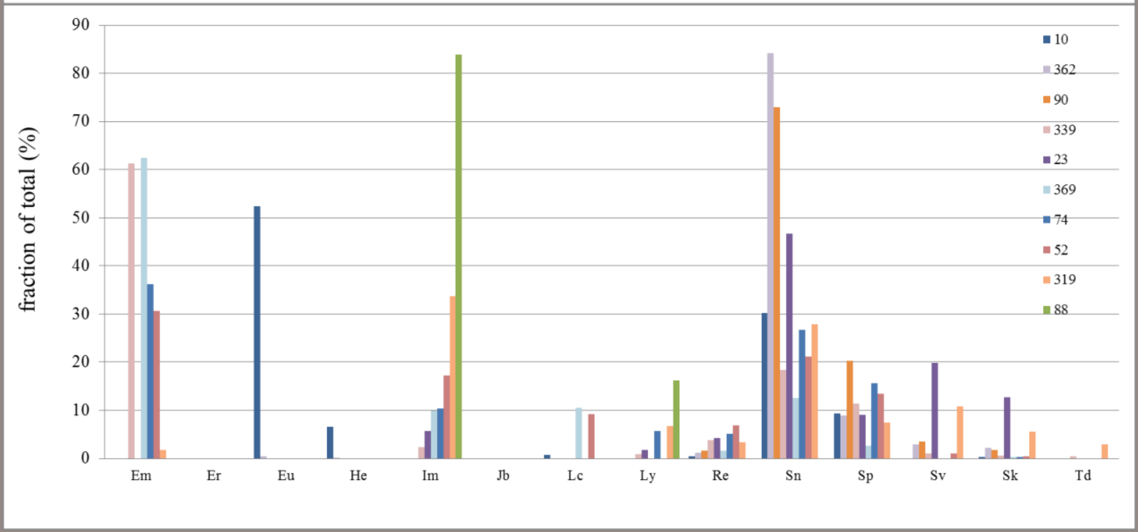


Patterns green and chamomile tea (>10/5 µg/l)

green



chamomile



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What about farm animals?

Animal feedstuffs: Alfalfa (lucerne)

	2006	2007	2008	2009	2010	2011	2012
No of samples	6	13	12	17	51	50	51
Positive	83%	85%	83%	88%	92%	86%	90%
Average content (µg/kg)	1440	225	716	621	225	265	356
Max (µg/kg)	3439	1409	6219	4507	2418	2027	4169
Samples >1000 µg/kg	3 (50%)	1 (8%)	1 (8%)	2 (12%)	4 (8%)	4 (8%)	6 (12%)

- In the Netherlands contamination of alfalfa with PAs remains high, notwithstanding the information provided to the industry

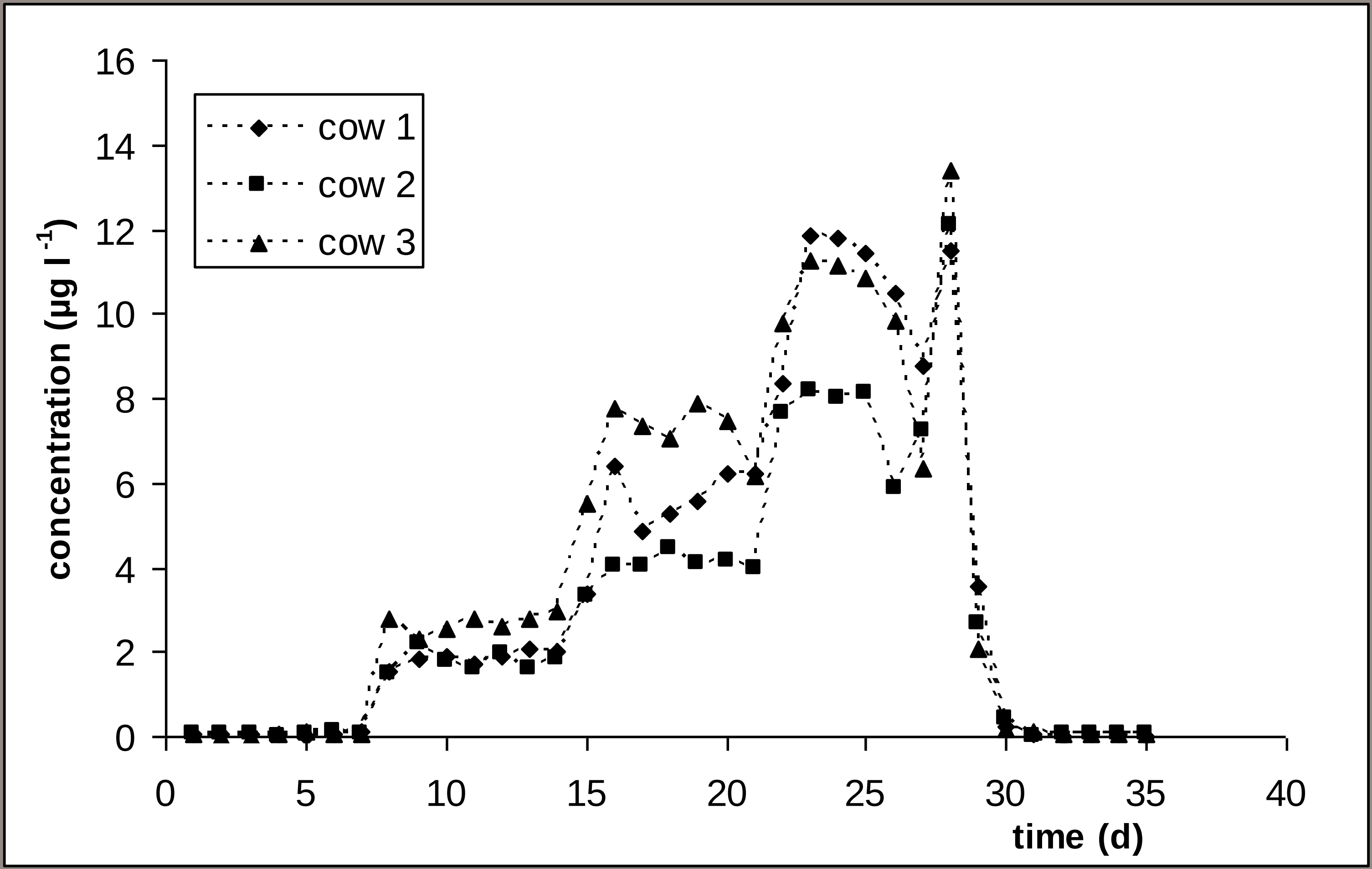
Source?

Common groundsel rather than ragwort

Transfer to milk: study design

- 3 cows fed (fistula) 2x/day with tansy ragwort (*Senecio jacobaea*)
  - Week 1: no ragwort
  - Week 2: 2x 25 g ragwort
  - Week 3: 2x 50 g ragwort
  - Week 4: 2x 100 g ragwort (1% of feed intake)
  - Week 5: no ragwort
- Collected:
  - Milk
  - Some urine and feces

PAs in evening milk



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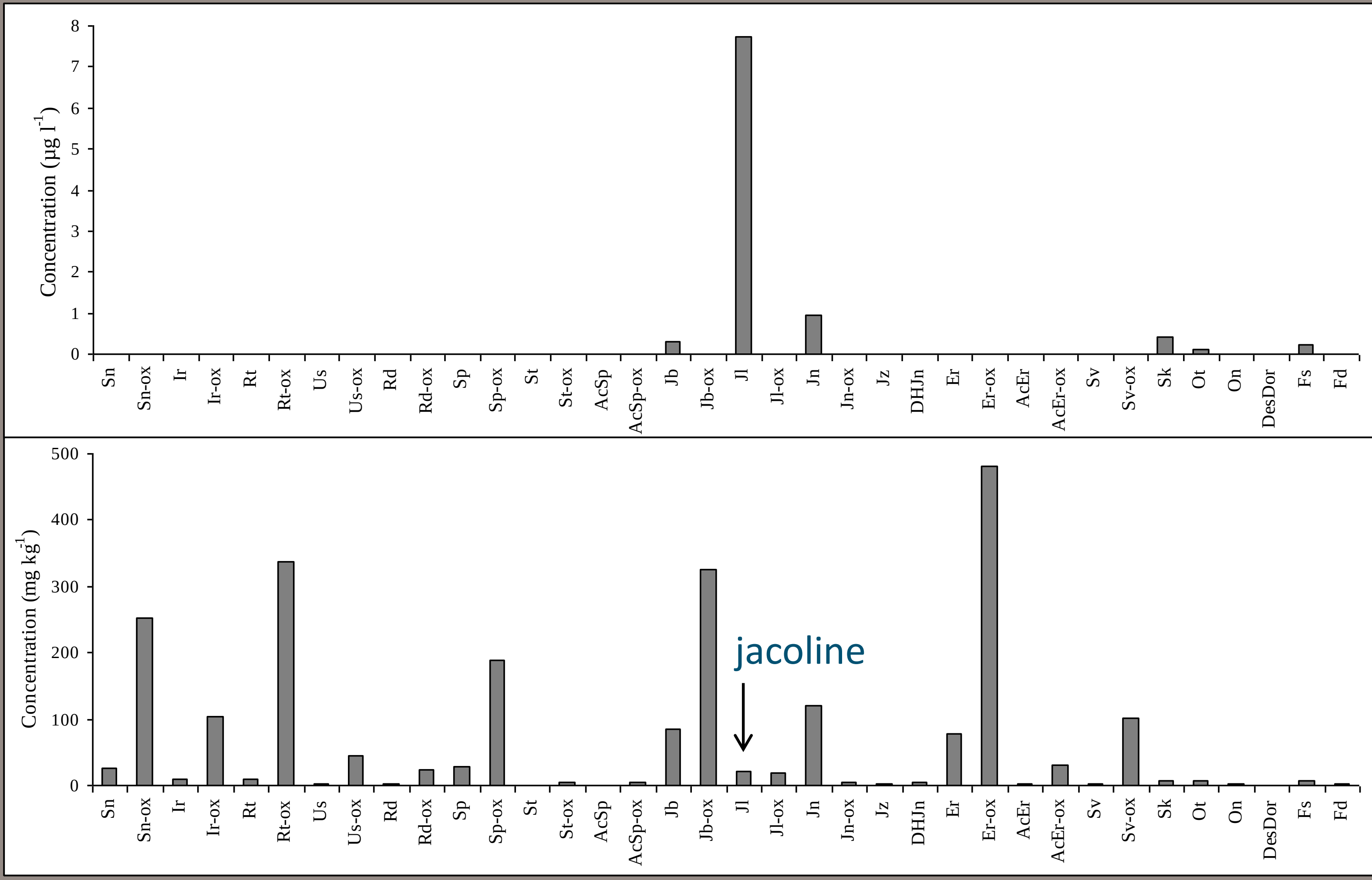
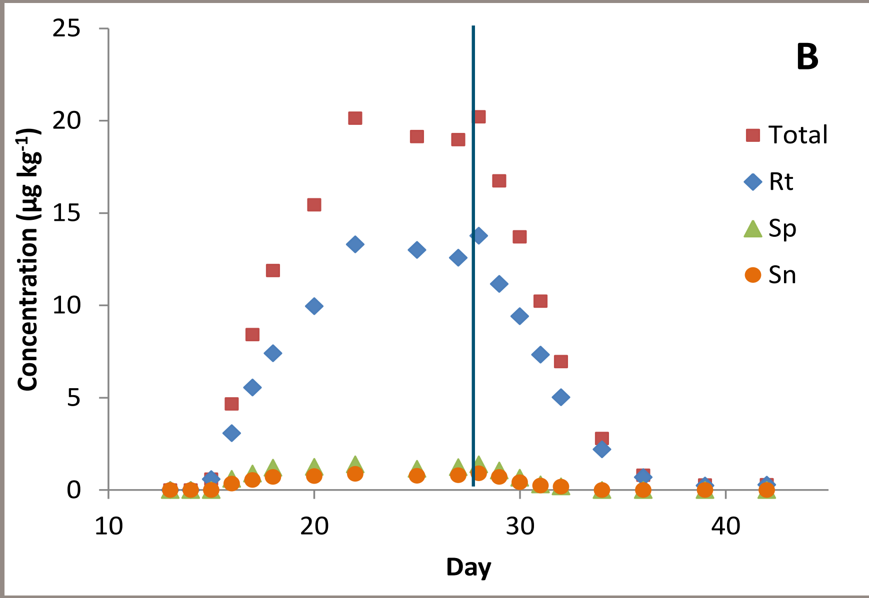
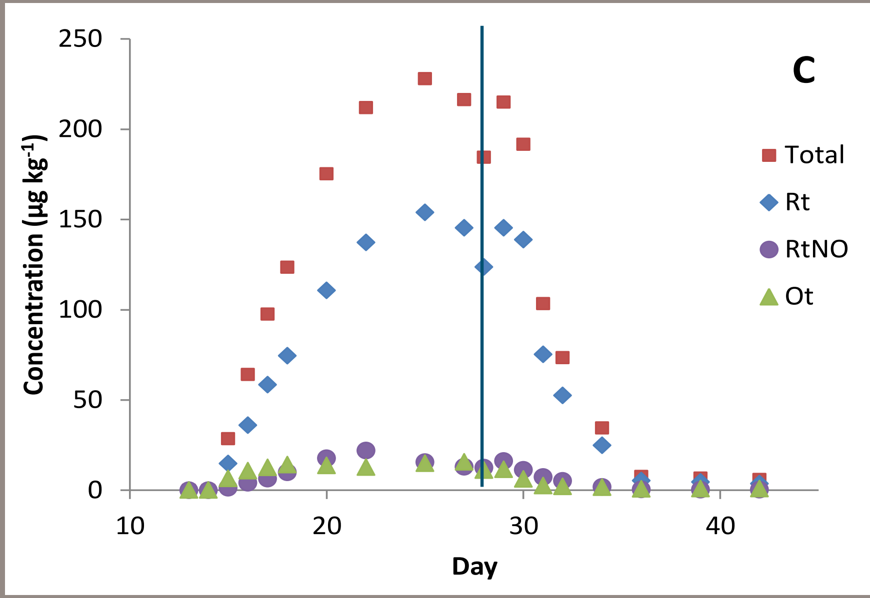
Milk versus plant material



PAs in eggs (Mulder et al., 2016)

- PAs primarily in yolk





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Questions?