VI Congresso Nazionale: Micotossine e Tossine Vegetali

10-12 June 2019

Plant toxins: is there a concern for human health due to the presence of alkaloids in food?

Katleen Baert

Scientific Officer

BIOCONTAM Unit

Trusted science for safe food

European Food Safety Authority


Quino-
lizidine
alkaloids
Pyrro-
lizidine
alkaloids
Glyco-
alkaloids
Opium
alkaloids
Tropane
alkaloids

Quinolizidine alkaloids in lupins and lupin-derived products

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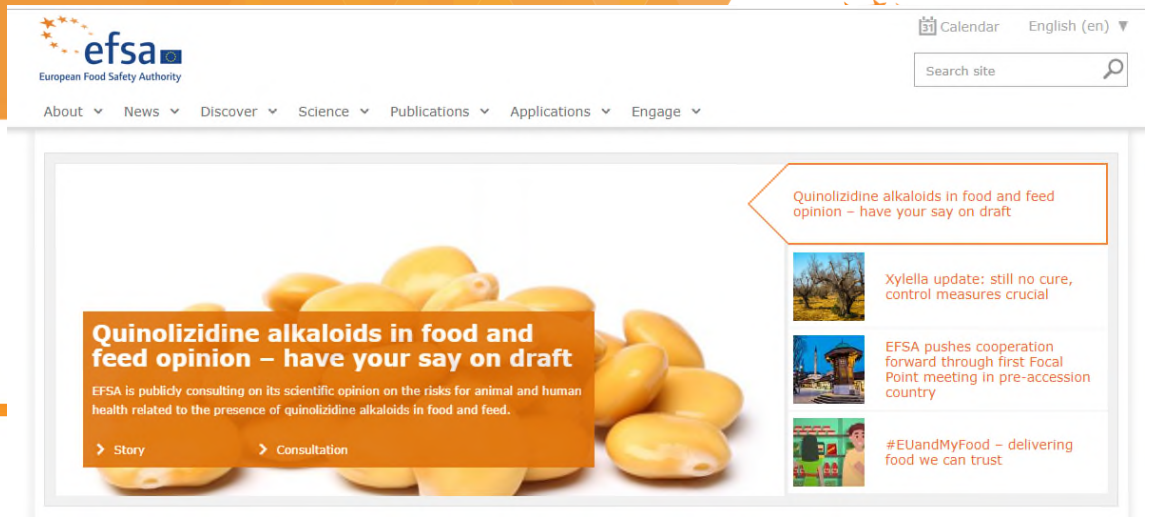

SCIENTIFIC OPINION

ADOPTED: DD Month 20YY

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Scientific opinion on the risks for animal and human health related to the presence of quinolizidine alkaloids in feed and food, in particular in lupins and lupin-derived products

EFSA Panel on Contaminants in the Food Chain (CONTAM)

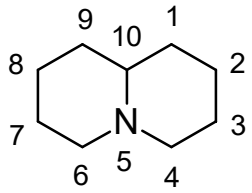
Dieter Schrenk, Laurent Bodin, James Kevin Chipman, Jesús del Mazo, Bettina Grasl-Kraupp, Christer Hogstrand, Laurentius (Ron) Hoogenboom, Jean-Charles Leblanc, Carlo Stefano Nebbia, Elsa Nielsen, Evangelia Ntzani, Annette Petersen, Salomon Sand, Tanja Schwerdtle, Christiane Vleminckx, Heather Wallace, Jan Alexander, Bruce Cottrill, Birgit Dusemund, Patrick Mulder, Davide Arcella, Katleen Baert, Claudia Cascio, Hans Steinkellner and Margherita Bignami

Endorsed for public consultation in May 2019

Quinolizidine alkaloids (QA)

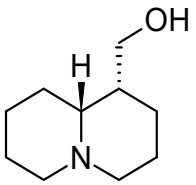
- **Lupin alkaloids** = QAs + other alkaloids such as piperidines (e.g. ammodendrine) and indoles (e.g. gramine).
- The present assessment: **QAs**.
- **Not included in the assessment**: antinutritional factors, the allergenic potential of lupin proteins and possible presence of phomopsins in lupins
- Lupin species and varieties that are relevant for animal and human consumption in Europe
  - *Lupinus albus*
  - *L. angustifolius*
  - *L. luteus*
  - *L. mutabilis*

Quinolizidine alkaloids (QA)

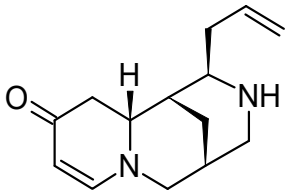


Quinolizidine

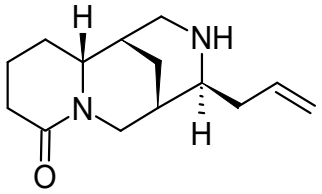
11 QAs have been selected based on their relevance with respect to occurrence in lupin species for human and animal consumption in Europe



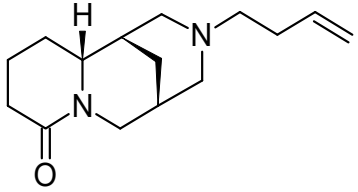
(-)-Lupinine



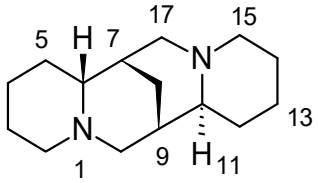
(-)-Albine



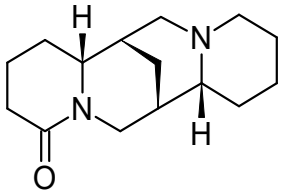
(-)-Angustifoline



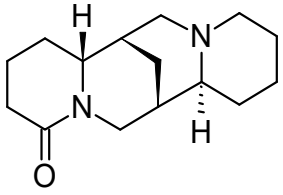
Tetrahydrorhombifoline



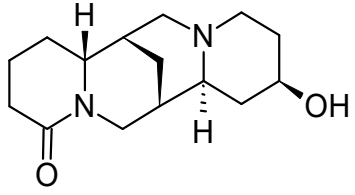
(-)-Sparteine



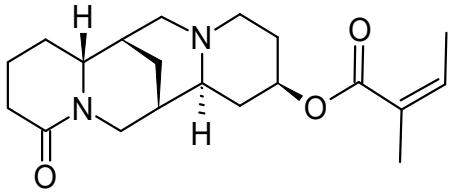
(+)-Isolupanine



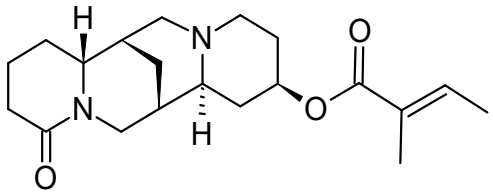
(+)-Lupanine



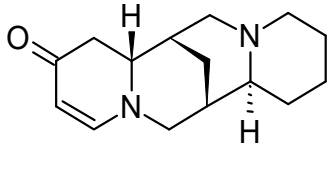
(+)-13α-Hydroxylupanine



13α-Angeloyloxylupanine



13α-Tigloyloxylupanine



(-)-Multiflorine

Toxicity in experimental animals

- Limited data
- Acute toxicity: Sparteine >> lupanine ~ 13α-OH-lupanine.
- Mice more sensitive than rats to acute toxicity of lupanine.
- Acute symptoms : death resulting from respiratory failure and toxic effects affecting the CNS.
- The similarity of the symptoms of intoxication support the conclusion of a similar mode of action of these QAs

Observations in humans

- Intoxication with lupin seeds do not occur frequently and rarely lead to a fatal outcome.
- Typical symptoms refer to the anticholinergic syndrome, are of neurological nature and may also affect the digestive and/or cardiovascular systems.
- Sparteine was used therapeutically in the past for both its antiarrhythmic and oxytocic properties in humans.
- The lowest oral dose reported with antiarrhythmic effects was 20 mg (equivalent to 0.16 mg sparteine/kg bw).

Possibilities for derivation of a HBGV

- **Critical effects**: anticholinergic effects and effects on electric conductivity in the heart following acute exposure to sparteine.
- **Reference point** (acute exposure): The lowest described single oral antiarrhythmic dose of 0.16 mg sparteine/kg bw.
- Group approach and applied the principle of dose-additivity with equal potencies of the QAs.
- A margin of exposure (MOE) approach was used.
- No reference point could be identified to characterise the risk following chronic exposure.

Occurrence in food

The Netherlands
540 analytical results
54 samples

University of Milan
495 analytical results
45 samples

1035 analytical results
99 samples

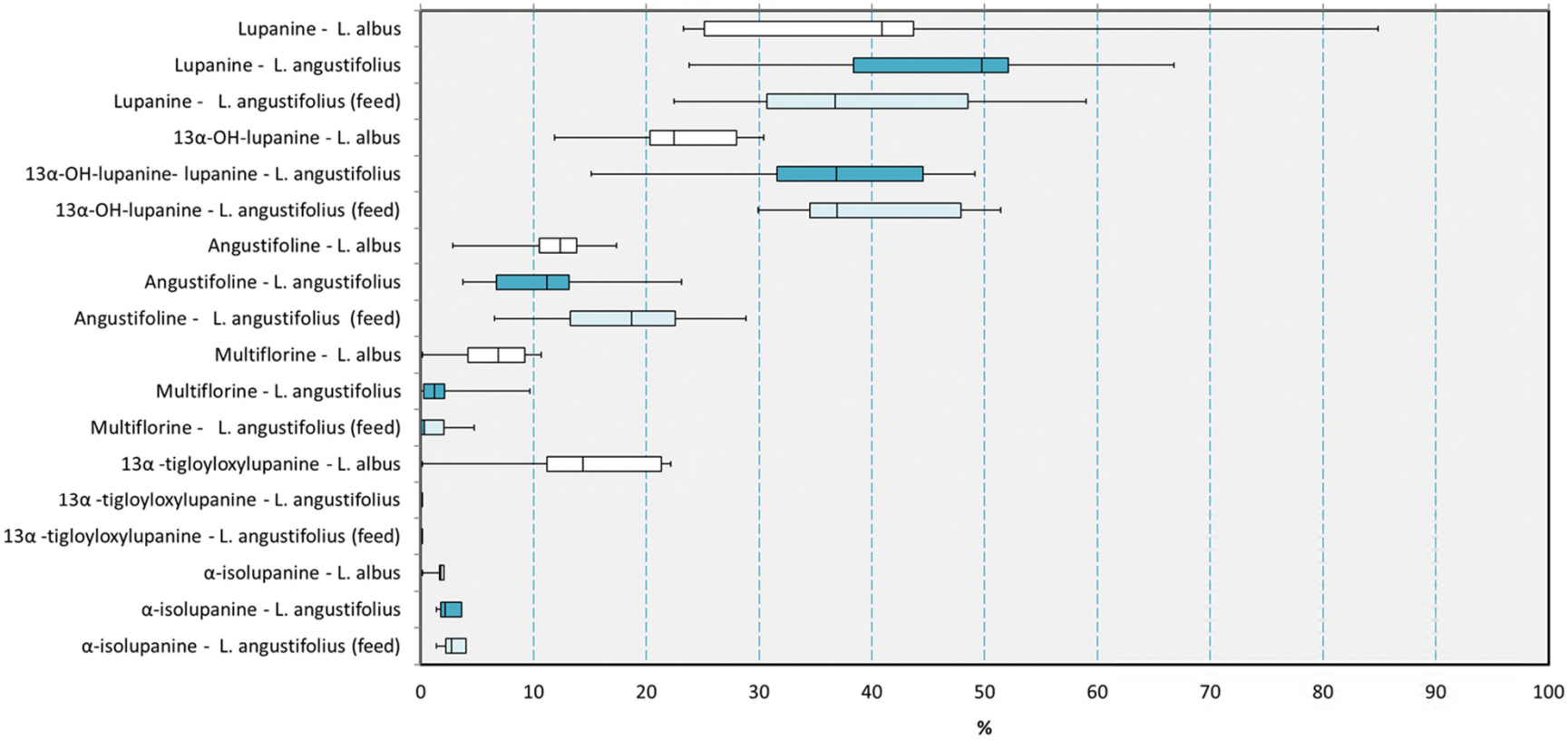
- **TotQA**= sum of the 6 most abundant QAs

(lupanine, 13α-OH-lupanine, angustifoline, multiflorane, 13α-tigloyloxylupanine, α-isolupanine)

- Highest mean concentrations of TotQA
  - 'lupins (dry) and similar-' (429 mg/kg)
  - lupin-based coffee imitate (powder) (331 mg/kg)

- Between 89 and 97% of the QAs present in seeds are removed by water treatment and boiling.

Contribution of single QAs to TotQA



White: lupin seed food samples of *L. albus* (n = 13)
Dark blue: lupin seed food samples *L. angustifolius* (n = 21)
Light blue: lupin seeds feed samples *L. angustifolius* (n = 11)

Acute dietary exposure

Due to the limited occurrence and consumption data => calculate acute dietary exposure only specific scenarios

Scenario	Occurrence data	Consumption data	Calculated exposure (µg/kg bw)
dry lupin seeds not debittered	High TotQA in dry lupin seeds	P95 lupin seeds adults	1700
dry lupin seeds debittered	High TotQA in dry lupin seeds but reduction of 89%	P95 lupin seeds adults	187
jarred lupin seeds in brine	Mean TotQA in jarred lupin seeds	P95 lupin seeds adults	44-46
lupin-based meat imitates	Mean TotQA in lupin-based meat imitates	P95 meat imitates adults	194-228

Risk characterisation

$$MOE = \frac{\text{Reference point (0.16 mg/kg bw)}}{\text{Exposure}}$$

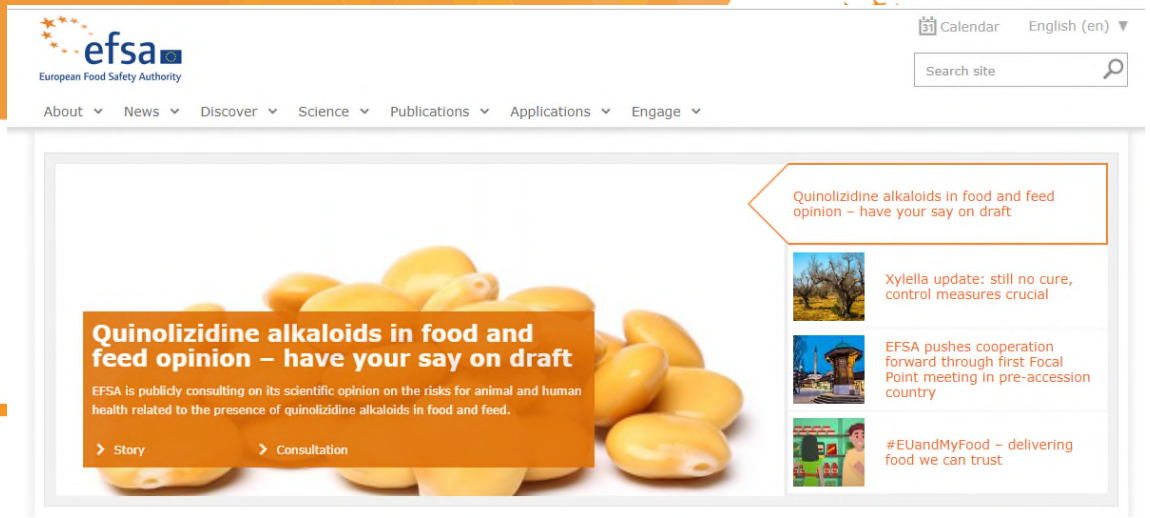
Scenario	Occurrence data	Consumption data	Calculated exposure (µg/kg bw)	MOE
dry lupin seeds not debittered	High TotQA in dry lupin seeds	P95 lupin seeds adults	1700	0.1
dry lupin seeds debittered	High TotQA in dry lupin seeds but reduction of 89%	P95 lupin seeds adults	187	0.9
jarred lupin seeds in brine	Mean TotQA in jarred lupin seeds	P95 lupin seeds adults	44-46	3.6-3.5
lupin-based meat imitates	Mean TotQA in lupin-based meat imitates	P95 meat imitates adults	194-228	0.8-0.7

Risk characterisation

- No full risk characterisation possible.
- Reference point is based on sparteine

  => Sparteine is assumed to be the most potent QA

  => MOEs > 1 are considered not to indicate a health concern.
- MOE values in the range of 0.1-0.8
  - Lupin seeds were not debittered
  - Consumption of lupin-based meat imitates
  - These MOEs may indicate a concern.
- MOEs are of lower concern or no concern
  - When a reduction factor for debittering is taken into account
- MOEs ≥ 1
  - Ready-to-eat lupin seeds that had an average QA content.



SCIENTIFIC OPINION

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Scientific opinion on the risks for animal and human health related to the presence of quinolizidine alkaloids in feed and food, in particular in lupins and lupin-derived products

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Public consultation until 5 July 2019

Opium alkaloids in poppy seeds

Trusted science for safe food

European Food Safety Authority

European

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 22 March 2018

doi: 10.2903/j.efsa.2018.5243

Update of the Scientific Opinion on opium alkaloids in poppy seeds

EFSA Panel on Contaminants in the Food Chain (CONTAM),
Helle Katrine Knutsen, Jan Alexander, Lars Barregård, Margherita Bignami, Beat Brüschweiler, Sandra Ceccatelli, Bruce Cottrill, Michael Dinovi, Lutz Edler, Bettina Grasl-Kraupp, Christer Hogstrand, Laurentius (Ron) Hoogenboom, Carlo Stefano Nebbia, Isabelle P Oswald, Annette Petersen, Martin Rose, Alain-Claude Roudot, Tanja Schwerdtle, Günter Vollmer, Heather Wallace, Diane Benford, Girolamo Calò, Albert Dahan, Birgit Dusemund, Patrick Mulder, Éva Németh-Zámboriné, Davide Arcella, Katleen Baert, Claudia Cascio, Sara Levorato, Marijke Schutte and Christiane Vleminckx

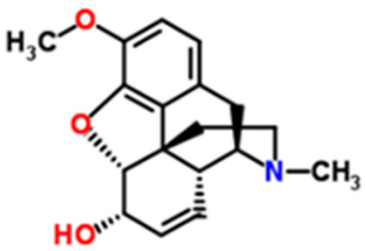
Introduction

- Poppy seeds are used in bakery products, on top of dishes, in fillings of cakes and in desserts and to produce edible oil
- Obtained from the opium poppy (*Papaver somniferum L.*)
- Opium alkaloids are present in the latex of the poppy plant
- Mature poppy seeds do not contain opium alkaloids, but can become contaminated due to insect damage to the capsule or through poor harvesting practices
- Cultivars
  - high and specific alkaloid content; pharmaceutical purposes; seeds are used as by-product for food use
  - low alkaloid content for seed/oil production

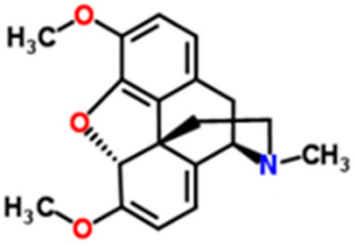
Introduction (2)

The principal phenanthrenes

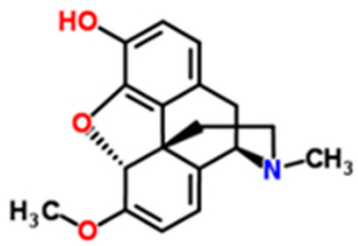
Morphine



Codeine

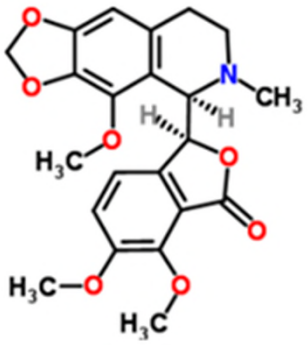


Thebaine

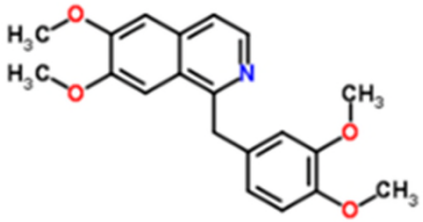


Oripavine

The principal benzylisoquinolines



Noscapine



Papaverine

Toxicity and critical effects

Morphine

- High affinity for the μ-opioid receptor as an agonist.
- Activation of μ-opioid receptor =>nausea, vomiting, sedation, drowsiness, euphoria, miosis, respiratory depression and obstipation => changes in attentiveness and reactive skills.
- Dependency potential

➡ Critical effects of morphine are on the central nervous system

- The lowest known single oral therapeutic dose reported is 1.9 mg morphine, corresponding to 27 μg/kg bw for an adult weighing 70 kg.

➡ Reference point: 27 μg/kg bw

Toxicity and critical effects

Codeine

- Metabolism: codeine -> morphine
  - dependent on CYP2D6 activity
  - Metabolic conversion ≤ 20%
- Pharmacology is strongly related to that of morphine
- The adverse reactions are similar but seen to a lesser extent at clinical doses.
- Dependency potential

➡ Critical effects the same as those of morphine

Toxicity and critical effects

Morphine & Codeine

- characterise the risks of combined exposure to morphine and codeine

- establish a group acute reference dose (ARfD) for morphine and codeine, expressed in morphine eq. using an equivalence factor of 0.2 for codeine

lowest known single oral therapeutic dose of 27 µg morphine/kg bw

uncertainty factor: **3**
LOEL -> NOEL;
LOEL was derived from patients

ARfD: 10 µg /kg bw

[Morphine equivalents] = [Morphine] + [Codeine * 0.2]

Toxicity and critical effects

Thebaine

- **No data** after oral or parenteral exposure of humans are available
- A contribution to morphine-like toxicity due to its possible metabolism into morphine and oripavine may occur but is expected to be small.
- Oral LD_{50} values in rodents indicate that thebaine is more acutely toxic than morphine.

→ Data are insufficient to characterise the hazard or to identify a factor for calculating morphine equivalents

Occurrence data

- Limited amount of data on food categories other than poppy seeds ➡ evaluate the alkaloid profile based on poppy seed samples only.
- 6,369 analytical results corresponding to 1,975 samples
- Large differences in opium alkaloid content in relation to the country of origin

Occurrence data

3 groups:

- ***'high-morphine' group***: poppy seed samples originating from Australia, China, France, Spain and the UK; assumed to represent primarily poppy seeds from varieties grown for pharmaceutical use;

- ***'low-morphine' group***: poppy seed samples originating from other countries; assumed to represent varieties grown for food use; some of these countries produce also varieties for pharmaceutical purposes;

- poppy seed samples with **unknown origin**.

➡ **Uncertainty in the applied division**

Occurrence data

Substance	Group	N	Concentration (mg/kg)	
			Mean	P95
Morphine	'high-morphine'	362	147	383
	'low-morphine'	1210	16.4	52.8
	Unknown	367	64.8	309
	Total	1939	50.1	240
Codeine	'high-morphine'	144	22.7	52.0
	'low-morphine'	1097	2.88	9.30
	Unknown	278	7.95	26.8
	Total	1519	5.82	21.0
Thebaine	'high-morphine'	123	92.5	334
	'low-morphine'	940	3.92	12.3
	Unknown	162	8.56	54.9
	Total	1225	13.5	68.4

Opium alkaloid ratio to morphine

Codeine

Group	N	Ratio to morphine			
		Median	P75	P95	Max
'high-morphine'	142	0.14	0.29	1.08	713
'low-morphine'	1086	0.14	0.20	0.51	0.97
Unknown	257	0.15	0.27	0.67	2.33
Total	1485	0.14	0.21	0.75	713

Thebaine

Group	N	Ratio to morphine			
		Median	P75	P95	Max
'high-morphine'	123	0.29	14.0	135	227
'low-morphine'	936	0.14	0.22	0.48	1.86
Unknown	143	0.12	0.19	0.52	1.10
Total	1202	0.14	0.24	0.84	227

Acute dietary exposure ~ other children (µg/kg bw per day

	Substance	Mean exposure			P95 Exposure		
		Min	Median	Max	Min	Median	Max
HIGH MORPHINE	Morphine	3.81	40.9	99.5	20.6	n.a.	284
	Codeine	0.59	6.31	15.4	2.80	n.a.	38.6
	Morph. equival.	3.94	42.3	103	21.0	n.a.	289
	Thebaine	2.39	25.7	62.5	18.0	n.a.	248
LOW MORPHINE	Morphine	0.42	4.56	11.1	2.84	n.a.	39.2
	Codeine	0.07	0.80	1.95	0.50	n.a.	6.90
	Morph. equival.	0.44	4.70	11.4	2.98	n.a.	41.0
	Thebaine	0.10	1.09	2.65	0.66	n.a.	9.09

⇔ Group ARfD of 10 µg/kg bw

Risk characterisation

Morphine & codeine

- *'High morphine' group*: mean and high levels of dietary exposure > group ARfD in most age groups by up to 33-fold.
- *'Low morphine' group*: exceedance of the group ARfD at high levels of dietary exposure in most surveys, but to a lesser extent at up to 4 to 5-fold.
- **Codeine** makes a minor contribution to exceedance of the group ARfD.
- The group ARfD is most likely to be exceeded when large portions or foods containing unprocessed poppy seeds are consumed.

Risk characterisation

Thebaine

- no quantitative risk characterisation => no health-base guidance value
- The estimated dietary exposures are slightly lower than those for morphine.
- the CONTAM Panel noted that LD_{50} values for thebaine are 3 to 10-fold lower than for morphine, suggesting that the estimated exposure levels might pose a health risk

Pyrrolizidine alkaloids in food

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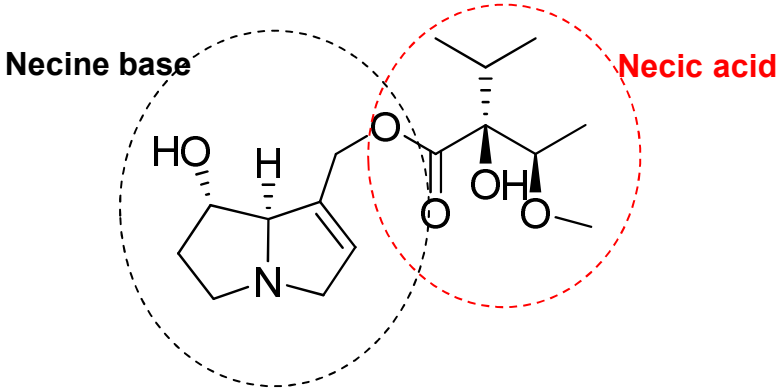
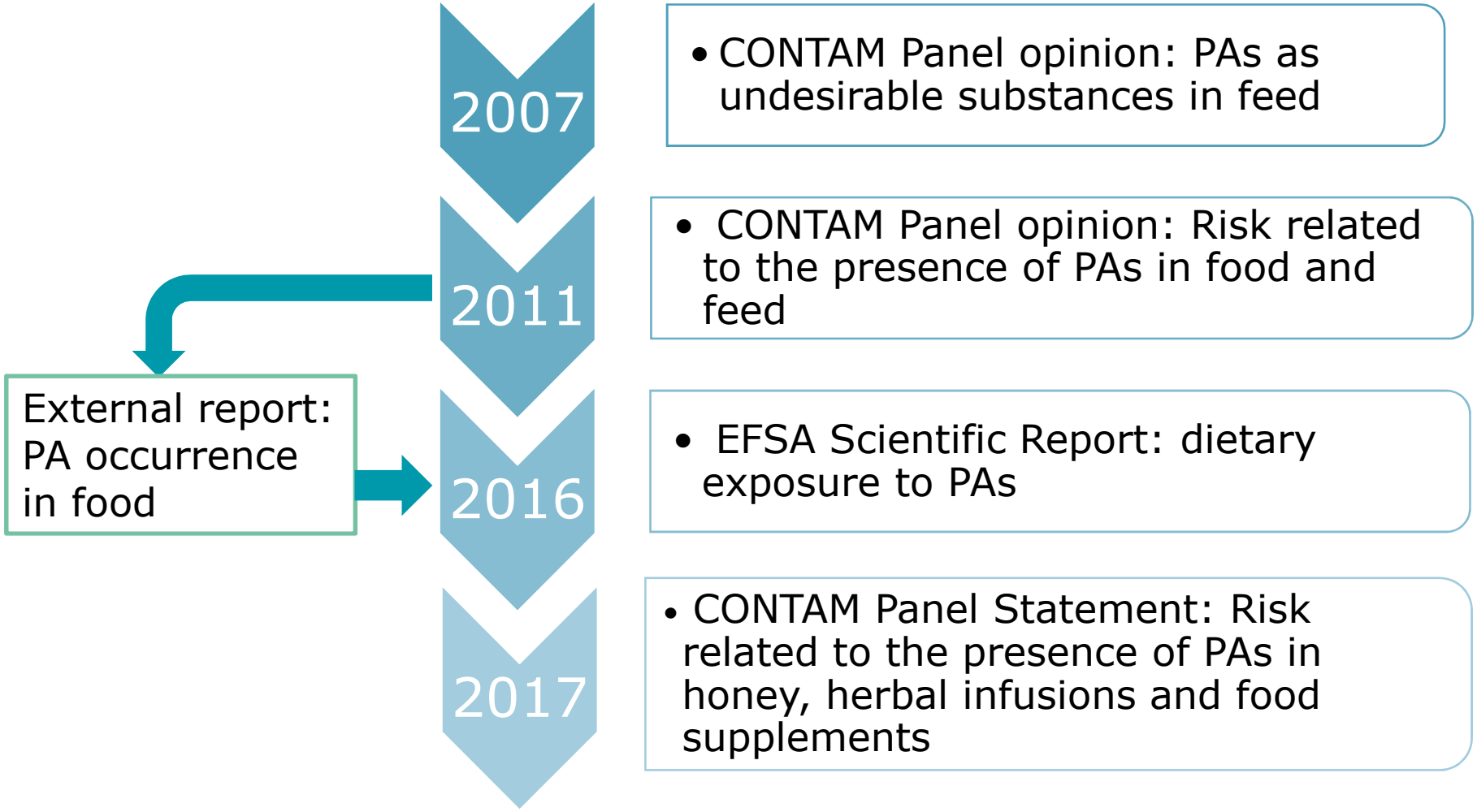
European Food Safety Authority

Introduction

- PAs are substances biosynthesised exclusively by plants.
- 600 known PAs, as result of combinations of different necine bases and necic acids.
- Necine bases can be 1,2-saturated or 1,2-unsaturated.
- Many PAs co-occur in 2 forms: PA and corresponding PA-N-oxide (PANO).
- **EFSA opinions are focused on 1,2-unsaturated PAs.**



Introduction
Chronology of EFSA activities on PAs



Tropane alkaloids

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European Food Safety Authority

EFSA Journal 2013;11(10):3386

SCIENTIFIC OPINION

Scientific Opinion on Tropane alkaloids in food and feed[1]

EFSA Panel on Contaminants in the Food Chain (CONTAM)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

On-going work: Glycoalkaloids

Request for a scientific opinion on the risks for animal and human health related to the presence of glycoalkaloids in feed and food, in particular in potatoes and potato-derived products

TERMS OF REFERENCE

In accordance with Art. 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for a scientific opinion on the risks for animal and human health related to the presence of glycoalkaloids in feed and food, in particular in potatoes and potato-derived products.

Acknowledgements

- Members of the **WG on alkaloids**
- Members of the **WG on opium alkaloids**
- Members of the **WG on quinolizidine alkaloids**
- Members of the **CONTAM Panel**
- **EFSA staff**

- **Member States - European countries**
- **Stakeholders**
  - ✓ occurrence data
  - ✓ consumption data

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