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Anwenderbündnis zum Erhalt homöopathischer Arzneimittel

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Facts about 400 cases of reported adverse events (including deaths) linked to Homeopathic Teething Tablets

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Press reports

Teething Tablets May Be Linked to 10 Children's Deaths, 400 Adverse Events: FDA

POSTED 2:12 PM, OCTOBER 13, 2016, BY CNN WIRE, *UPDATED AT 02:11PM, OCTOBER 13, 2016*

- September 30, 2016:
  FDA warns against the use of homeopathic teething tablets and gels: "Consumers should seek medical care immediately if their child experiences seizures, difficulty breathing, lethargy, excessive sleepiness, muscle weakness, skin flushing, constipation, difficulty urinating, or agitation after using homeopathic teething tablets or gels." (FDA Homepage)
- October 13, 2016 CNN "Ten deaths of children who used homeopathic teething tablets and 400 adverse events associated with the tablets have been reported to the US Food and Drug Administration, the agency said Wednesday."
- 01/27/2017 Laboratory Analysis of Homeopathic Teething Tablets: "FDA confirms elevated levels of belladonna in certain homeopathic teething products"
- 10.März 2017 Arzneimitteltelegramm:
  "Nebenwirkungen BELLADONNAHALTIGE HOMÖOPATHIKA … Schwere Störwirkungen und Todesfälle in den USA"
- April 13, 2017: "Nationwide Recall of Hyland's Baby Teething Tablets and Hyland's Baby Nighttime Teething Tablets Due to Mislabeling"

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Important Facts

which have not been discussed in the press reports:

1. **FDA found inconsistent amounts of Belladonna in Hyland‘s Teething tablets already in 2010; no laboratory- values have been published**
2. **There was a first product recall in 2010**
3. **Formulation of Hyland‘s Teething Tablets has been changed in 2011**
4. **The old formulation contained Belladonna D3**

Hylands Teething Tablets (Old formulation) on the market until 2010	**Hylands Baby Teething Tablets** (New formulation) on the market from 2011
Calcarea Phosphorica 3X HPUS	Calcarea Phosphorica 6X HPUS
Chamomilla 3X HPUS	Chamomilla 6X HPUS
Coffea Cruda 3X HPUS	Coffea Cruda 6X HPUS
Belladonna 3X HPUS D3	**Belladonna 12X HPUS D12**

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FDA U.S. FOOD & DRUG ADMINISTRATION

Results of the analysis of 411suspected cases (1993-2016) including deaths

Case reports (FDA Homepage):

Part 1: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/cderfoiaelectronicreadingroom/ucm548787.pdf

Part 2: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/cderfoiaelectronicreadingroom/ucm548711.pdf

Part 3: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/cderfoiaelectronicreadingroom/ucm548712.pdf

Laboratory analysis : https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm538669.htm

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	Year	1993	2003	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	?	TOTAL
	Hyl.Teeth.Tbl (old formula)	1	1	2	1	2	4	11	121	12	8	12	16	15	4	11	**221**
FDA Lab Analysis 2016 →	Hyl. Baby Teeth.Tbl (new formula)									5	20	20	34	37	19	5	**140**
	Hyl.Tbl (old or new)									2		2				1	**5**
FDA Lab Analysis 2016 →	Hyl.Nighttime Tbl.													5		3	**8**
	Hyland's Gel (separate)								1	1		4		1	2	1	**10**
FDA Lab Analysis 2016 →	CVS																**0**
	Hyl.Tiny Cold														1		**1**
	Humphreys								1	4							**5**
	Baby Orajel								2	4	2		2	2	1		**13**
	Not to be allocated														1	7	**8**
	Total	**1**	**1**	**2**	**1**	**2**	**4**	**11**	**125**	**28**	**30**	**38**	**52**	**60**	**28**	**28**	**411**

Red: Belladonna-containing preparations

The differentiation between the old and the new product was based on the year of the report, the name (old: Hyland`s Teething tablets; new: Hyland`s Baby teething tablets) and the scanned image of the packaging if available

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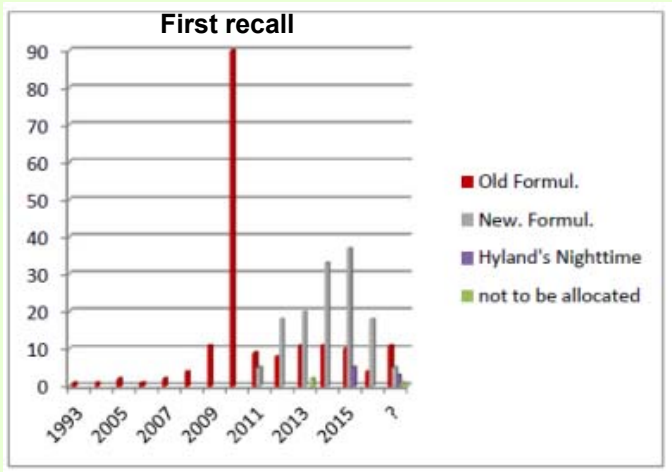
323 Serious adverse events

Serious criteria (ICH E2D Guideline):

- results in death,
- is life-threatening
  (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is a medically important event or reaction.

Year	1993	2003	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	?	Summe
Old Formul.	1	1	2	1	2	4	11	90	9	8	11	11	10	4	11	176
New. Formul.									5	18	20	33	37	18	5	136
Hyland's Nighttime													5		3	8
Not to be allacated											2				1	3
Total	1	1	2	1	2	4	11	90	14	26	33	44	52	22	20	323

2010



- Incomplete case reports; duplications
- Serious criteria were not fullfilled in many reports
- Most of the adverse events were in dead Belladonna-typical symptoms:
  - mostly seizures!
- Most of the cases are connected with the **old formulation**!
- **Incidence peak in 2010**
- There are reports involving the old formulation even after the first recall in 2010
- No case regarding CVS, the product with the highest found alkaloid levels

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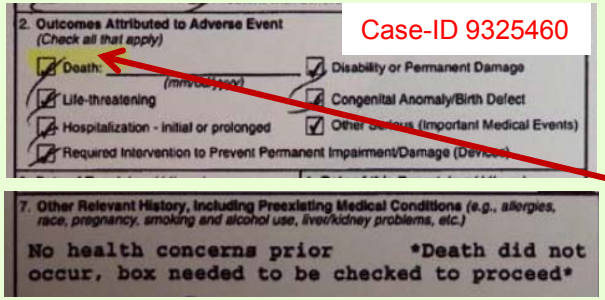
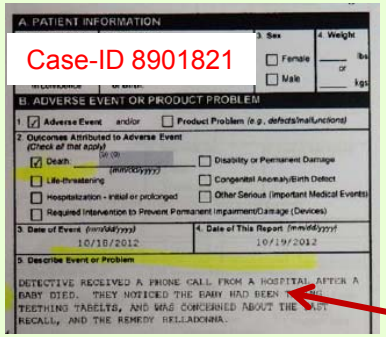
We found 8 not 10 deaths!

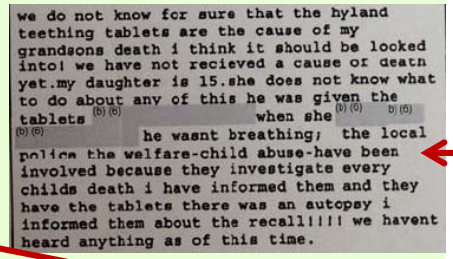
Examples:



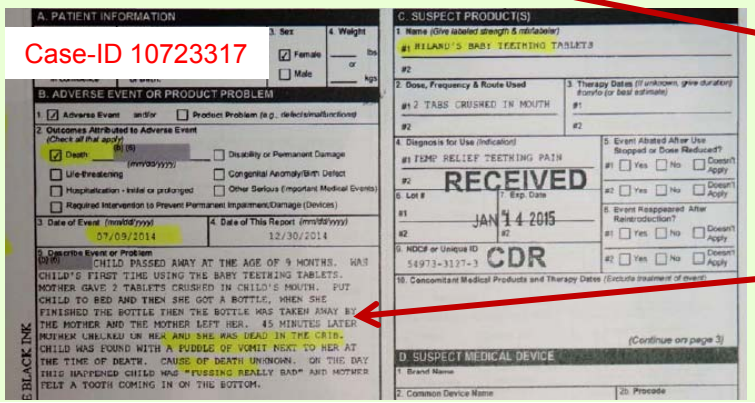
Case-ID 9325460



Case-ID 8901821


we do not know for sure that the hyland teething tablets are the cause of my grandsons death i think it should be looked into! we have not recieved a cause or death yet.my daughter is 15.she does not know what to do about any of this he was given the tablets when she he wasnt breathing; the local police the welfare-child abuse-have been involved because they investigate every childs death i have informed them and they have the tablets there was an autopsy i informed them about the recall!!!! we havent heard anything as of this time.

Case-ID 7744127



Case-ID 10723317

- No final causality assessment for all reports!
- One report concerns only Benzocain-containing Teething Gel
- in 2 of 10 reports field „death“ was chosen mistakenly in the report form
- in 6 of 8 reports the old formulation was involved; 4 reported in 2010, probably pushed by the FDA warnings
- in 2 of 8 reports the new formulation was involved
  - Vague inquiry from a detective without any further details about the case
  - Death caused by aspiration? Mother read in the internet “that Belladonna causing seizures in babies”; “mother does not have a cause of death or a death certificate”

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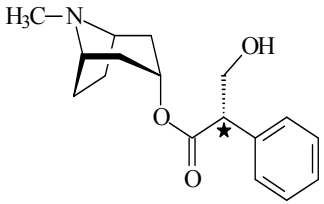
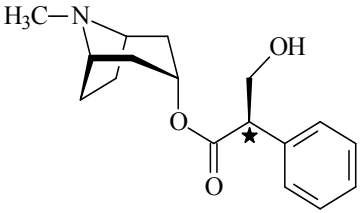
Belladonna alkaloids

Tropanalkaloids:



L-Hyoscyamin;
S-Hyoscyamin
(in fresh plant)

active

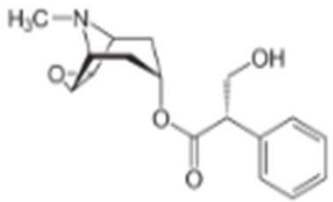


D-Hyoscyamin;
R-Hyoscyamin

inactive

Racemisation during drying process

Racemat: Atropin
(not in fresh plants)



Scopolamin

Actions:

- Parasympatholytic (anticholinergic)
- Spasmolytic
- positive dromotropic
- positive chronotropic
- psychotropic

Poisoning symptoms:

1. **Mydriasis**
2. **Redness of face and skin**
3. **Tachycardia**
4. **Dry mucous membrans with dry mouth/ Thirst**
5. Agitation/ Hallucination/ Seizures

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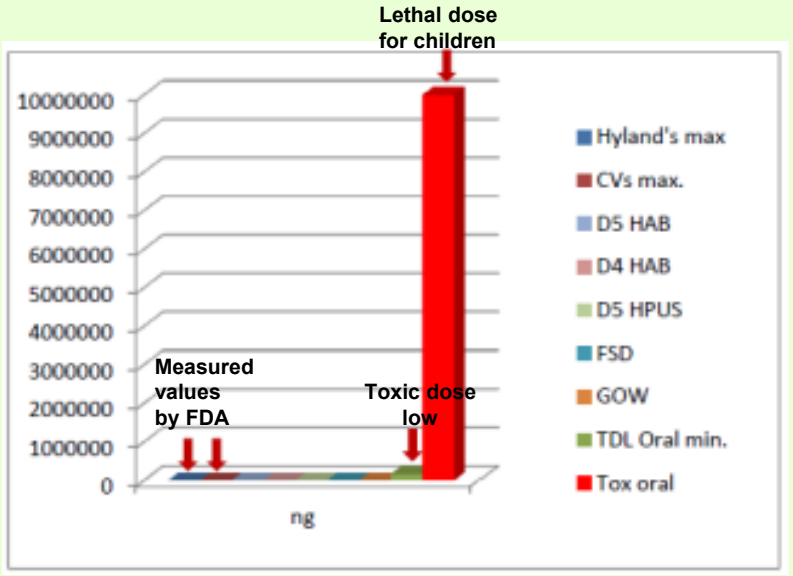
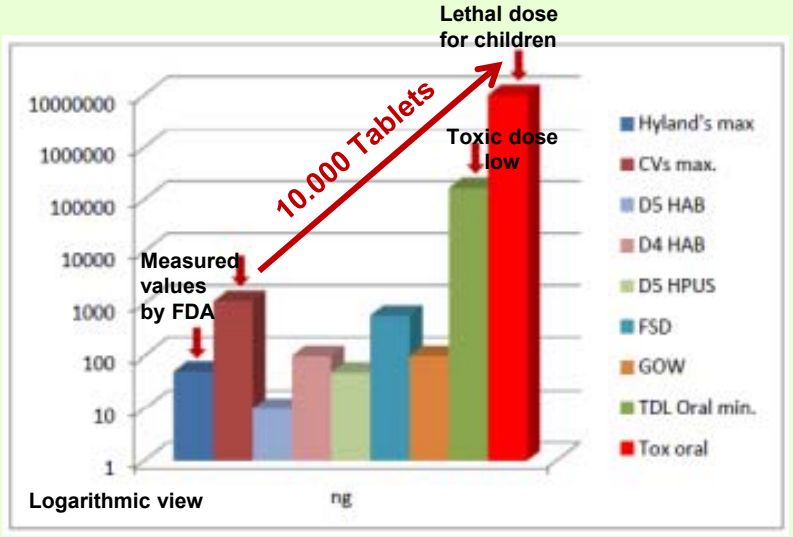
Toxicological data
in comparison with Lab values:

	Value [ng]	Alkaloid	Reference
Hyland's max./tablet	53,4	Scopolamin	FDA Laboratory Analysis of Hyland's Baby Natural Relief Teething Tablets
CVS max./ tablet	1.100	Atropin	FDA Laboratory Analysis of CVS Health Homeopathic Infants' Teething Tablets
1 g Bell D4 (HAB) **D4: OTC-Level** in Germany	100 (max)	Total amount of Belladonna alkaloids calculated as Hyoscyamin	HAB/ Ph.Eur. (Method 2a) **D4: "over the counter" (OTC) level;** Means: available in pharmacies without prescription by a physician in Germany **In US the OTC-level is D3!**
1 g Bell D5 (HAB)	10 (max)	Total amount of Belladonna alkaloids calculated as Hyoscyamin	HAB/ Ph.Eur. (Method 2a)
1 g Bell D5 (HPUS Class C)	50 (max)	Total amount of Belladonna alkaloids calculated as Hyoscyamin	HPUS Class C
FSD (D5; HAB)	600 ng/ 3 kg neonate/ day	Atropin	First list of FSD; HMPWG Homepage First Safe Dilution means: An intake of 10g of the preparation is safe for a daily intake lifelong calculated on a 3kg neonate
GOW per 1 liter drinking water	100		TrinkWVO (German Drinking Water Ordinance) 0,1 µg/l is a general benchmark (GOW) used in drinking water for substances which are not adequately assessed by toxicological criteria.
TDLlo oral (Toxic dose low)	165.000	Atropin	ChemIDplus-Datenbank https://chem.nlm.nih.gov/chemidplus/rn/51-55-8 The toxic dose low for atropine is 33 ug/ kg (33.000 ng/ kg) body weight – calculated for a 5 kg infant 165.000 ng
Tox oral	10.000.000	Atropin	Hagers Handbuch The lethal dose for infants may be less than 10 mg atropine.





1 bottle of CVS contains 135 Tablets

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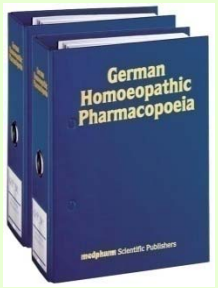
Differences between HPUS and GHP:



HPUS **Class M or Class C**	**GHP (HAB)/ Ph.Eur.** **Method 2a (Ph.Eur. 1.1.3)**
No exact trituration time	Trituration time: 1 hour
For preparation of MT: Fresh or dried plants are possible	For preparation of MT: Only fresh plants are allowed
Class C: MT = D1 Higher alkaloid content in D1	Further dilution step from MT to D1

HPUS HOMOEOPATHIC PHARMACOPOEIA of the United States

The Homœopathic Pharmacopœia of the United States

No exact trituration time!

33. CLASS F SOLID ATTENUATIONS: TRITURATIONS -- METHOD

33.1. Attenuations of solid medicinal raw materials are prepared by trituration of the medicinal raw material with lactose monohydrate. In calculating the ratio of raw material to diluent, the guidelines on water of hydration (see §1.7) apply. A mortar and pestle is used for small amounts; a mechanical triturator may be used for large amounts. The trituration process must be continued for a sufficient time period to ensure that a homogenous mass is prepared.

33.4. For hand triturations, one possible method to assure homogeneity is to place approximately one (1) part of lactose monohydrate in a mortar, add one (1) part of the raw material, and then cover with approximately one (1) part of lactose monohydrate. The mass should be mixed well to ensure the raw material is homogeneously dispersed in the lactose monohydrate. Add approximately two to three (2 - 3) parts of lactose monohydrate and mix well to ensure homogeneous dispersion. Finally, add sufficient lactose monohydrate to make a total of nine (9) [for centesimal attenuations: ninety-nine (99)] parts of lactose monohydrate and mix well to ensure homogeneous dispersion.

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Conclusions (1) :

1.
The laboratory values of Belladonna alkaloids in teething tablets found by FDA could only have been caused by a severe manufacturing error.
A product recall is absolutely understandable!

2.
There are no exact trituration times required in HPUS.
One explanation of the measured alkaloid values could be, that Belladonna has been only mixed in the preparation and not triturated or succussed step by step. Probably dried Belladonna plants have been used (Atropin was found).

3.
Even the inconsistent amounts of Belladonna alkaloids (found in 2016; new formulation) could not explain poisoning symptoms and cases of death.
A 5 kg infant must have taken 3000 tablets of the Hyland‘ s product with the found high alkaloid values to achieve the lowest known toxicological dose and 200.000 tablets for a lethal dose (of the CVS product 10.000 tablets). Even in very sensitive children toxicological relevant doses would not be achieved.

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Conclusions (2) :

4.
In most of the cases the old formulation (containing Bell D3) was involved.
Analogous manufacturing errors during preparation of the old formulation could result in really toxic concentrations of Belladonna alkaloids in the tablets.
FDA warnings should concentrate on remainder of the old formulation.

5.
Homeopathy must not be put under general suspicion if a manufacturer does careless work!

6.
Some of the Belladonna like symptoms could also have been caused by fever, teething or other typical problems in children.

7.
In Germany and Europe homeopathic medicinal products are controlled in the same manner as conventional drugs by the authorities and are safe!

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Thank you for your attention!

Questions?

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References:

Case reports; (downloaded in April 2017):

- www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/cderfoiaelectronicreadingroom/ucm548787.pdf
- www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/cderfoiaelectronicreadingroom/ucm548711.pdf
- www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/cderfoiaelectronicreadingroom/ucm548712.pdf

Laboratory analysis:

- https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm538669.htm

First Safe Dilution:

- http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/HMPWG/2016_11_HMPWG_First_List_of_FSD.pdf

ICH E2D:

- https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf

- DrugBase online: Hagers Enzyklopädie der Arzneistoffe und Drogen (Atropa bella-donna); Wissenschaftliche Verlagsgesellschaft Stuttgart (data status 24.01.2013)
- ChemIDplus Database: https://chem.nlm.nih.gov/chemidplus/rn/51-55-8

- http://www.aeha-buendnis.de
- „Homeopathic medicinal products in Europe are safe“ http://bit.ly/2qr42Xw
- „Facts about Homeopathic Teething Tablets“ http://bit.ly/2pEqkIM
- Detailed statement by Michael Frass: http://www.wisshom.de/index.php?menuid=358