Food and Agriculture Organization of the United Nations

World Health Organization

Guidance document on physical *Datura stramonium* seed contamination

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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
WORLD HEALTH ORGANIZATION
ROME, 2020

Required citation:
FAO and WHO. 2020. *Guidance document on physical Datura stramonium seed contamination*. Rome. https://doi.org/10.4060/cb2105en

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ISBN 978-92-5-133622-9 [FAO]
ISBN 978-92-4-001434-3 (electronic version) [WHO]
ISBN 978-92-4-001435-0 (print version) [WHO]

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Design and layout: Tomaso Lezzi

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ACKNOWLEDGEMENTS

This document was prepared by Mark Feeley under the technical review of FAO and WHO: Markus Lipp (FAO), Vittorio Fattori (FAO), Keya Mukherjee (FAO) and Kim Petersen (WHO). Gratitude goes to WFP (Virginia Siebenrok, Suvrat Bafna and Davor Janjatovic) for the feedback and insights provided throughout the development of the document.

Lastly, appreciation goes to Tomaso Lezzi for the graphic design and layout of the publication.

CHAPTER 1
BACKGROUND

Following a recent episode of human poisoning attributed to *Datura stramonium* seeds contaminating cereal products distributed by the United Nations World Food Programme (WFP), a Joint FAO/WHO expert meeting recommended guidance levels or operational limits for the combined sum of the two main tropane alkaloids (TAs) found in *D. stramonium*, hyoscyamine and scopolamine (FAO and WHO, 2020). These limits were based on concentrations in ready to consume WFP products but it was recognized that, for screening purposes, it would be beneficial if these limits could be expressed as seed contamination for two of the main cereal/legume ingredients, namely wheat and soybean.

Building on the deliberations of the FAO/WHO expert meeting, this document provides specific guidance on physical *Datura stramonium* seed contamination.

CHAPTER 2
INTRODUCTION

Datura spp. are herbaceous, leafy, flowering annual plants, approximately two meters in height. The leaves are alternate, 10–20 cm long and 5–18 cm wide (Fig. 1). The flowers are erect or spreading, trumpet shaped, 5–20 cm long and 4–12 cm wide at the opening, with colours varying from white to yellow, pink and pale purple (Fig. 2). The fruit is a spiny capsule 4–10 cm long and 2–6 cm wide, initially green coloured but becoming dull brown at maturity, splitting open into four chambers when ripe to release 1 300–30 000 seeds per plant. The seeds are almost dark brown to black, flat, kidney-shaped, surface irregular and pitted, 3–4 mm long, 2-3 mm wide (Fig. 3) (Weaver and Warwick, 1984). *Datura* is thought to have originated in Central America and has the following taxonomic tree:

Kingdom:	**Plantae – Plants**
Subkingdom:	**Tracheobionta – Vascular plants**
Superdivision:	**Spermatophyta – Seed plants**
Division:	**Magnoliophyta – Flowering plants**
Class:	**Magnoliopsida – Dicotyledons**
Subclass:	**Asteridae**
Order:	**Solanales**
Family:	**Solanaceae – Potato family**
Genus:	***Datura***

While *Datura* species have been deliberately cultivated for ornamental, traditional medicine, and pharmacological purposes, they are considered to be invasive/noxious weeds. *Datura* species can compete with food crops and cause economic losses, while all parts of the plants can contain high amounts of anticholinergic substances referred to as tropane alkaloids (TAs). TAs are nitrogenous secondary plant metabolites and occur naturally in plants. TAs can cause a variety of adverse effects related to their anticholinergic properties and may be fatal if ingested by humans and other animals, including livestock and pets. Recent reviews of the pharmacological and toxicological properties of TAs are available from EFSA (2013) and FAO and WHO (2020). There have been numerous reports of human poisonings, including mortalities, due to the accidental and/or deliberate ingestion of *Datura* plant parts (Fuchs *et al.*, 2011; EFSA, 2013; Adamse *et al.*, 2014; Chan, 2017; Fatur and Kreft, 2020; Kerchner and Farkas, 2020). While crops grown for human consumption do not naturally contain TAs, bulk commercial grains and seeds, such as wheat, rye, soybean, linseed, and maize, may be contaminated by TAs due to agricultural practices (EFSA, 2008; Adamse and van Egmond, 2010).

Of the 15–25 *Datura* species estimated to exist, *D. stramonium* L. is considered to be one of the world's most widespread weeds. *D. stramonium* is extensively distributed in temperate and tropical areas and is likely to be found in almost any summer crop (reported as a weed in more than 40 crops in almost 100 countries) (CABI, 2019).

FIGURE 1 ***DATURA STRAMONIUM* PLANT**

©Shutterstock/Gena Melendrez

FIGURE 2 ***DATURA STRAMONIUM*** **FLOWER**

©Shutterstock/ Melinda Fawver

FIGURE 3 ***DATURA STRAMONIUM*** **SEED POD AND SEEDS**

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FIGURE 4 ***DATURA STRAMONIUM* DIMENSION OF SEEDS**

©Adapted from the Canadian Food Inspection Agency Seed Program

CHAPTER 3

TROPANE ALKALOID CONTENT OF *D. STRAMONIUM* SEEDS

Tropane alkaloids (TAs) are found in many globally distributed Solanaceae species, with the principal genera including *Mandragora*, *Brugmansia*, *Duboisia*, *Hyoscyamus*, *Datura*, *Atropa*, and *Scopolia* (Griffin and Linn, 2000; Adamse *et al.*, 2014). Over 200 TAs have been identified but the exact concentration of specific alkaloids varies within genera, with major influences including species, cultivation, environment, geographic location, temperature, moisture, and storage. The TA content of plants can vary from leaf to leaf, plant to plant and season to season. The major tropane alkaloids, hyoscyamine and scopolamine, plus several minor tropane alkaloids have been identified in *Datura* species. Typical examples of minor TAs found in *D. stramonium* include tigloidin, aposcopolamine, apoatropin, hyoscyamine *N*-oxide and scopolamine *N*-oxide. While more than 67 alkaloids have been detected in *D. stramonium*, hyoscyamine and scopolamine predominate, accounting for up to 70–90 percent of total alkaloid content in various varieties, (Berkov *et al.*, 2006; El Bazaoui, 2011). Analysis of grain-based food samples collected in nine European countries supports the assumption that hyoscyamine and scopolamine are the most relevant tropane alkaloids. Hyoscyamine and scopolamine comprised 83 percent of the reported tropane alkaloid content when 24 different tropane alkaloids were being monitored (Mulder *et al.*, 2016). It should be noted that hyoscyamine is usually reported as atropine, the racemic mixture of the (+) and (-) hyoscyamine enantiomers. Most analytical methods do not allow for enantioselective separation of the two isomers. However, when chromatographic separation is achieved prior to quantification, the majority of hyoscyamine detected in *Datura stramonium* seeds is reported to be the (-)-hyoscyamine or "active" isomer (Marín-Sáez *et al.*, 2016).

Within the same *Datura* species, different varieties have also been shown to contain different concentrations of tropane alkaloids. For example, *D. stramonium* var. *tatula* L. plant parts have been reported to contain approximately two times greater concentrations of atropine (hyoscyamine) and scopolamine as compared to *D. stramonium* (Jakabová *et al.*, 2012).

While variability in the concentration of TAs in *D. stramonium* seeds is anticipated, the following (Table 1) information was used to develop average and range concentrations of the combined sum of the two main TAs, hyoscyamine and scopolamine. When values are being reported as total tropane alkaloids, 80 percent was applied to the total to estimate the approximate sum of (-)-hyoscyamine and scopolamine. Based on a reported *D. stramonium* seed moisture content of 8.5 percent (Oseni *et al.*, 2011), both wet weight and dry weight values were used as reported for statistical averaging.

TABLE 1 **REPORTED CONCENTRATIONS OF TAs IN *D. STRAMONIUM* SEEDS (mg/kg)**

STUDY	HYOSCYAMINE	SCOPOLAMINE	ΣTAs
Italy (Miraldi *et al.*,2001)	170-387**	12-89**	182-476**
Italy (Caligiani *et al.*, 2011)	1 283**	678**	1 961**
Poland (Mroczek *et al.*, 2006)	710-1 380**	520-1 275**	1 235-2 655**
USA (Friedman and Levin, 1989)	2 270 (1 690-2 710*)	530 (360-690*)	2 800 (2 050-3 400*)
USA (Dugan *et al.*, 1989)	2 710*	660*	3 370*
South Africa (Naudé, 2007)	557* (273-908)	587* (254-800)	1 114* (527-1 708)

* wet weight.
** dry weight.

Additional reports in the scientific literature have provided estimates of concentrations of TAs (typically only atropine reported) by weight of seed. In order to calculate properly, the approximate weight of *D. stramonium* seeds was also reviewed.

D. stramonium have relatively small seeds. Based on the following (Table 2), an average seed weight of 7.5 mg has been assigned.

TABLE 2 ***D. STRAMONIUM* SEED WEIGHT**

WEIGHT (mg)	REFERENCE
6.6	Naudé, 2007
9.0	Berkov, 2001
6.4	Queensland Government, 2015
8.0	http://data.kew.org/sid/weight.html
7.6	List and Spencer, 1979

* wet weight.
** dry weight.

The following has been documented about the amount of atropine in *D. stramonium* seeds:

> *D. stramonium* seeds have been reported to contain approximately 0.1 mg atropine (MMWR, 1995). Based on the average seed weight, this would represent 1.3 percent w/w or 13 000 mg/kg.

> *D. stramonium* seeds contain 0.4 percent atropine, and ten seeds equal 1 mg atropine or 400 mg (-)-hyoscyamine. (Artal, 2015). At 0.4 percent, this would represent 4 000 mg/kg atropine (hyoscyamine).

> One hundred *D. stramonium* seeds contain approximately 6 mg atropine, which would equal 0.8 percent w/w (Disel *et al.*, 2015). This would represent 8 000 mg/kg atropine (hyoscyamine).

> *D. stramonium* seeds contain approximately 0.1 mg of atropine per seed or 3–6 mg per 50–100 seeds (Goldfrank, 1994).

As these estimates have reported atropine (hyoscyamine) concentrations, in the range of 4 000–13 000 mg/kg, but no values for scopolamine, only the publications where both TAs have been analyzed will be used to estimate the average concentration on a per seed basis.

Based on the average results, using the lower values from Table 1 when ranges are reported, the average concentration of sum of hyoscyamine and scopolamine would be 1 554 +/- 474 mg/kg. Using the upper range values, the average concentration would be 2 261 +/- 456 mg/kg. On a per *D. stramonium* seed basis (7.5 mg), the average and upper range values would equal approximately 12 µg and 17 µg, respectively. This is in line with estimates of total alkaloid content of *D. stramonium* seeds being in the range of 0.25–0.36 percent (Naudé *et al.*, 2005; Mukhtar *et al.*, 2019). Additional reports have stated 1 g of *D. stramonium* seeds contain 2.9 mg atropine and 0.5 mg scopolamine (Krenzelok, 2010).

CHAPTER 4

SEED CONTAMINATION LIMITS

Visual inspection of cereal grains/legumes following harvesting can be part of an effective Good Agricultural Practices (GAP) program. Codex standards for various cereals and pulses include a provision that the products "shall be free from the following toxic or noxious seeds in amounts which may represent a hazard to human health", including *Datura* species (Codex, 2007). Currently, there is no applicable generic Codex standard for legumes which contains a quality factor provision for toxic or noxious seeds.

As an example of effective use of visual inspection, *Fusarium* Head Blight (FHB) is a common fungal disease affecting wheat, resulting in visually distinct Fusarium damaged kernels and the associated production of the mycotoxin deoxynivalenol or vomitoxin. Human visual inspection of wheat samples requires no specialized equipment and has been the traditional method for FHB assessment and in ensuring wheat-derived products meet international standards for deoxynivalenol.

Guidance or intervention levels recommended by the 2020 FAO/WHO expert meeting for hyoscyamine and scopolamine in WFP products, namely SUPER CEREAL, SUPER CEREAL PLUS and Lipid-Based Nutrient Supplements, were based on recommended intake quantities and population body weights. As the product ingredients had already been processed, assessment and compliance against these levels would require time and expense dependent chemical analysis using specialized equipment. As part of a GAP screening program for cereal grains and legumes, size exclusion and visual inspection of screenings could be implemented at an early stage post-harvest to ensure the final product meets the generic Codex standard of being free from noxious weeds in amounts that would represent a hazard to human health.

Using SUPER CEREAL as an example, guidance levels that would be health protective for adults in normal situations (no food security issues), based on an intake of 100 g/day, were recommended as 30 µg/kg for the combined sum of hyoscyamine and scopolamine. For emergency situations where food insecurity issues need to be taken into consideration, the guidance level for the same product that would be health protective for adults was recommended as 90 ug/kg. In comparison, an intervention threshold of 100 µg/kg buckwheat flour for the sum of atropine and scopolamine was derived by AFSSA in 2008.

The main ingredients for WFP SUPER CEREAL Wheat Soya Blend are 73.3 percent wheat and 25 percent soya bean. For SUPER CEREAL Wheat Soya Blend with sugar, 10 percent of the wheat ingredient is replaced with sugar. Average seed weights used for wheat and soya are 35 mg and 185 mg, respectively (http://data.kew.org/sid/weight.html).

In a worst-case scenario, the source of all TAs is attributed to one of the two main ingredients of SUPER CEREAL Wheat Soya Blend. Increasing or decreasing the percent contribution of any ingredient would have the effect of decreasing or increasing the *D. stramonium* seed contamination associated with the guidance levels.

Wheat: contamination of wheat with a TAs concentration of approximately 40 ug/kg and then used as an ingredient comprising 73.3 percent w/w of the SUPER CEREAL Wheat Soya Blend would result in a final concentration in the cereal of 30 µg/kg TAs, considering no contribution of TAs from other ingredients. Based on the average of 12 µg sum hyoscyamine/scopolamine per *D. stramonium* seed, 40 µg is equivalent to approximately 3.3 seeds. Using an average wheat seed weight of 35 mg, 1 kg of wheat seed would have approximately 28 500 seeds. Therefore, 3.3 *D. stramonium* seeds in 28 500 wheat seeds would provide a final TA concentration in the wheat seeds of 40 µg/kg. Presuming no loss during milling, when used at 73.3 percent w/w of the final cereal product, this would result in a final product TAs concentration of 30 µg/kg. For situations where food insecurity issues are to be taken into consideration, the guidance level of 90 µg/kg would be reached with the wheat seed contamination of approximately 122 µg or 10 *Datura* seeds per kg of wheat seeds. Applying the upper range of TAs concentration for *D. stramonium* seeds (17 µg) would reduce the allowable seed contamination to 2.3 and 7.2 seeds, respectively.

Soybean: contamination of soybean with a TAs concentration of approximately 120 µg/kg and then used as an ingredient comprising 25 percent w/w of the SUPER CEREAL Wheat Soya Blend would result in a final concentration in the cereal of 30 µg/kg, considering no contribution of TAs from other ingredients. Based on 12 µg sum of hyoscyamine/scopolamine per *D. stramonium* seed, 120 µg is equivalent to approximately 10 seeds. Using an average soybean seed weight of 185 mg, 1 kg of soybean seed would approximate 5 400 seeds. Therefore, 10 *D. stramonium* seeds in 5 400 soybean seeds would provide a final TAs concentration in the soybean of 120 µg/kg. Presuming no loss during milling, when used at 25 percent w/w of the final cereal product, this would result in a final TA concentration of 30 µg/kg. For situations where food insecurity issues are to be taken into consideration, the guidance level of 90 µg/kg would be reached with the contamination of 360 µg/kg or approximately 30 *Datura* seeds per kg of soybean seeds. Applying the upper range of TAs concentration for *D. stramonium* seeds (17 µg) would reduce the allowable seed contamination to 7 and 21 seeds, respectively.

Further consideration for use of soybean as a directly consumed food or the primary/sole ingredient in other soy foods, for example soy flour, soy protein, edamame, tempeh, natto or tofu, would increase the potential exposure and, concomitantly, require a reduction in the tolerable seed contamination in order not to exceed intakes as being health protective for the general population, as recommended by the FAO/WHO expert meeting. Based on a maximum one-day intake of 200 g for soybean/soy foods by adults (60 kg), when compared to the clinically significant minimal acute effect dose of 1.54 µg/kg body weight for TAs and a recommended composite margin of exposure (MOE) of 30, dietary exposures less than 51 ng/kg body weight/day would be considered as health protective for the general population. If total daily TAs exposure is provided by soybeans alone, maximum concentration of TAs in soybeans could not exceed 15 µg/kg (ppb). This would be equivalent to approximately 1.0 *D. stramonium* seed per kg of soybeans using the average TAs concentration of 12 µg/seed. For situations involving food insecurity, tolerable *Datura* seed contamination limits per kg of soybeans would increase by 3-fold (3 seeds). Increasing or decreasing the amount of soy consumed per day compared to the default 200 g/day value would have the opposite effect on the tolerable seed contamination amounts. While it would be expected that the lower body weights of infants and children would decrease the tolerable seed contamination recommendations, soybean amounts consumed per day for younger ages would likely be less than the 200 g value used for adults. While these seed contamination recommendations may be applied to product as sold, it should be recognized that various food processing and preparation techniques may decrease the final TAs concentration as consumed. For example, in the Perharič *et al.* study (2013) where buckwheat flour spiked with TAs was used to prepare a traditional buckwheat dish (žganci), the concentrations of (-/+)-hyoscyamine and (-)-scopolamine in the cooked buckwheat meal were reduced by approximately 58 percent and 37 percent, respectively, during food processing. Any processing factors applied to the *Datura* seed contamination recommendations would result in the tolerable *Datura* seed limits being increased accordingly.

Maize: using a similar scenario of direct consumption of maize either as a food or as the primary/sole ingredient in other maize-based foods, for example maize flour or meal, masa and porridges, recommendations for tolerable *Datura* seed contamination could be developed. Using a 200 g/day adult intake value for all maize products, and the assumption that TAs exposure is provided only from maize, maximum TAs concentration could not exceed 15 µg/kg (ppb) in order to remain health protective for the general population. This final TAs concentration would be reached with the presence of approximately 1 *Datura* seed per kg of maize. In situations involving food insecurity, *Datura* seed contamination could increase to approximately 3 seeds per kg of maize. Based on an average maize kernel weight of 245 mg, 1 kg of maize would comprise approximately 4 080 seeds. Increasing or decreasing the amount of maize consumed per day would have the opposite effect on the tolerable seed contamination amounts. While it would be expected that the lower body weights of infants and children would decrease the tolerable seed contamination recommendations, maize amounts consumed per day for younger ages would likely be less than the 200 g value used for adults. While these seed contamination recommendations may be applied to product as sold, it should be recognized that various food processing and preparation techniques may decrease the final TAs concentration in final foods as consumed. Any processing factors applied to the *Datura* seed contamination recommendations would result in the tolerable *Datura* seed limits being increased accordingly.

As a comparison, it has been reported that legislation in the Republic of South Africa had set allowable limits of *Datura* seed in grain for human consumption to 1 seed in 10 kg of maize, 3 seeds in 400 g ground nuts, and 5 seeds in 400 g soybeans. (Naudé *et al.*, 2005). As of 2002, the Republic of South Africa Foodstuffs, Cosmetics and Disinfectants Act has been updated to specify no more than 1 *Datura* seed per kg of various agricultural products, including maize, soya beans and wheat (Republic of South Africa, 2002). Currently, the Codex standard for maize (CODEX STAN 153-1985 (Rev. 1-1995)) and wheat (CODEX STAN 199-1995) contain provisions that the product shall be suitable for human consumption and free from "toxic or noxious seeds in amounts which may represent a hazard to human health", including *Datura* species.

CHAPTER 5
RECOMMENDATIONS

Based on the typical (30 µg/kg) and emergency (food insecurity) (90 µg/kg) guidance levels proposed by the FAO/WHO expert working group for WFP product SUPER CEREAL Wheat Soya Blend, estimated contamination by *D. stramonium* seeds required to achieve these levels have been proposed for the two main ingredients, wheat and soybean (Table 3).

TABLE 3 **ESTIMATED NUMBER OF *D. STRAMONIUM* SEEDS REQUIRED TO REACH GUIDANCE LEVELS IN WHEAT AND SOYBEAN**

GUIDANCE LEVEL (µg/kg)	DATURA SEEDS PER kg (average)	DATURA SEEDS PER kg (upper range)
30	3.5 (W)	2.3 (W)
	10 (S)	7.0 (S)
90	10 (W)	7.2 (W)
	30 (S)	21 (S)

(W) = wheat;
(S) = soybean

Following visual inspection of representative sampling of wheat or soya consignments, if on average greater than 3.5 or 10 *D. stramonium* seeds are identified per kg, the cereal/legume lot should either be rejected for use in formulating SUPER CEREAL Wheat Soya Blend, subjected to additional cleaning processes that are effective in removing foreign material on the basis of size, shape, and weight, assigned for use in SUPER CEREAL Wheat Soya Blend product destined for emergency or food insecurity situations or subject to analytical determination of hyoscyamine and scopolamine prior to food use. If cereal/legume lots are destined for use in formulating SUPER CEREAL Wheat Soya Blend which will be slated for possible food insecurity use and still exceed the proposed *Datura* seed limits, namely 10 and 30 for wheat and soybean, respectively, then the lots should either be rejected for human consumption subjected to additional cleaning processes that are effective in removing foreign material on the basis of size, shape, and weight, or subject to analytical determination of hyoscyamine and scopolamine prior to food use. Using the upper range of TAs concentrations in *D. stramonium* seeds would reduce the permissible number of seeds per kg of wheat or soya by approximately 30 percent while reducing the percent contribution either ingredient makes to a finished food would presumably increase the tolerable seed contamination.

Similar scenarios could be developed for other cereals, pulses and legumes when being directly consumed as foods and not as ingredients in WFP products. Compared to the clinically significant minimal acute effect dose of 1.54 µg/kg body weight for TAs and a composite margin of exposure (MOE) of 30, as recently recommended by the FAO/WHO expert working group, concentration of TAs in soybean or maize as directly consumed foods would need to be less than 15 µg/kg in order to be considered as health protective for the general population. This would be reached by a physical *Datura* seed contamination of approximately 1.0 *Datura* seed per kg of soybean or maize, based on the previous average *Datura* seed TAs concentration of 12 µg. For situations involving food insecurity, physical seed contamination would increase to approximately 3 *Datura* seeds per kg of either agricultural product.

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ANNEX A

TABLE A1 **UNCERTAINTIES IN THE RECOMMENDATIONS**

SOURCES OF UNCERTAINTY	DIRECTION[a]
Total measurement uncertainty in chemical analytical results	+/-
Assumption of equivalent potency of (-)-hyoscyamine and (-)-scopolamine	+/-
Accurate identification of *Datura* spp. seeds	+
Visual inspection being applied to representative cereal/legume lot samples	+/-
No loss of TA from grain/legume processing	+
Geographic variability in TA content of *D. stramonium* seeds	+/-
Standard deviation of average TA values per seed not considered	+/-
Consideration of TA contribution from more than a single ingredient	-

[a] + = uncertainty with potential to cause over-estimation of risk; - = uncertainty with potential to cause under-estimation of risk.

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ROME, ITALY

ISBN 978-92-5-133622-9

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CB2105EN/1/11.20