Netherlands Food and Consumer Product Safety Authority
Ministry of Agriculture, Nature and Food Quality

> Return address P.O. BoxP.O. Box 43006 3540 AA Utrecht

Head of Agency of the Netherlands Food and Consumer Product Safety Authority

Office for Risk Assessment & Research

Catharijnesingel 59
3511 GG Utrecht
P.O. Box 43006
3540 AA Utrecht
www.nvwa.nl

Contact person

T +31 88 223 33 33
risicobeoordeling@vwa.nl

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Advice from the Director of the Office for Risk Assessment & Research

Advice on MDMA in maize

Background

In March 2017 a cattle farmer spread manure across his farmland. The Environment Agency subsequently took a soil sample from the plot of land. Following an analysis by the Netherlands Forensic Institute (NFI) the soil sample was found to contain MDMA. In October 2017 the Netherlands Food and Consumer Product Safety Authority (NVWA) took samples of the maize that was growing on the plot of land. An analysis performed by RIKILT Wageningen University & Research found that these nine samples also contained MDMA.

These findings prompted the directorate Enforcement of NVWA to seek advice from the Office for Risk Assessment & Research (BuRO) on the risks of the consumption of MDMA-contaminated maize to public and animal health.

The following questions were addressed to BuRO:

1. What are the risks to animal health if the MDMA in the maize plant is fed to farm animals either in maize silage (whole plant with cob) or maize grain (cobs)?
2. What are the public health risks if consumers eat meat or drink milk from farm animals fed with MDMA-contaminated maize (see question 1)?
3. What are the public health risks if consumers consume MDMA-contaminated maize (cobs)?
4. How should the NVWA deal with any other substances (used or released in the synthesis of MDMA) that may be present in maize?
5. How should the NVWA deal with MDMA and any other substances (used or released in the synthesis of MDMA) that may be present in the soil and surface water?

Approach

BuRO performed a search of relevant literature in Google, Google Scholar and PubMed using combinations of the key words 'MDMA', 'synthesis' and 'toxicity'.

In addition, BuRO consulted the available MDMA expertise at the Dutch Health and Youth Care Inspectorate (IGJ) and the Netherlands Forensic Institute (NFI). As an additional source of information BuRO used the report 'Assessment of 3,4-methylenedioxy-N-methamphetamine (MDMA) in maize' published by the RIVM and RIKILT Front Office for Food and Product Safety in December 2015 (report no. V/090130, Appendix 1).

Finally, BuRO requested the RIVM-RIKILT Front Office for Food and Product Safety to conduct further research based on the above questions and the following three additional questions (see Appendix 2):

1. Has new literature become available, since the risk assessment issued by the Front Office in 2015, on the toxicity of MDMA, which provides greater insight into a possible 'safe' limit value for both humans and animals?
2. What uncertainties are there in the risk assessment process?
3. What other substances used or released in the synthesis of MDMA are expected to be found in chemical waste from drug production and in what concentrations?

Findings
In 2015 the RIVM-RIKILT Front Office for Food and Product Safety derived two health-based guidance values for the short-term and long-term exposure of humans to MDMA, namely an ADI[1] of 8.3 µg/kg body weight per day for short-term exposure and an ADI of 12.5 µg/kg body weight per day for long-term exposure.

An ADI of 125 µg/kg body weight per day has been derived for the exposure of animals to MDMA.

Three of the nine samples of maize silage contained a concentration of MDMA ranging between 12 and 17 µg/kg. None of the maize grain samples contained a concentration of MDMA higher than 10 µg/kg.

The maximum estimated intake for farm animals after the consumption of MDMA-contaminated maize is 1.2 µg/kg body weight per day (broiler chickens and laying hens). This intake is a factor of 100 lower than the (animal) ADI of 125 µg/kg body weight. The intake for other animal species is lower than for poultry. It can therefore be concluded that the concentrations of MDMA found are not expected to pose any health risks to farm animals if the maize plant is fed to farm animals either as silage maize (whole plant with cob) or grain maize (cobs).

The maximum estimated exposure of consumers to MDMA through the consumption of meat, milk and eggs from animals that have eaten MDMA-contaminated maize (indirect exposure) is 3.76 µg/kg body weight per day. The maximum estimated exposure of consumers to MDMA through the direct consumption of contaminated maize is 0.007 µg/kg body weight per day (60-kg adult) or 0.022 µg/kg body weight per day (20-kg child). Both the indirect exposure of adults and the direct exposure of adults and/or children is under the health-based guidance value for short-term exposure (8.3 µg/kg body weight per day). It can therefore be concluded that there are no public health risks if consumers consume meat or milk derived from farm animals that have been fed with MDMA-contaminated maize.

The estimated exposure described above contains uncertainties, which in most cases may lead to an overestimation, but occasionally to an underestimation of the actual exposure. The calculations made are so conservative that the

[1] This ADI has been derived for acute effects and it should therefore be regarded more as a reference dose (ARfD) rather than a health limit value for long-term exposure.

uncertainties have no impact on the conclusion drawn that the concentrations of MDMA measured in maize do not pose risks to humans and animals.

Various methods can be used to synthetise MDMA. Chemical waste from drug production can contain some MDMA in addition to various solvents, converted reagents and by-products.

At present, no information is available on the substances that could be present in the maize samples and their concentration levels. These samples must be analysed for this purpose.

MDMA and the substances stated above could enter the environment (soil and surface water). To that end, the NVWA might want to contact the colleague inspector responsible for this area at the Human Environment and Transport Inspectorate (ILT).

NVWA-BuRO recommendations
BuRO concludes that the concentrations of MDMA found in maize do not pose a risk to public health. However, there is a risk in terms of the adverse effects on the food safety system. The presence of MDMA and possibly other substances from the MDMA waste in maize is undesirable.

To the Head of Agency:

- Analyse, if there are indications of the production of MDMA, whether the residual waste from this process in the vicinity of the food crops grown, the maize silage and maize grain samples contain any (residues of) raw materials, solvents and (residues of) reagents used in the synthesis of MDMA.
- Should the analytical results give cause to do so, please notify the appropriate authorities of these results.

Yours sincerely,

Prof. Antoon Opperhuizen
Director of the Office for Risk Assessment & Research

SUBSTANTIATION

Background

MDMA (3,4-methylenedioxy-N-methamphetamine) is an amphetamine derivative that was patented in the early 20th century either for use as an appetite suppressant or as a precursor for therapeutic compounds. The toxicology of MDMA was analysed for the first time in the 1950s by the American army. In the 1980s MDMA was used during psychotherapy sessions. MDMA was said to increase the patient's self-confidence and to facilitate therapeutic communication. In 1985 the U.S. Food and Drug Administration (FDA) banned MDMA as a medicine. At the end of the 1970s MDMA was illegally launched on the market as Ecstasy. Nowadays Ecstasy is used primarily to induce the ability to dance all night non-stop (Green et al. 2003; Capela et al. 2009; White 2014).

Synthesis of MDMA

Various methods can be used to synthetise MDMA. MDP2P (3,4-methylenedioxyphenyl-2-propanone, also known as piperonyl methyl ketone or PMK) is usually used as the precursor. MDP2P is synthetised from piperonal, safrole or isosafrole and after reacting with methylamine is converted into MDMA. MDP2P can also be converted into MDEA (3,4-Methylenedioxy-N -ethylamphetamine) using ethylamine and into MDA (3,4-methyleendioxyamphetamine) using ammonia (Wikipedia[2]; Shulgin 1991). The synthesis route used depends on the availability of raw materials, solvents and reagents.

Since MDMA is the desired end product, it is plausible that the chemical waste from drug production contains a small quantity of MDMA and many solvents, converted reagents and by-products. The usual chemicals for the various synthetic routes of MDMA are described in a United Nations Office on Drugs and Crime (UNODC) document (UNODC 2011). Appendix 1 to the Front Office's report contains a list of raw materials and reagents used for the synthesis of MDMA. If the synthesis is executed carefully and efficiently, relatively few raw materials and reagents will be present in unchanged form in drug waste. This does not apply to solvents, which are in fact expected to occur in higher concentrations in chemical waste from drug production.

According to the Front Office, the following chemicals could potentially be found in chemical waste from drug production:

- (Residues of) raw materials: piperonal, piperonyl alcohol, PMK (3,4-methylenedioxy-phenyl-2-propanone), safrole, isosafrole, MDA (N-desmethyl MDMA), catechol and furthermore all by-products and intermediary products.
- Solvents: methanol, toluene, benzene, dimethylformamide, formamide, dichlormethane, diethyl ether and tetrahydrofuran.
- (Residues of) reagents: nitroethane, hydrobromide (HBr), hydrochloride (HCl), potassium hydroxide (KOH) and lithium, aluminium,zinc, mercury, copper and nickel sulphates.

In the Netherlands, MDMA is primarily synthesised from PMK. Depending on the step in the production process, the chemical waste from drug production contains the following chemicals: (1) water containing methanol or isopropyl alcohol and low concentrations of MDMA and PMK/reduced PMK, or (2) a (water) solution of

[2] https://en.wikipedia.org/wiki/MDMA#Synthesis Consulted on 16 November 2017.

hydrochloric acid containing acetone and low concentrations of MDMA and possibly PMK and reduced PMK (NFI 2015). The concentration of MDMA and PMK/reduced PMK in drug waste is around 2-10 mg/ml.

Other pollutants found in low concentrations in chemical waste from drug production are piperonal, safrole, isosafrole, N-acetyl-MDMA and N-formyl-MDMA, various aldol condensation products from acetone and various imines.

Effect of MDMA

MDMA is rapidly absorbed after oral intake. MDMA hardly attaches to proteins and is therefore primarily found in plasma. MDMA is largely metabolised by the liver and subsequently excreted in urine. The half-life of MDMA ranges between six and nine hours (Capela et al. 2009).

MDMA has an effect on the serotonergic system. Serotonin is a neurotransmitter in the brain that is excreted by synaptic vesicles and enables signals to be transmitted between the brain cells (neurons). After excretion, serotonin is reabsorbed into the synaptic vesicles. MDMA blocks this process to prevent serotonin from being reabsorbed and the level of serotonin in the bloodstream rises (Green et al. 2003; Capela et al. 2009).

Stimulation of the serotonergic system causes the 'desirable effects' of MDMA to occur, due to which a user has a lot of energy, feels happy and has a need to connect with others (White 2014). The recommended maximum dose for recreational use is 1 mg/kg body weight (Drugsinfoteam.nl). Higher doses increase the risk of adverse effects. The risks associated with the use of MDMA include anxiety and panic attacks, overheating, water poisoning, brain damage, liver and kidney damage and a higher heart rate and blood pressure (White 2014).

The risks of exposure to MDMA are higher for certain groups, such as young people, the mildly intellectually disabled and children whose parents have psychological or addiction problems (Front Office 2015).

Health-based limit values

Humans

In 2015 the Front Office derived two acceptable daily intake (ADI) values (Front Office 2015). The first is based on the fact that an XTC pill contains around 80 mg of MDMA and it is plausible that 50 mg of MDMA causes noticeable effects. This corresponds to an exposure of 0.83 mg/kg body weight per day for an adult (60 kg). Taking account of a safety factor of 100 (10 for extrapolating a LOEL to a NOEL, and 10 for the variation between people), this results in an **ADI of 8.3 µg/kg body weight per day**. This corresponds to 498 µg MDMA per day for a 60-kg adult. Since this ADI has been derived for acute effects, it should be regarded more as an acute reference dose (ARfD) rather than as a health limit value for long-term exposure.

The second ADI is based on a study of mice, in which the blood parameters indicating liver and kidney damage had risen. The no-observed-adverse-effect level (NOAEL) in this case is 1.25 mg/kg body weight per day. Taking account of a safety factor of 100 (10 for extrapolating the variation between animals and people, and 10 for the variation between people), an **ADI can be derived of 12.5 µg/kg body weight per day**. This corresponds to 750 µg MDMA per day for a 60-kg adult.

Animals

An ADI can also be derived for animals. Similar to humans, this is based on a study of mice, in which the blood parameters indicating liver and kidney damage had risen. The NOAEL is 1.25 mg/kg body weight per day. Taking account of a safety factor of 10 (for the variation between different animal species), an **(animal) ADI can be derived of 125 µg/ kg body weight per day**. This corresponds to 62,500 µg MDMA per day for beef cattle (500 kg), 78,125 µg per day for dairy cattle (625 kg), 12,500 µg per day for calves (100 kg) and pigs (100 kg), 213 µg per day for broiler chickens (1.7 kg), 238 µg per day for laying hens (1.9 kg), 56,250 µg per day for horses (450 kg), 9,375 µg per day for sheep (75 kg) and 5,000 µg per day for lambs (40 kg).

MDMA content measured in maize

The NVWA took samples of two types of maize on a plot of land on which manure had been spread that had been mixed with chemical waste from drug production, namely maize silage (whole plant with cob) and maize grain (cobs). RIKILT analysed the samples (table 1).

Table 1. Overview of the concentrations of MDMA measured by RIKILT in maize silage and grain on a plot of land on which manure had been spread that had been mixed with chemical waste from drug production.

Maize silage		Maize grain	
NVWA no.	MDMA (µg/kg)	NVWA no.	MDMA (µg/kg)
ST01	15	ST02	0.93
ST03	3	ST04	1.1
ST05	17	ST06	0.85
ST07	12	ST08	1.0
ST09	7.9	ST10	<10*
ST11	<10	ST12	<10
ST13	<10	ST14	<10
ST17	<10	ST16	<10
ST19	<10	ST18	<10
		ST20	<10

*contained a minute trace of MDMA (<10 µg/kg)

Three of the nine samples of maize silage contained a concentration of MDMA exceeding 10 µg/kg, i.e. 12 and 17 µg/kg. None of the maize grain samples contained a concentration of MDMA higher than 10 µg/kg.

Exposure to MDMA in maize

Farm animal exposure

The Front Office made a calculation of the exposure of various types of farm animals to MDMA through the consumption of contaminated maize (table 2). This is based on a worst-case scenario, in which the total food consumption per day consists of maize silage (except for calves, where the known consumption of maize silage was used). In reality the consumption of maize by farm animals is lower because they either do not eat maize silage but maize grain, and/or because a portion of their feed does not consist of maize but other crops.

Table 2. The intake of MDMA through maize consumption in various farm animals (based on 17 µg MDMA/kg maize).

	Body weight (kg) (OECD 2013)	**Feed consumption (kg/day) (OECD 2013)**	**MDMA intake (µg/kg/lg/day)**
Beef cattle	500	12	0.41
Dairy cows	625	25	0.68
Calves (0-3 months)*	100	2.72	0.46
Pigs	100	3	0.51
Broilers	1.7	0.12	1.2
Laying hens	1.9	0.13	1.2
Horse (sport/leisure)**	450	8.1	0.31
Sheep	75	2.5	0.57
Lambs	40	1.7	0.72

* Published in Van Raamsdonk 2007. Feed consumption relates specifically to maize silage.
** Published in Bikker 2009.

The maximum estimated exposure is 1.2 µg/kg body weight per day (broilers and laying hens). The exposure for other animal species is lower than for poultry.

Indirect consumer exposure
The Front Office calculated the indirect exposure of a consumer through the consumption of farm animals and related products (table 3). The following assumptions were applied to a worst-case scenario:

- 50% transfer to milk.
- An average daily milk yield of 30 litres (Van Raamsdonk 2007).
- Consumption of 1.5 litres of milk per day (Food Basket EC 2005).
- 50% transfer to eggs.
- Consumption of 2 eggs (100 g) per day (Food Basket EC 2005).
- 50% of the amount of MDMA in the feed eaten daily enters the piece of meat that is subsequently consumed according to the Food Basket (300 g, Food basket EC 2005).
- Consumption by an individual with 60-kg body weight.

Table 3. Indirect exposure of a consumer exposed to MDMA-contaminated maize via farm animal products.

	Consumer exposure to MDMA (µg/kg lg)
Beef cattle	1.7
Meat from dairy cows	3.5
Calves (0-3 months)	0.39
Pigs	0.43
Broilers	0.02
Meat from laying hens	0.02
Horses	1.1
Sheep	0.35
Lambs	0.24
Cow's milk	0.18
Egg	0.04
Food basket*	3.76

* 300 grams of meat, 2 eggs and 1.5 litres of milk.

The maximum estimated consumer exposure to MDMA through indirect exposure was 3.76 µg/kg body weight per day if both the meat, the milk and the eggs had been derived from animals that had eaten MDMA-contaminated maize. When looking at the consumption of one portion of meat/milk/egg, the maximum estimated exposure was 3.5 µg/kg body weight for the consumption of meat from a dairy cow.

Human exposure
All the concentrations of MDMA measured in grain maize were below 10 µg/kg. The exact value is not clear and therefore this example calculation assumes that the maize grain contained 10 µg/kg of MDMA. According to the Dutch National Food Consumption Survey, Dutch people (aged 7-69) eat an average of 44 grams of maize per day. The maize contained 0.44 µg of MDMA per portion. This produces an intake of 0.007 µg/kg body weight per day for an adult (60 kg) and an exposure of 0.022 µg/kg body weight per day for a child (20 kg).

The estimated exposure described above contains uncertainties, which in most cases may lead to an overestimation, but occasionally to an underestimation of the actual exposure. The calculations made are so conservative that the uncertainties have no impact on the final conclusion.

Effects of exposure to MDMA in maize
Farm animals
The maximum estimated exposure of farm animals following the consumption of MDMA-contaminated maize is 1.2 µg/kg body weight per day for both broilers and laying hens. This estimated exposure is a factor of 100 below the (animal) ADI derived of 125 µg/kg body weight for animals. The exposure for other animal species is lower than for poultry. It can therefore be concluded that the concentrations of MDMA found in maize are not expected to pose any health risks to farm animals.

Consumers
The maximum estimated consumer exposure to MDMA through indirect exposure is 3.76 µg/kg body weight per day if both the meat, the milk and the eggs had come from animals that had eaten MDMA-contaminated maize. This exposure is below the health-based guidance value for short-term exposure (8.3 µg/kg body weight per day). The consumption of products derived from farm animals that have eaten maize contaminated with MDMA in the concentrations found therefore does not pose any risks to public health.

The maximum estimated exposure of consumers to MDMA through the direct consumption of maize is 0.007 µg/kg body weight per day (60-kg adult) or 0.022 µg/kg body weight per day (20-kg child). The exposure of both adults and children is below the health-based guidance value for short-term exposure (8.3 µg/kg body weight per day).

Furthermore, it can be stated that the maximum intake of MDMA by a 60-kg adult is 498 µg before the health-based guidance value is exceeded. Based on an average daily consumption of 44 grams of maize, the permitted amount of MDMA in one kilogramme of maize is 11,318 µg of MDMA (11.3 mg/kg). This is a factor of 1,000 higher than the concentrations of MDMA actually found in maize. The direct consumption of maize contaminated with MDMA based on the concentrations found does not pose any risks to public health.

Conclusions

The concentrations of MDMA found are not expected to pose any health risks to both farm animals and consumers.

This risk assessment relates entirely to MDMA. It is plausible that the chemical waste from drug production contained a minimal amount of MDMA given that MDMA is the desired end product. In addition to MDMA, chemical waste from drug production could also contain other substances, such as residues of raw materials, solvents or residues of reagents that could potentially be harmful to animal and/or public health if it enters the food chain.

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Appendix 1. RIVM-RIKILT Front Office for Food and Product Safety (2015). Assessment of 3,4-methylenedioxy-N-methamphetamine (MDMA) in maize.

Appendix 2. RIVM-RIKILT Front Office for Food and Product Safety (2017). Risk assessment of 3,4-methylenedioxy-N-methamphetamine (MDMA) in maize.