National Institute for Public Health and the Environment
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WAGENINGEN UNIVERSITY & RESEARCH

FRONT OFFICE FOOD AND PRODUCT SAFETY

Risk assessment of 3,4-methylenedioxy-n-methamphetamine (MDMA) in maize

Risk assessment requested by:	NVWA–BuRO
Risk assessment performed by:	RIVM and RIKILT
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Subject

In 2015 the Front Office Food and Product Safety performed a risk assessment on MDMA in maize (RIVM-RIKILT, 2015). The Netherlands Food and Consumer Product Safety Authority (NVWA) has been regularly confronted in recent years with situations where waste from the production of illicit drugs (including MDMA and amphetamine) had been mixed with manure. The contaminated manure was subsequently spread on arable land, where crops such as maize are grown. This has again been discovered this year, and this time samples were taken of the maize growing on the field, which were subsequently analysed for the presence of MDMA.

Since MDMA is the end product of the illegal synthesis and should only be present in low concentrations, other possible substances (used or released in the synthesis of MDMA) are also expected to be present in the maize, perhaps even in higher concentrations.

Questions

In addition to the Front Office's risk assessment of 2015, NVWA-BuRO would like to receive answers to the following questions:

1. Has new literature become available, since the 2015 risk assessment issued by the Front Office, on the toxicity of MDMA that provides greater insight into a possible 'safe' limit value for both humans and animals?
2. What are the risks to animal and public health if MDMA-contaminated maize is used as animal feed (for cattle, dairy cows, calves, pigs, poultry, horses and goats) in the form of maize silage (whole plant with cob) or maize grain (cobs)? The concentrations found in maize should be taken into account.
3. What are the public health risks if an MDMA-contaminated cob is sold on the market as a food product?
4. What uncertainties are there in the risk assessment process?
5. What other substances used or released in the synthesis of MDMA are expected to be found in drug waste? What concentrations of these substances are expected to be present in drug waste?

Conclusions

1) No new literature has become available since 2015 to allow refinement of the limit value derived for both humans and animals in 2015.
2) In the MDMA concentrations found in maize, the maximum estimated exposure of farm animals is a factor of 1,000 lower than the no-observed-adverse-effect level (NOAEL) for mice. The human consumption of products derived from farm animals fed with maize containing MDMA does not exceed the health-based guidance value for short-term exposure (8.3 µg/kg bw/day) using the MDMA concentrations measured in maize. Risks to humans and animals can therefore be ruled out.
3) Humans only reach the health-based guidance value for short-term exposure through the consumption of 50 kg of maize kernels. From a public health perspective, the concentrations of MDMA found in maize (equivalent to the detection limit of 10 micrograms/kg at the most) therefore do not give a cause for concern.
4) There are various uncertainties in the derivations described, mainly due to the lack of data on the transfer of MDMA into edible products from farm animals. However, the calculations applied are so conservative that these uncertainties have no impact on the conclusion that the concentrations of MDMA measured in maize do not pose risks to humans and animals.
5) The waste produced during the production of MDMA differs for each synthetic route applied, in terms of both the substances and the concentrations. If the synthesis is executed carefully and efficiently, relatively few of the raw materials and reagents used will be present in unchanged form in drug waste. It is not known to what extent the synthesis is actually executed carefully. However, higher concentrations of the solvents used are expected to be present.

Introduction

In 2015 the RIVM-RIKILT Front Office performed a risk assessment on MDMA in maize following the discovery of a field of maize that earlier had been fertilised with manure mixed with chemical waste from drug production (XTC/MDMA). At that time, a health-based guidance value for short-term exposure had been derived of 8.3 µg/kg bw/day, based on the pharmacological effects in humans[1]. A health-based guidance value had also been derived for long-term exposure of 12.5 µg/kg bw/day, based on the adverse effects on blood parameters for mice (NOAEL 1.25 mg/kg bw/day). This NOAEL can be used to assess the risks to farm animals using a margin of exposure (MOE) approach. A maximum concentration of MDMA of 1 mg/kg of maize was used in the 2015 calculation. This resulted in no human health risks.

NVWA analysis data

The NVWA took samples of the maize growing in the field where drug production waste had been found this year. These samples were subsequently analysed for the presence of MDMA (table 1). The concentrations measured are as follows:

Table 1. MDMA concentrations measured in maize

Silage maize		**Grain maize**	
NVWA no.	MDMA (µg/kg)	NVWA no.	MDMA (µg/kg)
ST01	15	ST02	<10*
ST03	<10*	ST04	<10*
ST05	17	ST06	<10*
ST07	12	ST08	<10*
ST09	<10*	ST10	<10*
ST11	<10	ST12	<10
ST13	<10	ST14	<10

[1] Please note: the pharmacological effects occur at an earlier stage than the harmful effects.

Silage maize		Grain maize	
NVWA no.	MDMA (µg/kg)	NVWA no.	MDMA (µg/kg)
ST17	<10	ST16	<10
ST19	<10	ST18	<10
		ST20	<10

*contains a minute trace of MDMA (<10 µg/kg, but below the reporting limit).

Toxicity

The following was concluded on the toxicity of MDMA in the 2015 assessment:
The recommended maximum dose for recreational use is 1 mg/kg bw. Higher doses increase the risk of adverse effects. An XTC pill contains around 80 mg of MDMA. It is therefore plausible that 50 mg of MDMA will cause noticeable effects. For an adult with a body weight of 60 kg this means 0.83 mg/kg bw/day. Applying an uncertainty factor of 100 (from LOEL to NOEL and for intraspecies variation), this means an ADI of 8.3 µg/kg bw/day. Given that this concerns acute effects, this ADI should be regarded more as an acute reference dose (ARfD) rather than a health-based guidance value for long-term exposure.

A study with mice found that various blood parameters, which can be related to liver and kidney damage, had risen in male animals that had been exposed to a dose of 5 mg/kg bw/day and higher for 28 days. It was concluded from this reproductive toxicity study that MDMA has weak toxicity. Based on the effects on the blood parameters in male animals that had been exposed for a period of 28 days, the no-observed-adverse-effect level (NOAEL) was set at 1.25 mg/kg bw /day (Kwack et al., 2014). Based on this NOAEL, an ADI can be derived of 12.5 µg/kg bw per day, taking into account an uncertainty factor of 100 for inter- and intraspecies variation (RIVM-RIKILT, 2015).

For the years 2015-2018 (search date 27 November 2017), SCOPUS generated 589 hits based on a search performed with CAS numbers for MDMA or MDMA-HCl (CASREGNUMBER(42542-10-9 or 64057-70-1)). The titles were firstly scanned to determine whether there were any studies providing new information on the toxicity of MDMA. Where there was doubt and if the title appeared useful, the abstract was also examined. The vast majority of the publications relate to all kinds of pharmacological interactions, abuse, misuse, case studies or analytical methods. No studies have been published in the last three years that give a reason to change the NOAEL in animal studies or the guidance value for humans derived in 2015. This means that the risk assessment for humans will be calculated on the basis of the guidance value of 8.3 µg/kg bw per day derived in 2015. An MOE approach will be applied to the health risks to farm animals based on the NOAEL derived for mice.

Transfer data

A search in SCOPUS was performed for specific farm animal data based on the CAS numbers for MDMA or MDMA-HCI using the limiter: AND TITLE-ABS-KEY (cow OR cattle OR pig* OR chick* OR poultry OR milk OR egg* OR meat), without applying a limiter to the year. This search generated 57 hits dating back to 1988. These publications were similarly scanned for relevance according to title. A further search was performed specifically for data on the kinetics of MDMA based on the CAS numbers for MDMA and MDMA-HCI applying the limiter: (kinetic* OR adme) AND (half-life OR distribut*). This search generated 145 hits. No information was found on the kinetics of MDMA in farm animals. However, a number of publications were retrieved on the pharmokinetics of MDMA in rats, apes and humans. All three species have non-linear kinetics. For an oral dose of around 1.5-2 mg/kg body weight, the half-life of MDMA varied from 42 minutes in rats (Baumann), 1.8 hours in squirrel monkeys (Mueller 2008) to 10 hours in humans (Peira 2013, Farré 2015). This assessment assumes that the half-life of MDMA in farm animals will not be much higher than in humans.

Risk assessment

Farm animals
The maize silage contained 17 µg/kg at the most and the grain maize 10 µg/kg at the most. A calculation is shown below of the exposure of various types of farm animals to MDMA through the consumption of contaminated maize (see table 2). It 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 is used). In reality the consumption of maize by farm animals is lower because they either do not eat maize silage but grain maize, 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 bw/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.

According to the calculations in table 2, the highest estimated exposure equates to 1.2 µg/kg bw/day (for both laying hens and broilers). This exposure is a factor of 1,000 lower than the NOAEL for mice (1.25 mg/kg bw/day). This appears to be sufficient to compensate for any variation between animal species. 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.

Consumer exposure
Consumer exposure to MDMA was calculated for both direct consumption of maize and indirect consumption through meat and milk (see table 3). This was subsequently compared to the health-based guidance value for short-term exposure (8.3 µg/kg bw/day).

The following assumptions were made for indirect exposure through the consumption of edible products from farm animals:

- Similar to the 2015 assessment, the calculations below for a worst-case scenario assume 50% transfer into milk as well as an average daily milk yield of 30 litres per day (van Raamsdonk 2007) and consumption of 1.5 litres of milk per day (Food basket EC 2005).
- Furthermore, 50% transfer into eggs and consumption of 2 eggs (100 g) per day is assumed (Food basket EC 2005).
- The initial assumption is that 50% of the amount of MDMA in the feed eaten daily enters the portion of 300 g meat that is consumed daily according to the Food basket (Food basket EC 2005).
- Consumption by an individual with 60-kg body weight.

This is an extreme worst-case scenario. Should the outcome of this scenario indicate a risk, refined calculations should be made before drawing a conclusion.

Table 3. Consumer exposure through the consumption of farm animals

	Exposure to MDMA (µg/kg bw)
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.

Even in the unlikely event that both the meat, milk and eggs had been derived from animals that had eaten MDMA-contaminated maize, the intake of MDMA (3.76 µg/kg bw/day) is below the health-based guidance values for short- and long-term exposure (8.3 µg/kg bw/day and 12.5 µg/kg bw/day respectively). 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 following calculation can be made for direct exposure through the consumption of grain maize by humans:[2] The analysed grain maize contains 10 µg MDMA/kg at the most. To reach the health-based guidance value for short-term exposure, a quantity of 8.3*60/10 = 50 kg of grain maize must be eaten. From a public health perspective, the concentrations of MDMA found are not of concern.

Uncertainties

The derivatives described above contain uncertainties, which in most cases may lead to an overestimation but occasionally even to an underestimation, such as:

- The lack of data on the transfer of MDMA and any metabolites into milk, eggs and meat. To that end, a transfer rate of 50% for milk and eggs is assumed, which will probably lead to an overestimation of the risk. In addition, 50% of the MDMA is assumed to enter the portion of meat that will be consumed. Again, this most probably is an overestimation.
- The calculations with the food basket assume that the meat, milk and eggs are all derived from animals that have eaten MDMA-contaminated maize. This most probably is an overestimation.
- A production of 30 litres of milk was taken as the milk yield, which is an average of a cow's entire lactation cycle. Depending on the stage of milking the cow, this assumption may lead to an over- or underestimation of the concentration of MDMA in the milk when using an unchanged transfer rate (50%). However, the margin is so wide that an underestimation has no consequences for the risk assessment.
- All the feed consumed is assumed (except for calves) to consist of maize, specifically maize silage. This leads to an overestimation for animal exposure and hence for humans. The specific consumption of silage maize is assumed for calves.

[2] Please note: Only silage maize is grown in the Netherlands. The maize kernels from the cobs of silage maize are not used for human consumption.

- An animal is assumed to be slaughtered/milked/laying eggs shortly after the consumption of MDMA-contaminated maize. This will probably lead to an overestimation of the risk.
- The accumulation of MDMA through the consumption of maize by farm animals for a prolonged period of time has not been taken into account. However, in view of the expected relatively short half-life based on the data for rats, apes and humans, this will not have a substantial effect on the risk.

The calculations made are so conservative that these uncertainties have no impact on the conclusion drawn, i.e. that the concentrations of MDMA measured in maize do not pose risks to humans and animals.

Other substances
Various substances used and formed during the production of MDMA may be present in the chemical waste from drug production. Various methods can be used to prepare MDMA. The synthetic route used depends on the availability of raw materials, solvents and reagents. The waste produced during production will therefore differ per synthetic route. Since MDMA is the desired end product, it is plausible that the waste contains a relatively small amount of MDMA but many solvents, converted reagents and by-products.

Ample information is available on the synthesis routes of MDMA on the Internet. Given that trading in all the usual raw materials is regulated, there are no arguments for regarding one synthetic route more probable than another. For this reason, the chemicals used in all common synthetic routes according to the Internet have been taken into account.

The usual chemicals for the various MDMA synthetic routes are described in a United Nations Office on Drugs and Crime (UNODC) document (UNODC 2011). If the synthesis is executed carefully and efficiently, relatively few of the raw materials and reagents in this list (see Appendix 1) will be present in unchanged form in drug waste. It is not known to what extent the synthesis is actually executed carefully. The solvents used are expected to be present in higher concentrations in the drug waste.

The chemicals that could potentially be found in drug waste are summarised below. Knowledge of the actual situation in the Netherlands regarding the production of MDMA can probably be obtained from the Netherlands Forensic Institute (NFI).

(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, HBr, HCl, KOH, Li-sulfates, Al-sulfates, Zn-sulfates, Hg-sulfates, Cu-sulfates, Ni-sulfates.

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Appendix 1. Chemicals used in the manufacture of MDMA (After UNODC 2011)

Name	***CAS number***
Acetic acid	64-19-2
Acetone	67-64-1
Aluminum (metal)	91728-14-2
Aluminum chloride	7784-13-6
Aluminum chloride (anhydrous)	7784-13-6
Aluminum powdered	7429-19-5
Ammonia (gas)	1336-21-6
Ammonium acetate	8013-61-4
Ammonium chloride	1215-02-9
Ammonium hydroxide	1336-21-6
Baker's yeast	68876-77-7
Benzaldehyde	100-52-7
Benzene	71-43-2
Carbon dioxide gas	124-38-9
Charcoal	7440-44-0
Chloroform	67-66-3
Citrate buffer pH 6	
Copper metal	7440-50-8
Dimethylformamide	68-12-2
Ethyl alcohol	64-17-5
Ethyl ether	60-29-7
Formamide	75-12-7
Formic acid	64-18-6
Glacial acetic acid	64-19-2
Glucose	14431-43-7
Hydrobromic acid	10035-10-6
Hydrochloric acid	7647-01-0
Hydrogen bromide gas	10035-10-6
Hydrogen chloride gas	7647-01-0
Hydrogen gas	1333-74-0
Isopropyl alcohol	67-63-0
Lithium aluminum hydride	16853-85-3
Mercuric chloride	7487-94-7
Mercuric nitrate	10045-94-0
Mercury metal	9439-97-6
Methyl alcohol	67-56-1
Methylamine (40% solution in water)	74-89-5
Methylamine gas	74-89-5
Methylamine HCl	593-51-1
Methylformamide	123-39-7
Nitroethane	79-24-3
Palladium black	7440-05-3
Palladium chloride	7647-10-1
Palladium on barium sulfate	7440 -05-3
Paraformaldehyde	30525-89-4
Platinum (IV) dioxide (Adam's-type catalyst)	1314-15-4
Platinum metal	7440 -05-3
Potassium hydroxide (caustic pot-ash)	56-23-5
Pyruvic acid	113-24-6
Rainey nickel	7440-02-0

Sodium bicarbonate	144-55-8
Sodium borohydride	16940-66-2
Sodium bromide	7647-15-6
Sodium cyanoborohydride	25895-60-7
Sodium hydroxide (caustic soda)	1310-73-2
Sodium perborate	10042-94-1
Sodium percarbonate	15630-89-4
Sodium pyruvate	113-24-6
Sulfuric acid	7664-93-9
Tetrahydrofuran	109-99-9
Thiamine pyrophosphate	154-87-0
Toluene	108-88-3
Zinc metal	7440-66-6
Benzoquinone	106-51-4
N-Bromosuccinimide	75-18-3
Catechol	120-80-9
Cupric chloride	7447-39-4
Cuprous oxide	1317-39-1
Dibromomethane	74-95-3
Diethylamine	660-68-4
Ethylamine	506-58-1
Iron filings	7439-89-6
Isosafrole	120-58-1
Mercuric bromide	7789-47-1
3,4-Methylenedioxy-phenyl-2-propanone (PMK; 3,4-MDP-2-P)	4676-39-5
Piperonal	120-57-0
Piperonyl alcohol	495-76-1
Safrole	94-59-7
Sodium carbonate (soda ash)	497-19-8