National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

WAGENINGEN UNIVERSITY & RESEARCH

FRONT OFFICE FOOD AND PRODUCT SAFETY

Assessment of 3,4-methylenedioxy-N-methamphetamine (MDMA) in maize

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

A field of maize had been fertilised with manure mixed with chemical waste from illicit drug production (XTC/MDMA) earlier this year. Samples of the soil and the maize plants were taken in October. These samples were analysed by the Netherlands Forensic Institute (NFI). A very limited number of results are now available and they show that some drug-related substances were absorbed by the plants. The table below contains the data now known.

Plant number	Indicative concentration of amphetamine (µg/kg dried material)	Indicative concentration of MDMA (µg/kg dried material)
9	-	7
10	-	60
15	8	2
16	-	1

The results are indicative because the plant extraction may not have been optimal; the recovery was moderate. According to the NFI, the actual concentration of MDMA is unlikely to be higher than 1 mg/kg of dry material; it is not clear what this NFI statement is based on. This analysis centred on the green components; the maize kernels and the soil still need to be analysed. The amphetamine was not identified in the manure residues in the slurry tank earlier this year; it may have come from earlier manuring containing other waste. This question relates to the MDMA.

Question

NVWA-BuRO would like to receive an answer to the following questions:

1. What concentration of MDMA in the leaves and maize kernels fed to animals could have harmful effects on animals, and what concentration could be harmful to humans who consume products derived from these animals?
2. What uncertainties are there in the risk assessment?

Conclusions

1) Based on a maximum concentration in maize of 1 mg/kg, consumption of 15 kg (dry substance) of silage feed produced from this maize, a milk yield of 30 litres per day and 50% transfer into milk, the maximum concentration of MDMA in milk will be 0.25 mg/litres. The consumption of 1 litre of this milk by a 70-kg adult results in an exposure of around 3.5 µg/kg body weight/day. For a 20-kg child who drinks 0.5 litres, this results in an exposure of 6 µg/kg body weight/day. These maximum intakes are below the ADIs that can be derived based on the effects in humans or animals. The exposure of a cow is a factor of 50 below the NOAEL for mice and appears to be more than sufficient to compensate for interspecies differences.

   Under these conditions the maximum concentration of MDMA in silage feed would be 1.5 and 2 mg/kg of dry substance to rule out the risks of acute and chronic effects in humans, and 5 mg/kg of dry substance to prevent effects in cows.

2) The uncertainties, that could potentially lead to an overestimation, are the quality of the chemical analyses, the lack of transfer data and the lack of data on the toxic effects in humans, other than the effective dose.

3) This assessment is based solely on the concentrations of MDMA in maize. In addition to MDMA, however, chemical waste from drug production could also contain other substances that could also have been absorbed by the maize.

Transfer of MDMA into milk

MDMA, or 3,4-methylenedioxy-N-methamphetamine is the effective substance in the drug XTC. The maize in which residues of MDMA were found would have been processed into silage feed, which would probably have been fed to cattle. Only ruminants eat this type of silage feed; it is an important part of the diet of cattle and dairy cows. Van Raamsdonk et al. (2007) state an intake of 4.4 kg silage maize/day but in a recent animal test performed by Hoogenboom et al. (2015), the animals were fed 15 kg per day in accordance with practice. This assessment will therefore be performed for dairy cows, taking the transfer into milk as 'worst-case' situation. Exposure through meat consumption is regarded as, most probably, less worst-case than exposure through milk. Firstly, there is only a slight chance that the animals will be slaughtered shortly after they have eaten this feed and, secondly, people will not eat meat from those specific animals every day. Cows may be milked during a period in which they are regularly fed with this feed, and if transfer occurs, substances will enter the milk. Again in this case, the probability that people will only drink milk from cows that have eaten this maize is extremely low; however, in this assessment it is the 'worst-case' assumption.

No data are available on the transfer of MDMA into cow's milk. However, various websites provide warnings on the prolonged secretion of MDMA into breast milk (incidentally, without any literature references). This suggests that the substance could also enter cow's milk, which partly depends on the potential breakdown in the rumen but again this is not known.

It therefore seems prudent to assume a reasonable worst-case scenario, e.g. 50% transfer into milk of the amount of MDMA in the silage feed eaten. A concentration of 1 mg MDMA/kg of dry substance (ds) in silage feed amounts equals, with a daily intake of 15 kg ds silage feed, an intake of 15 mg MDMA per day. This equals to an exposure of 25 µg/kg body weight (bw)/day for a 600-kg cow. The average milk yield of a cow varies from 20 to 40 litres. If 50% MDMA is transferred from silage feed into milk and the daily milk yield is 30 litres, the concentration of MDMA in milk would be around 0.25 mg/litres.

Consumer exposure

The consumption of one litre of milk by a 70-kg adult would amount to an exposure of 0.25 mg or around 3.5 µg/kg bw/day. For a 20-kg child who drinks 0.5 litres, this results in an exposure of 0.125 mg or 6 µg/kg bw/day.

MDMA toxicity
MDMA affects the central nervous system, which causes users to experience mood-elevating effects. MDMA stimulates the release of serotonin in the brain and simultaneously blocks the reabsorption of serotonin, causing the serotonin levels in the bloodstream to rise. MDMA also has this effect on noradrenaline and dopamine, though to a lesser extent (www.drugsinfoteam.nl; Jerome 2006).

The recommended maximum dose for the recreational use of MDMA is 1 mg/kg bw (www.drugsinfoteam.nl). Higher doses increase the risk of adverse effects. The risks of using MDMA include psychological complaints and sleeping problems, liver and kidney damage, overheating, water poisoning and brain damage (www.drugsinfo.nl; www.jellinek.nl; Hall & Henry, 2006). Both single and repeated use of MDMA leads to an increased stress level, measured as the amount of cortisol (Parrot et al, 2014). The use of MDMA during pregnancy may lead to psychomotor abnormalities in babies (Parrot, 2013). A laboratory animal 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).

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 (www.drugsinfo.nl).

A safe dose of MDMA cannot yet be established with the current data. Based on the lowest dose with a pharmacological effect of 100 mg in humans, a safety factor of 100 (10 for the extrapolation of an effect level (LOEL) to a no-effect-level (NOEL) and 10 for intraspecies variation), in 2010 the National Institute for Public Health and the Environment (RIVM) established a preliminary acceptable daily intake (ADI) for MDMA of 17 µg/kg bw/day (RIVM, 2010). 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 a safety factor of 100 (again from LOEL to NOEL and for intraspecies variation), results in 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. Based on the NOAEL in mice of 1.25 mg/kg/bw/day, derived by Kwack et al (2014), an ADI can be derived of 12.5 µg/kg bw per day, taking account of an uncertainty factor of 100 for inter- and intraspecies variation.

Although both calculations include uncertainty, the ADIs calculated for the various effects are relatively close to each other.

However, this safety value is based only on MDMA. As the manure used for manuring had in this case been mixed with chemical waste from drug production, it is not improbable that other pharmacologically active substances (waste products from the XTC production process) were present in the manure and could have ended up on the maize. It seems plausible that most of the MDMA had been removed from the waste stream in order to produce XTC, and that the amount of these other substances could therefore potentially be larger than the remaining amount of MDMA.

Risk assessment
The maximum intake of 3.5 µg/kg bw/day calculated for an adult and 6 µg/kg bw/day for a child are lower than the ADI of 12.5 µg/kg bw/day based on the adverse effects on the blood parameters for mice and the ADI/ARfD of 8.3 µg/kg bw/day based on the pharmacological effects in humans.

The maximum estimated exposure for a dairy cow amounts to a dose of 25 µg/kg body weight (bw)/day. This is a factor of 50 lower than the NOAEL for mice and appears to be sufficient to compensate for any interspecies variations.

Under the earlier assumptions and based on the observed margins compared to the ADI/ARfD based on the pharmacological effects in humans and the ADI based on the reproduction effects in mice, the maximum permitted concentration of MDMA should be 1.5 mg/kg ds in silage feed to prevent adverse acute effects for humans and 2 mg/kg ds to prevent adverse chronic effects. Based on a desired margin of 10 compared to the NOAEL for mice, this amounts to 5 mg/kg ds for cows.

Uncertainties in the assessment

It should be noted that this derivation contains a large number of uncertainties, which may lead not only to an overestimation but perhaps even to an underestimation, such as the following:

- The quality of the analyses (underestimation, however, this has been taken into account by assuming 1 mg/kg ds; this has no consequences for the safe concentrations derived).
- It is unclear whether the analysis based on dry weight corresponds to dry substance. This may lead to an underestimation of the concentration, but a worst-case scenario is based on 1 mg/kg. This means that the risk is not underestimated.
- The lack of data on the transfer of MDMA and any metabolites into milk. To that end, a transfer factor of 50% is assumed, which will probably lead to an overestimation of the risk.
- A production of 30 litres of milk was taken as the milk yield, which is an average concentration for a cow's entire lactation cycle. Depending on the stage of milking the cow, this assumption may lead to an overestimation or an underestimation.
- The silage feed consumption is assumed to be 15 kg, which is far higher than the 4.4 kg stated by van Raamsdonk et al. (2007). This may lead to an overestimation for animal exposure and hence for humans. The acceptable concentration in maize could also be a factor of 3 or 4 higher.

References

Hall AP, Henry JA, Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management, British J Anaesthesia, 2006, 96 (6), p678-85

Hoogenboom, R.L.A.P., Klop, A. Herbes, R., Eijkeren, J.C.H., Zeilmaker, M.J., Vuuren, A.M. van, Traag, W.A., 2015. Carry-over of polychlorinated dibenzo-p-dioxins and dibenzo-furans (PCDD/Fs) and polychlorinated biphenyls (PCBs) in dairy cows fed smoke contaminated maize silage or sugar beet pulp. Chemosphere, 137, 214–220.

Jerome L, (=/-)-3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') Investigator's Brochure, 2007, MAPS: December 2007

Kwack SJ, Yoon KS, Lim SK, Gwak HM, Kim JY, Um YM, Lee JD, Hyeon JH, Kim YJ, Kim HS, Lee BM. A one-generation reproductive toxicity study of 3,4-methylenedioxy-N-methamphetamine (MDMA, Ecstasy), an amphetamine derivative, in C57BL/6 mice. Toxicol Environ Health A., 2014, 77(22-24), p1431-42.

Parrott AC, Montgomery C, Wetherell MA, Downey LA, Stough C, Scholey AB. MDMA, cortisol, and heightened stress in recreational ecstasy users, Behav. Pharmacol., 2014, 25 (5-6), p458-72

Parrott AC, Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research, Hum Psychopharmacol, 2013, 28 (4), p289-307

RIVM (2010). Report 703719064/2010, Drugs of abuse and tranquilizers in Dutch surface waters, drinking water and wastewater, 2010

van Raamsdonk L.W.D., Kan C.A., Meijer G.A.L. and Kemme P.A. (2007) Kengetallen van enkele landbouwhuisdieren en hun consumptiepatronen. RIKILT report 2007.010.

www.drugsinfo.nl, consulted on 12 November 2015

www.drugsinfoteam.nl, consulted on 12 November 2015

www.jellinek.nl, consulted on 12 November 2015

https://www.maps.org/research-archive/mdma/protocol/ib_mdma_new08.pdf