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**The Director of the directorate Enforcement of the
Netherlands Food and Consumer
Product Safety Authority**

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

Advice on 2,4-dinitrophenol (DNP)

**Office for Risk Assessment
& Research**

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Background

Dutch Customs has intercepted six different parcel post shipments containing 2,4-dinitrophenol (DNP) in capsules. The total amount found included three one-kilogramme packages of DNP. As a result of the find, the directorate Enforcement of the Netherlands Food and Consumer Product Safety Authority (NVWA) has requested the Office for Risk Assessment & Research (BuRO) to issue an advice on the harmful effects of DNP on public health.

Question

What concentration of DNP in capsules can damage human health?

As the question specifically concerns capsules containing DNP, the focus of this advice lies on oral exposure to DNP. Any other routes of exposure have not been taken into consideration.

Approach

BuRO conducted a literature study focusing on the question received. A search was performed for information on DNP on the websites of the European Chemicals Agency (ECHA), the Toxicology Data Network (TOXNET - U.S. National Library of Medicine), the U.S. Environmental Protection Agency (EPA), the Agency for Toxic Substances and Disease Registry (ATSDR) and the Dutch National Institute for Public Health and the Environment (RIVM). A further search was performed in Google Scholar and PubMed, using combinations of the key words '2,4-Dinitrophenol', 'DNP', 'weight loss' and 'supplement'. The draft advice was reviewed by the RIVM-RIKILT Front Office for Food and Product Safety. The Anti-Doping Authority of the Netherlands and the Dutch National Poisons Information Centre (NVIC) were also consulted on the dose and toxicity effects of DNP respectively.

Findings

Over the last century, reports have been published of dozens of people who had died after using DNP. The reported dose of DNP that causes people to die after intake varies from 1 to 3 grams per dose. After taking such a high dose of DNP, users may die as a result of overheating of their body (the thermogenic effect). A significant risk associated with DNP is the irreversibility of the thermogenic effect. Adverse effects also occur after

using small doses of DNP, such as skin lesions and cataracts and it also affects the cardiovascular and nervous systems.

DNP is a chemical substance that was marketed in the United States of America in the past as a medicine to treat obesity. It is available in capsules and in bulk through the Internet and sales are primarily aimed at bodybuilders. DNP is used, for instance, by bodybuilders to reduce subcutaneous fat.

The literature describes two toxicological guidance values for short-term exposure to DNP, namely a minimal risk level of 0.01 mg/kg of body weight per day and a 'derived no-effect level' (DNEL) of 0.014 mg/kg of body weight per day. The minimal risk level is an estimate of the daily exposure to a substance that causes no noticeable adverse health effects during a specific exposure period. A DNEL is the dose derived from a substance whereby no effects are observed as a result of short-term or long-term exposure. Two toxicological guidance values are also described for long-term exposure to DNP, namely a DNEL of 0.008 mg/kg of body weight per day and a reference dose (RfD) of 0.002 mg/kg of body weight per day. A reference dose is comparable to an acceptable daily intake (ADI) and provides an estimate of the amount of a substance that an individual may take on a daily basis, lifelong without any appreciable health effects.

Answers to the questions

Health effects cannot be ruled out for short-term exposure to DNP with the intake of 0.01 mg/kg of body weight per day (0.6 mg per day by a 60-kg adult) or for long-term exposure to DNP with the intake of 0.002 mg/kg per day (0.1 mg per day by a 60-kg a adult). The intake of 1-3 grams of DNP per dose can be lethal.

The literature shows that the dose of DNP varies but it is usually sold through the Internet in doses of 100-200 mg per capsule. RIVM has generally found around 120-200 mg of DNP in capsules that have caused complaints (such as nausea, yellow urine and hypothermia). These doses are far higher than the toxicological guidance values. Subsequently, the margin for the intake of a lethal dose is extremely small (factor 10).

NVWA-BuRO recommendations

- Prevent capsules containing DNP from being sold on the market due to the extremely harmful properties of DNP.
- Actively warn the public of the risks of taking capsules containing DNP.

Further action to be taken by BuRO

I will bring this matter to the attention of the European Food Safety Authority (EFSA).

Yours sincerely,

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

SUBSTANTIATION

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Background

2,4-Dinitrophenol (DNP) is a substance that was used for various purposes in the early 20th century (for example as a raw material for ammunition, dye or herbicide). In the early 1930s, Stanford University in the USA discovered that the intake of DNP by humans can lead to significant weight loss. From that time onwards, DNP was prescribed as a drug to treat conditions such as obesity. A few years later in 1938, DNP was prohibited as a medicine by the US Food and Drug Administration (FDA) because it was classified as 'extremely dangerous and not fit for human consumption' (Grundlingh et al., 2011) due to its side effects. DNP is also a prohibited substance for the consumer market.

Following an Interpol warning in 2015, the NVWA called on consumers to report the illegal sale of slimming aids. In addition to the NVWA, over the years various authorities in the Netherlands and abroad have warned for the adverse effects and risks of DNP (Anti-Doping Authority of the Netherlands 2014; NVWA 2015; Bundesinstitut für Risikobewertung (BfR) 2015; UK Food Standards Agency (FSA) 2015; Dutch National Poisons Information Centre (NVIC) 2015). Various media have also reported on deaths caused by the intake of DNP (Dutch magazine Muscle & Fitness 2017 and the Dutch daily newspapers Algemeen Dagblad (AD) 2016, De Gelderlander 2016 and NRC 2015).

What does DNP do?

DNP is an organic substance that is rapidly absorbed through oral intake, inhalation and the skin. A portion of DNP absorbed into the bloodstream, attaches to serum protein while the unattached portion penetrates the organs (such as the eye). DNP metabolises rapidly and is excreted in urine (ATSDR 1995).

DNP uncouples oxidative phosphorylation, due to which the energy produced by the citric acid cycle (Krebs cycle) is not stored as adenosine triphosphate (ATP) but is converted into heat (ATSDR 1995; Grundlingh et al., 2011).

Effects of oral exposure to DNP

Grundlingh et al. (2011) describe 36 fatalities linked to DNP for the first time in 1919 among workers in a French ammunition factory. During the period in which DNP was an authorised medicine, various fatalities were reported in the USA. During World War II Russian soldiers died because they had been administered DNP to warm up during the cold. Various fatalities were again reported in the period 2000-2010 when DNP was sold through the Internet (Grundlingh et al., 2011).

The main symptoms of severe acute toxicity are a combination of hypothermia, tachycardia, diaphoresis (sweating), tachypnea (abnormally rapid breathing) associated with cardiovascular collapse/cardiac arrest and death (Grundlingh et al., 2011). The reported dose of DNP that has caused people to die after intake varies between 1-3 gram per dose (Grundlingh et al., 2011; BfR 2015; POISINDEX® System). After taking such a high dose of DNP the user may die as a result of their body overheating (the thermogenic effect). A significant risk associated with DNP is the irreversibility of the thermogenic effect.

The main symptoms of chronic toxicity are skin lesions, cataracts, yellowish discolouration of the skin, sclera (white of the eye) and urine, effects on the blood, cardiovascular system and the nervous system (Grundlingh et al., 2001; BfR 2015).

Between 2009 and 2017 the Dutch National Poisons Information Centre (NVIC) received ten reports of patients who had developed various complaints following the oral intake of DNP, such as fever, rapid breathing, tightness in chest, a rash all over the body, nausea, vomiting, cardiac palpitations, pain during urination, yellow fluorescent urine, headache, dyspnea, muscle pain and kidney failure. The information on the doses they had taken varies from unknown, a few hundred milligrams for several days to a one-off dose of 3,000 milligrams. Various patients had purchased DNP through the Internet or the Deep Web/Dark Web. Two of the ten cases involved the same patient who had again been admitted to hospital for complaints a few years later.

Health-based guidance values

The Agency for Toxic Substances and Disease Registry (ATSDR 1995) has derived a minimal risk level for DNP of 0.01 mg/kg of body weight per day for short-term exposure amounting to 14 days or less. Based on a 60-kg adult the minimal risk level corresponds to 0.6 mg DNP per day. The minimal risk level is an estimate of the daily exposure to a substance that causes no noticeable adverse health effects during a specific exposure period. The minimum risk level is based on a 'lowest-observed-adverse-effect level' (LOAEL) of 1.2 mg/kg of body weight per day derived from a study of people, taking into account a safety factor of 100. A feeling of warmth, excessive sweating and weight loss (0.43 kg/week on average) was observed. The safety factor comprises a factor 10 for the variation between people and a factor 10 for using LOAEL instead of NOAEL ('no-observed-adverse-effect level').

The European Chemical Agency (ECHA) described a 'derived no-effect level' (DNEL) of 0.014 mg/kg of body weight per day for short-term exposure to DNP. A DNEL is the dose derived whereby no effects are observed as a result of short-term or long-term exposure. Based on a 60-kg adult, the DNEL corresponds to 0.9 mg DNP per day (ECHA 2017). ECHA also described a DNEL for long-term exposure to DNP, namely 0.008 mg/kg body weight per day (0.5 mg DNP per day for a 60-kg adult) (ECHA 2017).

The United States Environmental Protection Agency (US EPA 1995) has derived a reference dose (RfD) of 0.002 mg/kg of body weight per day (US EPA 1995). A reference dose is comparable to an acceptable daily intake (ADI) and provides an estimate of the amount of a substance that an individual can take on a daily basis, lifelong without any appreciable health effects. Based on a 60-kg adult, the RfD corresponds to 0.12 mg DNP per day. The RfD is based on a LOAEL of 2 mg/kg of body weight per day for the development of cataracts in humans, taking account of a safety factor of 1,000. The safety factor comprises a factor 10 for variation between people, a factor 10 for the extrapolation of a LOAEL to a NOAEL and a factor 10 for the extrapolation of subchronic exposure to chronic exposure.

Oral exposure to DNP

The literature (Grundlingh et al., 2011) showed that the dose of DNP varies, but it is usually sold through the Internet in doses of 100-200 mg per capsule. RIVM has generally found around 120-200 mg of DNP in capsules that have caused complaints (such as nausea, yellow urine and hypothermia). DNP is also sold in bulk. The target market are people who want to lose weight, but on the whole sales are specifically targeted towards bodybuilders. DNP is used by bodybuilders to reduce subcutaneous fat. A typical dosage regime is as follows: start with one capsule per day for a number of days; followed by an increase in the dose (Grundlingh et al., 2011). If the intended weight loss effect fails to occur immediately or quickly enough, the user usually increases the dose.

A study conducted by the KWR Watercycle Research Institute in 2016 revealed that DNP is available in waste water. The availability was higher around the period of bodybuilding contests (Causanilles et al., 2016).

At present insufficient information is available on the exact concentration of DNP in the capsules found. The literature showed that the dose of DNP varied, but it is usually sold through the Internet in doses of 100-200 mg per capsule. RIVM generally finds around 120-200 mg of DNP in capsules that have caused complaints.

Conclusions

Two guidance values have been derived for short-term exposure to DNP, namely a minimal risk level of 0.01 mg/kg of body weight per day and a DNEL of 0.014 mg/kg of body weight per day. If these guidance values are exceeded as a result of short-term exposure to DNP, health effects cannot be ruled out.

Two guidance values have also been derived for long-term exposure to DNP, namely a DNEL of 0.008 mg/kg of body weight per day and a reference dose (RfD) of 0.002 mg/kg of body weight per day. If these guidance values are exceeded as a result of long-term exposure to DNP, health effects cannot be ruled out.

The intake of 1-3 grams of DNP per dose can be lethal.

The literature showed that the dose of DNP varied, but it is usually sold through the Internet in doses of 100-200 mg per capsule. RIVM generally finds around 120-200 mg of DNP in capsules that have caused complaints. These doses are far higher than the toxicological guidance values. Subsequently, the margin for the intake of a lethal dose is extremely small (factor 10).

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