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EFSA STATEMENT

Potential risks for public health due to the presence of nicotine in wild mushrooms

(Question No EFSA-Q-2009-00527)

Issued on 07 May 2009

SUMMARY

The European Food Safety Authority (EFSA) received an urgent request on 27 April 2009 from the European Commission for a scientific opinion in relation to the risks for human health due to the presence of nicotine in wild mushrooms at concentrations up to 0.5 mg/kg. Considering the urgency of this request for advice, EFSA decided to issue a statement rather than an opinion.

The European Commission has been informed by food business operators that dried wild mushrooms (mainly *Boletus edulis*, but also truffles and chanterelles) may contain levels of nicotine higher than 0.01 mg/kg on a fresh weight basis. This is the default maximum residue level (MRL) set by Article 18.1.b of Regulation (EC) No 396/2005. According to the information received, 99% of samples tested from the 2008 production did not comply with the current MRL, irrespective of the wild mushrooms' origin, although most of them originated from China. No clear reason has thus far been established for this unexpected presence of nicotine in dried mushrooms.

Nicotine is a naturally occurring alkaloid in tobacco (*Nicotiana tabacum*) where it occurs at concentrations ranging from 2% to 8%. Low concentrations are also found in other plants belonging to the family of Solanaceae, such as tomatoes, aubergines, peppers and potatoes.

Nicotine is used as an insecticide. In European countries, the use of plant protection products containing nicotine will phase out by the latest in June 2010, but its use in Third Countries may continue and may lead to residues of nicotine in food.

Nicotine is rapidly absorbed through the oral cavity, lung, and gastrointestinal tract. The oral bioavailability of nicotine is incomplete because of hepatic first-pass metabolism, and usually ranges between 20% to 45%. The metabolism of nicotine is mostly mediated through the hepatic cytochrome P450 CYP2A6. Variants in the CYP2A6 gene have been associated with altered nicotine metabolism and with effects on smoking behaviour. Elimination half-lives

have been shown to range from 1.8 to 2.9 hours depending on the phenotypes, classified according to CYP2A6 activity.

Nicotine is acutely toxic by all routes of exposure (oral, dermal, and inhalation). Consistently with its action as agonist at the nicotinic receptors, it targets the peripheral and central nervous systems causing for example dizziness, salivation, increased heart rate and blood pressure.

EFSA established an acute reference dose (ARfD) of 0.0008 mg/kg body weight (b.w.), based on a lowest observed adverse effect level (LOAEL) of 0.0035 mg/kg b.w. for pharmacological effects after intravenous application of nicotine (i.e. slight, transient and rapidly reversible increase of the heart rate in humans), using an overall uncertainty factor of 10 and a correction factor of 0.44 for oral bioavailability of nicotine (extrapolation from the intravenous route to the oral route). The LOAEL is considered to be close to the no observed adverse effect level (NOAEL) and the overall uncertainty factor of 10 would be sufficient to cover the intra-species variability and the extrapolation from the LOAEL to NOAEL for the pharmacological effects.

Due to the short biological half-life of nicotine in humans, it does not accumulate in the body and the most sensitive effect of nicotine is considered to be its pharmacological effect on the cardiovascular system. Therefore, avoiding acute effects of nicotine would also protect from its chronic effects and EFSA established an acceptable daily intake (ADI[1]) for nicotine at 0.0008 mg/kg b.w. per day that is at the same level as the ARfD.

In order to assess the dietary exposure, EFSA used the occurrence data supplied by the Confederation of the Food and Drink Industries of the EU (CIAA). They included 176 analytical results with values between 0.21 and 9.9 mg/kg dried mushrooms, corresponding to 0.023 to 1.1 mg/kg expressed on fresh weight basis.

As far as consumption is concerned the highest levels were reported for Italy, for both adults and children, for wild mushrooms in general and also for the particular sub-category *Boletus edulis*.

Based on the above information EFSA performed both a long-term and a short-term exposure assessment. Long-term exposure scenarios based on mean nicotine concentrations (0.23 mg/kg) and high Italian consumers including children indicated nicotine exposure well below the ADI of 0.0008 mg/kg b.w. per day. The short-term exposure using the 95th percentile nicotine concentration reported (0.53 mg/kg) and taking into account high Italian adult consumers was estimated to be 0.0017 mg/kg b.w. per day which exceeds the ARfD 2-fold. Making the same calculations for Italian children the ARfD can be exceeded up to 4-fold. Exceeding the ARfD can lead to adverse health effects.

The European Commission requested assessment of a possible MRL for wild mushrooms. The results of the exposure assessment demonstrate that a residue level of 0.53 mg/kg is not safe and therefore it is necessary to propose a lower MRL that can be considered safe to consumers.

For **fresh wild mushrooms** a factor to cover unit-to-unit variability is normally included in the exposure assessment. Based on this assumption the highest level of nicotine which does not exceed the ARfD was calculated to be **0.036 mg/kg** (proposed MRL), corresponding to 0.32 mg /kg in dried mushrooms.

[1] For contaminants the term Tolerable Daily Intake (TDI) is used instead of ADI.

Should a MRL be set separately for bulked, dried mushrooms, unit-to-unit variability may not need to be taken into account. In this case the highest level of nicotine for **dried wild mushrooms** which does not lead to exceeding of the ARfD would then be **1.17 mg/kg** (expressed on dry weight basis).

It should be recognised that this statement was affected by a number of uncertainties and limitations. Consequently, EFSA recommends that the proposed MRL be considered on a temporary basis (Annex III of Regulation 396/2005). Finally, it is also noted that the monitoring recommended by the European Commission will provide data useful to derive a more robust basis for exposure assessment and MRL setting.

Key words: nicotine, wild mushrooms, cep, *Boletus edulis*, maximum residue level (MRL), Regulation (EC) No 396/2005, consumer risk assessment, acute reference dose (ARfD), acceptable daily intake (ADI)

ACKNOWLEDGEMENT

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BACKGROUND TO THIS REQUEST AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission has been informed by food business operators that dried wild mushrooms (mainly *Boletus edulis*, hereafter called ceps, but also truffles and chanterelles) may contain levels of nicotine higher than 0.01 mg/kg[2] (default level as set by Article 18.1.b of Regulation (EC) No 396/2005[3]). According to the information received, almost all wild mushrooms are affected, irrespective of their origin, although most of them originate from China. The data received from food business operators show that 99% of the 2008 production does not comply with the default limit of 0.01 mg/kg as set in the Regulation (EC) No 396/2005 and that residue levels found can be up to 6 mg/kg on the dried product.

Food business operators have been investigating on the reason of this unexpected presence of nicotine in dried mushrooms, but so far no clear causal link could be established. The nicotine residues found could be of various origin but also result from a combination of different factors:

1) Pesticide use. Nicotine is an insecticide and was recently evaluated under Directive 91/414/EEC[4] by the United Kingdom, which acted as Rapporteur Member State.
2) Inherent presence of nicotine in ceps, but also in other wild mushrooms.
3) Cross contamination due to bad practices in the storage/drying and packaging process (smoking people handling the mushrooms, cross contamination during storage, where storage rooms have been disinfected with nicotine, simultaneous drying of tobacco and mushrooms in the same room, presence of mushrooms in locations where smoking takes/has taken place). In addition nicotine might also be present as a consequence of unavoidable cross-contamination.

A monitoring and testing programme will be launched by food business operators at the start of the next season (June 2009). The European Commission will also ask the Member States to monitor the levels of nicotine in mushrooms as from the next season with a view to collect monitoring data and to have a clear understanding of the natural levels and unavoidable background presence that can be expected from various regions.

However, pending the submission of those data, urgent measures are needed to allow the placing on the markets of dried mushrooms from the 2008 season, provided that they are safe for our consumers.

TERMS OF REFERENCE

In accordance with Article 43 of Regulation (EC) No 396/2005, the European Commission asks the European Food Safety Authority to provide by 4 May 2009 a scientific opinion on the risks for human health related to a presence of nicotine in wild mushrooms up to 0.5 mg/kg.

[2] Recalculated on the fresh mushroom, to which the default level applies. According to information available the concentration factor as a consequence of drying is a factor of about 9.

[3] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC, OJ L 70, 16.3.2003

[4] Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.08.1991.

CLARIFICATION OF THE TERMS OF REFERENCE

EFSA agreed with the European Commission to provide a response by 7 May 2009. Considering the urgency of this request for advice and the lack of knowledge regarding the reason of elevated levels of nicotine in wild mushrooms, EFSA decided, in accordance with Art. 43 of Regulation (EC) No. 396/2005, to produce at this point an EFSA Statement rather than the requested EFSA Scientific Opinion.

The European Commission contact for this request clarified that it was essential to provide a proposal for a safe maximum residue level (MRL) to be established for fresh wild mushrooms if the value of 0.5 mg/kg was found not to be safe (Arena, personal communication).

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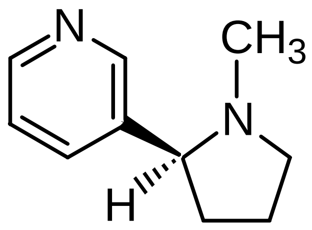
EVALUATION

1. Introduction

Nicotine is the main alkaloid in tobacco (*Nicotiana tabacum*) and other tobacco species where it occurs at concentrations ranging from 2% to 8%.



Nicotine: IUPAC name (S)-3-(1-methylpyrrolidin-2-yl)pyridine

Nicotine is synthesised in the tobacco root from ornithine and/or arginine by way of putrescine. Putrescine N-methyltransferase transfers the methyl moiety of S-adenosylmethionine to putrescine, thus forming N-methylputrescine which serves as a precursor of nicotine (Hibi *et al.*, 1994). Mushrooms are usually not reported as a significant source of nicotine, although both amino acids, ornithine and arginine have been identified in mushrooms (Ribeiro *et al.*, 2008).

Low concentrations were also measured in other plants belonging to the family of Solanaceae, such as tomatoes, aubergines, peppers and potatoes (Andersson *et al*., 2003). A study on dietary nicotine intake through consumption of Solanaceae performed by Siegmund *et al*. (1999) concluded that the mean daily dietary nicotine intake for the population of the countries for which consumption data were available is approximately 1.4 µg/person per day, 2.25 µg/person per day at the 95th percentile. This source of exposure was not further considered in this Statement.

Recently significant amounts of nicotine were detected in Germany in dried wild mushrooms (ceps) from China (BfR, 2009), raising questions about the origin of nicotine in these products and the possible concerns for human health.

The presence of nicotine in mushrooms may be the result of a pesticide use of nicotine which can be used as insecticide to control aphids, thrips, whitefly and other insects. It impacts on the nervous system of insects as agonist of nicotine acetylcholine receptors. The symptoms of exposed insects are typical of a neurotoxin and include loss of coordination followed by death. The use as a pesticide is possible at the growing stage, during storage or during transport. In European countries, the use of nicotine containing plant protection products will phase out by the latest in June 2010, but its use in Third Countries may continue and lead to residues of nicotine in food or feed.

Yunnan is known as the centre for the mushroom trade in China. Harvesting and subsequent handling of wild-grown mushrooms in the Yunnan province is very labour intensive and consists of a number of successive steps. Between each of the steps of the process, like picking, cleaning, slicing and drying, the semi-prepared products are offered on the open market. Thus, the products change hands many times. It is possible that nicotine is used at one (or several) of those steps to protect the product against insect infestation.

Yunnan is also the centre for Chinese tobacco production. Thus, besides its use as an insecticide, it is also possible that by-products from tobacco production are used as fuel for the drying process of mushrooms. Tobacco smoking is also common in the area and much of the processing of mushrooms takes place in confined areas that could harbour smoke in the air. Also, nicotine from the hands of the workers could find its way to the mushrooms.

Cep (*Boletus edulis*) is a member of a large genus, most of which are edible. It is common in woods in summer and autumn. The size can vary significantly; the cap may reach up to 25 cm in diameter and 1 kg in weight. Preliminary information on the international market for Chinese wild mushrooms in general and Boletus spp. in particular has been gathered from different websites of Chinese traders. Chinese companies offer Boletus spp. and other wild mushrooms in different forms:

- fresh;
- deep frozen;
- dried;
- in brine or vinegar (both whole or sliced).

According to the EUROSTAT trade data (2009), the EU imports dried, fresh and processed mushrooms from China. Figures are provided in detail in Appendix B. China is the predominant exporter of dried mushrooms to the EU, accounting for 75-82% of the total imports in the last three years. There is also significant intra-EU trade of dried mushrooms originated from local production or trade of imported quantities. The main exporters are the Netherlands and Germany and the main importers are Greece, Germany and the UK (the order is changing every year). According to the EUROSTAT (2009), “mushrooms and truffles, fresh or chilled” and “mushrooms and truffles prepared or preserved otherwise than by vinegar or acetic acid” imported in the EU from China are covering 10-12% and 98% respectively of the total EU imports of those commodities the last three years. The share of China in the total import figures for wild mushrooms in Italy was more than 40% in 2005 for the categories “dried” and “frozen”, with an increasing trend (Sitta and Floriani, 2008). The imported products may be then further processed, simply packed, or even only labelled by European companies.

Mushrooms are used both in home and industrial preparations in varying amounts depending on country and tradition. Fresh ceps are consumed raw, or in processed form like sautéed, cooked, fried etc.; similar uses may be partly shared by frozen cep as well. Home recipes in a country, like Italy, having in some areas a well established tradition for mushrooms suggest an amount of cep variable for a 4 person preparation in the range of roughly 400-1000 g. This corresponds to 100-250 g mushrooms per person.

Mushrooms may be used also as flavouring ingredient in composite food, like soups or risottos. Home recipes for mushroom cream soup or risotto suggest a range 50-150 g of mushrooms per person. These mushrooms may be fresh or re-hydrated from dry product (normally slices).

Industry offers a variety of mushroom flavoured packaged food using Boletus spp. and other wild species. Such products are offered both to final consumers and catering. Based on the percentage of mushrooms reported on the label and the suggested number of portions it is possible to calculate the amount of mushrooms per portion. This is normally in the range 5-25 g (expressed as fresh mushrooms).

Finally, the market of delicacies also uses preparations based on wild mushrooms (like ceps in marinade or ceps in olive oil). These products are often consumed as a starter or side dish. No portions are available for preserved mushrooms delicacies (in glass jars with vinegar and/or oil).

2. Legislative background

The use of nicotine as insecticide was evaluated in the framework of Directive 91/414/EEC in stage 4 with the United Kingdom being the designated Rapporteur Member State (RMS). The representative uses supported in the peer review process were the use of a fumigation formulation in glasshouse to protect fruiting vegetables, leafy vegetables, potatoes, against aphids, thrips, white fly green leaf hopper. Based on the Draft Assessment Report prepared by the Rapporteur Member State, the Standing Committee on the Food Chain and Animal Health concluded that the existing evidence is not sufficient to demonstrate a safe use of nicotine as a plant protection product with respect to operators, workers, bystanders and consumers. Thus, the evaluation under Directive 91/414/EEC resulted in a decision to not include nicotine in Annex I. This decision entered into force on 10 January 2009[5]. As a consequence, plant protection products containing nicotine as active substance have to be withdrawn by 8 June 2009. A period of grace can be granted by Member States for placing on the market and use of existing stocks of plant protection products until 8 June 2010.

In organic farming nicotine is not allowed to be used as pesticide (Regulation (EC) No 889/2008[6]).

As one of the regulatory contexts for nicotine is the pesticide legislation, the MRL provisions of Regulation (EC) No 396/2005 are applicable. This regulation establishes the legal limits for pesticide residues in food. Pesticide residues include active substances, metabolites and/or breakdown or reaction products of active substances currently or formerly used in plant protection products which are present in or on the food covered by Annex I to this regulation, including in particular those which may arise as a result of use in plant protection products, in veterinary medicine and as a biocide. For nicotine no specific MRLs have been established in Annex II or III of Regulation (EC) No 396/2005; therefore the default MRL of 0.01 mg/kg applies for all commodities of plant or animal origin, including all kind of cultivated or wild mushrooms. The MRLs established under Regulation (EC) No 396/2005 apply for fresh fungi (whole product), after removal of soil or growing medium. For processed products, the MRLs set for fresh products have to be recalculated using specific processing factors. According to the information provided by the food industry, for dried products a drying factor of 9 should be applied which accommodates for the loss of water in the drying process. The MRL of 0.01 mg/kg established by Regulation (EC) No 396/2005 entered into force on 2 September 2008. Before that data, national MRLs were applicable.

In the framework of the Regulation (EC) No 396/2005, EFSA is responsible for the risk assessment of MRLs.

3. Hazard identification and characterisation

For the hazard identification and characterisation studies from the Draft Assessment Report provided by the UK in 2007 (UK, DAR 2007) for registration purposes of nicotine as a plant protection product in the EU were considered.

In addition, reports from the German Federal Institute for Risk Assessment (BfR, 2009), the Agence Française de Sécurité Sanitaire des Aliments (AFSSA, 2009), the Nordic Council

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[5] Commission Decision of 8 December 2008 concerning the non-inclusion of nicotine in Annex I to Council Directive 91/414/EEC and the withdrawal of authorsations for plant protection products containing that substance. OJ L 5, 9.1.2009.

[6] Commission Regulation (EC) No 889/2008 of 5 September 2008 laying down detailed rules fort he implementation of Council Regulation (EC) No 834/2007 on organic production and labelling of organic products with regard to organic production, labelling and control. OJ L 250, 18.9.2008

(Andersson *et al*., 2003), United States Environmental Protection Agency (US EPA, 2008) and original research articles available in the public domain (NIH PubMed) were considered.

The review was thus based on information and toxicological data in the published literature, mainly based on human studies, providing few details of experimental protocols, dosing patterns or GLP status of studies cited.

Nicotine is an agonist to nicotinic receptors, which are located in the autonomous and peripheral nervous system, brain and spinal cord. In man, as in animals, nicotine has been shown to produce both behavioural stimulation and depression. Pharmacodynamic studies indicate a complex dose response relationship, due both to complexity of intrinsic pharmacological actions and to rapid development of tolerance (IPCS, 1991). Nicotine's effects depend on the dose, type of the exposure, and time elapsed since the exposure (BfR, 2009).

3.1. Absorption, distribution, excretion, metabolism

Nicotine is rapidly absorbed through the oral cavity, lung, and gastrointestinal tract. Absorption of nicotine across biological membranes depends on pH. In its ionised state, such as in acidic environments, nicotine does not rapidly cross membranes. The respiratory absorption of nicotine was found to be 60% to 80%. Nicotine base can be absorbed through the skin, and there have been cases of poisoning after skin contact with pesticides containing nicotine. Nicotine is poorly absorbed from the stomach because it is protonated (ionized) in the acidic gastric fluid, but is well absorbed in the small intestine, which has a more alkaline pH and a large surface area.

Following the administration of nicotine capsules or nicotine in solution, peak concentrations in blood are reached in about 1 h (Benowitz *et al*., 1991; Zins *et al*., 1997; Dempsey *et al*., 2004). The oral bioavailability of nicotine is incomplete because of the hepatic first-pass metabolism and ranges between 20% to about 45% (Andersson *et al*., 2003; Benowitz *et al*., 1991; Compton *et al*., 1997; Zins *et al*., 1997; Hukkanen *et al*., 2005). After intravenous administration, the highest levels of nicotine were found in spleen, liver, lungs and brain (UK DAR, 2007).

The metabolism of nicotine is mediated mostly through the hepatic cytochrome P450 CYP2A6 with the C-oxidation of nicotine to cotinine as the major detoxication reaction, followed by the hydroxylation of cotinine to 3-hydroxycotinine (Dorne *et al*., 2004; Hukkanen *et al*., 2005). The lungs and the kidneys are also partially involved in the metabolism of nicotine. Variants in the CYP2A6 gene have been associated with altered nicotine metabolism and with effects on smoking behaviour. A number of genotypes of CYP2A6 have been determined and a recent intravenous study (Benowitz *et al*, 2006b) classified subjects in three phenotypes according to CYP2A6 activity (fractional clearance of nicotine to cotinine and on plasma ratio of 3-hydroxycotinine to cotinine) with respective CYP2A6 activities and mean total plasma clearances of 100%, 80% and 50%, and 18.5, 15.5 and 11.7 ml/min/kg. Elimination half lives ranged from 1.8 to 2.9 hours between the three phenotypes (Benowitz *et al*., 2006b). Considering the short biological half-live of nicotine in humans, no accumulation of nicotine is foreseen.

Nicotine readily crosses the placenta. Nicotine is mainly excreted through urine, and faeces. The rate of nicotine excretion is influenced by the pH of the urine. When the pH of the urine is made alkaline, the proportion of uncharged nicotine increases and re-absorption of nicotine and as a result, less nicotine is excreted (UK DAR, 2007).

Recently, a mechanistic population model for the pharmacokinetics of nicotine, its primary (CYP2A6-generated) metabolite cotinine and 3-hydroxycotinine has been developed from sixty-six subjects receiving orally 2 mg of deuterium-labelled nicotine and 10 mg deuterium-labelled cotinine simultaneously. The model showed high correlation between nicotine clearance to cotinine and the 3-hydroxycotinine to cotinine concentration ratio in saliva supporting the idea that the 3-hydroxycotinine: cotinine ratio can be used as a predictor of CYP2A6 activity and nicotine clearance. The model-based analysis extends and further justifies this conclusion (Levi *et al.*, 2007a). This model has been applied to predict nicotine clearance using cotinine and 3-hydroxy-cotinine spot saliva samples (Levi *et al.*, 2007b).

A recent study (Yun *et al.*, 2008) in subjects exposed to transdermal nicotine patches administered as single and multiple doses, demonstrated that nicotine clearance in smokers is slower than in non-smokers: in smoking individuals nicotine induces glucuronidation, and higher plasma concentrations are thus maintained.

3.2. Acute Toxicity

3.2.1. Experimental data

Nicotine is acutely toxic by all routes of exposure (oral, dermal, and inhalation). The oral median lethal dose (LD_{50}) of nicotine is 50 mg/kg for rats and 3 mg/kg for mice (US EPA 2008).

3.2.2. Human data

The lethal dose of nicotine has been estimated to be 40–60 mg (0.6 to 1.0 mg/kg b.w.) for adults (Gosselin, 1988), and about 10 mg for children (Arena, 1974). Persons have widely different levels of tolerance to the toxic effects of nicotine. Apart from local caustic action, the target organs are the peripheral and central nervous systems. Nicotine is also a powerfully addictive drug. Poisoning in man is associated with a burning sensation in the mouth and throat, salivation, nausea, abdominal pain, vomiting and diarrhoea. Gastrointestinal reactions are less severe but can occur even after dermal and respiratory exposure. Systemic effects include: agitation, headache, sweating, dizziness, auditory and visual disturbances, confusion, weakness and lack of coordination. A transient increase in blood pressure, followed by hypertension, bradycardia, paroxysmal atrial fibrillation, or cardiac standstill may be observed. In severe poisoning, tremor, convulsions and coma occur. Faintness, prostration, cyanosis and dyspnoea progress to collapse. Death may occur from paralysis of respiratory muscles and/or central respiratory failure.

It is noted that in the Annex I to Directive 67/548/EEC[7] on Classification and Labelling of Dangerous Substances nicotine is currently classified as R25 and R27 (19th ATP) whereas salts of nicotine are classified as R26/27/28: “Very toxic by inhalation, in contact with skin and if swallowed”.

A report (Woolf *et al.*, 1997) on a postmarketing surveillance study over a 24-month period, involving 34 United States poison centres, was published in 1997. Patients were represented by 36 children aged 0 to 15 years (mean: 3 years) exposed to a Transdermal Nicotine Patch (TNP). Eighteen exposures were dermal; 18 additional children had bitten, chewed, or

[7] Annex I to Directive 67/548/EEC on Classification and Labelling of Dangerous Substances: nicotine. http://ecb.jrc.ec.europa.eu/classification-labelling/search-classlab/

swallowed part of a patch. Exposures were unintentional and transient (<20 minutes duration). Twenty-two children (64%) suffered no toxic effects from the TNP exposure: 13 of the 18 children (72%) with oral exposures and 9 of the 18 (50%) with dermal exposures remained asymptomatic. The 5 children who became symptomatic after an oral exposure to a TNP had only transient and local signs of toxicity; children with dermal exposures more often had systemic complaints. Seven of the nine children who were symptomatic after a dermal TNP exposure had nausea and/or vomiting. Five of the nine children were triaged to the emergency department and two were admitted. Fourteen children (39%) developed symptoms, including gastrointestinal distress (nausea, vomiting, diarrhea, abdominal pain), weakness, dizziness, or localized rashes. Occurrence of symptoms after a dermal exposure of children to a TNP was associated with an estimated nicotine dose of 100 µg (10 µg/kg b.w.). All children recovered fully (Woolf *et al*, 1997).

Lindgren *et al.* (1999) investigated the dose-response relationship for electroencephalographic parameters (EEG) and heart rate frequency over a wide range of intravenously infused nicotine doses in human volunteers. Fourteen regular smokers who had abstained from nicotine for at least 12 h were given intravenous infusions of 0, 3.5, 7, 14 and 28 µg/kg b.w. nicotine over 10 min in a single-blind randomised cross-over design and they were monitored for 120 minutes. Findings showed linear dose-related changes in EEG measures indicative of arousal, i.e., decrease in EEG delta and theta power, and increase in the alpha2 power, at all doses tested, markedly at 14 and 28 µg/kg b.w. Nicotine infusion caused heart rate acceleration (ranging from 8% to 20% of the baseline), with a highly significant linear trend contrast. The nicotine X time interaction was significant, with pronounced heart rate acceleration after infusion of the 14 and 28 µg/kg nicotine dose. Heart rate frequency returned back to a level comparable to the baseline within 2 hours from the end of the intravenous infusion. It is noted that changes in the heart rate frequency in the order of up to 50% of the baseline heart frequency are considered in a light physical exercise.

In a semi-blinded, within-subject, crossover study with inhaled nicotine, Benowitz *et al.* (2006a) examined plasma nicotine and cardiovascular responses in 12 healthy smokers receiving cigarettes with 5 graded nicotine contents (between 0.6 and 10.1 mg/cigarette). Non-abstinent smokers were asked to smoke on five subsequent occasions a research cigarette, each with a different nicotine content. Systemic nicotine exposure (0.26-1.47 mg per cigarette) varied linearly with the nicotine content of the cigarette (average intake of 13-43% of the cigarette's nicotine content). Cigarette smoking increased heart rate and decreased skin temperature, but the nicotine dose-response curve showed a flattening at higher doses, with a maximal response being observed from 8 mg of nicotine per cigarette. An increase in the heart rate was observed after a systemic dose of approximately 0.004 mg/kg b.w. equal to 0.26 mg in a 60 kg b.w. person (BfR, 2009). The effects on the blood pressure were not significant. The flat nicotine dose–cardiovascular response curve may be consistent with the tolerance of smokers to the cardiovascular effects of nicotine. In non-smokers stronger effects would possibly be observed (Benowitz *et al.*, 2006a).

3.3. Short term toxicity

Only limited animal experimental data are available for the evaluation of the toxic potential of nicotine as active substance in plant protection agents, in particular investigations are missing for chemical active substances, as required by the EU Directive 91/414/EEC (UK DAR, 2007).

In a subacute study (Yuen *et al*., 1995) on nicotine effects on the rat liver, nicotine hydrogen tartrate was administered to pregnant (n=16/group) and non-pregnant (n=24/group) female rats at doses of 54 and 108 μmol/L of drinking water (equivalent to 1.25 and 2.5 mg/kg b.w. per day) for 10 days. The animals exhibited mild fatty liver change, mild focal necrosis and mild dark cell change, with effects on the mitochondria, in a dose proportional manner.

Effects at the lower dose were not statistically significant, so the no observed adverse effect level (NOAEL) was identified as 1.25 mg/kg/day; the lowest observed adverse effect level (LOAEL) was identified as 2.5 mg/kg/day (Yuen *et al*., 1995 in US EPA 2008).

3.4. Genotoxicity

On the basis of the information reviewed in the published literature, nicotine was considered not mutagenic (UK DAR 2007).

3.5. Chronic toxicity and carcinogenicity

On the basis of the information reviewed in the published literature, nicotine was considered not carcinogenic. Chronic exposure was considered to lead to cardiovascular disease, hypertension, peptic ulcers and effects on the immune system (UK DAR 2007).

3.6. Reproductive and developmental toxicity

Nicotine rapidly crosses the placenta and enters the foetus. Cigarette smoking during pregnancy has been implicated in the increased risk of low birth weight, prematurity, spontaneous abortion, and perinatal mortality in humans. However controversial data exist for the adverse effects of nicotine per se in human studies. Furthermore, the effects of nicotine on birth weight or pups organ weight in rodent experimental models have either provided conflicting results or have not been investigated in a systematic fashion (Hussein *et al* 2007).

There is some evidence that effects may occur only at high nicotine doses. A 6 mg/kg b.w. per day nicotine dose administered throughout gestation to rats implanted with osmotic mini-pumps (plasma concentrations >100 ng/ml), did not result in any relevant adverse effects in the offspring (Hussein *et al*., 2007).

Another study in rats reported that low doses of nicotine injected subcutaneously (0.1 mg/ kg b.w. per day) from day 14 to the end of pregnancy had no effect on litter size or foetal development, but higher doses (1 mg/kg b.w. per day), comparable to those consumed by heavy smokers, reduced litter size and increased the number of still births (UK DAR 2007).

3.7. Neurotoxicity

Nicotine is an agonist at nicotinic receptors in the cholinergic peripheral and central nervous system. In man, as in animals, nicotine has been shown to produce both behavioural stimulation and depression (UK DAR, 2007).

3.8. Health-based guidance values

3.8.1. Existing health based guidance values

In 2007, nicotine was considered under the EU peer review process for pesticides, with the United Kingdom (UK) as the Rapporteur. The rapporteur considered the data available (as provided by the applicant) insufficient to set an Acceptable Daily Intake (ADI[8]) and an Acute Reference Dose (ARfD). Reports of human toxicity were considered in the draft assessment report. Clinical signs of toxicity were reported in humans at approx 0.03-0.8 mg/kg b.w. The lowest estimated systemic exposures of nicotine associated with adverse effects were reported to be <0.01 mg/kg b.w. per day based on a post-marketing surveillance, where US poison centres looked at reports of the poisoning of children exposed to transdermal nicotine patches (Woolf *et al.*, 1997). Taking 0.01 mg/kg b.w. per day as a lowest observed effect level (LOEL) and applying an uncertainty factor of 10 for intra species variability and 10 because the estimated LOEL was based on a limited data set, the rapporteur proposed an ARfD of 0.0001 mg/kg b.w. and an ADI of 0.0001 mg/kg b.w. per day (UK DAR 2007). The study by Lindgren *et al*., 1999 was not considered in the UK DAR.

During the re-registration process for nicotine in 2008, the US EPA based the setting of short term reference values on a NOAEL (for hepatotoxicity) of 1.25 mg/kg b.w., from a 10-day study in the rat by Yuen *et al*. (1995). An uncertainty factor of 1000 was applied accounting for intra- and inter-species variability and the uncertainties of the limited database. The reference value of 0.00125 mg/kg b.w. per day was mainly used for the assessment of short- and intermediate-term human health risks (operator exposure) associated with the current nicotine use pattern, as in the US nicotine is not used on any food and feed crops (US EPA 2008).

In February 2009, the BfR published a report concerning the potential acute risks deriving from the consumption of nicotine-contaminated mushrooms. The BfR established an ARfD for nicotine of 0.0008 mg/kg b.w. on the basis of a study by Lindgren *et al*. (1999) in humans who were injected nicotine intravenously. The lowest systemic nicotine dose, which caused an increase of heart rate, namely 0.0035 mg/kg b.w., was taken as the LOAEL (lowest observed adverse effect level) for humans. By applying a safety factor of 10 to account for the differences in sensitivity within the human population, and by assuming an oral bioavailability of 44% (Hukkanen *et al*, 2005), the final value of 0.0008 mg/kg b.w. was derived for the ARfD.

The Agence Française de Sécurité Sanitaire des Aliments (AFSSA) also prepared a report providing scientific and technical advice concerning mushroom contamination by nicotine and already made it available to EFSA. The AFSSA endorsed the ADI and ARfD of 0.0001 mg/kg b.w. per day, proposed by UK in 2007 (UK DAR, 2007).

[8] In the area of contaminants the term Tolerable Daily Intake (TDI) is used instead of ADI.

Tab. 3-1 Organisations establishing health based guidance values

Organisation	Key study	Administration	Endpoint	NOAEL (mg/kg b.w.)	UF*)	ARfD (mg/kg b.w.)	ADI (mg/kg b.w. per day)
UK PSD, 2007 AFFSA, 2009	Woolf *et al*. 1997 (human study)	Dermal, acute	Clinical symptoms	0.01 (LOEL)	100	0.0001	0.0001
US EPA, 2008	Yuen *et al*. 1995 (rat study)	Oral, 10 days	Hepatotoxicity	1.25	1000	Only AOEL derived (0.00125 mg/kg b.w. per day). No consumer exposure expected	
BfR, 2009	Lindgren *et al*. 1999 (human study)	I.v., acute	EEG and heart rate frequency changes	0.0035 (LOAEL)	10; 44% oral bioavailability	0.0008	0.0008

*) Uncertainty factor

3.8.2 Establishment of a health based guidance value by EFSA

The relevant exposure for consumers occurs through ingestion. The majority of clearly adverse effects (as currently available) have been reported for inhalation and transdermal exposure.

Within this context, EFSA considered two human studies, one from Lindgren *et al*. (1999), and one from Woolf *et al*. (1997) for the establishment of a health based guidance value. The study by Lindgren *et al*. has a single-blind randomised cross-over design, and is performed in adults under controlled conditions. Nicotine is applied intravenously and the dose definition is clear and monitored throughout the study. All effects including subclinical effects are recorded carefully. The study by Woolf *et al*. (1997) collected a number of acute symptoms in children after nicotine poisoning as reported in some US Poison Centres: the effects reported are clinical, mainly local for oral ingestion and systemic for transdermal exposure. Although both studies do not contain relevant information on the oral exposure, the results of the study by Lindgren *et al*., performed with intravenous administration of nicotine, can reliably be extrapolated to the oral route by using oral bioavailability data from pharmacokinetic studies. EFSA considered it as the pivotal study to derive a health based guidance value. In this study, a LOAEL of 0.0035 mg/kg b.w. for pharmacological effects (i.e. slight, transient and rapidly reversible increase of the heart rate in humans) was identified.

EFSA established an ARfD of 0.0008 mg/kg b.w., based on a LOAEL of 0.0035 mg/kg b.w. for pharmacological effects, using an overall uncertainty factor of 10 and a correction factor of 0.44 (Benowitz *et al*., 1991, BfR, 2009) for oral bioavailability of nicotine (extrapolation from the intravenous route to the oral route). The LOAEL is considered to be close to the NOAEL and the overall uncertainty factor of 10 would be sufficient to cover not only human variability but also the extrapolation from the LOAEL to NOAEL for the pharmacological effects observed at the LOAEL. EFSA considers that the same approach can be adopted for the derivation of an ADI, thus EFSA also established an ADI of 0.0008 mg/kg b.w. per day but noted some deficiencies in the toxicological database.

Table 3-2. Overview of the health based guidance values established by EFSA

	Source	Year	Value	Study relied upon	Uncertainty factor
ARfD	EFSA	2009	0.0008 mg/kg b.w.	Lindgren *et al.,* 1999	10
ADI	EFSA	2009	0.0008 mg/kg b.w. per day	Lindgren *et al.,* 1999	10

The usually applied default uncertainty factor for human variability includes both the variability in toxicokinetics and toxicodynamics, for which individual default uncertainty factors of 3.16 ($10^{0.5}$) have been proposed. Such values can be replaced by chemical specific adjustment factors when compound specific data are available (WHO-IPCS, 2005).

Metabolism of nicotine is mostly mediated via the CYP2A6 pathway. In a meta-analysis of toxicokinetic data for this route of metabolism, a pathway-related chemical specific adjustment factor of 1.7 was derived to cover the 95th percentile of the healthy adult population (Dorne *et al*., 2004). Recent polymorphism data for the elimination of nicotine via CYP2A6 also showed that slow metabolisers would be only 2-fold slower than fast metabolisers (Benowitz *et al*., 2006b). Taken together, the default uncertainty factor for toxicokinetics (3.16) applied by EFSA can be considered as rather conservative to cover human variability for nicotine elimination. In addition, the uncertainty factor for toxicodynamics (3.16) takes into account the potential subgroup sensitivity such as children.

4. Assessment of exposure

4.1. Occurrence of nicotine in wild mushrooms

The presence of significant amounts of nicotine in ceps were detected in Germany in late 2008. The “Chemischen und Veterinäruntersuchungsamt” (CVUA) in Sigmaringen when analysing 26 samples of sliced dried ceps found nicotine at levels ranging between 0.22 mg/kg to 5.87 mg/kg. The internet report from CVUA states that “at least a large proportion of the product originated from China”. To check the accuracy of the findings, CVUA Sigmaringen analysed also a fresh boletus mushroom in which no nicotine was detected, even after drying. Fifteen samples of other different dried mushrooms (including chanterelle, jelly ear, Shiitake- and oyster mushrooms) were then analysed and no nicotine was detected in these (CVUA Sigmaringen, 2008).

The Food Institute of the “Landesamt für Verbraucherschutz und Lebensmittelsicherheit” (LAVES) in Oldenburg tested three dry ceps where nicotine was detected between 2.62 and 2.91 mg/kg. In four other samples of ceps collected in Germany (fresh, deep frozen or dried) the content of nicotine was investigated with results below the limit of detection.

In a German risk assessment, results from commercial testing of 125 samples of dried mushrooms were used showing amounts of nicotine varying between 0.21 and 6.10 mg/kg. The samples with the highest values originated from China, whereas those with the lowest values came from Eastern Europe. In seven samples of fresh mushrooms nicotine was found at levels between < 0.005 and 0.13 mg/kg (BfR, 2009).

The Confederation of the Food and Drink Industries of the EU (CIAA) provided a report that included 176 analytical results from self-controls by industry and trade. These samples were analysed in official /accredited laboratories and seem to incorporate also the 125 results used in the German risk assessment. They reported values between 0.21 and 9.9 mg/kg dried mushrooms.

In conclusion, the occurrence data for nicotine in wild mushrooms are so far limited and insufficient to provide a clear picture of the situation. The available occurrence information for dried cep is summarised in Table 4-1; the data have been converted to fresh mushroom weight, in order to match consumption data which are presented in a subsequent section.

Table 4-1: Summary of the relevant available analytical results for the presence of nicotine in wild mushrooms. The nicotine content is expressed in mg/kg dried mushroom and converted to mg /kg fresh mushroom.

Data source	Nicotine content										
	mg/kg dried cep						mg/kg original fresh§ cep				
	No. of samples	Min	Median	Mean	P95	Max	Min	Median	Mean	P95	Max
CVUA	26	0.22	1.87	1.99	-	5.87	0.024	0.21	0.22	-	0.65
LAVES	3	2.62	-	-	-	2.91	0.29	-	-	-	0.32
CIAA	176	0.21*	2.05	2.05	4.78	9.9	0.023	0.23	0.23	0.53	1.1

§ A factor of 9 was adopted to recalculate the values from dry to fresh product.
* A single value of 0.005, much lower than all other values, has not been considered in the summary table since it probably referred to frozen or fresh products.

The CIAA results were used to calculate the exposure.

4.2. Mushroom consumption

For the specific case of the present statement, some European countries with quite recent and detailed food consumption data, were asked by EFSA to provide the information available concerning consumption of any of the following: *B. edulis*, wild mushrooms and total mushrooms, depending on the availability of these food descriptors in the database. In case that processed mushrooms (in particular dried mushrooms) were reported in the food consumption database, their weight was transformed into the fresh quantity by means of standard factors in order to obtain a total figure for the consumption of the different forms of mushrooms. Average and high percentiles of consumption were requested for the total population as well as for individual consumers, and this both in adults and in children. In order to assess acute consumption statistics, countries were asked to consider for the calculation of these figures only the days on which consumption took place.

Consumption data on mushrooms in adults were received from Ireland (Irish Universities Nutrition Alliance, 2001), Italy (Leclercq *et al.*, 2009), Finland (Paturi *et al.*, 2008) and France (Volatier, 2000) (Table 4-2). For children such information was provided for The Netherlands (Ocké *et al.*, 2008), Ireland (Irish Universities Nutrition Alliance, 2001), Belgium (Huybrechts, 2008), Italy (Leclercq *et al.*, 2009) and France (Volatier, 2000) (Table 4-3). Most of the countries were able to report consumption figures for total mushrooms whereas only Italy and Finland presented figures for the consumption of *B. edulis*.

The highest consumption levels were reported by Italy, in both adults and children, not only for the *B. edulis* but also for the total mushroom consumption and the consumption of wild mushrooms. Thus, the Italian consumption information was used to calculate exposure.

Table 4-2: Consumption of mushrooms in adults from some European Member States.

	Country	Age range (years)	Number of			Average body weight (kg)	Consumption (grams/kg body weight/day)									
							Total population*			Consumers only*			Consuming days only**			
			subjects	Consumers*	consuming days**		Mean	SD	95th perc.	Mean	SD	95th perc.	Mean	95th perc.	97.5th perc.	Max
Total mushrooms	**Ireland**	18-64	948	493	878	75.0	0.089	0.146	0.388	0.171	0.164	0.512	0.676	1.820	2.180	4.500
	Italy	> 18	2828	776	887	69.8	0.111	0.290	0.747	0.405	0.432	1.300	1.062	3.154	4.174	10.135
	France*,**	> 15	1474	847	303	66.4	0.052	0.115	0.319	0.090	0.140	0.376	1.610	3.850	4.310	8.470
	Finland	25 – 74	2038	206	230	77.6	0.031	0.127	0.231	0.300	0.280	0.836	0.544	1.640	2.060	3.060
Wild mushrooms	**Italy**	> 18	2828	776	887	69.8	0.111	0.290	0.747	0.405	0.432	1.284	1.062	3.154	4.174	10.135
	Finland	25-74	2038	181	203	77.6	0.027	0.118	0.182	0.300	0.270	0.836	0.540	1.640	1.960	2.970
Boletus edulis	**Italy**	> 18	2828	268	279	69.8	0.027	0.160	0.025	0.286	0.444	1.207	0.825	3.570	4.067	10.135
	Finland	25 – 74	2038	1	1	77.6	0.000	0.006	0.000	0.250	0.000	0.251	0.501	0.500	0.500	0.500

Table 4-3: Consumption of mushrooms in children from some European Member States.

	Country	Age range (years)	Number of			Average body weight (kg)	Consumption (grams/kg body weight/day)									
							Total population*			Consumers only*			Consuming days only**			
			subjects	Consumers*	consuming days**		Mean	SD	95th perc.	Mean	SD	95th perc.	Mean	95th perc.	97.5th perc.	Max
Total mushrooms	**Netherland**	2 - 6	1279	113	120	18.3	0.040	0.210	0.200	0.410	0.570	0.200	0.800	2.000	3.400	7.300
	Ireland	5 - 12	594	145	194	34	0.038	0.097	0.227	0.157	0.141	0.050	0.823	2.130	3.140	4.740
	Belgium	2.5 - 6.5	696	126	168	17.7	0.105	0.338	0.672	0.580	0.600	1.930	1.450	5.010	6.640	9.860
	Italy	3 - 6	68	10	10	19	0.114	0.369	1.221	0.775	0.667	2.033	2.325	6.098	6.098	6.098
	France*,**	3 - 14	1018	569	165	31.6	0.059	0.175	0.339	0.110	0.220	0.561	2.894	8.330	9.720	14.000
Wild mushrooms	**Netherlands**	2 - 6	1279	2	2	18.3	0.000	0.002	0.000	0.040	0.010	0.000	0.090	0.100	0.100	0.100
	Italy	3 - 6	68	10	10	19	0.114	0.369	1.221	0.775	0.667	2.033	2.325	6.098	6.098	6.098
Boletus edulis	**Italy**	3 - 6	68	2	2	19	0.001	0.006	0.000	0.035	0.004	0.038	0.105	0.113	0.113	0.113

Subjects= individuals who were interviewed **Consumers**=subjects who actually consumed mushrooms **Total Population**=statistics made on all subjects including non-consumers **Consumers only**=statistics made only persons consuming the product **Consuming days**=days in which mushrooms were actually consumed **Consuming days only**= statistics for only consumers and only the days of consumption.

* In France, figures calculated for the numbers of “consumers”, consumption in “total population” and in “consumers only” refer only to mushrooms consumed as such.

** In France, figures calculated for the numbers of “consuming days” and consumption in “consuming days only” refer to all mushrooms, including those consumed as such and those consumed in recipes.

4.3. Exposure estimates based on available occurrence data

Due to the availability of consumption data for wild mushrooms and the *Boletus edulis*, data concerning the consumption of total mushrooms were not used to estimate the exposure to nicotine in adults based on available occurrence. It should be noted that the consumption figures for some cases are particularly uncertain due to the limited number of consumers they are based on. This is the case of *Boletus edulis* for children in Italy, where the number of consumers is insufficient for any consideration; the category wild mushrooms is therefore preferred. The exposure is calculated for Italy, since this country appears to have a well established tradition of wild mushroom consumption, in particular ceps (Sitta and Floriani, 2008) and the consumption figures for wild mushrooms are the highest among the countries for which consumption data were available. It should be noted that for adults in Italy the consumption figures for wild mushrooms and for ceps are identical. This effect could be extrapolated for children, where no accurate data are available.

In order to assess potential long term dietary exposure to nicotine from wild mushrooms, the mean (0.23 mg/kg fresh cep) concentration calculated over the 176 samples reported by CIAA was used in combination with the mean (total population and consumers only) and 95th percentile consumption of wild mushrooms, for both Italian adults and children.

Acute potential dietary exposure to nicotine from wild mushrooms was calculated by using the mean and the 95th percentile of consumption of wild mushrooms, for both Italian adults and children, calculated considering the consuming days of consumption only. Two scenarios were considered concerning the occurrence: Scenario A utilises the 95th percentile (0.53 mg/kg fresh cep) calculated over the 176 samples reported by CIAA whereas Scenario B considers the maximum value (1.1 mg/kg fresh cep) found in the same samples. Results for the long term and acute exposure are reported in Tables 4-4 and 4-5, respectively. It is interesting to notice that the 95th percentile calculated over the 176 samples reported by CIAA and used under Scenario A is practically equal to the value mentioned in the above reported Terms of Reference, 0.53 vs. 0.50 mg/kg fresh cep. Exposure assessments calculated under Scenario A can therefore also be interpreted as an evaluation of that limit.

The calculated long term exposure to nicotine in wild mushrooms using the consumption recorded in Italy was for adults a mean of 0.026 and a 95th percentile of 0.172 μg/kg b.w. per day, and for children a mean of 0.026 and a 95th percentile of 0.281 μg/kg b.w. per day.

The highest calculated acute exposure to nicotine in wild mushrooms was for Italian children at 6.708 μg/kg b.w. per day.

Table 4-4: Long term exposure to nicotine from wild mushrooms and *Boletus edulis* in adults and children from some European countries.

Population group	Food item	Country	Age range (years)	Number of		Long term exposure (nicotine occurrence: 0.23 mg/kg)		
						Total population (µg/kg b.w. per day)		Consumers only (µg/kg b.w. per day)
				Subjects	Consumers	Mean	95th percentile	Mean
Adults	**Wild mushrooms**	Italy	> 18	2828	776	0.026	0.172	0.093
	Boletus edulis	Italy	> 18	2828	268	0.006	0.006	0.066
Children	**Wild mushrooms**	Italy	3 - 6	68	10	0.026	0.281	0.178
	Boletus edulis	Italy	3 - 6	68	2	0.000	0.000	0.008

Table 4-5: Acute exposure to nicotine from wild mushrooms and *Boletus edulis* in adults and children from some European countries.

Population group	Food item	Country	Age range (years)	Number of consuming days	Acute exposure (µg/kg b.w. per day)			
					Scenario A (nicotine occurrence: 0.53 mg/kg)		Scenario B(nicotine occurrence: 1.1 mg/kg)	
					Mean	95th percentile	Mean	95th percentile
Adults	**Wild mushrooms**	Italy	> 18	887	0.563	1.672	1.168	3.470
	Boletus edulis	Italy	> 18	279	0.437	1.892	0.908	3.927
Children	**Wild mushrooms**	Italy	3 - 6	10	1.232	3.232	2.558	6.708
	Boletus edulis	Italy	3 - 6	2	0.056	0.060	0.115	0.124

5. Exposure estimates compared to the health based guidance values set by EFSA

Results from the dietary exposure estimates based on the available occurrence data provided by CIAA (see Table 4.4. and 4.5.) were compared with the ARfD and ADI of 0.0008 mg/kg b.w. established by EFSA (see chapter 3.8.2).

5.1. Long term health effects:

Based on the long term exposure scenarios for Italian adults, that are assumed to be the highest mushroom consumers in Europe according to available information, mean exposure of 0.026 µg/kg b.w. and 95th percentile exposure of 0.172 µg/kg b.w per day were estimated when calculated over the total population and based on mean nicotine concentrations of 0.23 mg/kg in fresh wild mushrooms (Table 5.1). These levels are well below the ADI of 0.0008 mg/kg b.w. and do not raise concern for human health. There is also no concern for the health of children in Europe should they consume such wild mushrooms. The same conclusion holds true also when looking at mean exposure only for actual consumers of wild mushrooms. In addition, considering the short biological half-life of nicotine in humans (2-3 hours), no accumulation of nicotine is expected.

Table 5-1: Comparison of long term exposure to nicotine from wild mushrooms and *Boletus edulis* in adults and children for both general population and consumers only in relation to the ADI of 0.0008 mg/kg b.w.

	Type of mushroom	Total population mean exposure (µg/kg b.w. per day)	% of ADI	Total population 95th percentile exposure (µg/kg b.w. per day)	% of ADI	Consumers only mean exposure (µg/kg b.w. per day)	% of ADI
Adults	Wild mushrooms	0.026	3	0.172	22	0.093	12
	Boletus edulis	0.006	1	0.006	1	0.066	8
Children	Wild mushrooms	0.026	3	0.281	35	0.178	22
	Boletus edulis	0.000	0	0.000	0	0.008	1

5.2 Acute health effects

EFSA considers that a likely scenario for assessing the acute exposure to nicotine from wild mushrooms in adults and children would be using the 95th percentile concentration of nicotine reported in fresh mushrooms (0.53 mg/kg) and taking into account high Italian consumers (Table 5-2). Such a scenario would lead to exposure levels of 1.672 and 1.892 µg/kg b.w per day for wild mushrooms and *Boletus edulis*, respectively. Thus, considering exposure estimates at the 95th percentile level of both consumption and nicotine concentration, the ARfD could be exceeded by up to 2-fold. Applying the same calculations for children the ARfD can be exceeded up to 4-fold.

Table 5-2: Comparison of acute exposure to nicotine from wild mushrooms and *Boletus edulis* in adults and children in relation to the ARfD of 0.0008 mg/kg b.w.

	Type of mushroom	**95th percentile exposure (µg/kg b.w. per day)**	**% of ARfD**
Adults	Wild mushrooms	1.672	209
	Boletus edulis	1.892	237
Children	Wild mushrooms	3.232	404
	Boletus edulis	0.060	8

Overall, exceeding the ARfD can not be considered to be safe from a public health point of view. Hence, it is necessary to ascertain and derive a safe concentration of nicotine in mushrooms.

6. Assessment of the MRL proposal

6.1. Methodology of long-term and short-term consumer exposure in the framework of setting MRLs

In the framework of setting MRLs for pesticide residues the long-term and short-term dietary exposure calculation is performed according to the methodology developed by JMPR.

For **long-term consumer exposure** assessment the Theoretical Maximum Daily Intake (TMDI) is calculated according the following equation (WHO, 1989):

$$TMDI = \sum MRLi * Fi$$

MRL_i is the MRL for food commodity i

F_i is the mean consumption of food commodity i (normally derived for the total population).

For the purpose of this mandate, the safety assessment of the proposed nicotine MRL for wild mushrooms will be based on the food consumption of this food item only. Other food commodities are not included in the calculation of the overall dietary burden.

For the **short-term dietary exposure** the so-called International Estimated Short Term Intake (IESTI) (WHO, 1997) is calculated which requires data on:

- the large portion consumption, usually the 97.5th percentile from the single-day consumption reported in food surveys,
- typical unit weights of the edible part of the commodities
- the body weights of the population and
- the expected residue concentration.

For <u>fresh wild mushrooms</u> the exposure assessment has to be performed according to the following equation:

$$IESTI = \frac{U * (HR\, or\, HR - P) * \upsilon + (LP - U) * HR\, or\, HR - P}{bw}$$

LP Large Portion, the 97.5th percentile of portion sizes taken by people consuming the commodity (in kg of food per day). If estimates of LP are available from several countries, it is proposed to use the highest value (FAO/WHO 2003)

HR Highest residue in composite sample of edible portion found in supervised trials form which the MRL or STMR was derived (in mg/kg)

HR-P Highest residue in the processed commodity (in mg/kg), calculated by multiplying the highest residue in the raw commodity by the processing factor b.w. Mean body weight for the target population subgroup, in kg, for the country from which the large portion (LP) was derived

U Unit weight of the edible portion (in kg), mean or median value provided by the country in the region where the trials which gave the highest residue were carried out. It is calculated allowing for the percent edible portion

υ Variability factor - the factor applied to the composite residue to estimate the residue level in a high–residue single unit. It is defined as the residue level in the 97.5th percentile unit divided by the mean residue level for the lot

This equation takes into account a possible non-homogeneous distribution of residues among single units (e.g. single apples) making up a complete meal. The calculation is based on the assumption that the LP consists of more than one unit. The first unit consumed contains high residue concentrations (HR) multiplied by the variability factor whereas the rest of the large portion contains residues at the HR.

This variability of residue concentrations on food items is due to different factors affecting the deposition of pesticides during application on a crop or soil surface and the different rates of dissipation processes affecting residue levels in or on different parts of plant or plants of the same field (EFSA, 2005). At European level, usually a default variability of 7 is used for food items with a unit weight between 25 and 250 g, unless field trials data on unit-to-unit variability are available. For fresh wild mushrooms no information is available regarding the actual unit-to-unit variability. Since it is not clear whether the nicotine residues on wild mushrooms are a result of a pesticide use or whether other sources of contamination are relevant, the selection of the most appropriate variability factor should be considered carefully. It is also noted that discussions are ongoing whether the variability factor of 3, which is used by JMPR, should be taken over in the European approach to replace the variability factor of 5 and 7 (EFSA, 2005; EFSA, 2007a).

For the calculation of the nicotine exposure resulting from residues in wild mushrooms, the HR was replaced with the MRL proposal because no experimental data from supervised residue trials are available.

The unit weight of wild mushrooms may vary significantly. Therefore a good estimator of a realistic scenario has to be agreed which reflects the typical situation. EFSA performed a sensitivity analysis which allows to estimate the uncertainty resulting from the selection of this input parameter in the short-term intake calculations. This analysis should also consider the choice of the variability factor.

For processed commodities such as **dried wild mushrooms**, where bulking or blending is expected before the preparation of the single portion, the exposure assessment should be performed as described in the following equation without introducing a variability factor.

$$IESTI = \frac{LP * MRL}{bw}$$

6.2. Food consumption data used in the pesticide risk assessment

Food consumption data provided by Member States for the development of the EFSA PRIMo (Pesticide Residue Intake Model) (EFSA, 2007b) and which were made available for the assessment of the nicotine residues in mushrooms in the framework of this mandate are summarised in Tables 6-1 and 6-2. The figures refer to the raw, unprocessed fresh wild mushrooms as described in the food classification system of Regulation (EC) No 396/2005.

Table 6-1 Consumption data of wild mushrooms used for long-term dietary intake calculations of pesticide residues

Food commodity / code no.*)	Member State diet	Body weight (kg)	Average food consumption (g/kg b.w.per day)	Average daily food consumption (total population) (g /d)	Reference
Wild fungi (chanterelle, truffle, morel, cep)/ 280020	IT adult	69	0.111	7.66	Leclercq *et al*., 2009
	IT child	19	0.114	2.17	
	NL general	63	0.0019 **)	0.12	Dutch Food Centre, 1998
	NL child	17.1	0.0006 **)	0.1	
	DE child	16.15	0.0062	0.1	Banasiak *et al*., 2005
	FI adult	77.6	0.027	2.1	Paturi *et al*., 2008

*) Food classification according to Annex I of Regulation (EC) No 396/2005

**) The reported consumption figures refer to chanterelles.

Table 6-2 Consumption data on wild fungi used for short-term dietary intake of pesticide residues

Food commodity /code no.*)	Member State diet	Reported food consumptio n (g/kg b.w. per day)	Percentile	Body weight (kg)	Large portion (g/person)	Reference
Wild fungi (chanterelle, truffle, morel, cep)/ 280020	DE child	1.80	100	16.15	29.10	Banasiak *et al*., 2005
	NL general	5.29 **)	97.5	63.00	333.00	Dutch Food Centre, 1998
	NL child	0.82 **)	100	17.10	14.04	
	IT adult	4.17	97.5	69	291.4	Leclercq *et al*., 2009
	IT child	6.10	97.5	19	115.9	

*) Food classification according to Annex I of Regulation (EC) No 396/2005

**) The reported consumption data refer to chanterelle. No data are available for *Boletus edulis*

The acute exposure assessment is normally performed for the most critical diets for adult and children. The comparison of the available consumption data showed that the Italian adults and the Italian children have the highest consumption of fresh wild mushrooms; thus the short-term exposure assessment should be based on these consumer groups.

Member States also provided data on consumption of cultivated fungi (food classification code 280010). In most cases, the consumption of cultivated mushrooms is significantly higher than the consumption of wild mushrooms (0.775 g/kg b.w. per day for long-term dietary intake; 9.72 g/kg b.w. for short-term dietary intake). EFSA is of the opinion that the exposure assessment should be based on the specific consumption data of wild mushrooms because this is the more realistic scenario to answer the question of the European Commission.

6.3. Calculation of consumer exposure

6.3.1. Long-term exposure assessment

The expected long-term exposure is calculated with the amended EFSA PRIMo rev. 2 (EFSA, 2007b) in which the consumption data for wild mushrooms as reported in Table 6-1 were incorporated. In Table 6-3 the results of the expected long-term exposure resulting from wild mushrooms containing 0.5 mg/kg nicotine are summarised.

Table 6-3 Expected long-term dietary exposure resulting from nicotine residues of 0.5 mg/kg on fresh wild mushrooms

Member State diet	Expected long-term exposure (µg/kg b.w. per day)	Exposure expressed in % of the ADI
IT child (updated) mean total population	0.0570	7.1
IT adult (new data submission), mean total population	0.0555	6.9
FI adult (updated) mean total population	0.0135	1.7
DE child mean total population	0.0031	0.4
NL general mean total population	0.001	0.1
NL child mean total population	0.0003	<0.05

From the calculations presented in Table 6-3 it is concluded that a MRL of 0.5 mg/kg does not lead to a long-term dietary exposure exceeding the ADI.

Other food commodities derived from Solanaceae such as potatoes, eggplants, pepper are reported to contain nicotine (Andersson *et al*., 2003, Siegmund *et al*., 1999). However, the reported nicotine concentrations are not consistent. Further investigations would be necessary to obtain reliable values of nicotine which should then be included in the long-term exposure assessment. Due to the time constraints this was not possible in the framework of this mandate.

Other sources of nicotine exposure like smoking are also not included in the calculations presented in Table 6-3.

6.3.2. Impact assessment of unit weight and variability factor to be used in short term exposure assessment

For the short-term exposure calculations different scenarios were calculated to estimate the impact of the unit weights and the variability factor. Calculations were performed with variability factors 7 and 3. The selected unit weights were 25 g, 50 g and 100 g. The results for the critical European consumers (IT children and IT adults) of these different scenarios are summarised in Table 6-4. The detailed results of the calculations can be found in Appendix A.

Table 6-4 Short-term dietary exposure resulting from nicotine residues of 0.5 mg/kg on fresh wild mushrooms. Impact assessment of variability factor and unit weight.

IESTI calculation	Critical consumer	Variability factor	Expected short-term exposure (mg/kg b.w.)		
			Scenario 2 Unit weight 25 g	Scenario 1 Unit weight 50 g	Scenario 3 Unit weight 100 g
Wild fungi (chanterelle, truffle, morel, cep)/ 280020	IT child	3	0.0044	0.0057	0.0083
		7	0.0070	0.0109	0.0188
	IT adult	3	0.0024	0.0028	0.0035
		7	0.0032	0.0042	0.0064

The calculations show that both parameters, the variability factor and the unit weight, have an impact on the results. Specifically, a higher exposure is expected with higher unit weights and a higher variability factor.

EFSA concludes that a unit weight of 50 g (scenario 1) is a realistic estimator for the assessment of the safety of an MRL for fresh mushrooms which is not likely to underestimate the expected intake significantly, considering also the overall conservatism of the calculation.

EFSA also concludes that a variability factor of 7 should be used to assess the safety of a MRL proposal for fresh wild mushrooms. This conservative assumption is justified as no unit-to-unit variability is known. It would be desirable to derive data to determine the unit-to-unit variability on wild mushrooms in reality.

6.3.3. Short-term exposure assessment

From the short-term dietary exposure calculations for fresh wild mushrooms as presented in the Appendix A (scenario 1) it is concluded that a MRL of 0.5 mg/kg, based on an assumed unit weight of 50 g and a variability factor of 7 in the IESTI calculation, exceeds the ARfD for the critical European consumers. For the Italian child an exposure of 1368% of the ARfD is calculated, whereas for the Italian adult the exposure is 530% of the ARfD.

Under the same assumptions as scenario 1 (critical European consumers, variability factor 7, unit weight 50 g) a threshold MRL of 0.036 mg/kg is calculated (Appendix A, scenario 4); this residue concentration is the highest acceptable residue in fresh wild mushrooms which leads to less than 100% of the ARfD and is therefore considered as the maximum acceptable MRL for fresh wild mushrooms. (The threshold value in case the variability factor of 3 is applied, is 0.07 mg/kg (Appendix A, scenario 5)).

For bulked dried mushrooms the intake calculation was performed in scenario 6 (Appendix A). An MRL of 0.5 mg/kg expressed on fresh basis (corresponding to 4.5 mg/kg expressed on dried product) also leads to an exceedence of the ARfD (381% and 261% of the ARfD for Italian children and Italian adults, respectively). The threshold MRL for dried mushrooms is calculated in scenario 7 is 0.13 mg/kg for fresh mushrooms. This value corresponds to 1.17 mg/kg expressed on a dry matter basis.

CONCLUSIONS AND RECOMMENDATIONS

EFSA was asked to consider the possible health risks related to the presence of nicotine in wild mushrooms at concentrations up to 0.5 mg/kg.

- For this purpose EFSA established an ARfD of 0.0008 mg/kg b.w., based on an LOAEL of 0.0035 mg/kg b.w. for pharmacological effects, using an overall uncertainty factor 10 and a correction factor of 0.44 for oral bioavailability of nicotine. EFSA considers that the same approach can be adopted for the derivation of an ADI, thus EFSA also established an ADI of 0.0008 mg/kg b.w. per day but noted some deficiencies in the toxicological database.
- The Confederation of the Food and Drink Industries of the EU (CIAA) provided a report that included 176 analytical results of nicotine in mushrooms. These samples were analysed in official /accredited laboratories. They reported values between 0.21 and 9.9 mg/kg dried mushrooms, corresponding to 0.023 to 1.1 mg/kg expressed on fresh weight basis.
- The highest consumption levels were reported by Italy, in both adults and children, for wild mushrooms in general and also for the particular sub-category *Boletus edulis.*
- Based on the above information EFSA performed both a long-term and a short-term exposure assessment. Long-term exposure scenarios based on mean nicotine concentrations (0.23 mg/kg) and high Italian consumers including children indicated nicotine exposure well below the ADI of 0.0008 mg/kg b.w. per day. The short-term exposure using the 95th percentile nicotine concentration reported (0.53 mg/kg) and taking into account high Italian adult consumers was estimated to be 0.0017 mg/kg b.w per day which exceeds the ARfD 2-fold. Making the same calculations for Italian children the ARfD can be exceeded up to 4-fold.

Exceeding the ARfD can lead to adverse health effects. The results of the exposure assessment demonstrate that a residue level of 0.53 mg/kg is not safe and therefore it is necessary to propose a lower MRL that can be considered safe to consumers.

The European Commission requested assessment of a possible MRL of 0.5 mg/kg for fresh mushrooms. For **fresh mushrooms** a factor to cover unit-to-unit variability is normally included in the exposure assessment. Based on this assumption the highest level of nicotine which does not exceed the ARfD was calculated to be **0.036 mg/kg** (proposed MRL), corresponding to 0.32 mg/kg in dried mushrooms.

Should a MRL be set separately for bulked, dried wild mushrooms, unit-to-unit variability may not need to be taken into account. In this case the highest level of nicotine for **dried wild mushrooms** which does not lead to exceeding of the ARfD is **1.17 mg/kg** (expressed on dry weight basis).

It should be recognised that this statement was affected by the following uncertainties and limitations.

- The toxicological data package for setting health based guidance values was limited.
- A limited number of occurrence data were available to calculate exposure.

- As wild mushrooms are not a staple food, there is not a robust consumption database.
- Other dietary and non-dietary sources of nicotine exposure have not been taken into account.
- As discussed above, the establishment of MRLs is affected by several uncertainties which are discussed in section 6 (unit weight, unit-to-unit variability).

EFSA recommends the following:

- The proposed MRL should be considered suitable on a temporary basis only (Annex III of Regulation 396/2005).
- Finally, it is noted that the monitoring recommended by the European Commission will provide data useful to derive a more robust basis for exposure assessment and MRL setting.

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APPENDIX A: SHORT TERM DIETARY INTAKE CALCULATIONS

IESTI calculation

Active substance:	Nicotine
ARfD:	0.0008

Code no. (1)	Examples of individual products within the groups to which the MRLs apply	MRL input (mg/kg)	body weight (kg)	Large portion g/person	unit weight, edible portion (g)	case	variability factor	IESTI 1 (calculation with VF 7) mg/kg bw/day	% ARfD IESTI 1	alternative variability factor	IESTI 2 (calculation with alternative variability factor) (mg/kg bw)	% ARfD IESTI 2
Scenario 1	**Fresh mushrooms**											
	proposed MRL 0.5 mg/kg, IESTI case 2, unit weight 50 g, VF 7 or 3											
280020	Wild fungi- IT adult	0.50	69.80	291.35	50.00	2a	7	0.0042	529.5	3	0.0028	350.4
280020	Wild fungi- IT child	0.50	19.00	115.86	50.00	2a	7	0.0109	1368.0	3	0.0057	710.1
Scenario 2	**Fresh mushrooms**											
	proposed MRL 0.5 mg/kg, IESTI case 2 unit weight 25 g, VF 7 or 3											
280020	Wild fungi- IT adult	0.50	69.80	291.35	25.00	2a	7	0.0032	395.2	3	0.0024	305.6
280020	Wild fungi- IT child	0.50	19.00	115.86	25.00	2a	7	0.0070	874.5	3	0.0044	545.6
Scenario 3	**Fresh mushrooms**											
	proposed MRL 0.5 mg/kg, IESTI case 2 unit weight 100 g, VF 7 or 3											
280020	Wild fungi- IT adult	0.50	69.80	291.35	100.00	2a	7	0.0064	798.1	3	0.0035	440.0
280020	Wild fungi- IT child	0.50	19.00	115.86	100.00	2a	7	0.0188	2354.8	3	0.0083	1039.0
Scenario 4	**Fresh mushrooms**											
	threshold MRL 0.36 mg/kg for VF 7 IESTI case 2 unit weight 50 g,											
280020	Wild fungi- IT adult	0.036	69.80	291.35	50.00	2a	7	0.0003	38.1	3	0.0002	25.2
280020	Wild fungi- IT child	0.036	19.00	115.86	50.00	2a	7	0.0008	98.5	3	0.0004	51.1
Scenario 5	**Fresh mushrooms**											
	threshold MRL 0.07 mg/kg VF 3, IESTI case 2 unit weight 50 g,											
280020	Wild fungi- IT adult	0.070	69.80	291.35	50.00	2a	7	0.0006	74.1	3	0.0004	49.1
280020	Wild fungi- IT child	0.070	19.00	115.86	50.00	2a	7	0.0015	191.5	3	0.0008	99.4
Scenario 6	**Dried mushrooms**											
	proposed MRL 0.5 mg/kg, IESTI case 3											
280020	Wild fungi- IT adult	0.50	69.80	291.35		3	1	0.0021	260.9			
280020	Wild fungi- IT child	0.50	19.00	115.86		3	1	0.0030	381.1			
Scenario 7	**Dried mushrooms**											
	threshold MRL 0.13 mg/kg, IESTI case 3											
280020	Wild fungi- IT adult	0.13	69.80	291.35		3	1	0.0005	67.8			
280020	Wild fungi- IT child	0.13	19.00	115.86		3	1	0.0008	99.1			

APPENDIX B: TRADE DATA OF MUSHROOMS. SOURCE: EUROSTAT COMEXT DATABASE

Volume of the EU imports of different mushrooms commodities from China. Quantities in tonnes. Source Eurostat Comext database.

SITC	Commodity name	2006	2007	2008
05613	Dried mushrooms & truffles	3917	4656	5131
05458	Fresh or chilled mushrooms & truffles	1844	1405	1614
05674	Mushrooms & truffles prepared or preserved otherwise than by vinegar	56403	55463	46347

Volume of the EU imports of dried mushrooms from China. Quantities in tonnes. Source Eurostat Comext database.

REPORTER	2006	2007	2008
EU total	3917	4656	5131
GERMANY	1566	1653	1695
ITALY	759	1036	1485
FRANCE	867	1000	996
SPAIN	193	163	228
UNITED KINGDOM	124	199	193
NETHERLANDS	144	199	182
Other Member States	264	406	353

VOLUME OF IMPORTS AS REPORTED IN EUROSTAT ComExt DATABASE by SITC

Extracted on 2009/05/04 09:44:01

FLOW	IMPORT
INDICATORS	QUANTITY_IN_100KG
PARTNER	CHINA (PEOPLE'S REPUBLIC OF)
PRODUCT	05674-MUSHROOMS AND TRUFFLES PREPARED OR PRESERVED OTHERWISE THAN BY VINEGAR OR ACETIC ACID

REPORTER/PERIOD	2005	2006	2007	2008
EU27	612306	564033	554629	463468
GERMANY (incl DD from 1991)	305810	295195	308868	201185
NETHERLANDS	76658	63857	67500	91889
ROMANIA	123774	94811	57446	32561
SWEDEN	32587	32731	27611	31078
CZECH REPUBLIC (CS->1992)	22589	21400	29906	24832
SPAIN	4044	10955	12009	21428
GREECE	3382	2298	7033	14146
UNITED KINGDOM	15351	13767	13468	12335
FRANCE	2861	5240	9572	9661
SLOVENIA	2665	638	667	6297
FINLAND	4846	3976	2950	4250
AUSTRIA	3750	4342	3185	4131
SLOVAKIA	5849	2211	7343	3281
HUNGARY	4401	9625	4337	2245
ITALY	500	183	374	1790
DENMARK	551	584	810	696
ESTONIA	257	680	450	518
CYPRUS	198	1	9	303
PORTUGAL	65	61	30	273
POLAND	170	180		190
BELGIUM (and LUXBG -> 1998)	454	129	439	185
LITHUANIA	254	381		150
BULGARIA	1138	758	184	42
IRELAND	104	30	14	2
LUXEMBOURG	5			
LATVIA	43			
MALTA			424	

VOLUME OF IMPORTS AS REPORTED IN EUROSTAT
ComExt DATABASE by SITC

Extracted on 2009/05/04 09:44:01

FLOW IMPORT
INDICATORS QUANTITY_IN_100KG
PARTNER CHINA (PEOPLE'S REPUBLIC OF)
PRODUCT 05613 - MUSHROOMS AND TRUFFLES (dried, whole, cut, sliced, broken or in powder)

REPORTER/PERIOD	2005	2006	2007	2008
EU27	40725	39173	46557	51305
GERMANY (incl DD from 1991)	13765	15664	16528	16947
ITALY	9849	7592	10357	14845
FRANCE	8368	8671	9998	9963
SPAIN	1492	1927	1634	2279
UNITED KINGDOM	1445	1241	1989	1931
NETHERLANDS	2329	1439	1992	1815
POLAND	1127	647	774	769
CZECH REPUBLIC (CS->1992)	200	104	194	475
AUSTRIA	199	286	318	451
BELGIUM (and LUXBG -> 1998)	694	585	1437	424
PORTUGAL	296	205	579	424
SLOVENIA	36	26	131	230
LUXEMBOURG				133
DENMARK	39	63	33	117
LITHUANIA	8	61	102	102
BULGARIA	449	357	29	87
SWEDEN	45	65	122	82
ROMANIA	32	107	111	65
SLOVAKIA	117	18	37	59
FINLAND	13	4	6	35
IRELAND	3	15	97	21
HUNGARY	105	63	22	18
GREECE	101	30	31	16
MALTA			4	15
ESTONIA	3	1		2
CYPRUS		2	26	
LATVIA	10		6	

VOLUME OF IMPORTS AS REPORTED IN EUROSTAT ComExt DATABASE by SITC

Extracted on	2009/05/04 09:44:01
FLOW	IMPORT
INDICATORS	QUANTITY_IN_100KG
PARTNER	CHINA (PEOPLE'S REPUBLIC OF)
PRODUCT	05458-MUSHROOMS AND TRUFFLES, FRESH OR CHILLED

REPORTER/PERIOD	2005	2006	2007	2008
EU27	15648	18444	14047	16136
NETHERLANDS	6907	10576	8442	7749
UNITED KINGDOM	4456	3062	2624	2851
ITALY	416	38	842	1676
GERMANY (incl DD from 1991)	1327	1570	1193	1415
FRANCE	2018	1082	454	880
AUSTRIA	1	442	262	475
BELGIUM (and LUXBG -> 1998)	245	24	4	472
SPAIN	60	172	220	428
FINLAND				170
BULGARIA	134	4		18
DENMARK	1	183	2	1
HUNGARY	1	1	4	1
SLOVENIA	0	0		0
CYPRUS				
CZECH REPUBLIC (CS->1992)				
ESTONIA				
GREECE	81	1188		
IRELAND	1	42		
LITHUANIA				
LUXEMBOURG				
LATVIA				
MALTA				
POLAND				
PORTUGAL	0			
ROMANIA	0	0		
SWEDEN		60		
SLOVAKIA				

EXTRA EU27 Trade By SITC

2009/04/23 10:39:49
Extracted on

FLOW 1 - IMPORT
INDICATORS QUANTITY_IN_100KG
PERIOD Jan.-Dec. 2006
PRODUCT 05613 - MUSHROOMS AND TRUFFLES (dried, whole, cut, sliced, broken or in powder)

PARTNER/REPORTER	EU27		DE	IT	FR	ES	UK	NL	PO	BE	AT	SI	BU	CZ	PT	RO	HU	SE	DK	LT	SV	EL	IE	CY	FI	MT	EE	LU	LT
EU27_EXTRA	52224		18560	12819	11652	1953	1732	1701	748	612	508	483	358	234	209	176	118	99	81	70	42	30	24	5	5	4	1		
CHINA (PEOPLE'S REPUBLIC OF)	39173		15664	7592	8671	1927	1241	1439	647	585	286	26	357	104	205	107	63	65	63	61	18	30	15	2	4		1		
SERBIA (EU data from 01/06/05 ex CS)	4254		30	2606	1348				1		119	96					50									4			
FORMER YUGOSLAV REPUBLIC OF MACEDONIA	1530			1323	62							145																	
CHILE	1492		1143	120	214	2					13							0											
VIET-NAM	1358		637		169		180	106	96	17	2		1	116		1	5	3	1		24								
BOSNIA AND HERZEGOVINA	833		11	650	4						17	150							1										
INDIA	679		353		322		2											1							1				
PAKISTAN	516		37		459		6	7	0	2	5																		
RUSSIAN FEDERATION (RUSSIA)	420		295	83	24		1											3	10	4									
TURKEY	325		40	137	127		5			5	11																		
THAILAND	271		74	1	76	8	12	59			6	1		14		0		16	0				1	3	0		0		
SWITZERLAND (incl. LI->1994)	231		60		26		143											2											
MONTENEGRO (EU data from 01/06/05 ex CS)	193			135	7						41	10																	
KOSOVO (EU data from 01/06/05 ex CS)	185			140	45																								
HONG KONG	155		45		5		62	20										9	6				8						
UNITED STATES	91		55	2	14	2		18									0	0											
CROATIA	71				10						6	55																	
COUNTRIES AND TERRITORIES NOT SPECIFIED	68												0			68													
TAIWAN	61		54		4			1			2																		
JAPAN	52		14	8		3		21		3				0	3			0	0				0		0				
ECUADOR	48		29	15		4																							
MALAYSIA	41						41		0																				
ARGENTINA	32				25	7																							
MACAO	19						19																						
SINGAPORE	16						16																						
CANADA	14		6		8																								
INDONESIA (ID+TP from 77,excl. TP -> 2001)	14							14																					
BELARUS (BELORUSSIA)	13				5				3											5									
CAMEROON	12				12																								
NEPAL	12				12																								
KYRGYZ, REPUBLIC (ex KYRGYZSTAN->2005)	10				3			7																					
UKRAINE	9		4	5																									
IRAN, ISLAMIC REPUBLIC OF	6							6																					
SOUTH AFRICA (incl. NA ->1989)	6		6																										
COLOMBIA	4						4																						
COSTA RICA	3		3																										
KOREA, REPUBLIC OF (SOUTH KOREA)	3							3													0								
ALBANIA	2			2																									
BRAZIL	1		0					0							1														
MALAWI	1								1																				

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FLOW 1 - IMPORT
INDICATORS QUANTITY_IN_100KG
PERIOD Jan.-Dec. 2007
PRODUCT 05613 - MUSHROOMS AND TRUFFLES (dried, whole, cut, sliced, broken or in powder)

PARTNER/REPORTER	EU27		DE	IT	FR	UK	NL	ES	BE	PO	PT	AT	CZ	SI	RO	SV	BU	SE	LT	IE	DK	CY	EL	HU	FI	LT	MT	EE	LU
EU27_EXTRA	60405		20120	15516	12966	2372	2298	1705	1450	1012	580	555	415	358	206	157	148	142	128	98	62	37	33	24	8	6	5	4	
CHINA (PEOPLE'S REPUBLIC OF)	46557		16528	10357	9998	1989	1992	1634	1437	774	579	318	194	131	111	37	29	122	102	97	33	26	31	22	6	6	4		
CHILE	3620		2089	631	786		3	1		62		48																	
SERBIA (EU data from 01/06/05 ex CS)	2849		17	2179	491				2			115		42														3	
VIET-NAM (excl. NORTH -> 1976)	1572		682		288		118			175			181			120	3	3						2					
FORMER YUGOSLAV REPUBLIC OF MACEDONIA	1567			1392	96									18	60		1												
BOSNIA AND HERZEGOVINA	835		156	516	7							48		108															
RUSSIAN FEDERATION (RUSSIA)	578		224	218	62	1	1					12	29					3	18		10								
INDIA	464		235		197	28						1						3											
PAKISTAN	357		33		317	4	0		2	0		1						0											
TURKEY	263		10	38	174	15			4			5					17												
THAILAND	260		16		109	2	57	46	0			0	11					2			0	11	2		2		1	1	
HONG KONG	171		2		9	102	21										8	9		1	19								
ECUADOR	153		3	23	119			8																					
MONTENEGRO	143			143																									
SWITZERLAND (incl. LI->1994)	142		36		32	74																							
UNITED STATES	110		11		65	2	16	11		1		4					0								0				
KOSOVO (EU data from 01/06/05 ex CS)	96			6													90												
CANADA	83		4		73		2	3				1																	
NIGERIA	78					78																							
KYRGYZ, REPUBLIC (ex KYRGYZSTAN->2005)	75		11		64		0																						
CROATIA	71		12											59															
JAPAN	54		15	6	0	3	24		5		1			0		0		0							0				
MALAYSIA	44					44																							
ALBANIA	35														35														
COUNTRIES AND TERRITORIES NOT SPECIFIED	32						32																						
IRAN, ISLAMIC REPUBLIC OF	31						31								0														
TAIWAN	31		30				1											0											
AFGHANISTAN	25				25																								
NEPAL	20				20																								
ARGENTINA	18				16			2																					
MACAO	13					13																							
MOROCCO	11				11																								
UKRAINE	9			7								2																	
BELARUS (BELORUSSIA)	8																		8										
PHILIPPINES	6					6						0																	
SINGAPORE	6					6																							
KOREA, REPUBLIC OF (SOUTH KOREA)	5		5																										
QATAR	4				4																								
ZAMBIA	3					3																							
COTE D'IVOIRE	2				2																								
COLOMBIA	2					2																							
CUBA	1		1																										
MEXICO	1				1																								

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FLOW 1 - IMPORT
INDICATORS QUANTITY_IN_100KG
PERIOD Jan.-Dec. 2008
PRODUCT 05613 - MUSHROOMS AND TRUFFLES (dried, whole, cut, sliced, broken or in powder)

PARTNER/REPORTER	EU27		DE	IT	FR	ES	UK	NL	PO	AT	CZ	BE	SI	PT	DK	LT	LU	SE	BU	SK	RO	FI	CY	EL	HU	IE	MT	EE	LV
EU27_EXTRA	62152		20893	17907	12277	2469	2048	2006	899	686	658	453	438	427	162	157	133	118	110	100	66	35	31	20	20	21	15	3	
CHINA (PEOPLE'S REPUBLIC OF)	51305		16947	14845	9963	2279	1931	1815	769	451	475	424	230	424	117	102	133	82	87	59	65	35		16	18	21	15	2	
CHILE	3366		2344	163	849	7				3								0											
SERBIA (EU data from 01/06/05 ex CS)	1917		7	1306	352					163			88															1	
VIET-NAM (excl. NORTH -> 1976)	1637		785		360	94	5	20	130	10	160	10			1			16	3	41	1				1				
FORMER YUGOSLAV REPUBLIC OF MACEDONIA	758			699	48	1							9						1										
BOSNIA AND HERZEGOVINA	503		70	276	25					21			111																
RUSSIAN FEDERATION (RUSSIA)	355		202	88	59		2	2							2														
INDIA	326		226		93	1	1			4								1											
UNITED STATES	254		18	72	76	29	5	27		17	9							0				0			1			0	
TURKEY	250		20	135	57	2	10								16			1	9										
THAILAND	238		37		56	22		63			4	4			8			9				0	31	4					
MONTENEGRO	227			204	21	2																							
PAKISTAN	192		9		159		23	1										0											
SWITZERLAND (incl. LI->1994)	120		105	0	11		3			1																			
HONG KONG	97		4		7		30	28							17			9	2										
KOSOVO (EU data from 01/06/05 ex CS)	93			88															5										
CANADA	82		2		77	1		2		0																			
JAPAN	75		11	12	1	2	19	17		0	0	9	0	3	1			0			0	0							
ECUADOR	74		64		10																								
BELARUS (BELORUSSIA)	49															49													
TAIWAN	48		30		2			1		15															0				
KYRGYZ, REPUBLIC (ex KYRGYZSTAN->2005)	41		1		20			20																					
UKRAINE	35		10	10	3						6					6													
URUGUAY	23					23																							
ARGENTINA	21				14	6		1																					
COSTA RICA	9			9																									
NEPAL	8				8																								
SINGAPORE	8						8																						
IRAN, ISLAMIC REPUBLIC OF	7				3			4																					
KOREA, REPUBLIC OF (SOUTH KOREA)	7				1		6																						
CONGO, DEMOCRATIC REPUBLIC OF (ZAIRE ->1997)	5											5																	
CROATIA	5		1				1												3										
NIGERIA	5							4		1																			
COLOMBIA	4						4																						
ISRAEL (GAZA and JERICHO->1994)	4										4																		
ANTIGUA AND BARBUDA	2				2																								
AUSTRALIA	1											1																	
GUINEA	1							1																					

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FLOW 1 - IMPORT
INDICATORS QUANTITY_IN_100KG
PERIOD Jan.-Dec. 2006
PRODUCT 05613 - MUSHROOMS AND TRUFFLES (dried, whole, cut, sliced, broken or in powder)

PARTNER/REPORTER	EU27		UK	EL	DE	ES	FR	AT	PL	IT	BE	NL	IE	DK	HU	SE	EE	RO	LV	CZ	CY	SK	PT	BG	FI	SI	LT	MT	LU
EU27_INTRA	64125		13504	12873	6390	5113	4799	4269	4073	3686	1857	1473	1058	676	629	600	589	510	484	415	409	296	173	75	59	44	42	20	9
NETHERLANDS	17294		2462	10165	2332	4	502	73	2	26	1580		0	14	13	7	0	4	5	38	41		0		12	8			6
GERMANY	15866		1988	0		3486	868	3619	3772	196	48	663		452	136	176	7	32	9	211		117	41	5	19	9	12		0
FRANCE	6638		1088	2596	963	850		70	0	44	193	420	226	41	2	78		0		8	10	7	10		22	4	0	4	2
ITALY	4873		1725	76	252	305	827	154	98		25	374	277	158		6	0	375		45	20	67	1	31		21	29	7	0
BELGIUM	4820		2395	0	14	194	2168	0		41		7														0			1
DENMARK	3624		3361		20	0			166							77													
POLAND	3065		174		2540		89	55		93		5								62		46					1		
BULGARIA	2163				112	152	164	64		1628					2	19		22						0					
ROMANIA	1782						5	227		1051					465									34					
LITHUANIA	1067				11		7									7	574		468										
UNITED KINGDOM	981			0	17	101	23	1			6		555		7	230	0		0	41							0	0	
HUNGARY	496				24	14	26			355								77											
GREECE	338																				338								
IRELAND	311		311					0				0																	
AUSTRIA	299		0		66	6	1		28	186					0					10		0				2			
SPAIN	238						89			11	0	4		8		0							121	5					
SLOVENIA	87				23					55																		9	
CZECH REPUBLIC (CS->1992)	82				16				7						0							59							
CYPRUS	56			36			20															0							
SWEDEN	17						4				4			3											6				
SLOVAKIA	10							6							4					0									
FINLAND	8												0				8												
LUXEMBOURG	7						6				1																		
ESTONIA	2																		2										
PORTUGAL	1					1																							

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INDICATORS QUANTITY_IN_100KG
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PRODUCT 05613 - MUSHROOMS AND TRUFFLES (dried, whole, cut, sliced, broken or in powder)

PARTNER/REPORTER	EU27		EL	DE	UK	FR	ES	AT	PL	IT	LV	NL	BE	SE	IE	RO	DK	CY	PT	EE	CZ	BG	SK	HU	SI	LU	FI	MT	LT
EU27_INTRA	71518		14384	11260	9926	5648	4818	4728	4339	3733	2034	1596	1365	1227	1004	846	780	723	680	641	613	568	191	149	111	92	35	17	10
NETHERLANDS	17354		8066	2817	3558	409	795	42	222	43	10		987	9		0	50			10	252	21	1	5	7	31	19	0	0
GERMANY	15585		48		1802	1166	1548	4588	3908	545	22	833	41	192	44	33	301		1	2	229	25	130	99	15	1	10	0	2
FRANCE	7718		3525	654	1237		889	33	0	91	2	403	319	35	255	85	43	13	68		11			3	0	49	0	3	
ITALY	6882		1854	929	892	636	464	58	200		0	332	12	23	194	313	380	35	2	0	99	346	26	12	57	4		14	
POLAND	5588		2	4544	48	3	400	5		150	2	6		6		383					11		20						8
BELGIUM	5583		1	62	2266	2942	207	0		75		22									1					7			
LITHUANIA	3251			567	2	34				12	1998			20						618									
ROMANIA	2380			1012		4	22			1311												4		27	0				
BULGARIA	1932			370		211	112			1205				7		27							0						
UNITED KINGDOM	1482			7		13	60	1	0	0		0	5	884	511									1			0	0	
SPAIN	984			21	50	116			5	177		0					6		609										
CYPRUS	911		888	23																									
GREECE	704				6													675				23							
HUNGARY	462			70		44	300	1	0	45						2							0						
CZECH REPUBLIC	174			12					0	0		0										149	13						
AUSTRIA	165			113		0			0	9						3	0				5		1	2	32	0			
SLOVENIA	122					52		0		70																			
DENMARK	115				65	5	0		0					45															
SWEDEN	72			49		9			4	0										4							6		
PORTUGAL	31			10		0	21																						
FINLAND	13													6						7									
LUXEMBOURG	5					4							1																
SLOVAKIA	5																				5			0					

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FLOW 1 - IMPORT
INDICATORS QUANTITY_IN_100KG
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PRODUCT 05613 - MUSHROOMS AND TRUFFLES (dried, whole, cut, sliced, broken or in powder)

PARTNER/REPORTER	EU27		EL	UK	DE	PL	AT	SE	ES	IT	FR	LV	CZ	BE	NL	CY	DK	IE	EE	PT	BG	HU	RO	SK	SI	LU	LT	FI	MT
EU27_INTRA	55774		7953	6351	6331	4145	4070	3830	3562	3480	3478	2127	2052	1405	1125	1077	1023	822	737	626	449	377	300	162	113	72	59	39	9
NETHERLANDS	13707		5197	2488	1096	126	113	6	645	12	999	22	1731	1077			119				15	7	0	0	0	36	0	16	2
GERMANY	12690		20	674		3654	3840	247	1404	723	471	17	198	65	588	24	309	33	11	0	8	246	46	94	0	0	7	11	
FRANCE	5122		1647	945	964	21	20	23	520	205		0	8	220	280	4	39	190		2			0		1	32		0	1
ITALY	4925		10	1042	842	315	97	32	332		307	0	107	30	250	11	510	231	0	0	353	25	254	47	102	1	18	4	5
UNITED KINGDOM	4107				22			3428		63	143			3				368		0		79							1
BELGIUM	3362		529	1120					273	193	1238				5										0	3	1		
POLAND	3176		4	9	3059			7		24	15		8	3	2									12			33		
LITHUANIA	2895				3			40	13	10	17	2088					0		724										
ROMANIA	1417				32				11	1332	18											15			9				
GREECE	1101				39				0	1	1					1038					22								
BULGARIA	880				6			5	46	708	115												0						
SPAIN	817		50		17			6		24	50						46			624			0						
AUSTRIA	759		496		210	0				4	41		0		0							5	0		1	0		2	
HUNGARY	229				11		0		177	21	20																		
SLOVENIA	155									155				0															
DENMARK	134			21		20		36	57																				
CZECH REPUBLIC	98				17	4			3		14										51			9					
PORTUGAL	91				10				81	0	0																		
IRELAND	52			52							0																		
SWEDEN	38				1	5					26		0															6	
LUXEMBOURG	10										3			7															
CYPRUS	6				1					5																			
FINLAND	2																		2										
ESTONIA	1				1																								

GLOSSARY / ABBREVIATIONS

a.s.	active substance
ADI	acceptable daily intake
AOEL	Acceptable operator exposure level
ARfD	acute reference dose
b.w.	body weight
d	day
DAR	Draft Assessment Report (prepared under Directive 91/414/EEC)
EC	European Community
EFSA	European Food Safety Authority
EU	European Union
HR	highest residue
IUPAC	International Union of Pure and Applied Chemistry
i.v.	intraveous
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
MRL	maximum residue limit
MS	Member States
NOAEL	no observed adverse effect level
ppm	parts per million (10^{-6})
PRIMo	Pesticide Residues Intake Model
STMR	supervised trials median residue
TMDI	theoretical maximum daily intake
UF	uncertainty factor
WHO	World Health Organisation