SCIENTIFIC OPINION

Scientific Opinion on the risks for public health related to the presence of opium alkaloids in poppy seeds[1]

EFSA Panel on Contaminants in the Food Chain (CONTAM)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Poppy seeds are obtained from the opium poppy *(Papaver somniferum* L.). They are used in bakery products, on top of dishes, in fillings of cakes and in desserts and to produce edible oil. The opium poppy plant contains narcotic alkaloids such as morphine and codeine. Poppy seeds do not contain the opium alkaloids, but can become contaminated with alkaloids as a result of insect damage, or through poor harvesting practices. The European Commission asked the European Food Safety Authority (EFSA) to provide a scientific opinion on the risks for public health related to the presence of opium alkaloids in poppy seeds intended for human consumption. Following a call for data, EFSA received the results from analyses of opium alkaloids, primarily morphine, codeine, thebaine, papaverine and noscapine, in samples of poppy seeds, bakery products and baking ingredients. Based on the relative prevalence of the alkaloids present in poppy seed and food samples analysed, and on their pharmacological potency, the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) concluded that the risk assessment could be based on dietary exposure to morphine alone. The CONTAM Panel applied an uncertainty factor of 3 to establish from the lowest known single oral therapeutic dose of 30 µg morphine/kg body weight (b.w.) an acute reference dose (ARfD) of 10 µg morphine/kg b.w. Estimates of dietary exposure to morphine from foods containing poppy seed demonstrate that the ARfD can be exceeded during a single serving by some consumers, particularly children, across the EU. This risk assessment relates to poppy seed samples with an alkaloid profile comparable to that of the submitted data and should not be extrapolated to poppy seed samples with a qualitatively different alkaloid profile.

KEY WORDS

poppy seeds, morphine, codeine, dietary exposure, toxicity, pharmacology, acute reference dose (ARfD)

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SUMMARY

Poppy seeds are obtained from the opium poppy (*Papaver somniferum* L.). The latex (milky sap) of the opium poppy contains alkaloids, referred to here as opium alkaloids, including the narcotic agents morphine and codeine that have been used by man for the treatment of severe pain for generations. Opium alkaloids are also subject to misuse. The alkaloids are synthesised, stored and metabolised in the latex of the poppy plant. The latex permeates all parts of the plant, except the seeds and is to be found in particular in the pericarp of the capsule. The latex of the immature capsules, which is released by incisions and has dried, is called opium. Opium contains approximately 20 – 25 % alkaloids, of which around 50 different alkaloids have been isolated in pure form. The total alkaloid content of the poppy plant depends on various factors such as variety, location, soil conditions, fertilisation, climate, weather and harvesting time. Opium alkaloids can be divided into 2 distinct chemical classes, phenanthrenes and benzylisoquinolines. The principal phenanthrenes are morphine, codeine and thebaine, whereas the principal benzylisoquinolines are papaverine and noscapine. Morphine is generally the predominant alkaloid. *Papaver somniferum* varieties especially bred with high alkaloid content intended for pharmaceutical purposes are also used for production of poppy seeds for food use. Low morphine varieties of *Papaver somniferum* are available.

Poppy seeds are used as food in bakery products, on top of dishes, in fillings of cakes and in desserts and to produce edible oil. Whilst the seeds of the poppy plant do not contain the latex, they can become contaminated with alkaloids as a result of insect damage to the capsule, or through poor harvesting practices. Consumption of foods containing poppy seeds that are contaminated with opium alkaloids can lead to adverse health effects and to detectable contents of free morphine in blood as well as measurable concentrations in urine, sufficient to interfere with drug abuse testing. There are currently no European Union regulations relating to alkaloids in poppy seeds used in food, although Hungary has national maximum levels of 30 mg/kg for morphine, 20 mg/kg for noscapine, 40 mg/kg for morphine and noscapine, 20 mg/kg for thebaine and 20 mg/kg for codeine.

The European Commission asked the European Food Safety Authority (EFSA) to provide a scientific opinion on the risks for public health related to the presence of opium alkaloids in poppy seeds intended for human consumption, taking into account the situation for specific (vulnerable) groups of the population (e.g. high consumers, children, people following specific diets, etc.).

Today's state of the art methodology for the determination of alkaloids in poppy seed samples is liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Detection limits are usually considerably below 1 mg/kg for morphine and related opium alkaloids.

Following a call for data, EFSA received the results from the analysis of 1033 samples including altogether 2678 analytical results for opium alkaloids in poppy seeds (n = 785), and poppy seed-containing bakery products (n = 186) and baking ingredients (n = 62). Four European countries (Germany, Hungary, Austria and The Netherlands) provided data on morphine, codeine, thebaine, papaverine and noscapine. Australia provided data on morphine, codeine, thebaine and, in addition, on oripavine. Oripavine, a phenanthrene, is a biosynthesis precursor of morphine. In the submitted data, and in line with the literature, morphine was the major alkaloid in poppy seed samples. Moreover, morphine and codeine had a high level of co-occurrence, as did codeine and thebaine, and morphine and thebaine. There was a low level of co-occurrence of morphine, codeine and thebaine with noscapine. Based on the relative prevalence of the alkaloids present in poppy seed and food samples analysed and on their pharmacological potency, the Panel on Contaminants in the Food Chain (CONTAM Panel) concluded that the exposure assessment should focus primarily on morphine alone.

Poppy seed consumption varies broadly within the European Union. In some cultures, such as in Central-Eastern European countries, it is traditional to use poppy seeds widely in foods, and in specific instances sometimes in high amounts in bread, fine bakery ware, desserts and other dishes. For other consumers poppy seeds are commonly used as a condiment or decoration. Due to the limited

available data on consumption of foods containing poppy seeds, the CONTAM Panel adopted a number of different approaches to estimate dietary exposure to morphine. Since opium alkaloids act acutely, only acute dietary exposure was assessed. In each case lower and upper bound concentrations and mean and 95th percentile occurrence data were used. Firstly, mean exposure to morphine was estimated for three European countries where foods with high poppy seed content are popular and for which poppy seed consumption data were available in the Comprehensive European Food Consumption Database, together with the occurrence data for morphine in poppy seed samples. The estimated mean dietary exposures for the three countries ranged from 3.11 to 90.9 µg/kg body weight (b.w.) per day. The number of consumers in the Database was not sufficient to estimate high level exposure. Secondly, hypothetical single portion scenarios were developed based on recipes for foods with high content of poppy seeds, and the occurrence data for morphine in poppy seed samples. The estimated morphine exposure ranged from 37.8 to 200 µg/kg b.w. per portion for adults and was the highest for children within the age range of 3 to 10 years, at 47.8 to 252 µg/kg b.w. per portion. Thirdly, exposure was estimated based on occurrence data of morphine in poppy seed samples and consumption of bread or fine bakery ware with estimated high or low level poppy seed contents, assuming that certain groups of white bread or fine bakery ware consumed on one day contain poppy seeds. Estimated exposure from bread was lower than from fine bakery ware. For consumers of low poppy seed content foods, the estimated dietary exposure to morphine via fine bakery ware for adults ranged from 0.05 to 16.9 µg morphine/kg b.w. per day. The estimated dietary exposure was the highest for toddlers and ranged from 0.39 to 36.3 µg morphine/kg b.w. per day. The estimated exposures of other children and adolescents were between those of adults and toddlers. For consumers of foods with high poppy seed content, the estimated dietary exposure to morphine via fine bakery ware for adults ranged from 2.48 to 375 µg morphine/kg b.w. per day. The estimated dietary exposure was the highest for children within the age range of 3 to 10 years at 10.2 to 753 µg morphine/kg b.w. per day. The estimated exposures of toddlers and adolescents were between those of adults and other children. Since these exposure estimates are based on the reported data on concentrations of alkaloids in poppy seed samples, they do not necessarily reflect the exposure to morphine in the food as consumed. The alkaloid content of poppy seed samples and poppy seed containing foods can be reduced by several methods of pre-treatment and processing. Food processing may decrease the alkaloid content by up to about 90 %. The most effective methods include washing, soaking and heat treatments, as well as grinding and combinations of these treatments. If the concentrations are reduced by processing, the exposure would be up to 90 % lower.

Finally, exposure was estimated based on the occurrence data for morphine in bakery products, which were all for foods sampled in Germany, together with consumption data for countries where foods with high poppy seed content are popular. The estimated high exposure ranged from 0.50 to 14.6 µg/kg b.w. per day for adults. The exposure was the highest for children within the age range of 3 to 10 years at 1.88 to 30.7 µg/kg b.w. per day.

Morphine and codeine are readily absorbed from the gastrointestinal (GI) tract. The oral bioavailability of morphine is reduced by both Phase I and II pre-systemic metabolism in the GI tract and liver. Codeine is less susceptible to this pre-systemic effect. Extrapolation of codeine toxicity data from rats to humans is complicated by large differences in oral bioavailability and metabolism affecting the conversion to morphine. Oral bioavailability of papaverine, noscapine, thebaine and oripavine, appears to be low due to pre-systemic metabolism in the GI tract and liver primarily involving demethylation reactions but also glucuronidation.

The data on the pharmacology of morphine, codeine and the other opium alkaloids in poppy seeds indicate that morphine is the most pharmacologically active opiate compound, with codeine as the second. Morphine acts mainly via the opiate µ-receptor. And because of its widespread distribution in the body it exerts a number of different effects, both in the central nervous system and in the peripheral nervous system. Chronic and developmental toxicity of morphine have not been systematically evaluated. Morphine is genotoxic only *in vivo* but most likely by a non-DNA reactive mode of action. Although carcinogenicity data for morphine itself are lacking, based on the lack of

carcinogenicity of codeine which is extensively metabolised to morphine in rats, the CONTAM Panel concluded that morphine is unlikely to be carcinogenic. Codeine is not genotoxic *in vitro* or *in vivo*. The most prominent side effects of morphine and codeine are sedation and respiratory depression. Only very limited data are available for oripavine and thebaine. They show only partial agonistic activity at the μ-receptor, and thebaine has been shown to act as an antagonist at higher dosages. The benzylisoquinolines papaverine and noscapine do not show opiate-like behaviour, papaverine acting as a smooth muscle relaxant, and noscapine as an antitussive agent.

As morphine and codeine are in long-established use as human therapeutic agents and relevant human data are available, the CONTAM Panel decided to use these data as the primary basis for its risk assessment. Activation of the μ-opiate receptor by morphine leads to analgesia, euphoria, dependence, miosis, respiratory depression, cough calming and obstipation. Patients with pain tolerate larger doses of morphine than pain-free patients, without severe side effects. Therapeutic doses of morphine may also impair the ability to drive or to operate machinery due to changes in attentiveness and reactive skills. The pharmacology of codeine is strongly related to that of morphine, as it acts mainly as a precursor of morphine itself. Up to 20 % of codeine can be converted to morphine. The most frequent side effect of codeine is constipation. Other side effects include slight headaches, minor sleepiness, nausea sometimes linked with vomiting (particularly at the beginning of treatment) and a dry mouth. At higher doses impaired vision, respiratory depression and euphoria may also occur. The side effects of papaverine that occur after oral administration are dizziness, headache, drowsiness, tiredness, gastro-intestinal disturbance, flush, skin rash, tachycardia, sweating and hypotonia.

Since morphine-like central nervous effects have been observed in humans following consumption of a single portion of a meal containing opium alkaloid-contaminated poppy seeds, the CONTAM Panel considered it appropriate to base the risk assessment for poppy seeds on exposure to morphine. Because it is unlikely that morphine has genotoxic or carcinogenic potential at exposures relevant to dietary exposure from poppy seeds, establishing a health based guidance value is appropriate taking into account the short term nature of the effects of morphine, therefore the CONTAM Panel concluded that establishment of an acute reference dose (ARfD) was required. Ensuring exposure is below the ARfD would also protect against possible effects of repeated exposure and therefore establishing a Tolerable Daily Intake (TDI) was not necessary. The available data on central nervous effects following consumption of poppy seed-containing foods did not provide sufficient information on the dose response relationships for the alkaloids. The CONTAM Panel therefore decided to derive the ARfD from the lowest known single oral therapeutic dose used for treatment of pain or dyspnoea, which is 1.9 mg morphine, corresponding to 31.7 μg/kg b.w. for an adult weighing 60 kg. This lowest known single oral therapeutic dose, rounded to a single significant figure of 30 μg/kg b.w., is regarded by the CONTAM Panel as the lowest-observed-effect level (LOEL). It applies to children as well as adults since it is lower than the lowest known single oral therapeutic dose for children of 83 μg morphine/kg b.w. Furthermore, the LOEL is conservative, because it is uncertain whether side effects are actually observed following a single administration at this dose. The CONTAM Panel concluded that an uncertainty factor of 3 was sufficient to allow for extrapolation from the LOEL to a no-observed- effect level (NOEL), considering that the LOEL was derived from patients and not from the general population. The CONTAM Panel applied the uncertainty factor of 3 to establish from the LOEL of 30 μg morphine/kg b.w. an ARfD of 10 μg morphine/kg b.w. This is the dose of morphine from poppy seed-containing foods for which a person would not be expected to experience effects following consumption of one meal or total consumption within one day.

If poppy seeds are consumed as condiments or decoration in bread and fine bakery ware, it is possible that some consumers, particularly toddlers, will exceed the ARfD for morphine on rare occasions. A considerable proportion of consumers of foods that contain large amounts of poppy seeds, such as are common in Central-Eastern European countries, are likely to exceed the ARfD for morphine on at least some eating occasions. The highest estimates of morphine exposure are about 75-fold greater than the ARfD. Due to the lack of data on morphine in food as consumed, the exposure estimates based on morphine content of poppy seed samples do not take into account the effects of food

processing, which could, in some circumstances, result in reduction of the morphine content by up to about 90 %. Taking this reduction into account the ARfD is most likely to be exceeded when single large portions are consumed or if foods containing raw, unground poppy seeds are consumed.

There are few reports of side effects arising from traditional consumption of poppy seeds in foods, excluding instances of misuse. However, in the absence of formal reporting systems it cannot be assumed that such reactions do not occur from time to time.

Contrary to expectation, estimations of exposure to morphine based on data available for fine bakery products sampled in Germany, where foods with high poppy seed content are common, were very similar to those for foods using poppy seeds as condiments or decoration. This observation could be due to the influence of processing (e.g. baking) on the alkaloid levels in food and/or the measures that have been taken in Germany to reduce alkaloid contamination of poppy seeds.

This risk assessment relates to poppy seed samples with an alkaloid profile comparable to that of the submitted data and should not be extrapolated to poppy seed samples with a qualitatively different alkaloid profile.

The CONTAM Panel recommended that analysis of poppy seeds and poppy seed containing products should focus not only on morphine, but also on those alkaloids reported to be present, and their ratios to morphine. More data are required on levels of opium alkaloids in food products, on the varieties of poppy seeds that are available on the European market for food use, as well as on their alkaloid content (including alkaloid profile), and on consumption of poppy seed products.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Opium poppy Papaver somniferum is a traditional medicinal plant. Opium alkaloids are extracted from the dried milky latex of the immature seed capsules. Opium is the source of many opiates, including morphine, thebaine, codeine, papaverine, and noscapine of which morphine and codeine are two of the most well-known opium alkaloids.

Besides the medical importance of opium poppy, the seeds of the plant are also of importance as food: The mature seeds are used predominantly in poppy cakes but also in smaller amounts on rolls and bagels. Because of their high oil content, edible oil is also produced from the seeds.

Although the seeds may also contain alkaloids, they only occur naturally in traces. Studies on alkaloid levels in edible poppy seeds have, however, revealed that the levels vary markedly and have increased overall in recent years. Types of poppy, harvesting time and geographical origin could all influence the alkaloid levels. The main reason for the increase seems, however, to be the contamination of the seeds with alkaloid-containing capsule fragments or the milky latex. Possible causes could be recently introduced new harvesting methods in which the capsules are squashed and the milky latex released could contaminate the seeds.

The consumption of poppy seed-containing foods made of poppy seeds with increased level of alkaloids, could lead to the ingestion of significant morphine amounts. The overall range of adverse reactions could then occur, including central nervous and peripheral effects like impaired consciousness, respiratory disorders and cardiovascular effects.

A risk assessment on the risks of the presence of the opium alkaloids in poppy seeds is appropriate in order to be able to consider the need for legal measures in the frame of Council Regulation (EEC) No 315/93 of 8 February 1993 laying down Community procedures for contaminants in food[4] to protect public health.

In accordance with Article 36 of Regulation (EC) No 178/2002, a report "Scientific information on mycotoxins and natural plant toxicants" has been produced following a grant agreement between the European Food Safety Authority (EFSA) and the author(s) of the report (CFP/EFSA/CONTAM/2008/01). The report presents information, inter alia, regarding morphine in poppy seeds and is available on the EFSA website (http://www.efsa.europa.eu/en/scdocs/doc/24e.pdf)

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Art. 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion on the risks for public health related to the presence of opium alkaloids in poppy seeds intended for human consumption. For the assessment of the risks, the situation for specific (vulnerable) groups of the population (e.g. high consumers, children, people following specific diets, etc.) should be considered by including an exposure assessment for these specific groups.

[4] OJ L 37, 13.2.1993, p.1.

ASSESSMENT

1. Introduction

Poppy seed is an oilseed obtained from the opium poppy *(Papaver somniferum* L.). *Papaver somniferum* contains pharmacologically and toxicologically relevant active opium alkaloids. In this opinion the term opium alkaloids is used to describe the alkaloids produced by the poppy plant and not for opium as a product. The pharmacological characteristics of opium alkaloids have been known since ancient times. Extracts from the opium poppy have been used by man for pain relief for at least 3500 years (Bernáth, 1998). Other parts of the plant, namely poppy seeds, have been used as food and to produce edible oil (Nencini, 1997).

The consumption of foods containing poppy seeds contaminated with opium alkaloids, can lead to a range of adverse reactions. In addition, consumption of highly contaminated poppy seeds can lead to detectable contents of free morphine in blood as well as measurable concentrations in urine, sufficient to interfere with testing for drug abuse (Andresen and Schmoldt, 2004; Moeller et al., 2004; Rochholz et al., 2004).

1.1. Poppy seeds and opium poppy – botanical origin, ingredients, uses and cultivation

Papaver somniferum (opium poppy) belongs to the family of *Papaveraceae*. There are a wide range of cultivars and ecotypes grown all over the world, with the greatest economic importance in Asia. In the European Union (EU) the main poppy seed producing country is the Czech Republic with a production of about 50 000 tonnes of the seeds per year (Figure 1). *Papaver somniferum* is a crop plant and diverse varieties and sorts are cultivated, of which the characteristics like number of seeds, colour of seeds or production of alkaloids vary widely. The seeds are black, white, blue or brown; they are between 0.9 and 1.5 mm long and are kidney shaped (Gessner, 1974; Hoppe, 1975; Dejnega et al., 2002; Rochholz et al., 2004; Blaschek et al., 2006).

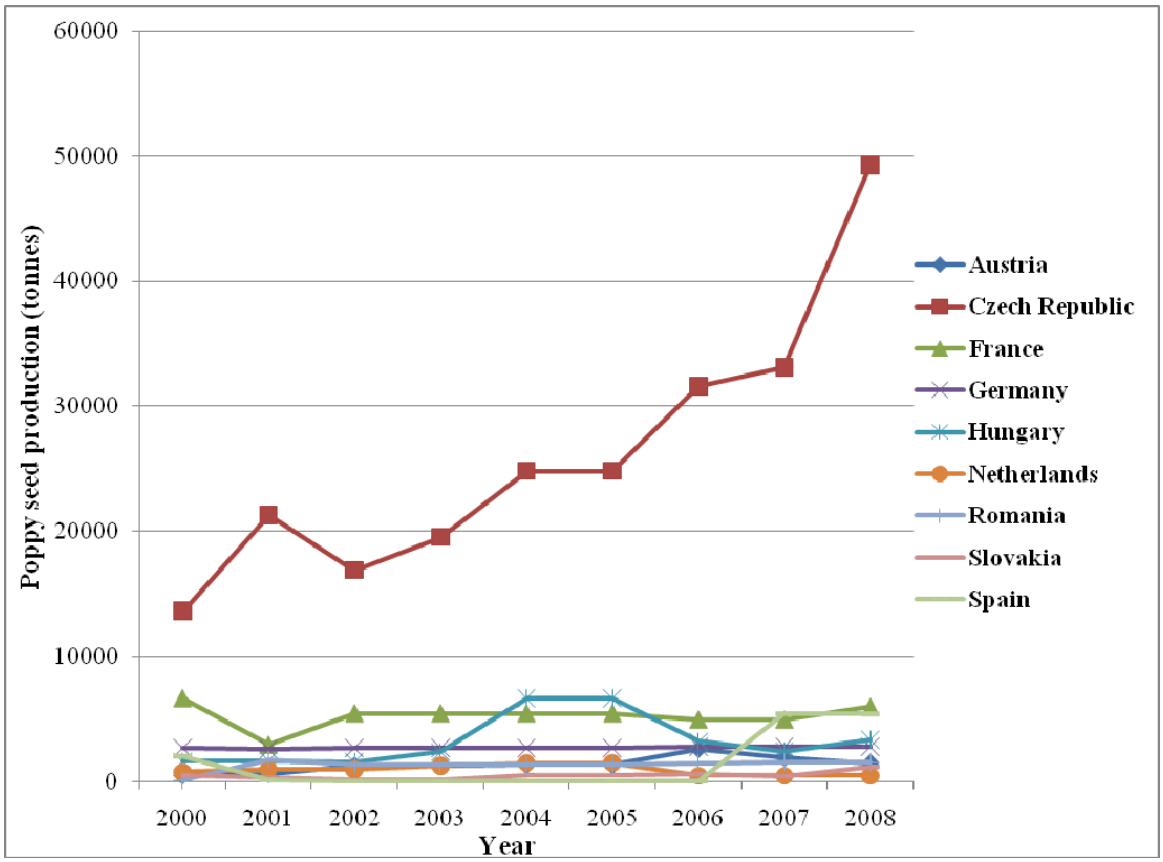


Figure 1: Poppy seed production in the EU countries in 2000-2008.[5]

In principle, a distinction is made between the more primitive "shaken poppy" whose capsules open with pores and "closed poppy" obtained through cultivation whose capsules remain closed (Dejnega et al., 2002; Blaschek et al., 2006). The Mediterranean wild strain is regarded as a sub-species of *Papaver somniferum* and is also termed *Papaver somniferum ssp.setigerum* (DC) Corb. (edible poppy) (Täufel et al., 1998). Poppy seeds are used in the food sector. They are used in bakery products, on top of dishes, in fillings of cakes and in desserts and to produce edible oil (Gessner, 1974; Hoppe, 1975; Dejnega et al., 2002; Rochholz et al., 2004; Blaschek et al., 2006). The oil content in poppy seeds varies between 32 % and 57 % (Azcan et al., 2004; Blaschek et al., 2006; Bernáth and Németh, 2009). Proteins (21 – 27 %), sugars (3 % pentosans) and lecithin (0.25 – 1 %) are further components of poppy seeds (Blaschek et al., 2006). The oil is obtained by solvent or mechanical extraction and the remaining poppy seed cake is crushed and used for cattle feed (Schiff, 2002; Azcan et al., 2004; Blaschek et al., 2006). Fatty acid compositions of poppy seed oil may be determined by gas chromatography – mass spectrometry (GC-MS). Major components were found to be linoleic acid (56 – 69 %), oleic acid (16 – 37 %), and palmitic acid (5 – 21 %) (Azcan et al., 2004; Blaschek et al., 2006). Besides food use as cooking oil and more recently as salad oil and dipping oil (Anonymous, 2011), poppy seed oil is also used for pharmaceutical, cosmetic and technological purposes (Bozan and Temelli, 2003; Azcan et al., 2004; Blaschek et al., 2006). Ethylesters of iodinated fatty acids of poppy seed oil are used for iodine supplementation in areas where iodized salt is not available (administration e.g. once a year orally or intramuscular (i.m.)) or as an iodinated radiographic contrast medium (e.g. Leverge et al., 2003; WHO, 2007; Martindale, 2010). The European Food Safety Authority (EFSA) Panel on food additives and

[5] Available from http://faostat.fao.org/site/567/DesktopDefault.aspx?PageID=567#ancor (Retrieved 15.03.2011).

nutrient sources added to food (ANS) has received a request from the European Commission[6] to provide a scientific opinion, based on its consideration of the safety of iodized ethyl esters of poppy seed oil as a source of iodine added for nutritional purposes to foodstuffs.

Papaver somniferum is cultivated for production of alkaloids and opium for pharmaceutical purposes (Dejnega et al., 2002; Blaschek et al., 2006). The alkaloids are synthesised, stored and metabolised in the latex (milky sap) which is located in a closely woven network of mutually anastomosal laticiferous tubes. The latex permeates all parts of the plant other than the seeds and is to be found in particular in the pericarp of the capsule (Gessner, 1974; Hänsel et al., 1999). The seeds do not contain milky sap (Frohne and Pfänder, 1987) and are described as being "free of morphine" in some older reference works (Hoppe, 1975; Gessner, 1974).

The latex of the immature capsules which is released by incisions and has dried is called opium. The opium contains approximately 20 – 25 % alkaloids of which around 50 alkaloids have been isolated in pure form up to now. The most active alkaloid of opium is morphine, which is also present in the largest amount (12 %, depending on origin, 7 – 20 %). Other important opium alkaloids are codeine (approximately 2 %; 0.3 – 6 %), thebaine (approximately 0.5 %; 0.2 – 1 %), papaverine (approximately 1 %; 0.5 – 3 %) and noscapine (5 %, 2 – 12 %; formerly described as narcotine) (Blaschek et al., 2006; Pelders and Ross, 1996; Bracher et al., 2010). Differing alkaloid levels for samples of the seeds have been reported in the more recent literature, ranging from not detectable up to 0.062 % for morphine, up to 0.0057 % for codeine, up to 0.0041 % for thebaine, up to 0.023 % for noscapine, and up to 0.0067 % for papaverine (Thevis et al., 2003; Moeller et al., 2004; Rochholz et al., 2004, 2005; Trafkowski et al., 2005). Poppy seeds themselves contain at maximum only very low levels of morphine and codeine, therefore poppy seed-related alkaloids mainly result from the contamination with capsule latex (Rochholz et al., 2004). The morphine content of seeds could be drastically reduced through washing (e.g. Lo and Chua, 1992; Andresen and Schmoldt, 2004). Contamination can result from insect damage or poor harvesting practices (Bernáth, 1998).

Alkaloids are found in other parts of *Papaver somniferum*, which besides opium are used to harvest the alkaloids. Poppy capsules without seeds contain the same active substances as opium but at a much lower concentration. Their morphine level fluctuates and is indicated as being between 0.12 and 0.89 % (Blaschek et al., 2006). Poppy straw (capsule with 5-10 cm stem parts) contains also mature deseeded capsules (morphine level: 0.015 up to 0.018 %) (Blaschek et al., 2006). Poppy roots were shown to have approximately 0.03 % morphine (Gessner, 1974).

The total alkaloid content of the plant, which depends on various factors (variety or sort, location, soil conditions, fertilisation, climate, weather, harvesting time), increases in the case of *Papaver somniferum* during growth up to the flowering period and then falls again (Kadar et al., 2001; Frohne and Pfänder, 2004; Blaschek et al., 2006). The alkaloid content also shows daily fluctuations with a minimum around noon and a maximum in the early hours of the morning. There may be a particularly marked drop in content when the alkaloids are washed out from the mature capsules by rain or dew (Blaschek et al., 2006).

There are ongoing extensive studies on selection of poppy genotypes offering a variety of different traits of both agronomic and commercial properties (e.g. Bernáth and Németh, 2009). Breeding methods aim to obtain poppy cultivars (*Papaver somniferum*) with either high alkaloid content (e.g. 1.5 – 2.5 % morphine or thebaine in the capsules) which are needed by the pharmaceutical industry, or with low morphine content (less than 0.1 % in the capsules). The latter cultivars are taken for poppy seed/oil production for culinary use (Bernáth and Németh, 2009).

Oripavine and thebaine are intermediates in the biosynthesis of morphine, which is possible via 2 pathways, as shown in Appendix A, Figure A1 (Millgate et al., 2004; Ziegler et al., 2009). Recently,

[6] Request for EFSA to provide a scientific opinion, based on its consideration of the safety and bioavailability of iodized ethyl esters of poppy seed oil as a source of iodine added for nutritional purposes to foodstuffs, question no EFSA-Q-2011-00034.

especially in Australia, poppy cultivars producing high yields of oripavine and thebaine rather than morphine and codeine have been developed because oripavine and thebaine are needed as precursors for the production of pharmaceuticals (Millgate et al., 2004). The predominance of one pathway over the other may depend on the relative activities of 3-O-methyl oxidase (involved in the production of oripavine) and 6-O-methyl oxidase (involved in the production of codeine) (Prajapati et al., 2002). Which alkaloids are formed and the amount depends on one hand on the genetic regulation of enzymatic processes in this pathway, but also on environmental factors (Bernáth et al., 1988; Németh-Zambori et al., 2011). Consequently, a very low correlation exists between the content of the individual alkaloids across different varieties (Dittbrenner et al., 2009; Shukla et al., 2010). All possible combinations of high content of an alkaloid with high or lower content of another alkaloid have been observed.

In some countries of Europe (e.g. Germany) only low-morphine varieties of *Papaver somniferum* are authorised for cultivation. They are exclusively destined for the production of seeds which are used in food or to produce oil and encompass for instance the varieties "Przemko", "Mieszko", "Edel-Weiß", "Edel-Rot", "Florian", "Josef", "Zeno" and "Zeno 2000" (Dejnega et al., 2002; Stolzenburg, 2006). However, there is poppy seed production for food use from *Papaver somniferum* varieties especially bred with high alkaloid content intended for pharmaceutical purposes (Fist et al., 2000).

1.2. Previous assessments

Due to the former occurrence of highly morphine contaminated poppy seeds (up to 330 mg morphine/kg) for food use on the German market, which were associated with cases of intoxication (e.g. BfR, 2005b) and possible drug abuse, the German Federal Institute for Risk Assessment (BfR) performed a risk assessment in 2005 (BfR, 2005a; Dusemund et al., 2010). For this purpose, human data on the pharmacological and toxicological effects of opium alkaloids known from medical uses were taken into consideration in addition to human case reports and experimental results. Being a potent analgesic used for short- and long-term treatment of severe pain, morphine has major effects on the central and peripheral nervous system by acting on the opioid receptors. Known adverse reactions of moderate morphine doses include sedation, drowsiness, nausea and vomiting. These symptoms have also partly been described by a consumer having eaten a dish sprinkled with approximately 75 g blue poppy seeds, containing 210 mg morphine/kg and 39 mg codeine/kg (corresponding to intake doses of 16 mg morphine or 260 µg morphine/kg body weight (b.w.) for an adult weighing 60 kg and 3 mg codeine or 50 µg codeine/kg b.w. for an adult weighing 60 kg). Additional side effects of medical use of morphine are cardiovascular effects and respiratory depression, which may have life-threatening consequences. BfR also took into account that long-term use can lead to tolerance development as well as psychological and physical dependence.

Based on the lowest known single oral therapeutic dose of 31.7 µg of morphine/kg b.w. (equivalent to 1.9 mg morphine/person for an adult weighing 60 kg) (Martindale, 2005, 2010), which is associated with pharmacological activity, BfR, by applying an uncertainty factor of 5, established a provisional daily upper intake level for morphine from poppy seeds. It is 6.3 µg morphine/kg b.w. per day (equivalent to 0.4 mg/person for an adult weighing 60 kg) and describes the intake which a person should not exceed during one meal or several meals spread over the day. The uncertainty factor of 5 took into account: (i) the existing uncertainty concerning the threshold doses of health-relevant effects, in particular psychomotor effects; (ii) possible interactions e.g. with other opium alkaloids in poppy seed samples, pharmaceuticals with central nervous activity and alcohol; (iii) the uncertainty arising from (i) and (ii) for workplace and traffic safety; (iv) the expected interindividual variations in sensitivity, and (v) the higher sensitivity in older people and in numerous clinical pictures. Based on an estimated high consumption of 100 g poppy seeds (two pieces of cake, each weighing 200 g, 25 % of poppy seeds) during one meal or several meals spread over the day, BfR proposed a guidance value of 4 mg morphine/kg at the maximum in poppy seeds. According to BfR, poppy seed batches exceeding this value should at least comply to a second "guidance value with consumption restrictions" amounting to a maximum of 20 mg morphine/kg. This could be tolerated on condition of a labelling notice that human daily intake should not be above 20 g of poppy seeds per day.

No other evaluations have been published.

1.3. Chemistry

Opium alkaloids can be divided into 2 distinct chemical classes, phenanthrenes and benzylisoquinolines. The principal phenanthrenes are morphine, codeine and thebaine whereas the principal benzylisoquinolines are papaverine and noscapine. In addition oripavine, a phenanthrene, is a biosynthesis precursor of morphine which is obtained in high yield for pharmaceutical use in certain *Papaver somniferum* cultivars.

Figure 2 shows the predominant alkaloids reported to be in poppy seed samples, namely morphine, codeine, papaverine, noscapine, thebaine together with oripavine along with their synonyms, molecular weights (MW) and their chemical abstract numbers (CAS). In contrast to morphine and codeine, the two morphinandienes thebaine and oripavine possess one additional double bond which affects the spatial structure and planarity of these compounds and might explain differences in affinity for the opiate receptors (see Section 7).

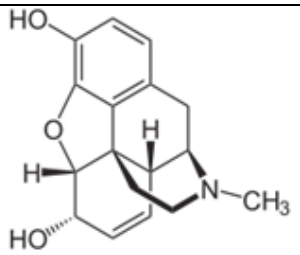
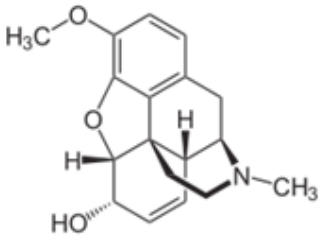
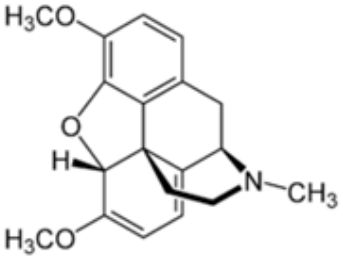
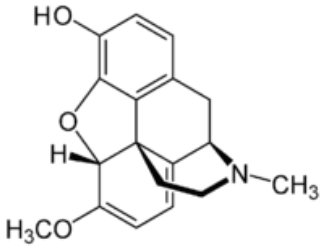
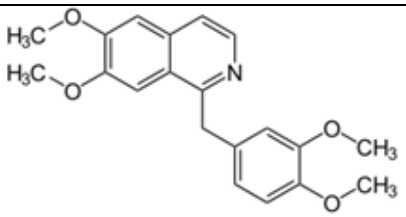
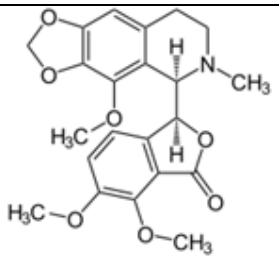
Compound	MW	CAS	Structure
Morphine Synonyms: 7,8-Didehydro-4,5α-epoxy-17-methyl morphinan-3,6α-diol (5R,6S,9R,13S,14R)-4,5-epoxy-N-methyl-7-morphinen-3,6-diol	**285.3**	**57-27-2**	
Codeine Synonyms: 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (5R,6S,9R,13S,14R)-4,5-epoxy-3-methoxy-N-methyl-7-morphinen-6-ol	**299.4**	**76-57-3**	
Thebaine Synonyms: 4,5α-Epoxy-3,6-dimethoxy-17-methyl-6,8-morphinadien 6,7,8,14-Tetradehydro-4,5-epoxy-3,6-dimethoxy-17-methyl-morphinan	**311.4**	**115-37-7**	
Oripavine Synonyms: 4,5α-Epoxy-6-methoxy-17-methylmorphina-6,8-dien-3-ol 6,7,8,14-Tetradehydro-4,5α-epoxy-6-methoxy-17-methylmorphinan-3-ol	**297.4**	**467-04-9**	
Papaverine Synonyms 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline	**339.4**	**58-74-2**	
Noscapine Synonyms: (3S)-6,7-Dimethoxy-3-[(5R)-4-methoxy-6-methyl-5, 6, 7,8-tetrahydro-1,3-dioxolo [4,5-g]isoquinoline-5-yl]isobenzo-furan-1(3H)-one	**413.4**	**128-62-1**	

Figure 2: Structures of opium alkaloids for which occurrence data were received (MW: molecular weight, CAS: chemical abstracts service).

1.3.1. Morphine

The phenanthrene alkaloid morphine is the main active component of opium. It is used for medicinal purposes as morphine sulphate pentahydrate (MW: 758.8 g/mol; CAS No.: 6211-15-0) or as morphine hydrochloride trihydrate (CAS No.: 6055-06-7, MW: 375.8 g/mol) (PH Eur., 2010; Martindale, 2010).

1.3.2. Codeine

The phenanthrene alkaloid codeine is the 3-methylether of morphine. It is normally used pharmaceutically in the form of its salts, e.g. as codeine phosphate hemihydrate (MW: 406.4 g/mol, CAS No.: 41444-62-6) (PH Eur., 2010; Martindale, 2010).

1.3.3. Thebaine

Thebaine contains the basic structure of morphinan, like morphine and codeine, and is classed as a phenanthrene alkaloid. It is a key intermediate in the biosynthesis of morphine in the poppy plant. Thebaine has seen ample use as a synthetic precursor to some of the medicinally most important opiate derivatives, such as buprenorphine, that is used in the treatment of pain, opiate and alcohol addiction as well as opiate overdose (Berényi et al., 2009).

1.3.4. Oripavine

Oripavine is a phenanthrene alkaloid that is formed in various species of the genus *Papaver*, including *P. bracteatum* Lindl and *P. orientale* L. In the last decade, a variety (a strain) of *P. somniferum* was created by plant breeders with a high content of oripavine and is now cultivated commercially on a considerable scale. Oripavine is easily convertible to thebaine. It is the parent compound from which a number of semi-synthetic opiates are derived.[7]

1.3.5. Papaverine

Papaverine is a benzylisoquinoline alkaloid. It is normally used pharmaceutically in the form of papaverine hydrochloride (MW: 375.9 g/mol, CAS No.: 61-25-6) (PH Eur., 2010; Martindale, 2010).

1.3.6. Noscapine

Noscapine (formerly narcotine) is also an alkaloid of the benzylisoquinoline type. For medical purposes it is also used as noscapine hydrochloride monohydrate (MW: 467.9 g/mol) (PH Eur., 2010; Martindale, 2010).

2. Legislation

2.1. Food

In order to protect public health, Article 2 of the Council Regulation (EEC) No 315/93[8] stipulates that, where necessary, maximum tolerances for specific contaminants shall be established. Thus a number of maximum tolerances for contaminants as well as natural plant toxicants are currently laid down in

[7] Available from http://www.who.int/medicines/areas/quality_safety/6.3Oripavine.pdf.
[8] Council Regulation (EEC) No 315/93 of 8 February 1993 laying down Community procedures for contaminants in food. OJ L 37, 13.2.1993, p. 1–3.

Commission Regulation (EC) No 1881/2006.[9] While maximum levels (MLs) for various mycotoxins were set for a number of food commodities, alkaloids in poppy seed samples in food are not regulated so far under this nor under another Regulation.

On a request of the EU Commission, the following 17 countries reported to have currently no legislation in place: Czech Republic, Denmark, Estonia, Finland, France, Ireland, Latvia, Luxembourg, Malta, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, The Netherlands and United Kingdom.

National maximum levels for content of opium alkaloids in poppy seed samples are only known from Hungary.[10] They are 30 mg/kg for morphine, 20 mg/kg for noscapine, 40 mg/kg for morphine and noscapine, 20 mg/kg for thebaine and 20 mg/kg for codeine.

In 2005, the BfR derived a provisional reference value for morphine in poppy seed samples of 4 mg/kg (BfR, 2005a). This BfR recommendation has been used as a basis for action but has not been incorporated in legislation.

Belgium has no national legislation on opium alkaloids in poppy seeds for food use. However, a legislation is in force which mentions the plant *Papaver somniferum* on the list of plants of which the use is forbidden in food, but allows an exception for the use of the poppy seeds on bakery products. As a consequence, in Belgium, poppy seeds can not be used in food in general, but only on bakery products. A royal decree on bread mentions that poppy seeds can be used on the surface of bread as decoration.

2.2. Narcotics

There is no uniform regulation on poppy cultivation in the EU. Some EU countries prohibit totally the production, some of them (like Germany) allow the low alkaloid containing varieties and others have other regulations. In Hungary e.g. the regulation states that there are two groups of poppy varieties: (1) industrial varieties of which the total content of opiate alkaloids is more than 0.7 % in the dry capsule, (2) food varieties with 0.7 % or less. For the first category, the regulation gives strict instructions on how to deal with the plant and seeds, with the poppy straw and the other plant parts. The producer of the food category has also some obligations.[11]

The cultivation of *Papaver somniferum* requires an exemption in the Federal Republic of Germany pursuant to the Narcotics Act (BtMG) [12] of 28 July 1981 § 3 and will only be granted for low morphine poppy varieties. Annex 3 to § 1 para 1 BtMG, which lists marketable and prescription narcotics, includes *Papaver somniferum* (plants and parts of plants), opium (the curdled sap of the plants which belong to the species *Papaver somniferum*), morphine and codeine. However, seeds of the plants belonging to the species *Papaver somniferum* (including the sub-species *setigerum*) are explicitly excluded. Annex 2 to § 1 para 1 BtMG, which lists marketable, non-prescription narcotics, indicates thebaine.

[9] Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. OJ L 364, 20.12.2006, p. 5–24.
[10] 17/1999. (VI. 16) EüM rendelet. az élelmiszerek vegyi szennyezettségének megengedhetö mértékéröl.
[11] 62/201 (III.18) Kormányrendelet "A kábítószer előállítására alkalmas növények termesztésének, forgalmazásának és felhasználásának rendjéről szóló 162/2003 (X.16) Korm rend módosításáról" (Goverment Decree on the cultivation, turnover and use of plants which may have narcotic effects, - a modification of the former one released in 2003).
[12] Gesetz über den Verkehr mit Betäubungsmitteln (Betäubungsmittelgesetz - BtMG, 28.07.1981).

3. Methods of analysis

The analysis of morphine, its metabolites and related opium alkaloids in poppy seed samples and biological samples, as well as the improvement in sensitivity and selectivity of analytical methods over the past 60 years has been summarized and reviewed by a number of working groups, such as Bratina et al. (1957), Wasels and Belleville (1994), Sproll et al. (2006) and Bosch et al. (2007). Earlier applied analytical methods were often limited to the determination of morphine and codeine. The extraction of the alkaloids from the poppy seed samples is generally performed by means of water or alcohol after acidification of the sample. Purification steps, such as liquid/liquid partitioning, use of ion exchangers as well as solid phase extraction (SPE) can be applied for the separation of the alkaloids from interfering substances. Initially morphine in poppy seed samples was determined gravimetrically with 4-chloro-1,3-dinitrobenzene or colorimetrically (Bratina et al., 1957). In 1965 Preininger et al. (1965) detected morphine and codeine in poppy seed samples by thin-layer chromatography (TLC). In addition to codeine and morphine, three more compounds: narcotine (noscapine), papaverine, and thebaine were detected in Indian and Dutch poppy seed samples using a GC-MS technique by Paul et al. (1996). The poppy seeds originated from India (off-white) and The Netherlands (slate-blue) and were purchased from local grocery stores in the United States of America (USA). Compared to the earlier used methodologies and high-performance liquid chromatography (HPLC) with ultra violet (UV) detection, which was also occasionally applied, GC-MS based methods offer the advantage of higher selectivity and sensitivity. A certain disadvantage is that the extracts have to be derivatized prior to gas chromatographic injection in order to increase the volatility of the opiates, their chromatographic separation and thus the sensitivity. In their review on GC-MS procedures Wasels and Belleville (1994) focus on different derivatization agents and conditions described in literature for the determination of opiates in various matrices.

Trenerry et al. (1995) developed a rapid method for the determination of morphine and related alkaloids, including codeine, thebaine, oripavine, papaverine, narcotine, narceine, cryptopine and salutaridine in crude morphine, poppy straw and opium preparations by micellar electrokinetic capillary chromatography (MEKC). The analytical separation took less than 10 minutes and the levels of morphine and related alkaloids determined by MEKC were in good agreement with those determined by HPLC.

Today's state of the art methodology for the determination of alkaloids in poppy seed samples is liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Sproll et al. (2006) describe a simplified LC-MS/MS procedure consisting of optimized cold extraction of the unground poppy seed sample with acidified methanol and improved chromatography with an alkaline gradient system on a pH-stable HPLC column. The detection limits obtained ranged between 0.07 mg/kg for both papaverine and noscapine and 0.3 mg/kg for both morphine and codeine. A major advantage of MS-based methods is the possibility of using isotope labelled standards, such as morphine-D_3 which not chromatographically but mass spectrometrically can be separated from their native analogues. By adding respective standards, the accuracy of the determination can be considerably improved.

Certified reference materials regarding food that contains opium alkaloids at relevant concentrations as well as international proficiency tests for their determination are lacking. There are also no harmonized performance criteria for respective analytical methods.

Whereas the above mentioned analytical methodologies are applied for the determination of opium alkaloids in food, immunological methods are now widely adopted as the initial screening test to detect opiates in urine because they have adequate sensitivity and pre-treatment of samples is often not required. As these methods are not used for food, they are beyond the scope of this opinion and thus not further described.

4. Occurrence of opium alkaloids in food

4.1. Previously reported occurrence results

There are significant variations in the content of morphine and other alkaloids in the varieties of poppy seeds grown for commercial use. According to international data, maximum contents of 620 mg/kg morphine, 57 mg/kg codeine, 230 mg/kg noscapine, 67 mg/kg papaverine and 41 mg/kg thebaine have been measured in poppy seed samples (Rochholz et al., 2004). Large variations in the levels have been found in samples from different origins. The highest morphine values have been reported in samples from Spain, Australia, India, Eastern Europe, The Netherlands and in samples of unknown origin (Rochholz et al., 2005). Large variations have been detected in the content, often with 30-50-fold differences but in some cases even 6000-fold differences in the same sample material between different batches (Thevis et al., 2003; Rochholz et al., 2004).

As mentioned by Rochholz et al. (2004), poppy seeds themselves may only contain very low levels of morphine and codeine. It has been described by Bernáth (1998) that there is a negative gradient in accumulation of alkaloids in the direction from capsule wall to placenta and further to seed. Maximum alkaloid content has been reported as about 23 % in the capsule wall, about 15 % in the placenta and only 3-4 % in the early stages of seed development. The alkaloid practically disappears from the seeds with seed colouring (Bernáth, 1998).

The main sources of morphine and other alkaloid compounds would be due to external contamination especially through inappropriate plant protection and harvesting-cleaning procedures (Andresen and Schmoldt, 2004; Rochholz et al., 2004, 2005; Bernáth and Nemeth, 2010). Other factors influencing the alkaloid contamination of poppy seeds and products are e.g. the variety of poppy plant and growth conditions like drought and mycotoxins as stress factors. In addition, insects may play a major role in the contamination of poppy seeds (Bernáth and Nemeth, 2010). These sources of variability are reflected in the different occurrence values obtained from poppy seed samples from different countries, brands and batches of products. The true origin of poppy seeds is, therefore, important information to be able to understand the variation in poppy seed alkaloid occurrence on the market. Mixing of poppy seeds from different origins could have a decreasing or increasing effect on the occurrence depending on the poppy seed batches that are combined. Factors affecting the content of poppy seed alkaloids are summarised in the Table 1.

Table 1: Factors affecting the alkaloid content of poppy seed samples and products.

Factor	Additional conditions	Effect	Quantity of effect	Reference
Variety / sort	Poppy varieties for pharmacological industry, Low-morphine poppy varieties	Significant variation in the morphine content	Morphine > 50 mg/kg, even > 500 mg/kg vs. < 1 mg/kg even ~ 0 mg/kg	Lo and Chua, 1992; Hayes et al., 1987; Stolzenburg, 2006
Growth, climate, weather		Increases during growth and falls after flowering period, disappears from the seeds by seed colouring. Daily fluctuation: max in early morning, minimum	3-4 % alkaloids in seeds during early development, ~ 0 % in mature seeds	Frohne and Pfänder, 1987; Bernáth,1998; Blaschek et al., 2006
Fertilisation	N-fertilisation P-fertilisation	Increase of alkaloids Decrease of alkaloids		Lachman et al., 2006
Harvesting (technology and time)	Manual cutting + shaking vs. mechanic squeezing / crushing of the capsules; Detrimental effect of immature capsules	Opium juice contaminates the seeds when capsules are cut and seeds put in containers. Higher risk to get the seeds contaminated by capsule wall powders produced by harvesting machines.	High variation	Andresen and Schmoldt, 2004; Moeller et al., 2004; Rochholz et al., 2005
Contamination due to pest damage		Seed contaminated due to stings of insects through the poppy seed capsule followed by a latex-seed contact (e.g. *Ceutorrynchus maculatus* insect)	High variation	Bernáth and Nemeth, 2010
Stress during growth	General/drought stress Mycotoxin stress	Increase of alkaloids / Morphine metabolised to bismorphine No significant difference		Szabo et al., 2003; Lachman et al., 2006; Morimoto et al., 2001 Szabo et al., 2003;
Washing	Acidic conditions 60°C	Marked reduction of morphine content	Up to 100 % Up to 90 % ↓	Rochholz et al., 2004; Sproll et al, 2007
Origin/country /location			e.g. Australian poppy seeds, morphine 90-325 mg/kg Turkish poppy seeds 4-5 mg/kg	Thevis et al., 2003; Hill et al., 2005
Batches/Brands			morphine 152 vs. 1 mg/kg	Thevis et al., 2003

4.2. Current occurrence results

Following a European Commission request, EFSA published in October 2010 a call for data, with the deadline of December 2010, inviting Member States, research institutions, academia and other stakeholders to submit data on the presence of opium alkaloids in poppy seed samples and composite food containing poppy seeds. The call requested data on six poppy seed alkaloids (morphine, codeine, thebaine, papaverine, noscapine and narceine). In addition, also data on other compounds could be submitted.

Since only one country had responded to the call by the first deadline, the submission deadline was extended to January 2011.

EFSA collected and evaluated the results reported from the analysis of 1033 food samples namely, bakery products (n = 186), baking ingredients (n = 62) and poppy seeds (n = 785), including altogether 2678 analytical results. Data were provided by four European countries (Germany, Hungary, Austria and The Netherlands) and Australia mainly covering the period from 2006-2010 with 11 samples from years before that. Data providers were asked to provide clarifications in case of unclear or missing detailed information and were contacted to confirm the final version of data included in the EFSA database.

4.2.1. Data collection summary

The source of the 2678 analytical results reported from the four European countries and Australia is illustrated in Table 2. Data on five poppy seed alkaloids of interest (morphine, codeine, thebaine, papaverine and noscapine) were obtained from Germany and on four from Austria and Hungary. From The Netherlands only data on morphine were received. Australia provided data on morphine, codeine, thebaine and in addition on oripavine. It needs to be mentioned that the reporting country does not necessarily correspond to the country of origin. No data were received on narceine or other alkaloids. No data were available regarding the cultivar of the submitted samples.

Table 2: Distribution of submitted analytical results for the six reported opium alkaloids in samples of poppy seeds and products across 4 European countries and Australia.

Reporting country	Number of analytical results submitted						
	Total	**Morphine**	**Codeine**	**Thebaine**	**Oripavine**	**Papaverine**	**Noscapine**
Austria	180	45	45	-	-	45	45
Germany	1255	561	374	143	-	90	87
Hungary	924	231	231	231	-	-	231
The Netherlands	131	131	-	-	-	-	-
Australia	188	55	43	47	43	-	-
Total	*2678*	*1023*	*693*	*421*	*43*	*135*	*363*

- no data submitted

4.2.2. Distribution of analytical results across different foods

The distribution of analytical results of different opium alkaloids to different foods is shown in Table 3. Details of the distribution of analytical results according to information provided by the data suppliers are provided in the Appendix B, Table B1. In Table 3, all different bakery products are pooled into one group, because certain bakery products contained a very limited number of analytical results. Also the three samples categorised by the data suppliers to be oil seeds were pooled together with poppy seed samples.

Germany was the only country providing opium alkaloid data analysed from bakery products and baking ingredients. Poppy seed data were provided by all countries that submitted data. No data on poppy seed oil were submitted.

Table 3: Distribution of analytical results reported for food categories.

Substance	Reporting country	Number of analytical results submitted			
		Total	Bakery products	Baking ingredients	Poppy seeds
Morphine	Austria	45	-	-	45
	Germany	561	186	62	313
	Hungary	231	-	-	231
	Netherlands	131	-	-	131
	Australia	55	-	-	55
Morphine, total		*1023*	*186*	*62*	*775*
Codeine	Austria	45	-	-	45
	Germany	374	89	47	238
	Hungary	231	-	-	231
	Australia	43	-	-	43
Codeine, total		*693*	*89*	*47*	*557*
Thebaine	Germany	143	49	16	78
	Hungary	231	-	-	231
	Australia	47	-	-	47
Thebaine, total		*421*	*49*	*16*	*356*
Oripavine	Australia	43	-	-	43
Oripavine, total		*43*	-	-	*43*
Papaverine	Austria	45	-	-	45
	Germany	90	25	8	57
Papaverine, total		*135*	*25*	*8*	*102*
Noscapine	Austria	45	-	-	45
	Germany	87	24	9	54
	Hungary	231	-	-	231
Noscapine, total		*363*	*24*	*9*	*330*
Overall, total		*2678*	*373*	*142*	*2163*

- no data submitted

4.2.3. Analytical methods used

The most used analytical methods were LC-MS and HPLC with standard detection (HPLC-UV or HPLC-fluorescence) with 1412 and 598 results, respectively (Figure 3).

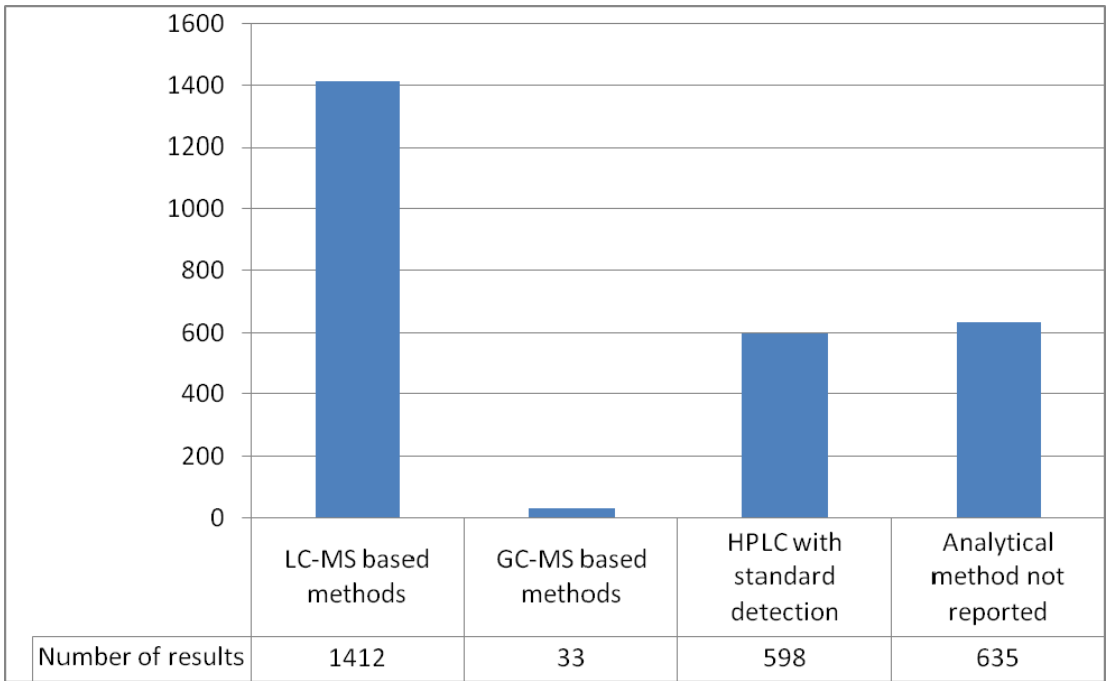


Figure 3: Distribution of analytical methods as reported (n = 2678).

Evaluation of the limits of detection (LOD) or limits of quantification (LOQ) reported shows that around 75 % of the LODs for morphine were under 1 mg/kg, with around half at or below 0.3 mg/kg. The maximum LOD for morphine was 10 mg/kg. The LOD for codeine was 0.5 mg/kg or below, for papaverine 0.3 mg/kg or below and for thebaine and noscapine 0.2 mg/kg or below in 95 % of the reported cases. The LOD for oripavine was not reported.

The proportion of analytical results reported for the individual poppy seed alkaloids in relation to the LOD, LOQ and detected values are shown in Figure 4. Morphine was quantified in more than 80 % of the samples, while the reverse was true for papaverine with less than 20 % of the results given as quantified.

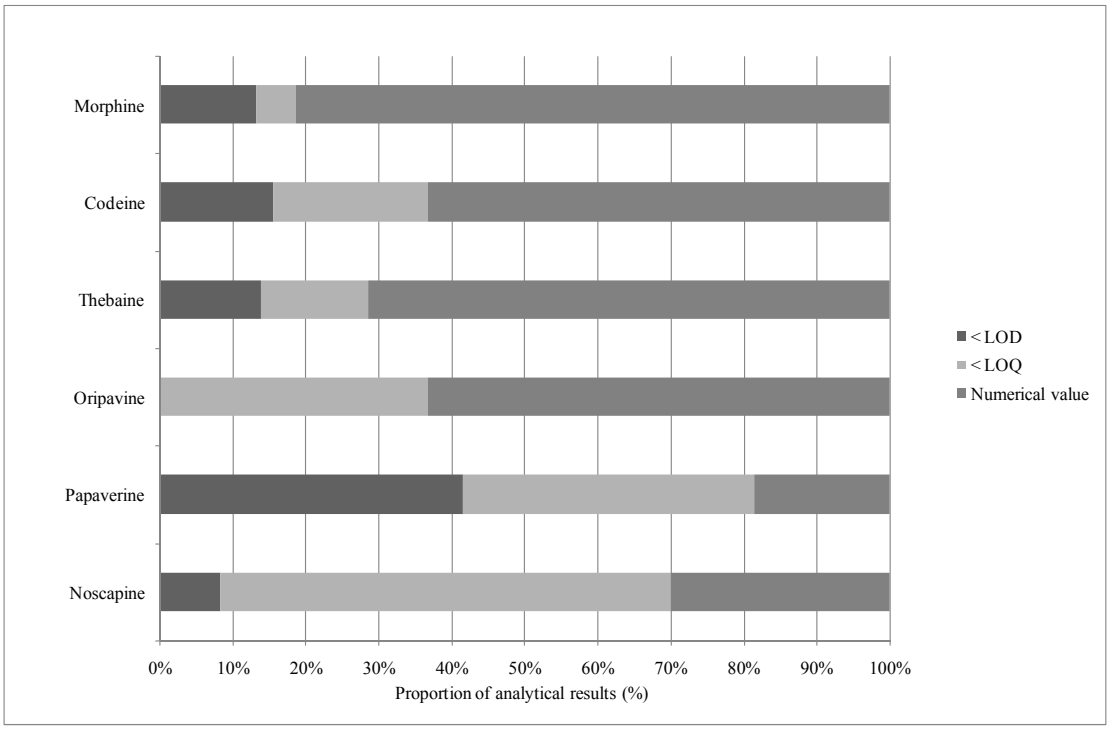


Figure 4: Proportion of results reported for the individual poppy seed alkaloids in relation to the limit of detection (LOD), limit of quantification (LOQ) and detected values.

4.2.4. Occurrence data by food group

Data providers were asked to codify all food descriptors according to the EFSA FoodEx Classification system (EFSA, 2011a).

FoodEx is a provisional food classification system developed by the DCM Unit (Dietary and Chemical Monitoring, former DATEX Unit), in 2009 with the objective of simplifying the linkage between occurrence and food consumption data when assessing the exposure to hazardous substances. It contains 20 main food groups (first level), which are further divided into food groups, having 140 items at the second level, 1261 items at the third level and reaching about 1800 end-points (food names or generic food names or food groups at the fourth level). It is based on a hierarchical coding system for easier cross-checking and it is structured with a child-parent relationship.

Occurrence data were provided in 10 food groups at levels 2, 3 and 4. Most of the data, 2163 analytical results out of 2678, were plain poppy seeds/oilseeds. The second largest pool of data included bakery products, with 373 analytical results classified into seven food groups (white wheat rolls; fine bakery ware; pastries and cakes; buns; cake from batter; fruit cake; croissant from puff pastry). The food group "fine bakery ware" is a level 2 food group in the FoodEx system including for example sweet pastries, as well as cakes and biscuits and was used by some data suppliers for classifying the samples. In addition, 142 analytical results for baking ingredients (e.g. poppy seed filling) were submitted.

Since the number of samples was very small in the FoodEx food groups of bakery products, the data were pooled together. Also data classified as oilseeds were pooled together with data classified as poppy seeds. A summary of the occurrence data by substance and food group is presented in Table 4.

Table 4: Summary of the poppy seed alkaloid occurrence data by substance and food group (mg/kg).

Substance	Food group	n	% LC	Median		Mean		P95[(a)]		Max	
				LB	UB	LB	UB	LB	UB	LB	UB
Morphine	Bakery products	186	57 %	0	1.00	0.53	0.98	3.00	3.00	8.20	8.20
	Baking ingredients	62	19 %	2.12	2.12	3.21	3.33	10.7	10.7	28.8	28.8
	Poppy seeds	775	9 %	10.0	10.0	38.20	38.53	202	202	630	630
Codeine	Bakery products	89	74 %	0	0.30	0.23	0.51	1.00	1.00	6.60	6.60
	Baking ingredients	47	26 %	0.90	0.90	1.08	1.18	3.30	3.30	4.10	4.10
	Poppy seeds	557	32 %	1.40	1.40	4.95	5.23	14.9	14.9	827	827
Thebaine	Bakery products	49	94 %	0	0.10	0.01	0.11	0.20	0.20	0.21	0.21
	Baking ingredients	16	50 %	0.03	0.11	0.17	0.23	0.80	0.80	0.80	0.80
	Poppy seeds	356	19 %	2.00	2.00	15.6	15.8	101	101	783	783
Oripavine	Poppy seeds	43	42 %	4.00	4.00	20.8	21.3	68.0	68.0	233	233
Papaverine	Bakery products	25	100 %	0	0.07	0	0.10	0	0.20	0	0.20
	Baking ingredients	8	38 %	0.13	0.20	0.14	0.18	0.35	0.35	0.35	0.35
	Poppy seeds	102	80 %	0	0.75	0.09	0.59	0.40	1.00	1.79	1.79
Noscapine	Bakery products	24	92 %	0	0.10	0.02	0.11	0.19	0.19	0.23	0.23
	Baking ingredients	9	56 %	0	0.10	0.27	0.33	1.36	1.36	1.36	1.36
	Poppy seeds	330	69 %	0	1.0	1.01	1.70	4.20	4.20	39.2	39.2

n: number of analytical results; LB: lower bound; UB: upper bound; P95: 95th percentile; LC: left censored data (values below the limit of detection or limit of quantification); Max: maximum.
(a): For some of the food groups, summary statistics (in particular high percentiles) may not be statistically robust due to the limited number of observations available.

4.2.5. Alkaloid profiles

While the typical prevalence of opium alkaloids has been described for *Papaver somniferum* in Section 1.1, it was considered helpful to test the hypothesis that the levels of opium alkaloids in the poppy seed samples that are the basis of this assessment conform to historical experience. Therefore, exploratory and statistical analyses of the collected occurrence data were performed.

Because occurrence data are characterised by measures that can only have positive values, a reported concentration in the sample below the LOD/LOQ leads to the statistical condition described as left-censored data (i.e., those data ≥0 but <LOD are lost to the distribution). These two essential characteristics of the collected data restrict the statistical analysis to those techniques that account for such facts (called survival analysis). A Kaplan-Meier estimate (non-parametric method) provided some insights into the distribution of the different alkaloids, and these exploratory analyses pointed out differences between the concentrations of alkaloids in the samples (data not shown). This finding was confirmed by Log-Normal models (parametric survival model), showing differences between the estimates obtained for each alkaloid (data not shown).

4.2.5.1. Co-occurrence

The co-occurrence of different alkaloids in poppy seeds was studied. It was considered that different pairs of alkaloids coexist if they were both quantified or if they were both below the LOD/LOQ level, if one was below the LOD/LOQ and the other one was quantified they were not considered coexistent. Figure 5 represents the level of agreement between each possible pair of the most common alkaloids presented as a percentage of the total number of samples. Morphine and codeine, codeine and thebaine, and morphine and thebaine had a high level of agreement, while the other pairs had a very low level of agreement indicating no or low co-occurrence. It is important to note that such comparisons should be made with caution, since they only reflect the submitted data on poppy seed samples from 2006 to 2010 and might refer to different numbers of observations.

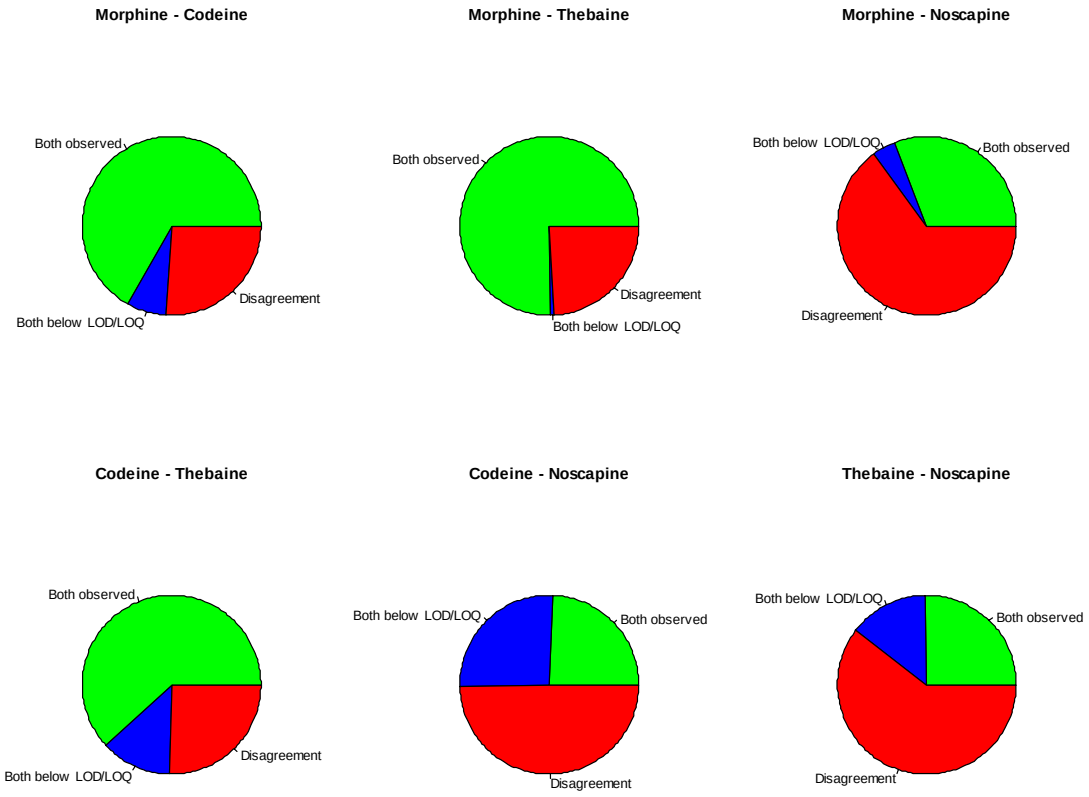


Figure 5: Pie chart showing level of agreement (percentage) for each alkaloid pair (green: both observed; blue: both below LOD/LOQ; red: disagreement).

4.2.5.2. Morphine being the minor alkaloid

To estimate the probabilities that morphine levels are lower than the levels of one of the other alkaloids, logistic models were fitted. This analysis was only done for 4 compounds which could have higher values compared to morphine. The following definitions were used to determine whether morphine was the minor.

- If morphine levels were not quantified (below LOD/LOQ), but the reported LOD/LOQ for morphine is below that for the other alkaloids, then it was considered that the event of interest has occurred, i.e. the morphine level was smaller than the level for the other alkaloids.
- If the observed levels of morphine are lower than the observed levels for the other alkaloids then in this case also the event of interest has occurred, i.e. the morphine level was smaller than the level for the other alkaloids.
- If the observed levels of morphine are below the LOD/LOQ levels reported for the other alkaloids, the case was considered as inconclusive.
- In any other case it is considered that the event of interest did not occur and that the morphine level was not smaller than the level for the other alkaloids.

The probability that the levels of morphine are lower than the levels of codeine was estimated to be 0.016 (95 % confidence interval (CI): 0.008, 0.029), which is low. It should be noted that from the 547 observations in which both morphine and codeine were reported, only 9 had morphine levels lower than the codeine levels. The probability that morphine levels are below thebaine levels was estimated to be 0.093 (95 % CI: 0.065, 0.126). Most of the poppy seed samples in which morphine levels were below thebaine levels were from Australia. This is presumably due to the use of different cultivars in the studied period which were likely specifically selected for use in the pharmaceutical industry.

Only 57 samples were reported by Australia, of which 43 were on morphine, codeine, thebaine and oripavine. From these only 14 had morphine levels higher than the levels of one of the other 3 alkaloids. Thus in 29 samples the level of morphine was below the level of another alkaloid, which was in general thebaine. These 21 had levels of morphine below the LOD/LOQ values, demonstrating differences with respect to the data provided by Australia and the European countries.

In the case of the Australian data, an analysis was made of whether the levels of morphine are lower than the oripavine levels. The estimated probability was 0.395 (95 % CI: 0.258, 0.544). From the 26 quantified oripavine observations 17 had lower levels of morphine compared to oripavine, with 10 of them not quantified for morphine.

4.2.5.3. Morphine being the major alkaloid

A multinomial model was used to estimate the probability that morphine could be considered as the major alkaloid present in the samples. In the evaluation, the following situations were considered as inconclusive events:

- if morphine levels were not quantified (below LOD/LOQ), but the reported LOD/LOQ for morphine is above one for the other alkaloids;
- if the observed levels of morphine are below the LOD/LOQ levels reported for the other alkaloids;
- if morphine levels were not quantified (below LOD/LOQ) and the other alkaloids are also below the LOD/LOQ levels.

Morphine was considered as the major alkaloid if the observed levels of morphine were greater than the observed levels of the other alkaloids. The model estimated that the probability of morphine being the major alkaloid was at least 8 times larger than the probability of morphine not being the major alkaloid. The probability of inconclusive results was about two times smaller than the probability that morphine was not the major alkaloid. Excluding the inconclusive results (only 3 % of the total number of observations) then the probability that morphine is the major alkaloid is estimated to be 0.921 (95 % CI: 0.896, 0.942). It is clear that such a high probability and narrow confidence interval indicates that morphine in general was the dominant alkaloid in poppy seed samples. Table 5 shows the percentage for each country of observations having morphine as the major alkaloid or not, or those inconclusive observations. It can be seen that only Australia had a larger percentage of observations for which morphine is not the major alkaloid, followed by Austria having two thirds of the observations for which morphine is the major alkaloid.

Table 5: Proportion of conclusive (morphine is the major/not the major) and inconclusive poppy seed samples with origin as reported by the submitting countries.

Origin	Morphine is the major	Morphine is not the major	Inconclusive
Australia	0.383	0.617	0.000
Austria	0.612	0.082	0.306
Unknown	0.929	0.059	0.012
Germany	0.950	0.000	0.050
Czech Republic	0.966	0.034	0.000
Hungary	0.988	0.012	0.000
European Union	1.000	0.000	0.000
Italy	1.000	0.000	0.000
The Netherlands	1.000	0.000	0.000
Poland	1.000	0.000	0.000
Slovakia	1.000	0.000	0.000
Turkey	1.000	0.000	0.000

4.2.5.4. Proportion of alkaloid content in poppy seed samples

Figure 6 shows a boxplot of the proportion (%) of each alkaloid within the total alkaloid content. It is clear from the graph that in general morphine represents the largest percentage of the total alkaloid content and the median is much larger for morphine than for the other reported alkaloids. Besides a high median value, morphine also showed a high variability of the percentage of the total alkaloids being morphine. This high variability was also observed for thebaine.

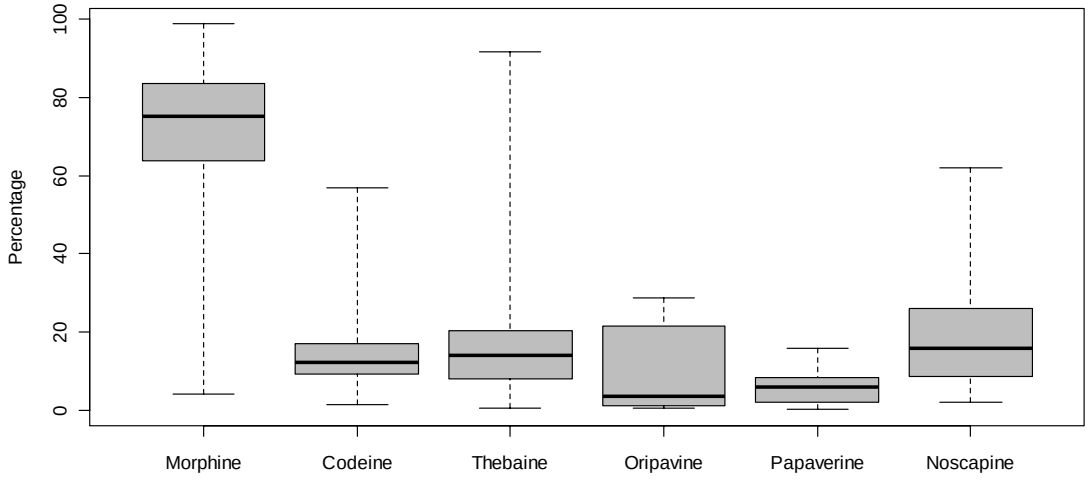


Figure 6: Boxplot of the percentages of each alkaloid compared to the total alkaloid content in the samples in which at least two alkaloids were quantified (the boxes indicate the 25th and the 75th percentiles, the ends of the whiskers represent the minimum and maximum and the dark black horizontal line represents the median).

When the sum is made up of morphine and codeine concentrations together (Figure 7), it is clear that in the majority of poppy seed samples, morphine and codeine account for more than half of the total alkaloid content, with 75 % of the samples having a morphine and codeine content that is higher than 70 % of the total alkaloid content. However, it should be noted that for oripavine only 3 observations were used, for thebaine 218 observations were used, for noscapine 80 and for papaverine only 20. This

exercise was repeated for each country separately, showing that the large variability of the percentage of morphine and thebaine of the total alkaloid content was mainly caused by Australian poppy seed samples.

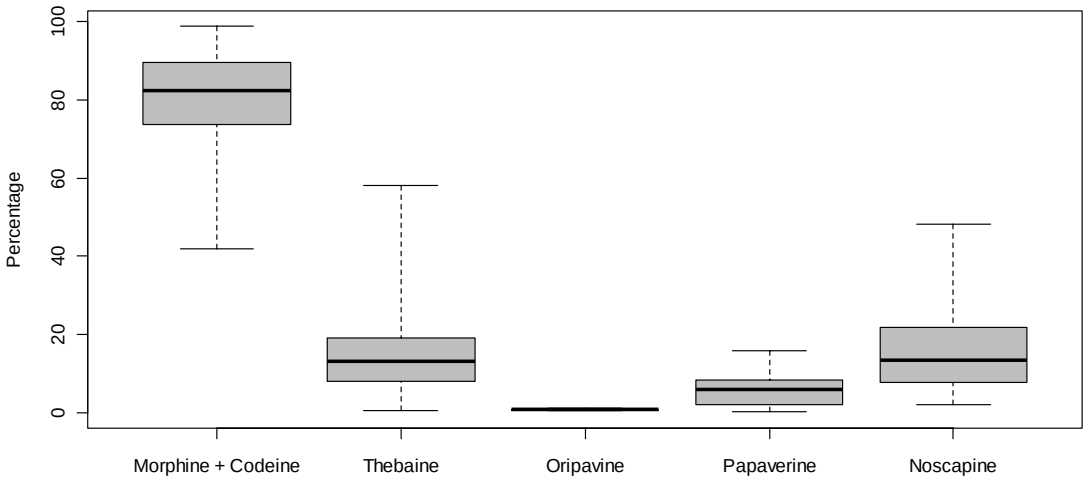


Figure 7: Boxplot of the percentages of each alkaloid compared to the total alkaloid content in the samples in which at least morphine, codeine and another alkaloid were quantified (the boxes indicate the 25th and the 75th percentiles with a thick black line at the medians, the ends of the whiskers represent the minimum and maximum).

Based on the performed analyses it can be concluded that morphine and codeine have a high level of co-occurrence as do codeine and thebaine and morphine and thebaine. The other pairs under study show a very low level of co-occurrence. In the data submitted by European countries, morphine is the major alkaloid in poppy seed samples. The data submitted by Australia show a different profile with higher levels of thebaine. It is known that in Australia certain varieties are produced for the extraction of oripavine and thebaine for pharmaceutical use by modifying the biosynthetic pathway of morphine (Millgate et al., 2004).

4.2.6. Overview of occurrence data used for exposure assessment

Due to the different nature of the alkaloid profile of the poppy seed samples submitted by Australia, and because it is unclear if these 55 samples are representative of Australian poppy seeds imported to the EU, the CONTAM Panel decided to exclude the Australian data and base the exposure assessment on the occurrence data for samples taken from the European market. Table 6 shows the summary statistics of the occurrence data of opium alkaloids in poppy seeds used for the exposure assessment in Section 6. As only Australia submitted data for oripavine, oripavine was not included in the exposure assessment.

Table 6: Summary statistics of the opium alkaloid occurrence data in poppy seed samples submitted by European countries (mg/kg).

Poppy seed alkaloid	n	Median		Mean		P95	
		LB	UB	LB	UB	LB	UB
Morphine	720	9.50	10.0	33.3	33.6	176	176
Codeine	514	1.50	1.50	2.85	3.09	13.9	13.9

Thebaine	309	1.60	1.60	3.23	3.40	12.2	12.2
Papaverine	102	0	0.75	0.09	0.59	0.40	1.00
Noscapine	330	0	1.00	1.02	1.70	4.20	4.20

n: number of analytical results; LB: lower bound; UB: upper bound; P95: 95th percentile.

Besides an estimation of the exposure based on occurrence results in poppy seed samples in combination with recipes, the exposure was also estimated by using occurrence data in bakery products. Table 7 gives an overview of the data used for the exposure assessment.

Table 7: Summary statistics of the opium alkaloid occurrence data in bakery products submitted by Germany (mg/kg).

Poppy seed alkaloid	n	Median		Mean		P95	
		LB	UB	LB	UB	LB	UB
Morphine	186	0	1.00	0.53	0.98	3.00	3.00
Codeine	89	0	0.30	0.23	0.51	1.00	1.00
Thebaine	49	0	0.10	0.01	0.11	0.20[(a)]	0.20
Papaverine	25	0	0.07	0	0.10	0[(a)]	0.20
Noscapine	24	0	0.10	0.02	0.11	0.19[(a)]	0.19

n: number of analytical results; LB: lower bound; UB: upper bound; P95: 95th percentile.
(a): If n < 60 then the calculated P95 should be considered as an indicative value only due to the limited dataset (EFSA, 2011b).

As discussed in Section 7.5., the CONTAM Panel considered application of a morphine equivalence approach in the risk characterisation. Therefore, a new occurrence variable, 'morphine equivalent', was estimated from the dataset by combining occurrence data on morphine and codeine by using an equivalence factor for codeine of 0.2 for each individual sample based on maximal metabolic conversion to morphine in CYP2D6 ultra-rapid metabolisers (≤20 %, see Section 7.1.2.3). The 'morphine equivalent' variable is consequently calculated for each sample as follows: 1* morphine (mg/kg) + 0.2 * codeine (mg/kg). Table 8 gives an overview of the summary statistics of the morphine equivalent in three food groups for samples that had both morphine and codeine analysed (n = 640). Comparison of the morphine equivalent values with only morphine values analysed for the same samples shows the major role of morphine in the exposure of the poppy seed alkaloids.

Table 8: Summary statistics of the morphine content and the morphine equivalent by food group (mg/kg) in the samples which were analysed for both morphine and codeine.

Food group	n	Median		Mean		P95[(b)]		Max	
		LB	UB	LB	UB	LB	UB	LB	UB
Morphine equivalent[(a)] based on samples in which both morphine and codeine were measured									
Bakery products	89	0	1.06	0.70	1.24	3.94	3.94	4.50	4.50
Baking ingredients	47	3.02	3.02	4.19	4.32	11.8	11.8	29.0	29.0
Poppy seeds	504	9.31	9.36	16.8	16.9	49.9	49.9	279	279
Morphine levels of samples in which both morphine and codeine were measured									
Bakery products	89	0	1.00	0.66	1.14	3.60	3.60	4.40	4.40
Baking ingredients	47	2.80	2.80	3.97	4.09	11.0	11.0	28.8	28.8
Poppy seeds	504	9.15	9.15	16.3	16.4	49.2	49.2	276	276

n: number of analytical results; LB: lower bound; UB: upper bound; P95: 95th percentile.
(a): The morphine equivalent is calculated as follows: 1* morphine (mg/kg) + 0.2 * codeine (mg/kg).
(b): For some of the food groups, summary statistics (in particular high percentiles) may not be statistically robust due to the limited number of observations available.

Comparison of the statistics for morphine equivalents with those for morphine alone in Table 8 reveals that codeine has a minor impact on the morphine equivalents. Therefore, the CONTAM Panel concluded that dietary exposure estimates for morphine alone should be used in the risk characterisation.

4.3. Food processing

The alkaloid content of poppy seed samples can be reduced by several means of pre-treatment and food processing. It has been shown that during the processing of food, alkaloid content may decrease by up to about 90 % and with pre-treatment and heat processes combined even almost totally (General et al., 2007; Lachenmeier et al., 2010). The most effective methods include washing and soaking, heat treatments using temperatures at least above 135°C, but preferably above 200°C, lower temperatures (e.g. 100°C) in combination with moisture or washing as well as grinding and combinations of the multiple treatments (Bjerver et al., 1982; Sproll et al., 2006; General et al., 2007; Sproll et al., 2007, Lachenmeier et al,. 2010).

Poppy seed containing foods go through several processes before being served. In the case of bread, often whole, untreated poppy seeds are used mainly as decoration and no other treatment than baking takes place. In other foods, poppy seeds are commonly ground before adding on top of a dish or before using in bakery products (Bernáth and Németh, 2010). Poppy seeds are also used as poppy seed filling, which is a combination of ground poppy seeds, sugar, liquid (water or milk) and possible additional ingredients and spices. The poppy seed filling is usually heat treated before use in the food preparation (General et al., 2007). Thus, poppy seeds in foods often go through a combination of different processing steps including grinding, mixing with liquid, heat treatment and sometimes even with several heat treatment steps. Although a single processing step may not have a major reducing effect on the poppy seed alkaloid content, e.g. 10 %-50 % reduction due to baking of whole poppy seeds on bread (General et al., 2007) or 25-34 % due to grinding of poppy seeds (Sproll et al., 2007), a combination of pre-treatment (e.g. processing of the poppy seed filling) followed by heat treatment (e.g. baking) may reduce the poppy seed alkaloid content down to non-detectable quantities (General et al., 2007). By the combination of washing and drying on a technical scale, General et al. (2007) achieved reductions of morphine concentrations also in highly contaminated batches of raw poppy seeds (original concentration varying from 50 up to 220 mg morphine/kg) down to concentrations below 4 mg

morphine/kg without loss of quality and organoleptic properties. The effects of different treatments on the reduction of poppy seed related alkaloids are summarised in the Table 9.

Morphine degrades in aqueous solutions with the formation of mainly pseudomorphine, a dimeric phenolic coupling product. The degradation of morphine is accelerated in the presence of oxygen and at higher pH of the solution, whereas temperature and light have only a minor influence on the degradation rate (reviewed in Vermeire and Remon, 1999). Based on low potency for binding to the μ-opioid receptor *in vitro* (Frölich et al., 2011), low penetrance into the central nervous system (CNS), and an inability to produce narcosis or respiratory depression *in vivo* (Misra and Mule, 1972), it appears that pseudomorphine does not possess appreciable morphine-like activity.

Table 9: Factors reducing the alkaloid content of poppy seeds and poppy seed products.

Factor	Additional conditions	Effect	Quantity of effect	Reference
Washing or soaking with water	Time (5 min) Increased time and temperature (30 s – 2 min - 30 min) in water of 15°C 60°C 100°C Single washing, slightly acidic conditions	Reduction in alkaloid content	46 % ↓ 60 % -75 % ↓ 80 % -95 % ↓ 80 % - 100 % ↓ 40 % ↓	Lo and Chua, 1992 Sproll et al., 2007 Bjerver et al., 1982
Temperature / heat treatment	Bread baking 135°C 220°C 200°C+grinding	Reduction in alkaloid content	~10-50 % ↓ ~30 % ↓ ~80-90 % ↓ ~90 % ↓	General et al., 2007 Sproll et al., 2006 Lachenmeier et al., 2010
Grinding	Oxygen (large active surface) Increased pH	Accelerated degradation rate of morphine, formation of pseudomorphine, improved aroma of the product	~25-34 % ↓	Sproll et al., 2006; Sproll et al., 2007; Vermeire and Remon, 1999
Light		Minor influence on the degradation rate		Sproll et al., 2007; Vermeire and Remon, 1999
Combined pre-treatment	Washing, 100°C, 1min +rosting 200°C, 20 min Washing, 100°C, 1min + drying (90°C, 120 min) Moisture with steam 100°C, 10 min+drying (90°C, 120 min) Moisture 100°C, 10min + grinding + drying (90°C, 120 min)	Reduction in alkaloid content	98-100 % ↓ 99 % ↓ 50-75 % ↓ 90-98 % ↓	General et al., 2007
Pre-treatement + baking	Grinding + baking Combined steam pre-treatment + grinding + baking Combined washing pre-treatment + grinding + baking	Major reduction in alkaloid content with combination of moisture and heat pre-treatment followed by dry heat treatment	80-95 % ↓ 90-95 % ↓ 100 % ↓	General et al., 2007

5. Food consumption

5.1. Sources of poppy seeds in the diet

Poppy seeds are mainly used in cereal products, i.e. breads and rolls as well as in fine bakery ware, but also as an ingredient in desserts and certain traditional composite dishes, especially in Central-Eastern European Countries. Consumption of poppy seed containing foods in Europe has been popular in the areas of Silesia, Bohemia, Moravia and Poland and in general in the areas influenced by the former Austro-Hungarian Empire. The popularity of these foods in western Germany has increased by eastern German bakers moving to western parts of the country after 1945 (General et al., 2007) (Figure 8). Today the consumption of poppy seed containing foods is common in Austria, the Czech Republic, Germany, Hungary, Poland, Slovakia and Slovenia. In these countries, poppy seeds are used widely in foods and in specific instances sometimes in high amounts in bakery products. Also, poppy seed containing dishes and desserts are common (Bernáth and Németh, 2010). Certain poppy seed containing traditional fine bakery wares (e.g. sweet poppy seed roll or strudel) are especially popular during Christmas and Easter times. These traditions can be found also in neighbouring countries like Lithuania, Latvia and in parts of Romania and Bulgaria (Biruté, 1998). For other consumers, poppy seeds are commonly used as a condiment or decoration in a restricted number of foods and in lower quantities.

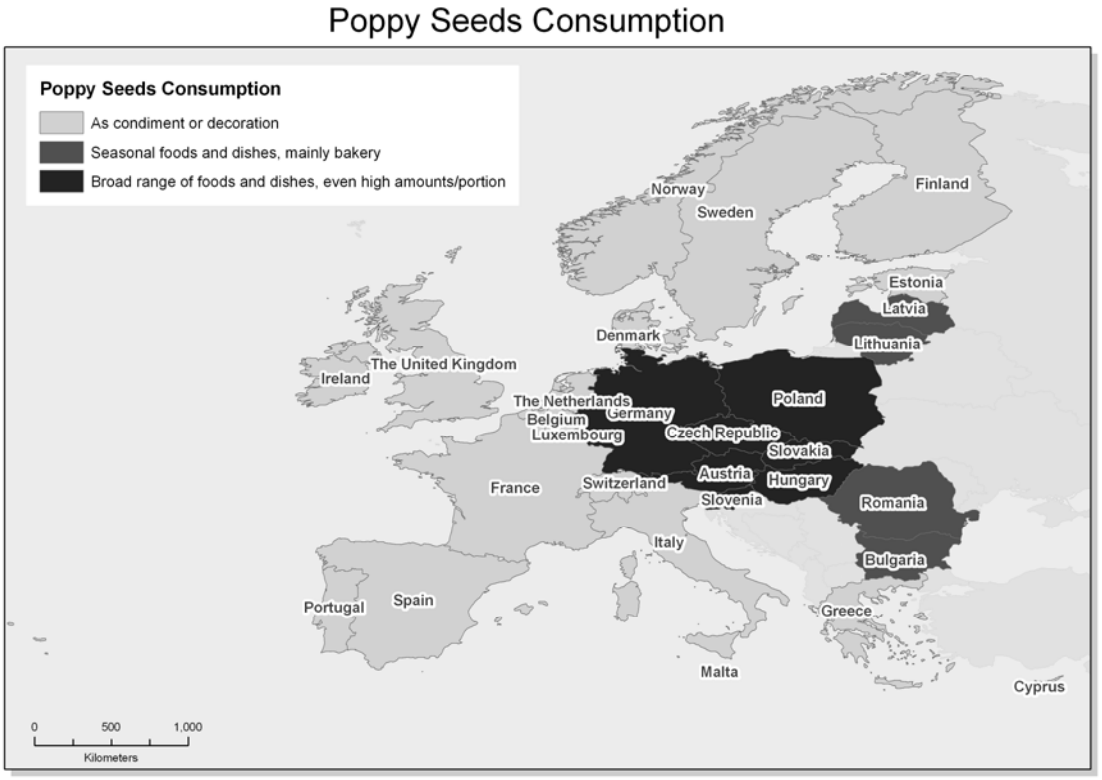


Figure 8: Poppy seed consumption in Europe[13,14,15] (Biruté, 1998; Bernáth and Németh, 2010).

[13] http://medlibrary.org/medwiki/Poppy_seed#European_cuisine.
[14] http://easteuropeanfood.about.com.
[15] EFSA/DCM, Expert Group on Food Consumption Data. Written communications from the country representatives.

5.2. EFSA's Comprehensive European Food Consumption Database

The CONTAM Panel considered that since opium alkaloids act acutely, it is appropriate to assess acute dietary exposure. Therefore, as suggested by the EFSA Working Group on Food Consumption and Exposure (EFSA, 2011a) all dietary surveys, including one day per subject, were used in the calculation of acute dietary exposure. Thus, for the present assessment, food consumption data were available from 32 different dietary surveys carried out in 20 different EU Member States as follows:

1. Infants: 2 Member States; 2 dietary surveys;
2. Toddlers: 8 Member States: 10 dietary surveys;
3. Other children: 14 Member States; 18 dietary surveys;
4. Adolescents: 12 Member States; 14 dietary surveys;
5. Adults: 20 Member States; 21 dietary surveys;
6. Elderly: 9 Member States; 9 dietary surveys;
7. Very elderly: 8 Member States; 8 dietary surveys.

Within the dietary surveys, subjects were classified in different age groups as defined below:

1. Infants: < 1 year old
2. Toddlers: ≥ 1 year to < 3 years old
3. Other children: ≥ 3 years to < 10 years old
4. Adolescents: ≥ 10 years to < 18 years old
5. Adults: ≥ 18 years to < 65 years old
6. Elderly: ≥ 65 years to < 75 years old
7. Very elderly: ≥ 75 years old

In particular, results from consumption surveys from 13 different Member States for children gathered by means of the EFSA Article 36 project "Individual food consumption data and exposure assessment studies for children" (acronym EXPOCHI) (Huybrechts et al., in press) were incorporated in the database. No data were available for infants, but it is unlikely that poppy seed containing foods are consumed by this age group. Consumption records were codified according to the FoodEx classification system, which was developed by the DATEX Unit in 2009 (EFSA, 2011a).

The dietary surveys considered for the acute dietary exposure assessment and numbers of subjects in the different age groups are presented in Appendix C, Table C1. Acute intake or exposure was based on consumers only and was expressed as exposure per consumption days. The "per day" consumption and exposure reported in Section 6 thus refers in this opinion to days when the food was consumed. Further details on how the Comprehensive Database is used are published in the Guidance of EFSA "Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment" (EFSA, 2011b).

The challenge with the EFSA food consumption database concerning poppy seed consumption is that poppy seed containing foods are rarely eaten in many countries. Only five countries provided any information on poppy seed consumption in their dietary surveys (Austria, Czech Republic, Germany, Hungary and Slovakia) and at most 2.96 % of children's and 2.91 % of adults' survey days[16] were reported to include poppy seeds in the dietary data (Table 10). The Member States used different types of food lists and recipe databases and often poppy seeds, being a minor ingredient, are not included. In addition, poppy seed containing foods are partly seasonal foods eaten during Christmas and Easter periods and national dietary surveys do not always cover these seasons. In the case of Bulgaria, Latvia, Poland and Slovenia, the surveys did not cover the Christmas and Easter seasons (Merten et al., 2011), when the poppy seed containing foods are traditionally consumed. Consequently, poppy seed consumption amounts obtained directly from the Comprehensive European Food Consumption Database are very low (Table 10) and possibly an underestimation of the true intake.

[16] Including elderly and very elderly.

Table 10: Poppy seed consumption according to the Comprehensive European Food Consumption Database.

Age class	Country	Total number of days	Number of consumption days[(a)]	Proportion of consumption days (%)	Average consumption (g per day)[(b)]
Toddlers					
	Germany	255	2	0.78	3.7
Other children					
	Czech Republic	778	23	2.96	6.5
	Germany, 2007	678	1	0.15	13.3
	Germany, 2008	669	1	0.15	1.2
Adolescent					
	Czech Republic	596	11	1.85	11.1
Adults					
	Austria	2123	6	0.28	2.5
	Czech Republic	3332	41	1.23	10.3
	Germany	20838	3	0.01	9.3
	Hungary	3222	58	1.80	8.4
	Slovakia	2763	13	0.47	33.8
Elderly					
	Hungary	618	18	2.91	6.9
Very Elderly					
	Hungary	240	3	1.25	7.5
Minimum			**1**	**0.01**	**1.2**
Median			**6**	**1.01**	**7.5**
Maximum			**58**	**2.96**	**33.8**

(a): Survey results with mean reported consumption of poppy seeds of < 10 consumption days/survey are excluded from further analyses.
(b): The poppy seed consumption ranged from 1 to 75 grams per day in the countries reporting poppy seed consumption in their surveys.

5.3. Recipes

To better evaluate poppy seed consumption, and thus opium alkaloid exposure, the levels of poppy seeds in foods were evaluated for European countries where poppy seeds are commonly used. Ranges of poppy seed content of 101 poppy seed containing foods based on recipe evaluations in seven countries, namely Austria, Czech Republic, Germany, Hungary, Lithuania, Poland, and Slovenia, are summarised in Table 11. More information on the poppy seed content in Europe is presented in Appendix C, Table C2. Poppy seed contents of the recipes were estimated based on the poppy seed proportion of the whole weight of the raw ingredients taking into account the possible weight losses during the food preparation (Bergstrom, 1994). Portion sizes were based on the information indicated in the recipe. If no information was available on the number of portions per recipe, mid-range portion sizes from picture books used in European dietary surveys were used for portion size estimation (Paturi et al., 2006; Rakicioglu et al., 2009). In cases where the portion indicated in the recipe was considered to be unrealistically high, the portion used in the estimations was decreased to be more realistic (e.g. in the case of the German Mohnpielen recipe, the indicated portion size of 495 g/portion was decreased to an arbitrary 200 g portion for this evaluation).

Table 11: Ranges of poppy seed content of European poppy seed containing foods (g/portion and g/100 g).

Food group	n	Poppy seed content (g/portion of food)[a],[b]			Poppy seed content (g/100g of food) [b]		
		Min	Med	Max	Min	Med	Max
Bread	9	0.3	1.1	6.0	0.9	2.5	17
Pastries and cakes	62	2.4	14	50	3.8	14	41
Biscuits and cookies	5	1.0	2.0	9.0	6.7	13	60
Savory main dishes	6	0.6	7.5	26	0.3	5.4	9.4
Sweet main dishes	5	26	39	83	13	18	35
Desserts	9	5.0	17	42	2.5	10	18
Poppy seed filling	2	20	-	23	40	-	46

n: number of recipes; Min: minimum; Med: median; Max: maximum.
(a): Portion estimated according to the published recipe or based on common portion sizes (Paturi et al., 2006; Rakicioglu et al., 2009).
(b): Weight changes were taken into account based on published values (Bergstrom, 1994).

The highest poppy seed contents per portion were found in a Polish noodle dish with poppy seeds (83 g/370g portion equivalent to 22.7 g/100 g), in a German dessert (Mohnpielen, 70 g/200 g portion equivalent to 35 g/100 g). Hungarian poppy seed cakes showed the highest poppy seed content in the fine bakery ware category with a poppy seed content being around 30 g/100g and poppy seed amounts ranging between 20-50 g/portion depending on portion size. These foods were used for acute exposure estimations for a hypothetical single portion. The Polish noodle dish and the German dessert Mohnpielen are examples of dishes that are commonly eaten as sweet main dishes in large portions but can also be eaten as dessert in smaller portions. The poppy seed cake chosen for children's single portion scenraios (containing 31g/100g) was not the highest in poppy seed content. It was chosen based on palatability and therefore reslistic example of children's consumption.

5.4. Food consumption data and estimates of acute poppy seed consumption for different age and consumer groups used for exposure assessment

Four different approaches were used to estimate acute opium alkaloid exposure.

First, poppy seed consumption as reported in the EFSA Comprehensive Database (Table 10) was used to estimate exposure to opium alkaloids.

Secondly, single portion scenarios with foods containing high poppy seed content were used. These scenarios were used to evaluate the exposure of individuals consuming foods containing high amounts of poppy seeds (approximately 20-35g/100g food). Table 12 gives an overview of the different single portion scenarios.

Thirdly, exposure to the poppy seed alkaloids was estimated using the occurrence data of opium alkaloids measured in fine bakery wares (German data only) in combination with the acute consumption data from the Comprehensive Database for countries in which consumption of foods with high poppy seed content is common (Table 13).

Finally, the exposures were assessed using food consumption data from the EFSA Comprehensive Database. These scenarios were estimating acute poppy seed consumption based on the assumption that either all bread eaten on one day would contain poppy seed or all fine bakery ware consumed on one day would contain poppy seeds. Different poppy seed contents for these food groups were assumed for the high poppy seed content and low poppy seed content as described in the linking table (Table 14).

These estimates were based on the food consumption shown in Tables 13 and 15 and the occurrence data based on analyses of poppy seeds. Food consumption is expressed as the average and the 95th percentile consumption and the distribution in surveys included as illustrated through the minimum, median and maximum among the surveys in each age group.

Table 12: Hypothetical single portion scenarios for high opium alkaloid exposure assessment.

Scenario	Age group	Body weight[(a)] (kg)	Poppy seed source	Food portion (g)	Poppy seed consumption	
					(g/meal)	(g/kg b.w.)
1	Toddlers	11.6	Poppy seed cake	50	15.5	1.3
2	Other children	21.6	Poppy seed cake	100	31	1.4
3	Adults	73	Poppy seed dessert ("Mohnpielen")	200	70	1.0
4	Adults	73	Sweet main dish (Noodles with poppy seeds)	370	83	1.1

b.w.: body weight.
(a): EFSA Comprehensive Food Consumption Database, median weights of all surveys.

Table 13: Summary statistics of consumption data for bread and fine bakery ware retrieved from the Comprehensive database for countries where foods containing high amounts of poppy seeds are common.

Population	Bread[(a)] consumption (g per day)						Fine bakery ware[(b)] consumption (g per day)					
	Average[(c)]			P95[(c)]			Average			P95		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Toddlers	6.1	7.8	34.8	16.7	23.7	72.5	8.0	10.8	40.1	26.0	30.2	116
Other children	13.8	29.5	48.8	43.0	70.0	162	14.6	32.5	83.0	42.0	85.4	240
Adolescents	42.1	52.6	193	113	135	455	49.5	73.8	134	132	200	420
Adults	18.7	49.7	202	60.0	125	421	11.7	60.5	130	38.2	170	348

P95: 95th percentile; Min: minimum; Med: median; Max: maximum.
(a): The bread scenario includes the food groups: wheat bread, rolls and unleavened crisp bread.
(b): The fine bakery scenario includes the food groups: pastries and cakes and biscuits and cookies.
(c): The average and P95 consumption data are calculated per food consumption survey. The minimum, median and maximum values for all surveys are included in the table to show the range in the dataset.

Table 14: Linking table of the scenarios used to estimate poppy seed alkaloid exposure using poppy seed containing food consumption from the EFSA Comprehensive food consumption database.

Scenario	FoodEx number	Selected food groups	Poppy seed content in recipes (g/100g of food)	
			high content [(a)]	low content [(b)]
Bread	A.01.04.001	White wheat bread and rolls	17	0.9
	A.01.04.005	Unleavened bread, crisp bread and rusk	17	0.9
Fine bakery	A.01.07.001	Pastries and cakes	41	3.8
	A.01.07.002	Biscuits (cookies)	60	6.7

(a): The maximum reported poppy seed content was used from the recipe database as described in Table 11.
(b): The minimum reported poppy seed content was used from the recipe database as described in Table 11.

Table 15: Summary statistics of consumption data for bread and fine bakery ware retrieved from the Comprehensive database for countries where foods most commonly containing low amounts of poppy seeds.

Population	Bread [(a)] consumption (g per day)						Fine bakery ware [(b)] consumption (g per day)					
	Average [(c)]			P95 [(c)]			Average			P95		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Toddlers	2.5	23.2	27.0	7.6	50.4	69.8	2.5	14.9	20.8	7.9	46.7	64.2
Other children	7.5	13.9	46.5	18.2	35.0	95.0	2.9	21.7	32.0	11.5	63.1	87.5
Adolescents	14.1	44.4	69.1	36.0	106	173	4.0	27.1	54.8	17.5	75.1	169
Adults	10.1	20.8	76.2	23.6	46.9	200	2.7	15.6	48.6	11.2	47.1	141

P95: 95th percentile; Min: minimum; Med: median; Max: maximum.
(a): The bread scenario includes the food groups: wheat bread, rolls and unleavened crisp bread.
(b): The fine bakery scenario includes the food groups: pastries and cakes and biscuits and cookies.
(c): The average and P95 consumption data are calculated per food consumption survey. The minimum, median and maximum values for all surveys are included in the table to show the range in the dataset.

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6. Exposure assessment of opium alkaloids in humans

6.1. Previously reported human exposure assessments

No published exposure assessments were identified.

6.2. Acute dietary exposure to opium alkaloids

Assessment of acute exposure to opium alkaloids was based on actual reported poppy seed consumption, on hypothetical single food scenarios and on hypothetical scenarios based on information obtained from European dietary surveys on consumption of major poppy seed sources as described in Sections 5.2-5.4. The exposure assessments carried out were:

1. Mean exposure to opium alkaloids based on reported poppy seed consumption in 3 countries recorded in the EFSA Comprehensive Food Consumption database (see Table 10) and occurrence data in poppy seeds (see Table 6).

2. Hypothetical single portion scenarios for consumers of foods with high poppy seed content (see Table 12), based on occurrence data in poppy seeds (see Table 6).

3. Acute exposure scenarios based on the Comprehensive database consumption data of countries where foods containing high amounts of poppy seeds are common (see Table 13), and occurrence data measured in food products in Germany (see Table 7).

4. Acute exposure scenarios based on the Comprehensive database information on bread consumption ("Bread" scenario) and fine bakery ware consumption ("Fine bakery" scenario), estimated poppy seed intake based on estimated high and low poppy seed content of foods (see Table 13-15), and occurrence data in poppy seeds (see Table 6).

Detailed results on exposure based on the above schemes with average and high (95^{th} percentile) consumption and mean and high (95^{th} percentile) occurrence values for five opium alkaloids separately, are presented in Appendix D.

Morphine is the major contributing opium alkaloid to exposure of all the five alkaloids covered in this opinion. Exposure to morphine in relation to poppy seed consumption according to all the different exposure scenarios tested for all age groups and based on mean and high (95^{th} percentile) occurrence values are summarised in Tables 16-20. The exposure to codeine and thebaine was about 7-8 % of that of morphine and exposure to papaverine and noscapine less than 3 % of that of morphine.

6.2.1. Acute dietary exposure to opium alkaloids based on reported poppy seed consumption

Only five countries had information on poppy seed consumption in the Comprehensive database, namely Austria, Czech Republic, Germany, Hungary and Slovakia. Only three countries had survey data that contained >10 poppy seed consumption days per survey, i.e. Czech Republic, Hungary and Slovakia. Due to the limited number of consumption days per survey, i.e. less than 60 days, the 95^{th} percentile of the poppy seed consumption was considered as unreliable and not included in the exposure assessment (EFSA, 2011b). Therefore, only the mean reported poppy seed consumption (Table 10) was included in the exposure assessment. Insufficient data were available for the toddler age group. Morphine exposure based on mean occurrence data ranged from 3.11 µg/kg b.w. per day to 17.4 µg/kg b.w. per day, being the highest among adults. The morphine exposure based on high (95^{th} percentile) occurrence data ranged between 16.4 µg /kg b.w. per day and 90.9 µg/kg b.w. per day

(Table 16). The detailed exposure to opium alkaloids based on reported poppy seed consumption is shown in Appendix D, Table D1.

Table 16: Summary of acute dietary exposure to morphine (µg/kg b.w. per day) based on average reported poppy seed consumption according to the Comprehensive European Food Consumption database

Population [a]	Exposure (µg/kg b.w. per day)			
	Mean occurrence		High occurrence (95th percentile)	
	LB	UB	LB	UB
Other children	9.16	9.25	48.3	48.3
Adolescents	8.06	8.14	42.5	42.5
Adults [b]	3.11	17.4	16.4	90.9

b.w.: body weight; LB: lower bound; UB: upper bound.
(a): Population groups with <10 consumption days have been excluded from this summary. Only one survey in the age groups "other children" and "adolescents" was available.
(b): For adults, several surveys had reported poppy seed consumption from > 10 consumption days. The LB value is calculated from the survey of which the average consumption was the lowest and the UB value is calculated from the survey of which the average consumption was the highest.

The limitations of the dietary surveys to capture poppy seed consumption accurately include possible lack of poppy seeds among the foods covered in the data collections, lack of poppy seeds in recipe databases used to calculate consumption of ingredients of composite dishes as well as limitations to capture seasonal consumption of poppy seeds. The seasonal consumption of poppy seeds is underestimated due to the fact that the time window of data collections does not always cover Christmas, New Year and Easter days, when poppy seed containing foods are consumed in high amounts in certain countries. This is reflected in this exposure assessment, which is based on reported poppy seed consumption only from a limited number of countries where the consumption of foods with high poppy seed content is common. None of the other countries had provided any poppy seed consumption to the Comprehensive database. This indicates on one hand that poppy seed consumption is not very common (low frequency of consumption) or that the data collection instruments (food list or recipe database used) do not include poppy seeds and poppy seed consumption is not recorded in these countries. If the consumption occasion in these countries is missed in the data collection, this may result in an underestimation of true acute poppy seed consumption and thus underestimate acute poppy seed alkaloid exposure.

On the other hand, due to the fact that the occurrence data are for raw poppy seeds, the above presented exposure assessment may overestimate the true exposure, because in this assessment the poppy seed occurrence values are on raw poppy seeds, which are seldomly consumed as such in foods. However, no information was available from the Member States on the processing of the poppy seed containing food products consumed in these surveys.

6.2.2. Acute dietary exposure to opium alkaloids based on hypothetical single portion scenarios

Estimates of acute exposure to opium alkaloids were based on scenarios for single portions of foods containing high amounts of poppy seeds, i.e. poppy seed cake, poppy seed dessert and a noodle dish with poppy seeds that is also served as a sweet main dish.

The detailed exposure to opium alkaloids from hypothetical single portion scenarios are shown in Appendix D, Table D2 and a summary of the morphine exposure estimates in Table 17.

Table 17: Summary of acute dietary exposure to morphine (µg/kg b.w. per portion) based on single portion scenarios for foods with high poppy seed content.

Scenario	Age group	Food (portion, g)	Poppy seeds		Exposure LB-UB (µg/kg b.w.) [(a)]	
			(g/portion)	(g/kg b.w.)	Mean occurrence	High occurrence (P95)
1	Toddlers	Poppy seed cake (50g)	15.5	1.3	44.4-44.9	235
2	Other children	Poppy seed cake (100g)	31	1.4	47.8-48.3	252
3	Adults	Poppy seed dessert (200g)	70	1.0	31.9-32.2	168
4	Adults	Noodles with poppy seeds (370 g)	83	1.1	37.8-38.2	200

b.w.: body weight; P95: 95th percentile; LB: lower bound; UB: upper bound.
(a): When the upper and lower bound value is equal, only one value is shown.

Combination of the mean occurrence data and consumption of poppy seed cake portions of 50 g and 100 g for toddlers and other children, respectively, resulted in a mean morphine exposure of 44.9 µg/kg b.w. for toddlers (based on UB occurrence data) and 48.3 µg/kg b.w. for other children (based on UB occurrence data). High exposure based on the 95th percentile of the opium alkaloid occurrence was 235 µg/kg b.w. for toddlers and 252 µg/kg b.w. for other children, respectively.

The exposures of adults' single portion scenarios varied between 31.9 and 38.2 µg/kg b.w. for mean occurrence, and between 168 to 200 µg/kg b.w. for high morphine occurrence.

The foods in the single portion scenarios presented here are those that could realistically also be consumed in larger portions or in multiple servings. If that would be the case, the exposure would increase accordingly. In addition, if a child (3-10 years of age) would consume a half portion (185 g) of an adult's portion (370 g) of the noodle dish the morphine exposure would be 337 µg/kg b.w.

It is well-known that the opium alkaloid content decreases during different processing steps, as described in Section 4.3. This effect would be the largest for poppy seed cake. This is because poppy seeds in cakes go through several processing steps before consumption. The seeds are normally ground before mixing into the batter and the batter is further heat treated (e.g. baked at 170°C for 60 minutes). In addition to the grinding, also mixing the ground seed into other ingredients of a moist batter may reduce the alkaloid content of poppy seeds due to the contact with water and air (oxygen). Although the temperature of the batter most probably will not reach temperatures over 100°C in the oven (Penfield and Campbell, 1990) due to the moisture content, it has been shown that the normal baking process can decrease the morphine content of a cake even to a non-detectable level after other processing steps (General et al., 2007). General et al. (2007) also showed that a combination of grinding of the seeds and baking can reduce the alkaloid content of a poppy seed cake by about 90 % from the original morphine content of the whole untreated seeds varying between 50-220 mg/kg. If this possible influence of processing on the morphine content is taken into account, the exposure of other children, which is the age group with the highest exposure on b.w. basis, would remain in excess of about 5 and 25 µg/kg b.w. for mean and high occurrence, respectively.

Also the sweet main dish Mohnpielen goes through a short heat treatment, but at a lower temperature and for a shorter time than baking of a poppy seed cake (Appendix C, Table C2). This results in a decrease of the opium alkaloid content to a lesser extent. Grinding alone of the seeds could cause a decrease of up to 25-34 % of the original opium alkaloid level (Sproll et al., 2007). Taking both the heat treatment and grinding into account, there might be a reduction of up to 50 %. If this possible influence

of processing on the morphine content is taken into account, the morphine exposure for adults would remain in excess of 84 µg/kg b.w. for the Mohnpielen.

Besides dishes with heated poppy seeds, it is also common to use unheated poppy seeds to sprinkle on top of dishes of which the treatment and the used quantity are very diverse depending on the recipe and the personal preferences. Although, unground poppy seeds are used, most recipes recommend using ground unheated poppy seeds. In the latter case only grinding has an influence on the opium alkaloid level and there might be a reduction of up to 25-34 %.

6.2.3. Acute dietary exposure to opium alkaloids based on occurrence data measured in food products (fine bakery ware)

As discussed in Section 4, the number of analytical results for food products was limited (n = 186 for morphine, n = 89 for codeine) and data were only submitted by Germany, a country where poppy seeds are used frequently in food products. The estimation of the exposure through occurrence data in food products is therefore limited to countries where foods with high poppy seed content are commonly eaten. As most submitted data on food products were on fine bakery ware, which is the most broadly consumed poppy seed-containing food, the exposure assessment was limited to these products. The consumption was calculated at the individual level for consumption days only and taking into account individual body weights. The morphine exposure results are summarised in Table 18 and detailed alkaloid exposures are presented in Appendix D, Table D3-D6.

Table 18: Summary of acute dietary exposure to morphine (µg/kg b.w. per day) based on occurrence data measured in bakery products and consumption data for countries where consumption of foods with high poppy seed content is common.

Population	Exposure (µg/kg b.w. per day)							
	Mean occurrence				High occurrence (P95)			
	Average consumption		High consumption		Average consumption		High consumption	
	Min[(a)],LB	Max[(a)],UB	Min,LB	Max,UB	Min,LB	Max,UB	Min,LB	Max,UB
Toddlers	0.36	3.07	1.09	8.38	2.01	9.37	6.15	25.5
Other children	0.33	3.46	0.90	10.1	1.88	10.6	5.11	30.7
Adolescents	0.55	2.28	1.74	7.54	3.10	6.96	9.84	23.0
Adults	0.09	1.80	0.30	4.79	0.50	5.48	1.70	14.6

b.w.: body weight; P95: 95th percentile; Min: minimum; Max: maximum; LB: lower bound; UB: upper bound.
(a): The average and high (95th percentile) consumption data are calculated per food consumption survey. The table shows the exposure for the minimum and maximum consumption values for all surveys.

6.2.3.1. Toddlers

The detailed acute exposure in toddlers to individual opium alkaloids from pastries, cakes and biscuits based on analysed fine bakery ware occurrence values is summarised in Appendix D, Table D3. Based on the mean and high (95th percentile) consumption and mean occurrence values, the morphine exposure varied in the range of 0.36 to 3.07 µg/kg b.w. per day and of 1.09 to 8.38 µg/kg b.w. per day, respectively. The corresponding exposures based on high occurrence values were in the range of 2.01 to 9.37 µg/kg b.w. per day and of 6.15 to 25.5 µg/kg b.w. per day, respectively.

6.2.3.2. Other children

The detailed acute exposure in children from 3 to 10 years of age to individual opium alkaloids from pastries, cakes and biscuits based on occurrence data for analysed bakery products is summarised in Appendix D, Table D4. Based on the mean and high (95th percentile) consumption and mean occurrence values, the morphine exposures were in the range of 0.33 to 3.46 µg/kg b.w. per day and 0.90 to 10.1 µg/kg b.w. per day, respectively. The corresponding exposures based on high occurrence values were in the range of 1.88 to 10.6 µg/kg b.w. per day, and of 5.11 to 30.7 µg/kg b.w. per day, respectively (Table 18).

The exposure is slightly higher than in toddlers, which reflects the larger consumption of fine bakery products on a body weight basis among children over 3 years of age compared to younger children.

6.2.3.3. Adolescents

The detailed acute exposure in adolescents (from 10 to 18 years) to individual opium alkaloids from pastries, cakes and biscuits based on analysed bakery products occurrence values is summarised in Appendix D, Table D5. Based on the mean and high (95th percentile) consumption and mean occurrence values, the morphine exposures were in the range of 0.55 to 2.28 µg/kg b.w. per day and of 1.74 to 7.54 µg/kg b.w. per day, respectively. The corresponding exposures based on high occurrence values were in the range of 3.10 to 6.96 µg/kg b.w. per day, and of 9.84 to 23.0 µg/kg b.w. per day, respectively (Table 18).

6.2.3.4. Adults

The detailed acute exposure in adults (>18 years) to individual opium alkaloids from pastries, cakes and biscuits based on analysed bakery products occurrence values is summarised in Appendix D, Table D6. Based on the mean and high (95th percentile) consumption and mean occurrence values, the morphine exposures were in the range of 0.09 to 1.80 µg/kg b.w. per day, and of 0.30 to 4.79 µg/kg b.w. per day for adults, respectively. The corresponding exposures based on high occurrence values were in the range of 0.50 to 5.48 µg/kg b.w. per day, and of 1.70 to 14.6 µg/kg b.w. per day, respectively (Table 18).

6.2.4. Acute dietary exposure to opium alkaloids based on consumption data and recipes for foods with high and low poppy seed content

The exposure to poppy seed alkaloids was estimated also based on food consumption data of the Comprehensive database combined with the poppy seed content information collected from recipes of poppy seed containing foods (Appendix C, table C2) and occurrence data of poppy seeds. Two food groups that are common sources of poppy seeds were in focus, namely bread and fine bakery ware.

The "bread" and "fine bakery ware" scenarios were calculated with maximum and minimum poppy seed content of the recipe information (e.g. white wheat bread and rolls and crisp bread decorated with poppy seeds as breads and poppy seed muffins and cakes as fine bakery ware). The exposure estimates were based on average and high (95th percentile) consumption and both mean and high (95th percentile) occurrence data.

The detailed exposures to individual opium alkaloids concerning the "Bread" scenario are presented in Appendix D, Tables D7-10 and summarised in Table 19. The corresponding results concerning the "Fine bakery ware" scenario are presented in Appendix D, Tables D11-14 and summarised in Table 20.

Table 19: Summary of acute dietary exposure to morphine (µg/kg b.w. per day) according to the "Bread" exposure scenario for high and low poppy seed content.

Scenario	Population	Exposure (µg/kg b.w. per day)							
		Mean occurrence				High occurrence (95th percentile)			
		Average consumption		High consumption		Average consumption		High consumption	
		Min[c], LB	Max[c], UB	Min, LB	Max, UB	Min,LB	Max,UB	Min,LB	Max,UB
High poppy seed content[a]	Toddlers	2.98	16.6	8.09	34.2	15.7	86.6	42.7	179
	Other children	3.35	16.8	10.1	39.1	17.7	87.8	53.3	204
	Adolescents	4.24	18.5	11.1	45.8	22.4	96.6	58.3	239
	Adults	1.56	16.5	4.39	34.3	8.20	85.9	23.2	179
Low poppy seed content[b]	Toddlers	0.08	0.67	0.27	1.56	0.44	3.52	1.49	8.14
	Other children	0.14	0.58	0.32	1.37	0.71	3.04	1.67	7.13
	Adolescents	0.10	0.47	0.25	1.12	0.52	2.45	1.31	5.83
	Adults	0.05	0.35	0.11	0.92	0.24	1.81	0.57	4.81

b.w.: body weight; Min: minimum; Max: maximum; LB: lower bound; UB: upper bound.

(a): Exposure scenario based on wheat bread consumption in countries where poppy seeds are commonly used in high amounts, high content of poppy seeds in bread and analysed opium alkaloid levels of poppy seeds.

(b): Exposure scenario based on wheat bread consumption in countries where poppy seeds are mainly used as condiment or decoration, low content of poppy seeds in bread and analysed opium alkaloid levels of poppy seeds.

(c): The average and high (95th percentile) consumption data are calculated per food consumption survey. The table shows the exposure for the minimum and maximum consumption values for all surveys.

Table 20: Summary of acute dietary exposure to morphine (µg/kg b.w. per day) according to the "Fine bakery ware" exposure scenarios for high and low poppy seed content.

Scenario	Population	Exposure (µg/kg b.w. per day)							
		Mean occurrence				High occurrence (95th percentile)			
		Average consumption		High consumption		Average consumption		High consumption	
		Min[(c)], LB	Max[(c)], UB	Min, LB	Max, UB	Min,LB	Max,UB	Min,LB	Max,UB
High poppy seed content[(a)]	Toddlers	11.1	46.6	31.4	117	58.4	243	167	613
	Other children	10.2	51.7	26.6	144	53.6	270	140	753
	Adolescents	14.8	33.7	45.8	106	78.2	176	242	555
	Adults	2.48	28.2	9.23	71.8	13.1	147	48.7	375
Low poppy seed content[(b)]	Toddlers	0.39	2.49	1.40	6.94	2.03	13.0	7.20	36.3
	Other children	0.16	2.31	0.69	6.43	0.83	12.1	3.66	33.6
	Adolescents	0.11	1.48	0.49	4.14	0.60	7.70	2.58	21.6
	Adults	0.05	1.10	0.23	3.23	0.28	5.76	1.23	16.9

b.w.: body weight; Min: minimum; Max: maximum; LB: lower bound; UB: upper bound.

(a): Exposure scenario based on fine bakery ware consumption in countries where poppy seeds are commonly used in high amounts, high content of poppy seeds in consumed foods and analysed opium alkaloid levels of poppy seeds.

(b): Exposure scenario based on fine bakery ware consumption in countries where poppy seeds are mainly used as condiment or decoration, low content of poppy seeds in consumed foods and analysed opium alkaloid levels of poppy seeds.

(c): The average and high (95th percentile) consumption data are calculated per food consumption survey. The table shows the exposure for the minimum and maximum consumption values for all surveys.

6.2.4.1. Toddlers

Based on the high (95th percentile) consumption of bread and high occurrence values of poppy seeds, the morphine exposure for toddlers varied from 42.7 to 179 µg/kg b.w. per day for high poppy seed foods, and from 1.49 to 8.14 µg/kg b.w. per day for low poppy seed foods, respectively (Table 19).

The corresponding morphine exposure estimates based on high consumption of fine bakery ware varied from 167 to 613 µg/kg b.w. per day for high poppy seed foods, and from 7.20 to 36.3 µg /kg b.w. per day for low poppy seed foods (Table 20).

6.2.4.2. Other Children

Based on the high (95th percentile) consumption of bread and high occurrence values of poppy seeds, the morphine exposure for other children varied from 53.3 to 204 µg/kg b.w. per day for high poppy seed foods and from 1.67 to 7.13 µg/kg b.w. per day for low poppy seed foods, respectively (Table 19).

The corresponding morphine exposure estimates based on high consumption of fine bakery ware varied from 140 to 753 µg/kg b.w. per day for high poppy seed foods, and from 3.66 to 33.6 µg /kg b.w. per day for low poppy seed foods (Table 20).

6.2.4.3. Adolescents

Based on the high (95th percentile) consumption of bread and high occurrence values of poppy seeds, the morphine exposure for adolescents varied from 58.3 to 239 µg/kg b.w. per day for high poppy seed foods and from 1.31 to 5.83 µg/kg b.w. per day for low poppy seed foods, respectively (Table 19).

The corresponding morphine exposure estimates based on high consumption of fine bakery ware varied from 242 to 555 µg/kg b.w. per day for high poppy seed foods, and from 2.58 to 21.6 µg /kg b.w. per day for low poppy seed foods (Table 20).

6.2.4.4. Adults

High consumption of bread and high occurrence values of poppy seeds resulted in a morphine exposure for adults from 23.2 to 179 µg/kg b.w. per day for high poppy seed foods, and from 0.57 to 4.81 µg/kg b.w. per day for low poppy seed foods, respectively (Table 19).

The corresponding morphine exposure estimates based on high consumption of fine bakery ware varied from 48.7 to 375 µg/kg b.w. per day for high poppy seed foods, and from 1.23 to 16.9 µg /kg b.w. per day for low poppy seed foods (Table 20).

The morphine exposure calculated based on the assumption that all wheat bread consumed during one day would contain high levels of poppy seeds was highest in adolescents, 58.3 - 239 µg/kg b.w. per day. For the corresponding morphine exposure based on the assumption that all bread consumed during one day would contain only low levels of poppy seeds, the estimated exposure was highest in toddlers ranging from 1.49 to 8.14 µg/kg b.w per day. The about 40-fold difference in the highest exposure estimates between consumers of high and low poppy seed containing bread is mainly based on the different content of poppy seeds in bread and not on the amount of bread consumed. For consumers of high poppy seed foods, the high poppy seed content in bread used for the calculations is possible, but rare. In addition, in the cases of both low and high poppy seed foods, the exposure assessment is likely to be an overestimate because the reduction in poppy seed alkaloid levels caused by the baking process could not be taken into account in this assessment. The morphine content may be lowered through bread baking for about 10-50 % assuming that unprocessed poppy seeds are used for the bread (General et al., 2007).

The morphine exposure calculated based on the assumption that all fine bakery ware consumed during one day would contain high levels of poppy seeds, was highest in children over 3 years of age ranging from 140 to 753 µg/kg b.w. per day for high consumers of the foods, when high occurrence values were the basis for the estimates. For the low poppy seed foods, the corresponding highest morphine exposure concerned toddlers and ranged from 7.20 to 36.3 µg/kg b.w. per day for high consumption, when high poppy seed alkaloid occurrence values were the basis for the estimates.

The morphine exposure based on consumption of fine bakery ware for countries where foods containing high levels of poppy seeds are common together with alkaloid levels in bakery products resulted in exposure estimates in the same range as calculated estimates consumers of low poppy seed foods (Tables 18 and 20). When calculating exposure with opium alkaloid levels analysed from bakery products, the exposure levels based on high occurrence values are clearly lower than estimated using a single portion approach or estimated based on consumption of fine bakery products with high poppy seed content. Since the bakery product consumption was based on consumption of all possible pastries, cakes and biscuits that could contain poppy seeds, these exposure results may overestimate the real exposure. However, the occurrence data for food products were only obtained from Germany, where several measures have been taken during the past years to decrease the opium alkaloid content of poppy seeds on the market and in processed foods (e.g. grinding and steaming or washing as pre-treatment of the seeds) (General et al., 2007; Lachenmeier et al., 2010). In countries where these kinds of measures are not in place, exposure could be higher.

6.2.5. Overall summary of the exposure assessment

Food based exposure to poppy seed alkaloids is mainly based on consumption of cereal products, i.e. breads and fine bakery ware containing poppy seeds (whole or ground) or processed poppy seed filling as ingredient. In addition, poppy seeds are a common ingredient in desserts and certain traditional composite dishes, especially in Central-Eastern European Countries. The exposure to poppy seed alkaloids in these countries is more common and high exposures more probable than where poppy seeds are used mainly as decoration or condiment.

Morphine is the major contributing opium alkaloid to exposure of all the five alkaloids covered in this opinion. The exposure to codeine and thebaine was about 7-8 % of that of morphine and exposure to papaverine and noscapine less than 3 % of that of morphine.

According to the hypothetical acute exposure scenarios of this opinion, the exposure to morphine may be for adults as high as 200 µg/kg b.w. per portion of Polish noodle dish. For children (3-10 years of age) the exposure may reach levels up to 252 µg/kg b.w. per portion of poppy seed cake if poppy seeds are highly contaminated (high occurrence levels). This high exposure can even be exceeded if raw poppy seed-containing foods are eaten in larger amounts or by children. Consuming half (185 g) of an adult's portion (370 g) of the noodle dish results in a morphine exposure of 337 µg/kg b.w. if eaten by a 3-10 year old child. If the influence of processing on the morphine content is taken into account, there might be a reduction of the estimated exposure. For example, the exposure from poppy seed cake consumption by children from 3 to 10 years of age would remain in excess of about 25 µg/kg b.w. per day if grinding and baking reduces the morphine content by up to 90 %.

This high intake could not be verified through the European dietary surveys (actual intake), since only a small number of consumers were evaluated during the data collection phases and due to limitations in capturing poppy seed consumption in general and capturing poppy seed containing seasonal food consumption in the surveys. The highest exposure based on poppy seed consumption reported in three European national dietary surveys and poppy seed occurrence values was 16.4 - 90.9 µg/kg b.w. per day among adults without taking any reducing effect of food processing into account in the assessment.

When the poppy seed alkaloid exposure due to consumed fine bakery ware was estimated based on consumption data from the Comprehensive Database and occurrence values of analysed fine bakery

products in Germany, the highest morphine exposure of 30.7 µg/kg b.w. per day was seen among children of 3-10 years of age.

In a "worst case scenario", in which all fine bakery ware contains a maximal poppy seed content according to European poppy seed recipes and based on occurrence values of analysed poppy seeds, a high morphine exposure of 753 µg/kg b.w. per day was estimated for children of 3-10 years of age. If the possible influence of grinding and baking is taken into account, the exposure would remain in excess of about 75 µg/kg b.w. per day.

The most exposed group was shown to be children of 3-10 years old on a µg/kg b.w. basis.

6.3. Other exposure via oral route

Poppy seeds are used traditionally as an ingredient in warm beverages for calming infants (e.g. poppy seed milk) and also deliberately in poppy seed tea as an agent of abuse or treatment for opioid dependency (Table 21) and incidents of poisoning have been reported (see Section 7.3.5.). The exposure of adults to morphine by the beverages listed in the Table 21 based on high occurrence (95^{th} percentile) values ranged from 72.1 to 721 µg/kg b.w. Heat treatment may reduce the alkaloid content to some extent, but the temperature during preparation will not exceed 100°C. The possible effect of soaking on the poppy seed alkaloid content in these beverages is not relevant, because the total liquid is consumed. The use of these beverages is not regarded as a food use in this opinion.

There is potential for additional exposure to some opium alkaloids and derivatives from licenced medicines (see Section 7.3.).

Table 21: Poppy seed use, content (g/portion and g/100 g) and morphine exposure (µg/kg b.w. per day) of selected European poppy seed beverages.

Country	Beverage	Recipe	Portion weight (g)	Poppy seeds (g/ portion)	Poppy seeds (g/ 100 g)	Exposure (µg/kg b.w.)[a]	Reference
Int[b]	Poppy seed milk	Seeds soaked in water for 4-5 hours	200	30	15	72.1	http://hubpages.com/hub/Poppy-Seeds-Milk-Khus-Khus-Milk
Germany	Poppy seed milk	200 g seed/500 ml milk	200	80	40	192	BfR, 2005a
Int.	Poppy seed tea	500 g seeds/2 l of water	500	100	20	240	http://www.zoklet.net/totse/en/drugs/otc/poppyseedteare179568.html
Germany	Poppy seed milk	400 g seeds/500 ml milk	200	160	80	385	BfR, 2005a
Int.	Poppy seed tea	1200 g seeds/2 l of water	500	188	38	452	http://www.zoklet.net/totse/en/drugs/otc/poppyseedteare179568.html
Int.	Poppy seed tea	Shaken 5 min and let sit for 10 min, repeated up to 1 hour (4 times)	300	300	100	721	http://www.zoklet.net/totse/en/drugs/otc/poppyseedteare179568.html

b.w.: body weight.
(a): Exposure calculated for an adult weighing 73 kg, based on 95th percentile occurrence data.
(b): Int: International.

7. Hazard identification and characterisation

7.1. Toxicokinetics

7.1.1. Morphine

7.1.1.1. Absorption

Based on studies using oral administration of radiolabelled material, morphine is considered to be extensively absorbed from the gastrointestinal (GI) tract of humans (Brunk and Delle, 1974) and rats (Walsh and Levine, 1975; Iwamoto and Klassen, 1977), mainly from the upper small intestine and, to a lesser degree, from the stomach. The absolute bioavailability (20 - 40 %) is reduced by pre-systemic metabolism in the GI tract and liver (Hardman et al., 1996; Forth et al., 2001). The systemic levels of morphine, codeine, and their glucuronides have been reported in humans following consumption of poppy seed food (Westphal et al., 2006).

7.1.1.2. Distribution

Morphine is distributed throughout the body, mostly (65 %) found in the kidneys, liver, GI tract, lungs and spleen, while lower levels (20 %) are present in the brain and muscles (Mullis et al., 1979). Though the brain is its primary site of action, morphine does not cross the blood-brain barrier easily, since 80 % is present in the ionised form. Following intravenous administration, morphine has an apparent volume of distribution ranging from 1 to 4.7 L/kg. Protein binding is reported to be 36 % and muscle tissue binding is reported to be 54 %. Morphine diffuses across the placenta, and traces also appear in milk and sweat (Martindale, 2010). Morphine glucuronides are subject to active transport out of tissues (e.g., hepatic multidrug resistance proteins (Mrp) 2 and 3 in mice (van de Wetering et al., 2007)) as is morphine via the P-glycoprotein in the human GI tract, but apparently not brain (Kharasch et al., 2003).

7.1.1.3. Metabolism

Morphine is metabolised via N-demethylation and O-glucuronidation in the gut and the liver. Glucuronidation is the predominant route of metabolism, producing morphine-3 glucuronide (M3G) (60 %) and morphine-6 glucuronide (M6G) (10 %) predominantly via uridine diphosphate (UDP)-glucuronysyltransferase (UGT) 2B7 and to a lesser extent UGT1A8, while approximately 5 % of the drug is N-demethylated into nor-morphine via the cytochrome P450 (CYP) enzymes CYP3A4 and CYP2C8 (Trescot et al., 2008). In addition other minor metabolites include morphine-3,6-diglucuronide, codeine and morphine-3-ethereal sulphate (AHFS, 2007). Total clearance of morphine by children less than 3 years of age through the developing capacity for UGT2B7-catalyzed glucuronidation is strongly influenced by age with an estimated exponential b.w. scaling factor of 1.44 (Knibbe et al., 2009). The pharmacological effects of morphine glucuronides differ profoundly in that M3G has no analgesic properties while M6G is more potent than morphine itself and can contribute to the overall analgesic effect of morphine.

7.1.1.4. Excretion

About 90 % of morphine is excreted in the urine within 24 hours mainly as M3G (up to 60 %), M6G, and only 2-12 % is excreted as morphine unchanged. Small amounts of morphine glucuronides are excreted in the bile, recirculated enterohepatically, resulting in another 7-10 % of the dose of morphine being excreted in faeces. The elimination half-life of morphine is approximately 120 minutes in humans (Trescot et al., 2008). Oral clearance of morphine is approximately 3-3.5 ml/min/kg b.w. (Eckardt et al., 2000). The fact that lower morphine doses are recommended for older patients has to do with the lower

distribution volume and reduced renal function (Martindale, 2005; Forth et al., 2001). Morphine is also excreted in milk; peak milk levels of 82 or 500 µg/L were observed after 2 doses of 4 mg epidural or 5 to 15 mg parenteral (intravenous (i.v.) or intramuscular (i.m.)), respectively, were administered postoperatively to lactating mothers (at least 1 month post partum) (Feilberg et al., 1989). The reported ratios for morphine concentrations in milk/maternal plasma from several studies appear to range from 0.1 to 4 (Willmann et al., 2009).

While drug interactions with morphine are believed to be rare, studies have shown that drugs that inhibit or induce UGT2B7 may alter the amount of M3G and M6G available and the overall elimination of morphine (Armstrong and Cozza, 2003; Kiang et al., 2005). Similarly, inhibition of P-glycoprotein efflux from the gastrointestinal tract by coadministration of quinidine increased the systemic bioavailability of morphine and its pharmacological actions in humans (Kharasch et al., 2003).

7.1.2. Codeine

7.1.2.1. Absorption

Codeine (as codeine phosphate) is readily absorbed from the gastro-intestinal tract following oral administration. Studies using oral administration of radiolabelled codeine demonstrated extensive absorption from the GI tract of rats (Yeh and Woods, 1969). The maximum plasma concentration is reached after around one hour (Reynolds, 1989; Forth et al., 2001). Bioavailability shows inter-individual variations of 40 – 70 % (Moffat, 1986; Forth et al., 2001).

7.1.2.2. Distribution

Codeine is distributed throughout the body with a volume of distribution of 3.5 L/kg (Moffat, 1986; Baselt and Cravey, 1989) after oral administration. Protein binding of codeine is about 25 % in human serum (Reynolds, 1989). Moffat (1986) states that plasma protein binding is about 7 to 25 %. Codeine penetrates the placental barrier and enters foetal circulation.

7.1.2.3. Metabolism

The most important biotransformations are O- and N- demethylations in the liver to morphine, norcodeine and nor-morphine, amongst others. CYP3A4 produces nor-codeine and UGT2B7 conjugates codeine, nor-codeine, and morphine to the corresponding 3- and 6- glucuronides (Moffat, 1986; Coffman et al., 1998). Because methylation of the hydroxyl group in the 3-position protects against the conjugating enzymes, pre-systemic metabolism of codeine in the GI tract and liver is less than morphine and therefore codeine has a higher oral-parenteral potency ratio (Gilman et al., 1985). The conversion of codeine to morphine occurs in the liver and is catalysed by CYP2D6. Approximately 6–10 % of the Caucasian population, 2 % of Asians, and 1 % of Arabs[17] are "poor metabolisers" (PM), because they have little CYP2D6 activity. Alternatively, CYP2D6 gene duplication produces a so-called "ultra-rapid" phenotype (UM) that is found in approximately 3 % of northern European whites, 5-10 % in southern European whites, and 10-30 % in Arabian and northeast African countries (Kirchheiner et al., 2007). The intermediate phenotype, characterized by the presence of two wild-type alleles, is referred to as extensive metaboliser (EM). Codeine is reportedly less effective for analgesia in EM and PM patients (Kirchheiner et al., 2007). Conversely, UM have been reported to produce up to 45-fold higher concentrations of morphine than PM after codeine administration (Yue et al., 1997). Drug interactions can also alter the CYP2D6-catalyzed metabolism of codeine to morphine (e.g., selective serotonin reuptake inhibitors, which inhibit) or CYP3A4-catalyzed N-demethylation (e.g., erythromycin, which inhibits or hypericin, which induces).

[17] Codeine Information – Facts. Available from http://codeine.50g.com/info/codeine.html. Retrieved 16.10.201013.

Since codeine has a low affinity for opioid receptors it is widely stated that its analgesic effects are due to metabolic conversion to morphine (Meyer, 2000); however, the recognition that codeine administration can produce analgesia in CYP2D6-deficient individuals (so-called "poor metabolisers", see above), is consistent with a therapeutic role for the major metabolite, codeine-6-glucuronide (C6G) (Vree er al., 2000). While the circulating concentrations of C6G are high in patients of all CYP2D6 phenotypes (Vree er al., 2000), its 440-fold lower affinity for μ-opioid receptors *in vitro* relative to morphine and 2.3-fold lower affinity than for codeine itself (Chen et al., 1991; Mignat et al., 1995), suggest that pharmacodynamic effects are derived from codeine and various metabolites, depending on CYP2D6 phenotype (see Sections 7.3.2.1. and 7.5.2.3.).

The CYP 2D6-catalyzed O-demethylation conversion of codeine to morphine has been investigated in 132 Swedish volunteers for whom CYP 2D6 status was established through debrisoquine hydroxylation measurements (Yue et al., 1989). The group was comprised of PM, EM, and UM phenotypes. After oral dosing with codeine phosphate (25 mg), codeine, C6G, nor-codeine-glucuronide, morphine, morphine-3-glucuronides (M3G) and morphine-6-glucuronides (M6G), and nor-morphine were measured in urine from these same individuals using HPLC (Yue et al., 1997). A log-linear relationship was observed between debrisoquine metabolic ratio (CYP 2D6 activity) and the % of O-demethylated codeine metabolites (i.e., morphine-derived) in urine. The range of conversion to morphine-derived species was from 0.34 to ± 0.14 % (n = 18) in PM, 1.7 to 8.7 % in EM, and 15 to ± 9.1 % (n = 24) in UM. Similar experimental design showed similar distributions of codeine conversion to morphine in German men (n = 26) where the mean conversion percentages were 0.4 % in PM, 7.7 % in EM, and 14 % in UM (range 8 to 18 %) (Kirchheiner et al., 2007). These ranges are also comparable to earlier reports of urinary morphine-derived metabolites from codeine (10-21 %) obtained using less reliable analytical methodology and without regard for CYP 2D6 status (Adler et al., 1955; Ebbighausen et al., 1973).

Absolute oral bioavailability of codeine in humans is approximately 5-fold greater than in rats (Shah and Mason, 1990); however, the amount of codeine converted to morphine is approximately 30-fold greater in the rat where the area under the curve (AUC) for morphine/AUC for codeine is 90 % vs. in humans where it is 2.7 % (Shah and Mason, 1990). As a result, internal exposures to morphine from a common oral dose of codeine would be predicted to be approximately 7-fold lower in humans relative to rats. While circulating levels of codeine and active metabolites are useful experimental metrics, it is their levels in the CNS that are believed to determine analgesia and other pharmacological/toxicological effects. Therefore, the CYP 2D6-mediated conversion of codeine to morphine within the CNS may also contribute (Sindrup et al., 1996).

7.1.2.4. Excretion

Codeine and its metabolites are almost fully excreted via the kidneys mainly as glucuronides (BfArM, 2007; Bracher et al., 2004). The codeine elimination half-life is 3 to 5 hours in healthy adults (Gilman et al., 1985); in the case of renal insufficiency it may be between 9 and 18 hours. The elimination of codeine is also slower in older people (BfArM, 2007). Eighty six percent of codeine is excreted within 24 hours, (Gilman et al., 1985; Moffat, 1986) mainly in urine as norcodeine, morphine and glucuronides. Negligible amounts of codeine and its metabolites are found in faeces (McEvoy, 1989). Of the 86 % excreted after an oral dose 40 to 70 % is free or conjugated codeine, 5 to 15 % free or conjugated morphine, 10 to 20 % is free or conjugated norcodeine; unchanged codeine accounts for 6 to 8 % of the dose excreted in urine within 24 hours but this can increase to 10 % if the urinary pH is decreased (Moffat, 1986).

Codeine is excreted in breast milk in which it reaches approximately a 2.5 fold higher concentration than that in maternal plasma (Willmann et al., 2009). The half-life is 3 hours. After administration of 60 mg codeine to breastfeeding mothers, codeine and morphine were detected in the plasma of the babies in probably sub-pharmacological concentrations (Meny et al., 1993). When mothers are treated with single therapeutic doses, a risk to the baby is unlikely except possibly for those maternal/fetal pairs

exhibiting the CYP2D6 ultra-rapid or extensive metabolizer phenotypes (Koren et al., 2006; Willmann et al., 2009).

7.1.3. Thebaine, oripavine, papaverine and noscapine

7.1.3.1. Absorption

Detailed absorption studies are not available for thebaine, oripavine, papaverine and noscapine, (the 3-O-dealkylated derivative of thebaine). However, bioavailability for all is apparently decreased by extensive pre-systemic Phase I and/or Phase II metabolism in the GI tract and the liver. Absolute bioavailability values have been reported in humans for papaverine (0.53, Ritschel and Hammer, 1977) and noscapine (0.30, Dahlström et al., 1982).

7.1.3.2. Metabolism

Metabolism of papaverine, noscapine and thebaine is thought to be dominated by CYP isoforms because papaverine is excreted primarily as the 4'-O-demethylated metabolite (Ritschel and Hammer, 1977), noscapine inhibits human CYP2C9 and CYP3A4 isoform-catalyzed reactions *in vitro* and inhibits S-warfarin metabolism in humans (Ohlsson et al., 2008), and thebaine is extensively converted to several O- and N-demethylated metabolites in mice, including oripavine (Misra et al., 1974). The conversion of thebaine to oripavine is catalyzed by CYP 2D1, the rat orthologue to human CYP 2D6 (Mikus et al., 1991). In addition, evidence has been reported showing the metabolic conversion of thebaine to morphine and codeine, albeit in very low amounts, in rat tissues (Donnerer et al., 1986; Kodaira and Spector, 1988). In addition, a number of phenolic opioids, including oripavine, are substrates for glucuronidation by UGT 2B isoforms (Coffman et al., 1998).

7.1.3.3. Excretion

Detailed excretion studies are not available for papaverine, noscapine and oripavine, but papaverine is excreted in human urine predominantly as Phase II conjugates of phenolic metabolites (Belpaire et al., 1978). Similarly, thebaine and metabolites are excreted primarily in urine (17 and 43 % for thebaine and total radioactivity) and also in faeces (4 and 8 %, respectively (Misra et al., 1974).

7.1.4. Concluding comments

Consumption of poppy seed-containing food produces measurable levels of morphine, codeine, and conjugated forms in people. The oral bioavailability of morphine is reduced by both pre-systemic Phase I and II metabolism in the GI tract and liver. Codeine is less susceptible to this effect. CYP2D6-mediated metabolism of codeine to morphine is thought to be important in codeine-mediated analgesia in all but the CYP2D6 PM phenotype. Extrapolation of codeine toxicity data from rats to humans is complicated by large differences in oral bioavability (lower in rat than in human) and metabolism in the conversion to morphine (greater in rat than in human). Oral bioavailability of papaverine, noscapine, thebaine and oripavine, appears to be low by virtue of pre-systemic metabolism in the GI tract and liver primarily involving demethylation reactions but also glucuronidation. The documented abilities of active transport proteins, including the P-glycoprotein, and CYP2D6 phenotype to modify the pharmacological effects of opium alkaloids suggests that mixture- and/or population-interactions could be relevant to poppy seed consumption in humans.

7.2. Toxicity in experimental animals

7.2.1. Morphine

7.2.1.1. Acute toxicity

Direct toxicity of morphine is related to its pharmacodynamic effect, i.e. stimulation of, preferentially, μ-opiate receptors, but because of the specific distribution of several opioid receptors (i.e., μ, κ, δ) the acute toxicity might be different in pattern between the animal species. Opiate receptor-specific responses are characterized by the feature that they can be antagonized with the antagonists naloxone and nalorphine. The μ-receptor is connected to a Gi-protein, so that responses to receptor activation and inactivation can be monitored (Nikolaev et al., 2007).

Frenk (1983) reported that high dosages (e.g. 300 mg/kg b.w. subcutaneous (s.c.)) in mice and rats induce convulsions, which might be non-specific effects as they are naloxone-insensitive. In some other species, the respiratory depression might be more important as the cause of death (Martindale, 2005). Using lower dosages a sedative effect is observed e.g. in cats (with 0.5-3.0 mg/kg b.w. intraperitoneal (i.p.)) and dogs (0.1-0.5 mg/kg b.w. s.c.), while with higher dosages (cats: 10-20 mg/kg b.w. i.p; dogs 10 mg/kg b.w. s.c.) increases in locomotor activity and emesis, respectively, can be induced (Cowan, 1993).

The oral LD_{50} of morphine in the rat is 335 mg/kg b.w., and in the mouse is 524 mg/kg b.w. (Peterson and Talcott, 2006). However, the acute toxicity of morphine in animals is not directly relevant in the framework of this report, as the effects of morphine on humans are well-known from the clinical literature (see Section 7.3.1.). This indicates that no extrapolation from animal data to humans is needed to characterise acute effects.

7.2.1.2. Repeat dose toxicity

A systematic study on the long-term toxic effects of morphine is not available in the public literature. Most of the studies on chronic administration are focused on tolerance and dependence and the regimens are not easily translated to oral administration as will occur with opiates in poppy seed. Van der Laan et al. (1988) has conducted studies in rats for 4 to 6 weeks with morphine mixed in the feed at concentrations of 1 or 2 g/kg, which led to clear opiate dependence, but no effects on body weight and feed intake. (Daily dose of morphine is equal to 100-200 mg/kg b.w. per os (p.o.)). A clear decrease in feed intake and body weight was observed when morphine was withdrawn resulting in a mild withdrawal syndrome characterized also by changes in spontaneous locomotor activity (Van der Laan and De Groot, 1988; Van der Laan et al., 1991). From this study it was not possible to establish a no-effect level. The pharmacological effects leading to physical dependence can be interpreted as adverse and were already observed at the lowest dose. In later studies lower concentrations of morphine were used (see Section 7.2.1.3.).

7.2.1.3. Immunotoxicity

As drug (opiate) abusers have a higher incidence of Hepatitis B or HIV infection, there was an interest to conduct studies focussing on the potential for immunosuppressive effect of opiates. In addition it became clear that lymphocytes have opiate receptors (Wybran et al., 1979) and are also able to produce pro-opiomelanocortin, which is the precursor of β-endorphin, a peptide hormone stimulating the μ-opiate receptor (Bryant and Holaday, 1993).

Immunosuppressive effects of morphine were described in the 1980's (Donahoe et al., 1985) as a decreased expression of the T-cell E-receptor. Others described suppression of antibody formation to sheep erythrocytes (Lefkowitz and Chiang, 1975), which is probably a T-cell dependent effect. These

effects are likely to be mediated by the opiate receptor, although rather high concentrations in the μM range were needed to show it consistently.

A National Toxicology Program (NTP) study (US Department of Health and Human Services, 1992) is available reporting the effect of morphine-pellet implantation on immunological endpoints. Dosages of 8, 25 and 75 mg/pellet implanted subcutaneously (leading to serum concentrations of 900-1610 ng/ml morphine) led to serious immunosuppression such as a decrease in spleen and thymus weight, associated also with several changes in immune cells. Innate immunity was suppressed as seen as a lower macrophage function, lower Natural Killer (NK)-cell activity and decreased serum C3 levels. The effects could be antagonized by naltrexone, supporting the involvement of the μ-opiate receptor, and partly by RU-486 indicating a possible role of corticosteroid effect.

Van der Laan et al. (1995) found dose-related effects of morphine and methadone of 6 weeks administration of orally administered morphine in rats (food-admixed with 0.25, 0.5, 1.0 g/kg morphine in feed and 0.2, 0.4, 0.8 g/kg methadone in feed). Serum concentrations were around 500 ng/ml for morphine (1.0 g/kg in food) and 150 ng/ml for methadone (0.8 g/kg in food) (Van der Laan et al., 1995), which are much lower than with pellet-administration in mice in the NTP-study mentioned earlier. The effects on the immune function were less severe than those found in mice, and in some cases organ-specific increases were observed instead of suppression. Increases in the mesenterial lymph node weight were observed with morphine and methadone as well. These changes occurred at dose levels that showed only marginal effects on relative liver, kidney and pituitary gland weight. The change in the lymph node was characterized as slight activation in follicles and an increased cell density of medullary cords. Functional tests revealed that morphine had no effect on the T-cell dependent response on Sheep Red Blood Cells (SRBC), but decreased the response to *Trichinella spiralis*. (De Waal et al., 1998). In another study morphine suppressed the NK cell population in spleen dose-dependently already at a dose of 0.25 g/kg in food, but enhanced the populations in lung and in the peritoneal cavity (Van der Laan et al., 1996). No No-Observed-Effect-Level (NOEL) could be established, but with this low dose the effects remained small. Methadone was found to decrease the NK cell population in all three organs at the level of 0.4 g/kg in food (with a NOEL of 0.2 g/kg in food), indicating that the response was not a simple stimulation of one opiate receptor.

These studies detected no other systemic toxicity, i.e. no change in body weight and food intake.

7.2.1.4. Reproductive and developmental toxicity

Morphine may depress sexual activity in male rats by lowering serum luteinizing hormone (LH) and testosterone (Cicero et al., 1976; Adams et al., 1993), effects that appeared to be reversible when morpine administration ended. The prenatal administration of morphine has also been associated with reduced testicular function and spermatogenesis (Siddiqui et al., 1995). In one report from Thailand, chronic exposure to morphine was associated with the induction of galactorrhea in male cynomolgus monkeys (Malaivijitnond and Varavudhi, 1998).

High dosages of morphine to dams caused CNS defects in fetal hamsters, which could be blocked by opioid antagonists (Geber and Schramm, 1975).

Teratogenic effects, such as exencephaly and cryptorchism were described also for mice (Harpel and Gautieri, 1968) using dosages of 100-500 mg/kg b.w. s.c., but were probably related to maternal toxicity (Khera, 1984) and could be blocked by administration of the opioid antagonist naloxone (Jurand, 1985). Lower dosages [10-70 mg/kg b.w. per day s.c. from Gestation Day (GD) 5 to GD 20 in osmotic minipumps] in rats (Fujinaga and Mazze, 1988) and rabbits (Raye et al., 1977) induced no malformations. In the studies on rats and rabbits the primary effect of morphine might be on food intake and b.w. rather than on organogenesis. In the rat study with plasma concentrations of 200 ng/ml (10 mg/kg b.w. perday) up to 670 (70 mg/kg b.w. perday) there was a general effect on body weight (around 20 %) but no malformations were observed, although there was a higher mortality of pups in

the morphine-treated groups at exposure of 35 mg/kg b.w. per day and higher, probably related to withdrawal symptoms. The s.c. dose of 10 mg/kg b.w. per day can be seen as the NOEL.

The rabbit study was conducted with daily s.c. dosing up to 50 or 100 mg/kg b.w., starting with incremental dosing in steps of 10 mg/kg b.w. per day. In spite of identical food intake by the mothers, morphine exposure resulted in a significant reduction in weight and length of the fetus and the weight of the placenta. Morphine given late during pregnancy is associated with placental vasoconstriction with a potential for general fetal effects (Raye et al., 1977).

More recent studies focus on neurobehavioural development in animals, also associated to the question of the effects of opiate addiction during pregnancy, even in case of therapeutic management of the mothers. Vathy (2002) showed that prenatal morphine exposure induces long-term alterations in the adult brain, not restricted to a single brain site or a single neurotransmitter. Other studies in rats included a morphometrical evaluation on the effect of morphine on the brain (Sadraie et al., 2008) or on neural tube development (Nasiraei-Moghadam et al., 2005) identifying another focus of adverse effects in this area. Human data will be discussed under Section 7.3.

There are data that morphine induces DNA damage in germ cells, e.g. in male mice (Badr and Rabouh, 1983) leading to decrease in progeny and early pregnancy loss. The dosages used are rather high, but dose–dependency was difficult to obtain. The later discussion on genotoxicity (see below) does not allow an easy interpretation of the data. Such phenomena on DNA-level are not necessarily the result from direct interaction between the compound and the DNA, but might be caused by other indirect mechanisms, e.g by a delay in transport of semen, as described also for 5HT-agonists, which effects is hypothesized to be mediated by decreasing oxytocin release (De Jong et al., 2007).

Furthermore, administration in the last phase or just before labour causes neonatal respiratory depression. The dosages required for this effect are in the order of magnitude of the therapeutic dose.

7.2.1.5. Genotoxicity

The genotoxicity of morphine is not completely clear. Morphine is non-mutagenic in the *Drosophila melanogaster* sex-linked recessive lethal mutation assay, and in the *Salmonella* or yeast test systems (reviewed by Madden et al., 1979). It did not induce chromosome aberrations in cultured human lymphocytes (Falek et al., 1972).

Morphine (single dose 20 mg/kg, i.p.) induced an increase in the frequency of micronuclei in splenocytes (Sawant and Couch, 1995), also in different mouse strains, DBA and C57BL/6 (Couch and Sawant, 1995). In a recent overview of the International Workshop on Genotoxicity Testing (IWGT) (Tweats et al., 2007) morphine has been discussed as an *in vivo* positive-only compound.

The explanation of this *in vivo* only effect is not fully clear but is likely to be by a non-DNA-reactive and opiate receptor-mediated mode of action, as it could be blocked by naloxone (Sawant and Couch, 1995). Furthermore, it was abolished in adrenalectomized rats. A role of glucocorticoids in these effects was strongly suggested, as plasma from morphine-treated animals (20 mg/kg i.p.) induces micronuclei formation in naïve lymphocytes *in vitro*, and this response is blocked by the steroid antagonist RU486 (Couch and Sawant, 1995).

Shuey et al. (2007) indicate that the increases induced by oxymorphone (also binding to the same μ-opiate receptor) in micronuclei might occurr secondary to hyperthermia, and not due to a direct genotoxic effect of morphine. The suggestion that reactive metabolites are formed in the *in vivo* situation (Li and Lin, 1998), is unlikely based on the role of the μ-receptor (Sawant and Couch, 1995). Opiate as well as glucocorticoid receptors may play a role in morphine-induced apoptosis associated with increased DNA-fragmentation.

It is not clear whether the DNA-damage induced by morphine in sperm cells mentioned in the previous paragraph (Badr and Rabouh, 1983) is mediated by a similar mechanism. The route of administration is the same and only the frequency of dosing (3 times a daily dose of 10-60 mg/kg) is higher with respect to this repeated dosing. It might be speculated that the effect on sperm-DNA is mediated by the same mechanism as the effect on lymphocyte DNA.

7.2.1.6. Carcinogenicity

Carcinogenicity testing has not been reported for morphine *per se*, although the NTP reported a chronic bioassay of codeine as described below (U.S. Department of Health and Human Services, 1996.) Since the AUC for metabolically produced morphine was approximately 90 % of that for codeine in rats treated orally with codeine (Shah and Mason, 1990) and 0.3- to 11-fold that for codeine given in the diet (Yuan et al., 1994), the observed absence of carcinogenicity in the codeine rat bioassay encompasses an assessment of morphine exposures of a similar magnitude. Dillenburg et al. (2008) studied the possibility that morphine (around 5 mg/kg b.w. per day after 23 weeks of administration as approaching opium ingestion in rural areas) would stimulate the carcinogenic action of diethylnitrosamine in the esophagus in rats, but did not observe an effect.

7.2.1.7. Concluding comments

Morphine is known as a potent pharmacologically active substance with its specific actions usually mediated via the specific μ-opiate receptor. Acute toxicity data in animals are available, but due to species-specific responses, the data are not easy to interpret with regard to their relevance for humans. As morphine is widely used in clinical practice for analgesia the human data are discussed later in this opinion.

Chronic toxicity has not been systematically evaluated. Some data reveal immunosuppressive actions of opiates at dosages that also induce physical dependence, which may be relevant for the sensitivity of opiate addicts to infectious agents.

The data in rats and mice clearly show the dose-dependency with marginal effects in rats at a serum concentration of 200 ng/ml, resulting from an oral dose of 60 mg/kg b.w. Developmental toxicity studies in animal species seemed to be not conclusive. Developmental abnormalities were observed in 2 out of 4 species but this difference in sensitivity might be rather a result of differences in exposure being lower in the species with no pronounced malformative effects (rats and rabbits). The (*in vivo* only) genotoxicity of morphine has been discussed for a long time, but there is growing evidence that these effects can be explained by an indirect, non-DNA reactive, mechanism of morphine, e.g. by inducing hyperthermia in certain species via an opiate receptor-mediated mechanism, which might be caused by species-specific systems. Although carcinogenicity data for morphine itself are lacking, based on the lack of carcinogenicity of codeine which is metabolised to morphine, the CONTAM Panel concluded that morphine is unlikely to be carcinogenic.

7.2.2. Codeine

7.2.2.1. Acute toxicity

For codeine, the acute oral, i.v. and s.c. LD_{50} values in rats are 427, 75 and 229 mg/kg b.w., respectively. In the case of codeine phosphate the acute oral, i.v., s.c. and i.m. LD_{50} values in rats are 266, 54, 365 and 208 mg/kg b.w., respectively (Sax and Lewis, 1989). The acute toxicity of codeine in animals is not directly relevant in the framework of this report, as the effects of codeine on humans are well-known from the clinical literature (see Section 7.3.2.). This indicates that no extrapolation from animal data to humans is needed to characterise acute effects in man.

7.2.2.2. Repeat dose toxicity

Codeine was examined and assessed by the American National Institute of Health (NIH) within the NTP (US Department of Health and Human Services, 1996). Male and female F344/N rats and B6C3F1 mice were given codeine (99 % pure) in feed for 14 days, 13 weeks or 2-years.

7.2.2.3. Subacute toxicity

14-day studies

F344/N rats were given 0, 1562, 3125, 6250, 12,500, or 25,000 ppm codeine in feed for 14 days, which resulted in daily doses of approximately 125, 250, 450, 650, or 750 mg codeine/kg b.w. to males and 125, 250, 500, 700, or 300 mg/kg b.w. to females (US Department of Health and Human Services, 1996). Dose-dependent deaths occurred from 6250 ppm. Final mean body weights and mean body weight gains of all exposed groups except 1562 ppm females were significantly lower than those of the controls. No chemical-related gross lesions were observed in rats at necropsy. Thickening of the forestomach mucosa (hyperplasia and hyperkeratosis) and lymphoid depletion of the thymus in exposed males and females and testicular degeneration in exposed males, observed primarily in the 12,500 and 25,000 ppm groups, were associated with decreased survival and increased morbidity in these groups.

B6C3F1 mice were given 0, 781, 1562, 3125, 6250, or 12,500 ppm codeine in feed for 14 days, which resulted in daily doses of approximately 150, 300, 600, 1300, or 3000 mg codeine/kg b.w. to males and 200, 400, 750, 1500, or 3000 mg/kg b.w. to females. All mice survived to the end of the study. The final mean body weight of the 3,125 ppm females was significantly greater than that of the controls; the final mean body weight of the 12,500 ppm females and the mean body weight gains of 12,500 ppm males and females were significantly lower than those of the controls. No gross or histopathologic lesions were attributed to codeine exposure (US Department of Health and Human Services, 1996).

13-week studies

Groups of 10 male and 10 female F344/N rats were given 0, 390, 781, 1562, 3125, or 6250 ppm codeine in feed for 13 weeks, which resulted in daily doses of approximately 25, 50, 100, 200, or 450 mg codeine/kg b.w. to males and 25, 50, 100, 250, or 500 mg/kg b.w. to females (US Department of Health and Human Services, 1996). There were no treatment-related deaths during the study. Final mean body weights and mean body weight gains of all groups of males and of females exposed to 1562, 3125, and 6250 ppm were significantly lower than those of the controls. Feed consumption decreased dose-dependently but transiently. There was a mild dose-dependent lymphopenia in females receiving 1562 ppm and above and in 6250 ppm males at the end of the study. There also was a minimal to mild macrocytosis that occurred in all exposed groups of males and in females exposed to 781, 3125, or 6250 ppm. No significant differences were observed in sperm morphology or vaginal cytology parameters. Absolute and relative adrenal gland weights of exposed males and of 3125 and 6250 ppm females were significantly greater. Absolute and relative liver weights of exposed males were significantly lower than those of the controls. Relative thymus weights of 3125 and 6250 ppm males were significantly lower than that of the controls. No treatment-related gross or histopathologic lesions were observed in male or female rats.

In B6C3F1 mice, groups of 10 males and 10 females were given 0, 390, 781, 1562, 3125, or 6250 ppm codeine in feed for 13 weeks, which resulted in daily doses of approximately 60, 120, 260, 460, or 1,000 mg codeine/kg b.w. to males and 60, 130, 280, 530, or 1200 mg/kg b.w. to females. Two male mice in the 3125 ppm group died during week 7. All other mice survived to the end of the study. Final mean body weights and feed consumption of exposed males and females were similar to those of the controls. Abnormal posture was observed in all exposed groups of males. There were no significant differences in hematology or urinalysis parameters in male or female mice. No significant differences in sperm morphology or vaginal cytology were attributed to codeine exposure. Absolute and relative

kidney weights of 3125 and 6250 ppm males were lower than those of the controls. No treatment-related gross or histopathologic lesions were observed in male or female mice (US Department of Health and Human Services, 1996).

7.2.2.4. Chronic toxicity and carcinogenicity

Groups of 60 male and 60 female F344/N rats were fed diets containing 0, 400, 800, or 1600 ppm codeine for up to 106 weeks, with 9 or 10 rats per group evaluated at 15 months (US Department of Health and Human Services, 1996). These exposure concentrations resulted in average daily doses of approximately 15, 30, and 70 mg codeine/kg b.w. to males and 15, 40, and 80 mg/kg b.w. to females. Survival of 400 ppm females was significantly greater than that of the controls; survival of all groups of exposed males and of 800 and 1600 ppm females was similar to that of the controls. The final mean body weight of high dose males and females was approximately 90 % of control. Treatment-related clinical findings were limited to ocular discharge in exposed males and females. Absolute and relative adrenal gland weights of 800 and 1600 ppm males were significantly greater than those of the controls at 15 months. There were no increased incidences of neoplasms attributable to codeine exposure at any site. At 2 years, there were exposure-related decreases in the incidences of adrenal medullary hyperplasia in males and females. The decreased incidences of benign phaeochromocytomas in males and mammary gland neoplasms in females were considered to be related to codeine exposure. Based on increases in adrenal gland weight the no-observed-adverse-effect level (NOAEL) can be concluded to be 15 mg/kg b.w. per day.

Groups of 60 male and 60 female B6C3F1 mice were fed diets containing 0, 750, 1500, or 3000 ppm codeine for up to 106 weeks, with 9 or 10 mice per group evaluated at 15 months. These exposure concentrations resulted in average daily doses of approximately 100, 200, or 400 mg codeine/kg b.w. to males and females. Survival of exposed males and females was similar to that of the controls. Mean body weights of 3000 ppm males and females were less than those of the controls from about week 13, and the final mean body weights of these groups were 86 % and 82 % those of the respective controls. There were no increased incidences of neoplasms attributable to codeine exposure at any site. At 15 months, the incidence of thyroid gland follicular cell hyperplasia in 3000 ppm males was significantly greater than that of the controls, and this lesion was observed in 1500 and 3000 ppm females. At 2 years, the incidences of follicular cell hyperplasia in all exposed groups of mice were significantly greater than those in the controls, but there were no increases in thyroid gland follicular cell neoplasms. The incidence of centrilobular fatty change in the liver of 3000 ppm males was significantly lower than that in the controls at 15 months, and the decreased incidence appeared to be related to exposure level. At 2 years, the incidences of eosinophilic foci, foci of fatty change, centrilobular cytomegaly, and centrilobular fatty change in 3000 ppm males were lower than those in the controls. The incidence of hepatocellular adenomas and the incidence of hepatocellular adenomas or carcinomas (combined) in 3000 ppm males and females were significantly lower than those in the controls; this was considered to be related to lower body weights in these groups (US Department of Health and Human Services, 1996). Based on the increased incidence of thyroid follicular cell hyperplasia at all dose levels at 2 years, the NOAEL was concluded to be less than 100 mg/kg b.w. per day.

In summary, codeine was tolerated in rats and mice for up to 2 years at dose levels of up to 70 and 400 mg/kg b.w. per day, respectively with no increased incidence of tumours at any site in either species. Slightly lower incidences of tumours in high dose animals of both species compared with control may have resulted from suppression of weight gain at this level. The latter effect on body weight confirmed that the doses evaluated were satisfactory in terms of meeting maximum tolerated dose (MTD) criteria. The chronic NOAELs for non-tumour endpoints were 15 mg/kg b.w. per day in for rats and less than 100 mg/kg b.w. per day in mice.

7.2.2.5. Immunotoxicity

To investigate the effects of centrally acting antitussive drugs, codeine and morphine, on the humoral immunity in the respiratory tract, male guinea pigs were immunized either systemically, i.p. or locally, intratracheally (i.t.), with SRBC. The development of plaque-forming cells (PFC) was determined using the spleen (S-PFC) and tracheobronchial lymph node cells (T-PFC). Codeine (15 mg/kg) given prior to the immunization inhibited the number of S-PFC. Codeine (3, 15 mg/kg) and morphine (1, 5 mg/kg) given before and after the immunization markedly inhibited the number of T-PFC, dose-dependently. These results indicate that codeine and morphine (see above) affect humoral immunity both locally in the respiratory tract and systemically, which cautions against use in respiratory diseases (Yanaura et al., 1983).

7.2.2.6. Developmental toxicology

In animal experiments on developmental toxicity in which codeine was given in the drinking water, NOAELs were established for developmental toxicity of 20 mg codeine/kg b.w. per day for hamsters and 150 mg/kg b.w. per day for mice whereas the NOAELs for maternal toxicity were 100 mg/kg b.w. per day for hamsters and 300 mg/kg b.w. per day for mice (Williams et al., 1991). Thus codeine showed evidence of selective fetal toxicity as seen by decreased fetal body weight at doses below those producing maternal toxicity in both species.

In an oral rat study at 10, 35 or 120 mg codeine/kg b.w. per day from GD 6 to 15 the highest dose induced embryolethality, but no malformations. In the case of oral administration of 5, 12.5 or 30 mg codeine/kg b.w. per day in rabbits from GD 6 to 18, no teratogenic effect was observed (Lehman, 1976). From these limited data it is concluded that even at dosages up to those inducing embryolethality there is no evidence of teratogenicity.

7.2.2.7. Genotoxicity

Codeine phosphate did not show any mutagenicity in tests involving four strains of *Salmonella Typhimurium* in the presence or absence of S9. Depending on the concentration it did, however, lead with and without metabolic activation to an elevated incidence of Sister Chromatid Exchanges (SCE) in Chinese Hamster Ovary (CHO) cells. Positive findings were, only obtained with concentrations in the cytotoxic range that caused cell cycle delay (U.S. Department of Health and Human Services, 1996). *In vivo*, codeine did not induce micronuclei or DNA strand breaks, measured by the comet assay, when administered orally to mice (Mittal et al., 2009).

For further findings of animal experiments, reference to the summary of the NTP report should be made (US Department of Health and Human Services, 1996).

It is concluded that there was no evidence of genotoxicity in the studies conducted.

The similar internal exposures (i.e., plasma AUCs) for both codeine and its active metabolite, morphine, in codeine-treated rats in the NTP 2-year study (Yuan et al., 1994) implies conclusions about carcinogenicity are equally applicable to both codeine and morphine.

7.2.2.8. Concluding comments

The relevance to humans of the acute toxicity data in animals are difficult to interpret, therefore it is preferable to refer to the data resulting from therapeutic use of codeine in humans (see Section 7.3.). Developmental studies did not indicate the presence of birth defects. Immunotoxicological findings showed that codeine may affect immunity responses. There was no evidence of genotoxicity using *in vitro* and *in vivo* studies. Long-term oral toxicity studies showed no evidence of carcinogenic activity of codeine in either male or female rats or mice. Decreased incidences of benign phaeochromocytomas of

the adrenal medulla in male rats and mammary gland fibroadenomas and fibroadenomas or adenocarcinomas (combined) in female rats together with a lower incidence of hepatocellular adenomas or adenomas and carcinomas (combined) in males and female mice treated at 400 mg/kg b.w. per day compared with controls may have been related to lower body weights in these groups, due to administration of high dosages of codeine.

7.2.3. Thebaine, oripavine, papaverine and noscapine

7.2.3.1. Thebaine

Data on toxicology of thebaine in the literature are scarce and rather old (1940-1980). Preininger (1972) indicated that thebaine is more toxic and less analgesic than morphine. Important pharmacological data are included in a report of the World Health Organization (WHO) Advisory Group on Narcotics, (WHO, 1980). The report refers mainly to other WHO reports and studies in Narcotic Research Groups, in which apparently the original data on thebaine have been published. The predominant effects of thebaine in animals were observed to be excitatory.

Thebaine induces analgesia in various species, but the effect varies with species and method applied, and some reports are negative. A "narcotic" effect including drowsiness was not observed in the mouse, guinea pig, rabbit, cat or dog. In rabbits, thebaine was able to antagonize morphine-induced respiratory depression.

Thebaine induces inhibition *in vitro* in the guinea pig ileum as well as in the mouse vas deferens, both indicative for a μ-opiate receptor mediated activity (WHO, 1980). Thebaine was, however, much less potent than morphine (0.07 %) and its effect could not completely be antagonized by naloxone, indicative of a different profile. Naloxone antagonized the convulsions induced by thebaine in mice, but with a higher dose as compared with antagonistic dose in relation to morphine.

There are a few suggestions that thebaine is rather a partial antagonist than a pure agonist. Although in rhesus monkeys severe withdrawal signs could be induced after stopping administration of thebaine, thebaine not only failed to suppress morphine withdrawal signs, but precipitated these withdrawal signs as well. This is supported by self-administration studies, as the reinforcing effect of thebaine could not be shown in a cross self-administration experiment with morphine, but only in a continous self-administration experiment with thebaine itself (Hartel et al., 1981).

Recent data with modern techniques confirm the partial agonistic character of thebaine on the opiate receptor (Nikolaev et al., 2007). The affinity of thebaine for the Gi-activity is 1000 times lower as compared with morphine.

Data on electroencephalogram (EEG) and behaviour of rabbits and cats show that morphine and thebaine produce biphasic effects on behaviour, with low doses (up to 1.5 mg/kg b.w., i.v.) being depressant and higher doses (10-20 mg/kg b.w., i.v.) excitatory (Navarro and Elliott, 1971). In cats, the depressant action of both morphine and thebaine is less prominent. In rabbits thebaine antagonized the effects of phenobarbital and potentiated those of caffeine. Also in other species convulsions and excitatory effects were observed, e.g. in skate, frog, sparrow, pigeon, mouse, and dog. The convulsive doses were around 20 mg/kg b.w. (s.c.).

With respect to toxicological endpoints thebaine is more acutely toxic than morphine. In animal experiments a LD_{50} of 114 mg/kg b.w. was determined in rats and a LD_{50} of 54 mg/kg b.w. in mice following oral administration (RTECS, 2003). No other animal experiments are available involving oral administration. Most of the comparative data have been obtained with subcutaneous administration.

No data on chronic dosing, immunotoxicity, genotoxicity, carcinogenicity and developmental toxicity of thebaine are reported.

7.2.3.2. Oripavine

Oripavine (3-O-demethylthebaine) is chemically similar to thebaine, and is its major metabolite. No further data on pharmacological data of oripavine itself are present in the public literature.

Richards and Sadée (1985) refer to a class of oripavines, including its derivatives etorphine, a potent μ-agonist (in use as a veterinary drug, e.g. in horses, and together with acepromazine to immobilize large animals), diprenorphine, a potent μ-antagonist, and buprenorphine, a mixed agonist-antagonist with a strong binding affinity. All three drugs showed lower δ-affinity than μ-affinity *in vivo*, whereas the κ-affinity for the three compounds was variable. Etorphine and diprenorphine are still in use in opioid receptor research as δ-receptor specific compounds (Eisinger and Ammer, 2011).

The WHO report on thebaine, mentioned above, also indicates that oripavine may be the most pharmacologically active metabolite of thebaine, but dependence studies with oripavine are lacking (WHO, 1980). Data from Nikolaev et al. (2007) confirm that oripavine is a full agonist at the μ opiate receptor, with an affinity 50-times lower than morphine.

7.2.3.3. Papaverine

Papaverine is an isoquinoline alkaloid with nonspecific relaxant effects on all types of smooth muscles, and is used for its vasodilatory and spasmolytic effects (Davila et al., 1990). Because of the observed human hepatotoxicity there are data on rat hepatocytes. The mechanism of action leading to hepatotoxicity is not fully clear. It might be immune-mediated or direct metabolite-involved. Acosta et al. (1980) indicates that the lag time of *in vitro* toxicity of papaverine (and in comparison paracetamol) might be due to the period needed for accumulation of toxic metabolites.

Lehoczky (1970a) has described the toxicity of papaverine in rats after subchronic administration of 45 days in dosages of 50 and 100 mg/kg b.w. (p.o.) daily. These doses were tolerated well in these animals as changes neither in blood cell parameters nor in histopathology of the gastrointestinal system, heart, liver, and kidneys were reported. The same group studied 6 months administration of 10 mg/kg b.w. papaverine (p.o. or i.m.) in dogs (Lehoczky, 1970b). Although the study did not describe specific toxicities associated with papaverine, the concluding summary indicates that the condition in papaverine-treated animals was less favourable as compared with those treated with bencyclan. The minimal toxic dose after 6 months in dogs can be taken as 10 mg/kg b.w. (p.o.).

7.2.3.4. Noscapine

Toxicity studies were conducted in 1943 (Krueger et al., 1943 cited by Winter and Flataker (1961)) indicating that noscapine is the least toxic of the opium alkaloids. In a more systematic study, Winter and Flataker (1961) described toxicity studies in rats, mice and dogs.

Acute toxicity studies in mice confirmed the low toxic profile as no LD_{50} could be established up to 3500 mg/kg orally. In rats the lethal dose was around 3000 mg/kg. In dogs antitussive effects could be demonstrated with dosages of 0.5 and 1.0 mg/kg, which is in the order of magnitude of the human therapeutic dose of 15-60 mg per adult. After i.v. administration in mice an LD_{50} could be established, which was not affected by nalorphine.

Sub-chronic toxicity was studied in dogs given a dose of 30 mg/kg b.w. orally for 13 weeks (5 times a week) and no toxic effects were observed in body weight, haematology, and histology of tissues. In rats noscapine was given admixed with the feed at dosages of more than 250 mg/kg b.w. up to 700 mg/kg b.w. per day, but no effects were observed.

Genotoxicity

In 1988 Ishidate and colleagues were the first reporting noscapine as being genotoxic by inducing polyploidy. The CHO-cell line was, however, inappropriate to be conclusive. A few years later similar findings were observed in CHO cell line V79 and in human lymphocytes (Gatehouse et al., 1991; Mitchell et al., 1991).

A serious concern was raised and noscapine was taken from the market in several countries waiting for further research. To clarify if noscapine would have an effect on germ cells *in vivo* a thorough analysis of mouse oocytes was conducted at doses of 20, 120 and 400 mg/kg b.w. (Tiveron et al., 1993). The data indicate that noscapine did not induce *in vivo* delay of the meiotic progression or induction of chromosome malsegregation. No increases in polyploidy or hyperploid oocytes were found. The difference between *in vitro* and *in vivo* results might be explained by the relatively long treatment (24 h) necessary to induce polyploidy *in vitro*. Such a long exposure period at this level will never be reached *in vivo* because of the pharmacokinetics of noscapine. Noscapine exhibits presystemic elimination resulting in a low systemic availability (Karlsson and Dahlström, 1990). A genetic risk of noscapine in humans at therapeutic dosages is therefore concluded to be very unlikely. Even the gastrointestinal tract being exposed to noscapine after oral administration to relatively high concentrations is unlikely to be a risk because of the short period that the cells are exposed to these concentrations (Rauws et al., 1997).

In more recent years another therapeutic application of noscapine has been discovered, i.e. as an orally effective anticancer drug. It was discovered that noscapine binds to tubulin and interferes with microtubule dynamics. In this way noscapine arrests a variety of mammalian cells including drug-resistant variants in mitosis targeting them for apoptosis. In this way noscapine inhibits murine melanoma and lymphoma as well growth of human breast tumors implanted in nude mice (Ye et al., 1998). In all these cases the toxicity remains low (Aneja et al., 2007). These effects can be seen by oral administration (via drinking water 15mg/ml, estimated dose around 1.2 mg/kg b.w.).

Developmental toxicity
Data on developmental toxicity of noscapine is scarce. The most recent report by Martindale (2010) just refers to genotoxicity data from 1991, discussed above.

There are confidential studies in the registration dossier of Kabi Pharmacia, showing no specific reproductive toxicity.

Carcinogenicity
Data on carcinogenicity testing with noscapine are not present in public literature. The use of noscapine as an antitussive drug is intended to be short-term, therefore not warranting life-time carcinogenicity studies in accordance with regulatory guidelines.

7.2.4. Concluding comments

The data on the pharmacology of morphine, codeine and the other opium alkaloids in poppy seed samples reviewed above indicate that morphine is the most active opiate compound, with codeine as the second. Morphine is known to act mainly via the most important opiate receptor, the μ-receptor, and because of its widespread distribution in the body it exerts a high number of different effects, both at the central nervous system and in the peripheral nervous system. Most pharmacological effects are well-characterized with respect to their dose-response character as well as with respect to tolerance development after repeated administration. The pharmacology of codeine is strongly related to that of morphine, as it acts mainly as a precursor of morphine itself (both in humans as in mammals) and codeine-6-glucuronide, which shows also agonistic activity at the the same μ-receptor.

For oripavine and thebaine only very limited data are available. They show only partial agonistic activity at the μ-receptor, and especially thebaine has been shown to act as an antagonist at higher dosages.

The other opium alkaloids reviewed, i.e. papaverine and noscapine, did not show opiate-like behaviour in their pharmacology, papaverine acting as a smooth muscle relaxant, and noscapine as an antitussive agent.

The toxicity of the opiates is strongly related to their pharmacological effects. Acute toxicity of morphine leads to sedation and respiratory depression, although at high dosages excitatory effects were observed, which could not be ascribed, however, to opiate receptor stimulation codeine as a less potent opiate hardly shows these excitatory effects. Repeated administration of morphine, such as in a subchronic 28-day oral route study, showed an immunosuppressive effect without further affecting body weight and organ weight indicative of a specific action on the immune system, while similar effects of codeine, although reported, were clearly expressed to a lower extent as with morphine.

Thebaine is claimed to be more toxic than morphine probably because of its opiate-antagonistic properties. This might be true too for oripavine, although not documented very well. Both alkaloids are only being used as precursors for other therapeutically useful derivatives.

The data on morphine and codeine indicate neither a direct genotoxic effect, nor a carcinogenic hazard. Developmental toxicity studies do not suggest a teratogenic effect for morphine or codeine, although higher dosages may lead to some degree of placental vasoconstriction leading to embryo-fetal toxicity.

In summarising the most prominent side effects of the most prominent opium alkaloids in poppy seed samples, morphine and codeine, are sedation and respiratory depression. As morphine and codeine are in use as human therapeutic compounds, no extrapolations have been conducted from the animal data as the human data are more relevant.

7.3. Human data

There are an enormous number of studies on morphine and codeine in the scientific literature, which have been extensively reviewed in the context of pharmaceutical uses. Therefore, the CONTAM Panel decided to use recent reviews in pharmaceutical reference books, such as Martindale (2010), as the primary basis for its review of the data.

7.3.1. Morphine

Morphine is the main active component of opium. It is used for medicinal purposes as morphine sulphate pentahydrate or as morphine hydrochloride trihydrate.

7.3.1.1. Pharmacodynamics

For opioids (agonists and antagonists with morphine-like activity including natural and syn-thetic opioid peptides) there are three types of receptors in humans, the mu (μ)-, delta (δ)-, and kappa (κ)-receptor. Morphine has high affinity to the μ-receptor as an agonistic ligand. Of the endogenous opioids the endorphins (endogenous opioids) are widespread in the organism and involved in controlling various body functions. Several mammalian species also contain endogenous morphine and codeine bio-synthesised from L-tyrosine, however, only in traces; their physiological relevance is unknown (reviewed in Stefano et al., 2008). Activation of the μ-receptors leads to analgesia, mainly on the supraspinal level, euphoria, dependence, miosis, respiratory depression, cough calming and obstipation. In addition to supraspinal there are also spinal points of attack (Amann and Zenk, 1996; Hänsel et al., 1999; Poeaknapo et al., 2004; Trescot et al., 2008; Aktories et al., 2009).

Morphine has an analgesic effect by targeting various levels of the CNS. It is well established that the analgesic effects of morphine arise from its ability to directly inhibit the ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that

descend from the midbrain via the rostral ventromedial medulla to the spinal cord dorsal horn. Opioid peptides and their receptors are found throughout these descending pain control circuits. It has been hypothesized that morphine creates an unrealistic feeling of well-being (euphoria) by increasing the release of dopamine in the *nucleus accumbens*. In this way, it reduces fear in conjunction with acute pain, which contributes also to the antinociceptive effect. People suffering from chronic pain do not benefit from these positive mental side effects but they are also not at risk of becoming dependent. There are reports of light-headedness, impaired consciousness and mood swings in the case of pain patients and healthy individuals after being given morphine. Miosis (pupil constriction) is a common occurrence following consumption of μ-receptor-agonistic opioids (Golianu et al., 2000; Brunton et al., 2006; Aktories et al., 2009).

Morphine depresses respiration leading in high doses of morphine poisoning to respiratory arrest. The primary mechanism of respiratory depression by morphine involves a reduction in the responsiveness of the brainstem respiratory centers to CO_2. Morphine also depresses the pontine and medullary centers contributing to the regulation of respiratory rhythmicity. Natural sleep also produces a decrease in the sensitivity of the medullary center to CO_2 and the effects of morphine and sleep are additive. Low-level respiratory depression can be triggered by morphine in healthy subjects, even at standard therapeutic doses, but not in patients suffering from severe pain (in the absence of underlying pulmonary dysfunction). In this case pain stimulates respiration and counteracts the morphine effect. In pain-free individuals therapeutic doses of morphine depress all phases of respiratory activity (rate, minute volume, and tidal exchange). The diminished respiratory volume is due to a slower rate of breathing. The reduction in respiratory rate caused by higher doses of morphine can initially be compensated consciously. In the case of a further increase in dose, periodic respiration and finally respiratory arrest can occur. The effect of morphine to reduce the sensitivity to hypercapnia[18] and to lower ventilation is used in the treatment of dyspnoea. As morphine dampens the reflex excitability of the cough centre in the *medulla oblongata*, it has an antitussive effect (Brunton et al., 2006; Wang and Teichthal, 2007; Koehler et al., 2010; Mahler et al., 2010).

The nausea and vomiting frequently induced by morphine also result from its effects on the *medulla oblongata*. However, they are temporary and disappear after repeated administration. In the case of bedridden patients, morphine does not influence blood pressure. Upon standing, therapeutic doses of morphine can produce a drop in blood pressure because of peripheral vasodilatation, reduced peripheral resistance and inhibition of the baroreceptor reflex (i.e., orthostatic hypotension). A low grade bradycardia (cardioinhibition) may occur. Central effects also include inhibition of the secretion of releasing hormones by the hypothalamus which regulate the pituitary gland. Effects on the hypophyseal-hypothalamic axis may lead to changes in the hormone status of corticoids, sex hormones, prolactin, and the antidiuretic hormone. Consequently, corresponding manifestations or clinical symptoms are possible. Finally, a drop in temperature and muscle rigidity are possible with further central effects of morphine (Golianu et al., 2000; Brunton et al., 2006; Aktories et al., 2009).

Morphine increases the tone of the GI tract and reduces motility with the consequence of spastic obstipation. Stomach motility is already reduced at relatively low doses of morphine. As a consequence of the contraction of the pylorus as well, the chyme only leaves the stomach slowly. In the ileum there is, in addition to increased tone, an inhibition of peristalsis. Colon peristalsis is slowed down and the defaecation reflex is suppressed. Morphine leads to a contraction of the gall bladder musculature and the *sphincter oddi* which leads to bile congestion. Therapeutic doses of morphine can increase the tone and amplitude of urethral contraction. Morphine leads to spasms of the bladder sphincter and inhibits the miction (bladder emptying) reflex. This means that, after administration of therapeutic doses of morphine, urinary retention may occur and catheterisation may be necessary. Therapeutic morphine doses can lead to a widening of blood vessels in the skin. Frequently, there is flushing of the face, neck and thorax which, in some cases, can also be attributed to histamine release. Furthermore pruritus (itching skin) can occur. In asthmatics bronchoconstriction may occur as a consequence of histamine

[18] Hypercapnia: too high concentration of CO_2 in blood.

release. From *in vitro* and animal studies different effects of morphine are reported on components of the immune system; however their clinical relevance cannot be assessed at the present time (Hardman et al., 1996; Aktories et al., 2009).

The pharmacological effects of morphine glucuronides differ profoundly in that M3G has no analgesic properties while M6G contributes to the overall analgesic effect of morphine (Wittwer and Kern, 2006; Van Dorp et al., 2008).

Morphine effects in healthy test persons in comparison to patients suffering from pain
Patients with pain tolerate larger doses of morphine than pain-free patients without severe side effects. The pain counteracts due to its stimulatory effect sedation and even respiratory depression (Twycross, 1990; Brunton et al., 2006). In contrast to patients with pain, healthy persons are more likely to show nausea, vomiting, feeling of drowsiness, difficulty in mentation, apathy and lessened physical activity in consequence of therapeutic doses of morphine (Brunton et al., 2006). In healthy individuals respiratory depression is observed after oral therapeutic standard doses of morphine (Aktories et al., 2009).

7.3.1.2. Therapeutic applications and dosage

Morphine is mainly administered via the oral or parenteral routes to treat severe and extreme pain (e.g. cancer-associated pain, postoperative pain). Furthermore, it is used as a hypnotic drug primarily when pain is the cause of insomnia. To alleviate dyspnoea morphine is administered in relatively low doses (Martindale, 2010). At very high doses it can be used as an anaesthetic.

Treatment of severe pain
The scientific literature points out the difficulty of establishing a standard dose for morphine due to a large variation in individual sensitivity to morphine in therapeutically desired effects and side effects (Hanks, 1995; BfArM, 2004). A slow titration starting at low oral doses is recommended to reduce the incidence of typical initial adverse events (drowsiness, dizziness, confusion, nausea, vomiting) and to achieve pain relief (Hanks, 1989; Pergolizzi et al., 2008). A dose range of 2.5 to 2500 mg (usually however below 100 mg) is given for oral pain therapy with morphine sulphate pentahydrate (equivalent to 1.9 mg – 1900 mg morphine) as the single dose to be administered every four hours (Martindale, 2005). Similar figures are reported by other authors indicating that oral doses are usually equivalent to 5 – 20 mg of morphine every 4 hours given as an aqueous solution of the hydrochloride or sulphate or as immediate-release or modified-release tablets (Martindale, 2010). These indications are in agreement with reports of Hanks et al. (2001) and Pergolizzi et al. (2008).

With immediate-release formulations, the maximum effect can be achieved in as little as 30 minutes after oral administration and the effect of a single dose lasts normally for 4 - 6 hours (Hardman et al., 1996; BfArM, 2004; Merck, 2010).

Sustained or modified release formulations are used to increase patient compliance. There is no evidence that the 12- or 24-hourly formulations are different in their relative analgesic potency compared to immediate-release formulations providing the same daily dose (Hanks, 1989; Klepstad et al., 2003; Pergolizzi et al., 2008).

Single doses of modified-release formulations for pain treatment of adults usually range from doses equivalent to 3.75 mg - 200 mg morphine resulting in doses of 7.5 - 400 mg morphine per day (corresponding to 0.125-6.67 mg/kg b.w. per day for an adult weighing 60 kg (BfArM, 2005)).

Older patients (over 75 years) may be more sensitive to morphine (Hardman et al., 1996). The dose must also be reduced in the case of hepatic insufficiency (Blaschek et al., 2006; Morant and Senn, 1991). An effect is, however, only to be expected from low doses in the case of opium alkaloid-naive patients who have not developed tolerance from prior treatment with opium alkaloids (Martindale, 2010).

Table 22 provides examples for a comparison of morphine doses recommended for pain therapy in children of different age and adults, referring to oral immediate-release forms (aqueous solutions or tablets) (BfArM, 2004; Merck, 2010).

Table 22: Examples of recommended doses for orally administered morphine for pain therapy in children and adults (immediate release forms).

Age Group (body weight (kg))	Single Dose Morphine Hydrochloride Trihydrate Dosage (*Equivalent Morphine Dosage*)		Total Daily Dose Morphine Hydrochloride Trihydrate Dosage (*Equivalent Morphine Dosage*)	
	Dose (mg) (BfArM, 2004; Merck, 2010)	**Dose (mg/kg b. w.)[a]**	**Dose (mg) (BfArM, 2004; Merck, 2010)**	**Dose (mg/kg b.w. per day)[a]**
Children up to 2 years (up to 12.5 kg)	Up to 2.5 *(Up to 1.9)*	0.20 *(0.15)*	Up to 22.5 *(Up to 17.1)*	1.80 *(1.37)*
Children 2 - 6 years (12.5 - 20 kg)	2.5 – 5 *(1.9 – 3.8)*	0.20 – 0.40 *(0.15 – 0.30)*	15 - 30 *(11.4 – 22.8)*	1.20 – 2.40 *(0.91 – 1.82)*
Children 6 -12 years (20 - 40 kg)	5 – 10 *(3.8 – 7.6)*	0.25 – 0.50 *(0.19 – 0.38)*	30 - 60 *(22.8 – 45.6)*	1.50 – 3.00 *(1.14 – 2.28)*
Adolescents 12 - 16 years (40 - 50 kg)	10 – 20 *(7.6 – 15.2)*	0.25 – 0.50 *(0.19 – 0.38)*	60 - 120 *(45.6 – 91.1)*	1.50 – 3.00 *(1.14 – 2.28)*
Adolescents > 16 years and adults (60 kg)	10 – 60 *(7.6 – 45.6)*	0.17 – 1.00 *(0.13 – 0.76)*	360 *(273.3)*	6.00 *(4.56)*

b.w.: body weight.

(a): Where dose ranges are shown, the dosage in mg/kg b.w. or mg/kg b.w. per day have been calculated using the lower body weight shown in the first column.

Carbajal and Simon (1995) indicate for morphine an initial daily dose of 0.5 up to 1 mg/kg b.w. per day as the lowest oral therapeutic dose for sedation and analgesia for children. It is divided into 6 individual doses, i.e. 0.083 up to 0.17 mg/kg/b.w., if not effective, it can be increased by 50 %. Histamine release, hypotonia and obstipation are indicated as the side effects of this dose. The dosage information does not refer to a specific children's age (Carbajal and Simon, 1995). It is assumed that the pharmacokinetics of morphine in children are similar to those of adults (Martindale, 2010). Neonates, however, have a longer half-life for morphine, because of their immature P-450 system and reduced renal clearance. Furthermore, the immature blood-brain barrier can lead in their case to elevated morphine concentrations in the brain. Neonates are known to develop convulsions (Golianu et al., 2000; Llewellyn et al., 2000) at body weight-adjusted doses of morphine that are otherwise routinely given to children. Attention is drawn to an elevated sensitivity of neonates vis a vis respiratory depression (Martindale, 2005).

Treatment of dyspnoea

Morphine has been advocated as a treatment for breathlessness/dyspnoea which may develop as a main symptom of several advanced lung or heart diseases (e.g. cancer, chronic obstructive pulmonary disease, lung emphysema) because it is known to reduce ventilatory drive in response to carbon dioxide, hypoxia and exercise. In addition, the sedating effect of morphine is expected to reduce anxiety (Poole et al., 1998). Thus the decrease in respiratory effort in the treatment of dyspnoea by morphine leading to a reduction in breathlessness is explained by multiple mechanisms of action, including reduction in ventilation, lowering of oxygen consumption, decreasing sensitivity to hypercapnia, reduction in the

central perception of dyspnea (similar to the reduction in the central perception of pain) and decrease of the anxiety associated with dyspnoea (Mahler et al., 2010).

Also for the treatment of dyspnoea in adults 2.5 mg of morphine sulphate (equivalent to 1.9 mg morphine corresponding to 31.7 µg/kg b.w. for an adult weighing 60 kg) is recommended as the lowest oral therapeutic single dose which could be applied every 4 hours resulting in a daily dose of 11.4 mg morphine per day (Davis and Percy, 2006; Martindale, 2010). In many publications the treatment of dyspnoea or breathlessness with morphine is endorsed and attempts are made to find low effective doses to decrease the occurrence of side effects (Boyd and Kelly, 1997; Schönhofer et al., 2001; Jennings et al., 2002; Abernethy et al., 2003; Berrill and Linnasne, 2003; Currow et al., 2011).

Abernethy et al. (2003) evaluated the efficacy of an oral sustained release form delivering 20 mg morphine sulphate per day (corresponding to 15.04 mg morphine per day) administered for 4 days. Participants reported significant improvement of refractory dyspnoea. The authors noted that the chosen daily dose of 15.04 mg morphine per day may be regarded as a relatively high dose in patients who are opioid naïve.

Ten patients with chronic heart failure entered a randomised, double-blind, placebo controlled, crossover pilot study to determine the efficacy of morphine for the relief of breathlessness. The active arm was 4 days of 5 mg[19] oral morphine four times daily (2.5 mg[19] morphine if creatinine >200 micromol/l). There were 2 days wash-out between active and placebo arms. Six out of ten patients indicated that morphine improved their breathlessness (Johnson et al., 2002).

In a very recent study on the treatment of chronic dyspnoea, 10 mg daily of sustained-release morphine sulphate (corresponding to 7.52 mg morphine per day) were administered to 83 participants, and increased in non-responders by 10 mg daily each week to a maximum of 30 mg morphine sulphate daily (corresponding to 22.56 mg morphine per day). The participants were withdrawn if there were unacceptable side effects or no response to the maximum dose. If participants had a 10 % improvement in dyspnoea over their own baseline, they joined a long-term study at that dose. For 70 % of the participants this dose was 10 mg morphine sulphate per day (corresponding to 7.52 mg morphine per day). The mean sustained release morphine dose was 16.5 mg morphine sulphate (corresponding to 12.4 mg morphine per day). Twenty-nine individuals withdrew from the study due to side-effects, 30 participants withdrew for other reasons. Benefit was maintained at three months for 28 (33 %) people. Ranking of breathlessness was reduced significantly (Currow et al., 2011).

Also in view of results showing the equivalence of immediate release forms and sustained release forms delivering the same daily dose of morphine (Hanks, 1989; Klepstad et al., 2003), it was concluded that results obtained in the study of Currow et al. (2011) with sustained release forms providing a mean of 12.4 mg morphine per day would be expected to be similar to those obtained following the administration of an immediate release form with 1.9 mg morphine applied every 4 hours resulting in a daily dose of 11.4 mg morphine per day.

7.3.1.3. Tolerance and dependence

Tolerance development as well as strong physical and psychological dependence occur in conjunction with the chronic intake of morphine and rank amongst its most important adverse reactions. Tolerance can occur in all patients and is not an indication of addiction. Cross-tolerance and cross-dependence develop solely between opioids interacting with the same receptor (Hardman et al., 1996; Forth et al., 2001). Tolerance being defined as the reduction in response (e.g. analgesia) to a drug after repeated administrations is high in the case of morphine and is indicated as a 10 to 20-fold dose increase.

[19] The authors do not indicate if they refer to a salt of morphine.

Tolerance concerns all opioid effects besides miosis and obstipation. There is lower tolerance of the respiratory depressive effect than, for instance, of analgesia (Forth et al., 2001; Aktories et al., 2009).

Dependence consists of two components. Psychological dependence is an initially controllable but later irresistible craving for the drug. It develops from the euphoria-including properties of morphine. Physical dependence is a condition in which the opioids are essential for normal functioning of the body. When the opioid is no longer taken, it manifests in the form of withdrawal symptoms (Aktories et al., 2009). A short-term intake of morphine is not linked to any risk of dependence (Blaschek et al., 2006). The risk of psychological dependence is reduced in patients suffering from chronic pain (Twycross, 1990).

7.3.1.4. Adverse reactions

In the literature it is pointed out that the effects of morphine in healthy individuals may deviate in some cases from those in pain patients. Patients with pain tolerate larger doses of morphine than pain-free patients without severe side effects. The pain counteracts due to its stimulatory effect sedation and even respiratory depression (Twycross, 1990; Brunton et al., 2006). The presence of opioid-sensitive pain protects against the respiratory depressant effect which may occur if the source of opioid-sensitive pain is removed (e.g. by surgery) (Hanks et al., 1981; McQuay, 1989; Koehler et al., 2010; Martindale, 2010). Also in a controlled study in human volunteers it has been shown that experimental pain stimulates respiration and attenuates morphine induced respiratory depression (Borgbjerg et al., 1996). The predominant symptoms in healthy, pain-free individuals given therapeutic doses are nausea and vomiting. Furthermore, there are symptoms of light-headedness, dizziness, difficulty in carrying out intellectual activities, apathy, reduced physical activity and constipation. Respiratory depression is discernible even with doses too small to disturb consciousness. In healthy individuals, signs of respiratory depression are observed after oral standard therapeutic doses of morphine. As the dose is increased, the subjective, analgesic and toxic effects, including respiratory depression, become more pronounced. In contrast to healthy individuals, pain-patients do not develop euphoria. Certain side effects are especially observed directly after onset of therapy in the opioid-naïve patient and attenuate with long-term administration due to tolerance development. This holds e.g. for sedation, drowsiness, confusion, nausea and vomiting (Brunton et al., 2006; Aktories et al., 2009; Martindale, 2010).

There are reports that one single administration of an opioid to a healthy opioid-naive test person leads to central nervous suppression and in psychomotor and cognitive tests to increased reaction time and impairment of motoric coordination, of short-term and longer lasting attentiveness as well as of short-term memory (Vainio et al., 1995). However, no corresponding dose-response data following oral administration are available. A threshold dose beyond which the onset of psychomotor impairment is to be expected following single oral administration of morphine is not known, but would be useful for assessing possible impacts for public safety on highways and in the workplace. In order to determine this threshold dose, double-blind placebo-controlled studies are needed in healthy individuals with a larger number of test persons in order to consider the expected interindividual. There is also a lack of knowledge on how to estimate the impact from possible interacting factors (e.g. alcoholic beverages).

Allergic phenomena and anaphylactoid reactions have been reported after administration of morphine but are uncommon (BfArM, 2005; Brunton et al., 2006).

In the case of well described adverse morphine reactions, a distinction can be made between those under normal and high therapeutic doses (see below). Further adverse reactions mentioned were orthostatic hypotension, neuroendocrine dysfunction (e.g. amenorrhoea), hyperalgesia and central sleep apnoea (Caldwell et al., 2002; BfArM, 2005; Brunton et al., 2006; Farney et al, 2003; Walker et al., 2007; Wang and Teichtahl, 2007; Mogri et al., 2008; Canadian Guideline, 2010; Martindale, 2010; Rote Liste, 2011).

Adverse reactions at usual doses in the treatment of severe pain:
Frequently: nausea, vomiting, obstipation, light-headedness, dizziness, headaches, mood swings (euphoria or dysphoria), changes in cognitive and sensory abilities (e.g. blocking of thought processes, perceptive disorders, confusion), changes in activation (mostly dampening), dryness of the mouth, flushed face, perspiration, restlessness, miosis, disruptions in bladder emptying, hypersensitivity reactions, pruritus.

Occasional: bradycardia, tachycardia, cardiac palpitations, hallucinations.

Adverse reactions at high doses in the treatment of severe pain:
Respiratory depression (death may occur from respiratory failure) and hypotension with circulatory failure and deepening coma, convulsions (particularly in children), muscle rigidity.

Effects on ability to drive and operate machinery
A warning is issued that the oral administration of morphine may impair the ability to drive or to operate machinery owing to changes in attentiveness and reactive skills (BfArM, 2005; Merck, 2010). This is to be expected in particular at the beginning of treatment and when combined with alcohol or sedatives (BfArM, 2005; Merck, 2010). While it is generally recognized that central nervous depression after a unique therapeutic dose of morphine has deleterious effects on reaction time and the speed at which motor tasks are performed, opinions currently differ as to whether steady, long-term treatment with tolerance development in pain patients leads to an impairment of their ability to drive. It seems to be subject to individual variations (Täschner, 1994; Hanks, 1995; Vainio et al., 1995; Strumpf et al., 1997; WHO, 1997; Larsen et al., 1999; Chapman et al., 2002; Kress and Kraft, 2005).

Selected reports on side effects: Low dose studies, studies for the treatment of dyspnoea
Daytime drowsiness, dizziness or mental clouding commonly occur at the start of treatment but resolve when patients are stabilized. Similarly nausea and vomiting, which are observed in up to two-thirds of patients when morphine is started, usually resolve while constipation continues. As a starting dose for opioid naïve patients 5 mg morphine[19] given 4-hourly are recommended (Hanks et al., 2001; Pergolizzi et al., 2008).

An open, uncontrolled study to evaluate the effectiveness of regular oral morphine as symptomatic treatment of dyspnoea in patients with advanced cancer was reported. Thirteen opioid naïve patients were assessed initially, and then 48 h and 7-10 days after starting treatment with oral modified-release tablets, giving twice daily a dose of 10 mg morphine sulphate (20 mg per day, corresponding to 15.04 mg morphine per day). Sedation was the main side effect significantly increased at 48 h. Dizziness or light-headedness was the second commonest side-effect. The authors concluded, that regular, titrated oral morphine may improve dyspnoea in some patients and that the high incidence of side effects, particularly sedation and dizziness, was of concern (Boyd and Kelly, 1997).

Orally administered sustained-release morphine sulphate was compared with placebo, in a randomized, double-blind, crossover trial with two 6-week treatment periods separated by a 2-week washout period, for the treatment of breathlessness in patients with severe chronic obstructive pulmonary disease. The dose of morphine sulphate was titrated from 10 mg daily (corresponding to 7.52 mg morphine per day) to 20 mg twice a day (corresponding to 30.08 mg morphine per day) as tolerated. Almost all the subjects experienced side effects related to morphine, primarly nausea or anorexia, constipation and drowsiness. The authors concluded that the treatment was not effective for the treatment of breathlessness in patients with severe chronic obstructive pulmonary disease (Poole et al., 1998).

In a study in which sustained release morphine sulphate was given in a daily dose of 20 mg (corresponding to 15.04 mg morphine per day) for the management of refractory dyspnoea 3 of 41 patients withdraw from the trial because of nausea and vomiting in two cases, and sedation in one case. Moreover constipation was a common side effect in this study (Abernethy et al., 2003).

As described in Section 7.1.1.2., Johnson et al. (2002) followed ten patients with chronic heart failure treated for 4 days with 5 mg[20] oral morphine (2.5 mg[20] morphine if creatinine > 200 micromol/l) four times daily. Six out of ten patients indicated that morphine improved their breathlessness. Sedation scores increased until day 3, reducing on day 4. Four patients developed constipation.

Currow et al. (2011) report on a very recent study on the treatment of chronic dyspnoea with morphine (see Section 7.3.1.2. for further details). Participants who had a 10 % improvement in dyspnoea over their own baseline joined a long-term study at that dose. For 70 % of the participants this dose was 10 mg morphine sulphate per day (corresponding to 7.52 mg morphine per day). The mean sustained release morphine dose was 16.5 mg morphine sulphate (corresponding to 12.4 mg morphine per day). Twenty-nine individuals withdrew from the study due to side effects, 30 participants withdraw because of other reasons. The side effects reported were drowsiness, confusion, constipation, nausea, vomiting, dizziness and hallucinations.

Forty-two healthy subjects were examined with polysomnography after a bedtime dose of placebo, sustained-release morphine sulphate-dose of 15 mg (corresponding to 11.55 mg morphine), or methadone (5 mg) on each of 3 different nights in a double-blind multiple crossover study in a sleep laboratory in the General Clinical Research Center at an academic medical center. Both opioid drugs significantly reduced deep sleep and increased stage 2 sleep (both $p < 0.01$); but neither of them had an effect on sleep efficiency, wake after sleep onset, or total sleep time. The authors concluded that single sustained-release doses of oral opioid medication can significantly affect sleep architecture in healthy adults. Furthermore, observed reductions in slow-wave sleep following opioid administration may have important implications for the pathogenesis of opioid-use related fatigue (Dimsdale et al., 2007).

Conclusions

The Panel concluded that with sustained release forms in the oral dose range of 7.5 to 15 mg morphine per day (corresponding to single doses of about 1.3 to 2.5 mg morphine taken every 4 hours) side effects such as sedation, dizziness or light-headedness occurred in the onset of therapy of opioid-naïve individuals. These symptoms are considered to be relevant for the ability to drive and operate machinery. This dose range is associated with nausea, vomiting and obstipation. Furthermore, a single low sustained release morphine bedtime dose of 11.55 mg has been shown to significantly affect sleep architecture in healthy adults and lead to reductions in slow-wave sleep. A threshold for the onset of these side effects is not described and it is not known if these side effects occur below the lowest known single oral therapeutic dose of 1.9 mg morphine. It has to be taken into account that healthy persons are considered to be more susceptible to side effects than patients with pain.

7.3.1.5. Interactions

A warning is issued about the following interactions of morphine in medicinal usage (BfArM, 2005; Merck, 2010):

- The parallel administration of morphine and other central depressant drugs like tranquillisers, anaesthetics, hypnotics and sedatives, neuroleptics, barbiturates, antidepressants, antihistamines/antiemetics and other opioids or alcohol can exacerbate the side effects of morphine at normal doses. This applies in particular to the possibility of respiratory depression, sedation, hypotonia or coma. Benzodiazepines may cause apnoea when given with opioids and are contraindicated for the treatment of patients with sleep apnoea (Brunton et al., 2006; Rote Liste, 2011).

[20] The authors do not indicate if they refer to a salt of morphine.

- Pharmaceuticals with an anticholinergic effect (e.g. psychopharmaceutics, antihistamines, antiemetics, drugs to treat Parkinson's Disease) can increase the anticholinergic side effects of opioids (e.g. obstipation, dryness of the mouth or miction disorders).

- The administration of cimetidine and other pharmaceuticals which strain hepatic metabolism can lead to elevated plasma concentrations of morphine (inhibition of degradation).

- Morphine can increase the effect of muscle relaxants.

- In the case of preliminary treatment of patients with specific antidepressants (MAO (monoamine oxidase) inhibitors) (within the last 14 days prior to opioid administration), life-threatening interactions with the CNS, respiratory and circulatory function have been observed after the administration of pethidine. This cannot be ruled out for morphine either. The parallel administration of rifampicin can weaken the effect of morphine.

7.3.1.6. Specific groups

Pregnant women

Morphine crosses the placental barrier. Adequate data are not available that would permit an assessment of the possible teratogenic risk for humans; however, based on a relatively small number of studied exposures, this agent does not appear to increase the incidence of birth defects in humans (Mellin, 1964; Heinonen et al., 1977). Placental vasoconstriction was observed in a woman at 27 weeks gestation who had been treated with morphine chronically for pain control (Collins et al., 2005). Administration of morphine to women during the third trimester was associated with a decrease in fetal breathing movements (Kopecky et al., 2000). The authors concluded that there was also evidence of placental vascular constriction with the potential for adverse fetal effects; however, their data did not show a significant change in measures of placental vasoconstriction.

Newborns of women addicted to morphine and other opioids may develop a withdrawal syndrome during the first several days of life (Cobrinik et al., 1959; Thajam et al., 2010). Respiratory depression and withdrawal symptoms occur in neonates particularly of dependent mothers. Furthermore, foetal cardiac frequency may be reduced. Other clinical signs in neonates are muscular hypertonus, hyperactivity, convulsions, shrill crying, tremor, vomiting, diarrhoea, sneezing and tachypnoae.

Delayed CNS development may be a consequence, as suggested from animal data (see Section 7.2.1.3.), but persistent human defects attributable to the drug alone are difficult to prove, on the one hand because of confounding factors involved in studies of human opiate users. On the other hand, it is difficult to determine neurobehavioural changes at an early age, as the children have to respond or have to use neurolinguistic tools (Jansson et al., 2009; Bandstra et al., 2010). However based on the available animal and human data, a strong case can be made for persistent alterations in neurobehavioral function attributable to opioid effects on the developing nervous system (Zagon and McLaughlin, 1984). The timing and dose of morphine that may be associated with such effects in humans is unknown.

The identification of threshold doses for developmental and reproductive toxic effects is not possible on the basis of the knowledge currently available.

Morphine can prolong or shorten the length of labour (BfArM, 2005; Merck, 2010).

Children

Children under the age of 1 can be more sensitive to the inhibiting effect of morphine on the respiratory function (BfArM, 2004; Merck, 2010).

The American Academy of Pediatrics has stated that the administration of morphine is normally compatible with lactation. Moreover, it also points out that there are no reports of adverse reactions in infants although measurable morphine levels may occur in their blood (Martindale, 2005).

Individuals at higher risks due to certain health conditions (contraindications)

It is known that patients with certain diseases and individuals under special health conditions are at higher risks for development of side effects of morphine, consequently precautionary measures or contraindications are recommended in the medical field due to corresponding known side effects of morphine.

Morphine is generally contraindicated in acute respiratory depression and obstructive airways disease, although opioids such as morphine are used in some forms of dyspnoea. Morphine must be used with caution in patients with compromised respiratory function (e.g. emphysema, apnoea, severe obesity). Morphine can aggravate central or obstructive sleep apnoea. (Brunton et al., 2006; Canadian Guideline, 2010; Martindale, 2010). Brunton et al. (2006) report: "In patients with cor pulmonale, death has occurred after therapeutic doses of morphine. Although many patients with such conditions seem to be functioning within normal limits, they are already using compensatory mechanisms, such as increased respiratory rate. Many have chronically elevated levels of plasma CO_2 and may be less sensitive to the stimulating actions of CO_2. The further imposition of the respiratory depressant effect of opioids can be disastrous".

Children with obstructive sleep apnoea and significant previous recurrent hypoxemia during sleep have been observed to have a higher sensitivity for morphine. This has been concluded from a study in 22 children aged between 19 and 79 months treated postoperatively after adenotonsillectomy with morphine intravenously (Brown et al., 2006).

Since morphine has an inhibitory effect on gastrointestinal motility it has to be avoided in patients at risk of paralytic ileus and has to be used only with caution in obstructive or inflammatory bowel disorders (colitis) (Martindale, 2010).

Morphine leads to histamine release, which can cause bronchoconstriction and vasodilation. Morphine has the potential to exacerbate asthma and should be avoided in patients having a history of uncontrolled asthma (Barnes and Chung, 1989; Brunton et al., 2006; Martindale, 2010). Patients with hypovolaemia and hypotension from other causes are considerably more susceptible to the vasodilatory effects of morphine (Brunton et al., 2006; Martindale, 2010).

Morphine has to be used with great caution in acute alcoholism and convulsive disorders (Martindale, 2010).

Morphine has to be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, renal or hepatic impairment, prostatic hyperplasia, shock, or myasthenia gravis (Martindale, 2010).

7.3.1.7. Intoxications

Acute morphine intoxication normally manifests as three symptoms: miosis, respiratory depression and unconsciousness (coma). Respiratory depression is the most important risk in conjunction with opioid overdose. The direct cause of death is respiratory arrest. For adults doses from 200 mg morphine may be acutely lethal (Frohne and Pfänder, 2004). Other sources give a range of 300 mg to 1500 mg for morphine hydrochloride trihydrate (equivalent to 228 mg-1139 mg morphine) for the oral lethal doses in the case of non-opiatedependent adults whereby babies and infants are far more sensitive (Bracher et al., 2010). In older literature there are data indicating that it is unlikely that a normal pain-free adult would die when given oral doses below 120 mg morphine (Brunton et al., 2006).

In individual cases morphine overdose leads to symptoms ranging from light-headedness and stupor to coma. Blood pressure initially remains normal but quickly decreases as intoxication advances. A persistent decline in blood pressure can lead to a state of shock. Tachycardia, bradycardia and rhabdomyolysis may occur. Body temperature decreases. The skeletal muscles relax; general convulsions may occur particularly in children. As a result of inadequate oxygen supply, any skin areas still receiving blood turn blue (cyanosis). Death is normally caused by respiratory insufficiency or complications like pulmonary oedema (Frohne and Pfänder, 2004; BfArM, 2005; Merck, 2010).

7.3.2. Codeine

Due to its antitussive and analgesic properties, codeine is currently one of the most commonly used drugs according to numerous reports including the WHO. Today most codeine is synthesized from morphine through the process of O-methylation. It was first isolated in 1832 in France by Pierre Robiquet. Numerous codeine salts have been prepared since the drug was discovered. The most commonly used are hydrochloride, phosphate, sulphate and citrate. Others include salicylates and barbiturates.

7.3.2.1. Pharmacodynamics, therapeutic applications and dosage

Codeine also binds with opioid receptors at many sites within the CNS to alter processes affecting both the perception of pain and the emotional response to it. While codeine thus has opiate-agonistic properties, precise sites and mechanisms of action have not been fully determined although it is thought that at least two of these types of receptor, μ and κ, mediate analgesia. Codeine is considered to be a prodrug, since it is metabolised *in vivo* to the primary active compounds morphine and codeine-6-glucuronide (C6G) (Srinivasan et al., 1997; Vree et al., 2000). Up to 20 % of codeine can be converted to morphine, with the remainder either free, conjugated to form C6G, or converted to norcodeine and hydromorphone. It is approximately one twelfth less potent than morphine as an analgesic and has a correspondingly lower dependence-liability than morphine (Vree et al., 2000).

Codeine is used to treat moderately severe pain and also acute diarrhoea but its main use is for the symptomatic treatment of dry coughs. The antitussive effect results from suppression of the cough reflex by acting on the *medulla oblongata* in the cough centre. This effect is far stronger than in the case of morphine. Additionally, codeine has slight sedating properties. The pharmacology is partly mediated by binding to the supraspinal opiate receptors (μ-receptors) where codeine has a relatively low affinity (Bracher et al., 2004; Martindale, 2005; BfArM, 2007).

For the treatment of cough, the following dose ranges shown in Table 23 are recommended (Grove et al., 1976).

Table 23: Recommended single and total daily doses for orally administered codeine salts presented as doses of codeine (= anhydrous codeine base, CAS No 57-27-2, MW: 285.3 g/mol) to treat dry cough (BfArM, 2007).

Age Group (body weight)	Single Dose mg codeine	Total Daily Dose mg codeine
Children aged between 2 – 6 years (up to 12.5 – 20 kg)	2.5 – 5 mg, can be repeated every 6 – 8 hours	Up to 30
Children aged between 6 – 12 years (20 – 40 kg)	5 – 15 mg, can be repeated every 6 – 8 hours	Up to 60
Adolescents over the age of 12 years and adults (40-60 kg)	15 – 44 mg, can be repeated every 6 – 8 hours; in individual cases up to 100 mg	Up to 200

7.3.2.2. Tolerance and dependence

Like all opioids, codeine has dependence potential, with longer term use and high doses resulting in tolerance and physical/psychological dependence. The risk of dependence is low compared to morphine. There is cross-tolerance with other opiates (Forth et al., 2001). However, the withdrawal symptoms are relatively mild.

7.3.2.3. Adverse reactions (healthy adults)

The adverse reactions to codeine are similar to those with morphine but seen to a lesser extent at clinical doses. In the case of chronic administration in usual doses, the most frequent side effect is constipation (Forth et al., 2001; Martindale, 2005). Frequent side effects also include slight headaches, minor sleepiness, nausea sometimes linked with vomiting (particularly at the beginning of treatment) and a dry mouth. At higher doses impaired vision, respiratory depression and euphoria may also occur (BfArM, 2007). In order to examine the dose-dependency of CNS-related impaired vision, test persons were given 30, 60 or 90 mg codeine phosphate. At the doses of 60 and 90 mg visuomotor co-ordination worsened and from 90 mg upwards dynamic visual acuity worsened. Sleepiness occurred at a dose of 90 mg codeine phosphate (Martindale, 2005) with the potential to affect the ability to drive and operate machinery. The interaction between codeine and alcohol or centrally active medicines leads to a major impairment of psychomotor performance. In a double-blind study the administration of 50 mg codeine phosphate alone or in combination with alcohol led to impaired ability in a driving simulation test (Linnoila and Häkkinen, 1974).

'Allergic' reactions to codeine do occur but rarely in a severe form (BfArM, 2007). Typically these result from the consequences of histamine release as a pseudo-allergic response.

7.3.2.4. Interactions

Based on the foregoing clinical pharmacology, the following warnings have been issued about interactions of codeine following oral administration in medicinal usage (BfArM, 2007). The sedating or respiratory depressive effect can be exacerbated by the parallel taking of codeine and other central depressants like sedatives, hypnotics or psychotropics (phenothiazines like chlorpromazine, thioridazine, perphenazine) as well as antihistamines (like promethazine, meclozine) and antihypertensives. Alcohol should be avoided when taking codeine as psychomotor abilities may be considerably diminished (supra-additive effect of individual components). In conjunction with tricyclic antidepressants (imipramine, amitriptyline) and opipramole, codeine-related respiratory depression may be exacerbated. The parallel administration of partial opioid agonists/antagonists like buprenorphine, pentacozine may weaken the effect of codeine.

7.3.2.5. Specific groups

Briggs et al. (1986) examined the results of 5 studies covering the maternal use of codeine during the first trimester of pregnancy. While there was no evidence to suggest a relationship to large categories of major or minor malformations, possible associations were found with respiratory malformations, hydrocephaly, pyloric stenosis, cardiac and circulatory system defects, cleft lip and palate, umbilical hernia and inguinal hernia, dislocated hip and other musculoskeletal defects. The associations of codeine and respiratory and heart malformation was statistically significant whereas the data on the remaining malformations were inconclusive. There are also reports of other malformations from epidemiological studies involving narcotic analgesics, including codeine (BfArM, 2007).

The following information is obtained from reprotox:[21] "More recently, a case-control study of 141 infants with cardiac malformations did not find any association with first trimester use of codeine (Shaw et al., 1992). No significant association with maternal use of codeine during the first trimester of pregnancy was seen in a case-control study of 538 fetuses and infants with neural tube defects (Shaw et al., 1998). Retrospective studies of human pregnancies that involved the first trimester use of codeine have associated this compound with a variety of anomalies, including respiratory tract malformation, pyloric stenosis, inguinal hernia, cardiac and circulatory system defects, and cleft lip and palate (Saxen, 1975; Heinonen et al., 1977; Rothman et al., 1979; Bracken and Holford, 1981). The absence of a consistent pattern in these retrospective associations, however, as well as criticisms of possible bias in the data collected for these observations, make it unjustified to consider codeine as causative of these malformations."

Attention is drawn to the difficulties in interpreting the available studies on development toxicity, e.g. as a consequence of multiple substance exposure (U.S. Department of Health and Human Services, 1996). For instance, studies on the use of codeine to treat pain and a high temperature did not reveal any elevated risk of malformation.

7.3.2.6. Intoxications

Acutely toxic doses of codeine produce unconsciousness, pinpoint pupils, slow and shallow respiration, cyanosis, weak pulse, hypotension and in some cases pulmonary oedema, spasticity and twitching of the muscles. The main and most dangerous effect is respiratory depression. Death from respiratory failure may occur within 2 to 4 hours after oral exposure (IPCS, 1990).

Hallucinations, trembling, uncontrolled muscle movements, mental depression and skin rash may be observed also.

The symptoms of codeine overdose are similar to those of acute morphine intoxication, which of course partly reflects the metabolism of codeine to morphine. Extreme respiratory depression is characteristic and ranks amongst the most frequent severe complications along with pulmonary oedema. Symptoms ranging from extreme sleepiness to stupor and even coma may occur. At the same time, this may be coupled with miosis, vomiting, headaches, urine and faeces retention, cyanosis, hypoxia, cold skin, skeletal muscle tone loss and areflexia and, in some cases, with bradycardia, syncopes and a drop in blood pressure. Particularly in children sometimes only cramps occur (Forth et al., 2001; Bracher et al., 2004).

In clinical terms toxic symptoms are to be expected in adults at a total dose of 0.5 – 1 g codeine (corresponding to 8.3 – 16.6 mg/kg b.w. for an adult weighing 60 kg).

7.3.3. Thebaine, oripavine, papaverine and noscapine

7.3.3.1. Thebaine

Since thebaine is not used pharmaceutically, but only as a starting substance for pharmaceutic synthesis, no information is available about its effects in humans.

7.3.3.2. Oripavine

Since oripavine is not used pharmaceutically, but only as a starting substance for pharmaceutic synthesis, no information is available about its effects in humans.

[21] www.reprotox.org.

7.3.3.3. Papaverine

Papaverine is normally used pharmaceutically in the form of papaverine hydrochloride. It is a myotropic spasmolytic agent which has a direct relaxing effect on smooth muscle. The spasmolytic effect is most pronounced on blood vessels including the coronary, cerebral, pulmonary and peripheral arteries. (AHFS, 1995; Blaschek et al., 2003; Bracher et al., 2010; Martindale, 2010). The effect is attributed to an inhibition of phosphodiesterase (Martindale, 2010). It does not bind to opioid receptors and it does not evoke tolerance and addiction. Papaverine hydrochloride relaxes the cardiac muscle, by directly depressing the excitability of the myocardium, prolonging the refractory period and depressing conduction. It has minimal CNS action, although large doses may have a depressant effect in some patients. Today, papaverine hydrochloride is only rarely used to treat spasms of the gastro-intestinal tract, bile ducts, urinary tracts and bronchi. Orally, 100 mg papaverine hydrochloride (equivalent to 90 mg papaverine) are administered several times daily. The maximum daily dose is indicated as 600 mg papaverine hydrochloride (equivalent to 542 mg papaverine). There was not sufficient evidence to establish the therapeutic value of papaverine hydrochloride and it has been discarded by most clinicians (AHFS, 1995; Bracher et al., 2010; Martindale, 2010).

The side effects which occur after oral administration are dizziness, headache, drowsiness, tiredness, gastro-intestinal disturbance, flush, skin rash, tachycardia, sweating and hypotonia. In conjunction with long-term administration eosinophilia, liver enzyme changes (reversible) and icterus may occur. Overdosage may lead to seizures (AHFS, 1995; Bracher et al., 2010; Martindale, 2010).

The effects of papaverine hydrochloride may be slightly potentiated by CNS depressants and synergism may result from combination with morphine (AHFS, 1995).

7.3.3.4. Noscapine

Noscapine is an opium alkaloid that is chemically related to papaverine. The therapeutic use as an antitussive compound was discovered and developed in the last century (e.g. Konzett, 1955). It does not bind to opioid receptors and is not, therefore, considered to be an opioid. It has neither an analgesic, respiratory depressive nor obstipating effect (Forth et al., 2001). It has no dependence potential (Forth et al., 2001). It has a weaker spasmolytic effect than papaverine. Noscapine demonstrates weak bronchiodilatory properties and stimulates respiration (Blaschek et al., 2003; Bracher et al., 2010). It is used to treat dry cough. For adults the dose is 25-50 mg 3 times daily, for children aged between 3 and 12, 12-25 mg 3 times daily and for children aged between 6 months and 3 years 6-12 mg 2-3 times daily (Blaschek et al., 2003; Bracher et al., 2010; Martindale, 2010). Slight sleepiness, light-headedness, dizziness, headaches, nausea and erythema are indicated as adverse reactions. Reactivity may be impaired (Blaschek et al., 2006; Bracher et al., 2010).

Noscapine may lead to the release of histamine. At high doses it triggers bronchoconstriction and temporary hypotonia (Hardman et al., 1996).

In a non-interventional controlled multicentre study performed by Dahlheim et al. (2010) in paediatric and general medical practices in Germany, 303 patients were orally treated with codeine or dihydrocodeine containing products (97 patients, mean treatment period: 6.8 days; no daily doses reported) or with noscapine containing products (206 patients; mean treatment period: 6.8 days; no daily doses reported). The objective of the study was to acquire valid data on the efficacy and tolerability of these drugs from medical practices. The principal finding of this study was that the antitussive effect of the drugs studied was similar, though the proportion of patients without cough at the end of treatment was higher in the noscapine group. No serious adverse drug reactions were reported in either groups and significantly fewer adverse drug reactions were reported in the noscapine group (2 patients: nausea) compared to the codeine/dihydrocodeine group (7 patients: headache, stomachache, obstipation, dizziness, drowsiness, breathlessness).

The use of noscapine as an anti-mitotic and tubulin-binding novel anti-cancer agent which can be used orally is reported to be investigated (Aneja et al., 2007; Mahmoudian and Rahimi-Moghaddam, 2009).

Pregnancy and lactation

The use of noscapine during pregnancy has been changed because of the discussion on its potential genotoxic effect, which was decided however, to be not relevant for humans (see Section 7.2.3.4). Before 1991, when the discussion started, the use of noscapine during pregnancy was acceptable when there was a medical need, indicating that until then no malformations were observed as being associated with its use.

At a maternal daily dose of 100 to 150 mg noscapine administered to 8 women, noscapine was only found in amounts of 11-83 ng/ml in milk (Martindale, 2010). At a maternal daily dose of 150 mg an uptake of at most 300 ng noscapine/kg b.w. was assumed from milk. A risk to babies from this dose was considered to be unlikely.

Intoxication

During the treatment of tumours orally administered doses in the range of 1 to 3 g were well tolerated by 80 % of patients. The other 20 % suffered from minor sedation, nausea and emesis. Signs of intoxication are only to be expected from a dose of 4 to 6 g per day upwards (Lasagna et al., 1961; Blaschek et al., 2006). Aktories et al. (2009) report cerebral convulsions as an effect of noscapine overdosage (no indication of dose).

7.3.4. Opium

Opium is the air-dried latex obtained by incisions from the unripe capsules of *Papaver somniferum L.* Assuming that the high alkaloid content in poppy seeds is caused by contamination with the latex or that opium alkaloids adhering to poppy seeds have a distribution pattern similar to that found in opium, then the scientific literature relating to the combined effects of the alkaloids in opium may be relevant for alkaloid-contaminated poppy seeds. The toxicity of opium, including possible lethal depression of the respiratory centre, is based primarily on the toxic effect of the main alkaloid morphine.

The overall effect of opium is a result of the combined effects of the individual opium alkaloids, which could be antagonistic, additive or synergistic. It can be assumed that codeine can increase the analgesic and hypnotic effects of morphine.

Opium has a paralysing effect on the CNS, particularly on the respiratory centre. The paralysing effect of morphine is said to be reduced in opium because of the antagonistic effect of thebaine (Blaschek et al., 1998; Blaschek et al., 2003). Noscapine also has a minor stimulatory effect on respiration. The peripheral effect of opium is mainly increasing the tonus of smooth muscles, in particular the sphincter muscles. According to Blaschek et al., (2006) papaverine and noscapine have a relaxing effect on intestinal muscles, thus prolonging absorption of opium alkaloids from the gastrointestinal tract and attenuating side effects of morphine, such as nausea and vomiting. The stimulating effect of morphine on smooth muscle is set against the spasmolytic effect of papaverine. Results of animal experiments show that papaverine may counteract under certain conditions the constipation associated with morphine dosage (Tucci et al., 2008). According to older data, the antidiarrhoeal effect of opium is due to the triggering of atonic obstipation (in contrast to the spastic effect of morphine).

7.3.5. Poppy seeds

In older toxicological standard literature it is reported that the consumption of large amounts of commercially available poppy seeds, e.g. in the form of desserts with approximately 10 – 20 % poppy

seeds or poppy seed cakes, can lead to light-headedness and enteroparesis in sensitive individuals (Wirth and Gloxhuber, 1981).

The symptoms described in a consumer complaint made to the German official food control coincided with the range of adverse reactions to morphine (BfR, 2005a). After eating a dish, which had been sprinkled with a mixture of ground poppy seed and sugar, a consumer observed an "uneasy feeling" in her head, had to vomit and felt like she had a hangover the next day. The person concerned had ingested approximately 75 g blue poppy seeds, containing 210 µg morphine/g and 39 µg codeine/g. This corresponds to intake doses of 16 mg morphine and 3 mg codeine.

Further information from forensic studies in test persons is available concerning the dose range at which morphine ingestion from poppy seeds can lead to adverse reactions.

Moeller et al. (2004) gave various poppy seed-containing products (rolls, cake) to five test persons (three men and two women, aged 22 – 43 years, body weight 55 - 102 kg). The morphine content of the poppy seed samples was 50 mg/kg, unfortunately the amounts of biscuits or poppy seeds consumed were not documented. Directly after consumption the test persons were examined by a trained policeman using a checklist for routine tests for drug consumption in car drivers. This test proved negative. A general practitioner also examined the test persons. Only one of the test persons (55 kg), who had eaten the largest amount of poppy seed cake, reported a slight drug effect involving light-headedness with reduced reaction time of the pupils. No free (unconjugated) morphine or codeine was found in the serum of any of the five test persons. However, after hydrolysis of the morphine conjugates morphine could be detected using GC-MS (highest value: 24 ng/ml). Morphine and codeine could be detected in the urine of all test participants following hydrolysis.

In the investigations by Westphal et al. (2006) and Rochholz et al. (2005) 20 test persons (8 females, 12 males) aged between 19 and 45 consumed between 25 and 250 g poppy seed in the form of poppy seed rice pudding and/or poppy seed cake within 90 minutes. They had been instructed to eat as much as they could. The two poppy seed batches used showed morphine levels of 72.4 mg/kg and 114.3 mg/kg (levels of codeine not indicated by the authors). Morphine intake ranged from 2.9 to 22.9 mg/person, corresponding subject to individual body weights to a range of 40.2 to 317.5 µg/kg b.w. Only half of the test persons had eaten that morning prior to the test. Serum was collected 1, 2, 4, 8, and 24 hours after the end of consumption and checked for the presence of free and conjugated morphine and codeine (for details see Westphal et al. (2006)). Already 1 hour after poppy seed consumption, levels of free morphine greater than 10 ng/ml were measured in 6 of the 20 volunteers. The authors pointed to 10 ng/ml of free morphine in serum being the recommended threshold for the proof of driving under the influence of drugs of abuse with regard to penalties on the basis of § 24a Street Traffic Law (StVG) [22]) in Germany (administrative offence). According to the results of this study, this threshold can be exceeded if the products consumed are made from poppy seeds with high morphine levels.

When the last blood samples were taken, the test subjects described their condition after ingesting poppy seeds. Seven test subjects (intake range: 8.3 to 18.1 mg morphine/person, corresponding to individual body weight-based doses of 109.6 to 274.2 µg morphine/kg b.w.) did not describe any effects, while the 13 others (intake range: 2.9 to 22.9 mg morphine/person, corresponding subject to individual body weights to 40.2 to 317.5 µg morphine/kg b.w.) indicated one or more of the following symptoms: tiredness, lack of drive and energy, difficulty concentrating headache dizziness ongoing dry mouth minor to severe nausea and vomiting, heavy tongue, and impaired field of vision (Westphal and Rochholz, 2005, personal communication). The symptoms listed, aside from "constricted pupils, heavy sweating and dry mouth", had been reported by the test subjects themselves. There was no medical observation as the experiment had not been designed to examine morphine symptoms. The lowest morphine dose at which adverse reactions (listlessness, shortage of power and sleepiness) were reported was also the lowest amount consumed with the poppy seeds meal (2.9 mg morphine/person

[22] Strassenverkehrsgesetz (StVG, 03.05.1909).

corresponding to 40.2 µg/kg b.w.). It can be assigned to a test person who only wanted to eat 25 g poppy seeds and for whom the detection of free morphine in serum was positive but not quantifiable since it was between the LOD of 0.74 ng/ml and the LOQ of 2.82 ng/ml. The authors expressed doubts about whether the symptoms could be attributed to the action of poppy seeds. At the next higher morphine intake level of 8.3 mg in absolute terms, equivalent to 109.6 µg/kg b.w., the test subject did not observe any adverse reactions. Out of the 8 test subjects who ingested 11.4 mg morphine in absolute terms (corresponding to individual body weight-based doses of 134.5 to 190.5 µg/kg b.w.) six test subjects described adverse reactions (nausea, reduced salvia, headaches, dizziness, tiredness, concentration problems) while 2 test subjects did not. At the highest morphine intake levels in the absolute range of 20.0 to 22.9 mg, corresponding to 228.6 to 317.5 µg morphine/kg b.w. all three test subjects manifested morphine-related effects such as e.g., mouth dryness up to 10 hours after intake, slight impaired field of vision, and constricted pupils.

Altogether the sensation of repletion, nausea and tiredness observed by some test persons cannot be interpreted unambiguously as effects of morphine since they could be triggered solely by consuming large amounts of fat-containing foods, but symptoms such as vomiting, dizziness, constricted pupils and dry mouth seem to be clearly linked to morphine intake. The experiment shows the high variation range of individual reactions to morphine intakes.

Bjerver et al. (1982) described an experiment in which 7 test persons consumed one or two pieces of a poppy seed cake, which contained 5 mg morphine per portion (levels of codeine not indicated by the authors). After intake of 5 - 10 mg morphine, obstipation was the only morphine effect observed.

In another study 12 test persons (7 female/5 male, age: 23-58 years) ate 1-4 pieces of poppy seed cake within 30 minutes. The morphine content of the baking poppy seed samples was 206 mg/kg in batch I and 0.6 mg/kg in batch II. The codeine content in batch I amounted to 5.6 mg/kg. In batch II codeine was not detected (LOD not given). Each test subject ingested between 9–55 g poppy seeds (the poppy seed batch used was not indicated). The blood concentration of free (unconjugated) morphine was 8.5 ng/ml after 4 hours in one person and 13.5 ng/ml after 4.5 hours in another. Free codeine in blood was below the limit of determination (not given). The only adverse reaction which occurred in all female test persons was a major sensation of repletion, in some cases nausea. The authors considered it was questionable whether these effects could be attributed to the content of alkaloids in the poppy seed samples or other ingredients. Other side effects like sleepiness, drop in blood pressure or tachycardia were not observed by the authors (Andresen and Schmoldt, 2004).

In other publications there were reports of a sensation of repletion, lethargy (Blaschek et al., 1998) or obstipation (Rochholz et al., 2004) as adverse reactions after consuming poppy seed-containing pastry without morphine or codeine intake being quantified.

Hayes et al. (1987) carried out blood tests in four test persons after consumption of 25 g poppy seeds with 294 mg morphine/kg and 14 mg codeine/kg, equivalent to intake of 7.5 mg morphine and 0.4 mg codeine. After hydrolysis with beta-glucuronidase they showed 82 - 131 ng total (conjugated and unconjugated) morphine/ml serum (2 hours after consumption). The concentration of codeine in serum exhibited a range of 4 to 11 ng/ml 3 hours after ingestion. However, they reported that none of the symptoms caused by morphine, like analytic or euphoric effects, were observed.

Finally, attention is drawn to one intoxication incident as a consequence of which BfR warned against using baking poppy seeds as a sedative for babies (Hanks, 1995). A 6-week old baby suffered from severe health impairment including respiratory depression and had to be taken to intensive care after consuming 75 ml of a milk preparation obtained after straining a mixture of 200 g poppy seeds and 500 ml milk. The morphine level in the serum of the baby on the following day was 4.3 ng/ml. The morphine and codeine content in the poppy seed samples used were determined to be 0.1 % and 0.003 % respectively.

In summary, primarily the investigation reported by Westphal et al. (2006) and Rochholz et al. (2005) are relevant for the purposes of risk assessment. This study shows that the consumption of poppy seeds leading to morphine intakes of 11.4 mg (corresponding to 134.5 – 190.5 µg/kg b.w.) or above must be assumed to be linked to the occurrence of adverse reactions typical for morphine. These findings are consistent with the data provided by the German official food control (light-headedness after intake of 16 mg morphine). Statements on possible adverse reactions at lower doses or about threshold doses, below which health impairment can be ruled out, cannot, however, be derived from the study by Westphal et al. (2006) as only 2 test persons in total were examined in the lower dose ranges. One report of adverse reactions, like e.g. sleepiness, at an intake of 2.9 mg morphine (equivalent to 40.2 µg morphine/kg b.w.) is questionable. Another report mentions obstipation as an additional adverse reaction from poppy seeds associated with morphine intake of 5 - 10 mg (Bjerver et al., 1982).

The results discussed above show that morphine intake from poppy seeds may be of the magnitude of therapeutic morphine doses. They may lead to the spectrum of adverse reactions known from medicinal applications.

It is pointed out that the findings of the available forensic studies are only of limited validity for risk assessment because the test design is oriented towards a different question (e.g. no double-blinding, no recording of sensitive psychomotorparameters, low number of test persons per dose group, no medical diagnosis).

Poppy seed allergy

Immediate-type allergy and anaphylaxis caused by poppy seeds have been described (Crivellaro et al., 1999; Frantzen et al., 2000; Keskin and Sekerel, 2006; Oppel et al., 2006; Panasoff, 2008).

Poppy seed misuse

King et al. (1997) report the case of a 26-year-old baker who had a witnessed first tonic-clonic seizure after which he was delirious and terrified and struggling against hallucinatory figures. At the time of the seizure he was drinking up to 2 l of tea each day made from 4 kg of poppy seeds. After the seizure he reduced this slightly. The authors report that his daily intake of morphine was as much as 280 mg. His morphine concentration in blood was nearly 3 mg/l after the seizure and nearly 2 mg/l 2-3 weeks later. The authors demonstrate the magnitude of the baker's tolerance to morphine by reporting that the average morphine concentration in blood of heroin addicts who die of overdose is 0.6 mg/l (range 0.1 to 3.0 mg/l). Opioid drugs in high dosage are a recognised cause of seizures in patients in hospitals (King et al., 1997).

In 2005 instructions were communicated on the internet on how to use citric acid to extract opium alkaloids for the purposes of misuse from the blue seeds available commercially. After ingesting an extract obtained from 640 g or 350 g poppy seeds by citric acid, signs of tiredness, inactivity and warmth are said to have occurred (Westphal and Rochholz, 2005, personal communication). From another source there are reports of euphoria, relaxation, inactivity, obstipation and abdominal pain following ingestion of an extract prepared with citric acid from 250 g blue poppy seeds (BfR, 2005a).

Poppy seeds in the treatment of dependency

Braye et al. (2007) studied the frequency and nature of poppy seed tea (PST) use by opiate-dependent patients in the form of a written questionnaire. PST is used commonly by opiate-dependent patients attending an alcohol and drug clinic in New Zealand. The study took place at the Community Alcohol and Drug Clinic, Wellington, New Zealand, and comprised 24 opiate-dependent patients attending the clinic. A total of 11 out of 24 (46 %) patients reported having used PST. In five patients currently using PST it represented the major source of opiates, and two had managed to withdraw from use of other opiates with regular PST use. In the four samples of PST which were prepared for analysis, the concentration of morphine ranged between 10 and 105 mg/kg of poppy seeds and the codeine concentration ranged between 3.1 and 11.2 mg/kg of poppy seeds. Different recipes to produce the

infusion were described, varying e.g. in terms of the use of cold or hot water, period of soaking and the use of acidity (citric acid, lemon juice). The patients daily use varied between 0.25 and 3 kg of poppy seed prepared in water. In all cases the PST was taken orally. The patients estimated that 1 kg of seeds had an effect equivalent to 45-160 mg (median 65 mg) of i.v. morphine. Patients reported a median onset of action of 15 minutes and an effect lasting a median of 24 hours. Physical effects reported by the PST users were vomiting, appetite suppression, muscle tightening, or a strange feeling in the legs and a slowing down in respirations. Psychological effects included a feeling of calmness, euphoria, and other symptoms of opiate use. The major limitation of PST use was considered to be the foul taste. The authors see a potential for PST to act as a "gateway drug" by inducing opioid dependence and introducing people to the culture of drug abuse.

Forensic aspects of poppy seed consumption

The detection of free morphine in serum is interpreted under forensic aspects as an indication of exposure to specific pharmaceuticals or drugs, i.e. morphine itself or heroin and codeine, which can be metabolically converted into morphine (Forth et al., 2001). The distinguishing specific metabolite of heroin, 6-acetylmorphine, occurs in blood only for a short period after heroin administration (Rochholz et al., 2005). According to more recent findings (Westphal et al., 2006) the detection of morphine in serum may also be linked to the consumption of poppy seeds containing higher levels of morphine (see above).

7.4. Pharmacokinetic and pharmacodynamic models for opioid alkaloids

A number of physiologically based pharmacokinetic-pharmacodynamic (PB-PK-PD) models that correlate plasma and tissue concentrations of opioids with their pharmacological effects are available and have been reviewed (Lötsch, 2005). A generic physiologically based pharmacokinetic (PBPK) model for morphine in adults was adapted for use in predicting pediatric plasma profiles using age-specific physiological and clearance parameters (Edginton et al., 2006). This model was further refined to relate morphine concentrations in mother/infant pairs derived from maternal consumption of codeine (Willman et al., 2009).

Studies linking pharmacokinetics and pharmacodynamics of morphine action and the role of active transport systems are available in both experimental animal models (Kalvass et al., 2007) and humans (Caraco et al., 1999).

7.5. Derivation of health-based guidance value

7.5.1. Derivation of an acute reference dose (ARfD) for morphine

Morphine is a highly potent narcotic agent that induces a range of toxicological and pharmacological central and peripheral effects (see Sections 7.2.1. and 7.3.1.).

Because morphine-like central nervous effects have been observed in humans following consumption of a single portion of a meal with opium alkaloid-contaminated poppy seeds (see Section 7.3.5.) it was considered appropriate to base its risk assessment for poppy seeds on exposure to morphine. Morphine exhibits genotoxicity *in vivo* only, which is most likely to be by a non-DNA reactive mode of action. The morphine metabolite codeine is not genotoxic or carcinogenic, and it is unlikely that morphine has genotoxic or carcinogenic potential at exposures relevant to dietary exposure from poppy seeds, therefore establishing a health based guidance value is appropriate. Taking into account the short term nature of the effects of morphine the CONTAM Panel concluded that establishment of an acute reference dose (ARfD) was required. Ensuring exposure is below the ARfD would also protect against possible effects of repeated exposure and therefore establishing a Tolerable Daily Intake (TDI) was not necessary.

The available data on central nervous effects following consumption of poppy seed containing foods did not provide sufficient information on the dose response relationships for the alkaloids. The CONTAM Panel therefore decided to derive the ARfD from the lowest known single oral therapeutic dose in humans.

Oral doses with sustained release forms in the range of 7.5 to 15 mg morphine per day (corresponding to single doses of about 1.3 – 2.5 mg morphine taken every 4 hours) side effects such as sedation, dizziness or light- headedness occurred in the onset of therapy of opioid-naïve individuals. These symptoms are considered relevant for the ability to drive and operate machinery. This dose range is associated with nausea, vomiting and obstipation. Furthermore, a single low sustained release morphine bedtime dose of 11.55 mg has been shown to significantly affect sleep architecture in healthy adults and lead to reductions in slow-wave sleep. A threshold for the onset of these side effects is not described and it is not known if these side effects occur below the lowest known single oral therapeutic dose of 1.9 mg morphine.

For the purposes of determining the lowest therapeutic dose, several datasets have been taken into account. In the treatment of pain or dyspnoea in adults a dose equivalent to 1.9 mg morphine (31.7 µg/kg b.w. for an adult weighing 60 kg) is mentioned in the literature as the lowest single oral therapeutic dose (Davis and Percy, 2006; Martindale, 2005, 2010). Dose ranges for pain therapy in oral pharmaceutical forms for children and adults are shown in Table 22. In order to be conservative the lowest known single oral therapeutic dose of 31.7 µg/kg b.w., rounded to a single significant figure of 30 µg/kg b.w., is regarded by the CONTAM Panel as the lowest-observed-effect level (LOEL). It applies to adults and children since it is lower than the lowest known oral single dose for children of 83 µg morphine/kg b.w.). The medical literature reports that some healthy opiate-naive individuals experience adverse reactions such as nausea, vomiting, light-headedness, dizziness, difficulties in carrying out intellectual tasks, apathy and reduced physical activity as well as other adverse reactions to usual therapeutic doses like dry mouth, obstipation, sleepiness and headache at low therapeutic doses. However, it is unclear if these reports relate to single administration or repeated doses over the course of a day.

Forensic studies by Westphal et al. (2006) and Rochholz et al. (2005) showed that morphine intake of 11.4 mg (equivalent to 135 to 191 µg/kg b.w.) from the matrix of poppy seeds led to symptoms typical for morphine: nausea, reduced salvia, headaches, dizziness, tiredness and concentration problems. As only two test subjects were tested with lower morphine intake, these investigations do not allow the identification of a threshold dose. Whether the symptoms (listlessness, shortage of energy, sleepiness) described by one of the two test subjects, who had ingested 2.9 mg morphine (equivalent to 40.2 µg/kg b.w.) should be doubted – as suggested by the authors - cannot be judged. Furthermore, it is uncertain whether a medical examination, which did not take place, would have revealed further effects.

Because morphine-like effects predominate from the exposure to poppy seeds containing opium alkaloids, it is appropriate to consider the LOEL of 30 µg morphine/kg b.w. derived from pharmaceutical formulations for treatment of pain and dyspnoea as a basis for the risk assessment for poppy seeds. This LOEL is considered to be relevant for sensitive individuals, since it is the lowest of the range of doses recommended for commencement of treatment. Furthermore, it is conservative, because it is uncertain whether effects are actually observed following a single administration at this dose, or only following repeated administration or possible titration to higher doses. Therefore, the CONTAM Panel concluded that an uncertainty factor of 3 was sufficient to allow for extrapolation from the LOEL to a NOEL considering that the LOEL was derived from patients and not from the general population. Additional uncertainty factors were not required since the NOEL relates to the entire population including children. The CONTAM Panel identified LOEL of 30 µg morphine/kg b.w. and applied an uncertainty factor of 3 to establish an ARfD of 10 µg morphine/kg b.w. This is the dose of morphine from poppy seed-containing foods that would not be expected to result in effects following consumption of one meal or total consumption within one day.

7.5.2. Consideration of combined effects of opium alkaloids in poppy seeds

When dealing with exposure to a complex chemical mixture, such as the opium alkaloids in poppy seeds, it is necessary to consider the possibility of additivity and/or divergent pharmacological/toxicological effects or interactions that may be associated with concurrent exposure. From the earlier Sections on toxicokinetics, toxicity in experimental animals, and human pharmacology it can be seen that the actions of different opium alkaloids show variations in potency and qualitative effects in large part based on binding affinity and activation of opioid receptors (e.g. the μ, κ, and δ opioid receptors). The activity is greatly affected by structural class (i.e., phenanthrene- vs. benzylisoquinoline-type) and molecular structural features but also by metabolic interconversion or detoxification via Phase I and II pathways. Consequently, consideration of the principal opium alkaloids by chemical class, their pharmacology, comparative pharmacokinetic and pharmacodynamic characteristics, and clinical sequelae following poisoning is important for determining any potential for conducting a comprehensive risk assessment.

The opium alkaloids found in the poppy seed samples reported were morphine, codeine, thebaine, oripavine, papaverine and noscapine (see Figure 2). These alkaloids can be divided into two distinct chemical classes, the phenanthrenes (morphine, codeine, thebaine and oripavine) and benzylisoquinolines (papaverine and noscapine), which affects their pharmacological characteristics as discussed below.

7.5.2.1. Phenanthrene alkaloids

Morphine is the major alkaloid in poppy seed samples (see Section 4.2.5.) and is considered the prototype narcotic drug against which all other opioids are compared. It is the principal poppy seed sample alkaloid. Its main effect is due to potent binding to and activation of the μ-opioid receptors in the CNS by morphine and M6G (see Sections 7.1.1.3 and 7.3.1.1). Its primary actions of therapeutic value are rapid analgesia and sedation.

Codeine is the second-most predominant alkaloid in poppy seeds samples (see Section 4.2.5.), and can be considered as a prodrug, since it is converted *in vivo* by CYP 2D6-mediated O-demethylation to the primary active compound, morphine. Morphine conversion rates of 1.7-8.7 % have been reported in extensive metabolisers, which comprise the majority of Caucasian populations. When poor and ultra-rapid metabolisers are considered, morphine conversion in the entire population ranges from 0.4 to 18 % (see Section 7.1.2.). In addition, codeine is converted by UGT-mediated glucuronidation to codeine-6-glucuronide (C6G), which also has opioid receptor binding activity (Srinivasan et al., 1997; Vree et al., 2000).

Thebaine is present in small amounts in poppy seed samples and is chemically related to morphine and codeine, but has stimulatory rather than depressant effects, causing convulsions similar to strychnine poisoning at higher doses. Thebaine is not used therapeutically, but is converted industrially into a variety of semi-synthetic alkaloids.

Oripavine is not found in traditional *P. somniferum* poppy seed samples but has recently been selected for in traditional plant breeding of *P. somniferum* for use as an industrial feedstock from which a number of semi-synthetic opiates are derived. Oripavine possesses analgesic properties like morphine, however it is not clinically used because of severe toxicity and a low therapeutic index. It is the major metabolite of thebaine. Oripavine has a potential for dependence, which is significantly greater than that of thebaine but less than that of morphine.

7.5.2.2. Benzylisoquinoline alkaloids

Papaverine's *in vivo* mechanism of action is not entirely clear, but inhibition of phosphodiesterase (PDE) (and subtypes) causing elevation of cyclic adenosine monophosphate (cAMP) levels is

significant. It may also alter mitochondrial respiration. Papaverine is used clinically primarily in the treatment of visceral spasm and vasospasm (especially those involving the heart and the brain), and occasionally in the treatment of erectile dysfunction.

Noscapine has none of the analgesic properties of morphine although it shares the antitussive activity.

7.5.2.3. Comparative receptor pharmacology

Morphine-like symptoms of sedation, drowsiness, nausea and vomiting have been described in cases of poppy seed poisoning, for example by a consumer having eaten a dish sprinkled with approximately 75 g blue poppy seeds, corresponding to intake doses of 260 µg morphine/kg b.w. and 50 µg codeine/kg b.w. Whilst the poppy seed sample consumed may also have contained some or all of the other poppy seed alkaloids, the pattern of symptoms is consistent with the overall picture resulting from morphine exposure.

Direct comparison of *in vitro* µ-opioid receptor activation (agonist) has been reported for phenanthrene-type opium alkaloids including morphine, codeine, oripavine, and thebaine (Nikolaev et al., 2007). The relative activities are: morphine (1); oripavine (0.02); codeine (0.001); and thebaine (0.001). There is no evidence that the benzylisoquinolines have activity through opioid receptors so this entire class of compounds will not contribute to receptor-mediated morphine-like effects. Therefore, based on receptor pharmacology alone, the morphine content in poppy seeds is predicted to provide approximately 98 % of the opioid-related pharmacological/toxicological effects. Clearly, these *in vitro*-derived estimates of pharmacodynamic activity do not incorporate important factors including kinetics of absorption, metabolism (e.g., codeine to morphine/M6G (see Sections 7.1.1.3 and 7.3.1.1) and C6G (see Section 7.1.2.3.) or thebaine to oripavine), clearance, or possible antagonism by other opium alkaloids that appear to act by alternative mechanisms (e.g., papaverine and noscapine). However, this analysis does provide a framework for a simplifying assumption in the risk assessment of poppy seeds based on morphine content alone, or on total morphine equivalence.

As seen in Figure 7, the combination of morphine and codeine comprises greater than 80 % of the sum of the opium alkaloids in poppy seed samples at the median of the submitted data. Based on direct receptor interactions and contribution to total alkaloids in poppy seed samples, codeine is also likely to make a negligible contribution to total morphine-like activity. However taking into account metabolic activation of codeine to morphine, a maximum morphine-equivalence factor of 0.2 can be assumed for codeine. Based on the receptor interactions and the minor contribution to total alkaloids in poppy seed samples, thebaine is likely to make a negligible contribution to total morphine-like activity. Papaverine and noscarpine are unlikely to contribute to total morphine-like activity and may act as antagonists.

The CONTAM Panel considered estimating morphine-equivalence based on morphine and codeine content. However, from comparison of the statistics for total morphine equivalents with those for morphine alone (Table 8), the Panel concluded that codeine has a minor impact and that the risk assessment could be based on morphine alone. However, this approach would not be appropriate for poppy seed samples with a qualitatively different alkaloid profile, e.g. derived from cultivars bred for high oripavine or thebaine yields.

8. Risk characterisation

In considering possible acute effects of morphine in poppy seed samples, it is necessary to consider estimates of acute exposure based on high-level consumption and high-level occurrence data. As seen in Tables 16-20, there is potential for the ARfD of 10 µg morphine/kg b.w. to be exceeded by a considerable proportion of consumers throughout the EU, on at least some eating occasions. There are few reports of adverse reactions arising from traditional consumption of poppy seeds in foods,

excluding instances of misuse. However, in the absence of formal reporting systems it cannot be assumed that such reactions do not occur from time to time.

For consumers that use poppy seeds as condiments or decoration on bread and fine bakery ware (Table 19-20), the estimated exposure from bread was for all age groups lower compared to fine bakery ware. For adults, the estimated high-level dietary exposures based on high consumption and high level occurrence of morphine in poppy seed samples range from 1.23 to 16.9 µg morphine/kg b.w. per day for fine bakery ware (minimum LB to maximum UB across countries). The equivalent range for the mean level of occurrence is 0.23-3.23 µg morphine/kg b.w. per day, which is below the ARfD. For average consumption by adults in these regions, all of the estimated exposures for adults are below the ARfD and not a health concern. As commonly observed, the highest estimated dietary exposures, expressed on a body weight basis, are for toddlers. Based on high consumption and high level occurrence of morphine the estimated dietary exposures of toddlers range from 7.20 to 36.3 µg morphine/kg b.w. per day for fine bakery ware (minimum LB to maximum UB across countries), with potential for exceeding the ARfD. However, these estimated exposures are on a daily basis, and the exposure could be divided over more than one meal. As the ARfD refers to a single eating occasion or the consumption within one day, it does not necessarily mean that a slightly exceeding of the ARfD by the consumption of poppy seed containing foods over several meals would be a health concern. At mean occurrence of morphine with average and high level consumption, the estimated exposures are below the ARfD. The estimated exposures of other children and adolescents are between those of adults and toddlers.

Morphine data were available for fine bakery products sampled in only one European country (Germany), which has introduced measures to reduce levels of opium alkaloids in poppy seeds. These products include foods with high poppy seed content, such as those traditionally consumed in Central-Eastern European countries. The estimates of dietary exposure for these products (Table 18) are very similar to those for the consumers using poppy seeds as condiments or decoration. These exposures could be lower than anticipated due to the influence of processing (e.g. baking) on the alkaloid levels in food and/or the measures that were taken in Germany. For adults, the estimated high level dietary exposures based on high consumption range from 1.70 to 14.6 µg morphine/kg b.w. per day (minimum LB to maximum UB across countries) and from 0.30 to 4.79 µg morphine/kg b.w. per day for high consumption and mean occurrence of morphine in poppy seed samples, respectively. The estimated dietary exposures of toddlers based on high level consumption range from 6.15 to 25.5 µg morphine/kg b.w. per day and from 1.09-8.38 µg morphine/kg b.w. per day for high level and mean occurrence of morphine in poppy seed samples, respectively. Again, it is possible that the poppy seed containing foods are eaten over a number of occasions throughout the day, and that morphine intake at a single eating occasion would not exceed the ARfD.

In addition, the CONTAM Panel estimated dietary exposure to morphine based on the data available for poppy seed consumption in Czech Republic, Hungary and Slovakia in the EFSA comprehensive database, and based on consumption of single portions of foods with high poppy seed content (Tables 16-17). In almost all scenarios and age groups, the estimated exposures exceed the ARfD, with the highest estimate about 25-fold greater than the ARfD.

It should be noted that food processing in some circumstances could result in reduction of the morphine content by up to about 90 %. However, the exposure estimates based on data for poppy seeds do not take into account the effects of food processing due to the lack of data on processed products. Taking this reduction into account the ARfD is most likely to be exceeded when single large portions are consumed or if foods containing raw, unground poppy seeds are consumed.

9. Uncertainty analysis

The evaluation of the inherent uncertainties in the assessment of exposure to opium alkaloids in poppy seed samples has been performed following the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2006). In addition, the report on

"Characterizing and Communicating Uncertainty in Exposure Assessment" has been considered (WHO/IPCS, 2008). According to the guidance provided by the EFSA opinion (2006) the following sources of uncertainties have been considered: assessment objectives, exposure scenario, exposure model, and model input (parameters).

9.1. Assessment objectives

The objectives of the assessment were clearly specified in the terms of reference. The CONTAM Panel assessed the new occurrence data that were collected by EFSA between October 2010 and January 2011. Acute exposure assessments were performed based on hypothetical scenarios and information obtained from the EFSA Comprehensive Food Consumption Database. In its risk assessment the CONTAM Panel derived an acute reference dose (ARfD) for morphine and took into account possible contributions of other opium alkaloids to morphine-like activity based on the data available for poppy seed samples in the EU. A risk assessment for oripavine was not possible, as only a small number of occurrence data were submitted by Australia and toxicological information was lacking. Overall, the uncertainty of the assessment objectives is considered to be low.

9.2. Exposure scenario/Exposure model

In response to EFSA's request to submit occurrence data on opium alkaloids in food, four European countries (Germany, Hungary, Austria and The Netherlands) and Australia submitted data on 1033 food samples, including bakery products (n = 186), baking ingredients (n = 62) and poppy seeds (n = 785). Altogether 2678 analytical results were received mainly covering the period from 2006-2010 with 11 samples from years before that. The amount of occurrence data submitted differs considerably depending on individual alkaloid and reporting country. A data gap exists regarding the occurrence of oripavine, since oripavine is generally not included in the analytical methods used in Europe. There is uncertainty in possible regional differences in opium alkaloid contamination of food commodities, and the CONTAM Panel recognized that the data set is not representative of poppy seed samples on the EU market. This especially applies to the dataset for poppy seed-containing foods, which were submitted by Germany only.

The alkaloid content and profile of opium poppies differs strongly between different cultivars and varies from high alkaloid content (e.g. 1.5-2.5 % morphine or thebaine in the capsules) to low morphine content (less than 0.1 % in the capsules). Therefore, the alkaloid content and profile is highly variable and increases the uncertainty regarding the used occurrence data.

The alkaloid content of poppy seed samples can be reduced by several means of pre-treatment and processing. It has been shown that food processing may decrease alkaloid content by up to 90 %. The most effective methods include washing and soaking, heat treatments at temperatures at least above 135°C, but preferably above 200°C, as well as grinding and combinations of these. As most results reported were from unprocessed poppy seeds, the effect of food processing could not be accounted for, which adds to the overall uncertainty.

Only five countries provided any information on poppy seed consumption in their dietary surveys (Austria, Czech Republic, Germany, Hungary and Slovakia) and at most 3 % among children and 2.9 % of the survey days were reported to include poppy seeds in the dietary recall data. The Member States used different types of food lists and recipe databases and often poppy seeds, being a minor ingredient, were not included. In addition, while poppy seed-containing foods are partly seasonal foods eaten during Christmas and Easter periods, not always covered by national dietary surveys. Consequently, the consumption data are not representative for the European population and presumably an underestimation of the actual intake.

Therefore, besides the reported poppy seed consumption, also scenarios were elaborated based on recipes. Ranges of poppy seed content of 101 European poppy seed-containing foods were considered in the exposure assessment, based on recipe evaluations in seven countries in which poppy seeds are commonly consumed. On one hand, single portion scenarios were elaborated for which portion sizes were based on the information indicated in the recipe. If no information on the number of portions per recipe was available, mid-range portion sizes from picture books used in European dietary surveys were used. In cases, where the portion indicated in the recipe was considered unrealistically high, the portion used in the estimations was decreased to more common one. On the other hand, consumption data for fine bakery ware and bread from the comprehensive database were used, assuming that all consumed bread or fine bakery ware contained poppy seeds on a consumption day. This leads presumably to an overestimation of the actual intake. The CONTAM Panel considers the uncertainty in the exposure assessment to be high.

9.3. Model input (parameters)

There are no prescribed fixed official methods for the analysis of opium alkaloids and laboratories can use any method of analysis, provided it can be demonstrated in a traceable manner that they fulfill the requirements according to ISO 17025. This may have added to the uncertainty in the analytical results. The limited number of isotope labeled internal standards and certified reference materials is a limitation when the method performance for the analytical procedures for analysis of opium alkaloids in food is assessed. This adds to the overall uncertainty in the analytical results.

9.4. Other uncertainties

The ARfD is derived from the lowest known single oral therapeutic dose of morphine. A range of adverse reactions is reported to occur during therapeutic use of morphine, but the extent to which these occur at the lowest known single oral therapeutic dose or even below is not clear. Furthermore, the medical literature refers to contraindications in which morphine treatment should be avoided. There is also uncertainty if the low doses that are efficient in the therapy of dyspnoea via the reduction of ventilatory drive may impose additional risks on persons with different forms of sleep apnoea or sleep disordered breathing.

The risk characterization is based on comparison of dietary exposure to morphine with the ARfD. The CONTAM Panel took into account possible contributions of codeine and thebaine to morphine-like activity. However, the available data did not allow non-morphine like activity of the opium alkaloids in poppy seeds to be taken into account, which could be relevant for poppy seeds with different alkaloid profiles. The assessment applies only to the profile of opium alkaloids in the poppy seed samples analysed in the data submitted by the EU countries, and does not apply to poppy seeds from other regions, for example grown for specific purposes, with different alkaloid profiles.

Opium alkaloids can have combined effects with other central depressant drugs and alcohol. The relevance of these to exposure to alkaloids in poppy seed containing foods is unclear.

9.5. Summary of uncertainties

In Table 24, a summary of the uncertainty evaluation is presented, highlighting the main sources of uncertainty and indicating an estimate of whether the respective source of uncertainty might have led to an over- or underestimation of the exposure or the resulting risk.

Table 24: Summary of qualitative evaluation of the impact of uncertainties on the risk assessment of the dietary exposure of opium alkaloids in poppy seeds.

Sources of uncertainty	Direction
Uncertainty in analytical results	+/-[(a)]
Use of occurrence data from few European countries	+/-
Limited data on processed foods	+
Limited data on poppy seed consumption across Europe	-
Use of scenarios based on the comprehensive database in which is assumed that all consumed bread or fine bakery ware contain poppy seeds during one day	+
Use of portion sizes from recipes	+/-
Uncertainty in the LOEL for establishing the ARfD for morphine	-

(a): + = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure/risk

The CONTAM Panel considered that the impact of the uncertainties on the risk assessment of exposure to opium alkaloids is considerable.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

General

- Poppy seeds are obtained from the opium poppy *(Papaver somniferum* L.). The latex (milky sap) of the opium poppy contains alkaloids such as morphine and codeine that are narcotic agents. They have been used by man for the treatment of severe pain for generations but are also subject to misuse.

- The seeds are used as food and to produce edible oil.

- *Papaver somniferum* varieties especially bred with high alkaloid content intended for pharmaceutical purposes are also used for production of poppy seeds for food use. Low morphine varieties of *Papaver somniferum* are available.

- Poppy seeds do not contain the latex, but can become contaminated with the alkaloids (referred to as opium alkaloids in this opinion) as a result of pest damage and during harvest.

- Opium alkaloids detected in samples of poppy seeds and poppy seed-containing foods include the phenanthrenes: principally morphine, codeine, thebaine and oripavine, and the benzylisoquinolines: principally papaverine and noscapine.

Methods of analysis

- Today's state of the art methodology for the determination of alkaloids in poppy seed samples is liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Detection limits are usually considerably below 1 mg/kg for morphine and related opium alkaloids. A major advantage of mass spectrometry- based methods is the possibility of using isotope labelled standards.

- So far, none of the methods mentioned have been validated by inter-laboratory studies. In addition, no certified reference materials or proficiency studies are available for the determination of opium alkaloids.

Occurrence

- EFSA received the results from the analysis of 1033 samples including altogether 2678 analytical results for opium alkaloids in poppy seeds and poppy seed containing foods. Four European countries (Germany, Hungary, Austria and The Netherlands) provided data on morphine, codeine, thebaine, papaverine and noscapine. Australia provided data on morphine, codeine, thebaine and in addition on oripavine.

- In the submitted data, and in-line with the literature, morphine was the major alkaloid in poppy seed samples. Moreover, morphine and codeine had a high level of co-occurrence as did codeine and thebaine, and morphine and thebaine. There was a low level of co-occurrence of morphine, codeine and thebaine with noscapine.

- The alkaloid content of poppy seed samples and poppy seed containing food can be reduced by several methods of pre-treatment and processing. Food processing may decrease the alkaloid content by up to about 90 %. The most effective methods include washing, soaking and heat treatments, as well as grinding and combinations of these treatments.

Exposure

- Due to the nature of the alkaloid profile of the poppy seed samples submitted by Australia, the CONTAM Panel excluded these data and based the exposure assessment on data for samples taken from the European market.

- Poppy seeds consumption varies broadly within the European Union. In some cultures, such as in Central-Eastern European Countries, it is traditional to use poppy seeds widely in foods, and in specific instances sometimes in high amounts in bread, fine bakery ware, desserts and other dishes. For other consumers, poppy seeds are commonly used as a condiment or decoration.

- Since opium alkaloids act acutely, only acute dietary exposure is assessed.

- Based on the relative prevalence of the alkaloids present in poppy seed and food samples analysed, and on their pharmacological potency, the CONTAM Panel concluded that the exposure assessment should focus primarily on morphine alone. However, this approach would not be appropriate for poppy seed samples in which morphine is not the predominant alkaloid, e.g. derived from cultivars bred for high oripavine or thebaine yields.

- The poppy seed consumption recorded in the Comprehensive European Food Consumption Database is very low possibly resulting in an underestimation of actual intake. Based on these data for average reported poppy seed consumption the dietary exposure to morphine, using lower and upper bound concentrations, for 3 European countries was the highest for adults and ranged from 3.11 to 90.9 µg/kg b.w. per day.

- Based on hypothetical single portion scenarios for consumers of foods with high content of poppy seeds, using upper bound concentrations, the exposure to morphine ranged from 37.8 to 200 µg/kg b.w. for adults and was the highest for children within the age range of 3 to 10 years, at 47.8 to 252 µg/kg b.w.

- Based on food consumption data from bread and fine bakery ware recorded in the Comprehensive European Food Consumption Database and assuming that all bread or fine bakery ware consumed in one day contain poppy seeds, it can be concluded that the exposure from bread is lower compared to fine bakery ware.

- For consumers of foods with low poppy seed content, the estimated dietary exposure to morphine via fine bakery ware for adults ranged from 0.05 to 16.9 µg morphine/kg b.w. per day. The estimated dietary exposure was the highest for toddlers and ranged from 0.39 to 36.3 µg morphine/kg b.w. per day. The estimated exposures of other children and adolescents are between those of adults and toddlers.

- For consumers of foods with high poppy seed content, the estimated dietary exposure to morphine via fine bakery ware for adults ranged from 2.48 to 375 µg morphine/kg b.w. per day. The estimated dietary exposure was the highest for other children and ranged from 10.2 to 753 µg morphine/kg b.w. per day. The estimated exposures of toddlers and adolescents are between those of adults and other children.

- These exposure estimates are based on the reported data on concentrations of alkaloids in poppy seed samples. If the concentrations are reduced by processing, the exposure could be up to 90 % lower.

- Based on morphine levels measured in food products, namely fine bakery ware, using lower bound and upper bound concentrations for 95th percentile occurrence data, the exposure was the lowest for adults, ranging from 0.50 to 14.6 µg/kg b.w. per day. The exposure was the highest for other children within the age range of 3 to 10 years, at 1.88 to 30.7 µg/kg b.w. per day.

Hazard identification and characterisation

Toxicokinetics

- The oral bioavailability of morphine is reduced by both Phase I and II pre-systemic metabolism in the gastrointestinal (GI) tract and liver. Codeine is less susceptible to this pre-systemic effect.

- Oral bioavailability of papaverine, noscapine, thebaine and oripavine, appears to be low due to pre-systemic metabolism in the GI tract and liver primarily involving demethylation reactions but also glucuronidation.

- The documented abilities of active transport proteins, including the P-glycoprotein, and CYP2D6 phenotype to modify the pharmacological effects of opium alkaloids suggests that mixture interactions- and/or genetic polymorphisms could affect poppy seed effects in humans.

Toxicity in experimental animals

- Morphine is genotoxic only *in vivo* but most likely by a non-DNA reactive mode of action. Codeine is not genotoxic *in vitro* or *in vivo*.

- Chronic and developmental toxicity of morphine have not been systematically evaluated. Although carcinogenicity data for morphine itself are lacking, based on the lack of carcinogenicity of codeine which is metabolised to morphine, the CONTAM Panel concluded that morphine is unlikely to be carcinogenic.

Human data

- Morphine has high affinity for the µ-opiate receptor as an agonistic ligand. Activation of µ-opiate receptors leads to analgesia, euphoria, dependence, miosis, respiratory depression, cough calming and obstipation. Patients with pain tolerate, without severe side effects, larger doses of morphine than pain-free patients. Therapeutic doses of morphine may also impair the ability to drive or to operate machinery due to changes in attentiveness and reactive skills.

- The lowest known single oral therapeutic dose reported is 1.9 mg morphine, corresponding to 31.7 µg/kg b.w. for an adult weighing 60 kg.

- The pharmacology of codeine is strongly related to that of morphine, as it is a precursor of morphine itself. Up to 20 % of codeine can be converted to morphine.

- Morphine and codeine have dependence potential, associated with longer term use and high doses that can result in tolerance.

- The most frequent side effect of codeine is constipation. Other frequent side effects include slight headaches, minor sleepiness, nausea sometimes linked with vomiting (particularly at the beginning of treatment) and a dry mouth. At higher doses impaired vision, respiratory depression and euphoria may also occur.

- For oripavine and thebaine only very limited data are available. They show only partial agonistic activity at the µ-receptor, and thebaine has been shown to act as an antagonist at higher dosages.

- Papaverine and noscapine do not show opiate-like pharmacology since papaverine acts as a smooth muscle relaxant that is most pronounced on blood vessels, and noscapine is an antitussive agent.

- The side effects of papaverine, that occur after oral administration, are dizziness, headache, drowsiness, tiredness, gastro-intestinal disturbance, flush, skin rash, tachycardia, sweating and hypotonia. In conjunction with long-term administration eosinophilia, liver enzyme changes (reversible) and icterus may occur. Overdosage may lead to seizures.

Derivation of health-based guidance value

- Since morphine-like central nervous effects have been observed in humans following consumption of a single portion of a meal containing opium alkaloid-contaminated poppy seeds, the CONTAM Panel considered it appropriate to base its risk assessment for poppy seeds on exposure to morphine.

- Taking into account the short term nature of the effects of morphine, the CONTAM Panel concluded that the establishment of an acute reference dose (ARfD) was required. Ensuring exposure is below the ARfD would also protect against possible effects of repeated exposure and therefore establishing a Tolerable Daily Intake (TDI) was not necessary.

- The available data on central nervous effects following consumption of poppy seed containing foods did not provide sufficient information on the dose response relationships for the alkaloids. The CONTAM Panel therefore decided to derive the ARfD from the lowest known single oral therapeutic dose of morphine.

- In order to be conservative, the lowest known single oral therapeutic dose of 31.7 µg/kg b.w., rounded to a single significant figure of 30 µg/kg b.w., is regarded by the CONTAM Panel as the lowest-observed-effect level (LOEL). It applies to children as well as adults since it is lower than the lowest known single oral therapeutic dose for children of 83 µg morphine/kg b. w.

- The CONTAM Panel applied an uncertainty factor of 3 to establish from the LOEL of 30 µg morphine/kg b.w. an ARfD of 10 µg morphine/kg b.w. This is the dose of morphine from poppy seed-containing foods for which a person would not be expected to experience effects following one meal or total consumption within one day.

- The CONTAM Panel considered estimating morphine-equivalence based on morphine and codeine content but concluded that codeine has a minor impact, so that the risk assessment was based on morphine alone.

Risk characterisation

- If poppy seeds are consumed as condiments or decoration on bread and fine bakery ware, it is possible that some consumers, particularly toddlers, will exceed the ARfD for morphine on rare occasions.

- A considerable proportion of consumers of foods that contain large amounts of poppy seeds, such as are common in Central-Eastern European countries, are likely to exceed the ARfD for morphine on at least some eating occasions. The highest estimates of morphine exposure are about 75-fold greater than the ARfD.

- Food processing in some circumstances could result in reduction of the morphine content by up to about 90 %. Due to the lack of data on morphine in food as consumed, the exposure estimates based on morphine content of poppy seed samples do not take into account the effects of food processing. Taking the possible reduction into account the ARfD is most likely to be exceeded when single large portions are consumed or if foods containing raw, unground poppy seeds are consumed.

- There are few reports of adverse reactions arising from traditional consumption of poppy seeds in foods, excluding instances of misuse. However, in the absence of formal reporting systems it cannot be assumed that such reactions do not occur from time to time.

- Contrary to expectation estimations of exposure to morphine based on data available for fine bakery products, sampled in Germany where foods with high poppy seed content are common, were very similar to those for the regions using poppy seeds as condiments or decoration. This observation could be due to the influence of processing (e.g. baking) on the alkaloid levels in food and/or the measures that have been taken in Germany to reduce alkaloid contamination of poppy seeds.

- A number of methods for reduction of opium alkaloids content in poppy seed containing foods are available.

- This risk assessment relates to poppy seed samples with an alkaloid profile comparable to that of the submitted data and should not be extrapolated to poppy seed samples with a qualitatively different alkaloid profile.

RECOMMENDATIONS

- There is a need for certified reference materials and defined performance criteria for the analysis of opium alkaloids in food

- The analysis of poppy seed samples and poppy seed containing products should focus not only on morphine, but also on those alkaloids reported to be present and their ratios to morphine.

- More occurrence data should be collected on opium alkaloids in food products.

- Information should be obtained on the varieties of poppy seeds that are available on the European market for food use, and their alkaloid content (including alkaloid profile).

- More data on consumption of poppy seed products should be obtained.

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APPENDICES

APPENDIX A

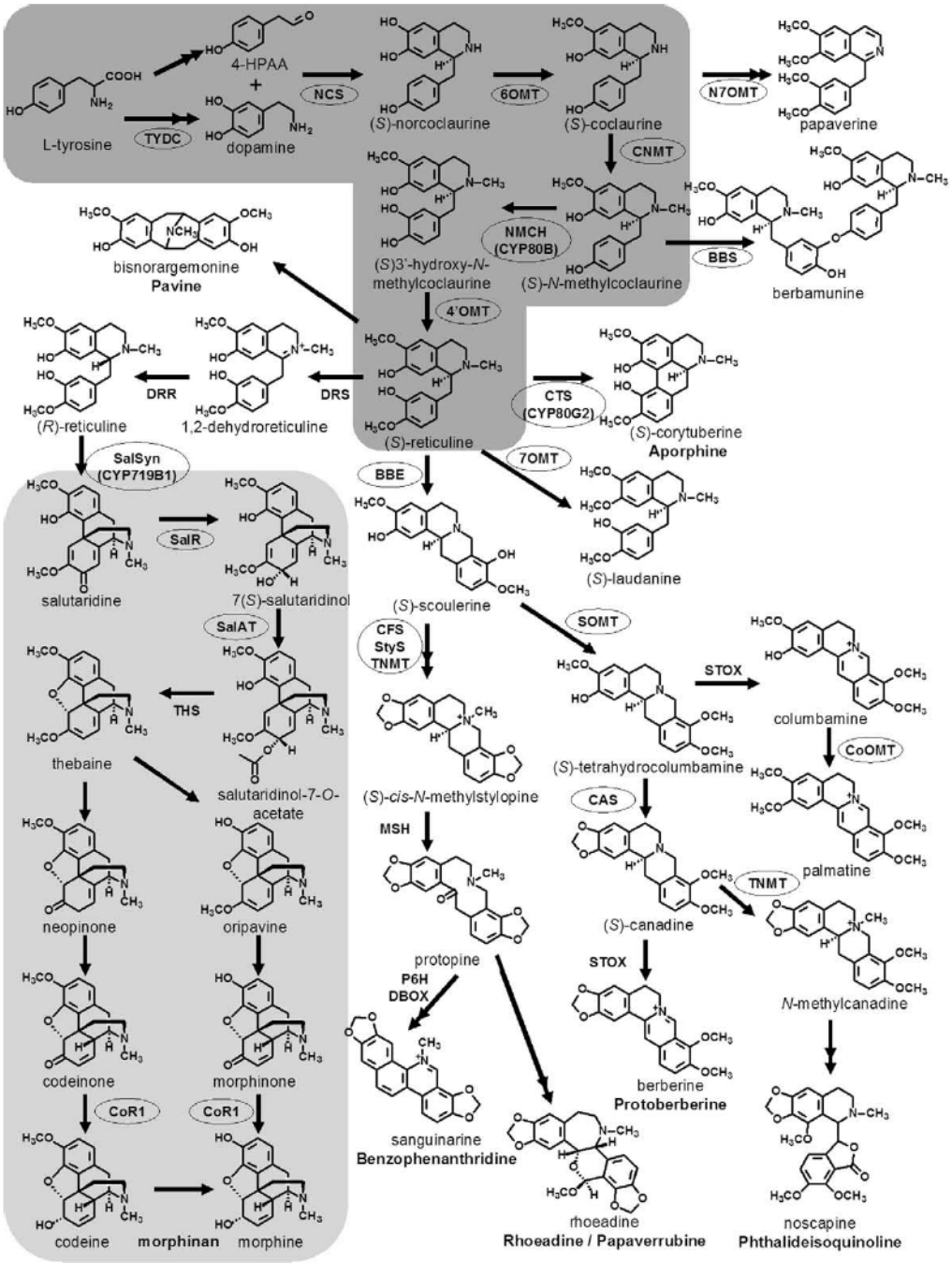

Figure A1:[23] Benzylisoquinoline alkaloid biosynthesis (Ziegler et al., 2009). Multiple arrowheads denote more than one enzymatic step. Arrows without labelling reflect conversions that have not been

[23] Reprinted from Phytochemistry, volume 70, Ziegler J, Facchini PJ, Geissler R, Schmidt J, Ammer C, Kramell R, Voigtländer S, Gesell A, Pienkny S and Brandt W, Evolution of morphine biosynthesis in opium poppy, 1696-1707, 2009, with permission from Elsevier.

enzymatically characterized. Enzymes that have been characterized are labelled, and those for which cognate cDNAs have been isolated are circled. The basic benzylisoquinoline pathway is shaded in dark grey, whereas the promorphinan and morphinan pathways are shaded in light grey. Abbreviations: 4-HPAA: para-hydroxyphenyl acetaldehyde; 40OMT: (S)30-hydroxy N-methylcoclaurine 40-O-methyltransferase; 6OMT: (S)-norcoclaurine 6-O-methyltransferase; 7OMT: (R,S)-reticuline 7-O-methyltransferase; BBE: berberine bridge enzyme; BBS: berbamunine synthase; CAS: (S)-canadine synthase; CFS: (S)-cheilanthifoline synthase; CNMT: (S)-coclaurine N-methyltransferase; CoOMT: columbamine O-methyltransferase; CoR1: codeinone reductase 1; CTS: (S)-corytuberine synthase (CYP80G2); DBOX: dihydrobenzophenanthridine oxidase; DRR: 1,2-dehydroreticuline reductase; DRS: 1,2-dehydroreticuline synthase; MSH: methylstylopine 14-hydroxylase; N7OMT: (S)-norreticuline7-O-methyltransferase, NCS, (S)-norcoclaurine synthase; NMCH: (S)-N-methylcoclaurine 30-hydroxylase (CYP80B subfamily); P6H: protopine 6-hydroxylase; SalAT: 7(S)-salutaridinol 7-O-acetyltransferase; SalR: salutaridine reductase; SalSyn: salutaridine synthase (CYP719B1); SOMT: scoulerine 9-O-methyltransferase; STOX: (S)-tetrahydroprotoberberine oxidase; StyS: (S)-stylopine synthase; THS: thebaine synthase; TNMT: tetrahydroprotoberberine N-methyltransferase; TYDC: tyrosine decarboxylase.

APPENDIX B

Table B1: Detailed summary table of the occurrence data (mg/kg).

Substance	Food group	n	% LC	Median[(a)]		Mean[(a)]		P95[(a)]		Max	
				LB	UB	LB	UB	LB	UB	LB	UB
Morphine	Wheat rolls, white	5	80	0	0.40	0.80	1.14	4.00	4.00	4.00	4.00
	Pastries and cakes	142	59	0	1.00	0.59	1.08	3.30	3.30	8.20	8.20
	Buns	26	23	0.34	0.54	0.40	0.57	1.00	1.00	1.10	1.10
	Fine bakery ware	9	100	0	0.30	0	0.61	0	1.00	0	1.00
	Baking ingredients	62	19	2.12	2.12	3.21	3.33	10.7	10.7	28.8	28.8
	Poppy seed	772	9	10.1	10.1	38.3	38.7	202	202	630	630
	Oilseeds	3	100	0	0.10	0	0.10	0	0.10	0	0.10
	Croissant from puff pastry	2	50	0.20	0.70	0.20	0.70	0.40	1.00	0.40	1.00
	Cake from batter	1	100	-	-	0	1.00	-	-	-	-
	Fruit cake	1	100	-	-	0	1.00	-	-	-	-
Codeine	Wheat rolls, white	2	100	0	0.40	0	0.40	0	0.50	0	0.50
	Pastries and cakes	77	70	0	0.40	0.27	0.54	1.20	1.20	6.60	6.60
	Buns	1	100	-	-	0	0.50	-	-	-	-
	Fine bakery ware	9	100	0	0.30	0	0.30	0	0.30	0	0.30
	Baking ingredients	47	26	0.90	0.90	1.08	1.18	3.30	3.30	4.10	4.10
	Poppy seed	554	31	1.40	1.40	4.98	5.26	14.9	14.9	827	827
	Oilseeds	3	100	0	0.10	0	0.10	0	0.10	0	0.10

Table B1: Continued.

Substance	Food group	n	% LC	Median[(a)]		Mean[(a)]		P95[(a)]		Max	
				LB	UB	LB	UB	LB	UB	LB	UB
Thebaine	Wheat rolls, white	2	100	0	0.15	0	0.15	0	0.20	0	0.20
	Pastries and cakes	37	97	0	0.10	0.01	0.11	0	0.20	0.21	0.21
	Buns	1	100	-	-	0	0.10	-	-	-	-
	Fine bakery ware	9	78	0	0.20	0.04	0.14	0.20	0.20	0.20	0.20
	Baking ingredients	16	50	0.03	0.11	0.17	0.23	0.80	0.80	0.80	0.80
	Poppy seed	356	19	2.00	2.00	15.6	15.8	101	101	783	783
Oripavine	Poppy seed	43	42	4.00	4.00	20.8	21.3	68.0	68.0	233	233
Papaverine	Wheat rolls, white	1	100	-	-	0	0.07	-	-	-	-
	Pastries and cakes	15	100	0	0.07	0	0.08	0	0.20	0	0.20
	Fine bakery ware	9	100	0	0.07	0	0.13	0	0.20	0	0.20
	Baking ingredients	8	38	0.13	0.20	0.14	0.18	0.35	0.35	0.35	0.35
	Poppy seed	102	80	0	0.75	0.09	0.59	0.40	1.00	1.79	1.79
Noscapine	Wheat rolls, white	1	100	-	-	0	0.10	-	-	-	-
	Pastries and cakes	22	91	0	0.10	0.02	0.11	0.19	0.19	0.23	0.23
	Buns	1	100	-	-	0	0.10	-	-	-	-
	Baking ingredients	9	56	0	0.10	0.27	0.33	1.36	1.36	1.36	1.36
	Poppy seed	330	69	0	1.00	1.02	1.70	4.20	4.20	39.2	39.2

n: number of analytical results; P95: 95th percentile; LB: lower bound; UB: upper bound; LC: left censored data (values below the limit of detection or limit of quantification.
(a): For some of the food groups, summary statistics (in particular high percentiles) may not be statistically robust due to the limited number of observations available.

APPENDIX C

Table C1: Dietary surveys considered for the acute dietary exposure assessment and number of study days in the different age classes.

Country	Dietary survey[a]	Abbreviation[b]	Number of study days							
			Total	Infants	Toddlers	Other children	Adolescents	Adults	Elderly	Very elderly
Austria	ASNS	AT	2123					2123		
Belgium	Diet_National_2004	BE/1	6328				1187	2648	1045	1448
	Regional Flanders	BE/2	1983		108	1875				
Bulgaria	NSFIN	BG/1	1204				162	691	151	200
Bulgaria	NUTRICHILD	BG/2	1723		856	867				
Cyprus	Childhealth	CY	909				909			
Czech Republic	SISP04	CZ	4706			778	596	3332		
Denmark	Danish_Dietary_Survey	DK	28795			3426	3348	1972	2159	140
Estonia	NDS_1997	EE	1866					1866		
Finland	DIPP	FI/1	4259		1486	2773				
	FINDIET_2007	FI/2	4076					3150	926	
	STRIP	FI/3	1000			1000				
France	INCA2	FR	28165			3315	6728	1572	1824	571
Germany	DONALD_2006	DE/1	909		276	633				
	DONALD_2007	DE/2	933		255	678				
	DONALD_2008	DE/3	921		252	669				
	National_Nutrition_Survey_I	DE/4	27852				2022	2083	4012	980
Greece	Regional_Crete	GR	2508			2508				
Hungary	National_Repr_Surv	HU	4080					3222	618	240
Ireland	NSIFCS	IE	6706					6706		
Italy	INRAN_SCAI_2005_06	IT	9921		108	579	741	6939	870	684
Latvia	EFSA_TEST	LT	3981			377	949	2655		
Netherlands	DNFCS_2003	NL/1	1500					1500		
	VCP_kids	NL/2	2558		644	1914				
Poland	IZZ_FAO_2000	PL	4134		79	409	666	2527	329	124
Slovakia	SK_MON_2008	SL	2763					2763		
Slovenia	CRP_2008	SI	407					407		

Table C1: Continued.

Country	Dietary survey[a]	Abbreviation[b]	Number of study days							
			Total	Infants	Toddlers	Other children	Adolescents	Adults	Elderly	Very elderly
Spain	AESAN	ES/1	828					828		
	AESAN_FIAB	ES/2	2974				226	2748		
	NUT_INK05	ES/3	2100			798	1302			
	enKid	ES/4	764		34	312	418			
Sweden	Riksmaten_1997_98	SE/1	8466					8466		
	NFA	SE/2	9922			5875	4047			
United Kingdom	NDNS	UK	12068					1206		

Table C2: European poppy seed recipes (n = 101), amounts of poppy seeds (g/common portion and g/100g) and information on processing of the food.

Food group	Country	Food name	Poppy seeds (g/ portion)	Portion weight (g, estimated)	Poppy seeds (g/ 100 g)	Temp (°C)	Time of heat treat. (min)	Notes	Reference
Biscuits and Cookies	Czech Republic	Loupáčky z domácí pekárny	1.0	15	6.7	180	15-20		http://www.srecepty.cz/ingredience/mak?pof_name=ingredient_recipes_693
Biscuits and Cookies	Latvia	Biscuits with poppy seeds	1.6	15	10.6	n.a	n.a		http://www.receptes.lv/
Biscuits and Cookies	Austria	Gespritzte Mohnkipferl	2.0	15	13.0	160	13		http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html
Biscuits and Cookies	Germany	Pflaumen - Mohn - Plätzchen	4.0	20	20.0	170	10		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Biscuits and Cookies	Lithuania	Poppy seed cookies	9.0	15	60.0	180	20-25	Blended into a paste	Lithuanian Traditional Foods, Baltos Lankos, Compiled by Biruté Imbrasiene
Bread	Germany	Knuspertoast	0.3	35	0.9	190	45	Portion=slice	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Bread	Germany	Gewürzbrot (Spicy bread)	0.3	35	0.9	190	45	Portion=slice	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Bread	Czech Republic	Housky se škvarkami (Braided roll with cracklings)	0.7	70	1.0	180	20		http://www.srecepty.cz/ingredience/mak?pof_name=ingredient_recipes_693
Bread	Poland	Chleb ziemniaczany z makiem (potato bread with poppy seeds)	0.7	35	2.0	190	45		http://allrecipes.pl/przepis
Bread	Austria	Cheese pretzels with poppy seeds	1.0	80	1.3	180	15	As decoration	http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html
Bread	Hungary	Mákos kenyér I.	1.2	35	3.5	180	50		Bernáth J and Németh E, 2010
Bread	Hungary	Mákos zsemble	1.5	50	3.0	200	20	As decoration	Bernáth J and Németh E, 2010.
Bread	Czech Republic	Sýrové spirály (Cheese spirals)	1.5	37	4.1	180	20		http://www.srecepty.cz/ingredience/mak?pof_name=ingredient_recipes_693
Bread	Germany	Gesundes und leichtes Weizenbrot mit Haferflocken und Mohn	2.3	35	6.6	220	25		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Bread	Germany	Mohn Brot/ Brot Rigan	6.0	35	17.1	150	70	Portion=slice	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Dessert	Austria	Mohnknödel auf Beerenragout (poppy seed dumplings with berries)	5.0	200	2.5	n.a	10	Ground poppy seeds. Boiled in salted water, at low heat 10min	http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html

Table C2: Continued.

Food group	Country	Food name	Poppy seeds (g/ portion)	Portion weight (g, estimated)	Poppy seeds (g/ 100 g)	Temp (°C)	Time of heat treat. (min)	Notes	Reference
Dessert	Latvia	Cream dessert with poppy seeds	6.7	150	4.5	-	-		http://www.receptes.lv/
Dessert	Germany	Germknödel mit Powidl	12.5	125	10.0	-	-	Ground raw poppy seeds sprinkled before serving.	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Dessert	Germany	Vanille - Mohn - Pudding	15.0	250	6.0	-	-		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Dessert	Hungary	Szolos mákhab kehelyben	16.5	165	10.0	-	-		Bernáth J and Németh E, 2010
Dessert	Germany	Mohneis (poppy seed ice)	21.9	125	17.5	-	-	Added raw	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Dessert	Hungary	Meggyes-mákos rétes (Sour cherry and poppy seed strudel)	24.2	200	12.2	200	35		http://www.nosalty.hu/mak_alapanyag_324
Dessert	Austria	Germknödel	25.0	250	10.0			Grated poppy seeds at room t.	http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html
Dessert	Hungary	Flódni rétes (strudel)	41.6	260	16.2	180	20		http://www.nosalty.hu/mak_alapanyag_324
Sweet dish	Hungary	Pozsonyi makos kocka	25.6	200	12.8	180	25		Bernáth J and Németh E, 2010
Sweet dish	Germany	Schlesische Mohnpielen (limited to 200 g/ portion)	36.0	200	18.0			Unground poppy seeds boiled into water	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Sweet dish	Hungary	Mákos nudli	38.9	250	15.6	-	-		Bernáth J and Németh E, 2010
Sweet dish	Germany	Mohnpielen	70.2	200	35.1	-	-	Ground	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Sweet dish	Poland	Kluski z makiem (noddles with poppy seeds)	83.0	370	22.7	-	-	Seeds simmered in hot water (15 min), ground	http://allrecipes.pl/przepis
Savory dish	Poland	Pikantne curry z kurczakiem (spicy chicken curry with poppy seeds)	0.6	200	0.3	-	-	Raw seeds	http://allrecipes.pl/przepis

Table C2: Continued.

Food group	Country	Food name	Poppy seeds (g/ portion)	Portion weight (g, estimated)	Poppy seeds (g/ 100 g)	Temp (°C)	Time of heat treat. (min)	Notes	Reference
Savory dish	Lithuania	Poppy seed potato dumpling	4.2	200	2.1	100	15	Added to the dough. Boiled	Lithuanian Traditional Foods, Baltos Lankos, Compiled by Biruté Imbrasiene
Savory dish	Germany	Mohn - Piroggen	5.0	88	5.7	175	20	Portion= piroggen	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Savory dish	Austria	Pork with sweet and sour poppy seed noodles	10.0	200	5.0	220	50	White poppy seeds	http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html
Savory dish	Austria	Salmon trout steak with dill sauce	15.0	160	9.4	n.a	n.a	Fried	http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html
Savory dish	Lithuania	Potato Soup whitened with poppy seed milk	26.4	300	8.8	n.a	n.a	Poppy seeds are grinded and boiled.	Lithuanian Traditional Foods, Baltos Lankos, Compiled by Biruté Imbrasiene
Beverages	Lithuania	Poppy seed "milk" (non-dairy)	24.0	200	12.0	-	-	Blended into a paste	Lithuanian Traditional Foods, Baltos Lankos, Compiled by Biruté Imbrasiene
Beverages	Lithuania	Poppy seed milk (non-dairy smoothie)	66.0	200	33.0	100	10	Seed pulp discarded	http://www.food.com/recipe/poppy-seed-milk-201222
Pastries and Cakes	Hungary	Citrommázas mákos muffin	2.4	60	4.1	180	25		Bernáth J and Németh E, 2010
Pastries and Cakes	Poland	Ciasto cytrynowo-makowe (Lemon poppy seed cake)	3.0	60	5.1	175	50		http://allrecipes.pl/przepis
Pastries and Cakes	Latvia	Wheaten rolls with poppy seeds	4.9	65	7.5				http://www.receptes.lv/
Pastries and Cakes	Czech Republic	Makové řezy	5.4	80	6.8	180	40		http://www.srecepty.cz/ingredience/mak?pof_name=ingredient_recipes_693
Pastries and Cakes	Germany	Apfel - Mohn - Marzipan - Torte	5.7	150	3.8	175	30		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Poland	Strucla makowa z gruszkami (poppy seed strudel with pears)	6.1	60	10.2	200	35		http://allrecipes.pl/przepis
Pastries and Cakes	Hungary	Mák Torta I	7.6	75	10.1	n.a	n.a		Bernáth J and Németh E, 2010
Pastries and Cakes	Slovakia	Poppy seed cake	8.2	75	10.9	Baked	n.a		http://www.gurman.sk/recept-makove-rezy-AAA0960/
Pastries and Cakes	Hungary	Mákos koszorú	8.3	80	10.4	180	45		Bernáth J and Németh E, 2010

Table C2: Continued.

Food group	Country	Food name	Poppy seeds (g/ portion)	Portion weight (g, estimated)	Poppy seeds (g/ 100 g)	Temp (°C)	Time of heat treat. (min)	Notes	Reference
Pastries and Cakes	Germany	Mohn - Quark - Torte	9.1	150	6.1	175	30	Ground	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Latvia	Cake with poppy seeds	9.2	70	13.2	n.a	n.a		http://www.receptes.lv/
Pastries and Cakes	Slovakia	Poppy seed cake from yeast dough	9.7	70	13.9	Baked	n.a		http://www.gurman.sk/recept-makove-jeze-AAA2230/
Pastries and Cakes	Germany	Möhren - Reis - Mohn Kuchen	9.8	80	12.3	150	85	Ground Portion=slice	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Czech Republic	Maková bábovka(Poppy Seed Cake)	10.0	75	13.3	180	40		http://www.srecepty.cz/ingredience/mak?pof_name=ingredient_recipes_693
Pastries and Cakes	Germany	Preiselbeer - Mohn - Torte	11.0	150	7.4	180	25		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Austria	Himbeer Mohn Torte	11.0	115	9.4	160	20		http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html
Pastries and Cakes	Hungary	Sült mákos tészta (Fried noddles with poppy seeds)	11.0	80	13.8	180	25		http://www.nosalty.hu/mak_alapanyag_324
Pastries and Cakes	Hungary	Kevert mákos sütemény	11.1	80	13.9	160	n.a	Ground	http://www.nosalty.hu/mak_alapanyag_324
Pastries and Cakes	Czech Republic	Cheesecake makovnik (Poppy seed cake)	11.4	80	14.3	n.a	30	Portion=slice Baked	http://www.srecepty.cz/ingredience/mak?pof_name=ingredient_recipes_693
Pastries and Cakes	Hungary	Meggyes-mákos szelet	11.5	125	9.2	200	20		http://www.nosalty.hu/mak_alapanyag_324
Pastries and Cakes	Germany	Russischer Mohnkuchen 2	11.7	80	14.6	200	30		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Germany	Russischer Mohnkuchen 1	11.8	80	14.8	180	60	Blue ground poppy seeds are added to cooked cake	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Hungary	Gyros citrommòazas màakos kocka	11.9	150	8.0	175	35	Ground	Bernáth J and Németh E, 2010
Pastries and Cakes	Hungary	Màkos kalàcs	12.7	120	10.6	180	30	Ground	Bernáth J and Németh E, 2010
Pastries and Cakes	Austria	Flower power Mohntorte	12.7	75	17.0	160	50		http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html

Table C2: Continued.

Food group	Country	Food name	Poppy seeds (g/ portion)	Portion weight (g, estimated)	Poppy seeds (g/ 100 g)	Temp (°C)	Time of heat treat. (min)	Notes	Reference
Pastries and Cakes	Hungary	Mákos és diós bejgli (Poppy seed and wallnut roll)	12.9	100	12.9	180	30		http://www.nosalty.hu/mak_alapanyag_324
Pastries and Cakes	Lithuania	Poppy seed cake	13.3	85	15.6	190	45	Blended into a paste	Lithuanian Traditional Foods, Baltos Lankos, Compiled by Biruté Imbrasiene
Pastries and Cakes	Germany	Mohnrolle	13.4	120	11.2	170	30	Ground	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Hungary	Afonyazselés maktorta	14.1	65	21.7	175	30	Ground	Bernáth J and Németh E, 2010
Pastries and Cakes	Hungary	Bögrés mçaktorta	14.1	70	20.3	180	20	Ground	Bernáth J and Németh E, 2010
Pastries and cakes	Germany	Mohn - Joghurt - Becherkuchen	14.4	125	11.5	180	45		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Hungary	Mákfelfújt csokoládémartással	14.4	60	24.0	170	3-4	Raw, ground	Bernáth J and Németh E, 2010
Pastries and Cakes	Hungary	Màkos-barracklekvaros pite	14.8	120	12.3	175	25		Bernáth J and Németh E, 2010
Pastries and Cakes	Hungary	Mazsolàs màkos rétes	14.8	32	41.1	180	25	Fresh ground poppy seeds	Bernáth J and Németh E, 2010
Pastries and Cakes	Hungary	Mákos szedres gombóc	14.9	120	12.4	200	n.a	Raw, ground	Bernáth J and Németh E, 2010
Pastries and Cakes	Germany	Mohntorte	15.0	80	18.9	150	25		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Austria	Feiner Mohnrehrücken	15.9	75	21.3	180	45		http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html
Pastries and Cakes	Hungary	Máklepény	16.0	75	21.3	Baked	30-40		Bernáth J and Németh E, 2010
Pastries and Cakes	Czech Republic	České buchty (Czech buns)	16.2	80	20.3	180	35		http://www.apetitonline.cz/recepty/745-ceske-buchty.html
Pastries and Cakes	Slovenia	"Prekmurska gibanica" (dough-pie)	16.5	140	11.8	Baked	60		http://www.kulinarika.net/english/food/recipe.asp

Table C2: Continued.

Food group	Country	Food name	Poppy seeds (g/ portion)	Portion weight (g, estimated)	Poppy seeds (g/ 100 g)	Temp (°C)	Time of heat treat. (min)	Notes	Reference
Pastries and Cakes	Hungary	Mákfelfújt	17.0	90	19.0	Baked	n.a		Bernáth J and Németh E, 2010
Pastries and Cakes	Germany	Mohn - Käse - Torte mit gemahlenem Mohn (Cheese cake with poppy seeds)	17.4	150	11.6	175	60	Ground	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Germany	Beas leckerer Mohnkuchen	18.3	70	25.9	160	45		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Hungary	Mákos-omlós kifli	18.6	90	21.0	180	20	Ground	Bernáth J and Németh E, 2010
Pastries and Cakes	Germany	Englischer Mohnkuchen	18.9	150	12.7	200	15	Ground	http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Slovenia	Potica (Poppy Seed Roll)	21.6	120	18.0	Baked	50		http://easteuropeanfood.about.com/od/polishdesserts/r/topielec.htm
Pastries and Cakes	Germany	Mohnstrudel	21.8	120	18.2	180	60		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Hungary	Mak Torta II	23.5	75	31.4	n.a	n.a	Ground	Bernáth J and Németh E, 2010
Pastries and Cakes	Poland	Makowiec (poppy seed roll)	24.1	120	20.1	350	30-35	Poppy seeds are first boiled	http://www.thefreshloaf.com/recipes/makowiec
Pastries and Cakes	Austria	Mohnrollen	24.7	120	20.6	175	14		http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html
Pastries and Cakes	Austria	Mohnstrudel aus Germteig (Poppy seed strudel from yeast dough)	24.8	150	16.5	170	40		http://www.ichkoche.at/cms/rezepte/rezeptsuche/index.html
Pastries and Cakes	Germany	Mohnkuchen	27.8	150	18.5	160	40		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Germany	Fruchtiger Hefezopf mit Mohn und Kirschen	28.8	150	19.2	175	50		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Germany	Mohn - Apfelkuchen mit Butterstreuseln (name modified)	30.0	150	20.0	180	60		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Hungary	Mákos pite	31.6	150	21.0	Baked	n.a		Bernáth J and Németh E, 2010

Table C2: Continued.

Food group	Country	Food name	Poppy seeds (g/ portion)	Portion weight (g, estimated)	Poppy seeds (g/ 100 g)	Temp (°C)	Time of heat treat. (min)	Notes	Reference
Pastries and Cakes	Czech Republic	Bábovka	34.5	125	27.6	Baked	50		http://allrecipes.pl/przepis
Pastries and Cakes	Czech Republic	Makový závin (Poppy Seed Cake)	37.5	219	17.1	Baked	60		http://www.srecepty.cz/ingredience/mak?pof_name=ingredient_recipes_693
Pastries and Cakes	Czech Republic	Bramborové lokše s mákem. (Potato pancakes with poppy seed)	38.0	370	10.3	n.a	30	Ground. Sprinkled on the surface before serving	http://www.srecepty.cz/ingredience/mak?pof_name=ingredient_recipes_693
Pastries and Cakes	Germany	Makowki	41.0	153	26.8	Low	30		http://www.chefkoch.de/rezepte/1035461208686047/Mohnpielen.html
Pastries and Cakes	Hungary	Macerás mákosguba	42.0	244	17.2	200	15		http://www.nosalty.hu/mak_alapanyag_324
Pastries and Cakes	Hungary	Mákosguba	42.0	205	20.5	150	50		http://www.nosalty.hu/mak_alapanyag_324
Pastries and Cakes	Hungary	Máktorta (Poppy Seed Cake)	50.0	185	27.0	170	60		http://www.nosalty.hu/mak_alapanyag_324
Baking ingredient	Slovakia	Poppy seed filling	20.0	50	40.0	n.a	n.a		http://www.gurman.sk/recept-makova-plnka-AAA2777/
Baking ingredients	Czech Republic	Sweet poppy seed filling for cakes	23.0	50	46.0	n.a	n.a	Ground	http://www.srecepty.cz/ingredience/mak?pof_name=ingredient_recipes_693

n.a.: information not available.

APPENDIX D

Table D1: Acute exposure (µg/kg b.w. per day) to five opium alkaloids for average consumers of poppy seeds according to the EFSA Comprehensive Food Consumption Database in different age groups based on average and high (95th percentile) occurrence.

Age group	Country	n [(a)]	Morphine		Codeine		Thebaine		Papaverine		Noscapine	
			LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Other children	Czech Republic	23	9.16/	9.25	0.78	0.85	0.89/	0.94	0.03	0.162	0.28	0.47
Adolescents	Czech Republic	11	8.06/	8.14	0.69	0.75	0.78/	0.82	0.02	0.143	0.25	0.41
Adults	Czech Republic	41	4.73/	4.77	0.41	0.44	0.46/	0.48	0.01	0.08	0.15	0.24
Adults	Hungary	58	4.06/	4.10	0.35	0.38	0.39/	0.41	0.01	0.07	0.12	0.21
Adults	Slovakia	13	17.2/	17.4	1.48	1.60	1.67/	1.76	0.05	0.305	0.53	0.88
Elderly	Hungary	18	3.11/	3.14	0.27	0.29	0.30/	0.32	<0.01	0.06	0.10	0.16
High occurrence (P95)												
Other children	Czech Republic	23	48.3	48.3	3.82	3.82	3.36	3.36	0.11	0.28	1.16	1.16
Adolescents	Czech Republic	11	42.5	42.5	3.36	3.36	2.96	2.96	0.10	0.24	1.02	1.02
Adults	Czech Republic	41	24.9	24.9	1.97	1.97	1.73	1.73	0.06	0.14	0.60	0.60
Adults	Hungary	58	21.4	21.4	1.69	1.69	1.49	1.49	0.05	0.12	0.51	0.51
Adults	Slovakia	13	90.9	90.9	7.19	7.19	6.32	6.32	0.21	0.52	2.17	2.17
Elderly	Hungary	18	16.4	16.4	1.30	1.30	1.14	1.14	0.04	0.09	0.39	0.39

b.w.: body weight; P95: 95th percentile; LB: lower bound; UB: upper bound;

(a): Surveys with <10 consumption days of poppy seeds are excluded of this table. Exposure assessment is based on average poppy seed consumption only, because none of the surveys exceeded the limit of 60 observations (consumption days) considered to be the minimum to reliably estimate high consumption (EFSA 2011b).

Table D2: Opium alkaloid exposure (µg/kg b.w., LB/UB) to hypothetical single portion scenarios based on mean and P95 occurrence values.

Scenario	Age group	Food (portion)	Poppy seeds (g/portion)	Body weight (kg)	Opium alkaloid	Mean exposure (µg/kg b.w.)	P95 exposure (µg/kg b.w.)
						LB-UB	LB-UB
1	Toddlers	Poppy seed cake (50g)	15.5	11.6	Morphine	44.5-44.9	235
					Codeine	3.81-4.31	18.6
					Thebaine	4.32-4.54	16.3
					Papaverine	0.12-0.79	0.53-1.34
					Noscapine	1.36-2.27	5.61
2	Other children	Poppy seed cake (100g)	31	21.6	Morphine	47.8-48.2	252
					Codeine	4.09-4.43	19.9
					Thebaine	4.64-4.88	17.5
					Papaverine	0.13-0.85	0.57-1.44
					Noscapine	1.46-2.44	6.03
3	Adults	Poppy seed dessert (200g)	70	73	Morphine	31.9-32.2	168
					Codeine	2.73-2.96	13.3
					Thebaine	3.10-3.26	11.7
					Papaverine	0.09-0.57	0.38-0.96
					Noscapine	0.98-1.63	4.03
4	Adults	Noodles with poppy seeds (370 g)	83	73	Morphine	37.9-38.2	200
					Codeine	3.24-3.51	15.8
					Thebaine	3.67-3.87	13.9
					Papaverine	0.10-0.67	0.45-1.14
					Noscapine	1.16-1.93	4.78

b.w.: body weight; LB: lower bound; UB: upper bound; P95: 95th percentile.

Table D3: Summary statistics of the exposure (µg/kg b.w. per day) to different opium alkaloids for average and high consuming (95th percentile) toddlers with mean and high occurrence (95th percentile) from the food group of "Fine bakery ware" for high poppy seed content based on analysed opium alkaloid content of bakery products.

Opium alkaloid	Exposure (µg/kg b.w. per day)											
	Average consumption						High consumption (P95)					
	MIN[(a)]		MED[(a)]		MAX[(a)]		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.36	0.66	0.49	0.91	1.66	3.07	1.09	2.02	1.42	2.64	4.51	8.38
Codeine	0.16	0.34	0.22	0.47	0.73	1.59	0.48	1.05	0.63	1.37	1.99	4.34
Thebaine	0.01	0.08	0.01	0.11	0.04	0.36	0.03	0.23	0.03	0.31	0.11	0.97
Papaverine	0	0.06	0	0.09	0	0.30	0	0.20	0	0.26	0	0.82
Noscapine	0.012	0.07	0.02	0.10	0.05	0.34	0.04	0.22	0.05	0.29	0.15	0.93
High occurrence (P95)												
Morphine	2.01	2.01	2.76	2.76	9.37	9.37	6.15	6.15	8.04	8.04	25.5	25.5
Codeine	0.67	0.67	0.92	0.92	3.12	3.12	2.05	2.05	2.68	2.68	8.51	8.51
Thebaine[(b)]	0.13	0.13	0.18	0.18	0.62	0.62	0.41	0.41	0.54	0.54	1.70	1.70
Papaverine[(b)]	0	0.13	0	0.18	0	0.62	0	0.41	0	0.54	01.70	1.70
Noscapine[(b)]	0.13	0.13	0.17	0.17	0.59	0.59	0.39	0.39	0.51	0.51	1.62	1.62

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.

(a): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

(b): The results based on high occurrence (P95) should be considered as indicative only due to the limited number of occurrence data (n < 60) (EFSA, 2011b).

Table D4: Summary statistics of the exposure (µg/kg b.w. per day) to different opium alkaloids for average and high consuming (95th percentile) children 3-10 years of age with mean and high occurrence (95th percentile) from the food group of "Fine bakery ware" for high poppy seed content based on analysed opium alkaloid content of bakery products.

Opium alkaloid	Exposure (µg/kg b.w. per day)											
	Average consumption						High consumption (P95)					
	MIN[a]		MED[a]		MAX[a]		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.33	0.62	0.77	1.42	1.86	3.46	0.90	1.68	2.08	3.98	5.43	10.1
Codeine	0.15	0.32	0.34	0.74	0.82	1.79	0.40	0.87	0.92	2.01	2.39	5.23
Thebaine	0.01	0.07	0.02	0.16	0.04	0.40	0.02	0.19	0.05	0.45	0.13	1.17
Papaverine	0	0.06	0	0.14	0	0.34	0	0.16	0	0.38	0	0.98
Noscapine	0.01	0.07	0.03	0.16	0.06	0.38	0.03	0.19	0.07	0.43	0.18	1.12
High occurrence (P95)												
Morphine	1.88	1.88	4.33	4.33	10.6	10.6	5.11	5.11	11.8	11.8	30.7	30.7
Codeine	0.63	0.63	1.44	1.44	3.52	3.52	1.70	1.70	3.93	3.93	10.3	10.3
Thebaine[b]	0.13	0.13	0.29	0.29	0.29	0.29	0.34	0.34	0.79	0.79	2.05	2.05
Papaverine[b]	0	0.13	0	0.29	0	0.70	0	0.34	0	0.79	0	2.05
Noscapine[b]	0.12	0.12	0.27	0.27	0.67	0.67	0.32	0.32	0.75	0.75	1.95	1.95

b.w.: body weight; P95: 95th percentile; Min: minimum: Med: median; Max: maximum; LB: lower bound; UB: upper bound.

(a): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

(b): The results based on high occurrence (P95) should be considered as indicative only due to the limited number of occurrence data (n < 60) (EFSA, 2011b).

Table D5: Summary statistics of the exposure (µg/kg b.w. per day) to different opium alkaloids for average and high consuming (95th percentile) adolescents with mean and high occurrence (95th percentile) from the food group of "Fine bakery ware" for high poppy seed content based on analysed opium alkaloid content of bakery products.

Opium alkaloid	Exposure (µg/kg b.w. per day)											
	Average consumption						High consumption (P95)					
	MIN[a]		MED[a]		MAX[a]		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.55	1.016	0.80	1.48	1.23	2.28	1.74	3.23	1.99	3.69	4.06	7.54
Codeine	0.24	0.53	0.35	0.77	0.54	1.18	0.77	1.67	0.87	1.91	1.79	3.91
Thebaine	0.01	0.12	0.02	0.17	0.03	0.26	0.04	0.37	0.05	0.43	0.10	0.87
Papaverine	0	0.10	0	0.14	0	0.22	0	0.31	0	0.36	0	0.74
Noscapine	0.02	0.11	0.03	0.16	0.04	0.25	0.06	0.36	0.07	0.41	0.13	0.84
High occurrence (P95)												
Morphine	3.10	3.10	4.52	4.52	6.96	6.96	9.84	9.84	11.3	11.3	23.0	23.0
Codeine	1.03	1.03	1.51	1.51	2.32	2.32	3.28	3.28	3.75	3.75	7.66	7.66
Thebaine[b]	0.21	0.21	0.30	0.30	0.46	0.46	0.66	0.66	0.75	0.75	1.53	1.53
Papaverine[b]	0	0.21	0	0.30	0	0.46	0	0.66	0	0.75	0	1.53
Noscapine[b]	0.20	0.20	0.29	0.29	0.44	0.44	0.62	0.62	0.71	0.71	1.46	1.46

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound

(a): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

(b): The results based on high occurrence (P95) should be considered as indicative only due to the limited number of occurrence data (n < 60) (EFSA, 2011b).

Table D6: Summary statistics of the exposure (µg/kg b.w. per day) to separate opium alkaloids for average and high consuming (95th percentile) adults with mean and high occurrence (95th percentile) from the food group of "Fine bakery ware" for high poppy seed content based on analysed opium alkaloid content of bakery products.

Opium alkaloid	Exposure (µg/kg b.w. per day)											
	Average consumption						High consumption (P95)					
	MIN[a]		MED[a]		MAX[a]		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.09	0.16	0.43	0.80	0.97	1.80	0.30	0.56	1.28	2.37	2.58	4.79
Codeine	0.04	0.08	0.19	0.42	0.43	0.93	0.13	0.29	0.56	1.23	1.14	2.48
Thebaine	0.002	0.02	0.01	0.09	0.02	0.21	0.01	0.06	0.03	0.27	0.06	0.56
Papaverine	0	0.02	0	0.08	0	0.18	0	0.05	0	0.23	0	0.47
Noscapine	0.002	0.02	0.01	0.09	0.032	0.20	0.01	0.06	0.04	0.26	0.09	0.53
High occurrence (P95)												
Morphine	0.50	0.50	2.45	2.45	5.48	5.48	1.70	1.70	7.23	7.23	14.6	14.6
Codeine	0.17	0.17	0.82	0.82	1.83	1.83	0.57	0.57	2.41	2.41	4.87	4.87
Thebaine[b]	0.03	0.03	0.16	0.16	0.37	0.37	0.11	0.11	0.48	0.48	0.97	0.97
Papaverine[b]	0	0.03	0	0.16	0	0.37	00.11	0.11	0	0.48	0	0.97
Noscapine[b]	0.03	0.03	0.15	0.15	0.35	0.35	0.11	0.11	0.46	0.46	0.93	0.93

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.

(a): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

(b): The results based on high occurrence (P95) should be considered as indicative only due to the limited number of occurrence data (n < 60) (EFSA, 2011b).

Table D7: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among toddlers and mean and high (95th percentile) alkaloid occurrence from the food categories of "Bread" with high poppy seed content.

Opium alkaloid	Exposure (µg/kg b.w. per day)											
	Mean bread[a] consumption[b]						High bread consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	2.98	3.01	3.71	3.75	16.4	16.6	8.09	8.17	10.9	11.0	33.9	34.2
Codeine	0.26	0.28	0.32	0.34	1.41	1.52	0.69	0.75	0.93	1.01	2.90	3.15
Thebaine	0.29	0.30	0.36	0.38	1.59	1.68	0.79	0.83	1.06	1.11	3.29	3.46
Papaverine	0.01	0.05	0.01	0.07	0.04	0.29	0.02	0.14	0.03	0.19	0.09	0.60
Noscapine	0.09	0.15	0.11	0.19	0.50	0.84	0.25	0.41	0.33	0.56	1.04	1.73
High occurrence (P95)												
Morphine	1.24	1.24	19.6	19.6	19.6	19.6	42.6	42.6	57.5	57.5	179	179
Codeine	1.24	1.24	1.55	1.55	6.85	6.85	3.38	3.38	4.55	4.55	4.55	4.55
Thebaine	1.09	1.09	1.36	1.36	6.02	6.02	2.96	2.96	4.00	4.00	12.4	12.4
Papaverine	0.04	0.09	0.04	0.11	0.20	0.49	0.10	0.24	0.13	0.33	0.41	1.02
Noscapine	0.38	0.38	0.47	0.47	2.07	2.07	1.02	1.02	1.38	1.38	4.28	4.28

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups wheat bread, rolls and unleavened crisp bread using high poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D8: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average andhigh (95th percentile) consumption among "other children" and mean and high (95th percentile) alkaloid occurrence from the food categories of "Bread" with high poppy seed content.

Opium alkaloid	Exposure (µg/kg b.w. per day)											
	Mean bread[(a)] consumption[(b)]						High bread consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	3.35	3.38	6.53	6.59	16.7	16.8	10.1	10.2	15.4	15.6	38.7	39.1
Codeine	0.29	0.31	0.56	0.61	1.43	1.55	0.87	0.94	1.32	1.43	3.31	3.59
Thebaine	0.33	0.34	0.63	0.67	1.62	1.70	0.98	1.03	1.50	1.58	3.76	3.95
Papaverine	0.01	0.06	0.02	0.12	0.05	0.30	0.03	0.18	0.04	0.27	0.11	0.69
Noscapine	0.10	0.17	0.20	0.33	0.51	0.85	0.31	0.52	0.47	0.79	1.19	1.98
High occurrence (P95)												
Morphine	17.60	17.60	34.4	34.4	87.8	87.8	53.3	53.3	81.4	81.4	204	204
Codeine	1.40	1.40	2.72	2.72	6.95	6.95	4.22	4.22	6.44	6.44	16.2	16.2
Thebaine	1.23	1.23	2.39	2.39	6.10	6.10	3.71	3.71	5.66	5.66	14.2	14.2
Papaverine	0.04	0.10	0.08	0.20	0.20	0.50	0.12	0.30	0.19	0.46	0.47	1.16
Noscapine	0.42	0.42	0.82	0.82	2.10	2.10	1.28	1.28	1.95	1.95	4.88	4.88

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups wheat bread, rolls and unleavened crisp bread using high poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D9: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among adolescents and mean and high (95th percentile) alkaloid occurrence from the food categories of "Bread" with high poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Mean bread[a] consumption[b]						High bread consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	4.24	4.28	6.04	6.10	18.3	18.5	11.1	11.2	14.8	14.9	45.4	45.80
Codeine	0.36	0.39	0.52	0.56	1.57	1.70	0.95	1.03	1.27	1.37	3.89	4.21
Thebaine	0.41	0.43	0.59	0.62	1.78	1.87	1.07	1.13	1.43	1.51	4.40	4.64
Papaverine	0.01	0.08	0.02	0.11	0.05	0.33	0.03	0.20	0.04	0.26	0.12	0.80
Noscapine	0.13	0.22	0.19	0.31	0.56	0.94	0.34	0.56	0.45	0.76	1.39	2.32
High occurrence (P95)												
Morphine	22.4	22.4	31.9	31.9	96.6	96.6	58.3	58.3	77.9	77.9	239	239
Codeine	1.77	1.77	2.52	2.52	7.65	7.65	4.61	4.61	6.17	6.17	18.9	18.9
Thebaine	1.55	1.55	2.22	2.22	6.72	6.72	4.05	4.05	5.42	5.42	16.6	16.6
Papaverine	0.05	0.13	0.07	0.18	0.22	0.55	0.13	0.33	0.18	0.44	0.55	1.36
Noscapine	0.54	0.54	0.76	0.76	2.31	2.31	1.39	1.39	1.86	1.86	0.55	1.36

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups wheat bread, rolls and unleavened crisp bread using high poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D10: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among adults and mean and high (95th percentile) alkaloid occurrence from the food categories of "Bread" with high poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Mean bread[a] consumption[b]						High bread consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	1.55	1.57	3.91	3.95	16.3	16.5	4.43	0.38	9.90	10.0	34.0	34.3
Codeine	0.13	0.14	0.34	0.36	1.40	1.51	0.38	0.41	0.85	0.92	2.91	3.15
Thebaine	0.15	0.16	0.38	0.40	1.58	1.67	0.43	0.45	0.96	1.01	3.29	3.47
Papaverine	0.00	0.03	0.01	0.07	0.04	0.29	0.01	0.08	0.03	0.18	0.09	0.60
Noscapine	0.05	0.08	0.12	0.20	0.50	0.83	0.14	0.22	0.30	0.51	1.04	1.73
High occurrence (P95)												
Morphine	8.20	8.20	20.6	20.6	85.9	85.9	23.1	23.1	52.2	52.2	179	179
Codeine	0.65	0.65	1.63	1.63	6.80	6.80	1.83	1.83	4.13	4.13	4.13	4.13
Thebaine	0.57	0.57	1.43	1.43	5.97	5.97	1.61	1.61	3.63	3.63	12.4	12.4
Papaverine	0.02	0.05	0.05	0.12	0.20	0.49	0.05	0.13	0.12	0.30	0.41	1.02
Noscapine	0.20	0.20	0.49	0.49	2.06	2.06	0.55	0.55	1.25	1.25	4.28	4.28

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups wheat bread, rolls and unleavened crisp bread using high poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D11: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among toddlers and mean and high (95th percentile) alkaloid occurrence from the food categories of "Bread" with low poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Mean bread[a] consumption[b]						High bread consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.08	0.08	0.59	0.59	0.67	0.67	0.27	0.27	1.33	1.34	1.54	1.56
Codeine	0.01	0.01	0.05	0.05	0.06	0.06	0.02	0.02	0.11	0.12	0.13	0.14
Thebaine	0.01	0.01	0.06	0.06	0.06	0.07	0.03	0.03	0.13	0.14	0.15	0.16
Papaverine	0.00	0.00	0.00	0.01	0.00	0.01	0.00	0.00	0.00	0.02	0.00	0.03
Noscapine	0.00	0.00	0.02	0.03	0.67	0.67	0.01	0.01	0.04	0.07	1.54	1.56
High occurrence (P95)												
Morphine	0.44	0.44	3.10	3.10	3.52	3.52	1.40	1.40	7.00	7.00	8.14	8.14
Codeine	0.03	0.03	0.25	0.25	0.28	0.28	0.11	0.11	0.55	0.55	0.65	0.65
Thebaine	0.03	0.03	0.22	0.22	0.25	0.25	0.10	0.10	0.49	0.49	0.57	0.57
Papaverine	0.00	0.00	0.01	0.02	0.01	0.02	0.00	0.01	0.02	0.04	0.02	0.05
Noscapine	0.01	0.01	0.07	0.07	0.08	0.08	0.03	0.03	0.17	0.17	0.20	0.20

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups wheat bread, rolls and unleavened crisp bread using low poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D12: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among other children and mean and high (95th percentile) alkaloid occurrence from the food categories of "Bread" with low poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Mean bread[a] consumption[b]						High bread consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.14	0.14	0.17	0.17	0.58	0.58	0.32	0.32	0.47	0.47	1.35	1.37
Codeine	0.01	0.01	0.01	0.02	0.05	0.05	0.03	0.03	0.04	0.04	0.12	0.13
Thebaine	0.01	0.01	0.02	0.02	0.06	0.06	0.03	0.03	0.05	0.05	0.13	0.14
Papaverine	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.02
Noscapine	0.00	0.01	0.01	0.01	0.02	0.03	0.01	0.02	0.01	0.02	0.04	0.07
High occurrence (P95)												
Morphine	0.71	0.71	0.88	0.88	3.04	3.04	1.66	1.66	2.47	2.47	7.13	7.13
Codeine	0.06	0.06	0.07	0.07	0.24	0.24	0.13	0.13	0.20	0.20	0.57	0.57
Thebaine	0.05	0.05	0.06	0.06	0.21	0.21	0.12	0.12	0.17	0.17	0.50	0.50
Papaverine	0.00	0.00	0.00	0.01	0.01	0.02	0.00	0.01	0.01	0.01	0.02	0.04
Noscapine	0.02	0.02	0.02	0.02	0.07	0.07	0.04	0.04	0.06	0.06	0.17	0.17

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups wheat bread, rolls and unleavened crisp bread using low poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D13: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among adolescents and mean and high (95th percentile) alkaloid occurrence from the food categories of "Bread" with low poppy seed content. .

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Mean bread[a] consumption[b]						High bread consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.10	0.10	0.24	0.24	0.46	0.47	0.25	0.25	0.61	0.62	1.11	1.12
Codeine	0.01	0.01	0.02	0.02	0.04	0.04	0.02	0.02	0.05	0.06	0.09	0.10
Thebaine	0.01	0.01	0.02	0.02	0.05	0.05	0.02	0.03	0.06	0.06	0.11	0.11
Papaverine	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.01	0.00	0.02
Noscapine	0.00	0.01	0.01	0.01	0.01	0.02	0.01	0.01	0.02	0.03	0.03	0.06
High occurrence (P95)												
Morphine	0.52	0.52	1.25	1.25	2.44	2.44	1.31	1.31	3.21	3.21	5.83	5.83
Codeine	0.04	0.04	0.10	0.10	0.19	0.19	0.10	0.10	0.25	0.25	0.46	0.46
Thebaine	0.04	0.04	0.09	0.09	0.17	0.17	0.09	0.09	0.22	0.22	0.41	0.41
Papaverine	0.00	0.00	0.00	0.01	0.01	0.01	0.00	0.01	0.01	0.02	0.01	0.03
Noscapine	0.01	0.01	0.03	0.03	0.06	0.06	0.03	0.03	0.08	0.08	0.14	0.14

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups wheat bread, rolls and unleavened crisp bread using low poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D14: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among adults and mean and high (95th percentile) alkaloid occurrence from the food categories of "Bread" with low poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Mean bread[a] consumption[b]						High bread consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.05	0.05	0.09	0.09	0.34	0.35	0.11	0.11	0.21	0.22	0.91	0.92
Codeine	0.00	0.00	0.01	0.01	0.03	0.03	0.01	0.01	0.02	0.02	0.08	0.08
Thebaine	0.00	0.00	0.01	0.01	0.03	0.04	0.01	0.01	0.02	0.02	0.09	0.09
Papaverine	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.02
Noscapine	0.00	0.00	0.00	0.00	0.01	0.02	0.00	0.01	0.01	0.01	0.03	0.05
High occurrence (P95)												
Morphine	0.24	0.24	0.49	0.49	1.81	1.81	0.57	0.57	1.12	1.12	4.81	4.81
Codeine	0.02	0.02	0.04	0.04	0.14	0.14	0.05	0.05	0.09	0.09	0.38	0.38
Thebaine	0.02	0.02	0.03	0.03	0.13	0.13	0.04	0.04	0.08	0.08	0.34	0.34
Papaverine	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.01	0.01	0.03
Noscapine	0.01	0.01	0.01	0.01	0.04	0.04	0.01	0.01	0.03	0.03	0.12	0.12

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups wheat bread, rolls and unleavened crisp bread using low poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D15: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among toddlers and mean and high (95th percentile) alkaloid occurrence from the food categories of "Fine Bakery" with high poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Average fine bakery ware[a] consumption[b]						High fine bakery ware consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	11.1	11.2	15.7	15.9	46.1	46.6	31.4	31.7	39.7	40.1	116	117
Codeine	0.95	1.03	1.34	1.46	3.95	4.28	2.69	2.92	3.40	3.69	9.95	10.8
Thebaine	1.07	1.13	1.52	1.60	4.48	4.71	3.05	3.21	3.86	4.06	11.3	11.9
Papaverine	0.03	0.20	0.04	0.28	0.13	0.82	0.09	0.56	0.11	0.70	0.31	2.06
Noscapine	0.34	0.57	0.48	0.80	1.41	2.36	0.96	1.60	1.22	2.03	3.56	5.93
High occurrence (P95)												
Morphine	58.4	58.4	82.8	82.8	243	243	166	166	209	209	613	613
Codeine	4.62	4.62	6.55	6.55	19.3	19.3	13.1	13.1	16.6	16.6	48.5	48.5
Thebaine	4.06	4.06	5.75	5.75	16.9	16.9	11.5	11.5	14.6	14.6	42.6	42.6
Papaverine	0.13	0.33	0.19	0.47	0.55	1.39	0.38	0.94	0.48	1.19	1.40	3.49
Noscapine	1.40	1.40	1.98	1.98	5.82	5.82	3.96	3.96	5.01	5.01	14.7	14.7

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups cakes, pastries and biscuits using high poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D16: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among other children and mean and high (95th percentile) alkaloid occurrence from the food categories of "Fine Bakery" with high poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Average fine bakery ware[a] consumption[b]						High fine bakery ware consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	10.2	10.3	22.9	23.1	51.2	51.7	26.6	26.9	64.6	65.2	143	144
Codeine	0.87	0.94	1.96	2.12	4.38	4.75	2.28	2.47	5.53	5.99	12.20	13.30
Thebaine	0.99	1.04	2.22	2.34	4.97	5.23	2.58	2.72	6.26	6.59	13.90	14.60
Papaverine	0.03	0.18	0.06	0.41	0.14	0.91	0.07	0.47	0.18	1.14	0.39	2.53
Noscapine	0.31	0.52	0.70	1.17	1.57	2.61	0.82	1.36	1.98	3.30	1.98	3.30
High occurrence (P95)												
Morphine	53.6	53.6	121	121	270	270	140	140	340	340	753	753
Codeine	4.24	4.24	9.55	9.55	21.4	21.4	11.1	11.1	26.9	26.9	59.6	59.6
Thebaine	3.72	3.72	8.39	8.39	18.8	18.8	9.76	9.76	23.7	23.7	52.4	52.4
Papaverine	0.12	0.31	0.28	0.69	0.62	1.54	0.32	0.80	0.78	1.94	1.72	4.29
Noscapine	1.28	1.28	2.89	2.89	6.46	6.46	3.36	3.36	8.14	8.14	18.0	18.0

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups cakes, pastries and biscuits using high poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D17: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among adolescents mean and high (95th percentile) alkaloid occurrence from the food categories of "Fine Bakery" with high poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Average fine bakery ware[a] consumption[b]						High fine bakery ware consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	14.8	15.0	23.2	23.4	33.3	33.7	45.8	46.3	55.1	55.7	105	106
Codeine	1.27	1.38	1.98	2.15	2.85	3.09	3.92	4.25	4.72	5.12	9.02	9.78
Thebaine	1.44	1.52	2.25	2.37	3.23	3.40	4.44	4.68	5.35	5.63	10.2	10.8
Papaverine	0.04	0.26	0.06	0.41	0.09	0.59	0.12	0.81	0.15	0.98	0.29	1.87
Noscapine	0.46	0.76	0.71	1.18	1.02	1.70	1.40	2.34	1.69	2.81	3.23	5.38
High occurrence (P95)												
Morphine	78.2	78.2	122	122	176	176	242	242	291	291	555	555
Codeine	6.19	6.19	9.67	9.67	13.9	13.9	19.1	19.1	23.0	23.0	44.0	44.0
Thebaine	5.44	5.44	8.49	8.49	12.2	12.2	16.8	16.8	20.2	20.2	38.6	38.6
Papaverine	0.18	0.45	0.28	0.70	0.40	1.00	0.55	1.38	0.66	1.66	1.27	3.16
Noscapine	1.87	1.87	2.92	2.92	4.20	4.20	5.78	5.78	6.95	6.95	13.3	13.3

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups cakes, pastries and biscuits using high poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D18: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among adults mean and high (95th percentile) alkaloid occurrence from the food categories of "Fine Bakery" with high poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Average fine bakery ware[a] consumption[b]						High fine bakery ware consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	2.48	2.50	11.5	11.6	27.9	28.2	9.23	9.32	32.9	33.2	71.1	71.8
Codeine	0.21	0.23	0.98	1.06	2.39	2.59	0.79	0.86	2.82	3.05	6.08	6.60
Thebaine	0.24	0.25	1.11	1.17	2.71	2.85	0.90	0.94	3.19	3.36	6.90	7.26
Papaverine	0.01	0.04	0.03	0.20	0.08	0.49	0.03	0.16	0.09	0.58	0.19	1.26
Noscapine	0.08	0.13	0.35	0.59	0.86	1.42	0.28	0.47	1.01	1.68	2.18	3.63
High occurrence (P95)												
Morphine	13.1	13.1	60.4	60.4	147	147	48.7	48.7	173	173	375	375
Codeine	1.03	1.03	4.78	4.78	11.6	11.6	3.85	3.85	13.7	13.7	29.7	29.7
Thebaine	0.91	0.91	4.20	4.20	10.2	10.2	3.38	3.38	12.1	12.1	26.0	26.0
Papaverine	0.03	0.07	0.14	0.34	0.34	0.84	0.11	0.28	0.40	0.99	0.85	2.13
Noscapine	0.31	0.31	1.45	1.45	3.52	3.52	1.16	1.16	4.15	4.15	8.97	8.97

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups cakes, pastries and biscuits using high poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D19: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among toddlers and mean and high (95th percentile) alkaloid occurrence from the food categories of "Fine Bakery" with low poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Average fine bakery ware[a] consumption[b]						High fine bakery ware consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.39	0.39	1.84	1.86	2.46	2.49	1.37	1.38	5.55	5.60	6.88	6.94
Codeine	0.03	0.04	0.16	0.17	0.21	0.23	0.12	0.13	0.48	0.52	0.59	0.64
Thebaine	0.04	0.04	0.18	0.19	0.24	0.25	0.13	0.14	0.54	0.57	0.67	0.70
Papaverine	0.00	0.01	0.00	0.03	0.01	0.04	0.00	0.02	0.02	0.10	0.02	0.12
Noscapine	0.01	0.02	0.06	0.09	0.08	0.13	0.04	0.07	0.17	0.28	0.21	0.35
High occurrence (P95)												
Morphine	2.03	2.03	9.72	9.72	13.0	13.0	7.20	7.20	29.3	29.3	36.3	36.3
Codeine	0.16	0.16	0.77	0.77	1.03	1.03	0.57	0.57	2.32	2.32	2.87	2.87
Thebaine	0.14	0.14	0.68	0.68	0.90	0.90	0.50	0.50	2.03	2.03	2.52	2.52
Papaverine	0.00	0.01	0.02	0.06	0.03	0.07	0.02	0.04	0.07	0.17	0.08	0.21
Noscapine	0.05	0.05	0.23	0.23	0.31	0.31	0.17	0.17	0.70	0.70	0.87	0.87

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups cakes, pastries and biscuits using low poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D20: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among other children and mean and high (95th percentile) alkaloid occurrence from the food categories of "Fine Bakery" with low poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Average fine bakery ware[a] consumption[b]						High fine bakery ware consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.16	0.16	1.49	1.51	2.29	2.31	0.69	0.70	3.86	3.90	6.36	6.43
Codeine	0.01	0.01	0.13	0.14	0.20	0.21	0.06	0.06	0.33	0.36	0.55	0.59
Thebaine	0.02	0.02	0.15	0.15	0.22	0.23	0.07	0.07	0.38	0.40	0.62	0.65
Papaverine	0.00	0.00	0.00	0.03	0.01	0.04	0.00	0.01	0.01	0.07	0.02	0.11
Noscapine	0.00	0.01	0.05	0.08	0.07	0.12	0.02	0.04	0.12	0.20	0.20	0.33
High occurrence (P95)												
Morphine	0.83	0.83	7.86	7.86	12.1	12.1	3.66	3.66	20.4	20.4	33.5	33.5
Codeine	0.07	0.07	0.62	0.62	0.96	0.96	0.29	0.29	1.61	1.61	2.65	2.65
Thebaine	0.06	0.06	0.55	0.55	0.84	0.84	0.25	0.25	1.42	1.42	2.33	2.33
Papaverine	0.00	0.00	0.02	0.04	0.03	0.07	0.01	0.02	0.05	0.12	0.08	0.19
Noscapine	0.02	0.02	0.19	0.19	0.29	0.29	0.09	0.09	0.49	0.49	0.80	0.80

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups cakes, pastries and biscuits using low poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D21: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among adolescents and mean and high (95th percentile) alkaloid occurrence from the food categories of "Fine Bakery" with low poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Average fine bakery ware[a] consumption[b]						High fine bakery ware consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.11	0.12	0.86	0.87	1.46	1.47	0.49	0.49	2.56	2.59	4.10	4.14
Codeine	0.01	0.01	0.07	0.08	0.13	0.14	0.04	0.05	0.22	0.24	0.35	0.38
Thebaine	0.01	0.01	0.08	0.09	0.14	0.15	0.05	0.05	0.25	0.26	0.40	0.42
Papaverine	0.00	0.00	0.00	0.02	0.00	0.03	0.00	0.01	0.01	0.05	0.01	0.07
Noscapine	0.00	0.01	0.03	0.04	0.04	0.07	0.02	0.03	0.08	0.13	0.13	0.21
High occurrence (P95)												
Morphine	0.60	0.60	4.52	4.52	7.70	7.70	2.58	2.58	13.5	13.5	21.6	21.6
Codeine	0.05	0.05	0.36	0.36	0.61	0.61	0.20	0.20	1.07	1.07	1.71	1.71
Thebaine	0.04	0.04	0.31	0.31	0.54	0.54	0.18	0.18	0.94	0.94	1.50	1.50
Papaverine	0.00	0.00	0.01	0.03	0.02	0.04	0.01	0.01	0.03	0.08	0.05	0.12
Noscapine	0.01	0.01	0.11	0.11	0.18	0.18	0.06	0.06	0.32	0.32	0.52	0.52

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups cakes, pastries and biscuits using low poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

Table D22: Summary statistics of the acute exposure (µg/kg b.w. per day) to opium alkaloids for average and high (95th percentile) consumption among adults and mean and high (95th percentile) alkaloid occurrence from the food categories of "Fine Bakery" with low poppy seed content.

Poppy seed alkaloid	Exposure (µg/kg b.w. per day)											
	Average fine bakery ware[a] consumption[b]						High fine bakery ware consumption (P95)					
	MIN		MED		MAX		MIN		MED		MAX	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Mean occurrence												
Morphine	0.05	0.05	0.34	0.34	1.09	1.10	0.23	0.24	0.97	0.98	3.20	3.23
Codeine	0.00	0.00	0.03	0.03	0.09	0.10	0.02	0.02	0.08	0.09	0.27	0.30
Thebaine	0.01	0.01	0.03	0.03	0.11	0.11	0.02	0.02	0.09	0.10	0.31	0.33
Papaverine	0.00	0.00	0.00	0.01	0.00	0.02	0.00	0.00	0.00	0.02	0.01	0.06
Noscapine	0.00	0.00	0.01	0.02	0.03	0.06	0.01	0.01	0.03	0.05	0.10	0.16
High occurrence (P95)												
Morphine	0.28	0.28	1.78	1.78	5.76	5.76	1.22	1.22	5.10	5.10	16.8	16.8
Codeine	0.02	0.02	0.14	0.14	0.46	0.46	0.10	0.10	0.40	0.40	1.33	1.33
Thebaine	0.02	0.02	0.12	0.12	0.40	0.40	0.09	0.09	0.36	0.36	1.17	1.17
Papaverine	0.00	0.00	0.00	0.01	0.01	0.03	0.00	0.01	0.01	0.03	0.04	0.10
Noscapine	0.01	0.01	0.04	0.04	0.14	0.14	0.03	0.03	0.12	0.12	0.40	0.40

b.w.: body weight; P95: 95th percentile; Min: minimum; Med: median; Max: maximum; LB: lower bound; UB: upper bound.
(a): Exposure scenario is based on the food groups cakes, pastries and biscuits using low poppy seed content and analysed opium alkaloid levels of poppy seeds.
(b): The average and P95 consumption data are calculated per food consumption survey. The table shows the exposure for the minimum, median and maximum consumption values for all surveys.

ABBREVIATIONS

ANS	The EFSA Panel on food additives and nutrient sources added to food
ARfD	acute reference dose
AUC	Area under the curve
BfR	Bundesinstitut für Risikobewertung/ the German Federal Institute for Risk Assessment
BtMG	Federal Republic of Germany pursuant to the Narcotics Act
b.w.	Body weight
C6G	codeine-6-glucuronide
cAMP	Cyclic adenosine monophosphate
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
CI	Confidence interval
CNS	Central nervous system
CONTAM Panel	The EFSA Panel on Contaminants in the Food Chain
CYP	Cytochrome P450
DCM	EFSA Unit on Dietary & Chemical Monitoring (former DATEX Unit)
EEG	electroencephalogram
EFSA	European Food Safety Authority
EM	Extensive metaboliser
EU	European Union
EXPOCHI	EFSA Article 36 project 'Individual food consumption data and exposure assessment studies for children'
GC-MS	Gas chromatography – mass spectrometry
GD	Gestation day
GI	Gastrointestinal
HPLC	High-performance liquid chromatography
i.m.	Intramuscular
i.p.	Intraperitoneal
i.t.	Intratracheal
i.v.	Intravenous
IWGT	International Workshop on Genotoxicity Testing
LB	Lower bound
LC	LC: left censored data (values below the limit of dection or limit of quantification)
LC-MS/MS	high performance liquid chromatography coupled to tandem mass spectrometry
LOD	Limit of detection
LH	luteinizing hormone
LOEL	lowest- observed-effect-level
LOQ	Limit of quantification
M3G	morphine-3 glucuronide
M6G	morphine-6 glucuronide
MAO	Monoamine oxidase
MEKC	Micellar electrokinetic capillary chromatography
ML	Maximum level
Mrp	Multidrug resistance proteins
MTD	Maximum tolerated dose
MW	Molecular weight
NIH	U.S. National Institute of Health
NK	Natural killer
NOAEL	No-observed-adverse-effect level
NOEL	No-adverse-effect level

NTP	U.S.National Toxicology Program
P95	95th percentile
PB-PK-PD	pharmacokinetic-pharmacodynamic
PBPK	physiologically based pharmacokinetic
PDE	Phosphodiesterase
PFC	plaque-forming cells
PM	Poor metabolisers
p.o.	Per os
PST	Poppy seed tea
s.c.	subcutaneous
SCE	Sister Chromatide Exchanges
SPE	solid phase extraction
S-PFC	Spleen- plaque-forming cells
SRBC	sheep red blood cells
StVG	Germany Street Traffic Law
TDI	tolerable daily intake
TLC	thin-layer chromatography
T-PFC	tracheobronchial lymph node plaque-forming cells
UB	Upper bound
UDP	Uridine diphosphate
UGT	UDP-glucuronysyltransferase
UM	Ultra-rapid metabolisers
USA	United States of America
UV	Ultra violet
WHO	World Health Organization