

BfR recommends provisional daily upper intake level and a guidance value for morphine in poppy seeds

BfR Health Assessment No. 012/2006, 27 December 2005

Poppy seeds are the mature seeds of opium poppy (*Papaver somniferum L.*). Because of their content of fatty oil and protein, they are used in the food sector in the manufacturing of bakery products and edible oil. Opium and its alkaloids can be obtained from the same plants from whose capsules the seeds are harvested. Opium is the name given to the dried milky sap which is obtained from the immature capsules. The most well known and most important opium alkaloid is morphine. Poppy seeds may also contain traces of alkaloids.

In April 2005 BfR issued a warning about damage to health from poppy seeds in a press release. A mother had used an old home remedy and given her six-week-old baby strained milk from poppy seed to treat its sleep problems. The child was rushed to hospital with respiratory disorders and impaired consciousness and treated there on suspicion of opiate intoxication. High levels of the alkaloids, morphine and codeine, were detected in its urine. In this context BfR pointed out that poppy seeds may contain varying amounts of morphine and codeine because of fluctuations in quality. Against this backdrop and following reports of the misuse of edible poppy seeds to produce drugs, BfR undertook a risk assessment of the occurrence of morphine in edible poppy seeds and issued an expert opinion on possible health risks for consumers.

The data on which the assessment is based showed that the morphine levels in edible poppy seeds vary considerably and have obviously increased recently. Types of poppy, harvesting time and geographical origin could influence the levels. The main reason is probably contamination of poppy seeds with alkaloid-containing capsule fragments and milky sap. The morphine levels could be drastically reduced by washing the seeds. Therefore, it is assumed that the elevated morphine levels in poppy seeds are linked to the recently introduced mechanical harvesting techniques in consequence of which the capsules are squashed.

Morphine is mainly used to treat severe pain. Adverse reactions include nausea, vomiting, light headedness, respiratory depression and cardiovascular effects. Long-term use can lead to tolerance development as well as psychological and physical dependence. Individual sensitivity varies markedly. This applies both to the desired effects and adverse reactions in medicinal usage. In animal experiments morphine had a negative impact on development and reproduction. Mutagenic effects were also observed. The lowest therapeutic single dose for oral intake is 1.9 mg morphine. Doses of this kind can be ingested from normal portions of foods containing poppy seeds contaminated with morphine. They can then elicit the related spectrum of adverse reactions. This is shown, for instance, by studies from forensic medicine. If a food contains larger amounts of poppy seeds from batches which have been contaminated to a high degree with morphine, morphine intakes may result in the worst case that are in the upper range of orally administered, therapeutic single doses or even higher. In cases like these, the risk of serious central nervous and peripheral effects like impaired consciousness, respiratory depression and cardiovascular effects has to be assumed.

It is clear that highly contaminated poppy seed batches of this kind are dangerous and not marketable. When, however, is the consumption of poppy seeds with lower morphine concentrations problematic in terms of health from the precautionary angle? In order to give official food control authorities an instrument to answer this question, BfR has established a "provisional daily upper intake level" for morphine. It is 6.3 microgram morphine per kilogram body weight per day. It indicates the morphine intake which should not be exceeded during

one meal or several meals spread over the day. Taking into account the estimated portions, this leads to a provisional guidance value for poppy seeds of a maximum of 4 microgram morphine per gram.

The Federal Institute for Risk Assessment calls on manufacturers to do everything in their power to reduce the levels of all pharmacologically active opium alkaloids in poppy seeds to the technically feasible minimum. BfR recommends that guidance values should also be established on this basis for other alkaloids contained in opium poppy: codeine, noscapine, papaverine and thebaine. Until there has been a successful change in production conditions for poppy seeds, BfR advises against excessive consumption of foods with a high level of poppy seeds particularly during pregnancy. Poppy seed cakes, poppy seed containing desserts like certain sweet puddings (Mohnpielen) and special traditional dishes sprinkled with poppy seeds like yeast dumplings (Dampfnudeln) may contain larger amounts of these seeds.

1 Subject matter of the assessment

The Federal Institute for Risk Assessment has expressed its opinion on the occurrence of morphine in edible poppy seeds and on limiting the morphine level of edible poppy seeds on health grounds. The regional authorities provided analytical data for this purpose. Based on these findings they had already voiced complaints about various batches of poppy seed samples on the grounds of elevated morphine levels pursuant to Article 14 paras 2a and 4 Regulation (EC) No 178/2002.

The current reason for assessment were media reports according to which by no means insignificant amounts of morphine had been detected in edible poppy seeds. Drug addicts were, therefore, using them to produce drugs. Hence, scientists urgently recommended the establishment of maximum levels for the morphine content of edible poppy seeds. Given the need for action from the food toxicological angle, the predecessor institute to BfR, the Federal Institute for Consumer Health Protection and Veterinary Medicine (BgVV) had drawn attention to this for the first time in 2002. At that time it had recommended recording data on the alkaloid content of poppy seeds and examining whether there was a need to establish corresponding purity and quality criteria.

2 Results

Based on pharmacological data, BfR has established "a provisional daily upper intake level" for morphine in poppy seeds. It is 6.3 µg morphine/kg body weight/day and describes the intake which a person should not exceed (referred to kg body weight) during one meal or several meals spread over the day. Considering the estimated portions, a provisional guidance level for poppy seeds of 4 µg morphine/g was derived from the provisional daily upper intake level. Manufacturers are called on to do everything in their power to reduce the contents of all pharmacologically active opium alkaloids in poppy seeds to the technologically feasible minimum. It is also recommended that guidance values should be established on this basis for codeine, noscapine, papaverine and thebaine. Therefore to the extent that the current data situation permits, provisional "orientation values" are indicated which would be acceptable from the health angle. Until there has been a successful change in the production conditions for poppy seeds, excessive consumption of foods with a high level of poppy seeds particularly during pregnancy is advised against.

3 Reasons

3.1 Risk assessment

3.1.1 Agent

Poppy seeds (*Semen Papaveris*) are to be assessed for their content of pharmacologically active alkaloids.

3.1.1.1 Poppy seeds and opium poppy – botanical origin, ingredients, use and cultivation

Poppy seeds are the mature seeds of *Papaver somniferum* L. (opium poppy), which belong to the family of *Papaveraceae*. The seeds are various shades of black, white, blue or brown; they are between 0.9 and 1.5 mm long and are kidney shaped (1 - 7).

Papaver somniferum is a crop plant and diverse varieties and sorts are cultivated. 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 (1, 2, 6). The Mediterranean wild strain is regarded as a sub-species of *Papaverum somniferum* and is also termed *Papaver somniferum* L.ssp.*setigerum* (DC) Corb. (edible poppy) (12). Poppy seeds are used in the food sector to produce bakery products and edible oil (3 - 7). The DAB 6 monograph "*Semen Papaveris*" (8) refers to the medicinal use of mature white poppy seeds. Poppy seed oil (*Oleum papaveris*) is also used for pharmaceutical and technological purposes (1).

Papaver somniferum is grown all over the world and has the greatest economic importance in Asia. The plant is not only used to produce seeds and oil but also alkaloids and opium (1, 2, 6).

The milky sap (latex) of the immature capsules which is released by incisions and which has dried on the capsule surface is called opium. It contains approximately 20 - 25% alkaloids of which around 50 alkaloids have been isolated in pure form up to now. The main 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%), noscapine (5%, 2 - 12%; formerly described as narcotine), narceine (approximately 0.5 %; 0.1 – 1.0%) and papaverine (approximately 1%; 0.5 - 3%) (1, 9).

The alkaloids are synthesised, stored and metabolised in the latex which is located in a closely woven network of mutually anastomosal laticiferous tubes. With the exception of the seeds, which are the only organ without milky sap, (11) it permeates all parts of the plant and is to be found in particular in the pericarp of the capsule (7, 9, 10). Varying amounts of the alkaloids have been detected in all parts of the plant. Differing alkaloid levels for the seeds have been indicated in the standard literature, which vary by several orders of magnitude. For instance, alkaloid concentrations have been reported in the trace range of < 0.0001% (9) as well as values of 0.005% (11) or 0.009% (1, 2) and 0.01% (3, 7). In the relevant literature codeine, thebaine, noscapine, papaverine, rhoeadine, the papaver rubines B, C, D, E and morphine are indicated as alkaloids which occur in very small amounts in the seeds (1, 2). However, some older reference works describe the seeds as being "free of morphine" (3, 7) (for further details see 3.1.1.3).

Higher alkaloid levels can be found in other parts of *Papaver somniferum*, which are described as drugs and/or used to harvest alkaloids. *Fructus papaveris* (poppy capsules without seeds) are specified in mature or immature stage in various national pharmacopoeia. The drugs contain the same active substances as opium but at a far higher dilution. Their morphine level fluctuates and is indicated as being between 0.12 and 0.89% (1, 2) or higher (7). What are more relevant for this assessment are possible indications that there may be a correlation between capsule form and seed colour on the one hand and morphine level on the other (1, 2). For instance, capsules of white or light seeds produced lower morphine yields than blue- or dark-seeded capsules. Maturation investigations led to varying results which means that the most morphine was found in the stadium of half ripeness and, in other cases, in the mature capsules (1, 2, 7). Mention should also be made of *Stramentum papaveris* (poppy straw), which contains mature deseeded capsules (morphine level: 0.015 up to 0.018%) (1, 2, 7) and *Radix papaveris* (poppy roots). They were shown to have approximately 0.03% morphine (7).

The total alkaloid content of the plant, which depends on various factors (variety or sort, location, soil conditions, climate, weather, harvesting time), increases in the case of *Papaver somniferum* during growth up to the flowering period and then falls again (1, 11). The alkaloid content also shows daily fluctuations with a minimum around lunchtime 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 (1).

In Europe (e.g. Austria and Germany) low morphine varieties of *Papaver somniferum* are authorised for cultivation. They are exclusively destined for the production of seeds which are used to manufacture bakery goods and oil. According to information from the Austrian Agency for Health and Food Safety/Institute for Seeds, Vienna (6) these seeds scarcely contain any alkaloids and no morphine. They encompass for instance the only variety "Przemko" authorised in Germany and the varieties "Edel-Weiß", "Edel-Rot", "Florian", "Josef", "Zero" and "Zero 2000" authorised in Austria (6).

Furthermore, in Europe, including the former Soviet Union, *Papaver somniferum* is mainly cultivated for direct alkaloid harvesting from capsules and poppy straw and parallel oil collection (1, 2). The cultivation of *Papaver somniferum* for opium production is limited, in accordance with the UN protocol from 1953, to Bulgaria, Greece, Iran, India, the former Soviet Union, former Yugoslavia and Turkey. Furthermore, there is illegal cultivation for the purposes of narcotics production (1, 2, 10).

3.1.1.2 Statutory provisions

The cultivation of *Papaver somniferum* L. requires an exemption in the Federal Republic of Germany pursuant to the Narcotics Act (BtMG) of 28 July 1981 § 3. It has only been granted for the low morphine opium poppy variety "Przemko" (cf. 3.1.1.1).

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.

Maximum values for the contents of opium alkaloids in poppy seeds are only known from Hungary (35). They indicate 30 µg/g for morphine, 20 µg/g for noscapine, 40 µg/g for morphine and noscapine, 20 µg/g for thebaine and 20 µg/g for codeine.

3.1.1.3 Analytical data on poppy seeds

Aside from the occurrence of alkaloids (cf. 3.1.1.1), poppy seeds contain 40 - 60% fatty oil whereby the white seeds contain more oil than the blue or grey ones. Poppy seed oil has the following composition of fatty acids: 62% linoleic acid, 30% oleic acid, 5% palmitic acid, 3% stearic acid. Furthermore poppy seeds contain 15 - 24% proteins, the enzymes diastase, emulsin and lipase, between 0.25 and 1 % lecithin and around 3% pentosane as sugar.

It is noted that the measurement data given below (Tables 1 - 6) were obtained using different, non-standardised extraction and analytical methods and are, therefore, only comparable to a limited degree.

3.1.1.3.1 Poppy seeds for sale in the German retail food trade

Data on the alkaloid content of poppy seeds in the German retail food trade were initially only available to BfR from forensics. Alkaloid concentrations in poppy seeds had been determined in studies investigating the association between the consumption of bakery goods containing poppy seeds and positive results in urine, blood and serum, saliva and hair analyses for opiates and the resulting problems for drug screening or doping controls (13, 14, 15, 22).

Table 1: Morphine levels and country of origin of poppy seeds which had been sold in the German retail food trade according to Thevis *et al.* (13).

Sample No.	Tradename/ Composition	Outlet	Origin	Morphine level (µg/g)
1	Neuform®	Health food store	Denmark	8.4
2	Neuform®	Health food store	Hungary	6.9
3	Müller's Mühle®	Supermarket	unknown	151.6
4	Insula®	Supermarket	unknown	2.1
5	FJD®	Supermarket	unknown	4.1
6	Rapunzel®	Health food store	Turkey	0.8
7	Davert®	Health food store	Turkey	0.9
8	Backmischung	Bakery	unknown	0.6

After enzymatic hydrolysis and liquid-liquid extraction by GC-MS, Thevis *et al.* (13) examined 8 products for their morphine level. In 5 samples it was between 0.5 µg/g and 5 µg/g, in 2 samples between 5 and 10 µg/g and in only one case 151.6 µg/g. The authors indicate that the high morphine content in sample no. 3 was confirmed by analysing a second package from the same batch, whereas other batches from the same manufacturer were only found to have low morphine concentrations of 1.1 µg/g. Furthermore, the authors note that all samples contained negligible amounts of codeine as well.

Trafkowski *et al.* (15) analysed 11 samples (7 unmixed poppy seeds and 4 baking mixtures) from the Bonn region using HPLC-MS/MS for their contents of codeine, morphine, noscapine and papaverine (5 g sample was extracted by ultrasound in 10 ml buffer, determination limits were only given for detection in body fluids. For urine analyses for codeine, morphine, noscapine and papaverine they were 5.5, 12.38, 1.56 and 0.33 ng/ml respectively. Three times the detection limit was taken for the determination limit.)

Table 2: Alkaloid levels in poppy seeds and poppy seed-containing products which had been purchased in the Bonn region, excerpt from Trafkowski *et al.* (15).

No.	Product	Concentration in poppy seed ($\mu\text{g/g}$)			
		Codeine	Morphine	Noscapine	Papaverine
1	Blaumohn Fa. ATCO	7.69	87.45	0.13	0.043
2	Blaumohn Fa. Neuforn	positive	0.00	0.00	0.000
3	Blaumohn Fa. Backstube	1.06	3.34	1.42	0.057
4	Blaumohn Fa. Märsch Import	0.82	3.65	1.57	0.057
5	Blaumohn Fa. Müller's Mühle	16.00	60.60	0.14	0.043
6	Blaumohn Fa. Davert	1.08	3.78	0.50	0.053
7	Blaumohn Rio Bravo	6.02	18.30	0.13	0.043
8	Mohn-Back Fa. Schwartau	0.29	2.61	0.00	0.000
9	Mohn-Fix Fa. Pichard-Dekor	0.27	2.69	0.00	0.000
10	Mohn Füllung Fa. Gold Puder	2.99	14.37	0.12	0.032
11	Mohn-Fix Fa. Backstube	0.22	1.51	0.08	0.000

The morphine contents in 7 samples were between 0 and 4 $\mu\text{g/g}$ and between 14 and 87.5 $\mu\text{g/g}$ for the other 4 samples. The codeine levels only exceeded 1.1 $\mu\text{g/g}$ in the case of the four last samples for which they ranged between 3 and 15 $\mu\text{g/g}$. Two other samples were noticeable which had a noscapine level between 1.4 and 1,6 $\mu\text{g/g}$ whereas the levels of noscapine in the other samples were between 0 and 0.50 $\mu\text{g/g}$. The papaverine concentrations in all samples fluctuated between 0 and 0.06 $\mu\text{g/g}$. It is noticeable that neither morphine, noscapine nor papaverine could be detected in one sample of blue poppy seeds. Codeine could be detected but the value was obviously below the determination level.

Furthermore, findings by Andresen and Schmoltdt (22) should be mentioned. They analysed two batches of poppy seeds following extraction by ethanol using GC/MS. The first batch from Australia contained larger amounts of morphine (207 $\mu\text{g/g}$) and codeine (5.5 $\mu\text{g/g}$). In the second batch from Asia far lower levels of alkaloids were detected: 0.6 μg morphine/g and no codeine.

Finally, measurement results on codeine and morphine levels in 48 poppy seed samples were recently made available by the Bavarian Regional Office for Health and Food Safety (LGL) which are given in Table 3. Measurements were taken using HPLC/DAD and secured using LC/MS/MS.

Table 3: Morphine and codeine levels in poppy seeds obtained in Bavaria
(n.n. = below the detection limit)

Sample No.	Origin if known	Morphine (µg/g)	Codeine (µg/g)
1		65	6.4
2		74	11.8
3		8	n.n.
4		66	8.6
5		10	n.n.
6		4	n.n.
7	Czech Republic	201	23.7
8		70	9.0
9		96	9.6
10	Russia (?)	4	n.n.
11	Turkey	5	n.n.
12	Denmark	25	2.0
13		90	7.1
14		98	9.8
15		7	n.n.
16		4	n.n.
17		8	n.n.
18		29	n.n.
19		46	n.n.
20		228	13.8
21		17	n.n.
22		8	n.n.
23		198	27.6
24	Turkey	3.10	1.80
25		35.40	2.60
26		95.50	14.00
27		7.30	n.n.
28		52.40	3.80
29		53.60	2.80
30		318.30	8.60
31		79.80	12.70
32		31.50	1.00
33	Czech Republic	30.60	n.n.
34		16.00	3.20
35		67.60	10.90
36		4.50	n.n.
37		34.90	n.n.
38		13.80	n.n.
39		60.80	7.20
40		78.90	12.20
41		77.60	14.10
42		64.50	5.10
43		9.10	n.n.
44		320.70	10.00
45		330.00	10.30
46		285.30	
47		203.20	
48		319.30	

Of the 48 samples which mainly consisted of blue poppy seeds, only 13 had a morphine level $\leq 10 \mu\text{g/g}$. Codeine was detected in one of these samples at a concentration of $1.8 \mu\text{g/g}$ but was not detectable in the other 12. In 10 out of 48 samples the morphine level was between $> 10 \mu\text{g/g}$ and $\leq 50 \mu\text{g/g}$ with codeine levels of maximum $3.2 \mu\text{g/g}$ or below the detection limit (no information available on the level). 16 samples showed morphine levels between > 50 and $\leq 100 \mu\text{g/g}$ together with codeine levels up to maximum $14.1 \mu\text{g/g}$. In the remaining 9 samples morphine levels were measured between $> 100 \mu\text{g/g}$ and maximum $330 \mu\text{g/g}$ which were coupled with codeine values up to maximum $27.6 \mu\text{g/g}$. It is clear that rising levels of morphine in the seeds are often coupled with elevated codeine values. Since the country of origin of the poppy seeds was only indicated in a few cases, no associations could be established between the alkaloid contents and geographical origin. It is noticeable that the poppy seeds of one manufacturer (sample nos. 3, 5, 17, 21, 22, 36, 38, 43) only contained relatively low morphine levels (8 samples: $\leq 17 \mu\text{g/g}$, of which 6 samples: $\leq 10 \mu\text{g/g}$). However, this could not be confirmed in other investigations (cf. Table 1, sample no. 3, and Table 2, product no. 5). This means that it might be by chance that several samples from the same or similar origin (e.g. same batch, same harvest) could have been investigated with, therefore, similar alkaloid contents. This might also be the reason why almost all (12 out of 13) blue poppy seed samples from another manufacturer (sample nos. 1, 2, 4, 9, 13, 14, 28, 29, 31, 35, 39 and 42) had morphine values between 50 and $100 \mu\text{g/g}$ and a high proportion (7 out of 10) of samples from a third manufacturer of blue poppy seed (sample nos. 19, 20, 30, 40, 44, 45, 46, 47 and 48) had morphine values over $200 \mu\text{g/g}$. Tracing the origin of poppy seeds from specific manufacturers might produce evidence of the causes of the low or high morphine concentrations in the poppy seeds. It is also interesting that the analyses of poppy seeds of the low morphine species "Przemko" by the official Bavarian food control authority, which had been cultivated in 2004 by the Regional Agency for Plant Cultivation in Forchheim, (Baden-Württemberg), revealed a morphine content of $3.5 \mu\text{g/g}$ and codeine was not detected.

Furthermore, the analytical data on one product of baking poppy seeds (0.1% morphine, 0.003% codeine) on sale in Germany should be mentioned. Their improper use as a milk extract recently led to severe health disorders in a six week old baby. It must be pointed out that the indicated morphine level of 0.1% (= $1000 \mu\text{g/g}$) clearly exceeded the morphine levels (cf. Tables 1 - 5) given for poppy seeds up to now and verification is recommended.

Overall, the analytical data situation on poppy seeds on sale in Germany must be described as very sparse as sample investigations are only available from a few regions in Germany and they are orientational in character. In almost all cases there are no details of batch number, country of origin, harvest years or botanical origin (cultivated types of opium poppy). Furthermore, apart from morphine it was mainly only codeine that was determined while data on the other relevant opium alkaloids are missing.

Finally, the findings of the Chemical and Veterinary Investigation Office (CVUA) Stuttgart should be mentioned. They determined $210 \mu\text{g}$ morphine/g and $39 \mu\text{g}$ codeine/g using LC-MS/MS in blue poppy seeds from one manufacturer and $120 \mu\text{g}$ morphine/g and $19 \mu\text{g}$ codeine/g in a poppy seed sugar mixture probably made from it. Consumption of the mixture had led to symptoms of disease in one patient.

3.1.1.3.2 Poppy seeds sold in the international retail food trade

The variations which occur in the alkaloid content of various poppy seeds and poppy seed-containing products are presented in more detail in a table prepared by Rochholz *et al.* (5) using a literature search. It also lists the values for poppy seeds on sale in Germany men-

tioned above (13) in the bottom row. Otherwise, it refers to samples collected around the world and is presented here in abbreviated form (Table 4) (5, 13, e.g. 16 - 21, 23). In some of the original works quoted (17, 21) a distinction is made for morphine and codeine contents between the "free" portion (dissolved from dust, capsule fragments and latex sticking to the outside of the seeds and from inside the seeds) and "bound" portion (released e.g. after acid hydrolysis). This is not included in the table.

Table 4: Alkaloid levels in various batches of poppy seeds and poppy seed-containing baking mixtures, according to Rochholz *et al.* (5).

Type of poppy seed	Morphine [$\mu\text{g/g}$]	Codeine [$\mu\text{g/g}$]	Other alkaloids [$\mu\text{g/g}$]
White poppy seeds	450		
Black poppy seeds	30		
Blue poppy seeds	2.6 - 107		
White poppy seeds	51.6 – 60.4		
Unknown	107 - 164	17.7 – 31.8	Thebaine: 8.2 – 20.7
Blue poppy seeds, baking poppy seeds	< 0.1 - 620	Codeine	Thebaine
Unknown	169	17	
Unknown	5.1 - 106	0.1 – 3.8	Thebaine: 0.3 - 14 Papaverine: 0 – 3.6
Poppy seed filling in bakery goods	24	0.36	Thebaine: 0.46 Papaverine: 0.05
Unknown	4 - 200		
Blue poppy seeds	0.5 - 15	0.1 - 3	
White poppy seeds	13	1.5	
Black poppy seeds	17 - 294	3 - 14	
White poppy seeds	58.4 – 62.2	28.4 – 54.1	
Blue poppy seeds, white poppy seeds	0.1 – 11.9	0.1 – 0.7	
Unknown	39 – 167	1.8 - 44	Thebaine: 1 - 41 Papaverine: 0.17 - 67 Noscapine: 0.84 - 230
Unknown	2 – 251	0.4 – 57.1	
Poppy seed filling in bakery goods	17.4 – 18.6	2.3 – 2.5	
Blue-black poppy seeds	0.964	0.79	
Unknown	0.6 – 151.6	low	

According to these international data, maximum contents of 620 $\mu\text{g/g}$ morphine, 57.1 $\mu\text{g/g}$ codeine, 230 $\mu\text{g/g}$ noscapine, 67 $\mu\text{g/g}$ papaverine and 41 $\mu\text{g/g}$ thebaine were measured in poppy seeds. No associations could be determined between the colour of the poppy seeds and alkaloid occurrence.

Table 5 gives the internationally published morphine contents of poppy seeds together with geographical origin. Table 5 can be seen as a supplement to Table 1. It contains data published by Möller *et al.* (24). Some of the samples listed in Table 5 are also to be found in Table 4.

Table 5: Morphine levels and countries of origin of poppy seeds which are sold in the retail food trade in various countries (supplement to Table 1)

No.	Outlet	Origin	Morphine content ($\mu\text{g/g}$)
9	Unknown	Australia	108
10	Unknown	Unknown	73.2
11	Unknown	Turkey	8
12	Unknown	Australia	200
13	Unknown	Hungary	44
14	Unknown	Spain	60
15	Unknown	Netherlands	5
16	Unknown	Poland	12
17	Bakery	Unknown	74
18	Unknown	Unknown	175
19	Unknown	Australia	120
20	Unknown	Hungary	12
21	Unknown	Denmark	10
22	Unknown	USA	4
23	Import business	Netherlands	100
24	Import business	Eastern Europe	39
25	Import business	Eastern Europe	151
26	Import business	Eastern Europe	67
27	Health food store	Denmark	2
28	Unknown	Turkey	0.5
29	Unknown	Hungary	1
30	Unknown	Unknown	58
31	Supermarket	India	167
32	Supermarket	India	39
33	Unknown	Australia	90
34	Unknown	Hungary	46
35	Unknown	Czech Republic	2
36	Unknown	Spain	251
37	Unknown	Turkey	5
38	Unknown	Turkey	27
39	Unknown	Netherlands	4
40	Retail trade Portland, Oregon	Unknown	294
41	Unknown	Singapore	58 – 62

Even if one looks at all the data presented, the low number of samples per country of origin and the variability of findings do not permit the establishment of a clear association between morphine levels and country of origin. It is, however, noticeable that all four seed samples from Australia have high morphine levels ($\geq 90 \mu\text{g/g}$, Table 5) (cf. also 15, 16, 18, 22). Of the eight samples listed from Turkey, $27 \mu\text{g}$ morphine/g is the highest value (Tables 1, 3, 5). In

the case of the four Danish samples the highest value measured was 25 µg morphine/g (Tables 1, 3, 5).

Of the 5 Hungarian poppy seed samples (Tables 1 and 5), 2 do not comply with the Hungarian provisions (cf. 3.1.1.2) and show morphine levels above 30 µg/g.

Table 6 below is taken from the recently published work by Rochholz *et al.* (30). It lists the samples, most of which are included in the preceding tables, by decreasing morphine levels. The finding described above is confirmed: the 9 Australian samples all have high morphine levels between 72 and 206 µg/g.

Table 6: Morphine levels and countries of origin of poppy seeds which were on sale in the retail food trade in various countries, listed by decreasing content.

Origin	Morphine µg/g	Origin	Morphine µg/g
Unknown	620	Netherlands	39
Unknown	450	Eastern Europe	39
Unknown	294	Unknown	33.2
Spain	251	Unknown	30
Australia	206	Unknown	29.5
Australia	200	Unknown	28
Unknown	175	Turkey	27
Unknown	169	Netherlands	19
India	167	Unknown	17
Unknown	164	Czech Republic	13.2
Unknown	151.6	Poland	12
Eastern Europe	151	Hungary	12
Australia	120	Denmark	10
Australia	114.3	Denmark	8.4
Australia	108	Turkey	8
Australia	107	Unknown	7.3
Unknown	107	Hungary	6.9
Australia	106	Turkey	5.1
Netherlands	100	Netherlands	5
Australia	90	Turkey	5
Unknown	85.5	Unknown	4.5
Unknown	84.5	Unknown	4.1
Unknown	74	Unknown	4
Unknown	73.2	Netherlands	4
Australia	72.4	Poland	2.7
Unknown	69.3	Unknown	2.6
Eastern Europe	67	Unknown	2.1
Unknown	63	Denmark	2
Unknown	62.2	Czech Republic	2
Unknown	60.4	Unknown	1.1
Spain	60	Hungary	1
Unknown	58.4	Turkey	0.9
Unknown	58	Turkey	0.8
Unknown	51.6	Turkey	0.66
Hungary	46	Asia	0.6
Hungary	44	Turkey	0.5

3.1.1.4 Possible causes of high alkaloid levels in poppy seeds

The reasons given for the, in some cases, high opiate contents of poppy seeds include the choice of less suitable botanical varieties (6), inopportune harvesting time (15, 22) and specific geographical origin (3.1.1.3.2). The contamination of poppy seeds with alkaloid-containing capsule fragments and latex seems to be another fundamental problem which could probably be solved by using less aggressive harvesting methods and/or cleaning procedures. For instance Rochholz *et al.* (5) believe that the poppy seeds themselves only contain very low levels of morphine and codeine and that these alkaloids only adhere as external contamination to the poppy seeds. They base this on findings that the morphine content of seeds could be drastically reduced through washing (e.g. 17, 22). For instance, Bjerver *et al.* (31) showed that 40 % of the total morphine content of blue poppy seeds could be removed by washing with slightly acidic water. The assumption by Andresen and Schmoldt (22) is discussed that the current elevated morphine levels in poppy seeds could be linked to a new machine harvesting technology introduced in recent years. This involves the squashing of the poppy seed capsules whereby the seeds are contaminated with the alkaloid-containing milky sap. The presence in particular of immature capsules has a detrimental effect (30). According to Andresen and Schmoldt (22), this procedure must be extended to include the careful washing of the seeds as the next step. The mechanical harvesting technique is used especially for "closed poppy" whose seed capsules remain closed even after ripening (cf. 3.1.1.1). In this way higher harvest yields are obtained than in the case of "shaken poppy" in which the seed capsules are emptied by hand or mechanically. Möller *et al.* (24) observed that the harvesting method used in low wage countries whereby the capsules are still cut open manually and the seeds collected in a container, leads to a lower contamination of the seeds with the milky sap.

There is no discussion in the literature whether the fact that poppy seeds are obtained from capsules, which had previously been scratched to obtain opium (3), could be a cause of the alkaloid contamination of the seeds. It may be that these seeds are primarily used to produce poppy seed oil (12) which is deemed to be free of alkaloids (7). In principle, the parallel use of opium poppy plants to harvest alkaloids and opium on the one hand (with the requirement of high alkaloid biosynthesis) and to harvest low alkaloid seeds on the other (for which low alkaloid varieties seem to be more suitable) implies contradictory preconditions when it comes to choosing species and varieties.

3.1.2 Hazard potential

3.1.2.1 Opium alkaloids and opium as medicinal products

In the following the pharmacokinetic and pharmacological data of the relevant opium alkaloids and opium known from their pharmaceutical application are summarized. In the case of the companion alkaloids and opium this information can only be orientational in character.

3.1.2.1.1 Morphine

The phenanthrene alkaloid morphine ((5R, 6S, 9R,13S,14R)-4,5-Epoxy-N-methyl-7-morphinen-3,6-diol, molecular weight (MW): 285.3, CAS No.: 57-27-2) is the main action component of opium. It is used for medicinal purposes as morphine sulphate pentahydrate (MW: 758.8; CAS No.: 6211-15-0) or as morphine hydrochloride trihydrate (CAS No.: 6055-06-7, MW: 375.8) (10, 39, 40).

3.1.2.1.1.1 Applications and dosage

Morphine is mainly administered via the oral or parenteral routes to treat severe and extreme pain (e.g. carcinoma 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 (38). At very high doses it can be used as an anaesthetic. The doses normally recommended for pain therapy in oral pharmaceutical forms are given in Table 7 below (42).

Table 7: Recommended single and total daily doses for orally administered morphine (42)

Age (body weight)	Single dose	Total daily dose
Children up to the age of 2 (up to 12.5 kg)	Up to 2.5 mg morphine hydrochloride equivalent to up to 1.9 mg morphine	Up to 22.5 mg morphine hydrochloride equivalent to up to 17.1 mg morphine
Children aged between 2 - 6 (up to 12.5 - 20 kg)	2.5 - 5 mg morphine hydrochloride equivalent to 1.9 – 3.8 mg morphine	15 - 30 mg morphine hydrochloride equivalent to 11.4 – 22.8 mg morphine
Children aged between 6 - 12 (20 - 40 kg)	5 – 10 mg morphine hydrochloride equivalent to 3.8 – 7.6 mg morphine	30 - 60 mg morphine hydrochloride equivalent to 22.8 – 45.6 mg morphine
Adolescents 12 - 16 years (40 - 50 kg)	10 – 20 mg morphine hydrochloride equivalent to 7.6 – 15.2 mg morphine	60 - 120 mg morphine hydrochloride equivalent to 45.6 – 91.1 mg morphine
Adolescents over the age of 16 and adults	10 – 60 mg morphine hydrochloride equivalent to 7.6 – 45.6 mg morphine	360 mg morphine hydrochloride equivalent to 273.3 mg morphine

The maximum effect can already be achieved 30 minutes after oral administration. The effect of a single dose lasts as a rule for 4 - 6 hours (38, 42). In the case of morphine sulphate pentahydrate, 2.5 mg (equivalent to 1.9 mg morphine) were mentioned in the literature as the lowest oral therapeutic single dose to treat cancer pain or dyspnoea in adults (39). Patients more advanced in years (as a rule over 75) may be more sensitive to morphine (1, 38, 39, 42). The dose must also be reduced in the case of hepatic insufficiency (1). In principle, a large variation in individual sensitivity to morphine can be assumed in the case of therapeutically desired effects and side effects (42, 44). The scientific literature points out the difficulty of establishing a standard dose for morphine. Rather a dose range of 2.5 – 2500 mg (usually however below 100 mg) is given for oral pain therapy with morphine sulphate pentahydrate as the single dose to be administered every four hours (39). An effect is, however, only to be expected from low doses in the case of opium alkaloid-naïve patients who have not developed tolerance from prior treatment with opium alkaloids (cf. 3.1.2.1.1.4) (39).

In their publication Carbajal and Simon (47) indicate for morphine an initial daily dose of 0.5 up to 1 mg/kg body weight/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/body weight. If the dose is not effective, it can be increased by 50 %. Histamine release, hypotonia and obstipation are indicated as the side effects of this dose (cf. 3.1.2.1.1.2). The dosage information does not refer to a specific children's age (47). It is assumed that the pharmacokinetics of morphine in children are similar to those of adults (39). However, neonates are the exception; because of their immature P-450 system and reduced renal clearance, they have a longer half-life for morphine. Furthermore, the immature blood-brain barrier can lead in their case to elevated morphine concentrations in the brain. Neonates already developed cramps (48, 49, 39) at morphine doses (referred to kg bodyweight) which are otherwise routinely given to children. Attention is drawn to an elevated sensitivity of neonates vis a vis respiratory depression (39).

3.1.2.1.1.2 Pharmacodynamics

For opioids (agonists and antagonists with morphine-like activity including natural and synthetic opioid peptides) there are three types of receptors in human beings. 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. The animal organism also contains endogenous morphine and codeine biosynthesised from L-tyrosine, however, only in traces; their physiological relevance is unknown. Activation of the μ -receptors leads to analgesia, mainly on the supraspinal (above the bone marrow) level, euphoria, dependence, miosis, respiratory depression, cough calming and obstipation (10, 32, 45, 46).

Central effects

Morphine has an analgesic effect by targeting various levels of the central nervous system (CNS). In addition to supraspinal there are also spinal points of attack. By increasing the release of dopamine in the *nucleus accumbens*, morphine creates an unrealistic feeling of well-being (euphoria). In this way, it reduces fear in conjunction with acute pain (anxiolysis). People suffering from chronic pain do not benefit from these positive mental side effects but they are not at risk of becoming dependent. The tranquillising, sedative-hypnotic effect can also be used for pain therapy. 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 an indication of the taking of μ -receptor-agonistic opioids. Respiratory depression triggered by morphine can be observed in healthy test persons in a less developed form already at therapeutic standard doses but not, however, in patients suffering from severe pain. In this case pain stimulates respiration and counters the morphine effect. 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 occurs and finally respiratory arrest. As morphine dampens the reflectory excitability of the cough centre in the *medulla oblongata*, it has an antitussive effect. The nausea and vomiting frequently induced by morphine also result from its effect 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. In the case of standing patients it does lead to a drop in blood pressure at therapeutic doses because of peripheral vasodilatation, reduced peripheral resistance and inhibition of the baroreceptor reflex. A low grade bradycardia (cardioinhibition) may occur. At high doses morphine can trigger cramps. 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, sexual hormones, prolactin and the antidiuretic hormone. Consequently, corresponding manifestations or clinical symptoms are possible. Finally, a drop in temperature and muscle rigidity (32, 38, 42, 48) can be mentioned as possible further consequences of central points of attack of morphine.

Peripheral effects

Morphine increases the tone of the gastrointestinal 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 defecation 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 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 (32, 38, 42).

3.1.2.1.1.2.1 Morphine effects in healthy test persons

In the literature it is pointed out that the effects of morphine in healthy test persons may deviate in some cases from those in pain patients. The predominant symptoms in healthy, pain-free individuals given therapeutic doses are nausea and retching. Furthermore, there are symptoms of light-headedness, dizziness, difficulty in carrying out intellectual activities, apathy and reduced physical activity. Only at higher doses do subjective analgesic and toxic effects increasingly occur, including respiratory depression (38).

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 co-ordination, of short-term and longer lasting attentiveness as well as of short-term memory (51). However, no corresponding dose-response data following oral administration are available. A threshold dose upwards of which the onset of psychomotor impairment is to be expected following single oral administration of morphine is not known, but is relevant for safety in road traffic and at 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 fluctuations. There is also a need to clarify possible interactions, e.g. with alcoholic beverages (cf. 3.1.2.1.1.5).

3.1.2.1.1.3 Pharmacokinetics – Warnings for lactation period

After peroral administration, morphine is relatively quickly absorbed from the gastrointestinal tract, mainly from the upper small intestine and, to a lesser degree, from the stomach. The low bioavailability (20% - 40%) in the case of peroral morphine administration can be attributed to presystemic elimination through metabolism in the intestinal mucosa and liver (intestinal and hepatic first-pass-effect) (42, 38, 39, 32). The plasma half-life of morphine is 2 – 3 hours. Around 30% of morphine is bound to plasma protein. Morphine spreads throughout the body with high tissue concentrations in the kidneys, liver, gastrointestinal tract, lungs and spleen and low concentrations in the brain and muscles (39, 42). Although the brain is the primary site of action of morphine, it has difficulty passing the blood-brain barrier since 80% is present in ionised form. In the liver and intestine morphine is mainly metabolised to morphine-3-glucuronide and in lower amounts to morphine-6-glucuronide whereby the latter contributes to its analgesic effect. The half-life of glucuronides is far longer than that of morphine. Morphine and its glucuronides are subject to enterohepatic circulation. Other active metabolites are, for instance, the oxidative metabolites, normorphine and codeine. 10% of the administered morphine is found in unchanged form in urine. Most of the metabolites are excreted via the kidneys (90 %), but also via the liver and gall bladder. The fact that lower morphine doses are recommended for older patients has to do with the lower distribution

volume and reduced renal function. Morphine can cross the placenta (32, 39, 42). Following the administration of therapeutic doses, morphine is detected in breast milk (39, 42).

Lactation

Morphine is excreted in human milk and reaches higher concentrations there than in the maternal plasma. As clinically relevant concentrations can be achieved in the infant, lactation is advised against (42) unless there is a strong therapeutic indication. So far there have been no reports of harm to babies following therapeutic applications. Hence, it is not normally deemed necessary to stop breastfeeding following the administration of a single dose of morphine (41). The American Academy of Paediatrics has stated that the taking of morphine is normally reconcilable with lactation. Moreover, it also points out that there are no reports of adverse reactions in babies although measurable morphine levels may occur in their blood (39).

3.1.2.1.1.4 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. They can occur in all patients and are not an indication of abuse. Cross-tolerance and cross-dependence develop solely between opioids interacting with the same receptor (32, 38).

Tolerance

Tolerance can be defined as the reduction in response (e.g. analgesia) to a drug after repeated administrations. The degree of achievable tolerance is high in the case of morphine and is indicated as a 10 to 20-fold dose increase. Tolerance concerns all opioid effects besides miosis and obstipation. There is lower tolerance of the respiratory depressive effect than, for instance, of analgesia (32).

Psychological and physical dependence

Dependence consists of two components. Psychological dependence is an initially controllable but later irresistible craving for the drug. It develops from the euphorising properties of morphine. Physical dependence is a condition in which the opioids are essential for the normal functioning of the body. When the opioid is no longer taken, it manifests in the form of withdrawal symptoms (32).

The short-term taking of morphine is not linked to any risk of dependence (1). The risk of psychological dependence is reduced in the case of the regular administration of morphine with even plasma effect levels concerning the analgesic range, as is the case in patients suffering from chronic pain. Physical and psychological dependences are frequent in the case of highly fluctuating plasma concentrations as occur in conjunction with abuse (1, 42).

3.1.2.1.1.5 Adverse reactions and resulting warnings

In the case of adverse morphine reactions, which have already been explained in part under 3.1.2.1.1.2., a distinction is made between those under normal and high therapeutic doses (38, 39, 41, 42).

Adverse reactions at normal doses:

Frequently: nausea, retching, 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:

Respiratory depression, hypotonia, cramps (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 (39, 42). This is to be expected in particular at the beginning of treatment and when combined with alcohol or sedatives (42). 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 (44, 51-56).

Pregnancy

Development and reproduction toxicity

Morphine crosses the placenta barrier (cf. 3.1.2.1.1.3.). Adequate data are not available for human beings which would permit an assessment of the possible teratogenic risk (42). However, there have been reports of a possible association with the elevated incidence of hernias. 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, cramps, shrill crying, tremor, vomiting, diarrhoea, sneezing and tachypnoeae. Delayed language development may also be a sequelae (1).

In published development toxicology studies, morphine was not administered orally but only subcutaneously or intraperitoneally (61-66). There were reports of, for instance, CNS malformations (65, 61, 69), retarded growth, reduced litter size, a higher number of stillbirths, increased mortality of offspring (62), rib and vertebrae coalescence (69) and cryptorchismus (failure of the testes to descend into the scrotum) (64). Furthermore, morphine affected male sexual behaviour and female fertility in various animal species (42). The derivation of threshold doses for development and reproduction toxic effects is not possible on the basis of the knowledge currently available.

Morphine may only be prescribed according to strict medical criteria during pregnancy in cases in which the benefits for the mother outbalance the risks for the child (41, 42).

Delivery

Morphine can prolong or shorten the length of labour. Neonates whose mothers were given opioid analgesics during labour should be monitored for signs of respiratory depression or withdrawal symptoms and, if necessary, treated with a specific opioid antagonist (42).

Children

In the case of children under the age of 1, morphine may only be administered with extreme caution as they are more sensitive to the inhibiting effect on respiratory function (42).

3.1.2.1.1.6 Experimental findings and resulting warnings

Genotoxicity/carcinogenicity

The Federal Institute for Medicinal Products and Medical Devices (BfArM) assesses genotoxicity based on the findings available to them as follows (42):

"There are clear positive findings on mutagenicity which indicate that morphine has a clastogenic effect and that it exerts such an effect also on germ cells. Hence morphine is to be considered as a mutagenic substance; an effect of this kind must also be assumed in human beings. - Morphine should only be taken in conjunction with safe contraception".

According to published investigations the *in vivo* administration of morphine to mice led to an increased incidence of chromosomal aberrations in bone marrow cells (57) and to the induction of micronuclei in bone marrow cells and lymphocytes (58, 59). Since the number of morphine-induced micronuclei in mice can be reduced through naloxone, an opioid antagonist, this genotoxic effect of morphine seems to be at least partially receptor-mediated (59). Since attempts failed to induce chromosomal aberrations or micronuclei *in vitro*, it is assumed that there is metabolic activation *in vivo*. In one *in vitro* test in human HUT-78 cells, morphine increased the mutation frequency and DNA damage (59). Tests on *Drosophila*, *Salmonella* and yeast cells were negative (59, 60).

No long-term studies in animals are available concerning the tumorigenic potential of morphine.

Reference has already been made in Chapter 3.1.2.1.1.5 to data on development and reproduction toxicology from animal experiments.

3.1.2.1.1.7 Clinical pictures for which precautionary measures or warnings are necessary

Application restrictions (medical supervision or, where appropriate dose reduction) are necessary in conjunction with the oral intake of morphine in the therapeutic range for the following diseases (41, 42):

- Opioid dependence
- Impaired consciousness
- Conditions in which a disorder of the respiratory centre and respiratory function is present or must be avoided
- Pulmonary heart
- Conditions involving elevated cerebral pressure unless ventilation is given
- Hypotension in the case of hypovolaemia
- Prostate hyperplasia with formation of residual urine (danger of bladder rupture through urine retention)
- Narrowing of the urinary tract or colics of the urinary tract
- Biliary tract diseases
- Obstructive and inflammatory intestinal diseases
- Pheochromocytoma
- Pancreatitis
- Hypothyroidism
- Epileptic seizures or increased susceptibility to cramps.

The following warnings are issued in conjunction with specific diseases or disease-related situations (42): morphine should be used with caution pre-operatively and post-operatively because of the higher risk of ileus or respiratory depression compared with non-operated individuals in the post-operative phase.

Given the analgesic effect of morphine, severe intraabdominal complications like intestinal perforation may be masked.

In the case of existing adrenal cortical insufficiency (e.g. Addison's Disease), the plasma cortisol concentration should be monitored and, where appropriate, replaced with corticoids.

3.1.2.1.1.8 Contraindications

Hypersensitivity to morphine, ileus and acute abdomen are listed as contraindications for morphine treatment (42).

3.1.2.1.1.9 Interactions

A warning is issued about the following interactions of morphine in medicinal usage (42): 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.

Pharmaceuticals with an anticholinergic effect (e.g. psychopharmaceuticals, 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 case of preliminary treatment to patients involving specific antidepressants (MAO inhibitors) (within the last 14 days prior to opioid administration), life-threatening interactions with the central nervous system, respiratory and circulatory function have been observed after the administration of pethidine. This cannot be ruled out for morphine either.

The parallel administration of rifampicine can weaken the effect of morphine.

3.1.2.1.1.10 Intoxications

Acute morphine intoxication normally manifests in the 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 (32). In individuals who do not show any tolerance development, serious toxic symptoms may already occur after the oral administration of 40 to 60 mg morphine (38). For adults doses from 200 mg morphine may be acutely lethal (11). Other sources give a range of 300 mg-1500 mg for morphine hydrochloride trihydrate (equivalent to 228 mg-1139 mg morphine) for the oral lethal doses in the case of non-opiate-dependent adults whereby babies and infants are far more sensitive (9). 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 (38).

In individual cases morphine overdose leads to symptoms ranging from light-headedness over stupor to coma. Blood pressure initially remains normal but quickly falls as intoxication

advances. A persistent drop in blood pressure can lead to a state of shock. Tachycardia, bradycardia and rhabdomyolysis may occur. Body temperature falls. The skeletal muscles relax; general cramps 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 (11,42).

3.1.2.1.2 Codeine

The phenathrene alkaloid codeine ((5R,6S,9R,13S,14R)-4,5-E poxy-3-methoxy-N-methyl-7-morphinen-6-ol, MW: 317.4, CAS No.: 76-57-3) 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, CAS No.: 41444-62-6) (39).

3.1.2.1.2.1 Applications

Codeine is used to treat moderately severe pain, acute diarrhoea but mainly for the symptomatic treatment of dry coughs. In the case of the latter the following dose ranges are recommended (43,67):

Table 8: Recommended single and total daily doses for orally administered codeine to treat dry coughs (67)

Age	Single dose codeine	Maximum daily dose codeine
2 – 6 years	2.5 – 5 mg, can be repeated every 6 – 8 hours	30 mg
6 – 12 years	5 – 15 mg, can be repeated every 6 – 8 hours	60 mg
Age 12 upwards	15 – 44 mg, can be repeated every 6 – 8 hours; in individual cases up to 100 mg	200 mg

Other sources indicate for children when codeine is administered orally as an antitussive agent 0.25 mg/kg body weight 4 – 6 times daily and as an analgesic 0.5 mg/kg body weight 4 – 6 times daily (9). For adults the orally administered single dose of codeine as an antitussive agent is 10 – 20 mg (maximum daily dose: 120 mg) and as an analgesic 15 – 60 mg (up to 6 times daily) (9). The lowest single dose indicated for children in the literature is 3 mg codeine for children aged 5 (39). The highest single oral dose indicated for children aged 12 upwards and adults is 0.1 g codeine (cf. Table 8) (9, 67).

3.1.2.1.2.2 Pharmacodynamics

Codeine has opiate-agonistic properties. It has an analgesic effect whereby it possesses around 1/12 of the pain- alleviating efficacy of morphine. Furthermore, it has an antitussive effect (suppresses the cough reflex) by acting on the *medulla oblongata* in the cough centre. This effect is far stronger than in the case of morphine. Furthermore, codeine has slight sedating properties. The effects are partly mediated by binding to the supraspinal opiate receptors (μ -receptors) whereby codeine has a considerably low affinity to the opiate receptors. The metabolite morphine is responsible for some of the effects (9, 67, 39).

3.1.2.1.2.3 Pharmacokinetics – Warnings for lactation period

Codeine is readily absorbed from the gastro-intestinal tract whereby, following administration of codeine phosphate, the maximum plasma concentration is reached after around one hour (32, 39, 67). Bioavailability shows interindividual variations of 40 – 70% (9). Because of the

OH group in the 3-position protected by methylation against the conjugating enzymes, codeine shows a lower first-pass effect than morphine. The most important biotransformations are O and N demethylations in the liver to, amongst others, morphine, norcodeine and normorphine. Codeine and its metabolites are almost fully excreted via the kidneys mainly as glucuronides (9, 67).

The codeine elimination half-life is 3 to 5 hours in healthy adults; in the case of renal insufficiency it may be between 9 and 18 hours. The elimination of codeine is also slower in old age (67).

Codeine penetrates the placenta barrier and enters foetal circulation.

Lactation

Codeine is excreted in breast milk in which it reaches a 2.5 fold higher concentration than in plasma. The half-life is 3 hours. After administration of 60 mg codeine to breastfeeding mothers, codeine was detected in the plasma of the babies in probably sub-therapeutic concentrations (39). When mothers are treated with single therapeutic doses, a risk to the baby is unlikely. However, adverse reactions cannot be ruled out in the infant following the administration of very high doses or repeated treatments with high doses during lactation. If therapy of this kind is necessary, mothers should refrain from breastfeeding during treatment (67).

3.1.2.1.2.4 Tolerance and dependence

Codeine has a primary dependence potential. In the case of longer use and high doses, tolerance and physical/psychological dependence develop. The risk of dependence is low compared to morphine. There is cross-tolerance with other opioids (32, 67).

In the case of an existing opiate dependence (also in remission), rapid relapses are to be expected. Codeine is used by heroin addicts as a substitute. Alcohol and sedative addicts also tend towards codeine abuse and dependence (67).

3.1.2.1.2.5 Adverse reactions and resulting warnings

The adverse reactions to codeine are similar to those with morphine. All the same, they are less developed in therapeutic doses. In the case of chronic administration in normal doses, the most frequent side effect is obstipation (32, 39). At high doses excitability and cramps particularly in children were frequently observed (9). At higher doses impaired vision, respiratory depression and euphoria may also occur (67).

The following are mentioned as frequent side effects: slight headaches, minor sleepiness, nausea sometimes linked with vomiting (particularly at the beginning of treatment) and a dry mouth.

Allergic reactions to codeine do occur but rarely in a severe form (67).

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 coordination worsened and from 90 mg upwards dynamic visual acuity worsened. Sleepiness occurred at a dose of 90 mg codeine phosphate (39).

Affects on ability to drive and operate machinery

A warning is issued that even when taken correctly, codeine can influence the capacity of reaction which means that the driving of vehicles, the operating of machinery and other dangerous activities are to be avoided at least during the first days of treatment. A decision about this is to be taken in each individual case bearing in mind individual reactions and the respective dose. The interaction between codeine and alcohol or centrally active medicines leads to a major impairment of psychomotor performance. This means that patients are not allowed to drive vehicles, operate machinery or engage in any other dangerous activities. 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 (70). There is no information available on a threshold value for codeine regarding impairment of psychomotor skills.

Pregnancy

In humans an association was observed between deformities of the respiratory tract and the medicinal use of codeine in the first three months of pregnancy. There are also reports of other malformations from epidemiological studies involving narcotic analgesics, including codeine (67). Attention is drawn to the difficulties in interpreting the available studies on development toxicity, e.g. as a consequence of multiple substance exposure (68). For instance, studies on the use of codeine to treat pain and a high temperature did not reveal any elevated risk of malformation. By contrast, other studies showed an association between maternal opiate administration (mainly codeine) and cleft lip and palate in children or highlighted postnatal development difficulties (68).

In animal experiments on development toxicity the NOAEL (no observable adverse effect level) of codeine was higher than the normal therapeutic doses. For instance in one study in which codeine was given with drinking water, 20 mg codeine/kg body weight/day was established for hamsters and 75 mg/kg body weight/day for mice as the NOAEL for development toxicity (71). For an adult weighing 60 kg the lower NOAEL (20 mg /kg body weight/day) has a margin of factor 120 to the lowest antitussive single dose of 10 mg codeine/person (167 µg/kg body weight) but only a margin of factor 10 to the highest antitussive daily dose of 120 mg codeine/person (2 mg/kg body weight).

In a rat study an embryotoxic effect was only observed at the highest dose following oral administration of 10, 35 or 120 mg codeine/kg body weight from the 6th to the 15th day of gestation. In the case of oral administration of 5, 12.5 or 30 mg codeine/kg body weight from the 6th to the 18th day of gestation, no teratogenic effect was observed (72).

Given the data available for humans and the reports of teratogenic potential from animal experiments, codeine may only be prescribed as medicine during pregnancy, particularly during the first three months, in line with strict therapeutic indication and careful weighing up of the risks and benefits (67).

In the case of imminent birth or imminent abortion, the use of codeine is contraindicated as codeine crosses the placenta barrier and can lead to respiratory depression in the neonate (67).

In the case of longer-term administration of codeine, an opioid-dependence can develop in the foetus. There are reports of withdrawal symptoms in neonates following the repeated administration of codeine in the last trimester of pregnancy (67).

3.1.2.1.2.6 Experimental findings

Genotoxicity/carcinogenicity

Codeine was examined and assessed by the American National Institute of Health (NIH) within the National Toxicology Programme (NTP) (68). There were no signs of carcinogenic activity of codeine from the two years feeding studies in rats and in mice.

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 dose it did, however, lead with and without metabolic activation to an elevated incidence of SCE (Sister Chromatide Exchanges) in CHO (Chinese Hamster Ovary) cells. Positive findings were, however, only obtained with doses in the cytotoxic range (68).

For further findings of animal experiments, reference to the summary of the NTP report is made (68).

Examination of documents relating to medicinal use showed that there were no indications of codeine having mutagenic or tumorigenic potential (42).

Findings from animal experiments on the development toxicity of codeine were already addressed in the previous chapter.

3.1.2.1.2.7 Clinical pictures for which precautionary measures or warnings are necessary

Application restrictions apply to the oral administration of codeineas medicine. Codeine should only be used after serious weighing up of the risk-benefit relationship in the case of:

- dependence on opioids,
- impaired consciousness,
- disorders of the respiratory centre (e.g. conditions involving high cerebral pressure) and respiratory function,
- parallel use of MAO inhibitors,
- chronic obstructive respiratory disorders(41, 67).

Higher doses of codeine should not be administered in cases of hypotension and parallel hypovolaemia.

Treatment of patients after a cholecystectomy should be handled with caution. As a consequence of the contraction of the *sphincter oddi*, heart attack-like symptoms and an exacerbation of symptoms may occur in the case of an existing pancreatitis.

At the beginning of treatment the individual reaction of the patient to codeine should be monitored in order to quickly identify any relative overdoses. This applies in particular to older patients with restricted renal function and respiratory function disorders (risk of a pulmonary oedema).

3.1.2.1.2.8 Contraindications

The following contraindications apply to orally administered codeine (67):

- over-sensitivity to codeine,
- respiratory insufficiency,
- respiratory depression,

- pneumonia,
- acute asthma attack,
- coma,
- children under the age of 2,
- imminent birth,
- imminent abortion.

3.1.2.1.2.9 Interactions

A warning is issued about the following interactions of codeine following oral administration in medicinal usage (67):

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 (supraadditive effect of individual components).

In conjunction with tricyclic antidepressants (imipramine, amitriptyline) and opipramole, codeine-related respiratory depression may be exacerbated.

The parallel taking of MAO inhibitors like tranlycypromine can lead an enhancement of effects on the central nervous system and other side effects on a non-foreseeable scale. Codeine may not, therefore, be administered until two weeks after the end of treatment with MAO inhibitors.

The effect of analgetics is enhanced. The parallel administration of partial opioid agonists/antagonists like buprenorphine, pentacozine may weaken the effect of codeine.

Cimetidine and other medicinal drugs, which influence hepatic metabolism, may increase the effect of codeine. During morphine treatment an inhibition of morphine degradation with consecutively elevated plasma concentrations was observed. Interaction of this kind cannot be ruled out for codeine.

3.1.2.1.2.10 Intoxications

The symptoms of codeine overdose are similar to those of acute morphine intoxication (cf. 3.1.2.1.1.10). Here, too, extreme respiratory depression is characteristic. It ranks amongst the most frequent severe complications along with pulmonary oedemas. Symptoms ranging from extreme sleepiness over stupor to 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 (9, 67).

In case of codeine intoxication the risk is deemed to be particularly high for children. This was shown by an evaluation of clinical data on acute codeine intoxications in 430 children (73). Out of 234 children who had been given more than 5 mg codeine/kg bodyweight, 8 suffered from respiratory arrest and required intensive care. 2 of them died. In the other cases one or more of the following symptoms were observed as a consequence of intoxication:

sleepiness, ataxia, miosis, vomiting, rashes, swelling, smarting of the skin but no life-threatening effects.

In clinical terms toxic symptoms are to be expected in adults at a total dose of 0.5 – 1 g codeine and in children from doses of 2 mg codeine/kg body weight upwards.

3.1.2.1.3 Papaverine

Papaverine (6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline, MW: 339.4, CAS No.: 58-74-2) is a benzyloisoquinoline alkaloid (10, 39); papaverine hydrochloride, MW: 375.8 (CAS No.: 61-25-6).

The myotropic spasmolytic papaverine has a direct relaxing effect on smooth muscle (1, 9, 32). The effect is attributed to an inhibition of phosphodiesterase (32, 39). It does not bind to opioid receptors. Today, papaverine is only rarely used to treat spasms of the gastrointestinal tract, bile ducts, urinary tracts and bronchi (9, 32). The oral dose is 0.1 g administered several times daily. The maximum daily dose is indicated as 600 mg papaverine hydrochloride (equivalent to 542 mg papaverine) (39).

After oral administration it is readily absorbed. Bioavailability is about 55 %. Nevertheless, efficacy is not reliable in the case of oral administration. Plasma protein binding is about 90%. Papaverine is mainly metabolised in the liver and excreted renally in the form of glucuronidated phenolic metabolites. The half-life is indicated as 0.5 to 2 hours.

The side effects which occur after oral administration are dizziness, headache, 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 (9, 39).

There are application restrictions for patients with glaucoma and prostate hypertrophy.

Increased intracranial pressure and atrioventricular block are contraindications (9).

There are strict therapeutic indications for pregnancy and lactation period (1).

Reduced efficacy of levodopa is stated as an interaction (39).

3.1.2.1.4 Noscapine

Noscapine ((3S)-6,7-Dimethoxy-3-[(5R)-5, 6, 7, 8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4, 5-g]isoquinoline-5-yl]phthalide (formerly narcotine, MW: 413.4, CAS No.: 128-62-1) is also an alkaloid of the benzyloisoquinoline type (10, 39).

Noscapine is an opium alkaloid which is chemically related to papaverine. It is a centrally acting cough suppressant. It does not react with opioid receptors and is not, therefore, considered to be an opioid. It has neither an analgesic, respiratory depressive or obstipating effect (32). Its antitussive effect is said to be weaker than that of codeine (1). It has no dependence potential (32). It has a weaker spasmolytic effect than papaverine. Noscapine demonstrates weak bronchodilatory properties and stimulates respiration (1, 9). 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 (1, 9, 39).

After oral administration noscapine is readily and quickly absorbed. Because of a first-pass effect bioavailability varies considerably intraindividually and interindividually. It is about 30%. The half-life is 1-4.5 hours; the antitussive effect lasts for 4-6 hours. Noscapine is excreted renally - to a low degree unchanged and, for the most part, in metabolised form (1, 9). Slight sleepiness, light-headedness, dizziness, headaches, nausea and erythema are indicated as adverse reactions. Reactivity may be impaired (9, 32).

Noscapine may lead to the release of histamine. At high doses it triggers bronchoconstriction and temporary hypotonia (38).

Hypersensitivity to noscapine is a contraindication (1, 9).

There are no reports of clinically relevant interactions (9).

Pregnancy and lactation

Noscapine is a poison of mitotic spindle formation. In contrast to other agents of this kind its interaction with tubuline dimers is reversible and depends on its concentration. Cell division in the metaphase is only stopped at noscapine concentrations equivalent to roughly 100 times the therapeutic daily dose for adults (150 mg). Given the elimination half-life of maximum 4.5 hours, the influencing of cell division at therapeutic doses is considered to be unlikely. Application during the first trimester of pregnancy should, however, only be undertaken in cases of strict therapeutic indications (1, 9, 39).

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 (39). At a maternal daily dose of 150 mg an uptake of 300 ng noscapine/kg body weight was assumed from milk. A risk to babies from this dose was considered to be unlikely. Hence, as also stated by the American Academy of Paediatrics (39), there are no objections to the therapeutic use of noscapine during lactation period (9).

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/day upwards (1).

3.1.2.1.5 Thebaine

Thebaine (6,7,8,14-Tetrahydro-4,5-epoxy-3,6-dimethoxy-17-methyl-morphinan, MW: 311.4, CAS No.: 115-37-7) contains the basic structure of morphinan like morphine and codeine. Therefore, it is classed as a phenanthrene alkaloid.

Since thebaine is not used pharmaceutically but only as a starting substance for pharmaceutical synthesis, no information is available about its effects in humans. In animal experiments a LD 50 of 114 mg/kg body weight was determined in rats and a LD 50 of 54 mg/kg body weight in mice following oral administration (76). No other animal experiments are available involving oral administration. From the experiments described and the scientific literature, it can be derived that it mainly has a stimulating effect on the CNS. In all animal species investigated it led to cramps (32, 75, 77). In rabbits thebaine antagonised respiratory depression caused by morphine (Table 9, 3.1.2.1.2) (74, 77). In a mixture with noscapine it provoked a strong respiratory stimulation. In a behaviour test in rhesus monkeys, at increasing doses, it manifested first tremor then cramp and light-headedness. Furthermore it was demonstrated

that, when applied at high doses over a longer period to rhesus monkeys, thebaine led to psychological and physical dependence (77).

3.1.2.1.6 Opium

Opium is the air-dried latex obtained by incisions from the unripe capsules of *Papaver somniferum* L. (cf. 3.1.1.1). Here, only brief attention will be paid to the effects of opium from the angle of alkaloid interactions. 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 statements in the scientific literature about the combined effects of the alkaloids in opium may be relevant for alkaloid-contaminated poppy seeds, too. 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 synergistic and antagonistic effects of the individual opium alkaloids (1, 2) which are presented in simplified form in Table 9.

Table 9: Central effects of opium alkaloids (presented in abbreviated form according to 1, 2)

	Morphine	Codeine	Thebaine	Papaverine
Analgesic effect	+++	++	-	-
Hypnotic effect	+++	+	-	-
Effect on the respiratory centre	Paralysing	-	Exciting	-

As shown by Table 9, it can be assumed that codeine can increase the analgesic and hypnotic effects of morphine. Morphine is said to have a higher analgesic effect than its morphine level would correspond to (1).

Opium has a paralysing effect on the central nervous system, particularly on the respiratory centre. The paralysing effect of morphine is said to be reduced in opium because of the antagonistic effect of thebaine (1, 2). Noscipine 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. The stimulating effect of morphine on smooth muscle is set against the spasmolytic effect of papaverine. 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).

3.1.2.2 Poppy seeds

3.1.2.2.1 Adverse reactions and intoxications after consumption of poppy seeds

Already in older toxicological standard works it is reported that the consumption of large amounts of commercially available poppy seeds, e.g. in the form of deserts with approximately 10 – 20% poppy seeds or poppy seed cakes, can lead to light-headedness and enteroparesis in sensitive individuals (28).

The symptoms described in a consumer complaint made to the official food control also agree with the range of toxicological actions of morphine. This complaint was passed on to us by. 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. The poppy seeds were deemed to have a health-injuring potential (within the intentment of Article 14 para 2a and para 4 of Regulation (EC) 178/2002).injury

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

Moeller *et al.* (24) gave various poppy seed-containing products (rolls, cake) to five test persons (three men and two women, aged: 22 – 43, body weight 55 - 102 kg). The morphine content of the poppy seeds was 50 µg/g; 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 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 GH/MS (highest value: 24 ng/ml). Morphine and codeine could be detected in the urine of all test participants following hydrolysis.

In the comprehensive investigations by Westphal *et al.* (29, 30) 20 test persons (8 female, 12 male) aged between 19 and 45 consumed between 25 g 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 µg/g and 114.3 µg/g. Only half of the test persons had breakfasted that morning prior to the test. Serum collected 1, 2, 4, 8 and 24 hours after consumption was found to contain morphine and codeine individually and together. When the last blood sample was taken the test persons described their condition since ingesting poppy seeds. 7 test persons did not describe any effects. By contrast, the 13 others indicated one or more of the following symptoms: tiredness, lack of drive, difficulty concentrating, headache, dizziness, ongoing dry mouth, minor to severe nausea down to vomiting, heavy tongue, impaired field of vision. Since the publications (29, 30) did not permit any allocation of the symptoms to the individual test persons and no relevant dose associations could, therefore, be identified, BfR got back to the authors who were so kind to provide more detailed information (33). In the case of the symptoms listed, aside from "constricted pupils, heavy sweating and dry mouth" all other symptoms had been observed by the test persons themselves. There was no medical observation as the experiment had not been designed to examine morphine symptoms. The codeine intake is not covered here. Reference is made to the original work.

The lowest morphine dose at which adverse reactions, i.e. listlessness, shortage of power and sleepiness were reported, was 2.9 mg in absolute terms and 40.2 µg/kg body weight. It can be assigned to test person T 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 detection limit of 0.74 ng/ml and the determination limit of 2.82 ng/ml. The authors voiced 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 body weight, the test person A did not observe any adverse reactions. Out of the 8 test persons who ingested 11.4 mg morphine in absolute terms, 2 did not observe any effects (test persons J and O). By contrast, 6 test persons described adverse reactions:

- Test person F (134.5 µg morphine/kg body weight) 10 - 12 hours after ingestion suffered from nausea without vomiting and reduced saliva,
- Test person H (190.5 µg morphine/kg body weight) suffered from slight nausea during the last bite,
- Test person K (142.9 µg morphine/kg body weight) suffered from tiredness and headaches (forehead and left half of head) about 7 hours after intake, dizziness whilst blood was being taken after 8 hours,
- Test person M (152.4 µg morphine/kg body weight) suffered from nausea, headache, tiredness, hiccups,
- Test person R (152.4 µg morphine/kg body weight) suffered from a sensation of repletion, nausea, problems concentrating, tiredness,
- Test person S (170.6 µg morphine/kg body weight) suffered from slight nausea.

Although the sensation of repletion, nausea and tiredness which occurred shortly after eating cannot be interpreted as specific effects of morphine since they could be triggered solely by consuming large amounts of fat-containing foods, the symptoms of test persons F and K do seem to be clearly linked to their morphine intake. At the next higher concentration range the three test persons D, B and G, whose morphine intakes were 13.0 (178.5), 14.5 (195.7), 14.3 (190.5) in absolute mg (relative in µg/kg body weight), did not observe any effects. Test person C with an absolute morphine intake of 14.5 mg (equivalent to 258.6 µg/kg body weight) noticed slight light-headedness, increasing nausea and vomiting and hiccups 8 hours after ingestion. In the dose range of absolute morphine intake of 17.1 – 18.1 mg, one test person (E, 274.2 µg/kg body weight) did not notice any effects whereas a second test person (I, 263.8 µg/kg body weight) observed headaches in the forehead area, slight nausea, tiredness, circulatory weakness 7 hours after intake and a third (P, 281.1 µg/kg body weight) abdominal pain and nausea. At the highest morphine intake levels in the absolute range 20.0 – 22.9 mg, all three test person manifested morphine-related effects: test person L (266.7 µg morphine/kg body weight) described slight nausea during the last bite, ongoing mouth dryness up to 10 hours after intake and slight light-headedness 2.5 hours after intake. Test person N (317.5 µg morphine/kg body weight) reported increasing tiredness up to 9 hours after intake, slight impaired field of vision and a heavy tongue. In test person Q the highest free morphine value in blood of 17.3 ng/ml was measured at a relative morphine intake of 228.6 µg morphine/kg body weight 1 hour after eating.

Directly after ingestion he manifested constricted pupils and heavy sweating in addition to tiredness and lack of drive as well as severe nausea which developed after 6 hours. Concentrations of free morphine in the serum of 10 ng/ml upwards (cf. 3.1.2.2.3 for recommendation of 10 ng/ml as the "cut-off value" regarding § 24 a StVG) with a 1-4 hour duration, where a calming effect on the organism is generally to be expected (30), were only observed in test persons who had ingested more than 14 mg morphine. However, the authors noticed that there was no direct proportionality between the ingested morphine amount (even if it were placed in relationship to body weight) and the morphine concentration in the serum. Even after intakes of more than 14 mg morphine, serum concentrations of free morphine resulted which were well below 10 ng/ml. Only in 2 out of 7 test persons, who had not observed any effects, were serum values of more than 10 ng/ml temporarily measured (B, G). The influence of abrosia prior to poppy seed consumption on the serum values or action was not observed. The experiment shows the major variation range of individual reactions to morphine intakes despite which a dose-dependent increase in the severity of the effects can be identified (e.g. from tiredness to light-headedness, from nausea to vomiting). Furthermore, the proportion of test persons undergoing adverse reactions increases at higher intake levels.

Bjerver *et al.* (31) describe an experiment in which 7 test persons consumed one or two pieces of a poppy seed cake, which contained 5 mg morphine per portion. 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 was 206 µg/g in batch I and 0.6 µg/g in batch II. Each test person ingested between 9 - 55g poppy seeds. The blood concentration of free morphine was 8.5 ng/ml after 4 hours in one person and 13.5 ng/ml after 4.5 hours in another. The only adverse reaction which occurred in all female test persons was a major sensation of repletion, in some cases nausea. The authors believe it is questionable whether these effects can be attributed to the content of alkaloids in the poppy seeds or other ingredients. Other side effects like sleepiness, drop in blood pressure or tachycardia were not observed by the authors (22).

In other publications there were reports of a feeling of and sensation of repletion, lethargy (2) or obstipation (5) as adverse reactions after consuming poppy seed-containing pastry without morphine intake being quantified.

Hayes *et al.* (23) carried out blood tests in four test persons after consumption of 25 g poppy seeds with 294 µg morphine/g and 14 µg codeine/g, equivalent to intake of 7.5 mg morphine and 0.4 mg codeine. After hydrolysis they showed 82 - 131 ng total morphine/ml serum (2 hours after consumption). However, they observed 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 (44). A 6-week old baby suffered from severe health impairment including respiratory depression and had to be taken to intensive care after its mother had given it 75 ml of a milk preparation obtained after straining a mixture of 200 g poppy seeds and 500 ml milk. In line with the investigations the morphine level in the serum of the baby on the following day was 4.3 ng/ml. 0.1 % morphine and 0.003 % codeine had been detected in the poppy seeds used (cf. 3.1.1.3.1).

By way of summary, it can be said that for the purposes of this risk assessment primarily the investigations by Westphal *et al.* (29, 30, 33) are relevant. This study shows that the consumption of poppy seeds leading to morphine intakes of 11.4 mg or 134.5 µg/kg body weight respectively, 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 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.* 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 body weight) is questionable. For morphine intakes of 5 - 10 mg from poppy seeds, another report mentions obstipation as a further adverse reaction (31).

The above experiments show that morphine intakes from the matrix of poppy seeds may, under the given circumstances, be on the scale of therapeutic morphine doses. They may also lead to the spectrum of adverse reactions familiar from medicinal applications.

It is pointed out that the findings of the available forensic studies are only reliable to a very limited degree when it comes to risk assessment because of the test design which is oriented towards a different question (e.g. no double-blinding, no recording of sensitive psychomotor

parameters, low number of test persons per dose group, no medical diagnosis). Hence, there is a need for investigations to fill in the identified gaps in knowledge.

3.1.2.2.2 Poppy seed abuse

On the Internet there are instructions about how to use citric acid to extract opium alkaloids from the blue seeds available commercially in Germany for the purposes of abuse. 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 (33). 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. There is a risk that opiate dependence could be triggered through this abuse (cf. 3.1.2.1.1.4).

3.1.2.2.3 Forensic aspects of poppy seed consumption

The detection of free morphine in serum is interpreted from the forensic angle as an indication of exposure to specific pharmaceuticals or drugs, i.e. morphine itself or heroin and codeine, which can be metabolised into morphine (32). According to more recent findings (29) the detection of morphine in serum may also be linked to the consumption of poppy seeds containing higher levels of morphine (cf. 3.1.2.2.1).

According to § 24 a Street Traffic Law (StVG) anyone who drives a motor vehicle under the influence of, e.g. morphine or heroin acts contrary to orders. An "influence" is assumed when morphine is detected in the serum. Only when morphine can be traced to the proper taking of a pharmaceutical prescribed for a concrete medical condition, has no regulatory offence been committed. The "Grenzwertkommission" which advises the Federal Ministry of Transport, Building and Urban Affairs currently recommends a serum concentration of 10 ng/ml as the cut-off value for free morphine below which no prosecution should be pursued. The exceeding of this value following the consumption of poppy seed-containing foods (cf. 3.1.2.2.1) creates a problematic assessment situation (29).

3.1.3 Exposure to poppy seeds

Poppy seeds are used directly or after kitchen processing e.g. with mills, through swelling, heating, cooking and/or baking in foods. No data are available on possible changes in contents or the bioavailability of the opium alkaloids by these processes. Hence, attention cannot focus here on such effects.

The poppy seed coating of rolls, bagels, muffins or other bakery products normally weighs between 1 and 4 g/piece (18, 20, 22). For cake preparation ground poppy seeds are mostly boiled in milk. This mixture is then baked with other ingredients without straining the milk. The poppy seed proportion in conventional recipes is between 10 - 30%, whereby 1 piece of cake from a bakery weighs between 150 g and 200 g.

Furthermore, other desserts like "Mohnpielen" contain up to 10 - 20% ground and cooked poppy seeds.

Finally poppy seeds (unprocessed) are sprinkled with sugar on traditional dishes like yeast dumplings. For the purposes of estimating the level of exposure, reference is made to the complaint addressed under 3.1.2.2.1 whereby a dish was sprinkled with 75 g blue poppy seeds as part of a mixture with sugar and then eaten.

Since poppy seeds contain a high level of fat (cf. 3.1.1.3), their intake is self-limiting by the high satiation value. What is of primary importance for risk assessments and maximum level derivations are the maximum intakes to be expected within the limits of normal consumption in the worst case. Orientation values can be taken from the test by Westphal *et al.* (33, 34) in which the test persons were instructed to eat as many poppy seeds as possible in the form of poppy seed rice pudding or homemade poppy seed cakes. Out of the 20 test persons one ate 25 g, eight 100 g, two 115 - 125 g, two 150 g, two 175/180 g, four 200 g and one 250 g poppy seeds. This test involved specially manufactured high content poppy seed preparations especially made for this purpose which were consumed under experimental conditions. For the purposes of this assessment, it seems realistic to take lower intake levels. In the risk assessment the worst case assumed is that an adult weighing 60 kg eats 150 g poppy seeds once a day during a meal. This corresponds for a cake with a 25% content of poppy seeds to three slices of 200 g or four slices of 150 g. The intake of 50 g poppy seeds once a day during a meal is considered to be moderate normal consumption. Intakes of > 50 g up to 100 g during one meal per day are regarded as high consumption. For children the example is taken of a 5-year-old girl weighing 14.6 kg (5th percentile) (50). Here the worst case assumed is the consumption of 75 g poppy seeds, corresponding to the consumption of one and a half 200 g pieces of cake during one meal a day. Moderate normal consumption is considered to be the intake of 25 g poppy seeds and high consumption the intake of 50 g poppy seeds during one meal a day.

3.1.4 Assessment and discussion

3.1.4.1 Analytical data on opium alkaloids in poppy seeds – orientational health assessment

The analytical data from various sources provide an overview of the contents of morphine and codeine detected in poppy seeds and also, in individual cases, for papaverine, noscapine and thebaine. Data on the identity (batch numbers, question of multiple sample collection from the same batch) and origin (e.g. geographical, botanical) of the samples are sparse. Because of the non-standardised analytical methods, comparison of the data from the various reports is only possible to a limited degree. Data are only available from a few regions in Germany.

For the purposes of this risk assessment it is assumed that, within normal consumption, an adult eats in the worst case 150 g poppy seeds (three 200 g pieces of cake with 25% poppy seed content) during one meal a day (cf. 3.1.3). If doses of the individual opium alkaloids are ingested in these portions which are within the range of therapeutic doses, then there is a health-injuring potential. On reaching the lowest known therapeutic dose, the occurrence of the described pharmacological effects must be considered in sensitive individuals (cf. 3.1.2.1).

3.1.4.1.1 Morphine

In the case of morphine, portions of up to 150 g poppy seeds in highly contaminated samples (content of up to 330 µg morphine/g, Table 3) would lead to intakes of up to 49.5 mg morphine. As this amount already exceeds the recommended highest oral single dose of 45.6 mg (Table 7), serious central nervous and peripheral effects are to be expected which include impaired consciousness, respiratory depression and cardiovascular effects. This is all the more so the case as it must be assumed that this mainly concerns the first-time intake of this amount of morphine by opioid-naïve, healthy individuals. By contrast, in the case of chronic pain therapy higher doses are normally only administered after longer treatment in the course of which tolerance has already developed. It can be assumed that frequent con-

sumption of morphine levels of this kind leads to the development of dependence. It is obvious that highly contaminated poppy seed batches of this kind are dangerous and not marketable. In Chapters 3.1.4.2 / 3.1.4.3 intake amounts/guidance values are established for morphine in poppy seeds. This aims at giving food control authorities decision support concerning the lower morphine concentrations in poppy seeds, upwards of which consumption must be deemed to be problematic also from the precautionary health angle.

3.1.4.1.2 Codeine

In the case of codeine, consumption of up to 150 g of the most highly contaminated poppy seed sample from Germany, which had already been focussed because of the high morphine values and which had a codeine content of 39 µg/g, would result in an intake of up to 5.85 mg codeine. In the worst case codeine intake would, therefore, in the case of adults be 1.7 times lower than the lowest indicated therapeutic single dose of 10 mg (cf. 3.1.2.1.2.1). For a 5-year-old child with a worst-case consumption of 75 g poppy seeds (cf. 3.1.3), the calculated intake for this sample would be 2.93 mg, which practically reaches the lowest single dose of 3 mg indicated for children of this age. The analogous calculation is even less favourable for the most highly contaminated poppy seeds from the international retail food trade, in which 57.1 µg codeine/g were detected.

High codeine levels only occurred in conjunction with high morphine contents (Tables 2-4). By contrast, poppy seed samples with morphine concentrations on the scale of the guidance value (cf. 3.1.4.3) mostly have codeine contents below the detection limit and in no case over 2 µg/g (Table 3: out of the 13 samples with morphine levels ≤ 10 µg/g 12 samples had codeine values below the detection limit and only one had a codeine level of 1.8 µg/g. Table 2: out of 7 samples with morphine levels ≤ 10 µg/g, the codeine contents of 4 samples were below 0.3 µg/g and of 3 samples below 1.08 µg/g). Hence, the establishment of a guidance value for codeine, to the extent that the proposed guidance value for morphine is used, is not considered to be absolutely necessary under aspects of health. Nevertheless, it is deemed wise in order to cater for the possibility that varieties of *Papaver somniferum* could, for instance, occur during the cultivation of low morphine types of poppy whose seeds have a different alkaloid pattern from the ones examined here. Since, furthermore, it can be assumed that codeine enhances toxicologically relevant morphine effects (e.g. central depressant), that it is difficult to estimate its further role in possible synergistic effects of opium alkaloids and that fundamental aspects of upholding purity and quality criteria have to be considered, the codeine contamination of poppy seeds should be kept as low as possible. Given the existing situation, no derivation of a guidance value is undertaken from the health angle. It is recommended to find out, which is the lowest level of codeine in poppy seeds that can be technologically met. The guidance value should not be higher than the range of maximum 1 - 2 µg codeine/g which can currently be derived from Tables 2 and 3. This leads, in a worst case consumption scenario of 75 g poppy seeds by a 5-year-old child, to a margin of factor 20 and 40 and in the case of high consumption of 50 g poppy seeds to a marginal factor 30 and 60 to the lowest known therapeutic single dose of 3 mg codeine.

3.1.4.1.3 Papaverine

The values measured in 11 samples from the German retail food trade were below 0.06 µg papaverine/g (Table 2), whereas levels of up to 67 µg papaverine/g (Table 4) have been published for the international retail food trade. Thus, in the worst case maximum exposures of up to 9 µg and 10 mg per person can result from the consumption of 150 g poppy seeds by an adult. The margin to the indicated therapeutic single dose of 100 mg is more than fac-

tor 10,000 for exposure to samples from the German food retail trade whereas for samples with papaverine levels of up to 67 µg/g there is only a margin of factor 10. The extreme variations in papaverine levels indicate that it is advisable, for the purposes of quality assurance, to define a maximum value which can be complied with through good manufacturing practice as the guidance value in terms of a purity requirement. It should be below 0.1 and 1 µg/g according to the current data available.

3.1.4.1.4 Noscapine

1.57 µg noscapine/g was the highest content found during the analysing of 11 poppy seed samples from the German market (Table 2). The highest value published for the international food trade was 230 µg noscapine/g (Table 4). In the worst case, consumption of 150 g poppy seeds by an adult would result in intakes of 236 µg and 34.5 mg noscapine. Whereas in the case of the first intake mentioned, which refers to samples from the German market, there is a margin of factor 106 to the lowest indicated single dose of 25 mg noscapine in adults, the intake of 34.5 mg noscapine is already within the range indicated for a single dose of 25 to 50 mg for the use of noscapine as an antitussive agent. In the case of the poppy seed sample with 230 µg noscapine, pharmacological effects must already be considered including the adverse reactions mentioned under 3.1.2.1.4 (e.g. sleepiness, light-headedness, impairment of reactivity, headaches, nausea). This means that this sample has health-injuring potential. Although no more details on the origins of the said batch and on the correctness of the measurement value are available, the data are nevertheless taken as an indication that poppy seeds may contain levels of noscapine which cannot be tolerated from the health angle. Particularly with a view to adverse noscapine reactions that could impair the ability to drive or operate machinery, the establishment of a provisional guidance value is recommended below the noscapine level of 2 µg noscapine/g that is considered to be compliant. It should reflect technological possibilities.

3.1.4.1.5 Thebaine

No analytical data are available for thebaine concerning poppy seeds available in the German retail food trade. The highest thebaine concentration recorded in Tables 1-6 was 41 µg/g (4). The few available measurements cannot be considered representative. Since only LD 50 values from animal experiments are available as oral effective doses, a risk assessment is scarcely sound. There is a margin of factor 540 between the lowest oral LD 50 of 54 mg/kg body weight in mice and the maximum intake of thebaine (0.1 mg/kg body weight) by an adult weighing 60 kg in the worst case of 150 g poppy seeds. Given the inadequate analytical and toxicological data available, no statements can be made about the need for guidance values for thebaine from the health angle. Given its obvious potential to produce dependence in rhesus monkeys, it is, however, advisable to define guidance values as purity criteria. Here the lowest technologically compliant value should be taken as the basis. As for thebaine a maximum level of 20 µg/g is established in Hungary (3.1.1.2), we can assume that this value can be met.

3.1.4.2 Derivation of intake levels for morphine in poppy seeds

Aside from the genotoxicity findings, what is important for the establishment of tolerable intake levels of morphine in food is the threshold dose upwards of which relevant health effects are to be expected in humans. A threshold dose of this kind cannot, however, be defined on the basis of existing data because of the diverse pharmacological and toxicological effects of morphine and the major variations in individual sensitivity (cf. 3.1.2.1.1.1). Nor is this described in the literature. What renders this situation even more difficult is the fact that data

from pharmaceutical applications of morphine can only be transferred to a limited degree to the consumption of poppy seeds as healthy test persons react differently from pain patients with respect to toxicologically relevant morphine effects (3.1.2.1.1.2), dose response relationships in patients treated with morphine can be shifted to higher dose ranges because of tolerance development and opioid-naïve healthy individuals are more sensitive to morphine than pain patients undergoing opiate treatment (3.1.2.1.1.4). Furthermore, morphine is normally given to seriously ill individuals who may react differently from healthy individuals to morphine because of specific disease-related impairments.

The pharmacological scientific literature shows that in adults a single oral effective dose of morphine is normally given as 7.6 mg/person (equivalent to 127 µg/kg body weight for an adult weighing 60 kg) (42) and in the lowest case as 1.9 mg/person (equivalent to 31.7 µg/kg body weight for an adult weighing 60 kg) (39) (3.1.2.1.1.1). At these therapeutic doses in line with the comments under 3.1.2.1.1.2 healthy individuals can be expected to develop at least nausea, retching, light-headedness, dizziness, difficulties in carrying out intellectual tasks, apathy and reduced physical activity as well as other adverse reactions to normal therapy doses (cf. 3.1.2.1.1.5) like dry mouth, obstipation, sleepiness and headache. In principle, variations in individual sensitivity must be taken into account. Psychomotor restrictions, which can impede the ability to drive a car or operate machinery, must be considered. They can be worsened by the parallel consumption of alcohol or pharmaceuticals affecting the central nervous system (cf. 3.1.2.1.1.5).

In line with this, forensic studies by Westphal *et al.* (29, 30) showed that morphine intakes of 11.4 mg (equivalent to 135 to 191 µg/kg body weight) from the matrix of poppy seeds also led to the above-listed symptoms typical for morphine (cf. 3.1.2.2.1). As only two test persons with lower morphine intakes were tested, these investigations do not permit any statements about a threshold dose. Whether doubt should be cast on the symptoms (listlessness, shortage of power, sleepiness) described by one of the two test persons, who had ingested 2.9 mg morphine (equivalent to 40.2 µg/kg body weight) – as suggested by the authors - cannot be assessed here. Furthermore, it is uncertain whether a medical examination, which did not take place, would have revealed further effects.

Therefore, regarding the central and peripheral adverse reactions, the lowest effective dose indicated for oral drug formulations for morphine of 1.9 mg (equivalent to 31.7 µg/kg body weight at a body weight of 60 kg) also seems to be transferable to the matrix of poppy seeds. Given

- the existing uncertainty concerning the threshold doses of health-relevant effects, in particular psychomotor effects,
- possible interactions e.g. with other opium alkaloids in poppy seeds, central nervous pharmaceuticals and alcohol,
- the uncertainty arising from the above situation for safety at the workplace and on the road,
- the expected interindividual variations in sensitivity and
- higher sensitivity in older people and in the case of numerous clinical pictures

according to common scientific practice the tolerable intake level should be at least ten times lower than the indicated lowest effective dose. The guidance values derived from this intake

for morphine in poppy seeds would, however, be so low that only a few batches at the present time could comply with them. As the indication of a "tolerable intake level" does not appear to be justified either given the genotoxic potential of morphine, a "provisional daily upper intake level" is recommended for the time being which is five times lower than the lowest effective dose. This appears justifiable when accompanied by recommendations to consumers to refrain from regular and excessive consumption of poppy seeds, and to manufacturers to exhaust all technological possibilities in order to reduce morphine contents in poppy seeds as far as possible. The "provisional daily upper intake level" is $6.3 \mu\text{g}/\text{kg}$ body weight. It indicates the daily dose of morphine from poppy seed containing foods which a person referred to kg body weight should not exceed during one meal or several meals spread over the day. It applies to adults and children (the intake of $6.3 \mu\text{g}/\text{kg}$ body weight is 13 times lower than the lowest known oral single dose for children of $83 \mu\text{g}$ morphine/kg body weight) (cf. 3.1.2.1.1.1).

3.1.4.3 Derivation of provisional guidance values for morphine in poppy seeds

In Chapter 3.1.3 "Exposure to poppy seeds" it was estimated how many poppy seeds an adult/a child could eat during a meal per day in the case of high or worst case consumption. The guidance values are determined on the basis of the estimated amount of 100 g poppy seeds eaten by adults which is regarded as a high level of consumption. If one takes the provisional daily upper intake level of $6.3 \mu\text{g}$ morphine/kg body weight/day established in Chapter 3.1.4.2 as the basis, then according to this an adult weighing 60 kg who eats 100 g poppy seeds should not ingest more than 0.38 mg morphine. This leads to a provisional guidance value of $4 \mu\text{g}$ morphine/g for poppy seeds. Based on the consumption of 150 g poppy seeds assumed in the worst case, this means a maximum intake of 0.6 mg morphine which is 3.2 times lower than the lowest therapeutic dose. In the case of sensitive individuals, too, the occurrence of central or peripheral effects are considered unlikely under these circumstances.

An exposure of maximum 0.2 mg morphine is calculated for children if the provisional guidance value is complied with using the example of a 5-year-old girl weighing 14.6 kg (5th percentile) (50) who has a "high consumption" of 50 g poppy seeds. The lowest known therapeutic dose for children of $83 \mu\text{g}$ morphine/kg body weight, i.e. 1.21 mg for a girl weighing 14.6 kg, is therefore undercut by factor 6.1. Based on the worst-case assumption of 75 g poppy seeds, this leads for the same child to a maximum intake of 0.3 mg morphine which has a margin of factor 4 to the lowest therapeutic dose. On these conditions, too, central or peripheral morphine effects are not to be expected.

Given the genotoxic potential of morphine (cf. 3.1.2.1.1.6), manufacturers are called on to take the appropriate steps to reduce the morphine levels in poppy seeds below the above-mentioned provisional guidance values. The regular and excessive consumption of foods with a high poppy seed content is advised against particularly during pregnancy.

Interim regulation

Since at least half of the samples examined are below the provisional guidance value of $4 \mu\text{g}$ morphine/g according to the results of Thevis *et al.* (13, Table 1) and Trafkowski *et al.* (15, Table 2), this value seems feasible. The most recent measurements of the Bavarian LGL on morphine levels in poppy seeds (Table 3) identified a trend towards far higher values and only 4 out of 48 sample had values $\leq 4 \mu\text{g}$ morphine/g. Hence, it must be assumed that the provisional guidance value of $4 \mu\text{g}$ morphine/g is not currently being complied with by the majority of poppy seed batches. Nor can it be achieved through cleaning and offcut. In this

situation, one possible management option, until the desired measures to reduce morphine contents in poppy seeds have taken effect (cf. 3.2), is compliance with the "provisional daily upper intake levels" for morphine through additional interim guidance values which are tied to the declaration of consumption restrictions on poppy seed packaging. Similar measures could be considered for processing plants. This presupposes that manufacturers determine morphine levels in each poppy seed batch.

a) Poppy seeds in the retail trade for direct sale to the consumer

A maximum value of 20 µg morphine/g is recommended as the "interim guidance value with consumption restrictions". Depending on the morphine level measured, the maximum daily portions given in Table 10 would result.

Table 10: Interim regulation: proposal for the declaration of maximum daily portions of poppy seeds depending on morphine level

Morphine level of poppy seeds µg/g	Maximum daily portion of poppy seeds to be declared
≤ 4	No declaration
> 4 up to 8	50 g
> 8 – 12	30 g
> 12 – 16	25 g
> 16 – 20	20 g

b) Poppy seeds for processing plants

Here, too, a maximum value of 20 µg morphine/g is recommended as the "interim guidance value with consumption restrictions". The information in Table 11 is based on the assumption that no more than 4 portions of poppy seed-containing foods (poppy seed rolls, poppy seed cake) should be consumed usually per day. Consequently, one portion should only contain one-quarter of the "provisional daily upper intake level" of 0.38 mg morphine, i.e. 95 µg morphine for an adult weighing 60 kg. It is recommended that for manufacturers of ready-to-eat foods the maximum poppy seed amount per portion for each poppy seed batch, which will depend on the morphine content of the batch, is indicated (cf. Table 11).

Table 11: Instructions for manufacturers of ready-to-eat foods concerning the levels of poppy seeds per portion which may not be exceeded depending on the morphine level

Morphine level of poppy seeds µg/g	Instructions for the production plant of the ready-to-eat food
≤ 4	No information
> 4 – 12	Maximum poppy seed amount per ready-to-eat portion: 8 g
> 12 – 20	Maximum poppy seed amount per ready-to-eat portion: 5 g

3.1.4.4 Forensic aspects

In case of compliance with the provisional daily upper intake level, even worst case morphine intakes (150 g poppy seeds) would still be considerably lower than the morphine dose of 14 mg indicated by Westphal *et al.* (33). When it is exceeded it can be assumed that the assessment value of 10 ng/ml free morphine in serum proposed by the "Grenzwertkommission" will be reached. The reaching of this value during traffic controls could thus no longer be at-

tributed to the consumption of poppy seed-containing foods as long as they complied with this guidance value. The same would probably apply to "false positive" findings after the consumption of poppy seed-containing foods during doping controls in sports medicine which are not discussed here (36, 37).

3.1.4.5 Abuse aspect

It can be assumed that poppy seeds, whose morphine content corresponds to the guidance value, are not likely to be misused for drug purposes since the morphine yields from the extraction processes described (cf. 3.1.2.2.2) are likely to be small.

3.1.4.6. Summary fundamental assessment

Poppy seeds are considered as foods which, according to scientific knowledge, themselves only contain very low levels of morphine (cf. 3.1.1.1). They are, therefore, exempted from the Narcotics Act (BtMG) (cf. 3.1.1.2). However, according to actual data normal consumption habits of poppy seeds could lead to an intake of the opiate morphine – obviously through contamination or the selection of false manufacturing conditions, respectively, (cf. 3.1.1.4) – which is on a par with therapeutic effective doses which are used to treat severe pain and are governed by the Narcotics Act. This situation is completely unacceptable. If morphine or opium components adhering to the seeds reach the market in this way, the question must be asked whether this does not, in fact, constitute an infringement of the Narcotics Act (BtMG). This also seems likely given the suitability of the seeds for abusive drugs production (cf. 3.1.2.2). From this obligatory results that under aspects of health assessment the situation is unacceptable within the framework of food legislation, too. Hence the regional authorities had already voiced complaints pursuant Article 14 paras 2a and 4 Regulation (EC) 178/2002. In order to have a clear basis for decision when poppy seeds batches showing borderline morphine contents have to be judged, it is recommended that the proposed provisional guidance for morphine should be applied. Every possible effort should be made to reduce the levels of all pharmacologically active opium alkaloids in poppy seeds to the lowest technically achievable minimum. It is recommended that guidance values be established on this basis too for codeine, noscapine, papaverine and thebaine. For this purpose, as far as the current data situation permits, provisional guidance values are indicated which are deemed acceptable from the health angle.

3.2 Action framework/measures

- It is recommended that each imported batch of poppy seeds currently placed on the market, be examined by manufacturers for its morphine content.
- Targeted efforts are deemed necessary in order to reduce the contents of pharmacologically active opium alkaloids, in particular morphine, to the technically feasible minimum. Research into the causes is deemed necessary. It is proposed that the reasons for high morphine contamination be identified by tracing the source (geographical origin, botanical origin/choice of varieties, cultivation conditions, climatic influence, harvest year, harvesting technique, cleaning conditions). Important data are expected when the above-mentioned parameters are compared between countries which primarily export products with a low level of contamination (e.g. Turkey) and those which supply batches with a high level of contamination (e.g. Australia).
- Consideration should be given to the aspects compiled in Chapter 3.1.1.4. For instance, it should be examined what successes could be achieved in reducing morphine levels by

improving harvesting and cleaning methods (e.g. removal of immature capsules, opening of capsules by hand, introduction of washing steps). Furthermore, it should be clarified whether poppy seeds with a high alkaloid contamination primarily originate from varieties of *Papaver somniferum* which are used because of high alkaloid production in parallel to alkaloid or opium harvesting.

- With reference to the low morphine content (3.5 µg/g) of seeds of the low morphine variety "Przemko" (cf. 3.1.1.3), it is recommended that the selection and cultivation of poppy varieties with a low morphine content be promoted. More information on this may be available from Austria (6) (cf. 3.1.1.1).
- It is recommended that official food control authorities be asked to carry out controls of poppy seed samples in all federal states (monitoring).
- It is recommended that standardised determination methods be elaborated for opium alkaloids from poppy seeds in order to guarantee the comparability of measurements taken.

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