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High capsaicin levels can harbour health risks

High levels of capsaicinoids can be ingested as a result of eating extremely spicy food or corn chips mixed with a capsaicinoid-rich *Capsicum* preparation, as well as in the context of chilli eating competitions. The Federal Institute for Risk Assessment (BfR) has taken reports of serious adverse health effects following oral intake of high doses of capsaicinoids as an opportunity to carry out a comprehensive review and evaluation of the literature published since 2011.

The BfR comes to the conclusion that an increased risk of gastric mucosal damage can be assumed even with intake levels that can be achieved through the traditional consumption of very spicy foods. The symptoms range from a burning sensation in the (upper) gastrointestinal tract, heartburn and reflux to nausea, vomiting and pain in the abdomen and chest. High intake levels can also cause circulatory problems such as cold sweats, changes in blood pressure and dizziness.

In some studies, intakes of 0.5 to 1 mg of capsaicinoids led to mild undesired effects such as a feeling of pressure and warmth or heartburn. The occurrence of pronounced adverse health effects is to be expected at intake levels of 170 mg. In the dose range between, adverse effects can occur. As the data basis is still insufficient, it is not possible to derive a specific dose above which the symptoms mentioned occur.

The studies analysed also suggest that, in addition to individual differencesregarding pungency perception, the type of food through which the capsaicinoids are ingested can also play a role. If one eats an entire or part of a capsaicin-spiced corn chip within a short period of time, the direct physical reaction may be different (more severe) than if one consumes the same amount in a complex dish over a certain period of time.

In the European Union and in Germany, there are currently no legally established maximum levels for capsaicinoids in food. The BfR does currently not have any estimates of the intake of capsaicinoids, particularly by the population in Europe or Germany. The BfR therefore advises caution when consuming foods that contain high levels of capsaicinoids, such as extremely hot chilli sauces or chilli extracts.

1 The BfR has updated its opinion in the light of information on the increased incidence of poisoning in children .Result

1.1 Objectives of the opinion

The reports of serious adverse health effects after oral intake of high doses of capsaicinoids, e.g. after excessive consumption of extremely spicy food or after eating corn chips mixed with a capsaicinoid-rich *Capsicum* preparation as well as in the context of chilli eating competitions, prompted the BfR to carry out a comprehensive review and evaluation of the literature published since 2011.

The research shows that the available information from human and animal studies does not allow a classical risk assessment and the derivation of a health-based guideline value as a basis for risk management measures. The following objectives are therefore defined for the opinion presented here:

(1) Compilation of information on the mechanism of action

For a more comprehensive understanding of the symptoms described in case reports, information on the mechanism of action is presented first.

(2) Identification of relevant toxicological endpoints

A comprehensive literature search was conducted to identify the animal data as well as human data from intervention studies and case reports that are relevant for a qualitative and/or quantitative assessment of the adverse effects of short-term capsaicinoid consumption and to evaluate the relevant toxicological endpoints.

Effects of chronic consumption of capsaicinoids via food are not the subject of this opinion.

(3) Identification of dose ranges at which adverse health effects were observed

Dose ranges at which adverse effects were observed are to be identified from the entirety of the studies relevant to the topic. They are intended to serve as a guide for risk management measures.

(4) Consideration of uncertainties

In addition to the incomplete data basis, the large number of different factors that influence the pungency perception of foods and preparations containing capsaicinoids is a source of uncertainty in the quantitative assessment of adverse health effects following short-term intake of capsaicinoids.

1.2 Results

In humans, short-term oral intake of capsaicinoids can lead to undesired health effects. The probability of occurrence and the severity of the symptoms depend in particular on the dose ingested, but also on numerous other factors.

(1) Information on the mechanism of action

The symptoms observed after acute ingestion of capsaicinoids indicate that the effects are primarily caused by the local effect in the gastrointestinal tract. These are associated with the triggering of pain and a locally occurring neurogenic inflammation. In addition, an activation of the immune system mediated via TRPV1 could also be (co-)responsible for certain effects.

The available mechanistic data, in particular the data on the TRPV1-mediated effects of capsaicinoids on sensory neurons and certain cell populations of the immune system, provide an incomplete picture of the mechanisms triggered by capsaicinoid intake.

(2) Relevant toxicological endpoints

The symptoms range from a burning sensation in the (upper) gastrointestinal tract, heartburn and reflux to nausea, vomiting and pain in the abdomen and chest. High intake levels can also cause circulatory problems such as cold sweats, changes in blood pressure and dizziness. However, the available data do not allow a clear characterisation of the dose-response relationships for the symptoms observed.

(3) Dose ranges at which adverse health effects have been observed

Based on the data currently available, it can be estimated that an intake of 0.5 to 1 mg of capsaicinoids can lead to mild undesired effects such as a feeling of pressure and warmth or heartburn. At intakes in the range of 170 mg, the occurrence of pronounced adverse effects is to be expected. In the dose range between, adverse effects can occur.

(4) Consideration of uncertainties

The capsaicinoid profile in the food matrix and individual factors that influence the perception of pungency among consumers lead to differences with regard to the quantitative assessment of the relationship between acutely ingested capsaicinoid quantities and the probability of occurrence and severity of health effects.

1.3 Conclusion

In view of the large number of different influencing factors and the incomplete data basis available, the health risks associated with the acute oral intake of capsaicinoids cannot be conclusively assessed.

To support risk management, dose ranges at which undesired health effects have been observed are shown in an orientation matrix for symptoms occurring in (healthy) humans after acute oral intake of different capsaicinoid doses, taking into account the form of administration (matrix) (Figure 2).

2 Rationale

2.1 Risk assessment

2.1.1 Agent

2.1.1.1 Capsaicinoids

Capsaicinoids are found as characteristic ingredients in various species of the genus *Capsicum* (family: Solanaceae (nightshade family)), whose fruits are used in a variety of ways as a vegetable and spice. Depending on genus, variety and capsaicinoid content, a wide variety of trivial names are also in common use (chilli, Spanish pepper, chilli pepper, cayenne pepper, etc.), some of which are also used differently from region to region. The compounds, together with small amounts of essential oil, are produced by glandular cells in the placental epidermis of the fruit and are responsible for the pungent flavour of *Capsicum* fruits (Peter 2001; Hänsel & Sticher 2007).

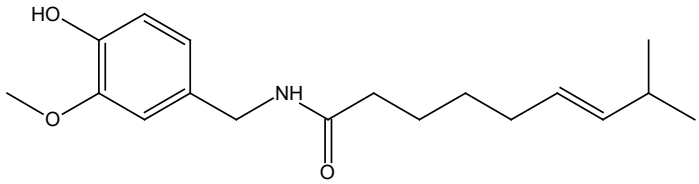
In chemical terms, capsaicinoids are acid amides made of vanillylamine and short-chain, branched fatty acids (Bracher *et al.* 2023). The colourless compounds are very lipophilic, volatile in steam and poorly soluble in water, but highly soluble in various organic solvents such as ethanol and chloroform (Hänsel & Sticher 2007). Capsaicinoids should not be confused with the capsinoids, which are also found in *Capsicum* species, have an ester structure instead of an acid amide structure and do not have any pungent properties (Akhtar *et al.* 2021).

There are various *Capsicum* species and numerous varieties whose fruits differ in size, shape, colour, ingredients and pungency. The fruits of *Capsicum annuum in* particular are used in the food sector. However, the fruits of the other domesticated species *Capsicum frutescens*, *Capsicum chinense*, *Capsicum baccatum* and *Capsicum pubescens* are also used. Contrary to popular belief, from a botanical point of view the fruits are not pods but berries. The two main capsaicinoids in the *Capsicum* species commonly used for consumption are capsaicin (vanillylamide of 8-methyl-6-nonenoic acid; (*E*)-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methylnon-6-enamide, CAS no. 404-86-4) and dihydrocapsaicin (CAS no. 19408-84-5). These two derivatives together make up around 80 to 90% of the total capsaicinoid content.

The content of capsaicinoids in the fruits depends on numerous factors, such as species and variety, and ranges from undetectable amounts to over 2% based on dry weight (Peter 2001; Hänsel & Sticher 2007; Bruneton 2008; Popelka *et al.* 2017). Thomas *et al.* detected 0.22 - 20 mg total capsaicinoids/g dry weight in different varieties of the *Capsicum* species *Capsicum annuum*, *Capsicium frutescens* and *Capsicum chinense* (Thomas *et al.* 1998). In addition to species and variety, other factors can also strongly influence the capsaicinoid content in the fruit - see also section 2.1.2.5.1. Within the fruit, the placental tissue contains the highest levels of capsaicinoids (Cisneros-Pineda *et al.* 2007; Akhtar *et al.* 2021). In addition, there is a high variability in the content of the individual capsaicinoids capsaicin, dihydrocapsaicin and nordihydrocapsaicin. For example, according to Jurenitsch *et al.*, the percentage of capsaicin, dihydrocapsaicin and nordihydrocapsaicin in the total capsaicinoid content in fruits of cultivated *Capsicum* species and varieties was 27 to 77% for capsaicin and 21 to 54% for dihydrocapsaicin (Jurenitsch *et al.* 1979). There are also smaller amounts of nordihydrocapsaicin and some minor acid amides such as homodihydrocapsaicin I and II,

caprylic acid vanillylamide and nonylic acid vanillylamide. In addition to capsaicinoids, the fruits also contain fatty oil, carotenoids, flavonoids, ascorbic acid and a complex mixture of volatile substances (Uarrota *et al.* 2021; Bracher *et al.* 2023; PubChem abgerufen am 2024-02-15).

A.



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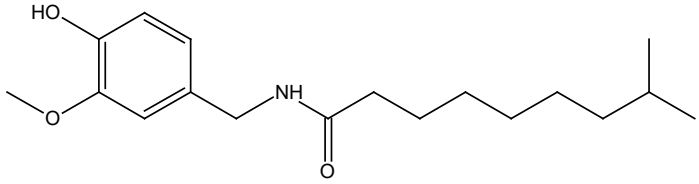

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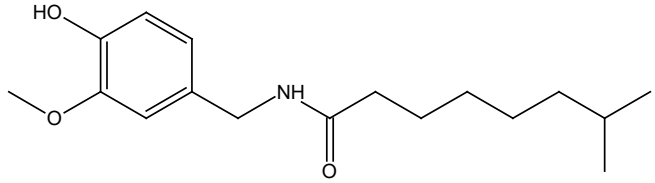

Figure 1: *Structural formulae of capsaicin (A), dihydrocapsaicin (B) and nordihydrocapsaicin (C).*

2.1.1.2 Foods containing capsaicinoids

In the food sector, the fruits of *Capsicum* spp. are used in a variety of ways, mainly as a vegetable or as a flavouring and pungent spice, depending on the degree of pungency. In addition to direct use, the production of various preparations is also widespread, for example "chilli sauces" and "oleoresins" (*Capsicum* extracts). The latter can in turn be used to flavour foods (Peter 2001; Ternes *et al.* 2007). Capsaicinoids are therefore mainly ingested through the use of preparations containing *Capsicum.*

2.1.1.2.1 Legal categorisation

In the European Union and in Germany, there are currently no legally established maximum levels for capsaicinoids in food. According to Annex III Part A of Regulation (EC) No 1334/2008, capsaicin is one of the substances which shall not be added as such to food.

Under Regulation (EU) 2015/2283 and Implementing Regulation (EU) 2019/1976, synthetically produced phenylcapsaicin may be placed on the market as a novel food and used in foods for special medical purposes and in food supplements for persons aged 11 years and older with a maximum level of 2.5 mg per day. Based on manufacturer data, it could be shown that phenylcapsaicin can be considered as a capsaicin analogue that leads to a half-maximal receptor activation compared to capsaicin considering the same dose (EFSA

2019).

2.1.1.2.2 Data on capsaicinoid uptake

Estimates of exposure to capsaicinoids, particularly for Europe and Germany, are not available to the BfR. Data on intake levels are subject to numerous uncertainties and can therefore only be used as a rough guidance. In general, strong regional differences in the consumption of foods containing capsaicinoids are observed. The average daily consumption of *Capsicum* spices in Thailand was estimated at 5 g/person (Monsereenusorn 1983), in Mexico at 20 g/person (Lopez-Carrillo *et al.* 1994), and in India with 2.5 g/person (Ancy *et al.* 2024). Assuming a capsaicinoid content of 1%, the daily intake of capsaicinoids in these countries would be 25 - 200 mg/person (SCF 2002). For the USA and Europe, the maximum daily intake of capsaicinoids from mild chillies and peppers was estimated at 1.5 and 0.5 mg/person respectively, assuming a capsaicinoid content of 0.3 and 0.1%. For Asian countries, the estimated intake levels are many times higher, for example for Korea and Thailand with a maximum daily intake of capsaicinoids of 80 and 50 mg/person when eating chillies with a capsaicinoid content of 1% (Govindarajan & Sathyanarayana 1991).

2.1.1.2.3 Quantification of the degree of severity

The degree of pungency of capsaicinoids or preparations containing chilli is traditionally expressed in so-called "Scoville Heat Units" (SHU). In an organoleptic method developed by pharmacist Wilbur Scoville in 1912, a specific amount of a preparation is dissolved in alcohol and then diluted with sugar water. A test group of five people determines the degree of dilution at which the pungent flavour is no longer perceptible, whereby three people must agree in their perception. The Scoville scale for estimating pungency is subject to numerous uncertainties due to the high variability of subjective pungency perception and can only be used as a rough estimate, but not for a reliable determination of the capsaicinoid content. Today, the degree of pungency is usually determined by analysing the capsaicinoid content. According to convention, 16 SHU corresponds to a capsaicin content of around 1 mg/kg (Peter 2001).

The pungency level of the two main derivatives capsaicin and dihydrocapsaicin is usually given as around 16,000,000 SHU each for the analytically pure substances, although individual studies also indicate differences in the pungency perception for the two substances (Krajewska & Powers 1988; Schneider *et al.* 2014b). The pungency level of nordihydrocapsaicin is stated to be around 9,000,000 SHU and is therefore comparatively lower (Todd *et al.* 1977). According to the Guinness Book of Records, the "Pepper X" variety is currently the hottest chilli in the world. Its heat level is given as 2,693,000 SHU (Guinness World Records abgerufen am 2024-02-15).

Based on a compilation by the CVUA Karlsruhe, the pungency levels of some preparations are listed below as examples. The SHUs are also converted into capsaicinoid contents using the above-mentioned conversion factor (16 SHU = 1 mg/kg capsaicin).

Table 1. *Pungency levels and calculated capsaicinoid contents in selected products[a] .*

Product	Scoville heat unit [SHU]	Capsaicinoid content [mg/kg]
Pepperoni	100 - 500	6 - 31

Sambal Oelek	1,000 - 10,000	63 - 625
Hot seasoning sauce on variety tabasco	2,500 - 8,000	156 - 500
Jalapeño chilli	2,500 - 8,000	156 - 500
Very spicy corn chip[b]	up to 316,000	up to 19,750
Chilli sauces	up to 865,000	up to 54,000
Pepper spray	2,000,000	125,000
Police pepper spray	5,000,000	312,500
Oleoresins (chilli extracts)	up to 11,000,000	up to 687,500

[a] *Exemplary indication of pungency levels in Scoville heat units (SHU) and the capsaicinoid content calculated from this (assumption: 16 SHU = 1 mg/kg capsaicinoid, results rounded). The information in lines 1 to 4 and 6 to 9 is based on data from a publication by the CVUA Karlsruhe (Baden Württemberg abgerufen am 2024-02-15).*
[b] *value reported by a food control authority*

2.1.2 Hazard identification and characterisation

2.1.2.1 Mechanisms of action

2.1.2.1.1 Capsaicinoid-mediated interactions with TRPV1

The effects of capsaicinoids are essentially mediated by agonistic binding to TRPV1 (*transient receptor potential cation channel subfamily V member 1*). This is a transmembrane, non-selective cation channel that can be activated by capsaicinoids, but also by an acidic environment and temperatures above 40 °C, for example (Caterina *et al.* 1997; Tominaga *et al.* 1998; Zhang *et al.* 2018; Thiel *et al.* 2020). The lower perception threshold for heat pain is also located in this temperature range (Yarnitsky *et al.* 1995). An acidic environment, which can also be found in inflamed tissue, for example, also leads to increased sensitivity of the receptor to other noxious substances. For example, a pH value of around 6.3 causes the channel to open at temperatures as low as 35 °C (Tominaga *et al.* 1998) which may explain the increased sensitivity to heat in inflamed tissues. Various other natural substances such as resiniferatoxin from the plant *Euphorbia resinifera*, spider venoms and some endogenous substances such as N-arachidonoyldopamine, N-oleoyldopamine and leukotriene B4 can also lead to activation of TRPV1 or increase its sensitivity to other noxious agents. In addition, various factors, e.g. messenger substances in inflamed tissues, can lead to increased expression of TRPV1 or an increase in its opening probability, and thus to an increased sensitivity of the nociceptive neurons to pain stimuli (Thiel *et al.* 2020).

2.1.2.1.2 Cellular effects of capsaicinoids

TRPV1 was initially found in sensory nerve cells (Caterina *et al.* 1997). The capsaicinoid-sensitive neurons are pseudounipolar nerve cells, most of which also contain the messenger substances substance P and CGRP (*calcitonin gene-related peptide*). The cell bodies of these neurons are located in the ganglia; the axon is divided into two branches. While one of the branches innervates the periphery and receives sensory stimuli from there (TRPV1 is also located on the peripheral axons), the other branch is responsible for the connection to the central nervous system. The activation of TRPV1 results in an influx of Ca^{2+} ions, among other things. The neuronal stimulus generated is transmitted to the central nervous system,

where it leads to the the perception of burning heat pain in the somatosensory cortex. At the same time, various messenger substances (substance P, CGRP) are released in the periphery of the stimulated nerve cells, which, among other things, activate the non-specific immune system and thus trigger local neurogenic inflammation, which is associated with the release of further inflammatory messenger substances. CGRP itself also has a vasodilatory effect. In addition, the Ca^{2+} influx triggers signalling cascades that result in altered gene expression and can therefore influence the sensitivity of the nociceptive nerve cells (Fischer *et al.* 2020; Thiel *et al.* 2020).

The expression of TRPV1 is not limited to nerve cells. Studies have shown that the TRPV1 receptor is also expressed in other tissues and by other cells, albeit at a lower expression level than in neurons. For example, the receptor is found in urothelial cells of the lower urinary tract (Birder *et al.* 2001) and in the keratinocytes of the skin epidermis layer (Denda *et al.* 2001). In primary keratinocytes, activation of TRPV1 can lead to Ca^{2+} -dependent release of proinflammatory signalling substances such as prostaglandin E2 and interleukin-8 (Southall *et al.* 2003) and thus contribute to immune responses. In addition, the expression of TRPV1 has been described in other non-neuronal primary cells, in epithelial and endothelial cells, fibroblasts, muscle cells, adipocytes and hepatocytes (Gunthorpe & Szallasi 2008; Russell *et al.* 2014).

The TRPV1 receptor of birds cannot be activated by capsaicinoids (Jordt & Julius 2002) . Birds can therefore also ingest very pungent *Capsicum* fruits and thus contribute to the dispersal of the seeds.

2.1.2.1.3 Immune cell-mediated local and systemic effects

2.1.2.1.3.1 Effect of cytokines, chemokines, lipid mediators and growth factors of immune cells on the sensitivity of peripheral nociceptors

In local inflammatory reactions, immune cells can modulate pain signals mediated by TRPV1 on nociceptors via the release of inflammatory mediators, both in their extent and in their stimulus thresholds, and thus control the signalling transduction directly and also in the short term (Baral *et al.* 2019). Mast cells, monocytes, macrophages, neutrophils and T cells can contribute to this signalling modulation at the peripheral nerve endings. Numerous studies have shown that, in addition to cytokines such as tumour necrosis factor-α (TNF- α), interleukin-1β (IL-1β), interleukin 6 (IL-6), chemokines such as C-X-C motif chemokine ligand 1 (CXCL1), growth factors such as nerve growth factor (NGF) and lipid mediators also influence the function of TRPV1 at the peripheral nerve endings (Baral *et al.* 2019). Prostaglandin E2 (PGE2), for example, can stimulate the phosphorylation of TRPV1 , which leads to an increase in the opening probability of the ion channel. In this state, opening can occur at 35 °C instead of over 40 °C (Chen *et al.* 2013). The nerve growth factor NGF released by immune cells can increase the translocation of TRPV1 to the outer membrane side of nociceptors in a short time and thus significantly increase the sensitivity of these nerve cells (Denk *et al.* 2017). While the effect of various mediators from specific immune cell populations on TRVP1 in nociceptors is well documented by numerous *in vivo* and *in* vitro studies, there are only a few reports specific to capsaicin responses in nociceptors that have been altered by immune effects. Pre-administration of capsaicin was found to attenuate inflammatory symptoms in an animal model of experimental autoimmune neuritis with fewer infiltrates in sciatic nerves and lower levels of TNF-α and interferon-γ while

increasing TRPV1 expression (Motte *et al.* 2018). According to these studies, capsaicin would tend to have anti-inflammatory and suppressive effects on immune cells. In addition to the modulating effects on peripheral neurons, immune cells can also influence neurotransmission directly at the synapses of the spinal cord after stimulation with capsaicin (Baral *et al.* 2019). Here, microglia, astrocytes and T cells can act on the endings of the dorsal root ganglia and thus on the excretion of adenosine triphosphate (ATP), glutamate and cytokines by releasing further cytokines and growth factors. On the other hand, these cells can modulate the second-order postsynaptic neurons and thus alter pain neurotransmission. Overall, these studies show that immune cells significantly influence the sensitivity of peripheral nociceptors via inflammatory mediators.

2.1.2.1.3.2 Interactions between capsaicin-stimulated nociceptors and immune cells

A number of publications show that the peripheral nervous system and the innate immune system can interact via the recognition of danger signals and the release of messenger substances. Following activation by higher temperatures, low pH or capsaicinoids as danger signals, TRPV1 on peripheral neurons can activate the non-specific immune system (Chiu *et al.* 2012).

Accordingly, in neurons of the dorsal root ganglia of mice in which the expression of TRPV1 was knocked out using genetic engineering methods, a response to capsaicin can no longer be triggered (Davis *et al.* 2000). Further evidence for signalling via TRPV1 in an inflammatory response was provided in a model of tissue injury-induced inflammation (Caterina *et al.* 2000). It was shown that there was only a slight hypersensitivity to thermal stimuli when the mice were TRPV1-deficient.

Various studies have shown that stimulated nociceptors have a direct effect on immune cells via the release of neurotransmitters and neuropeptides. However, there are only a few studies that have investigated this influence for the stimulus capsaicin (Pinho-Ribeiro *et al.* 2017). 500 nM capsaicin induced comparable amounts of CGRP in cultured neurons from dorsal root ganglia as neurons infected with the facultative pathogen *S. aureus* (Baral *et al.* 2018). In addition, there are numerous publications in the literature that demonstrate that nociceptors can influence different populations of immune cells in inflammatory situations via activation of TRPV1 (Baral *et al.* 2019).

When stimulated with the capsaicin analogue resiniferatoxin (RTX), nociceptors have been shown to control inflammatory responses of dermal dendritic cells and subsequently γδ T cells, as found in psoriasis and skin infections (Riol-Blanco *et al.* 2014). Although not explicitly shown in the study, CGRP is discussed as a candidate for the interaction of TRPV1-stimulated neurons with the investigated immune cells. In a model of chemical-induced contact dermatitis, knockout of the CGRP receptor demonstrated the importance of the neuropeptide in mediating T helper(h)-1 and Th2 responses (Mikami *et al.* 2011). According to this study, CGRP increases the release of interleukin 4 (IL-4) and thus Th2 responses and simultaneously inhibits interferon (IFN) -γ and Th1 responses in type IV hypersensitivity reactions such as contact allergy.

However, in these publications, other TRPV1 ligands were used as stimuli rather than capsaicin. The receptors for neuropeptides such as CGRP are expressed by dendritic cells, macrophages, mast cells, granulocytes and various subpopulations of T cells. In the scientific literature, the mechanism by which nociceptors stimulated by TRPV1 ligands tend to have an

inhibitory effect on immune cell-mediated inflammatory responses is known as the neuronal immune reflex arc (further details in the review article by (Andersson & Tracey 2012)). A neuronal immune reflex arc can also be considered as a possible mechanism of action for acute and adverse capsaicin effects.

2.1.2.1.3.3 Direct effects in TRPV1-stimulated immune cells

Among the cells of the innate immune system, the expression of TRPV1 and thus potential sensitivity to capsaicin was observed in monocytes, macrophages, dendritic cells, natural killer cells and neutrophils (Khalil *et al.* 2018).

In a macrophage study, the administration of capsaicin combined with increased expression of TRPV1 reduced lipid accumulation and TNF-α-induced release of the inflammatory proteins monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 2 (MIP-2) and IL-6 (Zhao *et al.* 2013). In pre-stimulated macrophages, capsaicin was able to significantly reduce the formation of inducible NO synthase (iNOS) and the formation of NO, as well as the production of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) (Kim *et al.* 2003). An anti-inflammatory potential of capsaicin was also confirmed in the publication by Zhang (Zhang *et al.* 2022). On the one hand, the release of TNF-α, IL-1β, IL-6 and NO in macrophages induced by the endotoxin LPS was significantly suppressed. On the other hand, in a mouse sepsis model with severe cytokine storm, a subcutaneous injection of capsaicin (dose: 0.5 - 2 mg/kg) significantly reduced the cytokine and lactate levels in serum, the occurrence of multi-organ failure due to inflammatory infiltrates in the kidney, lung, spleen and intestine, and increased the survival rate. In addition, capsaicin was able to reduce the increased concentrations of glucose transporter 1, pyruvate kinase M2, lactate dehydrogenase A, COX-2, lactate and PGE 2 caused by LPS. Similarly, an increased glycolysis rate via LPS, measured via the extracellular acidification rate and a reduced oxygen consumption rate - and thus an overall Warburg effect - could be specifically inhibited by capsaicin *in vitro.*

In addition to cells of the innate immune system, constitutive expression of the TRPV1 was found in mouse and human T cells. In this study, capsaicin stimulation (10 µM) induced Ca^{2+} -influx in Jurkat cells and naive T helper cells from murine spleen and this effect was almost completely inhibitable by knockdown of the receptor (Bertin *et al.* 2014). In transgenic mice with overexpression of TRPV1, however, Ca^{2+} -influx was greatly increased compared to wild-type cells. The electrophysiological and Ca^{2+} -binding tests of this study clearly show functional TRPV1 expression on primary cells of the adaptive immune system, the $CD4^{+}$-T cells.

In addition to immune cells in the gastrointestinal tract, immune cells in the oral mucosa could also be relevant as mediators of systemic-adverse effects when capsaicin is ingested orally as a food ingredient. In fact, certain dendritic cells, Langerhans cells, which are found particularly in the epidermis of humans and mice, can also be found in the mucosa of the oral cavity. These Langerhans cells are localised there suprabasally and form 2 - 8 % of the intra-epithelial cell component (Barrett *et al.* 1996) and are therefore potential target structures of capsaicin even before the gastrointestinal passage.

It is known that nociceptors innervate mucosal epithelia and can also mediate effects on immune cells such as T cells and dendritic cells locally in the mucosa via the release of CGRP.

In addition to this neuroimmuno crosstalk, the functional expression of TRPV1 in primary dendritic cells of the epidermal skin layer was also investigated in a recent publication (Mariotton *et al.* 2023). Here it was shown that 73 % of Langerhans cells from human epidermis expressed the extracellular epitope of the TRPV1 receptor. Even after stimulation with 10^{-5} M capsaicin, human Langerhans cell-like cells reacted with Ca^{2+} -influx. Thus, these experiments demonstrated both a functional expression of TRPV1 and a dose-dependency of TRPV1 stimulation by capsaicin. In further functional studies, it was observed that even low concentrations of capsaicin and CGRP induce the release of the chemokine CCL3 from Langerhans cells and can thus functionally inhibit the transmission of HIV-1 into the cells, for example. In T helper cells from human blood, stimulation with capsaicin alone was able to prevent direct infection with HIV-1. It appears mechanistically plausible that capsaicin, which induces Langerhans cells in the oral mucosa to release CGRP, can also contribute directly to vasodilatation and circulatory complications by activation of mast cells and histamine release. However, such a causal relationship has not yet been investigated in clinical or animal studies.

To summarise with regard to the immune system, it can be stated that

1. Capsaicin can modulate the function of TRPV1 at the peripheral nerve endings after stimulation of immune cells via the release of mediators.
2. Capsaicin can modulate immune responses following stimulation of nociceptors and a neuronal immune reflex arc.
3. Capsaicin can stimulate a number of lymphoid and myeloid immune cells expressing TRPV1, which then release peptide mediators such as CGRP.

2.1.2.2 Toxicokinetics

Animal studies have shown that capsaicin and dihydrocapsaicin are rapidly absorbed in the gastrointestinal tract after oral administration. Within 15 minutes, 30 - 50% of capsaicin or dihydrocapsaicin can be absorbed by the stomach alone (Donnerer *et al.* 1990). Findings by Kawada *et al.* (1984) indicate that absorption is by a non-active mechanism. However, according to observations by Donnerer *et al.,* absorption appears to be subject to a saturation effect at higher intake levels. After the administration of 50 µg/mL or 500 µg/mL capsaicin, about 5% or 25% of the capsaicin administered could still be detected in the gastrointestinal tract after 15 minutes, respectively (Donnerer *et al.* 1990).

In vivo studies on tissue distribution after oral administration of 30 mg/kg bw capsaicin to rats show that the highest concentration was measured in the blood and intestine 1 hour after administration. In the liver, the highest capsaicin concentration was reached 3 hours after administration and in the kidneys after 6 hours. While hardly any capsaicin was detectable in the blood after 24 hours, it took 96 hours until the capsaicin concentration in the intestine was also negligible.

Table 2. *Tissue distribution of orally administered capsaicin in rats*.*

Time (h)	Serum[1]	Blood[2]	Liver[3]	Kidney[4]	Intestine[5]
1	1.90 ± 0.18	11.11 ± 1.05	24.7 ± 2.10	3.61 ± 0.32	1057.0 ± 157.0
3	1.47 ± 0.09	8.59 ± 0.53	44.7 ± 3.37	5.71 ± 0.33	700.2 ± 42.2
6	0.93 ± 0.10	4.85 ± 0.59	14.8 ± 1,50	6.73 ± 0.45	249.3 ± 24.0

24	0.05 ± 0.01	0.29 ± 0.06	8.71 ± 2.55	3.35 ± 0.45	43.5 ±3.75
48	0.006 ±0.0001	0.035 ± 0.006	0.60 ±0.03	0.48 ± 0.09	1.14 ± 0.21
96	0.00	0.00	0.045 ± 0.005	0.00	0.72 ± 0.01
192	0.00	0.00	0.00	0.00	0.00

** n=6; dose 30 mg/kg bw (Suresh & Srinivasan 2010);[1] given in µg/mL;[2] given as µg/total blood;[3] µg/total tissue;[4] given as µg/total tissue;[5] given as µg/total tissue.*

A study in mice showed that after oral administration of 40 mg/kg of a capsaicinoid mixture consisting of 65% capsaicin and 35% dihydrocapsaicin, the half-life in the blood was 1.5 hours and the maximum plasma concentration was 16.7 ng/mL. The oral bioavailability is stated to be around 1 to 2% (Choi *et al.* 2013).

In a 28-day oral toxicity study in dogs, no capsaicin or dihydrocapsaicin was detected in the blood at any time point examined (0.25 - 4 h after administration), even at the highest administered dose of 0.9 mg/kg bw per day (Kuzma *et al.* 2019).

Due to almost complete metabolisation in the liver, the compounds are only available systemically to a limited extent (Kawada *et al.* 1984; Donnerer *et al.* 1990; Rollyson *et al.* 2014; Lu *et al.* 2017; Kuzma *et al.* 2019). A certain part of the metabolism already occurs in the intestinal lumen (Kawada *et al.* 1984; Donnerer *et al.* 1990; Rollyson *et al.* 2014; Lu *et al.* 2017; Kuzma *et al.* 2019), where a small portion of dihydrocapsaicin is hydrolysed to vanillylamine and 8-methylnonanoic acid when absorbed by the intestinal epithelial cells (Kawada *et al.* 1984).

The main part of the metabolisation is localised in the liver. The main metabolites in rats and dogs are 16-hydroxycapsaicin, 17-hydroxycapsaicin and 16,17-dehydrocapsaicin, which are formed by oxidation of the capsaicin or the hydroxylated metabolites. In addition to these metabolites, vanillylamine and vanillin have also been detected using microsomal preparations of the rat (Reilly & Yost 2006; Rollyson *et al.* 2014; Kuzma *et al.* 2019). Experimental animal studies have shown that the administration of 3 mg/kg capsaicin leads to a reduced expression of the xenobiotic-metabolising cytochrome P450 enzymes (CYP) CYP3A. This was demonstrated by reduced mRNA and protein levels of the enzymes (Zhai *et al.* 2013).

In a further study in rats, the metabolism of radiolabelled dihydrocapsaicin and unlabelled capsaicin was investigated. The parallel degradation of the two substances indicates comparable absorption and biotransformation (Donnerer *et al.* 1990).

When studying the metabolism of capsaicinoids in rats, Kuzma *et al.* found that capsaicinoids are also metabolised to glucuronides by UDP-glucuronyl transfer, which are then excreted into the intestinal lumen (Kuzma *et al.* 2015). Another study showed that 48 hours after oral administration of 20 mg/kg bw dihydrocapsaicin to rats, partially non-metabolised dihydrocapsaicin (8.7% of the total dose) and the metabolites vanillylamine (4.7%), vanillin (4.6%), vanillyl alcohol (37.6%) and vanillic acid (19.2%) were detected in the urine. 10% of the non-metabolised dihydrocapsaicin was found in the faeces (Kawada *et al.* 1984).

The fact that only a small proportion of non-metabolised capsaicinoids is excreted is consistent with the studies by Suresh and Srinivasan, in which a total of 0.1% of the

administered dose of capsaicin was detected in the urine and 6.3% in the faeces (Suresh & Srinivasan 2010). Leelahuta *et al.* also found 7.6% and 10.2% of capsaicin in its free form in the urine and faeces, respectively, 24 hours after administration of 47.5 mg/kg capsaicin. About 5% of glucuronidated capsaicinoids were detected in both urine and faeces (Leelahuta *et al.* 1983).

Compared to the data from various animal studies, there is only limited human data available. In a crossover study, 12 volunteers were given 5 g *Capsicum* with an average of 27 mg capsaicin. Capsaicin was absorbed so quickly that it was detectable in the plasma after only 10 minutes. The half-life in plasma was 25 minutes. The low maximum plasma concentration of 2.5 ng/mL indicates a rapid first-pass effect (Chaiyasit *et al.* 2009).

Metabolism studies using human microsomal preparations identified further metabolites that are formed by hydroxylation, dehydration or O-demethylation as well as combinations thereof. Furthermore, glutathione conjugates were also detected, which were formed both directly from capsaicin and from the metabolites (Reilly *et al.* 2003; Qin *et al.* 2019). The formation of capsaicin metabolites is catalysed by a number of cytochrome P450 isoenzymes (mainly CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP2E1) (Reilly & Yost 2006). It has also been shown *in vitro* that capsaicin can inhibit the human cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP3A4 (Babbar *et al.* 2010; Takanohashi *et al.* 2010; Pandit *et al.* 2012; Shamsi *et al.* 2017).

The extent to which the results described from the animal studies can be transferred to humans is unclear, as there is no meaningful data on the species-specific differences in the metabolism of capsaicinoids.

2.1.2.3 Animal experimental data on acute toxicity

As part of a comprehensive literature search, animal studies on acute toxicity following oral intake of capsaicin or capsaicinoids or chilli (peppers, powder, etc.) were evaluated. Relevant data on acute toxicity were only identified for capsaicin, not for other capsaicinoids. One criterion for the results of the animal studies to be considered in the assessment is the indication of the dose of capsaicin or a possible extrapolation from the administered substance to the capsaicin intake.

Toxicological studies carried out on various animal species show a significant variability in the LD_{50} of capsaicin depending on the type of application, animal species and sex. The LD_{50} describes the median lethal dose of a substance that is likely to lead to death within the period of investigation in 50% of those animals exposed. Table 3 shows the LD_{50} values for rats and mice, which were determined after a single dose by oral gavage. The animals died within a few minutes ($\geqslant$ 4 to 26 minutes) after administration of capsaicin. Convulsions and changes in the gastric mucosa were observed in the exposed animals. Saito *et al.* also observed gaitabnormalities, dyspnea and erythema of the skin (Glinsukon *et al.* 1980; Saito & Yamamoto 1996).

Further animal studies on the lethal dose of orally administered capsaicin have not been identified. In this context, the study by Winek *et al.* should also be mentioned, in which the LD_{50} of a chilli sauce based on *Capsicum* fruits (*Capsicum frutescens*) was investigated. The LD_{50} of the sauce, which was administered once by gavage, was 23.58 (18.7 - 29.8) mL/kg bw for the male Sprague Dawley rats and 19.52 (15.64 - 24.35) mL/kg bw for the females. The

authors do not indicate the capsaicin content in the sauce used.Due to the very different product-specificquantities of capsaicin, no extrapolation to the LD_{50} for capsaicin can be made, especially as the sauce used in the study is a mixture of different substances (including vinegar). Hypothermia, tachypnea and lethargy were observed in the animals prior to the onset of death, which occurred 24 hours (in some cases up to 72 hours) after administration of the substance. Pathologically, no ulceration, perforation nor bleeding of the gastrointestinal tract and no macroscopic changes in the organs were observed (Winek *et al.* 1982).

Table 3. *Details of the studies examining LD_{50} in rats and mice after acute administration of capsaicin by gavage.*

Animal species Gender	Solvent	LD_{50} (95 % CI)*	Symptoms	Reference
Mice	Propylene glycol		Increased salivation, tonic-clonic convulsions, dyspnea, tremor, cyanosis, gait abnormalities, bradypnea, erythema of the skin (sometimes more severe symptoms in rats) Stomach: focal slight erosions, ulcers with increased mucus, partly hemorrhages of the gastric fundus Liver, gallbladder (mice only), kidney: no macroscopic changes	(Saito & Yamamoto 1996)
Male		118.8 (96.9 - 145.6)		
Female		97.4 (68.8 - 137.4)		
Rat	Propylene glycol			
Male		161.2 (126.1 - 206.3)		
Female		148.1 (120.5 - 1821)		
Mice	Ethanol, Tween 80, NaCl		Stomach: desquamatic necrosis with increased gastric mucus material, pale basophilic cytoplasm and vacuolization of the chief and parietal cells Other organs: no significant histopathological changes	(Glinsukon *et al.* 1980)
Male		60 - 75		
Mice	DMSO		Convulsions	
Male		190 (122 - 294)		

** Information on the acute lethal dose 50% (LD_{50}) and the 95% confidence interval (CI) in [mg/kg bw].*

The data available with regard to the acute toxicity of capsaicin in animal models, in particular on the symptoms and on the dose-response relationship, is very limited.

After an exposure time of more than 15 minutes, the intragastric administration of a 10 % aqueous extract of *Capsicum* fruits (10 g ground fruits in 100 mL 0.85 % NaCl solution, 2 mL application volume) and 0.014 % capsaicin (in 0.85 % NaCl solution, 2 mL application volume) in male Sprague Dawley rats led to damaged mucosal cells in the duodenum, which increased with increasing exposure time (up to 60 minutes). The authors assume that the amount of capsaicin administered (approximately 1 mg/kg bw) is equivalent to the average intake level of capsaicin consumed with a single meal by the rural Thai population (Nopanitaya & Nye 1974)

The aim of the study by Zhao *et al.* was to improve the solubility and oral bioavailability of capsaicin by encapsulating the substance (hydroxypropyl-β-cyclodextrin (HP-β-CD) complex) and the resulting reduction in irritation. Animals were also treated with non-encapsulated capsaicin in the study. Acute administration of 90 mg/kg "free" capsaicin by gavage in male Sprague Dawley rats fasted for 24 hours showed irritation of the gastric mucosa with altered cell structures in histopathological examination after 2 hours (Zhao *et al.* 2016) (Table 4).

Table 4: *Details of the studies following acute peroral administration of capsaicin or capsaicin-containing substance in animal studies.*

Animal species Gender	**Substance**	**Solvent**	**Dose**	**Symptoms**	**Reference**
Rat Male	Capsaicin	CMC-Na solution	0,014 %	Duodenal mucosa: (ultra-)structural changes, including swelling of microvilli, increased number of free ribosomes and lysosomes	(Nopanitaya & Nye 1974)
	Capsicum extract		10 %		
Rat Male	Capsaicin	NaCl solution	90 mg/kg	Gastric mucosa: altered cell structure, inflammatory cell infiltration, changes in cell nucleus (rhexis, pyknosis)	(Zhao *et al.* 2016)

In summary, only few data is available regarding the acute toxicity of capsaicin, particularly with respect to the dose-response relationship. In the identified studies, capsaicin was administered exclusively by gavage. Results by use of non-oral routes were not considered. The few available data show a strong variability of LD_{50} values in mice between 60 and 294 mg/kg bw and in rats between 120.5 and 206.3 mg/kg bw. Prior to death, increased salivation, seizures, tremors and dyspnea were also observed in the exposed animals indicating neurological disorders.

Microscopic and macroscopic examinations of the exposed animals show that in particular damage to the gastric and intestinal mucosa occurs when capsaicin is administered acutely. However, due to the study design of the acute toxicity studies, it cannot be determined up to which dose range the gastrointestinal effects do not occur . Okumi *et al*. observed inhibited gastric acid secretion in mice after acute peroral administration of 30 or 100 mg/kg bw capsaicin. Lower doses (1, 3 or 10 mg/kg bw) showed no reduction in basal gastric acid secretion (Okumi *et al.* 2012). Adverse effects in other organs were not described in the identified studies, however, these were not always systematically investigated.

Results from subacute studies (up to 28 days), which are not addressed in detail in the opinion due to the research question, support the observations regarding adverse health effects in the gastrointestinal tract after acute administration of capsaicin. Xiang *et al.* observed histopathological changes in the jejunum (reduced villus length and crypt depth) and increased concentration of the pro-inflammatory cytokine IL-1ß, reduced IL-10 concentration, an anti-inflammatory cytokine, as well as increased serum levels of the

neuropeptides substance P and CGRP in male mice after intragastric administration of 40, 60 or 80 mg capsaicin (in physiol. NaCl solution)/kg bw for 7 days. For the medium and highest dose group, but not at 40 mg/kg bw/d, reduced goblet cell count was also observed. In the highest dose group (80 mg/kg bw/d), increased infiltration of inflammatory cells and increased TNF-α levels in the stomach, jejunum, ileum and colon were also observed (Xiang *et al.* 2022). In a study by Tang *et al.,* which investigated the protective properties of Qingke β-glucan after capsaicin-induced gastrointestinal damage, increased serum levels of inflammatory parameters, gastric mucosa erosion, gastric ulcers and sporadic perforation as well as damaged intestinal villi were observed after administration of 20 mg capsaicin (in soya oil)/kg bw via gavage in male mice for 28 days (Tang *et al.* 2021). Further subacute studies in rodents show that adverse health effects in the gastrointestinal tract associated with inflammation and structural and functional changes can occur with an orally administered capsaicin dose in the single or double-digit mg range (per kg bw) (Nopanitaya & Nye 1974; Kaur *et al.* 2017; Mao *et al.* 2023).

2.1.2.4 Human data

2.1.2.4.1 Intervention studies

Relevant studies were identified following a comprehensive literature search. The main criterion for inclusion was that preparations containing capsaicinoids were ingested orally. In addition, only studies in which the amount of capsaicinoids taken up was reported or could be inferred were generally considered.

Numerous intervention studies have been published in the scientific literature in which either healthy volunteers or patients were administered preparations containing capsaicinoids orally. Depending on the research question, these were often administered in the form of capsules containing capsaicin or *Capsicum* powder, but also, for example, via meals flavoured with *Capsicum*, "chilli sauces" and other preparations. In some studies, the substance was ingested once, while in other studies the effects were investigated after repeated ingestion. Most of the studies identified focussed on the assessment of desirable health effects of capsaicin or *Capsicum.* Undesirable health effects were not systematically investigated in most studies. In general, it was reported that the intervention was well tolerated. This applies, for example, to a number of studies in which the influence of 12 mg capsaicin (capsules) on physical performance was investigated (Opheim & Rankin 2012; de Freitas *et al.* 2018a; de Freitas *et al.* 2018b; de Freitas *et al.* 2022; Simões *et al.* 2022). There are also numerous other studies in which no adverse effects were reported after even higher intakes of up to 150 mg capsaicin (Glickman-Weiss *et al.* 1997; Yoshioka *et al.* 1999; Shin & Moritani 2007, 2008; Chaiyasit *et al.* 2009). These studies will not be described in detail here, as the design was focussed on desirable health effects and adverse effects, if any, were only marginally addressed.

The occurrence of adverse health effects following oral intake of capsaicin has only been described in detail in a few human intervention studies. Studies in which adverse effects were reported are described in more detail below. The focus here is on studies in which the adverse effects were already observed after short-term intake in healthy participants. In addition, only studies in which the intake was either with food or in capsule/tablet form or directly into the stomach are described here. Studies in which a solution containing capsaicinoids was slowly infused directly into the oesophagus or certain sections of the

intestine were used to answer specific questions. They are not addressed here due to the highly artificial method of application. The most common adverse effects observed were gastrointestinal effects - in particular a burning sensation in the upper gastrointestinal tract, abdominal pain, heartburn and reflux.

In a randomised and double-blind study conducted by Myers *et al.* in the USA, the effect of *Capsicum* powder on the gastric mucosa was investigated in eight adult male subjects in a crossover design. The design of the study does not fulfil the criteria listed above (indication of capsaicinoid intake obligatory) with regard to the selection of relevant studies for the questions in this statement. The study is nevertheless listed here in detail, as it was included in the earlier BfR statement (BfR 2011) and had a significant contribution to the assessment of the health risk following the consumption of foods with a very high capsaicin content. In the study by Myers *et al.,* three doses of *Capsicum* powder (0.1, 0.5, 1.5 g) were tested on different days, each suspended in 100 mL of distilled water. Distilled water and 625 mg aspirin served as negative and positive controls, respectively. The capsaicinoid content in the *Capsicum* powder used is not known. Due to the high variability of the capsaicinoid content in *Capsicum* fruits, it is therefore not possible to draw any reliable conclusions about the amount of capsaicinoids ingested. If the value of 0.14% for the capsaicin content in chilli quoted in the work by Myers *et al.* is taken into account, this results in a calculated intake of 0.14, 0.7 and 2.1 mg capsaicin per person - however, these values are subject to great uncertainty. According to the authors, the intake of 1.5 g of cayenne pepper corresponds to the intake from a very spicy meal. For the study, gastric lavage was first performed on the respective test days and the test suspension was then infused directly into the stomach via a probe. After an exposure time of 30 minutes, the gastric juice was removed together with two further gastric lavages. After a further 10 minutes, three more gastric lavages were performed. The lavage fluid was analysed for various markers. Compared to the control, a dose-dependent increase in DNA was found, which was regarded as a marker for increased cell shedding. This increase was statistically significant in the lowest and highest dose groups. Only in the lowest dose group, a marginal increase in blood was detected, which was statistically significant but negligibly small. In addition, a correlation was seen here with a pronounced sensitivity in an individual participant. Further, a statistically significant increase in pepsin, the parietal cell fraction and potassium was found in the highest dose group. Potassium was also significantly increased in the lowest dose group. The inter-individual range of variation with regard to the analysed endpoints was very large both in the three dose groups and in the controls (Myers *et al.* 1987).

In a follow-up study from the same working group, the influence of *Capsicum* on the gastric mucosa was investigated using video endoscopy on 12 test subjects in a randomised, single-blind (endoscopist) crossover study. Each of the participants ate four different test meals: a reference meal, a spicy Mexican dish with 30 g fresh jalapeño chillies, a pepperoni pizza and the reference meal together with 1,950 mg aspirin as a positive control. Shortly before the meal and approximately 12 hours after the test meals, the gastric mucosa was examined endoscopically for visual damage. After consumption of the spicy meals, isolated erosions were detected in individual cases, but on average relevant mucosal damage was only detected for the positive control meal with aspirin. In a further sub-experiment, a *Capsicum*-containing sauce was applied directly into the stomach of the participants via a probe. In this experiment, pronounced mucosal bleeding was found four hours after application; a gastroscopy performed 48 hours later no longer revealed any evidence of mucosal damage. In order to determine the effect of the acetic acid contained in the sauce, a further partial

experiment was carried out with 30 g of freshly chopped jalapeño chillies, which were also applied directly into the stomach. An endoscopy performed after 24 hours showed no evidence of mucosal damage (Graham *et al.* 1988). In addition to the acetic acid, however, the different matrix could also be (partly) responsible for the deviating findings.

In a non-blinded, placebo-controlled crossover study conducted in the USA, Nelson *et al.* investigated the effect of capsaicin on thermoregulation in eight healthy male volunteers. At a room temperature of 38 °C, they ingested a dose of 2 mg capsaicin/kg bw via gelatine capsules together with a meal, which corresponds to an intake of around 174 mg for an average body weight of around 87 kg. All test subjects complained of nausea and cramps that lasted for several hours - even after the end of the heat exposure. One subject required medical treatment and had to discontinue the study. The pronounced adverse effects prompted the researchers, after consultation with the responsible ethics committee, to refrain from further studies with a similar design (Nelson *et al.* 2000).

In a double-blind, randomised, placebo-controlled crossover study conducted in Belgium on 10 participants, Lee *et al.* infused 20 mL of a *Capsicum*-containing sauce with a total of 0.84 mg capsaicin or saline solution into the stomach. Compared to the control group, the only statistically significant adverse effect in the *Capsicum* group was a burning sensation in the stomach area. The scores for nausea, flatulence, bloating and discomfort were also slightly higher after *Capsicum* intake. However, these effects did not reach statistical significance compared to the placebo group (Lee *et al.* 2004).

In a study conducted in Austria, Hammer and Vogelsang investigated the effect on the gastrointestinal tract after peroral administration of a capsule containing 0.75 mg capsaicin in 32 participants. Mild adverse effects were reported, which included a feeling of pressure, warmth and heartburn. The symptoms started about 10-15 minutes after taking the capsule and disappeared within 2 hours. In a preliminary study involving a small number of participants, no adverse effects were observed at a dose of 0.25 mg capsaicin, but pronounced discomfort (feeling of pressure and heartburn) was reported at a dose of 1.5 mg capsaicin, so this dose was not used for further studies (Hammer & Vogelsang 2007).

Gonlachanvit *et al.* investigated the effects of *Capsicum* administration in a placebo-controlled, randomised cross-over study conducted in Thailand on 38 healthy individuals, among others. The participants received either a standard meal together with a placebo capsule, a standard meal flavoured with 2 g *Capsicum* powder plus a placebo capsule or a standard meal with 2 g *Capsicum* powder in capsule form. The intake of 2 g corresponded to 1.87 mg capsaicin. In the healthy participants, the intake of *Capsicum* only caused a slight burning sensation in the abdomen compared to the standard meal. The form of application had no influence (Gonlachanvit *et al.* 2009).

In a double-blind, placebo-controlled crossover study by Cao *et al.,* 42 healthy participants received either a capsule containing 0.5 mg capsaicin or placebo every 15 minutes until a moderate pain level was reached for at least 5 minutes. A moderate pain level was defined in this study as at least 30 out of 100 mm on a horizontal VAS (*visual analogue scale*). The study was conducted in Singapore. A moderate level of pain in the upper gastrointestinal tract was achieved in 38 participants after capsaicing, and in only one person after placebo administration. On average, this was achieved after 2 capsules, corresponding to 1 mg capsaicin. In 16 people, a moderate level of pain was achieved after just one capsule. In contrast, only a mild level of pain (VAS: 4 and 23 mm) was observed in two male participants

even after 8 capsules, corresponding to 4 mg capsaicin. Two female participants reported severe nausea before a moderate level of pain was reached. It is not reported after which amount of intake the nausea occurred in the test subjects. In addition to pain, other adverse effects were also reported in the study, in particular bloating and nausea. However, these were not systematically recorded in this study (Cao *et al.* 2011).

Milke *et al.* administered 12 healthy volunteers in a randomised study 3 x 1 g *Capsicum* powder with meals on one day and investigated the effect on oesophageal reflux. The study was conducted in Mexico. Six of the participants were given *Capsicum* of the Ancho variety with a capsaicin content of 0.488 mg/g and six participants were given *Capsicum* of the Cascabel variety with a content of 0.88 mg/g. It was found that there was an increased frequency of reflux after consumption of both varieties, but the increase was only statistically significant in the participants who received *Capsicum* of the Cascabel variety (Milke *et al.* 2006).

In a randomised crossover study conducted in Thailand, Chatsantiprapa *et al.* investigated the effect of *Capsicum* intake on the autonomic nervous system and metabolic functions in 33 healthy participants. The investigated intake amount of about 0.4 mg/kg bw total capsaicin (about 25 mg per person) was ingested by the participants via a rice dish (16.96 - 24.40 mg capsaicin plus 4.86 - 6.99 mg dihydrocapsaicin per dish). A rice dish without added *Capsicum* served as a control. A slight but significant increase in systolic blood pressure and a decrease in the rMSSD parameter for heart rate variability were observed. In addition, a slight but significant decrease in body temperature was reported in the participants (Chatsantiprapa *et al.* 2014).

2.1.2.4.2 Case reports

A report by Bartholomew *et al.* describes the case of a 51-year-old man who had two episodes of severe watery diarrhoea within about 3 years. A radiographic examination showed diffuse inflammation from the stomach to the ileocecal valve. The medical history revealed that approximately 40-50 jalapeños had been consumed on the eve of each of the diarrhoea episodes, which was considered to be the presumed cause of the symptoms (Bartholomew & Carlson 1994).

Snyman *et al.* report a case in South Africa in which an eight-month-old boy suffered from a severe cough for seven days and diarrhoea and vomiting for three days and was admitted to hospital with shock, acidosis, central convulsions, prerenal failure and septicaemia. The boy died of heart failure on the same day. He had previously been orally administered an infusion of a red powder containing "red pepper", which was used as a traditional remedy (name in Afrikaans: "Rooipoeier") (dose and frequency unknown). Capsaicin was detected in the powder. Pathological examination revealed that the liver was discoloured and enlarged (Snyman *et al.* 2001).

Patané *et al.* report two cases in which a hypertensive crisis occurred in one male person each. In one case, this was associated with an acute myocardial infarction and increased levels of thyroid-stimulating hormone. In both cases, the patients had consumed large quantities of peppers and chilli peppers on the previous day. No further details on the exact amount consumed have been reported (Patanè *et al.* 2009; Patanè *et al.* 2010).

Arens *et al.* report on a case in the USA in which a 47-year-old man ate "Bhut Jolokia" chilli together with a burger as part of a chilli eating competition. This type of chilli has a heat level of over 1,000,000 SHU. The amount consumed has not been reported. After consumption, the patient felt severe pain in his mouth. After drinking six large glasses of water, very severe vomiting occurred, resulting in oesophageal rupture (Arens *et al.* 2016).

A report by Sogut *et al.* describes a case in which a 25-year-old man suffered an acute myocardial infarction after taking capsules containing *Capsicum* for five days in order to lose weight. According to the report, such capsules often contain 400 to 600 mg *Capsicum* powder. The exact amount ingested is not known (Sogut *et al.* 2012).

Furthermore, a case of a 41-year-old male patient was described who took *Capsicum* pills for three months to lose weight and without cardiovascular risk factors suffered an acute myocardial infarction. The authors speculate that the subchronic intake of capsaicin could have triggered a coronary syndrome. A hypertensive circulatory status due to activation of the sympathetic nervous system was suspected. In addition, a vasospastic component due to continuous capsaicin-induced endothelin release may have been present. The exact amount of capsaicinoids ingested is not known in this case either (Sayin *et al.* 2012).

A similar case was reported by Akçay *et al.* In this case, a 21-year-old patient presented to the emergency department with chest pain after taking *Capsicum* pills twice a day for two days, the last pill one hour before the onset of chest pain. A myocardial infarction was diagnosed. As there were no other risk factors for coronary heart disease, the use of *Capsicum* pills was discussed as a possible cause (Akçay *et al.* 2017). However, it should be noted here that both the US FDA (Food and Drug Administration) and German authorities have issued a public warning for the preparation mentioned, as the undeclared active ingredient sibutramine was found in analytical tests. Sibutramine was used as a drug for weight reduction. In 2010, the authorisation was withdrawn due to its high risk of cardiovascular side effects (PZ 2014, abgerufen am 2024-03-11; FDA 2015).

Boddhula *et al.* report on the case of a 34-year-old man who experienced repeated "thunderclap headaches" over several days immediately after eating "*Carolina Reaper" Capsicum* during a chilli eating competition. A reversible cerebral vasoconstriction syndrome (RCVS) was diagnosed using computer tomography and the consumption of *Capsicum was* held responsible for the symptoms (Boddhula *et al.* 2018).

Taylor *et al.* report on a case in the USA in which a 15-year-old boy developed severe headaches and pronounced hypertension after two days of eating *Capsicum* of the "*Carolina Reaper*" variety as part of a courage test. This *Capsicum* variety can reach pungency levels of over 2,000,000 SHU. The amount ingested is not known. In the clinic, a reversible cerebral vasoconstriction syndrome was diagnosed, which was accompanied by a cerebral infarction and cortical oedema (Taylor *et al.* 2020).

The best documented case can be found in a report by Koprdova *et al*. A 27-year-old man suffered severe abdominal pain about 2.5 hours after eating four *Capsicum* fruits of the "Bhut Jolokia" variety (over 1,000,000 SHU) and other extremely spicy foods as part of a qualification for a chilli eating competition and had to be hospitalised. The amount of capsaicin ingested with the food was retrospectively estimated to be at least 600 mg. In contrast to the very severe abdominal pain, the further clinical, laboratory and radiological

examinations were largely unremarkable. The condition improved with the administration of painkillers within 30 hours (Koprdova *et al.* 2020).

As an increased incidence of cases of poisoning in children and adolescents has currently been observed, particularly after the consumption of corn chips, which apparently contained high levels of capsaicinoids, the BfR has also conducted a request to the German poison information centres on documented cases in connection with the consumption of such products in the period from 2021 to October 2023 and from November 2023 to March 2024.

The poison information centres recorded 73 enquiries in the period up to October 2023, with most of the documented cases involving children and adolescents. An asymptomatic course was reported for seven enquiries, mild symptoms for 55 enquiries and moderate symptoms for eight enquiries. The severity of three enquiries could not be assessed. The symptoms included in particular gastrointestinal complaints (especially nausea, vomiting, abdominal pain), which in some cases were accompanied by circulatory complaints (e.g. cold sweats, changes in blood pressure, dizziness). In 40 of the enquiries, spicy chips or similar products were reported as the source of exposure. Where reported, the quantity ingested was generally one chip or less; only one enquiry documented the consumption of 17 chips and another enquiry reported the consumption of a larger quantity of chips. The number of asymptomatic cases for the enquiries relating to spicy chips was two, while 31 mild and 6 moderate symptoms were reported. In one case, it was not possible to categorise the severity. A total of 32 enquiries were recorded for the enquiry period from November 2023 to March 2024. Here, too, the documented cases mainly concerned children and adolescents who usually consumed a part of such a product or 1 to 2 whole chips. Four cases were reported as symptom-free exposures. Mild symptoms were reported in 21 cases and seven cases showed moderate symptoms (including 2 cases in combination with caffeine). The symptoms included in particular mucous membrane irritation and gastrointestinal complaints (nausea, vomiting, abdominal pain) and in some cases circulatory problems (e.g. cold sweats, palpitations (tachycardia)). However, the case reports do not allow any conclusions to be drawn about the quantities of capsaicinoids ingested, as no details of the capsaicinoid content were reported.

2.1.2.5 Factors influencing the pungency perception of foods and preparations containing capsaicinoids

2.1.2.5.1 Capsaicinoid profile in *Capsicum* preparations

Both the content and the composition of the various capsaicinoid derivatives in the fruits of different *Capsicum* species depend on numerous factors. The degree of pungency is influenced by the genome of the plant and the environmental conditions. In addition to the species and variety, other influencing factors include the age and nutritional status of the plant, climatic conditions (e.g. temperature and light), geographic location, soil moisture, fertilisation, cultivation conditions and the time of harvest. Studies report on the accumulation of capsaicinoids in *Capsicum* fruits depending on the age, size and developmental stage of the fruit (Mueller-Seitz *et al.* 2008; Antonio *et al.* 2018; Uarrota *et al.* 2021).

Due to the described differences in terms of capsaicinoid content and composition, both the pungency and other sensory properties such as the flavour or the duration of pungency of products containing *Capsicum* can vary greatly. In addition, production and processing

methods also play a role with regard to the capsaicinoid content and the perception of pungency of foods containing capsaicinoids. For example, the type and the size of chopping as well as the type of drying of *Capsicum* fruits influence the degradation of capsaicinoids and thus also the pungency level (Kirschbaum-Titze *et al.* 2002). The group of capsaicinoids is relatively stable compared to other pungent compounds, such as those found in garlic, and *Capsicum* fruits or products containing *Capsicum* only lose their pungency to a limited extent through normal cooking or storage processes. Studies show a maximum degradation of capsaicinoids of 30 % with prolonged cooking and high temperatures (Ornelas-Paz *et al.* 2010; Si *et al.* 2014; Bustamante *et al.* 2021).

2.1.2.5.2 Individual factors influencing consumers' perception of pungency intensity

With regard to the individual perception of the pungency intensity of products containing capsaicinoids, in addition to the content and profile of the capsaicinoids, subjective perception, genetic and environmental factors as well as the composition of the respective food or meal are relevant (Todd *et al.* 1977; Törnwall *et al.* 2012; Siebert *et al.* 2022).

As indicated above, capsaicinoids activate the vanilloid receptor TRPV1, which leads to a non-selective inward cation current, subsequent depolarisation and possibly generation of action potential as well as the release of neurotransmitters and the resulting signal transduction and pain sensation. TRPV1 is polymodal and is activated not only by vanilloids but also by other stimuli such as heat (threshold >42 °C), low extracellular pH values (proton sensor; pH <6) or under strong alkaline conditions as well as other exogenous and endogenous factors (including ethanol, endocannabinoids, derivatives of arachidonic acid and lipids) (Caterina *et al.* 1997; Tominaga *et al.* 1998; Caterina & Julius 2001; Dhaka *et al.* 2009).

TRPV1 activation can be increased if several stimuli are present at the same time. For example, an increased pungency perception of capsaicin was observed at higher temperatures (Sizer & Harris 1985). However, other factors also influence the perceived pungency. Schneider *et al.* systematically investigated the impact of food ingredients on pungency intensity and confirmed that the perception of pungency decreases with complex food matrix. Important factors are starch, sugar and fat content in the food. However, the data are inconsistent to what extent these ingredients reduce or change the pungency perception of food. It has been described that the threshold for capsaicin in oil is significantly higher than in water due to its lipophilic properties (Lawless *et al.* 2000; Schneider *et al.* 2013). The amount of fat in preparations containing *Capsicum* can therefore affect the perception of pungency. In this context, high-fat milk, for example, is also used for neutralisation after consumption of spicy foods, probably justified by the fact that the components in the milk influence the capsaicin binding to the receptor. However, a general statement that fat- or oil-based capsaicinoid-containing food matrices generally have a lower pungency intensity compared to their low-fat analogues cannot be made due to the great variety of factors (Nasrawi & Pangborn 1990; Baron & Penfield 1996; Emrick *et al.* 2005; Kostyra *et al.* 2010; Schneider *et al.* 2014b).

Data on thresholds for capsaicinoids with regard to the activation of the TRPV1 receptor on the tongue and other oropharyngeal regions vary widely and range from 0.15 to over 1 µM (Jurenitsch *et al.* 1979; Rozin *et al.* 1981; Sizer & Harris 1985; Schneider *et al.* 2014a). Taking into account the molar mass (capsaicin: 305.4 g/mol; dihydrocapsaicin: 307.4 g/mol), this would correspond to a concentration of around 50 to 300 µg/L. In a study by Yoshioka *et al.,*

in which 16 Japanese test subjects consumed 30 mL of a soup (approx. 50 °C) with different levels of "*red pepper*", a capsaicin concentration of around 300 µg/L was considered as spicy, a 60-fold higher concentration of 18,000 µg/L was consideredas very spicy and a concentration of 42,000 µg/L, which was a good 2-fold higher, was perceived as too spicy. The inter-individual variability was high; while some participants already perceived a concentration of 3,750 µg/L of capsaicin as too spicy, for other test subjects the threshold was 60,000 µg/L (Yoshioka et al. (Yoshioka *et al.* 2004). No uniform conclusions can be drawn with regard to the thresholds of the two main representatives capsaicin and dihydrocapsaicin. On the one hand, comparable thresholds and Scoville units are described for these capsaicinoids (around 16,000,000 SHU), on the other hand, some studies also indicate different threshold values (Krajewska & Powers 1988; Schneider *et al.* 2014a).

The variability between the threshold determined in the numerous studies could be explained by methodological differences (e.g. variability with regard to stimulation modes/location or the volume of stimuli administered). As the sensitivity to capsaicinoids varies greatly from person to person and can be influenced by numerous factors, a direct comparison of capsaicinoid thresholds is only possible to a limited extent.

In addition to the described sensitisation of TRPV1 through numerous direct and indirect mechanisms, a " development of tolerance " to capsaicinoids can also be observed. Repeated (tachyphylaxis) or prolonged (desensitisation) stimulation by capsaicin can lead to a decrease in TRPV1 activity with a reduced or even absent neuronal response and the resulting inhibition of pain development and transmission to subsequent nociceptive stimuli ("functional" desensitisation ("cross-desensitisation")) and to capsaicin itself ("pharmacological" desensitisation). In addition to changes in the expression of TRPV1, the depletion of peripheral neuropeptide vesicles after activation of the nociceptors and the reversible degeneration of nociceptive afferents also play a role here (Szolcsányi 2004; Touska *et al.* 2011). This selective defunctionalisation of nociceptive afferents is considered to be the basis for the use of capsaicin (formulations) as an analgesic or for the treatment of painful diseases (Knotkova *et al.* 2008).

It has been described that high concentrations and continuous application of capsaicinoids can have a neurotoxic effect at . In newborn rats, for example, subcutaneous treatment with 50 mg capsaicin/kg bw led to irreversible ablation of the afferent C-fibres (Nagy *et al.* 1980). Accordingly, the "development of tolerance" could be a negative feedback mechanism that prevents overstimulation of activated neurones.

The underlying mechanisms of desensitisation after, for example, repeated consumption of products containing capsaicinoids are very complex and depend, among other things, on the stimulus concentration and duration, the intracellular and especially the extracellular calcium concentration and various other factors, such as the dephosphorylation of TRPV1 by calcineurin, a calcium-dependent phosphatase (Szallasi & Blumberg 1999). In addition, reversibility of autodesensitization and resulting reduction of TRPV1 activity are also reported. (Green 1996; Mandadi *et al.* 2004)

In addition to the numerous factors described above that influence the perception of pungency, individual susceptibility to capsaicinoids also plays a significant role. Studies have shown, for example, that patients with stomach problems such as functional dyspepsia or reflux disease (GERD/NERD) react more sensitively after consuming products containing capsaicinoids compared to the control group and report abdominal pain and heartburn,

however, Hammer *et al.* also discuss desensitisation mechanisms after long-term administration of capsaicin (Hammer *et al.* 2008; Hammer & Führer 2017; Patcharatrakul *et al.* 2020).

2.1.3 Assessment of undesired health effects after short-term intake of capsaicinoids

2.1.3.1 Identification of relevant toxicological endpoints

The available human data (intervention studies, case reports) show that the oral intake of capsaicinoids can cause undesired health effects at high intake levels. Due to the low systemic bioavailability after oral exposure, it seems likely that the effects observed in humans are primarily caused by the local irritant effect in the gastrointestinal tract, which is associated with the triggering of pain and locally occurring neurogenic inflammation. In addition, an activation of the immune system mediated via TRPV1, for example, could also be (co-)responsible for certain effects or intensify local irritant effects.

For a qualitative and/or quantitative assessment of adverse health effects following short-term ingestion of capsaicinoids, data on dose-response relationships for a relevant toxicological endpoint are required. The available mechanistic data, in particular the data on the TRPV1-mediated effects of capsaicinoids on sensory nerve cells and certain cell populations of the immune system, cannot be used for a qualitative and/or quantitative assessment. They also provide an incomplete picture of the mechanisms that lead to the observed symptoms triggered by the intake of capsaicinoids. The available human data as well as the data from animal experiments do not allow a clear characterisation of the dose-response relationship for the various symptoms occurring after ingestion of foods containing capsaicinoids. From the entirety of the studies, dose ranges can be broadly specified at which certain effects were observed.

In animal studies, gastric mucosal damage and other structural changes in the gastrointestinal tract were observed. In rodent studies, effects in the gastrointestinal tract occurred after oral (acute as well as subacute) administration of capsaicin doses in the single and especially double-digit mg range (per kg bw). Indications of inflammatory processes in the gastrointestinal tract after capsaicin administration were only described in animal models after repeated capsaicin administration (subacute). Depending on study design and sex, the LD_{50} values after oral administration were between 60 and 294 mg/kg bw in mice and between 120.5 and 206.3 mg/kg bw in rats. Seizures, tremors and respiratory disturbances occurred in the animals. These symptoms have not yet been reported in humans after acute ingestion of high doses of capsaicin.

The symptoms addressed in human studies focus in particular on the gastrointestinal tract and include a burning sensation in the (upper) gastrointestinal tract, heartburn, reflux, nausea, vomiting and pain in the abdomen and chest. If large amounts are ingested, circulatory symptoms may also occur - for example, cold sweats, changes in blood pressure and dizziness. The likelihood and severity of symptoms depend on the dose ingested, but also on numerous other factors. Based on the studies analysed, it can be concluded that the effects of capsaicinoids are largely dependent on the food matrix and other influencing factors.

2.1.3.2 Orientation matrix for dose ranges at which certain effects have been observed

From the data as a whole, it can be concluded that undesired health effects can only be attributed to a very limited extent to defined intake levels of capsaicinoids.

Even at very low doses, a localised burning sensation can be felt in the mouth. With increasing doses, from an intake of around 0.5 to 1 mg per person, symptoms that are generally considered undesirable can occur, such as a burning sensation in the upper gastrointestinal tract, heartburn, reflux and mild abdominal pain (Lee *et al.* 2004; Milke *et al.* 2006; Hammer & Vogelsang 2007; Cao *et al.* 2011). In other studies, however, significantly higher doses were tolerated without adverse effects being reported (Glickman-Weiss *et al.* 1997; Yoshioka *et al.* 1999; Shin & Moritani 2007, 2008; Chaiyasit *et al.* 2009; Opheim & Rankin 2012; de Freitas *et al.* 2018a; de Freitas *et al.* 2018b; de Freitas *et al.* 2022; Simões *et al.* 2022).

Clearly pronounced symptoms were observed in a study conducted in the USA (Nelson et al. (Nelson *et al.* 2000) after healthy male volunteers were given a dose of 2 mg capsaicin/kg bw (corresponding to 174 mg per person). All participants complained of nausea and cramps that lasted for several hours. One subject required medical treatment. In the dose range between, adverse effects can occur (Figure 2).

Very strong effects were described in a case report after a male participant in a chilli eating competition had ingested an estimated dose of over 600 mg. In this case, hospitalisation was required (Koprdova *et al.* 2020). The ingestion of this amount of capsaicinoids appears plausible as the cause of the symptoms described. However, the other case reports and reports of poisoning in Germany described in Chapter 2.1.2.4.2 are difficult to interpret in terms of causality. Furthermore, a dose-response relationship cannot be derived for any of the other case reports due to the lack of information on intake quantities.

Differences in the relationship between acutely ingested capsaicinoid quantities and the probability of occurrence and severity of health effects are due, among other things, to the capsaicinoid profile in the food matrix as well as individual factors that influence the perception of pungency intensity among consumers (see section 2.1.2.5). For example, it is to be expected that a certain intake amount is more likely to cause a more pronounced adverse effect if it is ingested via a single bolus (e.g. via a single corn chip in a "hot chip challenge"), as in this case conscious countermeasures in accordance with the body's own warning signals after ingestion are only possible to a limited extent than if the same amount is consumed via a complex dish spread over a certain period of time.

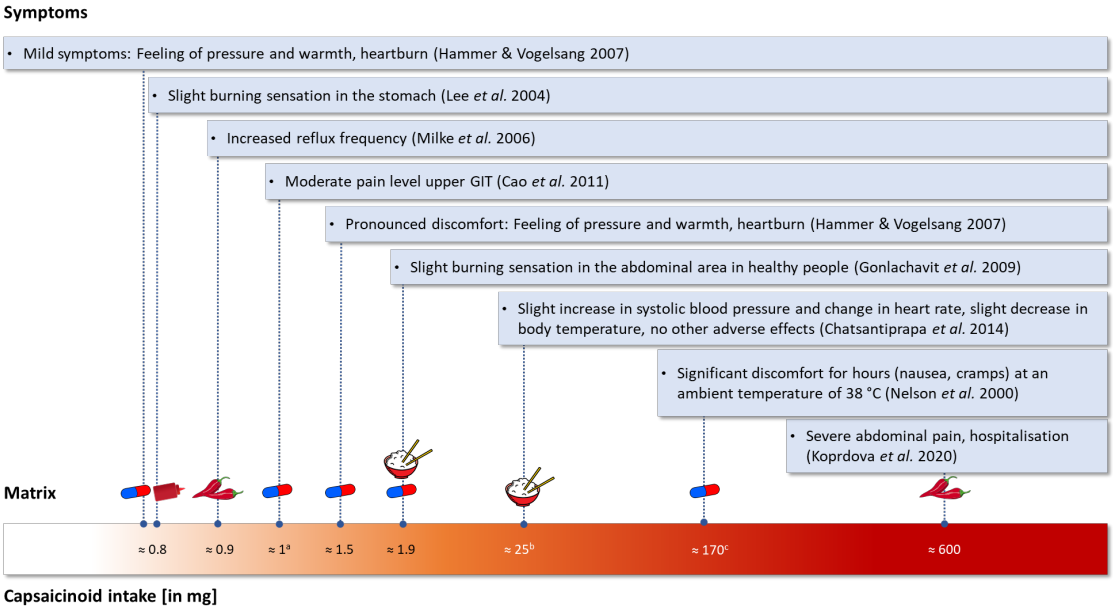

Figure 2: *Orientation matrix for symptoms occurring in (healthy) humans after acute intake of different capsaicinoid doses, taking into account the form of administration (matrix). Studies in which no adverse effects were reported are not included.* [a] *Occurrence of a moderate pain level (median), in some participants already at 0.5 mg, in others only at higher doses;* [b] *dosage in the study was about 0.4 mg/kg bw;* [c] *dosage in the study was 2 mg/kg bw at an average body weight of 87 kg. GIT = gastrointestinal tract. Image sources: www.pixabay.de.*

Further information on the BfR website on capsaicinoids

Spicy test of courage: Extremely spicy foods can be particularly harmful to children's health (German): https://www.bfr.bund.de/cm/343/scharfe-mutprobe-extrem-scharfe-speisen-koennen-besonders-kindern-gesundheitlich-schaden.pdf

High capsaicin levels - interim report on the update of the risk assessment (German): https://www.bfr.bund.de/cm/343/hohe-capsaicin-gehalte-zwischenbericht-zur-aktualisierung-der-risikobewertung.pdf

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