Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

VKM Report 2016: 32

Risk assessment of "other substances" – Curcumin

Opinion of the Panel Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2016: 32
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Risk assessment of "other substances" – Curcumin

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Assessed and approved

The opinion has been assessed and approved by Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Members of the panel are: Inger-Lise Steffensen (Chair), Ellen Bruzell, Berit Granum, Ragna Bogen Hetland, Trine Husøy, Jens Rohloff, Trude Wicklund.

(Panel members in alphabetical order after chair of the panel)

Acknowledgment

The Panel on Food Additives, Flavourings, Processing Aids, Material in Contact with Food and Cosmetics has answered the request from the Norwegian Food Safety Authority. Project leader from the VKM secretariat has been Gro Haarklou Mathisen. Ellen Bruzell is acknowledged for her valuable work on this opinion. Jan Alexander (the Scientific Steering Committee), Åshild Krogdahl (the Scientific Steering Committee) and Helle Margrete Meltzer (former member of Panel on Nutrition, Dietetic Products, Novel Food and Allergy) constituted a reference group and are acknowledged for their valuable comments and suggestions on this opinion.

Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the risk of "other substances" in food supplements and energy drinks purchased in Norway. VKM has assessed the risk of doses in food supplements and concentrations in energy drinks given by NFSA. These risk assessments will provide NFSA with the scientific basis while regulating the addition of "other substances" to food supplements and other foods.

"Other substances" are described in the food supplement directive 2002/46/EC *as substances other than vitamins or minerals that have a nutritional and/or physiological effect*. It is added mainly to food supplements, but also to energy drinks and other foods. VKM has not in this series of risk assessments of "other substances" evaluated any claimed beneficial effects from these substances, only possible adverse effects.

The present report is a risk assessment of curcumin, and it is based on previous risk assessments and articles retrieved from literature searches.

According to information from NFSA, curcumin is an ingredient in food supplements purchased in Norway. NFSA has requested a risk assessment of 300, 600 and 900 mg/day of curcumin in food supplements. The intake of curcumin was estimated for the age groups children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years). Other sources of curcumin, such as foods and cosmetics, have not been included in the present risk assessment.

Curcumin is the main ingredient in the spice turmeric, which is derived from the ground rhizomes of the plant *Curcuma longa* Linn. Other curcuminoids in turmeric are demethoxycurcumin and *bis*-demethoxycurcumin (EFSA, 2010). Curcumin is used as a food additive (E100) and is a spice component, such as in turmeric and curry. The absorption of curcumin is low, and the absorbed curcumin is efficiently metabolised by the liver and excreted into the biliary system. The curcumin plasma levels peak within 2 hours of administration, and complete clearance occurs within a few hours thereafter (Heger et al., 2014).

Maximum curcumin intake from food as food additive and spice combined has been reported to be 2.3 and 1.6-7.6 mg/kg bw per day for adults and children (1-10 years in the case of food additive; 5-12 years in the case of spices), respectively (EFSA, 2010).

An acceptable daily intake (ADI) of 0-3 mg/kg bw per day was allocated by JECFA (2004), based on the NOAEL from a multigeneration reproductive toxicity study in rats (Ganiger, 2002; Ganiger et al., 2007). Based on the same study, EFSA established an ADI of 3 mg/kg bw per day (EFSA, 2010).

For children (10 to <14 years), the estimated daily intakes of curcumin were 6.9, 13.8 and 20.7 mg/kg bw per day from daily doses of 300, 600 and 900 mg curcumin, respectively, from food supplements.

For adolescents (14 to <18 years), the estimated daily intakes were 4.9, 9.8 and 14.7 mg/kg bw per day from daily doses of 300, 600 and 900 mg curcumin, respectively, from food supplements.

For adults (≥18 years), the estimated intakes were 4.3, 8.6 and 12.9 mg/kg bw per day from a daily intake of 300, 600 and 900 mg curcumin, respectively, from food supplements.

The intake from all three doses of curcumin exceeded the ADI value of 3 mg/kg bw per day for all age groups.

VKM concludes that a daily intake of 300, 600 or 900 mg of curcumin in food supplements may represent a risk of adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Short summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet, NFSA), assessed the risk of daily intake of 300, 600 and 900 mg of curcumin in food supplements. For the risk characterisation, the value used for comparison with the estimated exposure are the ADI of 3 mg/kg bw per day, based on a multigeneration reproductive toxicity study in rats.

VKM concludes that a daily intake of 300, 600 or 900 mg of curcumin in food supplements may represent a risk of adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Key words: Adverse health effect, curcumin, food supplement, negative health effect, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, VKM

Sammendrag på norsk

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved tilsetting av «andre stoffer» i kosttilskudd og energidrikk som selges i Norge. VKM har risikovurdert ulike doser brukt av kosttilskudd og konsentrasjoner i energidrikker oppgitt fra Mattilsynet. Disse risikovurderingene vil gi Mattilsynet vitenskapelig grunnlag for å regulere andre stoffer.

«Andre stoffer» er beskrevet i kosttilskuddsdirektivet 2002/46/EC som *stoffer som har en ernæringsmessig og/eller fysiologisk effekt, og som ikke er vitaminer og mineraler*. De tilsettes i hovedsak til kosttilskudd, men også til energidrikker og andre næringsmidler. I disse risikovurderingene har VKM ikke sett på påståtte gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

Denne rapporten er en risikovurdering av kurkumin, og den er basert på tidligere risikovurderinger og artikler hentet fra litteratursøk.

I følge informasjon fra Mattilsynet er kurkumin en ingrediens i kosttilskudd som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere inntak på 300, 600 and 900 mg/dag av kurkumin i kosttilskudd. Inntak av kurkumin ble beregnet for aldersgruppene barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Andre kilder til kurkumin, som mat og kosmetikk, er ikke inkludert i denne risikovurderingen.

Kurkumin er hovedbestanddelen i krydderet gurkemeie, som utvinnes fra jordstenglene til planten *Curcuma longa* Linn. Øvrige kurkuminoider i gurkemeie er demetoksykurkumin og *bis*-demetoksykurkumin (EFSA, 2010). Kurkumin brukes som tilsetningsstoff i mat (E100) og det forekommer som en komponent i krydder, slik som i gurkemeie og i krydderblandingen karri. Kurkumin har lav absorpsjon. Absorbert kurkumin blir effektivt metabolisert av leveren og videre skilt ut i gallen. Plasmanivåene av kurkumin er på det høyeste i løpet av 2 timer etter inntak, og etter ytterligere et par timer er alt kurkumin skilt ut (Heger et al., 2014).

Det maksimale, samlede inntaket av kurkumin fra mat i form av tilsetninsstoff og krydder har blitt rapportert å være henholdsvis 2,3 og 1,6-7,6 mg/kg kroppsvekt per dag for voksne og barn (1-10 år gjelder ved inntak av tilsetningsstoff; 5-12 år for krydder) (EFSA, 2010).

Et akseptabelt daglig inntak (ADI) på 0-3 mg/kg kroppsvekt per dag ble satt av JECFA (2004) basert på NOAEL fra en flergenerasjonsstudie av reproduksjonstoksisitet i rotter (Ganiger, 2002; Ganiger et al., 2007). EFSA etablerte en ADI på 3 mg/kg kroppsvekt per dag basert på den samme studien (EFSA, 2010).

For barn (10 til <14 år) var det beregnede daglige inntaket av kurkumin 6,9, 13,8 og 20,7 mg/kg kroppsvekt per dag fra daglige doser på henholdsvis 300, 600 og 900 mg kurkumin fra kosttilskudd.

For ungdom (14 til <18 år) var det beregnede daglige inntaket av kurkumin 4,9, 9,8 og 14,7 mg/kg kroppsvekt per dag fra daglige doser på henholdsvis 300, 600 og 900 mg kurkumin fra kosttilskudd.

For voksne (≥18 år) var det beregnede daglige inntaket av kurkumin 4,3, 8,6 og 12,9 mg/kg kroppsvekt per dag fra daglige doser på henholdsvis 300, 600 og 900 mg kurkumin fra kosttilskudd.

Inntaket fra alle tre kurkumindoser overskred ADI-verdien på 3 mg/kg kroppsvekt per dag i alle aldersgrupper.

VKM konkluderer at daglig inntak av dosene 300, 600 og 900 mg kurkumin fra kosttilskudd vil kunne representere en risiko for negative helseeffekter for barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Kort sammendrag

På oppdrag fra Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved inntak av 300, 600 og 900 mg kurkumin i kosttilskudd. I risikokarkarakteriseringen ble en ADI-verdi på 3 mg/kg kroppsvekt sammenlignet med den beregnede eksponeringen. ADI-verdien var basert på en flergenerasjonstudie av reproduksjonstoksisitet i rotte.

VKM konkluderer at daglig inntak av dosene 300, 600 og 900 mg kurkumin fra kosttilskudd vil kunne representere en risiko for negative helseeffekter for barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Abbreviations and glossary

Abbreviations

ADI - acceptable daily intake
ADME - absorption, distribution, metabolism and excretion
bw - body weight
CA - chromosomal abberations
CHO - Chinese hamster ovary cells
DMSO - dimethyl sulfoxide
EC_{50} - half maximal effective concentration
EFSA - European Food Safety Authority
EMEA - European Medicines Agency
FAO - Food and Agriculture Organization of the United Nations
FDA - Food and Drug Administration, US
GRAS - Generally Recognized As Safe (FDA)
JECFA - Joint FAO/WHO Expert Committee on Food Additives
L./Linn. - Linnaeus (the Latin name of Carl von Linné) (in botany, the authority responsible for naming a species is added to the name in the binomial nomenclature system)
LD_{50} - median lethal dose
LOAEL - lowest observed adverse effect level
LOEL - lowest observed effect level
MNPCE - micronucleated polychromatic erythrocyte
NCI - National Cancer Institute (US)
NFSA - Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NOAEL - no observed adverse effect level
NOEL - no observed effect level
NSAIDS - non-steroidal anti-inflammatory drugs
NTP - National Toxicology Program (US)
RCT - randomised, controlled trial
SCE - sister chromatid exchange
SCF - Scientific Committee on Food (EU)
TA - toxin/antitoxin
VKM - Norwegian Scientific Committee for Food Safety [Norw.: - Vitenskapskomiteen for Mattrygghet]
WHO - World Health Organization

Glossary

"Other substances": a substance other than a vitamin or mineral that has a nutritional or physiological effect (The European Parliament and the Council of the European Union, 2006).

"Negative health effect" and "adverse health effect" are broad terms. VKM uses the definition endorsed by EFSA for "adverse effect": a change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (EFSA, 2006; WHO, 1994).

Background as provided by the Norwegian Food Safety Authority

«Other substances» are substances other than vitamins and minerals, with a nutritional and/or physiological effect on the body. "Other substances" are mainly added to food supplements, but these may also be added to other foods and beverages, such as sports products and energy drinks. Ingestion of these substances in high amounts presents a potential risk for consumers.

In Norway, a former practice of classification of medicines had constituted an effective barrier against the sale of potentially harmful "other substances". Ever since this practice was changed in 2009, it has become challenging to regulate and supervise foods with added "other substances". Meanwhile, in the recent years, the Norwegian market has witnessed a marked growth in the sales of products containing "other substances". In 2011, food supplements containing "other substances" constituted more than 50% of the market share.

While within the European Economic Area, these substances fall under the scope of the European Regulation (EC) No. 1925/2006 on the addition of vitamins, minerals and certain other substances to foods and the European Regulation (EC) No 258/97 concerning novel foods and novel food ingredients, "other substances" remain largely unregulated. In order to ensure safe use of "other substances" many countries have regulated their use at a national level. For example, Denmark regulates these substances in a positive list, i.e. a list of substances with maximal daily doses, permitted for use in food supplements and other foods (FVM, 2014).

The Norwegian Food Safety Authority (NFSA) is working on the establishment of a regulation on the addition of "other substances" to foods at a national level. The regulation will include a list of substances with permitted maximal doses, based on the substances and doses found in products on the Norwegian market. In preparation for a regulation, NFSA has therefore requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of "other substances" found on the Norwegian market. NFSA, in consultation with the industry, has compiled a list of "other substances" found in products marketed in Norway. Only substances with a purity of minimum 50% or concentrated 40 times or more have been included in the list. Substances regulated by other legislations like those for novel foods, food additives, flavourings, foods for special medical purposes etc., have been excluded from the list.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of curcumin in food supplements at the following doses: 300, 600 and 900 mg curcumin/day.

NFSA requested VKM to assess the safety of "other substances" (in accordance with the guidance document developed in Phase 2) at the doses specified (Phase 3). The safety assessments of "other substances" present in food supplements shall be carried out for a general population, ages 10 years and above.

Assessment

1 Introduction

"Other substances" are described in the food supplement directive 2002/46/EC *as substances other than vitamins or minerals that have a nutritional and/or physiological effect,* and may be added to food supplements or e.g. energy drinks (The European Parliament and the Council of the European Union, 2006).

This risk assessment regards the substance curcumin *per se*, and no specific products.

VKM has in this series of risk assessments of "other substances" not evaluated documentation of any claimed beneficial effects from these substances, but merely possible adverse effects at specified doses used in Norway. Thus, potential high intake consumer groups of the substance might not be identified and included in this assessment.

According to information from the Norwegian Food Safety Authority (NFSA), curcumin is an ingredient in food supplements purchased in Norway. NFSA has requested a risk assessment of the intake of 300, 600 and 900 mg curcumin per day from food supplements. The total exposure to curcumin from other sources than food supplements, such as foods and cosmetic products, is not included in the risk assessment.

Curcumin is the main component in turmeric, which is derived from the ground rhizomes of the plant *Curcuma longa* Linn (L.). Other curcuminoids in turmeric are demethoxycurcumin and *bis*-demethoxycurcumin (EFSA, 2010). Curcumin is used as a food additive (E100), and turmeric is both used as a spice by itself and in spice mixtures such as curry. The food colourant curcumin (E100) consists of three curcuminoid components: curcumin ((1E,6E)-1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), ($C_{21}H_{20}O_6$), desmethoxycurcumin ($C_{20}H_{18}O_5$) and bis-desmethoxycurcumin ($C_{19}H_{16}O_4$) (EFSA, 2010). The absorption of curcumin is low, and absorbed curcumin is efficiently metabolised by the liver and excreted into the biliary system (Heger et al., 2014).

Maximum curcumin intake from food as food additive and spice combined has been reported to be 2.3 and 1.6-7.6 mg/kg bw per day for adults and children (1-10 years in the case of food additive; 5-12 years in the case of spices), respectively (EFSA, 2010).

2 Hazard identification and characterisation

2.1 Literature

The present risk assessment is based on previous risk assessments of curcumin and articles retrieved from a literature search.

2.1.1 Previous risk assessments

Safety evaluation of certain food additives and contaminants (JECFA). Prepared by the Sixty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2004)

A temporary ADI of 0–1 mg/kg bw per day for curcumin was previously established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). In this report, the results from a multigeneration study by Ganiger (2002) were available for evaluation. Taking into account all of the data evaluated previously, the Committee withdrew the temporary designation and allocated an ADI of 0–3 mg/kg bw per day for curcumin, based on the NOAEL (No Observed Adverse Effect Level) of 250–320 mg/kg bw per day in the multigeneration reproductive toxicity study in rats, and the application of a safety factor of 100 (for more details of this animal experiment, see 2.4.3).

Assessment report on *Curcuma longa* L. rhizoma. Committee on herbal medicinal products (HMPC). European Medicines Agency (EMEA, 2010). (Doc. Ref.: EMEA/HMPC/456848/2008)

The report addresses the herbal substance *Curcuma longa* L. rhizoma (turmeric), herbal preparations or combinations thereof and their occurrence in the EU. The report is based on collected non-clinical and clinical data. Overviews were given of turmeric/curcumin with respect to pharmacology, pharmacokinetics and toxicology. Curcumin is contraindicated in patients with obstruction of the biliary tract. Concerning "overdose" and adverse effects, the committee concluded that no toxic effects were observed after three months of oral intake of 8 g or 2.2 g of turmeric (equivalent to 180 mg of curcumin) per day for four months. Overall conclusions on clinical safety were expressed as follows: "*No serious side effects have been reported up to now. Furthermore, the chemical composition of Curcuma longa L. does not give any reason for concerns regarding safety. Potential interactions between Curcuma longa L. and NSAIDs, antiplatelet agents, antihyperlipidemics and immunosuppressants have been reported, but this has not been clinically proven. Curcuma longa L. cannot be recommended in children under the age of 18 years, neither during pregnancy nor lactation, due to lack of data*".

VKM notes that the conclusion regarding lack of toxic effects assessed three months after oral intake for four months was not based on optimal clinical studies of curcumin with healthy subjects. Rather, the following literature was cited: one study that used curcumin oil (curcuminoids may not be present), two studies performed in cancer patients (Cheng et al., 2001; Sharma et al., 2004), one study that did not mention curcumin, a monograph of a collection of curcumin studies and a review. Clinical data were very limited.

Scientific Opinion of the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) on the re-evaluation of curcumin (E100) as a food additive. The European Food Safety Authority (EFSA, 2010)

Studies with curcumin or purified extracts of turmeric (the rhizome compound from which curcumin is derived) consisting of the three curcuminoids in varying proportions were included in this opinion. Animal studies revealed that curcumin is rapidly metabolised and excreted mainly via faeces. Based on human studies, EFSA regarded it as unlikely that substantial concentrations of curcumin occur in the body after ingestion at doses up to 12 g/person (171 mg/kg bw per day for a 70 kg person) (Cheng et al., 2001).

Regarding acute oral toxicity studies, EFSA claimed that since the time JECFA (2004) evaluated four such studies, no new studies were published. It was noted that the acute toxicity of curcumin was low. The LD_{50} value in mouse and ratafter oral dosing was >10 g/kg bw per day (about 79% curcumin purity) (Lilja et al., 1983). Lower LD_{50} values were reported in other studies, but without specifications of the curcumin purity (EFSA, 2010).

Evaluation of *in vitro* and *in vivo* data indicating curcumin genotoxicity led EFSA to conclude that these effects should not be disregarded and, in particular, that the available *in vivo* genotoxicity studies were insufficient to eliminate the concerns regarding genotoxicity. However, EFSA noted that tumorigenic effects observed by NTP (1993) were of benign rather than malign nature, were not dose-dependent, were in line with historical control values and were not consistent across sexes and/or species. Thus, EFSA concluded, as did JECFA, that curcumin was not carcinogenic, and that this perception eliminated the concerns over genotoxicity.

An ADI of 3 mg/kg bw per day was established, based on a multigeneration reproductive toxicity study (OECD Testing guideline 416) in rats fed curcumin up to 21 weeks in the parental generation (P) and 24 weeks in the F1 generation (until weaning from lactation of offsprings) followed by weight gain assessment in the P, F1 and F2 generation. The rats were fed diets with curcumin concentrations of 0, 1500, 3000 or 10000 mg/kg diet. These concentrations were equal to 0, 130-140, 250-290 or 850-960 mg/kg bw per day for males and 0, 160, 310-320, or 1000-1100 mg/kg bw per day for females. The NOAEL was 250-290 mg/kg bw per day for males and 310-320 mg/kg bw per day for females since decreased body weight gain in the F2 generation was observed at the highest dose level (850-960 mg/kg bw per day for males and 1000-1100 mg/kg bw per day for females; for more details, see 2.4.3) (Ganiger et al., 2007). An uncertainty factor of 100 was applied. EFSA concluded

that intake estimates for 1-10-year-old children at the mean and the 95th percentile were above the ADI in some European countries (EFSA, 2010).

GRAS Notification for Curcumin Preparation (Curcumin C3 Complex®) from Soni & Associates (FL, USA; agent for Sabinsa Corp., NJ, USA) to The Food and Drug Administration (FDA, USA) and Agency Response Letter GRAS Notice (GRN) No. 460 (FDA, 2013)

Sabinsa Corporation through its agent Soni & Associates provided notice of a claim that the food ingredient curcumin preparation (Curcumin C3 Complex®) is exempt from premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because it has been determined to be Generally Recognized As Safe (GRAS), based on scientific procedures. An Expert Panel ("modelled after that described in section 201 of the Federal Food, Drug, and Cosmetic Act"; CVs of the panel members were attached) has evaluated the scientific toxicological and safety information. The Expert Panel Statement included a chapter on animal and human toxicology studies (absorption, distribution, metabolism and excretion (ADME), acute and short-term, subchronic and chronic studies, carcinogenicity, genotoxicity, reproductive and developmental toxicity as well as sensitisation and allergenicity studies).

According to the Panel, the curcumin preparation in question was extracted from the rhizomes of *Curcuma longa* L. (turmeric). It contained >95% curcuminoids of which 70-80% was curcumin. The other curcuminoids in the mixture, *bis*-demethoxycurcumin and demethoxycurcumin were present in percentages of 2.5-6% and 15-25%, respectively. The preparation was intended for use as a flavouring agent (flavour enhancer) and as an antioxidant in several food categories at use levels up to 20 mg curcumin/serving. The curcumin preparation was not proposed for uses in foods formulated for babies or toddlers, nor in meat or poultry products. The intended use of Curcumin C3 Complex® was estimated to result in a maximum daily intake of 180 mg curcumin/person (2.6 mg/kg bw per day for a 70 kg person).This intake was characterised as "90th percentile all-user". The allocated ADI of 3 mg/kg bw per day by JECFA (2004) and EFSA (2010) was the basis for comparison of the proposed intake of Curcumin C3 Complex®.

The response letter from the FDA concluded that the agency had no questions regarding Sabinsa's information, as well as other information available to FDA, regarding Sabinsa's conclusion that curcuminoids is GRAS under the intended conditions. FDA noted that the agency had not made its own determination regarding the GRAS status.

2.1.2 Summary of previous risk assessments

In the present opinion, VKM uses the ADI of 3 mg curcumin/kg bw per day set by EFSA (2010) based on a multigeneration reproductive toxicity study in rats.

2.1.3 Literature search

A literature search was performed in EMBASE and MEDLINE in June 2015 in order to retrieve publications on adverse effects caused by curcumin. In addition, a search for publications exclusively on genotoxicity was performed in Pubmed in March 2016. The search strategies are included in Appendix 1.

2.1.3.1 Publication selection and data extraction for the first literature search

The first literature search (June 2015) identified 242 articles. In the primary screening, titles and abstracts of all publications retrieved were independently screened against the inclusion criteria checklist.

Inclusion criteria checklist:

- Adverse effects in relation to the substance alone are addressed
- Route of exposure for humans is oral
- Route of exposure for animals is oral, in addition, subcutaneous exposure is included if the toxicokinetic is equal to oral exposure
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal absorption and metabolism of the assessed substance
- Animal model studies address adverse effects relevant to human health

The inclusion criteria checklist was developed by members of the VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the VKM Panel on Nutrition, Dietetic Products, Novel Food and Allergy. Articles that did not appear to meet the inclusion criteria were excluded from further analysis. In situations where it was unclear whether the publication was of relevance to the study, it was retained for further screening. The primary screening was performed independently by two persons.

The full text of articles that passed the primary screening was retrieved for secondary screening. In this screening, the full text articles were reviewed and compared against the inclusion criteria checklist. The secondary screening was performed by one person.

The secondary screening resulted in 7 publications that were included in this report (see Figure 2.1.3.1-1).

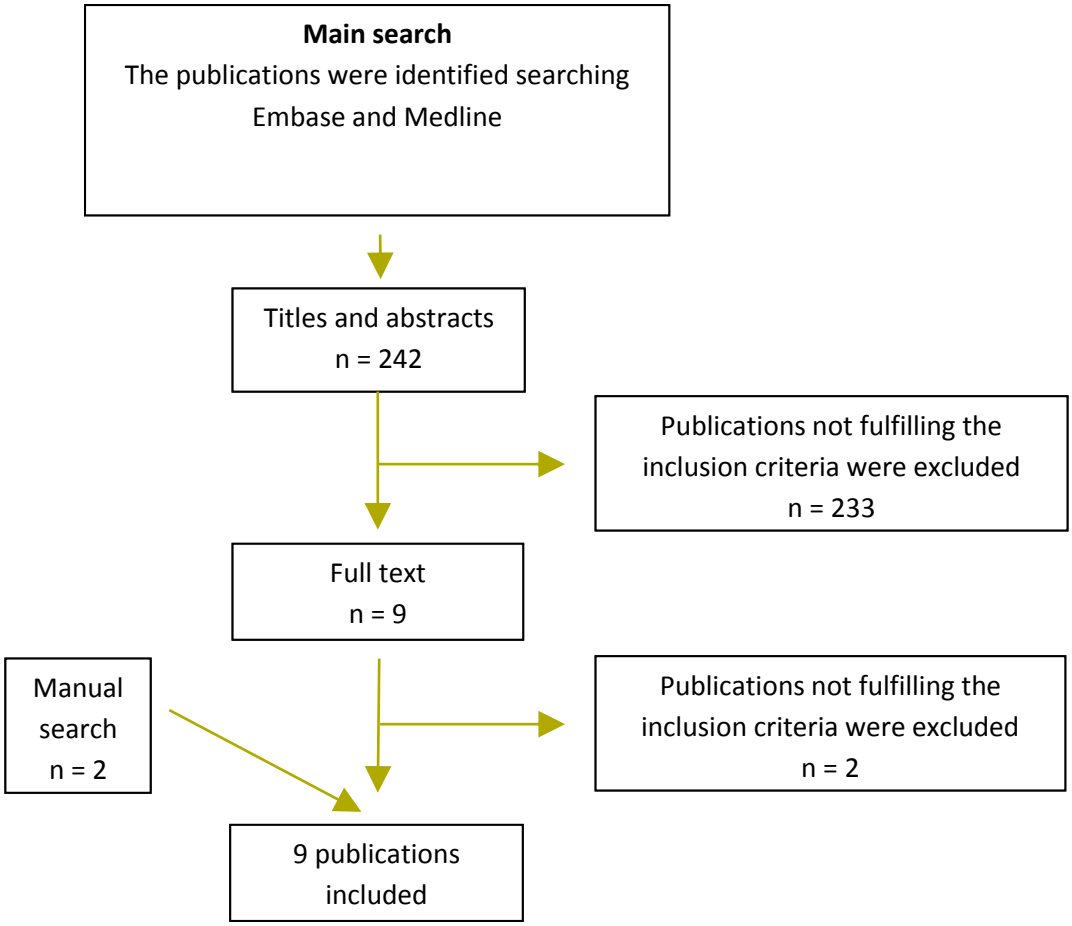


Figure 2.1.3.1-1: Flowchart for the first literature search (June 2015) for curcumin and the subsequent publication selection.

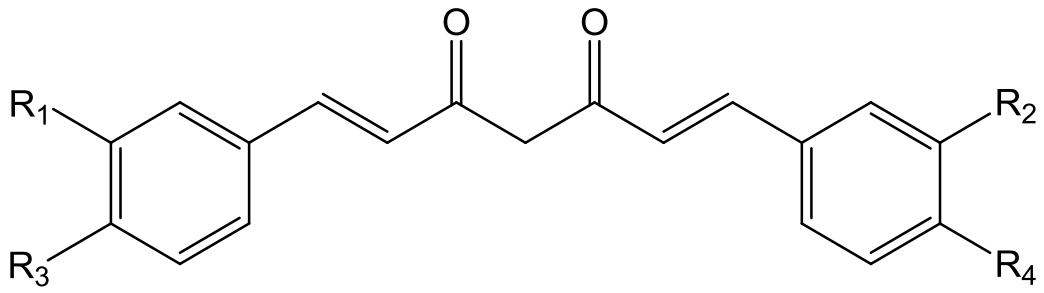
2.2 General information

2.2.1 Chemistry

Curcumin, an orange-yellow crystalline powder, is a polyphenolic compound [(1E,6E)-1,7-*bis*-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], with the molecular formula $C_{21}H_{20}O_6$ and molecular weight of 368.39 g/mol (CAS no. 458-37-7). When curcumin is used as a food colourant (E100) it also contains the curcuminoids demethoxy- and *bis*-demethoxy-derivatives with molecular formulas $C_{20}H_{18}O_5$ and $C_{19}H_{16}O_4$ and molecular weights of 338.39 (CAS no. 33171-16-3) and 308.39 g/mol (CAS no. 33171-05-0), respectively (EFSA, 2010; Heger et al., 2014). The food supplements on the Norwegian market consist of >90% curcuminoids with carrier substances constituting the rest (personal communication, NFSA 2016). Synonyms of the curcuminoids are *e.g.* turmeric yellow, kurkum, INS no 100(i), CI natural yellow 3, and diferoylmethane. EINECS number is 207-280-5 and Colour Index Number is CI 75300. Curcumin is lipophilic and has low solubility in water at acidic and physiological pH, it hydrolyses rapidly under alkaline conditions and it is susceptible to photochemical degradation (Tonnesen and Karlsen, 1985; Tonnesen et al., 1986; Tønnesen and Karlsen, 1985).

Curcumin undergoes hydrogen bonding and hydrophobic interactions, binds covalently (Michael acceptor) and can chelate (non)metal cations (Heger et al., 2014). Curcumin may interfere with manganese and iron (Chin et al., 2014; Schmitz et al., 2014).

The structural formula of the curcuminoids is shown in Figure 2.2.1-1.



Curcuminoid, molecular formula	R_1	R_2	R_3	R_4
Curcumin, $C_{21}H_{20}O_6$	$-OCH_3$	$-OCH_3$	-OH	-OH
Demethoxycurcumin, $C_{20}H_{18}O_5$	$-OCH_3$	-H	-OH	-OH
Bis-demethoxycurcumin, $C_{19}H_{16}O_4$	-H	-H	-OH	-OH

Figure 2.2.1-1 The structural formulas of the three curcuminoids: curcumin and its demethoxy- and *bis*-demethoxy derivatives (EFSA, 2010; Tovsen et al., 2014).

2.2.2 Occurrence

Curcumin is derived from the ground rhizomes of the plant *Curcuma longa* Linn (L.) (turmeric). Purified curcumin powder is obtained by solvent extraction of turmeric and further extract crystallisation (EFSA, 2010). It is worth noting that turmeric oil, although obtained from the same plant, does not necessarily contain curcuminoids. Turmeric oleoresin, on the other hand, contains 25-35% curcuminoids after extraction and distillation of turmeric powder (3-5% curcuminoids) (FDA, 2013). A final food additive/flavouring agent product may contain >95% curcuminoids (80% curcumin) after treatment of the turmeric oleoresin with isopropyl alcohol (FDA, 2013).

Curcumin is authorised for use as a food additive (E100) in beverages and foodstuffs (EU directive 94/36/EC). According to this directive, purity is specified as not less than 90%. Other ways of exposure are through the use of spices, such as turmeric and curry (a spice mixture containing turmeric) (EFSA, 2010), and in medicinal use inside EU and to a larger extent and with long traditions outside the EU, especially in Asia (EMEA, 2010). Curcumin is used in cosmetics as an antioxidant and colourant (CosIng, 2015).

2.3 Absorption, distribution, metabolism and excretion (ADME)

2.3.1 In humans

Studies in humans suggest that substantial concentrations of curcumin are unlikely to be present in the body (plasma, urine) after ingestion of doses up to 12 g/day (171 mg/kg bw per day for a 70 kg person) due to low absorption (curcumin concentrations in the submicromolar-to-low nanomolar range have been found in blood after oral intake of up to 12 g (Heger et al., 2014)). and rapid metabolism and excretion (EFSA, 2010). This conclusion was based on the following study: In a dose escalation study performed in USA of a commercial curcuminoid formulation (C3 Complex™, Sabinsa Corporation) on a mixture of three curcuminoids from the plant *Curcuma longa* L., maximum tolerated dose and detection of curcumin in serum were assessed for 72 hours (Lao et al., 2006). Twenty-four healthy adults, 13 males and 11 females, with mean age of 34 years (range: 19-74 years), either African-Americans or Caucasians, received a single dose of the curcumin product. Three subjects were entered consecutively at doses of 0.5, 1, 2, 4, 6, 8, 10 or 12 g taken with water and a standard meal. The subjects had normal organ function and had not consumed any curcumin-rich food within the previous 14 days. In two subjects who received 10 or 12 g curcumin, the serum level was 30.4, 39.5 and 50.5 ng/ml (baseline: 6 ng/ml) and 29.7, 57.6 and 51.2 ng/ml (baseline: trace) after 1, 2 and 4 hours, respectively. In the subjects who were adminstered 0.5-8 g and in the remaining subjects at the 10 and 12 g dose levels, no curcumin was detected in serum after 1-4 hours (Lao et al., 2006). Baseline values were obtained just prior to curcumin intake and were reported for the subjects with increased serum concentrations only. The limit of chromatography detection of curcumin was 31 ng/ml. Thus, values close to and below this number are uncertain.

The peak plasma levels of curcumin were estimated to be 2 to 3 orders of magnitude lower than its *in vitro* IC_{50} (half maximal inhibitory concentration) values (mean ± SD: 21 ± 17 µM, n= 309, clustered data), even when quantities up to 12 g of curcumin were ingested (Heger et al., 2014). Curcumin, a lipophilic compound, is ineffectively transported across the intestinal mucosa into the circulation (see *e.g.* Holder et al., 1978). The low absorption (and bioavailability) of curcumin is thought to be partly due to its adherence to the enteral mucosa (retaining curcumin), limiting its uptake by enterocytes through lowering of the pre-epithelial curcumin concentration gradient and impairment of the transmucosal passage. Further, curcumin is conjugated with glutathione (GSH) in the intestinal mucus. The curcumin molecules that are taken up by enterocytes are subsequently excreted apically or predominantly biotransformed before undergoing apical and basolateral transport. Curcumin is efficiently metabolised by the liver and excreted into the biliary system. Excretion via the urinary system occurs only to a limited extent (Heger et al., 2014). In a study including 24 patients with conditions indicating a high risk of malignancy, curcumin of purity 99.3% was given for 3 months starting at 0.5 g and given stepwise until 12 g/day. Serum curcumin levels peaked within 1-2 hours of administration and reached a maximum of about 2 µM after an oral dose of 8000 mg. Complete clearance occurred within a few hours thereafter (Cheng et al., 2001).

Curcumin metabolites are the results of mainly enzyme-driven processes and are, in these cases, end products of reductase-mediated methine bridge hydrogenation, sulfation and glucuronidation and protein complexation. Examples are curcumin sulfate and curcumin glucuronoside, hexahydrocurcumin and octahydrocurcumin (hexahydrocurcuminol) (Heger et al., 2014).

2.3.2 Animal studies

In mice and rats, curcumin is poorly absorbed, rapidly metabolised and excreted mainly through faeces, and low to negligible amounts are present in urine and plasma (EFSA, 2010).

MF1 mice (20 females, 20 males, age not given) were administered 220 mg/kg bw curcumin, and adult B6C3F1 mice (50 females, 50 males) were administered 10 mg/kg bw curcumin, both strains by oral gavage ((Tullberg et al., 2004); unavailable to VKM, cited by EFSA (2010)). EFSA (2010) commented that extremely low plasma levels were detected, given the high dose administered. The plasma concentration of curcumin was was lower in males, suggested to be caused by more extensive first pass metabolism in males (EFSA, 2010).

Five studies on rats (some included mice as well) were described in (EFSA, 2010). After oral gavage with a single dose of 1 g/kg bw of curcumin (in arachis oil) given to five male Sprague-Dawley rats (2-4 months old; weighing 200-300 g), 65-85% of the dose was eliminated in the faeces within 72 hours, and excretion was highest during the initial 48 hours. Curcumin was detected in plasma of one of four animals after 3 hours, whereas urinary excretion was negligible. The biliary concentration of curcumin was measured to 1 µg/ml after 30 min and remained stable throughout the experiment. The amount collected in

the bile during 3 hours was less than 0.0006% of the dose. After 3 hours, about 0.015% of the administered curcumin had accumulated in the liver, kidneys and body fat. Perfusion of curcumin through the dissected liver in an artificial perfusion system resulted in a transitory increase in bile flow; 10% of the dose was excreted in the bile within 3 hours after administration. Of the curcumin excreted in the bile, 49% was in the conjugated form (EFSA, 2010; Wahlstrom and Blennow, 1978).

In male Sprague-Dawley rats (250-300 g) receiving a single oral dose of 0.6 mg ^{3}H-labelled curcumin, 89% of the dose was excreted in the faeces and 6% in the urine within 72 hours (Holder et al., 1978). When labelled curcumin was administered to cannulated rats by intravenous injection, 85% of the dose was recovered in the bile after 6 hours. The major metabolites detected by mass spectroscopy were the glucuronides of tetrahydrocurcumin and hexahydrocurcumin, while minor metabolites were dihydroferulic acid and ferulic acid (EFSA, 2010; Holder et al., 1978). The number and age of rats were not given.

Pharmacological effects in dams and their suckling neonates after turmeric or curcumin administration to the dams indicated that turmeric or curcumin can be transferred through lactation (Singh et al., 1995).

Male albino Wistar rats weighing 150-200 g (age of rats were not given) were administered a suspension of 400 mg of curcumin in water containing 0.1% Tween 20 by gavage (Ravindranath and Chandrasekhara, 1980). About 40% of the dose was excreted unchanged in the faeces over a 5-day period (n=32). The authors assumed that the remaining 60% of the curcumin was absorbed. Curcumin was not detected in the urine, but there was increased excretion of conjugated glucuronides and sulphates in the urine (n=5). Negligible amounts of curcumin were found in the blood, liver and kidney.

Rats (F344/N; 10 male, 10 female) were fed diets containing 0, 1000, 5000, 10000, 25000, or 50000 ppm turmeric oleoresin (the organic extract of turmeric) in a 13-week study. The same number and sex distribution of B6C3F mice were fed diets of the same doses of the same compound. Discoloration of the fur was reported in both species and discoloured faeces in rats receiving 50 g/kg bw curcumin in their food daily (equal to 2 g/kg bw per day) was observed (NTP, 1993).

2.4 Toxicological data/Adverse effects

2.4.1. Genotoxicity

2.4.1.1 In vitro studies

In vitro studies included in EFSA (2010)

Ames and recombination assays

Curcumin (concentrations not given) was inactive in the *Salmonella* test using strains TA98 and TA100 (Kawachi et al., 1980). Curcumin was also inactive when tested in concentrations of 1.28, 6.4, 32.0 and 160 µg/plate in the *Salmonella* test using TA1535, TA98 and TA100 strains with or without exogenous metabolic activation (liver S9 fraction) (Jensen, 1982). Further, curcumin (79-85% curcumin compound I, CAS No. 458-37-7) was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 with or without exogenous metabolic activation (S9) (NTP, 1993). No mutagenicity was observed after exposure to curcumin of purity up to 85% using Ames assays (TemaNord, 2002). Genotoxicity studies on curcumin (curcumin preparations of up to 85% purity or of unknown purity) did not reveal mutagenic activity in bacteria) (JECFA, 1996, 2004) (EFSA, 2010). Curcumin (concentrations not given) induced recombination in a recombination assay (*Bacillus subtilis*) (Kawachi et al., 1980).

Chromosomal aberrations (CA) and micronuclei tests

Curcumin induced chromosomal aberrations in hamster lung fibroblasts (Kawachi et al., 1980). Curcumin in a 79-85% purity preparation induced small but significant chromosomal aberrations (without S9) (NTP, 1993).

Curcumin (concentrations not given) did not induce sister chromatid exchanges (SCE) using hamster lung fibroblasts and human embryo fibroblasts (Kawachi et al., 1980). Neither did curcumin induce SCE in Chinese hamster ovary cells (CHO) *in vitro* (Au and Hsu, 1979). However, curcumin in a 79-85% purity preparation induced SCE (with S9) in CHO cells (NTP, 1993).

Genotoxicity studies on curcumin (curcumin preparations of up to 85% purity or of unknown purity) or turmeric revealed only equivocal activity in assays for the induction of chromosomal aberrations (EFSA, 2010; JECFA, 1995; JECFA, 2004). No mutagenicity was observed after exposure to curcumin of purity up to 85% using assays studying chromosomal aberrations (TemaNord, 2002).

Exposure to curcumin gave an increase in micronuclei in HepG2 cells (human hepatocytes) at a curcumin concentration of 8 µg/ml (Cao et al., 2007).

Comet assay and other DNA damage tests
In the Comet assay, curcumin (10-50 µM) alone induced DNA strand breaks in human lymphocytes and gastric mucosa cells *in vitro*. Curcumin was also shown to work in an additive fashion with hexavalent chromium, a well-known mutagen and carcinogen (Blasiak et al., 1999). Curcumin induced DNA damage (Comet assay) at concentrations ranging between 2.5-40 µM as well as damage in mitochondrial and nuclear DNA (staining for 8-hydroxydeoxyguanosine) in HepG2 cells (Cao et al., 2006).

Urbina-Cano et al. (2006) evaluated the *in vitro* effect of 50 µM curcumin in the presence of increasing concentrations of copper (10, 100 and 200 µM) to induce DNA damage in Balb/c mouse lymphocytes by the Comet assay. A concentration of 50 µM curcumin in the presence

of 100-200 µM copper induced DNA damage in murine lymphocytes. Curcumin did not inhibit the oxidative DNA damage caused by 50 µM H_2O_2 in mouse lymphocytes. Moreover, 50 µM curcumin alone was capable of inducing DNA strand breaks under the tested conditions.

DNA chromosomal damage (test not given) in CHO cells after exposure to 10 µM curcumin was reported by Antunes et al. (1999).

EFSA concluded that, based on the *in vitro* studies, the concern regarding genotoxicity were not eliminated (EFSA, 2010).

In vitro studies 2010-2016

Ames and recombination assays
A commercial, formulated curcumin product, consisting of curcuminoids (92.5%) in addition to essential oil of turmeric (containing turmerone)(BCM-95®/Biocurcumin™, Arjuna Natural Extracts Ltd., Aluva, India), was assessed against *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 with and without metabolic activation (S9 liver fraction) (OECD Guidelines no. 471) at concentrations of 1000, 2000, 3000, 4000 and 5000 µg/plate. Curcumin had no genotoxic effects in any of the strains with or without metabolic activation (Aggarwal et al., 2016). One of the authors had affiliations to the company which provided the product, but no information about conflicts of interest was reported.

Chromosomal aberrations and micronucleus test
In a study designed to assess curcumin attenuation of quinocetone-induced oxidative stress and genotoxicity in human hepatocyte L02 cells (Dai et al., 2015), curcumin (purity ≥98%; Aladdin Reagent Co., Ltd., Shanghai, China) was also assessed alone as a control substance in the micronuclei assay at concentrations 2.5 and 5 µM. Curcumin did not induce an increase in the frequency of micronuclei compared to vehicle control (0.1% DMSO).

Curcumin produced significant increases in micronucleus formation in the p53-compromised rodent cell lines V79 (Chinese hamster lung fibroblasts, male), CHO and CHL (Chinese hamster lung fibroblasts, female) at lowest positive doses of 4, 12 and 14 µg/ml, respectively (Fowler et al., 2012). In the human p53-functional primary cultures of peripheral blood lymphocytes and the TK6 lymphoblastoid cell line, significant increases in micronucleus formation were produced at curcumin concentrations (lowest positive dose) of 31 and 16 µg/ml, respectively. Curcumin did not induce any micronuclei in HepG2 cells (human hepatocytes). The conditions under which curcumin induced micronuclei in TK6 cells coincided with apoptosis. The authors noted that rodent p53-compromised cell lines were more susceptible to giving misleading results ("false positives").

In another a study comparing different cell lines (human versus rodent and p53-competent versus -deficient (mutant)) for their suitability in micronucleus induction (i.e. to avoid "false positives") (Whitwell et al., 2015), curcumin (CAS no. 458-37-7; purity≥98%; Sigma, UK) was assessed in the micronucleus assay in the presence and absence of cytochalasin B (CB).

In CB presence, curcumin induced micronuclei at 7, 10 and 14 µg/ml in WIL2-NS cells (human, p53 deficient) and at 6 and 9 µg/ml in TK6 cells (human p53-competent). In the absence of CB, curcumin at concentrations of 2.5-25 µg/ml in L5178Y cells (mouse lymphoma, p53 deficient) induced micronuclei frequencies. Thus, curcumin induced micronuclei responses in three cell lines of either human or rodent origin and with different p53-status.

In a study assessing dose differences in DNA damage and genotoxicity of curcumin (Sun et al., 2013), curcumin (purity not given; Sigma-Aldrich, St. Louis, MO, USA) in concentrations 3-6 µM induced increases in micronuclei up to 6-fold in HT1080 cells (human fibrosarcoma, p53 wild-type).

Comet assay and other DNA damage tests
In a study designed to assess curcumin attenuation of quinocetone-induced oxidative stress and genotoxicity in human hepatocyte L02 cells (Dai et al., 2015), curcumin (purity≥98%; Aladdin Reagent Co., Ltd., Shanghai, China) was also assessed alone as a control substance in the comet assay at concentrations 2.5 and 5 µM. DNA strand-breaks were assessed as % tail DNA, tail length and tail moment. Curcumin DNA damages were similar to vehicle control values (0.1% DMSO).

In a study assessing dose differences in DNA damage and genotoxicity of curcumin (Sun et al., 2013), curcumin (purity not given; Sigma-Aldrich) induced DNA damage (measured by the biomarker phospho-H2AX) in HT1080 cells with LOEL of 3-8 µM (EC_{50}: 11 µM).

2.4.1.2 Summary of in vitro genotoxicity studies

Curcumin did not induce gene mutations in several strains, with or without metabolic activation, in Ames test. However, one *in vitro* study found that curcumin induced recombination in *Bacillus subtilis*. Curcumin induced chromosomal aberrations, micronuclei and DNA strand breaks in several studies. Thus, curcumin apparently has a genotoxic potential *in vitro*. VKM notes that several studies had limitations, such as questionable solubility of curcumin in aqueous solutions and unknown pre-exposure degradation due to photochemical instability of curcumin.

2.4.1.3 In vivo studies

An overview of *in vivo* studies investigating curcumin and genotoxicity is given in Table 2.4.1.3-1.

Table 2.4.1.3-1 An overview of animal studies investigating curcumin and genotoxic effects (M: male; F: female). Positive: curcumin induced genotoxicity; negative: curcumin did not induce genotoxicity.

Reference	Study and number of animals	Dose in treatment group	Total study length	Genotoxic outcome
Studies described in EFSA Opinion, 2010				
Vijayalaxmi, 1980	Micronucleus test (8 F); bone marrow chromosomes (5 M, 5 F); dominant lethal mutations (15 M/45 F) in Swiss albino mice	0.5% turmeric/0.015% curcumin (purity unknown) in the feed (20 mg/kg bw per day)	12 weeks	Negative
Giri et al., 1990	Tests for SCEs (Swiss albino male mice; 40 M) and CA on bone marrow (Swiss albino male rats ; 30 M) and -?	5 animals per dose/controls; SCE: 5, 10, 25, 50, 100, 200 mg/kg bw (i.p.); CA: 100, 200, 500, 1000 ppm in diet for 3, 6 and 9 months	9 months (CA study)	Positive
Nair et al., 2005	Nuclear and mitochondrial etheno-DNA adduct formation in Long-Evans Cinnamon rats (18 M)	0.5% curcumin (95% purity) in the diet	2 weeks	Positive
El-Makawy & Sharaf, 2006	Micronucleus and CA tests in male Wistar rats (10 animals/dose)	Curcumin spice (not described) given orally, corresponding to 0.5, 5, 10, 25 and 50 mg/kg bw	4 weeks	Positive
Studies published 2010-2016				
Papież, 2013	DNA damage in bone marrow cells (comet assay) (6 M/group) in brown-Norway rats	Curcumin (80.1% purity), 0, 100 and 200 mg/kg bw (gavage)	7 days	Negative
Zheng et al., 2015	Micronucleus and CA tests in bone marrow cells of Balb/c mice (4 animals per test; sex unknown)	Curcumin (>98% purity) in nanoparticles, curcumin equivalent dose: 100 mg/kg bw	2 days	Negative
Aggarwal et al., 2016	Micronucleus (Swiss albino mice; 10 M/10 F per group) and CA tests (Wistar albino rats; 30 M, 30 F per group)	Single dose: 2000 mg/kg bw of curcumin product (92.5%) BCM-95®/Biocurcumin™ (gavage)	Micronucleus test: 24 and 48 h post-exposure detection; CA test: 18 and 42 h post-exposure detection	Negative
Eke et al., 2016	Micronucleus test and DNA damage (comet assay) (Swiss albino rats; 6 M per group)	Curcumin (>99% purity), 80 mg kg bw alone (or in combination with PFOS) (by gavage)	30 days	Negative
Khatik et al., 2016	Micronucleus and CA tests in Balb/c mice (4 animals per test; sex unknown)	Curcumin (>98% purity) curcumin equivalent dose: 100 mg/kg bw by gavage	2 days (gavaged once daily)	Negative

In vivo studies included in EFSA (2010)

Results from several animal genotoxicity tests on weanling Swiss albino mice fed control diets or diets containing 0.5% turmeric (curcumin content unknown) or 0.015% curcumin of unknown purity (equivalent to 20 mg/kg bw per day) for 12 weeks revealed no effect in the

micronucleus test (eight females/group) using bone marrow, no cytogenetic effect on the bone marrow chromosomes (five males/five females per group) assessing breaks and deletions and polyploid cells, and no effect in a dominant lethal mutation test (15 males/45 females per group) assessed with live and dead embryos (Vijayalaxmi, 1980).

Curcumin (Gurr, Searle Diagnostics, England; purity not given; curcumin dissolved in distilled water) was injected intraperitoneally in concentrations of 5, 10, 25, 50, 100 and 200 mg/kg bw in male Swiss albino mice (weight ca. 30 g) or given in the diet for 3, 6 or 9 months in the feed in concentrations of 100, 200, 500 or 1000 ppm to rats (weight ca. 90 g at study start). Positive control was 2.5 mg/kg bw mitomycin C. A significant increase in SCEs was observed in all the concentrations in mice, except the two lowest curcumin concentrations (5 and 10 mg/kg bw). The two high concentrations of curcumin (500 and 1000 ppm in the feed) induced significant increase in CAs in bone marrow chromosomes during the 9 month treatment of rats. CAs were scored according to WHO (1985) (Giri et al., 1990).

In a study using 18 male Long-Evans Cinnamon rats (40-60 g) exposed to 0.5% curcumin (95% purity) in the diet (19 control animals), etheno-DNA adduct formation was enhanced 9- to 25-fold in nuclear DNA and 3- to 4-fold in mitochondrial DNA after treatment for 2 weeks (Nair et al., 2005). It was noted that this rat strain is a model for human Wilson's disease and develop chronic hepatitis and liver tumors owing to accumulation of copper and induced oxidative stress. No positive control was reported.

In a male Wistar rat study (10 animals/dose) the animals were given a suspension of curcumin spice (not further described) orally, corresponding to 0.5, 5, 10, 25 and 50 mg/kg bw in 1 ml distilled water daily for 4 weeks (El-Makawy and Sharaf, 2006). Curcumin caused a statistically significant dose-dependent increase in the number of micronucleated polychromatic erythrocytes (MNPCEs) and in the frequencies of total CAs over the control (bone marrow cells were used in both studies). CAs assessed were hypo-, hyper- and polyploid, chromatid gap, chromatid break, chromosome break, fragments, deletions and centromeric attenuations. The lowest dose that caused increased frequency (4-fold) in the micronuclei test compared to negative control was 5 mg/kg bw. The frequency of CAs induced by the highest dose tested, 50 mg/kg bw, was similar ($p>0.05$) to that of the positive control (25 mg/kg cyclophosphamide positive control was injected i.p. as a single dose).

EFSA (2010) payed particular attention to the detection of chromosomal aberrations and DNA adducts in the *in vivo* genotoxcity tests for curcumin. EFSA further noted that the *in vivo* genotoxicity studies were insufficient to eliminate the concern regarding genotoxicity (EFSA, 2010).

In vivo studies 2010-2016

The effect of curcumin (CAS no. 458-37-7; 80.1% purity, Sigma-Aldrich, St. Louis, MO, USA) and (-)-epicatechin on DNA damage induced by the cytostaticum etoposide was investigated (Papiez, 2013). Male Brown Norway (BN/CrlCmd) rats (216±14 g) were administered 0, 100

and 200 mg/kg bw of curcumin dissolved in 0.5 ml corn oil by oral gavage for 7 days alone or in addition to 50 mg/kg bw of etoposide administered i.p. for 3 days (n=6 animals per experimental group). Bone marrow from the mice was used to assess DNA damage using comet assay (strand-breaks and oxidative DNA damage as percentage of DNA in the comet tail). Curcumin did not induce DNA damage compared to the control group receiving corn oil only.

In a study primarily addressing physical chemical properties of phosphatidylserine chitosan nanoparticles loaded with curcumin (>98% purity, Sigma-Aldrich, St. Louis, MO, USA) (nanoparticle size: 220±3.67 nm), the micronucleus test and a chromosomal aberration assay (detection of metaphase cells) were performed in bone marrow cells from Balb/c mice (sex not given; 25±5 g: n= 4 per test) (Zheng et al., 2015). The "curcumin equivalent dose" in the nanoparticles was 100 mg/kg bw and was given for 2 days. The frequencies of micronuclei and chromosomal aberrations in the curcumin nanoparticle groups were not statistically different from the negative control values.

A commercial, formulated curcumin product, consisting of curcuminoids (92.5%) in addition to essential oil of turmeric (containing turmerone) (BCM-95®/Biocurcumin™, Arjuna Natural Extracts Ltd., Aluva, India), was assessed in the bone marrow CA test in Wistar albino rats (160-200 g; 30 males, 30 females) and erythrocyte micronucleus test in Swiss albino mice (20-25 g; 10 males, 10 females) (Aggarwal et al., 2016). In the CA test 2000 mg/kg bw of curcumin was given as a single dose orally (gavage). Total aberrations, number of cells with aberrations and mitotic index were assessed after 18 and 42 hours. The CA tests were negative for the curcumin product. Bone marrow from the mice was collected after 24 and 48 hours in the erythrocyte micronucleus test. No significant changes in the micronuclei were detected compared to negative controls. In assessment of acute toxicity in this study, the LD_{50} for rats was determined to be >5000 mg/kg bw. VKM notes that one of the authors had affiliations to the company which provided the product, and that no information of conflicts of interest was reported.

In a study addressing the role of curcumin in preventing perfluorooctane sulfonate (PFOS)-induced genotoxicity, one dose of curcumin (80 mg/kg bw; >99% purity; Sigma, St. Louis, MO, USA) by gavage was administered alone and in combination with PFOS (0.6, 1.25 and 2.5 mg/kg bw) to male Swiss albino rats (180-200 g) for 30 days at 48 hours intervals (six animals per study group) (Eke and Celik, 2016). Micronucleus test and comet assay for assessment of DNA damage were performed in rat peripheral blood. There were no increases in the frequency of micronuclei or DNA damages (expressed as genetic damage index and percent damaged cells) compared with negative control values for the group that was given curcumin alone.

Phospholipid complexes of curcumin (>98% purity, Sigma-Aldrich, St. Louis, MO, USA) were prepared and characterised as a means to improve drug delivery in cancer therapy (Khatik et al., 2016). The curcumin complexes consisted of either phosphatidylcholine or hydrogenated soya phosphatidylcholine. Balb/c mice (25±5 g; sex not given) were gavaged with curcumin

in either phospholipid complex at an "equivalent concentration" of 100 mg/kg bw per day for 2 days. The micronucleus test and a chromosomal aberration assay (detection of metaphase cells) (n= 4 animals per test) were performed in bone marrow cells from the mice. The phospholipid complexes of curcumin did not induce an increase in the frequency of micronuclei and chromosomal aberrations were comparable to control values. Gap chromosomal aberrations and aneuploid cells were recorded, but the authors decided not to include these findings in the percent chromosomal aberration calculations.

2.4.1.4 Summary of in vivo genotoxicity studies

Several negative *in vivo* micronuclei and chromosomal aberration studies of curcumin have been published. However, these studies had several limitations, such as lack of information on purity of curcumin, questionable solubility of curcumin in aqueous solutions, unknown pre-exposure degradation due to photochemical instability, a single dose used and/or lack of confirmation of cytotoxicity in the bone marrow. VKM is therefore of the opinion that the available *in vivo* studies are insufficient to completely eliminate the possibility that curcumin may be genotoxic.

2.4.1.5 Genotoxicity of metabolites

NTP (1993) reviewed genotoxicity data of two minor components of turmeric oleoresin, namely cineol and caprylic acid. Cineol was negative in the *B. subtilis* recombinant assay (Oda et al., 1978) and the *S. typhimurium* gene mutation test (Haworth et al., 1983). Cineol did not induce chromosomal aberrations, but did increase the frequency of SCEs, in CHO cells in the absence of S9 (Galloway et al., 1987). Caprylic acid was also nonmutagenic in *S. typhimurium* (NTP, 1993; Zeiger et al., 1988). The polyphenol vanillin, a curcumin catabolite generated *in vitro* (Heger et al. 2014) enhanced chromosome aberrations induced by alkylating agents in CHO cells (Matsumura et al., 1993).

2.4.2 Human studies

An overview of the included studies investigating curcumin and adverse health effects in humans is given in Table 2.4.2-1.

Table 2.4.2-1 An overview of human studies investigating curcumin and adverse health effects (M: males; F: females).

Reference	Study design/participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Duration of the study	Adverse effect
			Curcumin	Control				
Abidi et al. (2014)	RCT of 77 adult patients suffering from bronchial asthma receiving standard therapy +/- curcumin. Seventeen patients were lost during follow-up	India	30 (16 M and 14 F; group received standard asthma therapy + curcumin)	30 (14 M and 16 F; control group received standard asthma therapy)	1000 mg curcumin/day (Indsaff & Charak International Pvt. Ltd., India)	Dyspnoea; wheezing; cough; chest tightness; nighttime asthma symptoms; change in the pre-bronchodilator; haematological improvement; change in post-bronchodilator; C-reactive protein; adverse events	30 days	Curcumin-treatment group: 5 events (3 weight gain; 1 headache; 1 insomnia). Control group: 4 events (1 decreased appetite; 1 headache; 2 insomnia.
Sanmukhani et al. (2014)	RCT of adult patients with major depressive disorder receiving curcumin +/- fluoxetine or fluoxetine only	India	Group 2 (curcumin): 20 (5 M and 15 F); 2 withdrawals Group 3 (curcumin + fluoxetine): 20 (6 M and 14 F); 2 withdrawals	Group 1 (fluoxetine): 20 (10 M and 10 F); 3 withdrawals	1000 mg curcumin/day (BCM-95®: patented, registered form of curcumin) +/- fluoxetine	Response rate (Hamilton Depression Rating Scale)(HAM-D_{17}); mean change in HAM-D_{17} score after 6 weeks; vital signs; physical examination; lab. tests; electrocardiogram; investigator's opinion on global tolerability	6 weeks	Group 2: gastritis and nausea Group 3: gastritis, giddiness, hot flushes, nausea, photosensitivity Group 1: gastritis, mouth ulcers. No significant difference in vital signs, physical exam, etc. (described in endpoints) from baseline.
Chandran and Goel (2012)	Randomised, controlled, open labelled, pilot study with adult patients suffering from active rheumatoid arthritis receiving curcumin +/- diclofenac or diclofenac only	India	Group 1 (curcumin): 15 (2 M and 13 F) Group 2 (curcumin + diclofenac): 15 (4 M and 11 F)	Group 3 (diclofenac): 15 (1 M and 14 F)	1000 mg curcumin/day (BCM-95®: patented, registered form of curcumin) +/- diclofenac	Reduction in Disease Activity Score; ACR criteria for reduction in tenderness and swelling of joint scores; physical examination and various blood chemistry parameters	8 weeks	Group 1: mild fever and throat infection Group 2: one case of worsening of condition Group 3: itching and swelling around eyes/dimness of vision; worsening of condition; increase in SGPT and SGOT (probably related to drug).

Reference	Study design/participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Duration of the study	Adverse effect
			Curcumin	Control				
Belcaro et al. (2010)	Controlled (randomisation not reported) study with adult patients suffering from knee osteoarthritis (recruited from a database) receiving "best available treatment" +/- curcumin	Italy	50 (23 M and 27 F); 5 withdrawals	50 controls (28 M and 22 F); 6 withdrawals	200 mg curcumin/day (Meriva®): curcumin-phosphatidylcholine phytosome complex)	WOMAC score; Kernofsky Performance Scale Index;treadmill walking performance; inflammatory markers and erythrocyte sedimentation rate	8 months	None adverse effectzs were reported.
Hanai et al. (2006)	RCT/placebo study of patients suffering from ulcerative colitis, 13-65 years, in remission period	Japan	45 (23 M and 22 F); group received curcumin + sulfasalazine or mesalamine (2 withdrawals)	44 (26 M and 18 F; group received placebo + sulfasalazine or mesalamine) (5 withdrawals)	2 g curcumin/day (in cellulose/maltitol)	Relapse at 6 and 12 months (ulcerative Clinical Activity Index (CAI)> 4); CAI and Endoscopic Index scores before and after treatment; adverse events	6 months	Nine adverse events in seven patients: sensation of abdominal bulging, nausea, transient hypertension (patient was in curcumin group and withdrew from the study) and transient increase in the number of stools (events not related to group).
Sharma et al. (2004)	15 adult patients (50-70 years) diagnosed with adenocarcinoma of the colon or rectum (advanced) in a Phase I clinical trial of oral curcumin	UK	1) 0.45 g/day: 0 M/3 F 2) 0.9 g/day: 1 M/2 F 3) 1.8 g/day: 1 M/2 F 4) 3.6 g/day: 3 M/3 F	None	0.45 (n=3), 0.9 (n=3), 1.8 (n=3) and 3.6 (n=6) g/day curcumin (C3 Complex, Sabinsa Corporation, NJ, USA; one 500 mg capsule consisted of 450 mg curcumin, 40 mg desmethoxycurcumin and 10 mg *bis*-demethoxycurcumin), single batch to each of 4 groups	Glutathione S-transferase activity, levels of a deoxyguanosine adduct (M1G) formed via oxidative DNA damage and inducible prostaglandin E2 (PGE2) levels were measured in blood leukocytes	4 months	Dose-limiting toxicity was not observed. Curcumin was well tolerated at all dose levels. One patient in the 0.45 g/day curcumin dose group and one patient in the 3.6 g/day curcumin dose group reported diarrhea. Four patients had elevated levels of serum alkaline phosphatase and three patients had elevated level of lactate dehydrogenase (group unspecified).

Reference	Study design/participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Duration of the study	Adverse effect
			Curcumin	Control				
Shoba et al. (1998)	Ten healthy male adults, ages 20-26 years, were given curcumin alone and, after a two week wash-out period, curcumin + piperine orally in a randomised cross-over trial	India	10 (8 subjects completed)		33 mg/kg bw curcumin powder (commercial), 333 mg/kg bw piperine	Maximum level and time to reach serum curcumin concentration, absorption and elimination half-lives, AUC, volume distribution, total clearance, relative bioavailability	Single dose, serum concentration assessed during 6 hours	None reported. Two withdrawals due to non-medical reasons

One study of healthy humans and six studies on patients with diseases with varying degree of malignancies were found in the literature. The studies on patients did not include any healthy controls.

An open labelled, randomised, single centre study from India by Abidi et al. (2014) described the treatment effect of curcumin in adult patients (18-55 years) suffering from bronchial asthma as "add-on" therapy in addition to standard asthma therapy. Originally, 77 patients were recruited, but 17 were lost during follow-up. Thirty patients (16 males, 14 females) received standard therapy in addition to curcumin (1000 mg/day; 17 mg/kg bw per day (mean)) The curcumin capsules CUR-500 (curcumin 500 mg) were given twice daily (M/s Indsaff & Charak International Private Limited, Batala, Punjab, India). The control group (n=30) (14 males and 16 females) received standard therapy which consisted of budesonide 100 µg, formoterol 6 µg; acebrophylline 100 mg; montelukast 10 mg; levocetirizine 5 mg for 30 days. The predefined end-points were clinical assessment of dyspnoea, wheezing, cough, chest tightness and specific nighttime asthma symptoms, change in pulmonary function test values, haematological improvement, C-reactive protein (CRP) and adverse events. There were no statistically significant differences in the number of adverse effects between the two study groups. Five events were recorded in the curcumin-treatment group: weight gain (3); headache (1); insomnia (1)) four events in the control group: decreased appetite (1); headache (1); insomnia (2).

In a randomised, observer-masked, three parallel treatment arms trial from India, adult patients (29-47 years) with major depressive disorder received curcumin with or without fluoxetine (antidepressant) or fluoxetine alone for 6 weeks (Sanmukhani et al., 2014). Subjects in the curcumin only group (n=20; 5 males, 15 females; 2 withdrawals) were given a dose of 1000 mg curcumin/day (BCM-95®, Arjuna Natural Extracts, Kochi, Kerala, India; a patented, registered form of curcumin containing 88% curcuminoids with 7% volatile oils from the rhizomes of *Curcuma longa* L.) The weights of the participants were not reported. The dose given is equal to 14.3 mg/kg bw per day for a 70 kg adult. Subjects in the group given both curcumin and fluoxetine (n= 20; six males, 14 females; 2 withdrawals) received 1000 mg curcumin/day and 20 mg fluoxetine (0.3 mg/kg bw per day of fluoxetine for a 70 kg adult). The same fluoxetine dose was given to the control group, fluoxetine alone (n=20; 10 males, 10 females; 3 withdrawals). The primary efficacy measure was response rate (Hamilton Depression Rating Scale)(HAM-D_{17}). Screening visit included vital signs, physical examination and electrocardiogram. The final visit included laboratory tests, electrocardiogram and investigator's opinion on global tolerability. In addition, treatment emergent adverse events were assessed at each of four visits. Adverse events were reported as follows: curcumin alone group: gastritis (1) and nausea (1); curcumin and fluoxetine group: gastritis (1), giddiness (1), hot flushes (1), nausea (1), photosensitivity (1); fluoxetine group: gastritis (1), mouth ulcers (1). There were no significant differences in vital signs, physical exam, laboratory tests and electrocardiogram from baseline.

In a randomised, single-blinded, pilot clinical trial from India, adult patients (18-65 years; mean age 47.9 years) suffering from rheumatoid arthritis received curcumin alone or

combined with diclofenac sodium (an NSAID class of drug) or diclofenac alone for 8 weeks (Chandran and Goel, 2012). Subjects in the curcumin only group (n=15; two males and 13 females) received 1000 mg curcumin per day (BCM-95®, Arjuna Natural Extracts, Kochi; Kerala, India; a patented, registered formulation of curcumin). The weights of the participants were not reported. The dose given is equal to 14.3 mg/kg bw per day for a 70 kg adult. Subjects in the group given both curcumin and diclofenac (n=15; four males, 11 females) received 1000 mg curcumin/day and 100 mg diclofenac (1.4 mg/kg bw per day for a 70 kg adult). The same diclofenac dose was given to the control group, diclofenac alone (n=15, one male, 14 females). The primary end-point was reduction in Disease Activity Score and secondary end-points were American College of Rheumatology criteria for reduction in tenderness and swelling of joint scores. Monitoring of vital signs, physical examinations and various blood chemistry parameters were performed bi-weekly. The occurrence of adverse events was the primary safety variable. Adverse events were reported as follows: curcumin alone group: mild fever and throat infection; curcumin and diclofenac group: one case of worsening of condition; diclofenac only group: itching and swelling around eyes/dimness of vision, worsening of condition, increase in serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) (liver enzymes; according to the authors, these were probably related to the drug).

In an Italian study with adult patients suffering from knee osteoarthritis the subjects received either the "best available treatment", defined by each patient's general practitioner or a combination of "best available treatment" and curcumin for 8 months (Belcaro et al., 2010). The subjects were recruited from a database (San Valentino vascular screening project). Randomisation was not reported. The curcumin group (n=50; 23 males, 27 females; five withdrawals, mean age 43.6 years) received 200 mg curcumin/day (Meriva®): curcumin-phosphatidylcholine phytosome complex, Sigmar Italia S.p.A.) (the dose is equivalent to 2.9 mg/kg bw per day in a 70 kg adult) in addition to "best available treatment". The control group (n=50; 28 males, 22 females; six withdrawals) was not explicitly defined, but drugs mentioned were NSAIDs (dose and type not given) and 2 g/day of acetaminophen or 200 mg/day of celecoxib "as needed and according to physician's recommendations. Endpoints were The Western Ontario and McMaster Universities Arthritis Index (WOMAC) score; Kernofsky Performance Scale Index; treadmill walking performance; inflammatory markers, oxidative stress status and erythrocyte sedimentation rate. Assessment of adverse effects was neither described nor reported. However, the curcumin product was referred to as" safe" in the abstract. The authors reported conflict of interest.

A Japanese study by Hanai et al. (2006) studied the efficacy and safety of curcumin for the maintenance of remission in ulcerative colitis. Eighty-nine patients (13-65 years) who were suffering from ulcerative colitis and were in the remission period were recruited. They were treated with either a combination of curcumin and sulfasalazine or mesalamine (n=45 for both combinations; 23 males, 22 females; 2 withdrawals) or a placebo combined with sulfasalazine or mesalamine (n= 44; 26 males, 18 females (5 withdrawals) for 6 months. The curcumin dose was 2000 mg/day (in cellulose/maltitol; both curcumin and placebo were prepared by API Co, Ltd., Gifu, Japan) (equivalent to 28.6 mg/kg bw per day for adults and

approximately 33 mg/kg for adolescents), the sulfasalazine dose was 1.0-3.0 g/day and the mesalamine dose was 1.5-3.0 g/day. End-points were proportion of patients relapsing at 6 and 12 months (ulcerative Clinical Activity Index (CAI)> 4); CAI and Endoscopic Index scores before and after treatment; adverse events. Nine adverse events were reported in seven patients (some patients experienced more than one event): sensation of abdominal bulging, nausea, transient hypertension (the patient was in the curcumin group and withdrew from the study) and transient increase in the number of stools (events were not related to group). One patient, who was a regular alcohol drinker, had elevated γ-guanosine triphosphate levels.

Fifteen adult patients diagnosed with adenocarcinoma of the colon or rectum in a Phase I clinical trial of oral curcumin were recruited in the United Kingdom (Sharma et al., 2004). Doses of either 0.45 (n=3; no males, three females), 0.9 (n=3; one male, two females), 1.8 (n= 3; one male, two females) or 3.6 (n=6; three males, three females) g/day curcumin (C3 Complex, Sabinsa Corporation, NJ, USA; one 500 mg capsule consisted of 450 mg curcumin, 40 mg desmethoxycurcumin and 10 mg *bis*-demethoxycurcumin) for up to 4 months were given in a single batch to each of four patient groups. The doses are equivalent to 6.4, 12.6, 25.7 and 51.4 mg/kg bw, respectively for a 70 kg adult).There was no control or placebo group. Levels of curcumin and its metabolites in plasma, urine and feces were investigated. Glutathione S-transferase activity, levels of a deoxyguanosine adduct (M_1G) formed via oxidative DNA damage and inducible prostaglandin E_2 (PGE_2) levels were measured in blood leukocytes. Dose-limiting toxicity was not observed. The authors reported that curcumin was well tolerated at all dose levels. One patient in the 0.45 g/day curcumin dose group and one patient in the 3.6 g/day curcumin dose group reported diarrhea 1 and 4 months into treatment, respectively (NCI, 1999)(toxicity grade 2: moderate). Four patients had elevated levels of serum alkaline phosphatase (NCI grade 1 (mild) in two patients and grade 2 (moderate) in two patients) and three patients had elevated level of lactate dehydrogenase. The authors did not specify to which groups these four patients belonged.

An Indian randomised, cross-over study was designed to investigate bioavailability and pharmacokinetic profile of curcumin by the complementary intake of piperine in healthy human volunteers (Shoba et al., 1998). Ten male adults (of which eight completed the study), aged 20-26 years with mean weight of 60 kg, were given single oral doses of 2 g curcumin powder in capsules (33 mg/kg bw) alone and 2 g pure curcumin powder in combination with 20 mg piperine powder (333 µg/kg bw) separated by a two week wash-out period (Sami Chemicals and Extracts, Bangalore, India), both products swallowed with water. Blood samples were taken at several time points up to 6 hour post-drug exposure. Pharmacokinetic parameters studied were maximum serum concentration, time to reach serum curcumin concentration, absorption and elimination half-lives, area under the concentration time curce (AUC), volume of distribution, total clearance and relative bioavailability. Adverse effects were not specified by the authors. However, according to the authors, both curcumin alone and in combination with piperine was well tolerated and there were no adverse or untoward reactions. Two subjects dropped out of the study for non-medical reasons.

2.4.2.1 Interactions

Curcumin inhibits platelet aggregation *in vitro* (Shah et al., 1999; Srivastava et al., 1995), and thus, a potential for curcumin supplementation to increase the risk of bleeding in people taking anticoagulant or antiplatelet medications (e.g. aspirin, heparin, and warfarin) was suggested by the Linus Pauling Institute, Micronutrient Information Center (LPI-MIC) (Linus Pauling Institute, 2016) in a continuously updated website report of curcumin (chapter under "dietary factors; phytochemicals"). EMEA (EMEA, 2010) reported that curcumin showed inhibitory activity against platelet aggregation mediated by collagen and arachidonic acid, yet only a weak or no inhibitory effect against platelet activating factor or thrombin activated platelets. EMEA (2010) concluded that although potential interactions between *Curcuma longa* L. (turmeric, which contains curcuminoids) and antiplatelet agents have been reported, such interactions have not been clinically proven. This is also the case for interactions of curcumin with pharmaceuticals such as NSAIDs, antihyperlipidemics and immunosuppressants.

Curcumin inhibited the therapeutic effect induced by cytostatics when dissolved in DMSO (to increase solubility) in breast cancer cells *in vitro* and *in vivo* (Somasundaram et al., 2002). In contrast, curcumin given as food supplement (no solvent added) did not exert pharmacological activity in a human study on patients with hepatic metastases from colorectal cancers. The authors questioned the ability of curcumin to exert such effects in tissues distant from the gastrointestinal tract (Garcea et al., 2004). The Linus Pauling Institute Micronutrient Information Center concluded that since the issue of adequate curcumin concentrations in cancerous tissue is unresolved, women undergoing chemotherapy for breast cancer should avoid curcumin supplements (Linus Pauling Institute, 2016). VKM supports this conclusion and further notes that the contrasting results between the studies of Somasundaram et al. (2002) and Garcea et al. (2004) in part may be explained by different absorption and curcumin uptake in tissue due to the use of different solvents in the two studies.

Curcumin appears to be toxic to cancer cells, but cytoprotective to healthy cells, owing in part to its strong antioxidative capacity (Heger et al., 2014). Curcumin possesses several chemical properties that facilitate intermolecular interactions, among these are H-bond donating and acceptor capacity, a high partition coefficient (log P) and (non)metal chelating ability. The direct molecular targets of curcumin are the ErbB (epidermal growth factor) family of receptor tyrosine kinase. Further, curcumin has been shown to modulate protein kinase C-signalling, interfere with prostaglandin synthesis and can bind to DNA. Further, curcumin has been identified as a direct vitamin D receptor agonist (Heger et al., 2014). However, the *in vivo* impact of the latter is unknown.

2.4.2.2 Allergic sensitisation (including adjuvant effects)

According to the EFSA report on re-evaluation of curcumin as a food additive, no relevant data on curcumin-induced food allergy or intolerance were found in the literature (EFSA, 2010).

One patient reported an unspecified rash after intake of a single dose of 8000 mg C3 *Complex*™ (mixture of three curcuminoids) in a dose escalation study with healthy adults by Lao et al. (2006). The effect was grade 1, defined as mild adverse events according to NCI, Common Toxicity Criteria version 2.0.

Photosensitivity was reported by one person in a group of 20 given 1000 mg curcumin (mixture of three curcuminoids) and 20 mg fluoxetine (in itself a potential photosensitising agent) (http://www.wellnesspharmacy.net/photosensitivity.pdf)) in combination in an RCT study (n= 60) on the efficacy and safety of curcumin in major depressive disorder (Sanmukhani et al., 2014) (see 2.4.6. vulnerable groups). It is unknown if the reported effect was due to curcumin, fluoxetine or the combination.

As noted in the EFSA (2010) report, several cases of contact dermatitis and contact urticaria are described in the literature after topical exposure of curcumin or curcumin-derivative containing products, e.g. cosmetics, milled powder or spices (Liddle et al., 2006; Thompson and Tan, 2006). In EMEA (2010), two studies reporting cases of allergic contact dermatitis, one reporting scalp itching after topical use of curcumin for 18 months and one reporting allergic reactions revealed by patch testing in persons already exposed to curcumin, were included. The relevance for oral intake of food supplements is unknown.

2.4.2.3 Summary human studies

Aside from gastrointestinal symptoms, few adverse events have been reported in human studies after curcumin intake in the range 2.9 – 51.4 mg/kg bw per day: one case of photosensitivity (when taken together with the antidepressant fluoxetine), one case of elevated level of serum alkaline phosphatase and three cases of elevated levels of lactate dehydrogenase. The human studies were not specifically designed to study adverse events and most did not include healthy control subjects. Curcumin may interact with chemotherapeutics. Some cases of contact dermatitis and contact urticaria after topical exposure to curcumin have been described.

2.4.3 Animal studies

An overview of the included studies investigating curcumin and adverse health effects in animals is given in Table 2.4.3-1.

VKM notes that turmeric oleoresin contains other substances in addition to curcumin(oids) although it represents the major component. Thus, any toxicity observed after exposure to e.g. turmeric oleoresin may not be due to curcumin alone.

Table 2.4.3-1 An overview of animal studies investigating curcumin and adverse health effects.

Reference	Study	Number and dose in treatment group	Total study length	Adverse effect
Short-term and subchronic toxicity				
Lv et al. (2014)	Effect of curcumin (+/- micelle encapsulation) accumulation and antitumour activity in EMT6 breast tumour-bearing female Kunming mice	18 animals divided in three groups were treated daily with either 10 mg/kg bw curcumin (dissolved in ≤10% DMSO), 10 mg/kg bw curcumin loaded in PAE-b-PEG micelles or physiological saline (PBS) alone	9 days	No deaths or body weight loss compared to PBS control; no acute toxicity as assessed by histopathological abnormalities, degeneration, lesions or necrosis observed (heart, lungs, liver, spleen and kidney).
Chronic toxicity and carcinogenicity				
NTP (1993)	Toxicology and carcinogenesis studies of turmeric oleoresins in F344/N rats and B6C3F1 mice	Rats and mice were fed *ad libitum* 0, 2, 10 or 50 g/kg diet of turmeric oleoresin For rats (60 animals/sex/dose), the curcumin doses were 0, 80/90, 460/440 and 2000/2400 mg turmeric oleoresin/kg bw per day in males and females, respectively. For mice (60 animals/sex/dose), the curcumin doses were 0, 220/320, 520/1620 and 6000/8400 mg turmeric oleoresin/kg bw per day in males and females, respectively (60 animals/sex/dose)	2 years	Female rats: increased incidences of clitoral gland adenomas in the groups exposed to 440 and 2000 mg/kg bw per day (not dose-related). Male mice: increased incidence of hepatocellular adenoma after intake of 520 mg/kg bw per day, and occurrence of carcinomas of the small intestine after intake of 220 and 520 mg/kg bw per day Female mice: increased incidence of hepatocellular adenomas after intake of 1620 mg/kg bw per day and pituitary gland adenomas after 8400 mg/kg bw per day
Reproductive and developmental toxicity				
Chen et al. (2010)	Effect of curcumin on ICR mice embryonic development such as embryonic attachment, outgrowth *in vitro*, and *in vivo* implantation	Mouse blastocysts were incubated *in vitro* with 0 μM (control), 6, 12 and 24 μM curcumin and implanted in the uterus of 40 mice	24 hours (curcumin incubation of blastocysts)	The highest concentration caused lower implantation rate, increased resorption of postimplantation embryos in mouse uterus and decreased fetal weight in the embryo transfer assay
Ganiger et al. (2007)	Multigeneration, reproductive toxicity study in Wistar rats (OECD Testing guideline 416) (basis for ADI (EFSA, 2010))	Rats (30 animals/sex/dose) of parental and F1 generation were fed diets containing curcumin at a concentration of 0, 1500, 3000 or 10 000 mg/kg of diet (equal to 0, 130–140, 250–290 or 850–960 mg/kg bw/day in males and 0, 160, 310–320 or 1000–1100 mg/kg bw/day in females)	Total periods of treatment were 21 weeks for the parental generation and 24 weeks for the F1 generation until weaning of their pups (F2)	The mean body weights of the F2 offspring (both sexes combined) were significantly decreased on postnatal days 1 and 7 at the intermediate dose, and on postnatal days 7, 14 and 21 at the highest dose

Short-term and subchronic toxicity

Lv et al. (2014) investigated the toxic effect of curcumin accumulation and antitumour activity in 18 EMT6 breast tumour-bearing Kunming female mice for 9 days in a study aimed at improving the antitumour activity of curcumin in overcoming the problem of poor water solubility. Hence, curcumin was encapsulated in a di-block copolymer micelle. The mice were divided in three groups and treated daily with either 10 mg/kg bw curcumin (dissolved in ≤10% DMSO), 10 mg/kg bw curcumin loaded in PAE-b-PEG (poly(anhydride-ester)-b-poly(ethylene glycol)) micelles or physiological saline (PBS) only without curcumin. There were no deaths or body weight loss compared to PBS control, no acute toxicity as assessed by histopathological abnormalities, and no degeneration, lesions or necrosis observed (heart, lungs, liver, spleen and kidney).

Chronic toxicity and carcinogenicity

NTP (1993) reported the results of long-term studies in which F344/N rats (60 animals/sex/dose) and B6C3F1 mice (60 animals/sex/dose) were fed *ad libitum* diets containing 0, 2, 10 or 50 g/kg diet turmeric oleoresin (79-85% curcumin; CAS no. 458-37-7) for 2 years. For rats, the daily doses were 0, 80/90, 460/440 and 2000/2400 mg turmeric oleoresin/kg bw per day in males and females, respectively. For mice, the daily doses were 0, 220/320, 520/1620 and 6000/8400 mg turmeric oleoresin/kg bw per day in males and females, respectively.

For mice, the NTP concluded that there was equivocal evidence of carcinogenic activity of turmeric oleoresin in the male mice based on a marginally increased incidence of hepatocellular adenoma at the 10 g/kg diet level, and the occurrence of carcinomas of the small intestine in the 2 and 10 g/kg diet groups. For the female mice, the NTP concluded that there was equivocal evidence of carcinogenic activity of turmeric oleoresin based on an increased incidence of hepatocellular adenomas in the 10 g/kg diet group (EFSA, 2010).

The NTP concluded that there was no evidence of carcinogenic activity of turmeric oleoresin in the male rats administered 2, 10 or 50 g/kg feed, but equivocal evidence of carcinogenic activity of turmeric oleoresin in the female rats based on increased incidences of clitoral gland adenomas in the groups exposed to 10 and 50 g/kg feed (440 and 2000 mg turmeric oleoresin/kg bw per day) (NTP, 1993).

Although statistically significant increases in the incidences of hepatocellular adenomas (10 g/kg feed, males and females), small intestinal carcinomas (2 and 10 g/kg feed, males) and pituitary gland adenomas (50 g/kg feed, females) in mice and clitoral gland adenomas (10 and 50 g/kg feed, females) in rats were observed (NTP, 1993), JECFA (2004) concluded that these effects were not dose-related and that curcumin was not a carcinogen.

EFSA (2010) summarised that all statistically significant effects noted by the NTP (1993) referred to benign neoplastic lesions (adenomas) and that the incidences for malignant neoplastic lesions (carcinomas), including the carcinomas of the small intestine in male mice, did not reach statistical significance. EFSA also noted that the effects observed were not

dose-dependent, were in line with historical control values and were not consistent across sexes and/or species. Further, EFSA claimed that hepatocellular tumours occurring in untreated and treated B6C3F1 mice were not relevant for humans, and therefore gave support to JECFA (2004) in their view that curcumin is not carcinogenic.

VKM agrees with EFSA and NTP in that curcumin is not carcinogenic based on the study by NTP (1993). Therefore, VKM supports the use of ADI in risk assessment of curcumin. However, as opposed to the view of EFSA regarding carcinogenic effects, VKM notes that the carcinogenicity study by NTP does not eliminate the possibility that curcumin may be genotoxic *in vivo*, considering the positive results in several genotoxicity tests. Furthermore, VKM notes that regarding the use of the historical control data to evaluate the significance of the clitoral gland adenomas and carcinomas in rats in the NTP study, these control data were from 2007, while the study was performed in 1993. There may be discrepancies between controls from populations 14 years apart, such as changes in diet (occurred in 1995).

Reproductive and developmental toxicity

Chen et al. (2010) investigated the effect of curcumin on Imprinting Control Region (ICR) mouse embryonic development such as embryonic attachment, outgrowth *in vitro*, and *in vivo* implantation. Mouse blastocysts were incubated *in vitro* with 0 µM (control), 6, 12 and 24 µM curcumin (Sigma, St. Louis, MO, USA) for 24 hours. Mouse blastocysts were harvested from 40 nulliparous female mice (6-8 weeks old). Pseudopregnant dams produced by ICR females (white) mated with vasectomised males (C57BL/6J) (black) were recipients for embryo transfer. The surrogate mice were killed on day 18 post-coitus, and the frequency of implantations was calculated as the number of implantation sites per number of embryos transferred. *In vitro* curcumin-treated (24 µM) blastocysts was associated with lower implantation rate, increased resorption of postimplantation embryos in mouse uterus and decreased fetal weight in the embryo transfer assay.

EFSA (2010) described a study by Ganiger et al. (2007) who conducted a multigeneration, reproductive toxicity study in Wistar rats (Hsd Cpb:WU) according to OECD Testing guideline 416 using curcumin (99% purity; Spices Research Foundation, Anavathil, Cochin, Kerala, India). The study was reported to and evaluated by JECFA (2004). Rats (30 animals/sex/dose) were fed diets containing curcumin at a concentration of 0, 1500, 3000 or 10 000 mg/kg of diet (equal to 0, 130–140, 250–290 or 850–960 mg/kg bw/day in males and 0, 160, 310–320 or 1000–1100 mg/kg bw/day in females) starting from 10 weeks before the mating period and throughout mating. The treatment of females continued throughout pregnancy and lactation weaning of the offsprings (F1 and F2). The total periods of treatment were 21 weeks for the parental generation (P) and 24 weeks for the F1 generation. On postnatal day 4, the litter sizes of the F1 offspring were standardised to a maximum of eight animals. After weaning, 30 males and 30 females of the F1 generation were selected to become the parents of the F2 generation. Parents were observed for clinical signs, body weights, food intake, cohabitation interval and duration of gestation. Pups were weighed on postnatal days 1, 4, 7, 14 and 21. All parents, F1 weanlings not selected for

mating and all F2 weanlings were subjected to complete necropsy at terminal sacrifice. The following indices were calculated: male and female fertility index, percentage of matings resulting in pregnancy, number of implantations, percentage of pregnancies resulting in birth of live litters, percentage of live pups born, post-implantation loss, mean litter size and mean viable litter size, live birth index and percentage survival of pups at postnatal days 4, 7, 14 and 21. Ovaries, uterus, vagina/cervix, testes, epididymides, seminal vesicles, prostate, coagulating glands, liver, kidney, pituitary and adrenals glands were examined histologically.

Ganiger et al. (2007) reported no treatment-related clinical signs of toxicity, ophthalmological changes or mortality during the study. Further, during the premating period, there were no treatment-related effects in group mean body weights and net body weight gains or food consumption between treated and control animals of either generation. During days 10–15 of gestation there was a dose-related decrease in body weight gain in the dams of the parental generation, which was statistically significantly different from that of controls (body weight gains were >80% than that of controls) at the intermediate and highest doses (Ganiger, 2002; JECFA, 2004). At this time, body weights were reported to be below the range of values for the historical controls. However, maternal body weights did not differ significantly between groups at the end of gestation. The mean body weights of the F2 offspring (both sexes combined) were significantly decreased on postnatal days 1 and 7 at the intermediate dose, and on postnatal days 7, 14 and 21 at the highest dose. A dose-related trend was apparent, but the effect was small, with average body weights being >90% that of the control pups, and the observed changes were reported to be within the range of the data for historical controls. There were no other effects on general health, body weight, pup survival and fertility indices in either generation. The effects at the intermediate dose were observed at isolated time-points only and were considered to be incidental. JECFA considered that the small body weight reduction in the F2 pups of the F1 group fed the highest dose prevented this dose level from being the NOAEL, and therefore the intermediate dose, equal to 250–320 mg/kg bw/day fed to the F1 generation, was considered by JECFA to represent the NOAEL. JECFA allocated an ADI for curcumin of 0-3 mg/kg bw/day based on the intake of 250-320 mg/kg bw/day in the mid-dose group as the NOAEL (JECFA, 2004).

Ganiger et al. (2007) concluded that the NOAEL for reproductive toxicity of curcumin, fed in the diet for two successive generations to rats in this study, was 10 g/kg, which is equivalent to 847 and 959 mg/kg bw per day for male rats and 1043 and 1076 mg/kg bw per day for females in the P and F1 generations, respectively. However, EFSA considered the decreased body weight gain in the F2 generation observed at the highest dose levels (fed the P and F1 generations) to be an adverse effect and agreed with the NOAEL allocated by JECFA of 250-320 mg/kg bw/day (EFSA, 2010).

2.4.3.1 Interactions

In an animal model of breast cancer, dietary curcumin inhibited cyclophosphamide-induced tumor regression (Somasundaram et al., 2002).

Two animal studies indicated that curcumin may interfere with manganese (Mn) and iron (Fe) (Chin et al., 2014; Schmitz et al., 2014). The effect of chronic inhalation of a manganese mixture (manganese (III) acetate and manganese (II) chloride, 20:40 mM) was evaluated in mice together with curcumin supplemented in the diet (500 or 1500 ppm in food pellets). Curcumin alone produced similar deleterious effects as did Mn, i.e. disturbed motor performance as well as the short- and long-term spatial memory when evaluated in behavioural tests. In hippocampal tissue, the combined Mn and curcumin exposure significantly increased the levels of Mn and Fe, and decreased the levels of dopamine and serotonin (Schmitz et al., 2014). The authors indicated that increased Fe levels could be a result of the pro-oxidative effect of curcumin and that primary accumulation in the hippocampus (relative to other brain sites) may be associated with oxidative stress.
In a dietary supplementation study in mice given 0.2% (by weight) curcumin in the feed, a significant reduction in Fe stores in the liver and spleen was observed compared to non-supplemented mice. Also, liver hepcidin and ferritin expression were suppressed. The suggested mechanisms for these results were the Fe chelating ability of curcumin since curcumin has the ability to chelate dietary trace elements. Further, it was suggested that the observed decrease in Fe stores could be attributed to curcumin's anti-coagulant activity (Chin et al., 2014).

2.4.3.2 Allergic sensitisation (including adjuvant effects)

There was no information concerning allergic sensitisation or allergy adjuvant effects in the animal studies reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of allergic sensitisation or allergy adjuvant effects.

2.4.4 *In vitro* studies

Interactions
Antunes et al. (1999) found that curcumin potentiated the DNA damaging effect of the free radical generator and the cancer drug doxorubicin. Curcumin was also shown to work in an additive fashion with hexavalent chromium, a well-known mutagen and carcinogen (Blasiak et al., 1999; EFSA, 2010).

2.4.5 Mode of action for adverse effects

According to a review by Heger et al. (2014) and references therein, curcumin has been characterised as a DNA and RNA binding agent although the latter binding occurs with lower affinity. Curcumin was found to bind to the minor groove of DNA in a pH- and sodium concentration-dependent manner. Several studies have demonstrated that curcumin induces DNA damage in cancer cells, leading to cell cycle arrest and apoptosis. A suggested mechanism responsible for these effects is direct curcumin-induced DNA damage through

oxidation of guanine residues to 8-oxo-guanine. Curcumin-mediated impairment of DNA repair mechanisms contributes to the observed DNA damage. There are indications that curcumin induces both double and single strand DNA breaks.

2.4.6 Vulnerable groups

An Indonesian study by (Rasyid et al., 2002) was conducted to determine a dosage capable of producing an increase in gallbladder contraction by 50% and to define whether there is any linear relationship between the doubling of curcumin dosages and the doubling of gallbladder contraction. According to the authors, curcumin may be useful in preventing gallstone formation due to its ability to cause gallbladder contraction.The randomised, single-blind, three-phase, crossover design study included healthy adults volunteers (n=12; eight males, four females) ages 20-50 years, who were given either curcumin (Merck Schudchardt, Munich, Germany) or the placebo amylum (Shangi, Java, Indonesia). The numbers in each group was not reported. Dosages of 20, 40 and 80 mg synthetic curcumin were given each subject prior to gallbladder volume and contraction examination by the use of ultrasonography. The dosage capable of producing an increase in gallbladder contraction by 50% was 40 mg curcumin. A linear relationship between doubling curcumin dosage and doubling of contraction was not proven (Rasyid et al., 2002).

Linus Pauling Institute (2016) concluded that although curcumin could decrease the risk of gallstone formation by promoting gallbladder emptying, it could potentially increase the risk of symptoms in people who already have gallstones. According to the National Institutes of Health, National Center for Complementary and Integrative Health (USA), curcumin is contraindicated for use in subjects with gallstones and obstructed bile passages (NIH/NCCIH, 2016). This view is supported by EMEA (2010).

EMEA (2010) concluded that there are indications that turmeric and/or curcumin can be transferred through lactation. This view was substantiated by a study in which pharmacological effects were observed in dams and their suckling neonates after administration of turmeric and/or curcumin. Since safety during pregnancy and lactation has not been established due to lack of data, EMEA (2010)concluded that the use of curcumin during pregnancy and lactation is not recommended.

Dietary curcumin has been shown to inhibit chemotherapy-induced tumour regression in an animal model (Somasundaram et al., 2002) (See 2.4.2.1 Interactions). Women undergoing chemotherapy for breast cancer should avoid curcumin supplements according to Linus Pauling Institute (2016).

Nair et al. (2005) described the connection between increased levels of redox-active free copper ions in the liver of Long-Evans Cinnamon rats and production of hydroxyl radicals that attack DNA and initiate lipid peroxidation. The authors showed that these processes were further enhanced by dietary curcumin generating DNA damage and suggest that curcumin treatment for preventive measures of patients with liver diseases and hepatitis C infections

would be contra-indicative. Accumulation of copper ions in the liver and hepatic injury was positively correlated in humans (Hatano et al., 2000).

2.5 Summary of hazard identification and characterisation

Curcumin is the main ingredient in turmeric, which is derived from the ground rhizomes of the plant *Curcuma longa* L. (turmeric). Curcumin is used as a food additive (E100) and as a spice when present in turmeric and curry (EFSA, 2010). Curcumin is lipophilic and has low solubility in water at acidic and physiological pH, it hydrolyses rapidly under alkaline conditions and it is susceptible to photochemical degradation (Tonnesen and Karlsen, 1985; Tonnesen et al., 1986; Tønnesen and Karlsen, 1985).

The absorption of curcumin is low, and the absorbed curcumin is efficiently metabolised by the liver and excreted into the biliary system. The curcumin plasma levels peak within 2 hours of administration, and complete clearance occurs within a few hours thereafter (Heger et al., 2014).

Curcumin did not induce gene mutations in several strains, with or without metabolic activation, in Ames test. However, one *in vitro* study found that curcumin induced recombination in *Bacillus subtilis*. Curcumin induced chromosomal aberrations, micronuclei and DNA strand breaks in several studies. Thus, curcumin apparently has a genotoxic potential *in vitro*. VKM notes that several studies had limitations, such as questionable solubility of curcumin in aqueous solutions and unknown pre-exposure degradation due to photochemical instability of curcumin.

Several negative *in vivo* micronuclei and chromosomal aberration studies of curcumin have been published. However, these studies had several limitations, such as lack of information on purity of curcumin, questionable solubility of curcumin in aqueous solutions, unknown pre-exposure degradation due to photochemical instability, a single dose used and/or lack of confirmation of cytotoxicity in the bone marrow. VKM is therefore of the opinion that the available *in vivo* studies are insufficient to completely eliminate the possibility that curcumin may be genotoxic.

Curcumin is not carcinogenic based on animal studies (NTP, 1993).

An ADI of 0-3 mg/kg bw per day was allocated by JECFA (2004), based on a NOAEL for reduction in body weight in F2 animals in a multigenerational reproductive toxicity study in rats by (Ganiger et al., 2007). Based on the same study, EFSA supported the ADI of 3 mg/kg bw per day set by JECFA (EFSA, 2010).

Serious adverse effects of intake of curcumin in the range of 2.9-51.4 mg/kg bw per day were not observed in the human studies published after EFSA (2010). Therefore, in the present risk assessment, the value used for comparison with the estimated exposure in the risk characterisation is the ADI of 3 mg/kg bw per day.

Cases of contact dermatitis and contact urticaria were described in the literature after topical exposure of curcumin. However, the relevance of these findings for oral intake of food supplements is unknown.

Potential vulnerable groups for curcumin exposure are patients under chemotherapy for breast cancer, patients with gallstones and obstructed bile passages as well as liver diseases and hepatitis C infections.

There are indications that turmeric and curcumin can be transferred through lactation (EMEA, 2010).

3 Exposure / Intake

3.1 Food supplements

NFSA requested VKM to perform a risk assessment of 300, 600 and 900 mg/day of curcumin in food supplement for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years). The default body weights (bw) for these groups as determined by EFSA were used: 10 to <14 years; 43.4 kg, 14 to <18 years; 61.3 kg and adults; 70.0 kg (EFSA, 2012).

The estimated intake of curcumin from food supplements for the various age groups is presented in Table 3.1-1.

From a daily dose of 300 mg curcumin, the calculated intake levels are 6.9, 4.9 and 4.3 mg/kg bw per day for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

From a daily dose of 600 mg curcumin, the calculated intake levels are 13.8, 9.8 and 8.6 mg/kg bw per day for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

From a daily dose of 900 mg curcumin, the calculated intake levels are 20.7, 14.7 and 12.9 mg/kg bw per day for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

Table 3.1-1 Estimated daily intake of curcumin (mg/kg bw per day) from food supplements for the various age groups.

	Daily doses		
	300 mg	600 mg	900 mg
Children (10 to <14 years)	6.9 mg/kg bw per day	13.8 mg/kg bw per day	20.7 mg/kg bw per day
Adolescents (14 to <18 years)	4.9 mg/kg bw per day	9.8 mg/kg bw per day	14.7 mg/kg bw per day
Adults (≥18 years)	4.3 mg/kg bw per day	8.6 mg/kg bw per day	12.9 mg/kg bw per day

3.2 Other sources

EFSA (2010) stated that the intake of curcumin from the normal diet amounts to less than 7% of the ADI. Maximum curcumin intake from food as food additive and spice combined has been reported to be 2.3 and 1.6-7.6 mg/kg bw per day for adults (>18 years) and children (1-10 years for food additive; 5-12 years for spices), respectively (EFSA, 2010).

Curcumin is used in cosmetics as an antioxidant and colourant (CosIng, 2015).

4 Risk characterisation

4.1 Food supplements

NFSA requested VKM to perform a risk assessment of the doses 300, 600 and 900 mg/day of curcumin in food supplements for the general population, ages 10 years and above.

The value used for comparison with the estimated exposure in the risk characterisation is the ADI of 3 mg/kg bw per day. The ADI was based on the NOAEL of 290 and 320 mg/kg bw per day for males and females, respectively, from the multigeneration reproductive toxicity study for a decreased body weight gain in the F2 generation observed at the highest dose level fed the parental and F1 generations, and an uncertainty factor of 100. The total periods of treatment were 21 weeks for the parental generation and 24 weeks for the F1 generation (until lactation weaning of the F2 pups).

For children (10 to <14 years), the estimated intake ranged from 6.9 to 20.7 mg/kg bw per day, all above the ADI.

For adolescents (14 to <18 years), the estimated intake ranged from 4.9 to 14.7 mg/kg bw per day, all above the ADI.

For adults (≥18 years), the estimated intake ranged from 4.3 to 12.9 mg/kg bw per day, all above the ADI.

5 Uncertainties

5.1 Hazard identification and characterisation

Several of the human studies referred to are RCTs, with varying degrees of randomisation and patients under medical treatment as control groups. A majority of the studies were specifically designed to investigate the positive effects of curcumin, not negative effects. Also, in several *in vitro* studies performed between 2010 and 2016, potentially advantageous pharmacological effects of curcumin as well as curcumin absorption enhancing formulations, such as nanoparticles, were investigated. Some of these studies investigated curcumin in combination with other compounds not representative of food supplements, and when curcumin was investigated alone (as a study control) often only one dose was tested.

There are conflicting data regarding potential genotoxic effects of curcumin although EFSA (2010) noted in their re-evaluation that the assessed studies give reason to eliminate the concerns for genotoxicity and carcinogenicity. VKM notes that the carcinogenicity study by NTP does not fully eliminate the possibility that curcumin may be genotoxic considering the positive results in several genotoxicity tests (NTP, 1993). Furthermore, VKM notes that there are uncertainties in the use of the historical control data used with the clitoral gland adenomas and carcinomas in rats. These were from 2007 while the study was performed in 1993. There may be discrepancies between controls from populations 14 years apart, such as change in diet (occurred in 1995).

Based on an animal study, there were indications that turmeric and curcumin can be transferred through lactation (EMEA, 2010).

5.2 Exposure

With use of the default (mean) body weight of an age (population) group, the variance in all individuals in the group will not be covered.

6 Conclusions with answers to the terms of reference

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority (NFSA), assessed the risk of curcumin in food supplements (300, 600 and 900 mg per day). The present risk assessment is based on previous risk assessments of curcumin and a literature search.

The ADI value used for comparison with the estimated exposure in the risk characterisation is 3 mg/kg bw per day based on a multigeneration reproductive toxicity study in Wistar rats. The treatment periods were 21 and 24 weeks for the parental and F1 generation, respectively. The F1 generation was dosed until lactation weaning of the F2 pups.

Serious adverse effects of intake of curcumin in the range of 2.9-51.4 mg/kg bw per day were not observed in the human studies published after EFSA (2010). VKM performed a re-evaluation of the ADI of 3 mg/kg bw per day allocated by JECFA (2004), supported by EFSA (2010), and agrees with EFSA and NTP in that curcumin is not carcinogenic based on the study by NTP (1993). Therefore, VKM supports the use of ADI in risk assessment of curcumin. In the present risk assessment, the value used for comparison with the estimated exposure in the risk characterisation is the ADI of 3 mg/kg bw per day.

For children (10 to <14 years), the estimated intake ranged from 6.9 to 20.7 mg/kg bw per day, for adolescents (14 to <18 years), the estimated intake ranged from 4.9 to 14.7 mg/kg bw per day, and for adults (≥18 years), the estimated intake ranged from 4.3 to 12.9 mg/kg bw per day. Thus, the intake from all three doses of curcumin exceeded the ADI value of 3 mg/kg bw per day for all age groups.

VKM concludes that a daily intake of 300, 600 or 900 mg of curcumin in food supplements may represent a risk of adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

An overview of the conclusions is presented in Table 6.1. Estimated exposures (above the value for comparison) are shown in red.

Table 6.1 An overview of the conclusions on curcumin. Red: estimated exposure may represent a risk of adverse health effects.

Food supplement / Age groups	Curcumin		
	300 mg	600 mg	900 mg
Children (10 to <14 years)			
Adolescents (14 to <18 years)			
Adults (≥18 years)			

7 Data gaps

- There are few studies on negative health effects related to curcumin in children and adolescents.
- No studies were found on effects of curcumin in lactating women and no relevant studies were found on pregnant women.
- Human RCT studies on adverse effects after chronic oral exposure to curcumin in healthy subjects are lacking.

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9 Appendix

Search Strategy for the first literature search (June 2015):

Database: Ovid MEDLINE(R) <1946 to June Week 1 2015>, Embase <1974 to 2015 June 16>

1. curcumin*.ti. (11287)
2. (curcumin* adj3 (risk* or safety or adverse or reaction* or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or consequence* or toxicity or toxic)).tw. (778)
3. 1 and 2 (732)
4. (conference abstract* or letter* or editorial*).pt. (4464924)
5. 3 not 4 (679)
6. limit 5 to (danish or english or norwegian or swedish) (657)
7. remove duplicates from 6 (379)
8. limit 7 to yr="2010 -Current" (242)

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Search Strategy for the second literature search (March 2016):

Database: Pubmed

1. turmeric (3584)
2. curcuma longa (2602)
3. curcumin (8904)
4. genotoxicity (12197)
5. turmeric OR curcuma longa OR curcumin AND genotoxicity (31)