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Risk assessment of butylated hydroxytoluene (BHT)

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

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Norwegian Scientific Committee for Food and Environment (VKM)
Po 4404 Nydalen
N – 0403 Oslo
Norway

Phone: +47 21 62 28 00
Email: vkm@vkm.no

vkm.no
vkm.no/english

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Risk assessment of butylated hydroxytoluene (BHT)

Preparation of the opinion

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) appointed a project group to answer the mandate. The project group consisted of six persons, including a project leader from the VKM secretariat. Two external referees commented on and reviewed the opinion. The VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics evaluated and approved the final opinion.

Authors of the Opinion

Members of the project group that contributed to the drafting of the opinion (in alphabetical order after chair of the project group):

Trine Husøy - Chair of the project group and Chair of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health

Monica Andreassen - Member of the project group until August 31, 2018. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health.

Inger Therese Laugsand Lillegaard – Member of the project group. Affiliation: VKM

Gro Haarklou Mathisen – Member of the project group and project leader. Affiliation: VKM

Jens Rohloff – Member of the project group and member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) Norwegian University of Science and Technology

Jostein Starrfelt – Member of the project group. Affiliation: VKM

Members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics that contributed to and approved the opinion:

In addition to Trine Husøy and Jens Rohloff, these were (in alphabetical order):

Ellen Bruzell – Member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) Nordic Institute of Dental Materials

Monica Hauger Carlsen - Member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) University of Oslo

Tove Gulbrandsen Devold - Member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) Norwegian University of Life Sciences

Berit Granum - Member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health

Josef Daniel Rasinger - Member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) Institute of Marine Research

Camilla Svendsen - Member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health

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VKM would like to thank Hubert Dirven (Norwegian Institute of Public Health) and Robin Ørnsrud (Institute of Marine Research) for their valuable comments through critical review of the draft opinion. VKM emphasises that the referees are not responsible for the content of the final opinion. In accordance with VKM's routines for approval of a risk assessment, VKM received the referees' comments before evaluation and approval by the Panel and prior to publication.

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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Short summary

Butylated hydroxytoluene (BHT, E321) is a synthetic antioxidant authorised as food and feed additive in the EU. In addition, BHT is used in e.g. cosmetics and food contact materials. To our knowledge, risk assessments including exposure estimates for BHT from multiple sources and exposure pathways have not been performed.

BHT is characterised by extensive use and multiple exposure sources and routes. Therefore, it is important that these sources and routes are included in the estimations to arrive at the most accurate picture of the population's exposure. In addition, the main sources contributing to the exposure should be identified.

Toxicity
An acceptable daily intake (ADI) of 0.25 mg/kg bodyweight (bw) per day was established by EFSA based on effects on the litter size and pup body weight in two 2-generation studies in rats (EFSA, 2012). The ADI was based on the no observed adverse effect level (NOAEL) of 25 mg/kg bw per day in these two studies and an uncertainty factor of 100. The ADI was used as reference point for BHT toxicity in this risk assessment.

Exposure
The exposure was estimated for «realistic» and «high» scenarios. The consumption data used for the exposure estimation were from Norkost 3 (foods), EuroMix (foods and personal care products) and the Environmental Protection Agency (US; indoor dust). The concentration data used were from scientific literature, and identified through literature searches. The concentration data for the exposure estimation from foods and PCPs were limited and therefore considered to be the largest source of uncertainty in the exposure estimates.

Data considered most realistic for the Norwegian exposure were used for «realistic» exposure estimation, whereas the «high» exposure scenario was a worst-case estimation representing a risk assessment for potentially high consumers. To calculate the total internal exposure, absorption factors for BHT uptake from the gastrointestinal tract and skin were used.

BHT reaching the physical barriers in the body was defined as external exposure, and the absorbed BHT was defined as total internal exposure.

The «realistic» total internal exposure from all routes, for the lowest 5 and the highest 95 percentile, was estimated to be within 1.4 – 9.7 µg BHT/kg bw per day for females and 0.8 – 9.7 µg BHT/kg bw per day for males. The 50 percentile was estimated to be within 3.5 – 4.2 and 2.2 – 2.8 µg BHT/kg bw per day (rounded numbers) for females and males, respectively. The «high» total internal exposure from all routes, for the lowest 5 and the highest 95 percentile, was estimated to be within 23 – 281 µg BHT/kg bw per day for females and 9 - 319 µg BHT/kg bw per day for males. The 50 percentile was estimated to be

within 85 – 111 and 46 – 61 µg BHT/kg bw per day (rounded numbers) for females and males, respectively.

The predominant route of exposure is oral intake; on average 80% of the internal exposure in females is from food, dust and oral intake of PCPs, while for males even more (92%). Sources of BHT exposure were mainly from food through oral intake (females 41%, males 59%, with substantial contributions also from PCPs through oral uptake (females 38%, males 34%) and through dermal uptake from PCPs (females 21%, males 7.1%). The main contributors to the estimated dietary «realistic» external exposure were the food groups «milk, cream, ice cream», followed by «chewing gum» and «fatty fish». The personal care product categories «body lotion» and «deodorant»» were the two major contributors to the estimated dermal «realistic» external exposure. Oral exposure from personal care products was mainly from toothpaste.

Risk characterisation and conclusions

Both «realistic» and «high» total internal BHT exposure was used in the risk characterisation. The estimated «realistic» exposure was below the ADI for both women and men. The 50 percentile of the estimated «high» exposure (the worst-case estimation representing a cautious risk assessment approach) was below the ADI, whereas the 95 percentile was above the ADI. Thus, a small fraction of the population may exceed the ADI and be at risk for negative effects on reproductive health.

The Panel concludes that BHT exposure is unlikely to cause adverse health effects in adults.

Key words: BHT, butylated hydroxytoluene, cosmetics, external exposure, food, indoor air, indoor dust, total internal exposure, Norwegian Scientific Committee for Food and Environment, personal care products, risk assessment, VKM.

Kort sammendrag

Butylert hydroksytoluen (BHT, E321) er en syntetisk antioksidant som er tillatt brukt i mat og fôr i EU. BHT brukes i tillegg i en rekke andre typer produkter, for eksempel i matkontaktmaterialer, kosmetikk og kroppspleieprodukter.

Siden BHT brukes i så mange ulike typer produkter, er det viktig at hovedkildene til BHT eksponering er inkludert når det beregnes hvor mye BHT vi får i oss. På denne måten kan vi få et best mulig nøyaktig bilde av befolkningens eksponering. I tillegg bør kildene som bidrar mest til eksponeringen identifiseres.

Toksisitet
EFSA (2012) etablerte en grense for hva som er et akseptabelt daglig inntak (ADI) basert på to 2-generasjonsstudier i mus. ADI-verdien på 0.25 mg/kg kroppsvekt per dag var basert på redusert kullsttørrelse og kroppsvekt hos nyfødt avkom. Usikkerhetsfaktoren var 100. Denne ADI-verdien ble brukt som referansepunkt for toksisitet i denne risikovurderingen.

Eksponering
Eksponering ble beregnet for to ulike scenarioer, henholdsvis «realistisk» og «høy» eksponering. Data på inntak/bruk var fra studiene Norkost 3 (mat), EuroMix (mat og kosmetikk) og den amerikanske miljøvernetaten Environmental Protection Agency (USA; husstøv). Opplysninger om mengde BHT i mat, kosmetikk og husstøv ble funnet i vitenskapelig litteratur ved litteratursøk. Mangelen på konsentrasjonsdata ble ansett å være den største kilden til usikkerhet i beregningene av eksponering.

Konsentrasjonsdataene som ble ansett som mest realistiske for norske forhold ble brukt til å beregne «realistisk» eksponering. Scenarioet med "høy" eksponering var en verstefalls-estimat.

BHT som nådde de fysiske barrierer i kroppen ble definert som ekstern eksponering, mens absorbert BHT ble definert som total intern eksponering.

I beregningen av den totale interne eksponeringen ble det brukt absorpsjonsfaktorer for BHT-opptak fra mage-tarmkanalen og for opptak over hud. «Realistisk» total intern eksponeringen ble estimert til å være innenfor 1,4 – 9,6 og 0,8 – 9,7 µg BHT/kg kroppsvekt per dag for henholdsvis kvinner og menn. 50-persentilen ble estimert til å ligge innenfor 3,5 - 4,2 og 2,2 - 2,8 µg BHT/kg kroppsvekt per dag for henholdsvis kvinner og menn. «Høy» total intern eksponeringen ble estimert til å være innenfor 23 - 281 og 9 - 319 µg BHT/kg kroppsvekt per dag for henholdsvis kvinner og menn. 50-persentilen ble estimert til å være innenfor henholdsvis 85 - 111 og 46 - 61 µg BHT/kg kroppsvekt per dag (avrundet tall) for kvinner og menn.

Den dominerende eksponeringsveien er oralt inntak; gjennomsnittlig er 80% av den interne eksponeringen hos kvinner fra mat, støv og oralt inntak av kosmetikk og kroppspleieprodukter, mens for menn enda mer (92%). Kilder til eksponering for BHT var hovedsakelig fra mat gjennom oralt inntak (41 % for kvinner, 59 % for menn), med betydelige bidrag også fra kosmetikk og kroppspleieporodukter gjennom oralt opptak (38 % for kvinner, 34 % for menn) og dermal opptak (21% for kvinner, 7,1 % for menn).

Matvaregruppene «melk, fløte, iskrem», fulgt av «tyggegummi» og «fet fisk» var de viktigste matvarekildene. Tannkrem var den viktigste kilden til oralt inntak fra kosmetikk og kroppspleieprodukter, mens det var produktkategoriene «kroppslotion» og «deodorant» som var de to viktigste bidragsyterne til opptak fra hud.

Risikokarakterisering og konklusjoner

Risikoen ble vurdert for både «realistisk» og «høy» total intern BHT eksponering. I det «realistiske» scenarioet lå den estimerte totale BHT-eksponeringen under ADI for både kvinner og menn. I det «høye» scenarioet (verstefalls-estimatet) lå 50 persentilen under ADI, mens 95 persentilen lå over. Det vil si at en liten brøkdel av befolkningen kan overstige ADI og være utsatt for negative effekter på reproduktiv helse.

Panelet konkluderer med at det er lite sannsynlig at eksponering for BHT vil forårsake skadelige helseeffekter hos voksne.

Abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
BHT	butylated hydroxytoluene
bw	body weight
DMSO	dimethyl sulfoxide
dw	dry weight
KBS	food composition database (in Norwegian: kostberegningssystem)
LB	lower bound
LOD	limit of detection
LOQ	limit of quantitation
MB	middle bound
NOAEL	no observed adverse effect level
OIM	observed individual mean
PCPs	personal care products
RCT	randomised controlled trial
RoB	risk of bias
UB	upper bound
WoE	weight of evidence

Organisations

EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization of the United Nations
IARC	International Agency for Research on Cancer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
OECD	Organisation for Economic Co-operation and Development
SCF	Scientific Committee for Food
VKM	Norwegian Scientific Committee for Food and Environment
WHO	World Health Organization

Solvents

ACN	acetonitrile
ACN:Pen	acetonitrile:Pentane
DCM	dichloromethane
EtAc	ethyl acetate
EtOH	ethanol
HSSPME	headspace-solid-phase microextraction
HS	headspace
Hx	hexane
MeOH	methanol
SFE	supercritical fluid extraction

SPME	solid-phase microextraction

Method used for chemical analysis

GC-FID	gas chromatography flame ionisation detector
GC/MS	gas chromatography mass spectrometry
GC–MS/MS	gas chromatography tandem mass spectrometry
GC-MS SIM	selective ion monitoring gas chromatography mass spectrometry
HPLC-DAD	high-performance liquid chromatography diode-array detector
HPLC-ED	high performance liquid chromatography electrochemical detection
HPLC-MS/MS	high-performance liquid chromatography tandem mass spectrometry
HPLC-UV	high-performance liquid chromatography ultraviolet detection
HPLC UV+ECD	high-performance liquid chromatography ultraviolet detection/electrochemical detection
HPLC UV/VIS	high performance liquid chromatography ultraviolet and visible light detection
HS-GC/MS	headspace gas chromatography mass spectrometry
LC/MS	liquid chromatography mass spectrometry
LC-MS/MS	liquid chromatography tandem mass spectrometry

Definitions

Food group
A food group is a collection of foods that share similar nutritional properties and/or have the same usage. The food groups used in this assessment are grouped according to the KBS food groups (food composition database, University of Oslo).

Lower bound (LB)
Lower bound estimates were calculated by substituting values below the limit of detection (LOD) or limit of quantification (LOQ) for an analytical method with the number zero.

Medium bound (MB)
Medium bound estimates were calculated by substituting values below the LOD or LOQ with values set to half of the LOD or LOQ.

Observed individual means (OIMs)
Observed individual means refer to chronic exposure estimated by the arithmetic mean intake for each individual. The method does not allow the inclusion of covariables and cofactors in the exposure assessment, and the method is known to overestimate the upper tail of the exposure distribution.

Upper bound (UB)
Upper bound estimates were calculated by substituting values below the LOD or LOQ with values set equal to the LOD or LOQ.

Background

Butylated hydroxytoluene (BHT, E321) is a synthetic antioxidant authorised as a food and feed additive in the EU. BHT is also used in e.g. personal care products and food contact materials (the limit for migration is 3 mg/kg).

BHT has been assessed/evaluated by several competent bodies, including e.g. the EU Scientific Committee for Food (SCF), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA). An acceptable daily intake (ADI) of 0.25 mg/kg bw per day was established by EFSA (EFSA, 2012) based on effects on the litter size and pup body weight. The no observed adverse effect level (NOAEL) of 25 mg/kg bw per day was derived from two 2-generation studies in rats and application of an uncertainty factor of 100.

To our knowledge, risk assessments including exposure estimates for BHT from all sources and exposure pathways have not been performed. The extensive use of BHT necessitates a risk assessment for the Norwegian population. Therefore, the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics of the Norwegian Scientific Committee for Food and environment (VKM) proposed to perform a risk assessment of BHT that includes exposure estimations from several sources and exposure pathways.

Terms of reference

The overall aim of this opinion is to assess whether the exposure of BHT from foods, personal care products, indoor air and indoor dust constitute a health risk to the Norwegian population.

The sub-objectives are

- To calculate human BHT exposure from several sources with available concentration data.
- To evaluate the adverse effects of BHT in humans and animals via any relevant route of exposure and to characterise the hazard by using benchmark dose modelling if the ADI needs to be revised.
- To evaluate the scientific evidence through a weight of evidence (WoE) approach.
- To describe the uncertainty both qualitatively and quantitatively and to perform sensitivity analyses to identify the parameters that contribute most to the uncertainty.
- To identify and describe knowledge gaps.

The target population for this assessment is the adult Norwegian population, both sexes.

Assessment

1 Introduction

Butylated hydroxytoluene (BHT, E321) is a synthetic antioxidant. The substance is used to help preserve and stabilise the flavour, colour, freshness and nutritive value of foods and animal feed products. BHT can improve the stability of pharmaceuticals, fat-soluble vitamins, personal care products (PCPs), biomaterials, petroleum products, synthetic rubbers and plastics, and it serves as an antiskinning agent in paints and inks (EFSA, 2012; IARC, 1987; OECD, 2002; Wang et al., 2016b).

BHT is authorised as a food additive for use in fats and oils (only for the professional manufacture of heat-treated food), in frying oil and frying fat (excluding olive pomace oil), in lard, fish oil, beef, poultry and sheep fat. BHT is permitted in amounts up to 100 mg/kg fat. In addition, BHT is permitted in chewing gum alone or in combination with other antioxidants such as gallates, tert-butylhydroquinone and butylated hydroxyanisole at a maximum level of 400 mg/kg chewing gum (Lovdata, 2008). BHT is authorised for use up to 400 mg/kg in food supplements as defined in Directive 2002/46/EC (European Parliament). BHT is also authorised for use in feed for all species or categories of animals except dogs (European Commission, 2003). Thus, the presence of BHT in foods may be due to its use as food additive, by transfer from animal feed to food, by migration from food contact materials or from the environment.

The use of BHT in PCPs must follow the principle that cosmetic products must be safe when used under normal or reasonable forseeable conditions of use (Lovdata, 2013). Otherwise, there are no specific conditions for BHT use in PCPs. The presence of BHT in PCPs may be due to use as a preservative or due to migration from packaging materials.

EFSA has established an ADI for BHT of 0.25 mg/kg bw per day (EFSA, 2012). The ADI was based on a NOAEL of 25 mg/kg bw per day derived from two 2-generation studies in rats based on effects on litter size, sex ratio and pup body weight gain during the lactation period, using an uncertainty factor of 100.

A protocol for the risk assessment of BHT was developed (VKM, 2018) in which the scope and sub-objectives of the assessment were described. The protocol also includes the literature search strategy, the inclusion/exclusion criteria, the approach for evaluation of the quality of the included data, the methods used for exposure estimation and the evaluation of the uncertainty.

2 General information

The molecular formula of BHT (E321) is $C_{15}H_{24}O$ and the molecular weight is 220.36 g/mol. BHT is a lipophilic compound with an octanol/water partition coefficient (log P_{ow}) of 5.1, melting point of 70°C, and a topological polar surface area of 20.2 $Å^2$. The IUPAC name is 2,6-di-tert-butyl-para-cresol, the CAS Registry Number is 128-37-0 and the EINECS number is 204-881-4 (EFSA, 2012; IARC, 1987; OECD, 2002). BHT is classified by IARC in group 3 as not classifiable as to its carcinogenicity to humans (IARC, 2019).

The structural formula is presented in Figure 2-1.

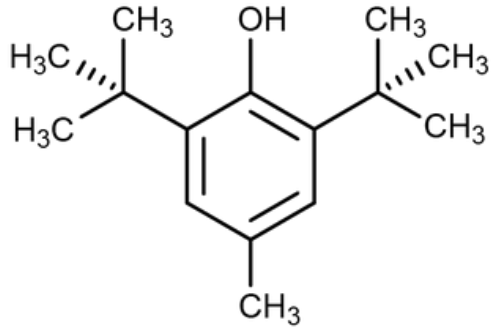

Figure 2-1. Structural formula of butylated hydroxytoluene (BHT, E321).

BHT is extensively used as an antioxidant in a wide range of products as described in the introduction (Chapter 1).

Potential oxidation products or transformation products of BHT is not included in the current assessment. Compared to other phenolic antioxidants such as BHA (butylated hydroxyanisole) and TBHQ (tert-butylhydroquinone), BHT shows relatively stronger volatilisation at elevated temperatures during e.g. food baking and frying (Nieva-Echevarria et al., 2015). Common routes of BHT oxidation include hydroxylation or hydroperoxylation at the C4-position (EFSA, 2012).

3 Hazard identification and characterisation

The hazard identification and characterisation steps were based on previous reports and risk assessments of BHT as well as articles retrieved from literature searches.

An overview of the sub-questions adressed in the hazard identification and characterisation steps is given in Table 3-1.

A full systematic procedure was applied to identify articles reporting on adverse health effects in humans and/or animals. A narrative approach was used in the studies on genotoxicity and toxicokinetics.

Table 3-1. Sub-questions addressed in the hazard identification and characterisation steps.

No.	Sub-questions	Approach
1	Is BHT exposure related to adverse health effects in humans? Identify target organs.	Systematic
2	Is exposure to BHT related to adverse health effects in animals? Identify target organs.	Systematic
3	Is BHT associated with changes at the molecular level such as mutation and other genotoxicity endpoints?	Narrative
4	What is the nature of any dose-response relationship between BHT and relevant endpoints in the target organs in human and/or animal studies?	Systematic
5	What is the ADME* in humans and in different animal species/strains?	Narrative
6	Is there a difference in ADME* between humans and animals?	Narrative
7	Are the included human/animal studies biased according to the defined criteria?	Risk of bias evaluation

*ADME - absorption, distribution, metabolism, excretion

3.1 Previous evaluations and assessments

Several evaluations and assessments of the safety of BHT have been performed. The latest is the re-evaluation by the European Food Safety Authority (EFSA, 2012). This assessment includes evaluations and assessments performed by the International Agency for Research on Cancer (IARC), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Organisation for Economic Co-operation and Development (OECD) and the Scientific Committee on Food (SCF) (EFSA, 2012; IARC, 1987; JECFA, 1996; OECD, 2002; SCF, 1989). EFSA established an ADI for BHT of 0.25 mg/kg bw per day. The ADI was based on the NOAEL of 25 mg/kg bw per day, which was derived from two 2-generation studies in rats, using an uncertainty factor of 100.

3.2 Articles

3.2.1 Literature search, publication selection and data extraction

Literature searches, from 2012 to the search date (see Appendix 10.1 for detailed description), were performed in Ovid MEDLINE(R), Embase, Web of Science, Cochrane Database of Systematic Reviews and Epistemonikos to retrieve publications on adverse health effects related to BHT exposure. The search strategy, including the time-period for the search, is included in the Appendix (Chapter 10.1). Two persons independently selected pulications according to the inclusion/exclusion criteria checklists (Appendix, Chapter 10.2.1). The first screening, based on analysis of title/abstracts, resulted in 29 articles. The full texts of the articles that passed the primary screening were retrieved for the secondary screening, with application of the very same inclusion/exclusion criteria. The secondary screening resulted in 13 articles. An overview of the publication selection is given in Figure 3.2.1-1.

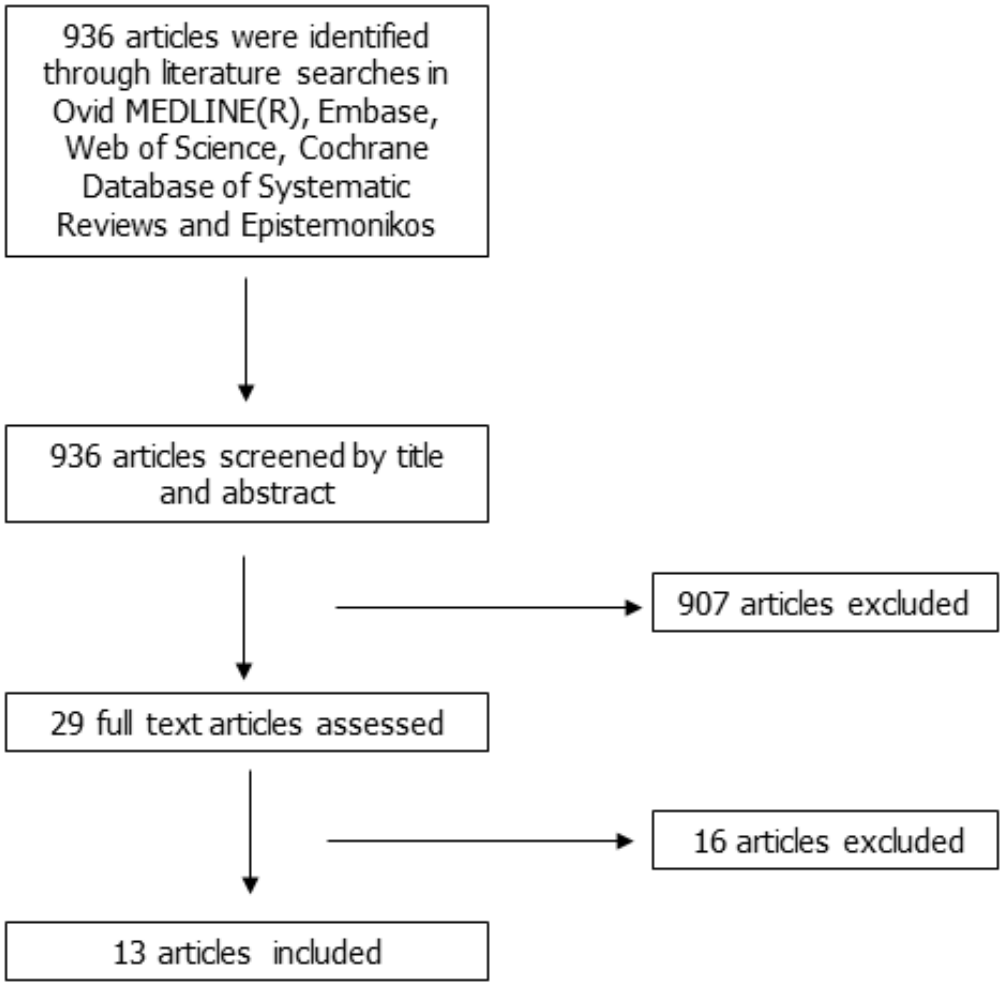

Figure 3.2.1-1. Flow diagram for publication selection (to retrieve articles on adverse health effects related to BHT).

Ten of the included articles were reviews and risk assessments. The reference lists of these articles were screened to check for additional relevant original studies, but no additional studies were identified. An overview of the three included original studies is given in Table 3.2.1-1.

Table 3.2.1-1 Overview of the included original studies.

Reference	Aim of the study	Study design /Participant characteristics	Country	Number in treatment group	BHT dose	Number in control group	Treatment of control group	Total study length	Main endpoints studied
Negritto et al. (2017)	Delineate the mechanism of phenol toxicity in yeast	Yeast	US	n=4	12 different concentrations were each tested in quadruplicates	-	Dimethyl sulfoxide (DMSO)	-	Levels of growth inhibition induced by the phenols; ability of X-phenols to induce DNA damage or breaks.
Pop et al. (2013)	Evaluate possible endocrine disruptive effects of BHT	Effects of BHT, at concentrations higher than the average diet exposure, on genital female tract was investigated using the immature rat uterotrophic assay Wistar female rats 17-21 days	Romania	Three experimental groups, each consisting of ten animals	75 mg/kg bw	Two control groups, each consisting of ten animals	17-beta estradiol (positive control) was given by subcutaneous injection at a dose of 20 µg/kg	Chemicals were administered once per day for three consecutive days in the morning between 9-10 a.m. Rats were sacrificed 24 hours after the last treatment	Absolute and relative uterus weights and endometrial epithelium thickness.

Reference	Aim of the study	Study design /Participant characteristics	Country	Number in treatment group	BHT dose	Number in control group	Treatment of control group	Total study length	Main endpoints studied
Ma et al. (2013)	Investigate interaction of BHT with DNA	*In vitro* study The binding properties of BHT with calf thymus DNA in simulated physiological buffer (pH 7.4) were investigated using ethidium bromide dye as a fluorescence probe using various spectroscopic techniques	China	-	0 to $3.27x10^{-5}$ mol/L				Intercalation of BHT molecules into the base pairs of ctDNA

Negritto et al. (2017) aimed to delineate the mechanism of phenol toxicity in yeast through testing of a series of phenols, including BHT. BHT showed no significant genotoxicity (no increase in deletion events) to *Saccharomyces cerevisiae* and caused only weak growth defects (the half maximal inhibitory concentration was 0.13 mM).

Pop et al. (2013) investigated possible endocrine disruptive effects of BHT using the immature rat uterotrophic assay. Wistar female rats, 17-21 days old, were given suspensions of BHT (75 mg/kg bw) for three consecutive days. Absolute and relative uterus weights were significantly decreased, whereas no significant effect on endometrial epithelium thickness was observed.

The binding properties of BHT, 0 to $3.27x10^{-5}$ mol/L, with calf thymus DNA were investigated using ethidium bromide dye as a fluorescence probe (Ma et al., 2013). BHT molecules were shown to intercalate into the base pairs of calf thymus DNA. This finding was supported by the observation of a competitive interaction between BHT and the ethidium bromide probe with calf thymus DNA.

Risk of bias, relevance of endpoint and weight of evidence were evaluated for the original study by Pop et al., (2013), but not for the two original studies on genotoxicity as the approach for studies on genotoxicity was narrative.

3.2.2 Evaluation of risk of bias

Risk of bias was evaluated for the study by Pop et al. (2013) according to (NTP/OHAT, 2015). In the evaluation of risk of bias, the following was included:

- Aspects that introduced a systematic difference between the control and the exposed group only (e.g. non-randomised allocation of animals to study groups).
- Aspects that potentially affected, to the same extent, control and exposed study groups (e.g. the reliability of the method used to test the outcome).

Two members of the project group performed the evaluation independently. The response options for each question were «Definitely low risk of bias (++)», «Probably low risk of bias (+)», «Probably high risk of bias (-)», «Definitely high risk of bias (--)». The results of the evaluation are presented in Table 3.2.2-1.

Table 3.2.2-1. Evaluation of risk of bias.

Reference	Question	Domain	Rating (++, +, -, --)
Pop et al. (2013)	Were experimental conditions identical across study groups?	Performance	++
	Were outcome data completely reported without attrition or exclusion from analysis?	Attrition	++
	Can we be confident in the exposure characterisation?	Detection	+

Reference	Question	Domain	Rating (++, +, -, --)
	Can we be confident in the outcome assessment?	Detection	+
	Were the statistical methods and the number of animals per dose group appropriate?	Other sources of bias	-
Conclusion			+ Probably low risk of bias

3.2.3 Evaluation of relevance of the endpoints for the target population

Two members of the project group independently evaluated the relevance of the endpoint endocrine disruptive effect for the human population studied by Pop et al. (2013). They concluded that the endpoint «uterus weight in rats» was considered to be relevant for an assessment of potential risks in humans. However, recent reports indicate that the use of diverse animal models and various endpoints might be more effective to characterise endocrine disruptive effects, thus limiting overreliance when using only one animal model (Patisaul et al., 2018).

3.2.4 Weighting the body of evidence (WoE)

To study the strenght of an association between BHT and a subsequent effect, an initial confidence rating of the included original studies was performed. The following four descriptors were used to determine this initial level of of confidence (NTP/OHAT, 2015):

- Controlled exposure conditions
- Exposure preceding the effect onset
- Outcome being assessed at individual level (i.e. not through population aggregate data)
- Presence of an appropriate comparison group

Fulfilment of all features received an initial rating of high confidence (++++). Lower ratings, i.e. moderate (+++), low (++) or very low (+), correspond to the number of features fulfilled. Considerations on whether the exposure preceded the outcome was done at internal validity level (RoB, see 3.1.2.3), which fulfilled this aspect. For the included randomised controlled trial (RCT) studies, the Panel considered that fulfilment of all features would receive an initial rating of high confidence (++++).

The further procedure for the evaluation of confidence in the evidence was a modified version from NTP/OHAT (2015), downgrading or upgrading the confidence in the evidence. Risk of bias, relevance of endpoints, unexplained inconsistency and imprecision downgrade the confidence in the evidence, whereas large effect (e.g. incidence, degrees of severity), dose-response relationship, consistency across study design (dissimilar populations, animal models, species or gender), consistency in direction of effect and confounding (if all relevant

confounders are described and considered) upgraded the evidence. The overall confidence in the evidence was graded into high confidence, moderate confidence, low confidence and very low confidence, and were defined as follows:

- High confidence (++++) in the association between exposure to the substance and the outcome. The true effect is highly likely to be reflected in the apparent relationship.
- Moderate confidence (+++) in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship.
- Low confidence (++) in the association between exposure to the substance and the outcome. The true effect may be different from the apparent relationship.
- Very low confidence (+) in the association between exposure to the substance and the outcome. The true effect is highly likely to be different from the apparent relationship. This statement may give the impression that a true effect is different from the one observed. However, an additional explanation is given in the OHAT Handbook (NTP/OHAT, 2015) (in Figure 2, OHAT Framework for Systematic Review and Evidence Integration, Step 6): where for low or no evidence for a health effect, the evidence is termed «inadequate». Furthermore, it is stated that «... a conclusion of «Very Low Confidence» suggests that further research is very likely to have an impact on confidence in the apparent relationship».

The results of the WoE evaluation are presented in Table 3.2.4-1.

Table 3.2.4-1. Weighting the body of evidence.

Endpoint: Endocrine disruptive effect									
	Elements triggering downgrading				**Elements triggering upgrading**				**Confidence level**
	Risk of bias	Relevance of endpoint (animal studies only)	Unexplained inconsistency	Imprecision	Large effect	Dose-response relationship	Confounding	Consistency	
Pop et al. (2013) **Initial rating: +++**	**No serious concern**	**No serious concern**	**Serious concern** For BHT the uterine weight was significantly lower, while the uterine wall thickness was significantly higher after BHT exposure. The increased thickness should result in higher uterine weight.	**Serious concern** The measurement of uterine wall thickness was not well described. Short study duration of only three days	**Medium changes** Significant decrease in uterus weight, and increase in uterine wall thickness	**No** Only one single concentration tested at level of 3x NOAEL	**No**	**Not applicable**	++ to +

The overall confidence in the evidence for each endpoint/group of endpoints was transformed to likelihood as shown in Table 3.2.4-2.

Table 3.2.4-2. Set of terms used to transform the final rating of confidence in the evidence per endpoint of all relevant randomised controlled trials (RCTs) to overall likelihood.

Likelihood of an association between BHT and the effect under consideration	Summary confidence range levels
Very likely	++++
Likely	From ++++ to +++
As likely as not	From +++ to ++
Unlikely	From ++ to +
Very unlikely	+

Since the confidence level in the study by Pop et al. (2013) was ++/+, an association between BHT and the reported effect was considered unlikely and the study was not used for the hazard identification and characterisation.

3.3 Absorption, distribution, metabolism and excretion (ADME)

According to EFSA (2012), absorption, distribution, metabolism and excretion (ADME) of BHT have been studied in mice, rats, rabbits, chickens, monkeys and humans.

BHT is rapidly absorbed from the GI tract after oral exposure, and we therefore assumed a 100% absorption of BHT in the GI tract. According to Lanigan et al. (2002), *ex vivo* and *in vivo* studies indicated that <4% of BHT penetrated the skin. However, the studies cited in Lanigan et al. (2002) have weaknesses leading to uncertainties with respect to the dermal absorption. Even though dermal application produces systemic exposures to BHT or its metabolites, the magnitude of internal exposure is lower than that seen in studies using the oral route.

BHT is generally distributed to the liver and to body fat, and accumulation in fatty tissue in rats have been reported. According to EFSA (2012), the accumulation of BHT in fatty tissue is higher in humans than rats.

The BHT metabolism is complex, and important species differences are likely, considering the differences reported in the literature. More than 40 metabolites have been identified. Oxidation of one or both of the tert-butyl groups of BHT, with a following glucuronidation, is seen as one of the main metabolites in humans. It is not known whether the BHT quinone methides, a compound likely to be responsible for lung toxicity in mice, is formed in humans.

After a single BHT dose (20 or 500 mg/kg bw) to mice, the half-life in the stomach, intestine, liver and kidney was 9-11 hours. When daily doses (20 mg/kg bw/day) were given to mice for 10 days, the half-life in blood, liver, kidney lung and testis was reported to be 5-15 days. A daily dietary dose of BHT in rats for 35 days resulted in a maximum concentration of BHT in fatty tissue after 10 days. EFSA (2012) did not report on the half-life of BHT in the fatty tissue. The half-life in humans was studied in two men who were given a single oral dose of

40 mg/kg [^{14}C] BHT. In the first 24 hours, 50% was excreted, followed by a slower excretion that occurred for the next 10 days. In total, 63-67% of the dose was excreted.

BHT is mainly excreted via urine and faeces, but while excretion in faeces is the dominant pathway for rats and mice, including enterohepatic circulation, the main excretion route in humans is via the urine. This is likely due to the size of the metabolites, and different cut-off in rats and humans regarding the molecular size that can be excreted in the urine.

3.4 Toxicological data

A systematic literature search was performed to identify publications indicating that the ADI established by EFSA needed to be revised. No such publications were identified. As a result, the ADI of 0.25 mg/kg bw per day established by EFSA derived from two 2-generation studies (EFSA, 2012), is used for the risk characterisation in the present assessment. Both studies are described in EFSA (2012). The short description is from EFSA (2012):

In the 2-generation study by Olsen et al. (1986), Wistar rats in groups of 60, 40, 40 and 60 per sex were given 0, 25, 108, or 276 mg BHT/kg bw per day (males) and 0, 26, 106 and 287 mg BHT/kg bw per day (females) in the diet. After 13 weeks the rats (F0) were mated. Offspring (F1) in groups of 100, 80, 80, and 100 per sex were given the same doses as the F1 generation, except for the highest dose that was lowered to 250 mg BHT/kg bw per day due to effects on the kidney. When the F1 rats were 144 weeks, the study was terminated. The number of litters with ten or more pups decreased significantly ($P<0.001$) with increasing BHT dose (10.9, 9.6, 10.3 and 9.1 number of pups), and at weaning the offspring showed a reduction of body weight compared to the control animals (7%/5%, 11%/10%, and 21%/16% for males/females). A dose-related increase in hepatocellular adenomas (males and females) and carcinomas (males only) of the mid and high dose group was observed, with a carcinoma incidence of 8-12/99 at the highest dose. Tumours were also found in other organs, but their incidence were not statistically significantly different from that in controls. The study was terminated when the rats in the F1 generation were 144 weeks old.

Based on the study by Olsen et al. (1986; described in the EFSA Opinion), EFSA concluded that based on the effects on litter size and pup body weight gain during the lactation period, in the reproduction segment of the study, the NOAEL for non-neoplastic effects was 25 mg/kg bw per day. This NOAEL also covered the observed increase in hepatocellular adenomas and carcinomas.

In the 2-generation study by Price (1994; described in the EFSA Opinion), Wistar rats, 6 males and 48 females aged 13 and 9 weeks, respectively, were given 0, 25, 100 or 500 mg BHT/kg bw in the diet per day for 3 weeks prior to mating. The litters were either culled or augmented to comprise eight pups and were fed BHT concentrations corresponding to the diets fed to their parents, with the exception that the highest dose was reduced to 250 mg/kg bw per day. At 22 months, the study was terminated. In the first 5 weeks of BHT administration, lower body weight gain was noted in males given the highest-dose. Body

weight gain in all other treatment groups was similar to that in controls for both males and females. At the sacrifice on day 20 of gestation, both absolute and relative liver weights of the dams were increased in a dose-related manner, statistically significant at the high dose. No effect of treatment was evident on reproductive parameters. There was a slight decrease, but not dose related, in the numbers of pups per litter in the low and high-dose groups. In the high-dose group, the body weights of the pups were significantly lower than controls at birth (10%), and at days 6 (12%) and 21 (21%) of lactation. A dose-dependent increased mortality (2%, 8%, 12% and 15%) of the pups were observed, and body weights of the F1 males were lower in the high-dose group compared with controls. A dose-related increase was observed in relative, but not absolute liver weights at the high dose. At 22 months, there was a higher incidence of eosinophilic and basophilic foci in the liver of the high-dose group. The study by Price (1994) supported the NOAEL of 25 mg BHT/kg bw per day derived from the Olson study (1986), where effects on the litter size and pup body weight were confirmed. No increase in hepatocellular adenomas and carcinomas was reported in Price (1994).

3.5 Summary of the hazard identification and characterisation

The hazard identification and characterisation are based on previous reports and risk assessments of BHT and articles retrieved from literature searches. The most recently published opinion on BHT is the re-evaluation performed by EFSA (2012). EFSA established an ADI for BHT of 0.25 mg/kg bw per day. The ADI was based on a NOAEL of 25 mg/kg bw per day derived from two 2-generation studies in rats based on dose-related effects on litter size and pup body weight gain during the lactation period, using an uncertainty factor of 100. This NOAEL also covered the observed increase in hepatocellular adenomas and carcinomas. Note that the BHT metabolism is complex and important species differences are likely. On main metabolites in humans, one or both of the BHT tert-butyl groups are oxidated followed by glucuronidation. The half-life in humans was studied in two men given a single oral dose of BHT; 50% was excreted the first 24 hours, followed by a slower excretion for the next 10 days. In total, 63-67% of the dose given was excreted. BHT has been reported to accumulate in fatty tissue (EFSA, 2012).

Systematic literature searches were performed to identify publications potentially indicating that the ADI established by EFSA needed to be revised. Thirteen articles of the 936 obtained from the literature search were included, and only three were original studies. Risk of bias, relevance of endpoint and weight of evidence were evaluated for one of the original studies (Pop et al., 2013), but not for the two original studies on genotoxicity as the approach for studies on genotoxicity was narrative. The results reported by Pop et al. (2013) did not indicate that the ADI established by EFSA needed to be revised.

Since none of the included studies indicated a need for revision of the ADI established by EFSA (2012), the Panel concluded that the ADI of 0.25 mg/kg bw per day will be used in the risk characterisation.

4 Exposure

An overview of the sub-questions addressed in the exposure assessment is given in Table 4-1.

Table 4-1. Exposure assessment sub-questions.

No.	Sub-questions
1	What are the exposure levels and sources of BHT from foods?
2	What are the exposure levels and sources of BHT from personal care products?
3	What are the exposure levels and sources of BHT from indoor dust?
4	What are the exposure levels and sources of BHT from indoor air?
5	What is the total internal exposure to BHT?
6	What is the total exposure to potential harmful BHT/BHT metabolites?

BHT reaching the physical barriers in the body was defined as external exposure. The total amount of absorbed BHT was defined as total internal exposure. All potential toxic internal BHT (BHT and/or toxic BHT metabolites) was defined as total exposure to potential harmful metabolites. In order to estimate external exposure, total internal exposure and total exposure to potential harmful metabolites (Figure 4-1), the following choices were made in accordance with the protocol (VKM, 2018).

The BHT exposure was estimated for adults, based on BHT concentrations in food, PCPs and indoor dust, data on consumption (food, PCPs and indoor dust) and inhalation (indoor dust and indoor air), individual body weights, and data on absorption of BHT from the gastrointestinal tract/skin/lungs:

- Concentration; data on BHT in foods, PCPs and indoor dust, identified through literature searches and in previous reports, were compiled in a database. Data on BHT in indoor air were not identified, and the exposure level from indoor air was therefore not estimated (subquestion 4).
- Consumption; the national food consumption survey Norkost 3 (n=1787) provided data on individual food consumption (Totland et al., 2012), and the human biomonitoring study EuroMix (n=144) provided individual data on both food consumption and use of PCPs (Husoy et al., 2019). For consumption of indoor dust, standard exposure values from EPA were used.
- Body weight; to calculate BHT exposure per kg body weight per person, individual body weights were used for the studies Norkost 3 and EuroMix. Body weights were self reported in these studies. If body weights were not given in Norkost 3, mean body weights were imputed; 69.2 kg for women (n=29), and 86.2 kg for men (n=1). The mean body weight of 65 kg was used for three women in the EuroMix study.
- Absorption from the gastrointestinal tract/skin/lungs; absorption factors were derived from the literature.

The exposure was estimated for «realistic» and «high» scenarios (Table 4-2). In the «realistic» exposure scenario we aimed to use the concentration data considered the most

realistic for the Norwegian exposure, whereas more conservative choices were used for the «high» exposure scenario. In the «realistic» food exposure scenario, main food groups were divided into sub-groups to specify the occurrence estimate for the food groups «cereals, bread, and cake», and «fish and seafood». Only concentration data from Europe and USA that fulfilled the quality criteria were applied. In the «high» exposure scenario, main food groups, and all concentration data that fulfilled the quality criteria, regardless of country of origin, were applied. For consumption of indoor dust, a central tendency exposure factor was used in the «realistic» scenario whereas the upper percentile was used in the «high» exposure scenario (EPA., 2011). The 50 percentile for the applied PCP, as reported in studies from Europe and USA, were used in the «realistic» scenario, whereas maximum amounts were included in the «high» scenario (Ficheux et al., 2016; Garcia-Hidalgo et al., 2017; Loretz et al., 2006). Thus, the «high» exposure scenario is a worst-case estimation representing a risk assessment for potentially high consumers.

Table 4-2. An overview of the «realistic» and «high» exposure scenarios.

		«Realistic» exposure scenario	**«High» exposure scenario**
BHT concentrations	Foods	Mean of all concentration data from Europe and USA	Mean of all identified concentration data
	PCPs	Mean values (only articles from Europe and USA included), values <LOD were replaced with 0 *	Maximum values (articles from Europe, USA and Asia included), values < LOD were replaced by LOD *
	Dust	Greek data (Wang et al., 2016a)	Japanese data (Wang et al., 2016a)
Use/consumption	Foods	Survey data (amount consumed (g))	Survey data (amount consumed (g))
	PCPs	Survey data (frequency of use) 50 percentiles of amounts used (only articles from Europe and USA included) **	Survey data (frequency of use) 95 percentiles of amounts used (only articles from Europe and USA included) **
	Dust	Central tendency exposure factors (EPA; 2011)	Upper percentile exposure factor (EPA, 2011)

* Data from Europe and USA were prioritised over Asian data (Akkbik et al., 2011b; Alvarez-Rivera et al., 2014a; Boussenadji et al., 1993; Capitán-Vallvey et al., 2002; Celeiro et al., 2014; Myers et al., 2015; Sanchez-Prado et al., 2010).

**The French study was prioritised over the Swiss study: the Swiss study was prioritised over the US study (Ficheux et al., 2016; Garcia-Hidalgo et al., 2017; Loretz et al., 2006).

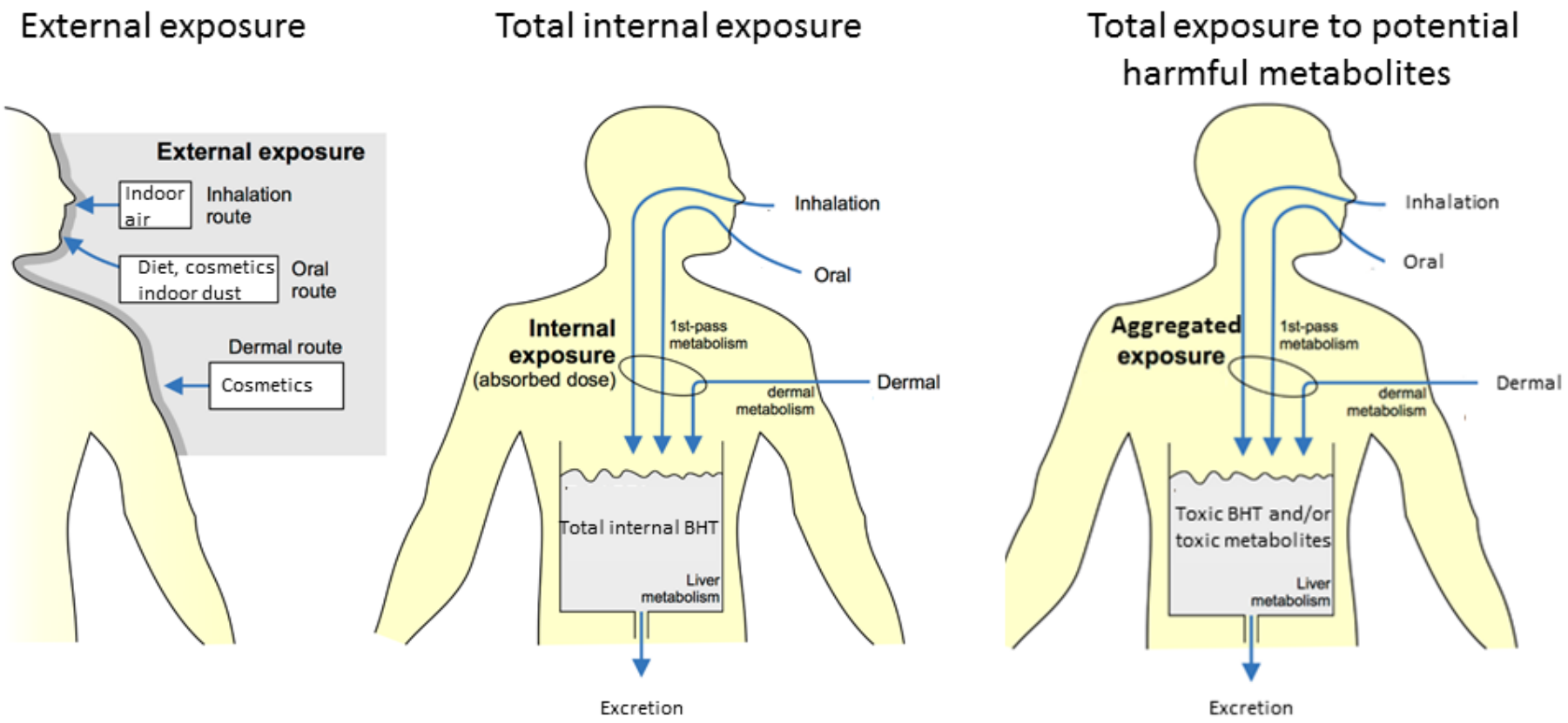

Figure 4-1. An overview of external exposure, total internal exposure (i.e. absorbed dose) and total exposure to potential harmful metabolites (toxic dose) (modified from (EFSA CEF Panel, 2015). For the external exposure through the oral route we differentiated between exposure from dust, diet, and personal care products.

4.1 BHT concentrations in foods, PCPs and indoor dust

Five reports with relevant BHT concentration data were included in the current assessment. In addition, literature searches were performed to retrieve articles with BHT concentration data. A BHT concentration data base was created from the included literature. An overview of the BHT concentrations in foods and PCPs is given in Tables 4.2.1-1 and 4.3.5-1, respectively.

4.1.1 Reports

Exposure of children and unborn children to selected chemical substances. Survey of chemical substances in consumer products No. 158 April 2017, Ministry of Environment and Food of Denmark (Danish Environmental Protection Agency et al., 2017)

The Danish Environmental Protection Agency assessed whether there may be a risk of the overall exposure of children under 3 years and pregnant women/unborn children to endocrine disrupting substances and chronic neurotoxic substances. The content of BHT was measured in a variety of PCPs, and ranged from (in weight %) 0.0029 to 0.064 in body oil, <0.0002-0.23 in body lotion, 0.0071-0.22 in face cream, 0.0009-0.32 in sunscreen/after sun and 0.052-0.23 in deodorants. It was concluded that «*Among the evaluated substances, the most significant endocrine disruptors to which children under 3 years and pregnant women/unborn children may be exposed are dioxins/PCBs, phthalates (DEHP, DBP, DiBP), bisphenol A, BHA and BHT*».

Report to the Swedish EPA (the Health-Related Environmental Monitoring Program) Phenolic substances in food – analytical survey of 11 phenols in Swedish Market Basket samples from 1999, 2005 and 2010 (Livsmedelsverket et al., 2014)

The report included food samples for analyses taken from the sample bank of Market Basket samples at the Swedish National Food Agency, comprising samples obtained in 1999, 2005 and 2010. Final analytical determination was made by GC-MS/MS. BHT levels in several foods were determined, including cereals, pastries, dairy, eggs, sugar sweets, meat, fats, fish, potatoes, vegetables, fruit, and beverages. The limits for detection (LOD) for BHT given as ng/g fresh weight, was 0.1 for 10 g, 1 for 5 g and 1 for 1 g fat samples. The limits for quantification (LOQ), given as ng/g fresh weight, was 1.5 for 10 g, 3 for 5 g and 15 for 1 g fat samples. For beverages (50 mL), LOD was 0.1 and LOQ was 0.3.

Screening program 2014. Organic phosphites, selected PBT substances and non-target screening (Norwegian Environment Agency et al., 2014).

Upon assignment from the Norwegian Environment Agency, the Norwegian Institute for Water Research (NIVA) and the Norwegian Institute for Air Research (NILU) performed a screening of organic phosphites and selected persistent, bioaccumulative and toxic compounds in freshwater and marine environments, including BHT. The analysis was performed using an Agilent 5973MSD GC/MS system and a Restek Sil5-MS GC-column. BHT was determined in shrimps, herring, cod liver, mysis, whitefish and brown trout.

Monitoring Programme for Residues of Therapeutic Agents, Illegal Substances and other Undesirable Substances in Farmed Fish, Annual Report 2010, NIFES (NIFES et al., 2011)

BHT was analysed using reverse phase HPLC and fluorescence detection. The concentration range for BHT in farmed salmon fillets was <LOQ-8.9 mg/kg, the mean concentration was 3.7 mg/kg fillet. The concentration of BHT in farmed trout fillet was 0.6 mg/kg wet weight. The LOD, wet weight in muscle in µg/kg was 14. The LOQ, wet weight in µg/kg, was 45. The results showed that BHT was carried over from the feed to fish fillets.

Screening of selected new organic contaminants 2004. Brominated flame retardants, perfluorinated alkylated substances, irgarol, diuron, BHT and dicofol (NIVA et al., 2005)

The results of a screening survey on contaminants, including BHT, in the Norwegian environment were presented in the report. The survey was carried out on behalf of the Norwegian Pollution Control Authority by NIVA, NILU and the Norwegian Centre for Soil and Environmental Research. The analysis was performed using an Agilent 5973MSD GC/MS system and a Restek Sil5-MS GC-column. The concentration of BHT in blue mussels and cod liver was analysed. None of the blue mussel samples had BHT concentrations above the LOD. For cod liver, the observed concentrations of BHT were 1.4 and 3.1 ng/g wet weight. The LOD was 0.1-0.2 ng/g wet weight.

4.1.2 Articles

Literature searches were performed to retrieve publications with data on BHT concentrations in foods, PCPs, indoor air and indoor dust. The first searches identified 3711 articles, the second identified 708 articles. For search strategies, see Appendix 11 (Chapter 11.1.1 and 11.1.2). Two persons independently selected pulications according to the inclusion/exclusion criteria checklists (Chapter 11.2.1). First, titles and abstracts were screened. Next, the full texts of the articles that passed the primary screening were retrieved for screening against the inclusion/exclusion criteria checklist. The data quality of the included articles was evaluated and rated. This evaluation included rating of the sample extraction method, the instrumental analysis, the validation of the method and the data presentation. The rating was deduced according to a scale of rates from 1 (lowest quality) to 5 (highest quality). The individual rates were weighted as follows to get the total rate: 1/5 from sample extraction, 1/5 from instrumental analysis, and 3/5 from validation and data presentation. Only articles with a total rate of ≥ 3.5 was used for the exposure assessment. The rating of all the included studies is shown in Chapter 11.2.2.

The final database consisted of data from the included reports and data from 29 articles; 20 which reported concentrations in food-items, nine which reported concentrations in PCPs and two which reported concentrations in dust. An overview of the publication selection is given in Figure 4.1.2-1.

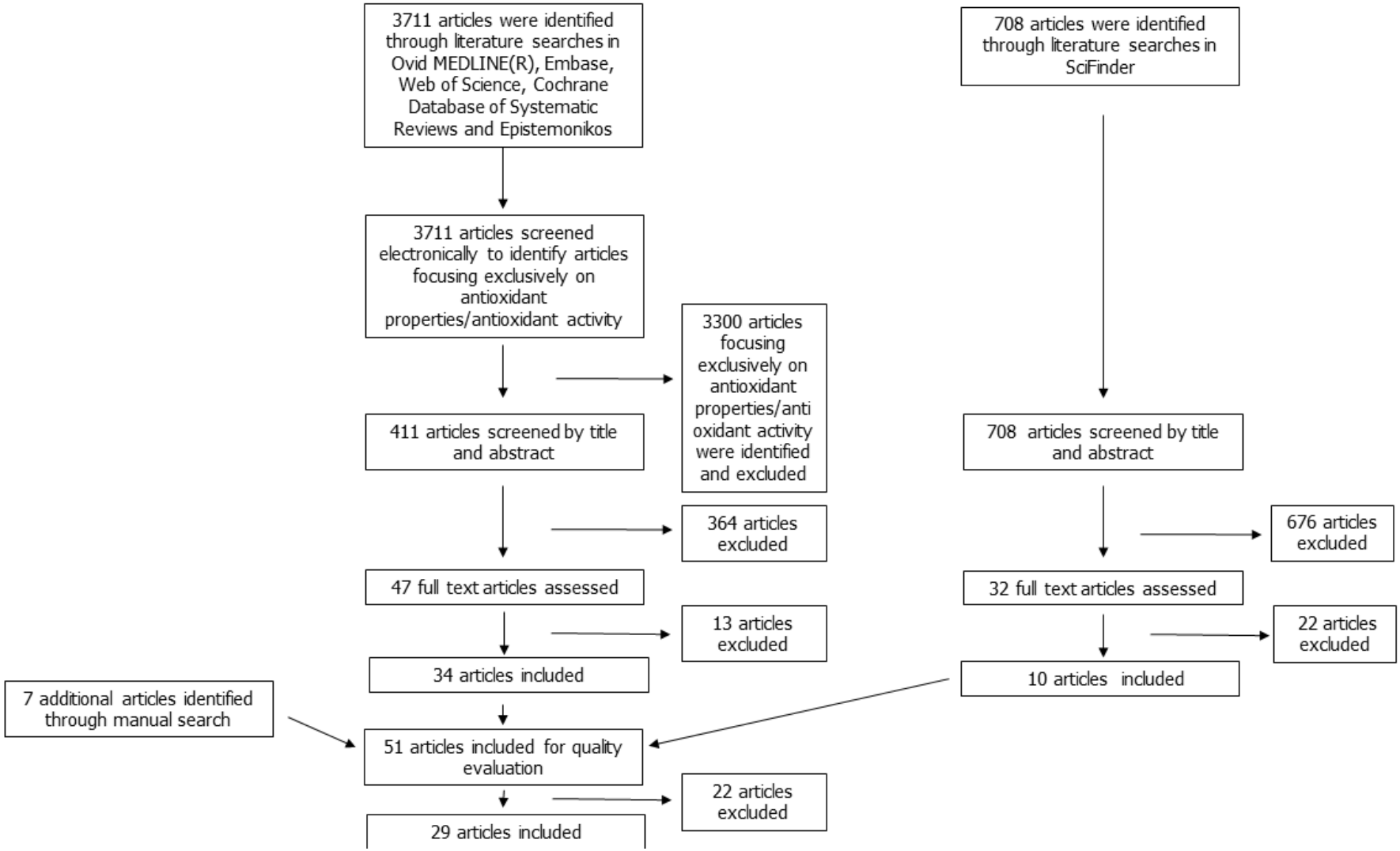

Figure 4.1.2-1. Flow diagram for publication selection aiming to retrieve articles with data on BHT concentrations in foods, PCPs, indoor air and indoor dust.

Concentrations on BHT in indoor air were not identified; therefore, it was not possible to include estimations of BHT exposure from indoor air in the assessment (subquestion 4).

4.2 External BHT exposure from foods and beverages

4.2.1 BHT in foods and beverages

In the «realistic» exposure scenario only concentrations from Europe and USA were included. The number of BHT datapoints included in this scenario were 259. Of the 20 food groups with assigned BHT values, 11 had a sample number below ten. The food group «cereals, bread and cakes» was divided in the sub groups «bread and cereals» and «cakes and biscuits», and «fish and seafood, wild» were divided in the sub food groups «fish, wild», «fish, freshwater», «shrimps and mussels», and «fish liver» (Table 4.2.1-1).

All BHT concentrations were included in the «high» exposure scenario estimations, regardless of country of origin. The number of BHT datapoints included in this scenario were 412. Of the 21 food groups with an assigned BHT value, 14 had a sample number below ten. Furthermore, the group «cereals, bread and cakes» was treated as one food group, and «fish and seafood, wild» was treated as one food group (Table 4.2.1-1). This implies that all foods in the given food group gets the same concentration.

The food groups «vegetable cream», «cheese», «margarine and butter», «mayonnaise», «fish oils», and «starchy snacks» were only included in the «high» exposure scenario due to lack of concentration data from Europe and USA. The food groups «various oils», and «chewing gum» had concentration values both from within and outside Europe/USA; therefore, the concentration values used for the «high» and the «realistic» scenarios were different. For the other food groups (Table 4.2.1-1), the BHT concentrations were the same for both the «realistic» and the «high» exposure scenarios.

In the «high» and the «realistic» exposure scenarios, the BHT concentrations were given as lower bound, medium bound and upper bound concentrations (Chapter 11.3). The lower bound was calculated by substituting values below the limit of detection (LOD) or limit of quantification (LOQ) for an analytical method with the number zero. The medium bound was calculated by substituting values below the LOD or LOQ with values set to half of the LOD or LOQ. The upper bound was calculated by substituting values below the LOD or LOQ with values equal to the LOD or LOQ. Concentration values above LOD/LOQ were kept unchanged.

Lower, upper and middle bound concentrations were not very different for most of the foods (Table 4.2.1-1), and had little impact on exposure estimates (not shown). The following analyses were based on middle bound concentrations for the «realistic» or «high» exposure scenarios.

Table 4.2.1-1 BHT content in different foods and food groups, µg/kg wet weight.

Food group	n	Lower bound	Middle bound	Upper bound
Cereals, bread and cakes[1]	11	2.1	15.8	29.4
Bread and cereals[2]	4		2.6[a]	
Cakes, biscuits[2]	5	2.6	2.9	3.2
Instant noodles[1,2]	1		0.7[a]	
Potatoes[1,2]	4	0.5	0.6	0.8
Vegetables[1,2]	5	0.1	0.3	0.5
Fruit[1,2]	4	1.5	1.5	1.6
Meat, meat products[1,2]	6	0.1	0.3	0.5
Pepperoni[1,2]	14		23586[a]	
Fish and seafood, wild[1]	76	1.5	1.6	1.6
Fish, wild[2]	15	1.6	1.6	1.7
Fish, freshwater[2]	24	0.9	0.9	0.9
Shrimp and mussles[2]	19	0.5	0.5	0.6
Fish liver[2]	18	3.4	3.5	3.5
Fish, farmed[1,2]	60	2644	2645	2646
Egg[1,2]	4	0.3	0.5	0.6
Dairy[1,2]	26		249[a]	
Milk, goat[1,2]	8		147[a]	
Coffee creamer[1,2]	1		0.7[a]	
Vegetable cream[1]	9		45500[a]	
Cheese[1]	2		71900[a]	
Margarine and butter[1]	49		92039[a]	
Various oils[1]	53	43138	43153	43168
Various oils[2]	14	6.2	6.2	6.2
Mayonnaise[1]	6		48117[a]	
Fish oil[1]	5		144140[a]	
Sweets, chocolate[1,2]	4		3.9[a]	
Chewing gum[1]	35		218232[a]	
Chewing gum[2]	10		135132[a]	
Starchy snacks[1]	7		46200[a]	

[1] Used in «high» exposure scenario: all concentration data that fulfilled the quality criteria, regardless of country of origin.
[2] Used in «realistic» exposure scenario: concentration data from Europe and USA that fulfilled the quality criteria.
[a] All analysed values were above LOQ.

4.2.2 Intake of foods and beverages

Food intake from the Norkost 3 survey and the EuroMix study was used for the exposure estimations (Husoy et al., 2019; Totland et al., 2012).

The national dietary survey Norkost 3 was conducted in 2010/2011, and 1787 adults (925 women and 862 men) aged 18-70 participated (Totland et al., 2012). Norkost 3 was based on two 24-hour recalls by telephone surveys, performed at least one month apart. Food

portions were presented in household measures or estimated from photographs. Norkost 3 did not include use of PCPs.

EuroMix is a biomonitoring study (Husøy et al., 2019). The participants were recruited among employees from governmental institutes and authorities, and universities in the counties Oslo and Akershus in Norway between September 2016 and November 2017. The study population of 144 consisted of 100 females aged 24-72 years and 44 males aged 25-72 years. The recording and sampling period consisted of two times 24 hours, with 2-3 weeks between the sampling periods. During the two sampling periods, the participants were asked to fill in a weighed food diary, a cosmetic diary and a questionnaire with personal information. The participants were instructed to weigh and record all intakes of food and beverages for 24 hours. The participants did not record the amount of PCP products applied in the dairies, only the frequency.

The EuroMix population represents a healthy group of Norwegians with a high level of education whereas Norkost 3 is a national food consumption survey more representative for the general population (Husoy et al., 2019; Totland et al., 2012).

4.2.3 Exposure estimates from foods and beverages

The external exposure of BHT from diet, normalised by bodyweight (bw) was summed up for all foods and beverages on an individual level:

External BHT exposure from diet (µg/kg bw per day) = Amount of food and drink consumed (g/day) x BHT concentration (µg/g) / individual bw (kg)

External BHT exposure from dietary intake was estimated using both Norkost 3 and EuroMix. For both studies, individual exposures were calculated for «realistic» and «high» exposure scenarios using summary statistics on the observed individual means (OIM) (Table 4.2.3-1). This is the classical approach for exposure estimation. In the «high» exposure scenario, the estimated exposure was 1-2 orders of magnitude higher than in the «realistic» exposure scenario.

Table 4.2.3-1. External exposure to BHT from foods and beverages based on observed individual means (OIMs) and middle bound concentrations.

Survey – exposure scenario	Mean	5 percentile	Median (50 percentile)	95 percentile
	µg BHT/kg bw per day			
EuroMix (n=144) – «realistic»	1.6	0.09	1.0	4.7
EuroMix (n=144)– «high»	71	12	56	188
Norkost 3 (n=1787) – «realistic»	2.5	0.14	1.6	8.0
Norkost 3 (n=1787) – «high»	75	19	65	164

The mean contribution of BHT from foods and beverages, in µg BHT/day and in percentage, is shown in Table 4.2.3-2. The mean contribution from the food groups «milk, cream, ice cream», «chewing gum» and «fatty fish» is approximately similar for the «high» and «realistic» exposure scenarios and ranges from 30 to 119 µg BHT per day. The mean contribution from the food groups «cheese» and «margarine and butter» is around 2000 µg BHT per day for the «high» exposure scenario, whereas it is not included in the «realistic» estimates. BHT is not authorised for use in cheese in EU (Directive No 95/2/EC). Although BHT is permitted as an additive in amounts up to 100 mg/kg fat in frying fat/margarine and frying oils, excluding olive oil, we did not identify any studies reporting concentrations of BHT in these foods in Europe/USA. In 2012 the industry did not report any use of BHT in frying oil and fat (EFSA, 2012).

If «cheese» and «margarine and butter» in Norway contain BHT, whether it be as additive or transferred from feed, the «realistic» exposure scenario leads to underestimation. For chewing gum, we assumed that all BHT from the chewing gum was absorbed. This is very likely an overestimation (Lin et al. 2003; Nunn 1991; Verhagen et al. 1991).

Table 4.2.3-2 Contribution of BHT from different food groups to the estimated «realistic» and «high» BHT exposure (in %). Consumption is based on Norkost 3.

Dietary sources	Contribution of different food groups to the estimated mean «realistic» BHT exposure	Contribution of different food groups to the etimated mean «high» BHT exposure
Cheese	na	46%
Margarine and butter	na	41%
Fish oil	na	5%
Milk, cream, ice cream	43%	3%
Chewing gum	40%	2%
Fatty fish	17%	1%

na: No concentration data from Europe/USA.

In the «realistic» exposure scenario the two food groups «milk, cream, ice cream» and «chewing gum» are the main BHT sources. In the «high» exposure scenario, the two food groups «cheese» and «margarine and butter» are the main BHT sources.

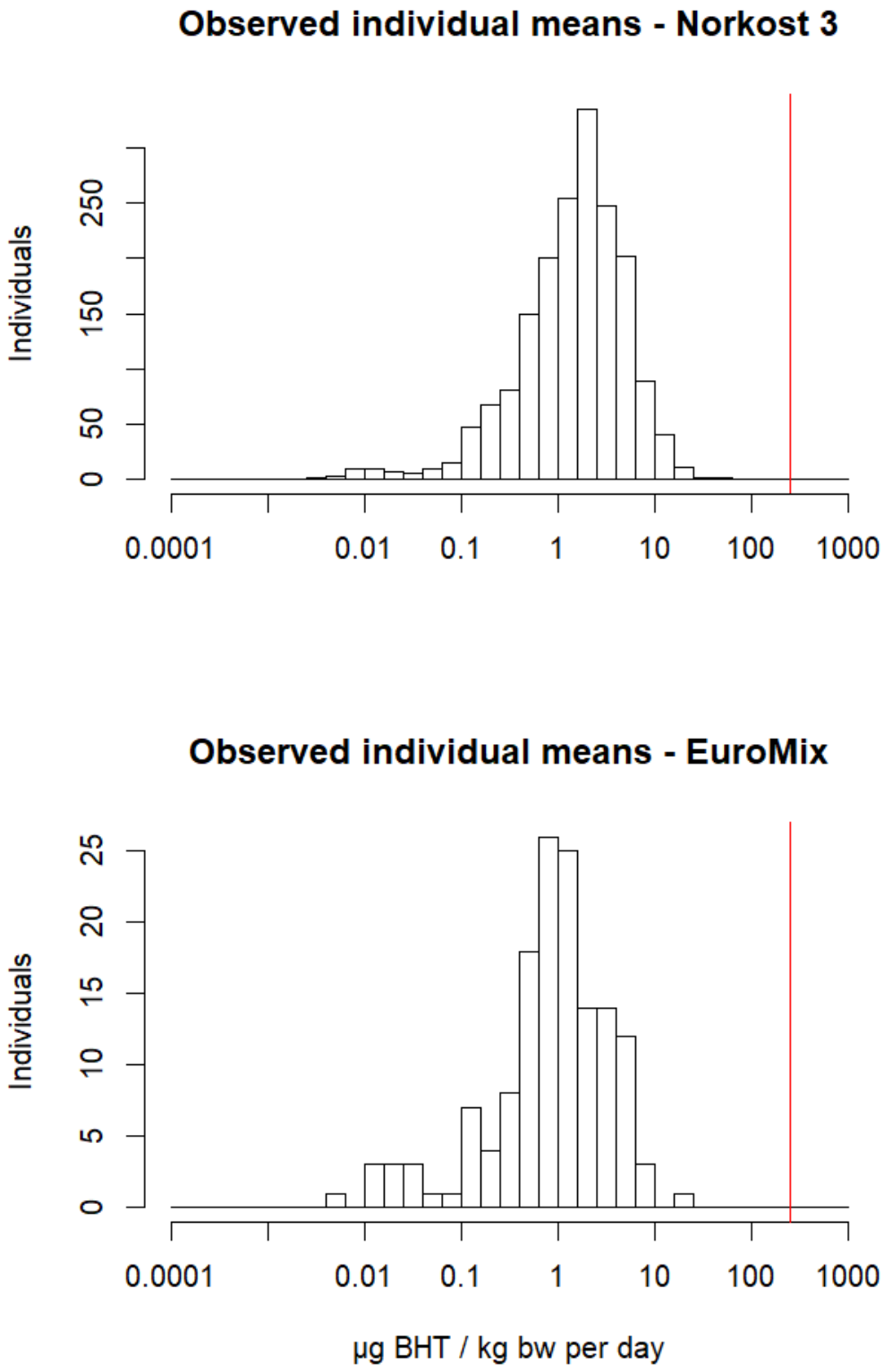

Figure 4.2.3-1. Histograms of observed individual mean exposures from diet using the «realistic» middle bound exposure dose (in µg BHT/kg bw per day) in Norkost 3 (Totland et al., 2012) and EuroMix (Husøy et al., 2019). The red line indicates the ADI at 250 µg/kg bw per day. Note the logged x-axis.

4.3 External BHT exposure from PCPs

PCPs were divided in product categories as predefined in EuroMix (Husøy et al., 2019). Only products used by the EuroMix participants for which concentration data had been found were included in the exposure estimation.

4.3.1 Frequency of use

In EuroMix, the frequency of use was recorded in a diary which allowed for detailed description of time of application and brand names of the PCPs used. The reported frequencies were used in both the «realistic» and «high» exposure scenarios.

4.3.2 BHT in PCPs

Concentrations of BHT in PCPs were obtained from the literature (see Chapter 4.1). When multiple data were available for a product, data from Europe and USA were prioritised based on the assumption that products available in Europe and USA are similar to products on the Norwegian market. Other concentration data were only used if no data from Europe and USA were available.

For the «realistic» exposure scenario, the mean BHT concentrations were used and the non-detects were replaced by 0. For the «high» exposure scenario, the highest BHT concentrations were used and the non-detects were replaced by the LOD value.

Concentration data for BHT in facial moisturiser and mouthwash were not identified. These products were reported used by the EuroMix participants, but not included in the exposure assessment due to the lack of concentration data.

4.3.3 Amount per application

PCP amounts used per application were not recorded in the EuroMix study and had to be obtained from the literature. Only publications reporting amounts used per application were considered, and those with separate data for men and women were prioritised. If multiple data on amounts used per product were available, we assumed that Norwegian PCP use might be closest to other European countries, and the data were prioritised as follows: 1) French, 2) Swiss, 3) USA and 4) Japanese. The French data by Ficheux et al. (2016) were prioritised over the Swiss data by Garcia-Hidalgo et al. (2017) because the weight of PCP products before and after use was reported, which we considered being a more precise metod than the picture method used by Garcia-Hidalgo et al. (2017). Note that the amount of product used per application in some cases can be sex-specific, e.g. men use more shower-gel and less shampoo than women do. If the amount applied was measured for more than one product in a category within a study, the mean of the 50-percentile and the 95-percentile were used for the «realistic» and the «high» exposure scenarios, respectively (Table 4.5.3-1), from that study.

Data for amount applied of antibacterial hand sanitisers were not identified. In the exposure estimations, we assumed that the amount applied was similar to the amount applied of hand cream.

4.3.4 Retention factors (RFs)

The retention factor (RF) is the fraction of a PCP available for uptake after application. Dermal and oral RFs depend on how products are applied (i.e. leave-on or rinse-off products) and are therefore given for product categories and are independent of the chemical. The mean values for the RFs were adopted from the Scientific Committee on Consumer Safety Notes of guidance (SCCS, 2018) and Dudzina et al. (2015), and are shown in Table 4.3.5-1.

4.3.5 Exposure estimates from personal care products (PCPs)

The external BHT exposure from PCPs, normalised by body weight (bw) was calculated using the following equation, summing over all products:

External BHT exposure from PCP (µg / kg bw per day) = Frequency of application (per day) x Amount per application (g) x BHT concentration (µg/g) x Retention factor (oral and/or dermal) / Individual bodyweight (kg)

An overview of the parameters used to estimate exposure from PCPs is given in Table 4.3.5-1. In the table, the realistic and high amount applied per application (for males and females), the realistic and high concentrations, and the retention factors for each product category are given. Lastly, the percentage of users and mean number of applications per day (for users) are given.

Table 4.3.5-1. The parameters used to calculate BHT exposure from PCPs. A detailed description of the parameters are given in 4.3.1, 4.3.2, 4.3.3 and 4.3.4. The last two columns show the fraction of individual-days with usage of the product as well as mean number of applications.

Product category	Expoure route	Realistic amounts per application [g]		High amounts per application [g]		BHT concentrations [µg/g]		Retention factors		Usage in EuroMix	
		Females	Males	Females	Males	Realistic	High	Dermal	Oral	Users (%)	Mean number of applications per day for users
Shower gel	Dermal	8	8.5	23.2	26.2	0.16	0.16	0.01	–	75.7	0.9
Shampoo	Dermal	8.1	5.1	25.3	13.9	0	4.1	0.01	–	61.1	0.7
Conditioner	Dermal	7.5	5.2	27	7.2	71.1	71.1	0.01	–	41.7	0.7
Deodorant	Dermal	0.8635	0.96375	2.5549	2.67945	269.78	700	1.00	–	86.1	1.0
Facial cleanser	Dermal	2.7287	2.789	8.0408	6.753	85.2	85.2	0.01	–	41.7	1.1
Body lotion	Dermal	7.55	5.1	23.55	19.6	285.734	2201	1.00	–	36.8	0.8
Anti-wrincle cream	Dermal	0.512	0.725	1.8997	0.7708	13.405	26.81	1.00	–	9.7	1.0
Sunscreen	Dermal	1.45	2.35	7.9	4.8	7.4225	14.5	1.00	–	13.2	0.7
Toothpaste	Oral	1.085	1.4155	3.004	2.8143	200	200	–	0.20	98.6	1.7
Lip gloss/ stick/balm	Oral	0.0125	0.02	0.0357	0.0458	1201.88	2996	0.10	0.90	38.2	1.8
Foundation	Dermal	0.091	0.6	0.370725	1.2	50	100	1.00	–	27.8	0.8
Intimate soap	Dermal	2	–	6.5	NA	0.16	0.16	0.01	–	4.9	0.6
Hand cream	Dermal	0.877	1.39	2.734	3.0622	187.76	354.24	1.00	–	22.2	1.3
Foot cream	Dermal	2.734	3.312	8.3724	8.4868	187.76	354.24	1.00	–	4.9	0.6
Hair styling products	Dermal	2.8653	1.9295	8.4952	6.5691	183.33	220	0.10	–	18.8	1.0
Hair treatment rinse off	Dermal	10.8	–	37.7	–	183.33	220	0.01	–	5.6	0.7

Product category	Expoure route	Realistic amounts per application [g]		High amounts per application [g]		BHT concentrations [µg/g]		Retention factors		Usage in EuroMix	
Eye make-up products	Dermal	0.0068	–	0.02285	–	34.5	34.5	1.00	–	38.2	1.2
Rouge and powder	Dermal	0.0093	–	0.0349	–	34.5	34.5	1.00	–	14.6	0.8
Make-up remover	Dermal	2.0114	0.3	5.3226	0.8	43.9	43.9	1.00	–	6.2	0.7
Shaving products	Dermal	7.5333	2.82	25.3667	10.04	30.6	30.6	0.01	–	7.6	0.7
Antibac	Dermal	0.877	1.39	2.734	3.0622	200	200	1.00	–	3.5	6.9
Oils	Dermal	1.8012	2.0975	3.9967	9.007	863.33	1540	1.00	–	4.9	0.7
Handsoap	Dermal	1.9875	2.9	4.8952	7.261	31,3	93,3	0.01	–	95.1	9.1

Oral and dermal external exposure to BHT through PCPs were estimated for the «realistic» and the «high» exposure scenario for all individuals in the EuroMix study (Table 4.3.5-2). To quantify the different sources of BHT from PCPs, we summed up exposure from each category across all individual-days for dermal exposure.

Table 4.3.5-2. Oral and dermal external exposure to BHT through PCPs. Exposures are observed individual mean using parameters for «realistic» and «high» exposure given in Table 4.3.5-1 with reported frequencies of use.

Route - exposure scenario	Mean	5 percentile	50 percentile (median)	95 percentile
	µg/kg bw per day			
Dermal – «realistic»	16	0.12	5.2	50
Dermal – «high»	270	0.88	37	985
Oral – «realistic»	1.3	0.59	1.3	2.4
Oral - «high»	4.1	1.3	3.4	8.9

«Body lotion» and «deodorant» were the two major contributors to the dermal «realistic» exposure scenario for both females and males. For females, exposure from «body lotion» and «deodorant» were 63% and 18% respectively. For males, exposure from «body lotion» and «deodorant» were 47% and 42%, respectively. Other minor sources were hand cream (females: 5%, males: 5%), oils (females: 6%, males: 0%), antibac (females: 4%. males: 3%), hand soap (females: <1%, males: 1%) and foot cream (females: 2%, males: 0%).

Oral exposure from PCPs is mainly from toothpaste (females: 85% and males 100%) with a smaller contribution (15 %) from lip gloss/stick/balm for females.

Overall, the main route of external BHT exposure from PCPs (i.e. oral vs dermal) is dermal for both males and females, with only 6.7% of all BHT exposure from PCPs through oral intake in females and 15.9% in males. Note however, that this is not accounting for different levels of absorption of BHT through dermal and oral exposure (see below).

4.4 External BHT exposure from indoor dust

The external BHT exposure from dust was estimated as follows:

External BHT exposure from dust (µg/kg bw per day) = BHT concentration in dust (µg/mg dry weight) x Intake of settled indoor dust (mg/day) / body weight (kg)

Due to lack of data on intake of settled indoor dust, the standard factors for intake of settled indoor dust of 20 mg/day (central tendency) or 60 mg/day (upper percentile) for adults in EPA's exposure toolbox were used (EPA., 2011). The intake of 20 mg/day (central tendency) settled indoor dust was used for the «realistic» exposure scenario whereas the intake of 60

mg/day (upper percentile) settled indoor dust were used for the «high» exposure scenario (EPA, 2011).

Wang (2016a) reported concentrations of BHT in house dust from 12 different countries, including median, minimum and maximum values. We assumed that the samples from Greece were most likely to be similar to Norwegian conditions and these were therefore used in the «realistic» exposure scenario, whereas the Japanese values were used in the «high» exposure scenario. The median, minimum and maximum values reported in Wang et al. (2016) indicated that the distribution of BHT concentrations in dust deviated from a normal distribution and had a right skew. This means that the average (or expected) BHT concentration, i.e. the arithmetic mean, was higher than the median. To properly account for variability and to arrive at chronic levels of exposure from dust particles, the values reported in Wang et al. (2016) were therefore used to estimate a log-normal distribution for concentrations in dust. The mean of the log-normal (not to be confused with the mean of the values; it refers to the mean on the log-scale) was set to log(median). The standard deviation was then estimated by optimisation, finding the value most likely to produce a maximum or minimum equal to that reported by Wang et al. (2016), given the number of samples reported. For the Greek data, these standard deviations were 0.65 and 1.75. We used the midpoint of the two standard deviations found by optimisation to approximate the mean concentration of BHT in dust. In realistic exposure from dust, the mean concentration was estimated to be 2652 µg BHT / kg dust (dry weight; dw), using parameters [μ = log(1330) and σ = 1.175], and for high levels of exposure (Japanese values, μ = log(8210), σ = 0.85), the concentration was 11782 µg BHT/kg dust dw. Thus, the average exposure from dust, used as input to the combined exposure (see below), was set to 0.053 µg / day for all adult individuals assuming a daily dust ingestion of 20 mg and an expected concentration of 2652 µg BHT/kg dust. Note that table 4.4-1 gives exposure both per individual and per standard kg body weight (70 kg). The exposure per individual was used in the combined exposure (see below), where individual body weights from the Euromix survey was used for normalisation.

The estimated external exposure to BHT through indoor dust is shown in Table 4.4.1.

Table 4.4-1. External exposure to BHT through settled indoor dust. Using concentrations of BHT in dust from Greece (realistic) and Japan (high), a log-normal distribution was assumed to arrive at 'mean' concentrations.). Following standard values for dust intake from EPA, exposure in µg/ per day is given in the two rightmost column, with the last column normalised by standard body weight of 70 kg.

Exposure scenario	Mean BHT in dust from log-normal (µg/g dw)	Daily ingestion of dust (g/day)	Exposure non-normalised (µg /day)	Exposure normalised by body weight (µg / kg bw per day)
Greek concentrations	2.652	0,020 (low)	0.053 (low)	0.00076 (low)
		0,060 (high)	0.16 (high)	0.0023 (high)
Japanese concentrations	11.782	0,020 (low)	0.24 (low)	0.0034 (low)
		0,060 (high)	0.71 (high)	0.010 (high)

4.5 Total internal exposure

Bivariate statistical models fitted to oral and dermal intakes were utilised to estimate total internal exposure. We added the dietary intake from food, the oral intake from PCPs (in EuroMix) and an average ingestion of dust for the oral route, resulting in 284 (140 individuals on two days + 4 individuals on 1 day) individual-day exposures of both oral and dermal routes. The goal of analysing oral and dermal exposure together was to determine whether individuals who have above average intake of BHT through their diet also have an above average exposure through the dermis. If there is a correlation (or covariance) between these routes, treating routes as independent will bias the estimates. We use the fitted models to draw daily exposures for many individuals over 365 days to predict chronic exposures for both pathways. These are finally added to yield a distribution of total internal exposure.

4.5.1 Absorption factors for BHT

BHT is rapidly absorbed in the gastrointestinal tract after oral exposure, and we therefore assumed a 100% absorption of BHT in the gastrointestinal tract (EFSA, 2012).

The studies on dermal absorption cited in Lanigan et al. (2002) showed absorption values ranging from 0.4% to 14.4%. The original studies were not available, thus, the Panel could not adequately assess the strengths and weaknesses of the studies to be able to define a key study. The three studies used *ex vivo* pig or rat skin models or *in vivo* guinea pig model. Pig skin resembles human skin and is thus a better model than *ex vivo* rat and *in vivo* guinea pig. Using the *ex vivo* pig skin model, the absorption value was found to be 0.4% (without adding 1-2 standard deviations to the final absorption value). However, the exposure period before wash-off of the test solution was only 30 minutes and not 8 hours that better resembles exposure from leave-on cosmetic products. A longer exposure period would likely result in a higher absorption value than 0.4%. Physical and chemical properties such as molecular weight > 500 Da, octanol/water partition coefficient (log P_{ow}) ≤ -1 or ≥4, topological polar surface area > 120 $Å^2$ and melting point > 200 °C indicate a very low dermal absorption. With regard to BHT, the log P_{ow} is 5.1, however the other properties are not indicative of a very low dermal absorption. The Panel therefore decided to use the absorption factor of 4% as indicated in Lanigan et al. (2002).

4.5.2 Modelling approach

Exposure from dietary intake and PCPs (both from EuroMix) and assumed exposure from dust were analysed using a generalised linear mixed model framework implemented in the *R* statistical software (R Core Team, 2018). Bayesian statistical models were used to remove the day-to-day variation that has a tendency to lead to overestimation of variability, and particularly the tails of the exposure distribution, when using OIMs. Using a multivariate model (i.e. a model predicting oral and dermal exposure) also allows for appropriate quantification of the potential covariance between exposure from diet and other sources. This is detailed below.

The basics of the statistical model is to predict all the individual-day datapoints of oral intake and dermal uptake using a model with fixed and random effects. Fixed effects refer to parameters that are estimated to predict the exposures. In the presented models we utilise sex as a fixed effect for dermal exposure (for other models tested see 4.5.3). This means that the model quantifies how males and females differ *on average* in their daily exposure levels for oral exposure. When having estimated such an effect of sex it is easier to predict population relevant exposures; in the case of EuroMix, 100 of 144 participants are females, and just presenting the OIMs for the intake (as in Table 4.2.2.2) is misleading, particularly if females have a different intake *on average*. By estimating the effect of being male or female on exposure we can correct for this bias in the representativeness of the survey.

The second part of a mixed model is the random effects. Most basic statistical models assume that differences between a prediction and a data-point is distributed according to some density (usually the normal distribution). A hierarchical model, on the other hand, assumes that the difference between a prediction based on the fixed effects and the actual observations can be partitioned into several sources of variability. In trying to arrive at exposure estimates that represent *chronic* exposure, i.e. long-term level of exposure, an ideal model should remove variability in exposure from day to day within individuals, but keep variability between individuals as we wish to characterise the exposure for the whole population. Using a hierarchical model we will not only be able to estimate the effect of (and thus correct for) males and females being different on average in their exposure, we will also be able to estimate whether or not males and females differ in their variability in exposure. In other words, we can correct for the possibility that male individuals vary more in their chronic exposures than females.

Finally, when applying multivariate models with fixed and random effects, we can also directly estimate the covariance between oral and dermal exposure between individuals. This is necessary to evaluate whether individuals with high oral exposure also have high dermal exposure, and whether females and males differ in the correlation between exposure routes.

These corrections (based on *mean*/fixed effects and *variances*/random effects) were performed by simulating data according to the estimated parameters. Just as one can draw random numbers from a normal distribution with a given mean and standard deviation one can also draw exposures according to a model fit. In all models we partition variability in observation into variance between individuals (as random effects) and variance between days (as residuals). While our data was only collected for 2 days, we can simulate a large number of individuals and simulate 365 daily exposures, of which we calculate an individual mean. We thus arrive at a distribution of expected chronic exposures. These simulations were implemented using custom made functions in *R*.

4.5.3 Models of BHT exposure

4.5.3.1 Fixed effects and model selection

Initially 12 models were fitted to the data with four different structures assumed for the variances (see 4.5.3.2 and Table 4.5.3.2-1) combined with three model structures of fixed

effects. Daily exposure were normalised by body weight (yielding two variables; oral *and* dermal exposure in µg BHT/kg bw) and then log-transformed. For each variance structure a model with fixed effects of sex and age within each sex for both variables (oral and dermal) was fitted. In all cases, the parameter estimates for age effects overlapped with 0. A model with no age effects but with fixed effect for oral exposure, indicating that males and females do differ in both oral and dermal exposure, on average. We also tested models with no fixed effect of sex on exposure, but they had a worse fit in terms of *DIC* (deviance information criterion). There is also little evidence for exposure to BHT having a relationship with age, both for dermal and oral exposure. The four final models (with different variance structures only) included fixed effects of sex on dermal exposure and oral exposure. Models with fixed effects of age and fixed effect only for oral exposure are not further discussed and were not used for simulating chronic exposures.

4.5.3.2 Random effects

The hierarchical model posits two levels of variability; one among individuals and one among observations (i.e. days) per individual.

Model 1 assumes no difference in the degree to which males and females vary; four variance parameters were estimated: variance among individuals for oral (1) and dermal (2) route and variance between days for oral (3) and dermal (4) exposure. In this model, the only difference between males and females is in their *mean* exposure levels forexposure. In other words, exposure estimates using model 1 will not take into account the possibility that dermal and oral exposure correlate. Estimates using this model would be the same as modelling oral and dermal route independently.

Model 2 posits that variation between individuals are the same for males and females, but explicitly estimates the *covariance,* i.e. to which degree individuals who have «high» exposure through the oral route also have high (or low) exposure through the dermis. In this case, we directly estimate if there is a correlation between BHT exposures orally and dermally, but assume that males and females vary in the same manner.

Models 3 and 4 posits that the error structures are similar as models 1 and 2, but that these (co-)variances are potentially different between males and females.

Model 3 ignores correlation in exposures between the oral and dermal route, but allows males and females to have different level of variance(s) between individuals.

Model 4 is similar to model 2, where the covariance/correlation between oral and dermal exposure is explicitly estimated. However, in model 4 the covariance routes can differ between the sexes. In other words, females can potentially have a positive correlation between oral and dermal exposure, while males have a negative correlation.

The fit of all four models with fixed effect of sex on oral and dermal exposure and different variance structures are shown in Figure 4.5.3-1, and detailed in Table 4.5.3-1.

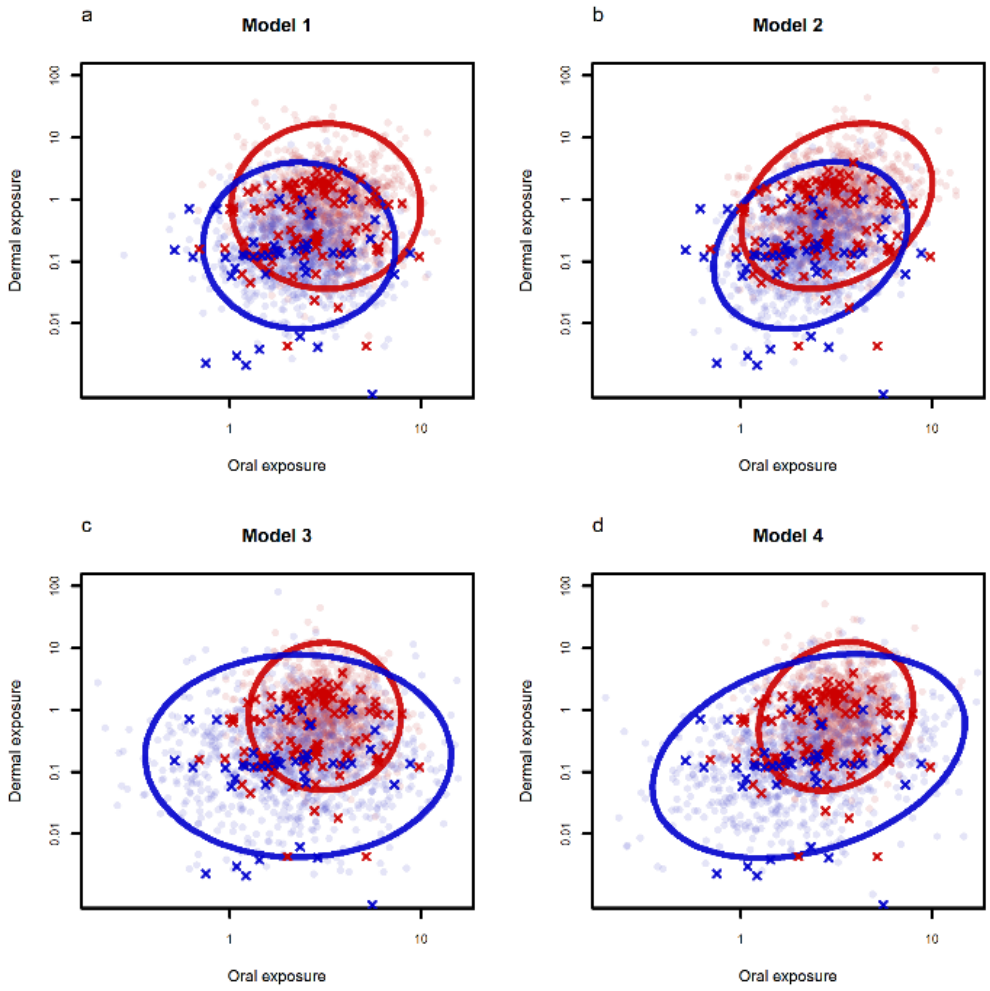

Figure 4.5.3-1. Results from models 1- 4 with contribution to internal exposure from oral intake on the x-axis and dermal exposure on the y-axis (adjusted for adsorption). The strongly coloured crosses are observed individual means (OIMs), whereas the lightly coloured dots are simulated/drawn from the model fit (red – females, blue – males). The ellipses encircle the 95-percentile for the predicted chronic exposures. Assuming the same structure of variability in males and females (Model 1 & 2) leaves the ellipses identical in shape, and the sexes differ only in mean exposures. In model 3 & 4 males and females were assumed to have different levels of variability among days and among individuals. As seen by the wider ellipse, males vary much more in both exposure routes. Note that all models use a log-transformation of the daily exposures. According to the Deviance information criterion (DIC) model 3 and 4 fits the data best with similar DIC values outperforming models with same variances for both sexes.

After the models were fitted to the data and model checks were performed, we utilised the estimated parameters to perform posterior predictive simulations. Essentially, we simulated exposures according to the model to form more robust exposure estimates. The OIMs approach will reduce the variability in exposure slightly compared to using all person-day exposure (i.e. not calculating individual means), but the modelling approach allows us to sample any number of days to estimate long-term average exposures. In our simulations we draw 50 000 «individuals» for each sex and draw 365 «daily» exposures (in µg BHT/kg bw) for each individual, and then calculate a mean exposure for each individual (Figure 4.5.3-1). We thus capture the variability between individuals, but reduce the variability between days to approximate a chronic exposure given the data and our model.

Table 4.5.3-1. Model summary: Models 1-4 differ in the variance/covariance structure estimated. The simplest model (Model 1) does not differentiate individual level effects between sexes, i.e. males and females were assumed to have the same variation in exposure between days and between individuals. For all models we assumed that the residual variance, i.e. the variability within individuals but between days, were the same for females and males. All models were analysed with exposure on a log scale, but simulated exposures are on the real scale. The Deviance information criterion indicates that models 3 & 4 fit the data better. We simulate chronic exposures based on all four models.

Model	Variance between individuals	Rationale / assumption	Fixed effects	DIC	Notes of variances
1	Same for females and males, one variance for each route	Males and females exhibit same degree of variability of exposure	Sex	1751	
2	Same for females and males, one variance for each route and a covariance between routes	Males and females exhibit same degree of variability, and individuals with high/low exposure through the oral route can also have high/low exposure through the dermal route	Sex	1750	
3	Males and females have different between- individual variances (no covariance)	Males and females differ in their variance for each route	Sex	1739	Males vary about twice as much between individual and between days as females for both oral and dermal exposure
4	Males and females have different between-individual variances and covariance	Males and females differ in their variance and covariance for each route	Sex	1738	Both males and females show tendency of positive individual level covariance between exposure through dermal and oral routes.

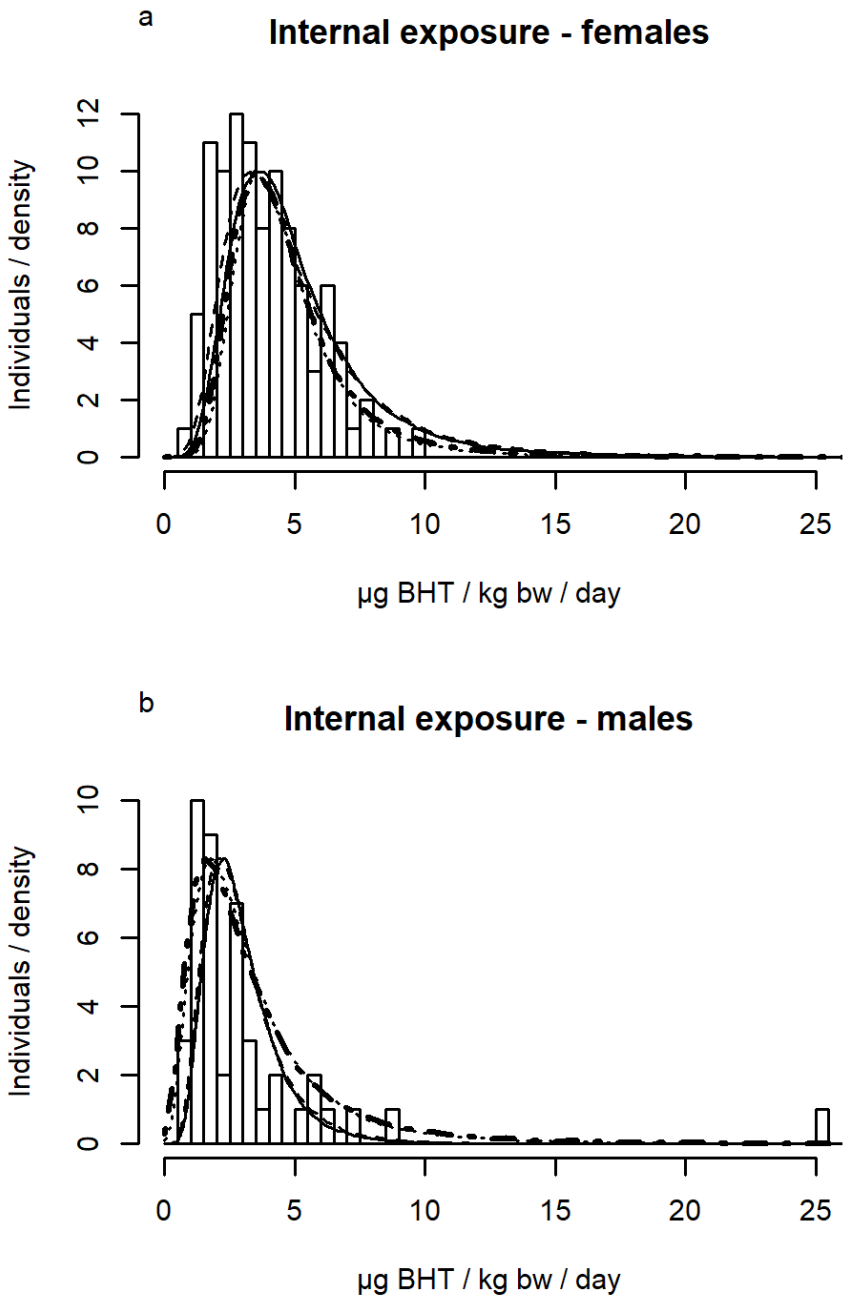

Figure 4.5.3-2. Total internal exposure using the EuroMix study and realistic middle bound concentrations for diet, realistic exposure assumptions for PCPs and Greek concentrations for mean oral exposure from dust. Histograms show the OIMs for females (top) and males (bottom). Lines are density distributions for the four different models presented in Table 4.5.3-1. Model 1 (full line), model 2 (dashed line), model 3 (dotted line), model 4 (dash-dotted line). The different models does not affect the estimates for females (lines are almost entirely overlapping), but models with variance parameters for each sex leads to more variation in exposures for males (dotted and dash-dotted lines). While the simulated exposures are from four different assumption on the variance structure, the predicted chronic exposures are remarkably similar

Total internal exposure as estimated through OIMs and the four statistical models (1-4) applied on the EuroMix survey is shown in Table 4.5.3-2. All four models were applied to daily oral and dermal exposures normalised by weight, using the most realistic combination of parameters for diet, PCPs and dust.

In addition to the «realistic» exposure scenarios we also calculated «high» exposure, combining the upper bound from the concentrations found in food (Table 4.2.1-1), the «high» exposure scenario of amounts and concentrations for PCP exposures (Table 4.3.1-1) and concentrations in dust from a ese study (Table 11.6-1). Results from this «high» exposure scenario is given in Table 4.5.3-3.

Table 4.5.3-2. «Realistic» total internal exposure, in µg BHT/kg bw per day, as estimated through observed individual means (OIMs) and the four statistical models (1-4).

«Realistic» exposure	Mean	5 percentile	50 percentile (median)	95 percentile
OIMs – females	3,8	1,4	3,5	7,0
OIMs – males	3,2	0,8	2,2	7,2
Model 1 – females	5,3	2,1	4,5	11
Model 1 – males	3,0	1,3	2,7	5,8
Model 2 – females	5,3	1,9	4,3	12
Model 2 – males	3,0	1,2	2,6	6,0
Model 3 – females	4,9	2,3	4,3	9,1
Model 3 – males	3,7	0,9	2,8	9,2
Model 4 – females	4,9	2,2	4,2	9,6
Model 4 – males	3,7	0,8	2,7	9,7

Overall using the OIMs and the two best fitting models (3 and 4), the «realistic» total internal exposure from all routes was estimated to be within 1.4 – 9.6 µg BHT/kg bw per day for females and 0.8 – 9.7 µg BHT/kg bw per day for males. The 50 percentile was estimated to be within 3.5 – 4.2 and 2.2 – 2.8 µg BHT/kg bw per day for females and males, respectively. Note that males have on average lower exposure, but vary more between individuals and have similar upper tails as females.

The predominant route of exposure is oral intake; on average 80% of the internal exposure in females is from food, dust and oral intake of PCPs, while for males even more (92%). Note that the models explicitly estimating the covariance between oral and dermal intake show a positive correlation for both males and females, i.e. «high» exposure dermally was correlated with higher exposure through the oral route.

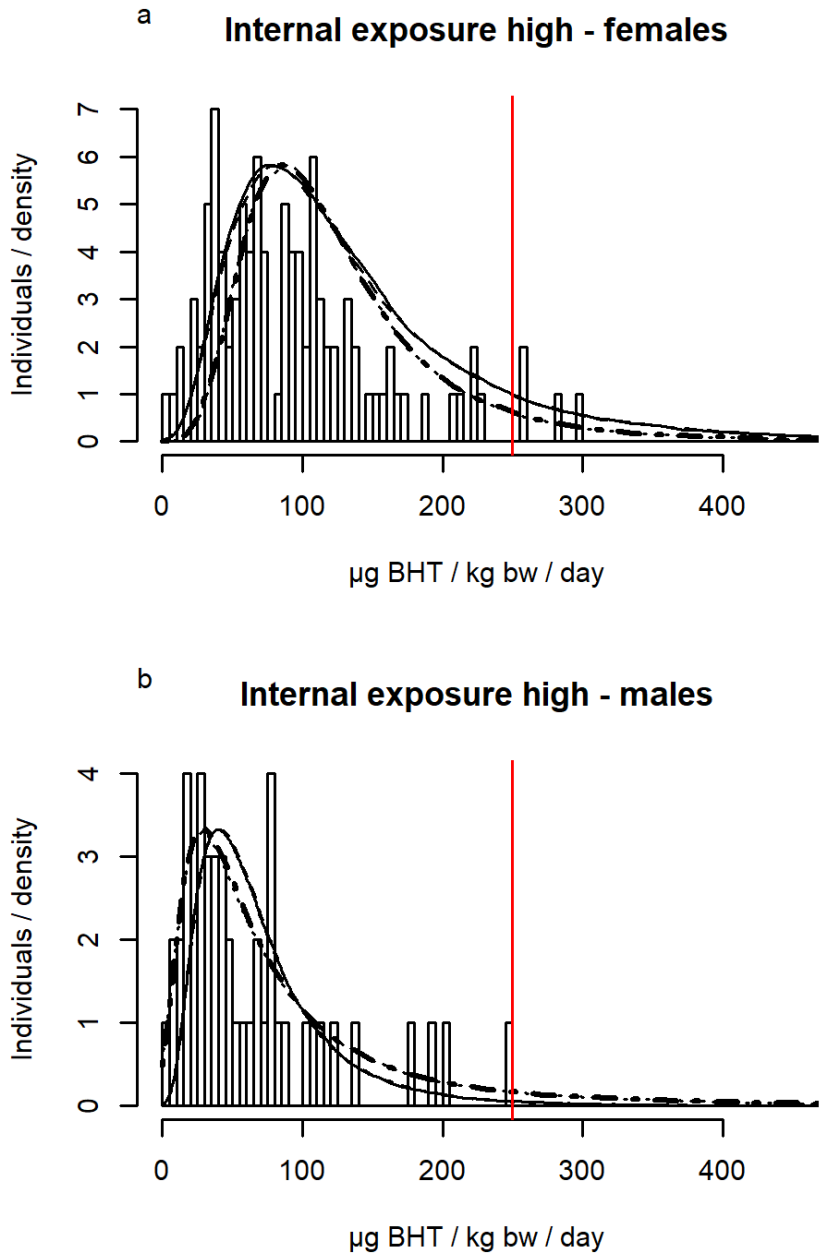

Figure 4.5.3-3. «High» exposure, combining the upper bound from the concentrations found in food, the «high» exposure scenario of amounts and concentrations for PCP exposures and concentrations in dust from a Japanese study (Wang et al., 2016a). Red is ADI of 250 µg/kg bw per day. Histograms are OIMs and lines show distributions of the simulated exposures (full line: model 1, dashed line: model 2, dotted line: model 3 and dashed dotted line: model 4).

Table 4.5.3-3. «High» total internal exposure (food, PCPs, and dust), in µg BHT/kg bw per day. OIMs: Observed individual means.

«High» exposure	Mean	5 percentile	50 percentile (median)	95 percentile
OIMs – females	94	23	85	224
OIMs - males	64	9	44	190
Model 1 – females	146	39	114	347

«High» exposure	Mean	5 percentile	50 percentile (median)	95 percentile
Model 1 – males	74	20	59	176
Model 2 – females	147	40	115	349
Model 2- males	74	20	59	174
Model 3 – females	132	48	110	277
Model 3 – males	102	13	60	309
Model 4 – females	134	48	111	281
Model 4 - males	104	13	61	319

Including estimates from OIMs and the two best fitting models, the «high» total internal exposure from all routes was estimated to be within 23 – 281 µg BHT/kg bw per day for females and 9 – 319 µg BHT/kg bw per day for males. The 50 percentile was estimated to be within 85 – 111 and 46 – 61 µg BHT/kg bw per day for females and males, respectively.

4.5.4 Contributions to exposure

To evaluate the relative contributions to exposure, dermal exposure was corrected using the absorption factor (0.04) and the four different routes (diet/oral, PCP/oral, dust/oral and PCP/dermal) on exposure were normalised by individual body weight. Their overall contribution to total exposure was then quantified (i.e. all absorption corrected internal exposure across all 144 individuals in Euromix). The percentage contributions to overall exposure of BHT is given in Table 4.5.4-1.

Table 4.5.4-1. Contributions to internal exposure calculated by taking the overall percentage contribution across individuals.

Mean contribution across individuals	Diet / oral (%)	PCP / oral (%)	Dust / oral (%)	PCP / dermal (%)
All	46	37	0.02	17
Females	41	38	0.02	21
Males	59	34	0.02	7.1

Sources of BHT exposure were mainly from food through oral intake (females 41%, males 59%, see Table 4.5.4-1), with substantial contributions also from PCPs through oral uptake (females 38%, males 34%) and through dermal uptake from PCPs (females 21%, males 7.1%).

The best fitting model predicted that for males, about 82% of the total internal exposure were derived from oral ingestion, and among individuals the median percentage from oral ingestion was 93% (median within males) and similarly for females (69% and 79%). This clearly showed that the main route for exposure to BHT was oral. The models did not distinguish the different sources for the oral intake.

4.6 Total exposure to harmful metabolites

Due to the complex metabolism of BHT, the total exposure to potential harmful metabolites was not estimated.

4.7 Summary of the exposure estimations

Due to lack of concentration data, BHT exposure from indoor air (sub-question 4) was not estimated. Due to the complex metabolism of BHT, the total exposure to potentially harmful BHT metabolites (sub-question 6) was not estimated.

The exposure was estimated for «realistic» and «high» exposure scenarios. The BHT concentrations in foods were identified in literature. In the «high» exposure scenario, all concentration data were included regardless of country of origin. In the «realistic» exposure scenario, only concentration data from Europe and USA were included. The consumption data used were from Norkost 3 and EuroMix. The concentrations of BHT in PCPs were identified through literature searches, and the consumption data were from EuroMix. The concentrations of BHT in indoor dust were identified through literature searches, and the consumption was based on standard exposure factors from EPA (2011).

External exposure - BHT reaching the physical barriers in the body
The food group «milk, cream, ice cream», followed by «chewing gum» and «fatty fish» were the main contributors to the estimated dietary «realistic» external exposure. The two food groups «cheese» and «margarine and butter» were not included due to lack of concentration data from Europe/USA. However, these two food groups contributed most to the BHT exposure in the «high» exposure scenario. The main route of BHT exposure from PCPs (i.e. oral vs dermal) was dermal. The PCP categories «body lotion» and «deodorant» were the two major contributors to the estimated dermal «realistic» external exposure.

Total internal exposure – absorbed BHT
To calculate the total internal exposure, absorption factors for BHT uptake from the gastrointestinal tract and dermal BHT uptake were derived from the literature.

Overall, the «realistic» total internal exposure from all routes was estimated to be within 1.4 – 9.6 µg BHT/kg bw per day for females and 0.8 – 9.7 µg BHT/kg bw per day for males. The 50 percentile was estimated to be within 3.5 – 4.2 and 2.2 – 2.8 µg BHT/kg bw per day for females and males, respectively.

Overall, the «high» total internal exposure from all routes was estimated to be within 23 – 281 µg BHT/kg bw per day for females and 9 - 319 µg BHT/kg bw per day for males. The 50 percentile was estimated to be within 85 – 111 and 46 – 61 µg BHT/kg bw per day for females and males, respectively.
The predominant route of exposure is oral intake; on average 80% of the internal exposure in females is from food, dust and oral intake of PCPs, while for males even more (92%). Sources of BHT exposure were mainly from food through oral intake (females 41%, males 59%, with substantial contributions also from PCPs through oral uptake (females 38%, males 34%) and through dermal uptake from PCPs (females 21%, males 7.1%).

5 Risk characterisation

As reference points for BHT toxicity, the Panel used the ADI of 0.25 mg/kg bw per day established by EFSA (EFSA, 2012), based on effects on the litter size and pup body weight. Both «realistic» and «high» total internal BHT exposure was used in the risk characterisation.

The «realistic» total internal exposure, from all routes, was estimated to be within 1.4 – 9.6 µg BHT/kg bw per day for females and 0.8 – 9.7 µg BHT/kg bw per day for males. The 50 percentile was estimated to be within 3.5 – 4.2 and 2.2 – 2.8 for females and males, respectively. The «high» total internal exposure from all routes was estimated to be within 23 – 281 µg BHT/kg bw per day for females and 9 - 319 µg BHT/kg bw per day for males. The 50 percentile was estimated to be within 85 – 111 and 46 – 61 for females and males, respectively. Figure 5-1 gives an overview of the estimated exposure compared to the ADI.

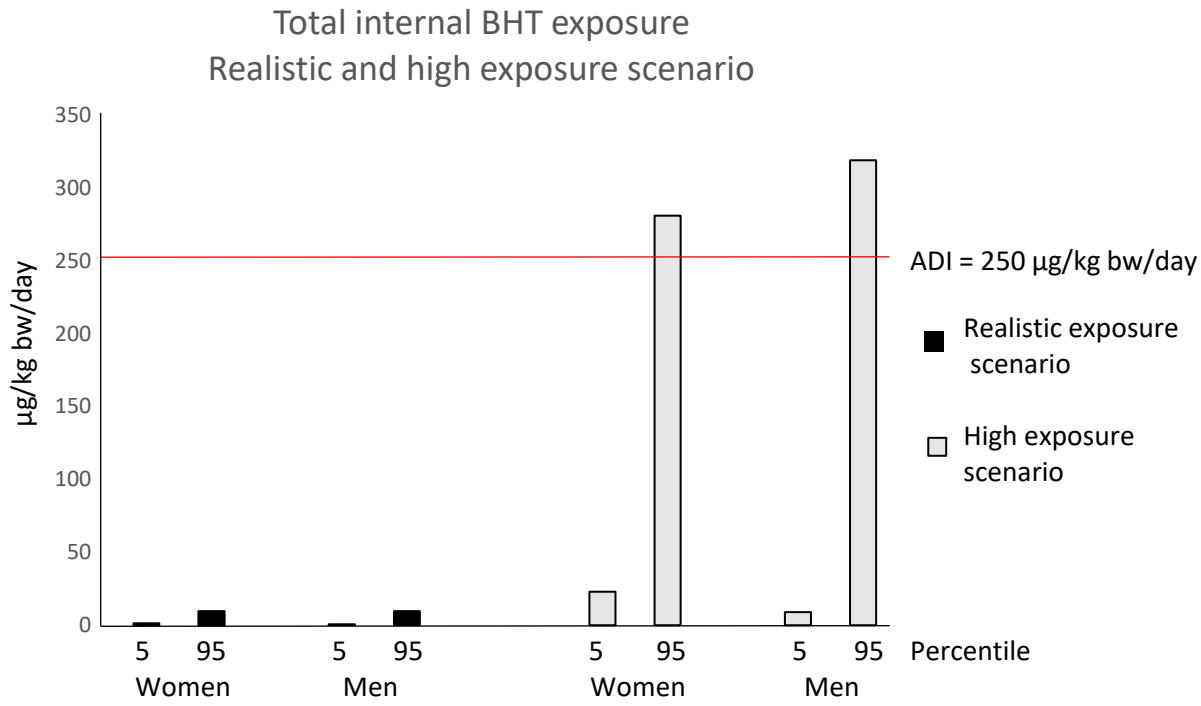

Figure 5-1. The total internal BHT exposure (from food, PCPs and indoor dust), both «realistic» and «high» exposure scenario (in µg/kg bw/day), for women and men. On the high end of the high scenario both males and females are predicted to exceed the ADI.

The estimated «realistic» BHT exposure is below the ADI for both women and men. The 50 percentile of the estimated «high» exposure for both men and women is below the ADI, whereas the 95 percentile is above the ADI.

6 Uncertainties

6.1 Uncertainties in the hazard identification and characterisation

The main sources to uncertainty in the hazard identification and characterisation are presented qualitatively in Table 6.1-1. The possible impact on the hazard identification and characterisation was evaluated by expert judgement, and both the main sources to uncertainty and the possible effects are presented in the table.

Table 6.1-1. Qualitative evaluation of uncertainties in the hazard identification and characterisation.

Endpoint	Source of uncertainty	Direction
ADME	The BHT metabolism is complex and differs considerably between rats and humans. Rats mainly excrete BHT in the feeces, while BHT is mainly excreted in the urine in humans. BHT is also shown to accumulate to a higher degree in fatty tissue in humans than in rats.	-
Hepatocellular adenomas and carcinomas	The duration of the study by Olsen et al. (1986) was 144 weeks, which is considerably longer than indicated in the OECD guidelines. This may influence the outcome of the study. However, this is mostly relevant for the development of hepatocellular adenomas and carcinomas, and not the reproduction effects (litter size and pup body weight gain) on which the ADI is based.	-/+

\+ Overestimation
\- Underestimation

6.2 Uncertainties in the exposure estimation

The main sources to uncertainty in the exposure estimates are presented in Table 6.2-1. The possible impact of the uncertainty on the exposure estimates was evaluated by expert judgement, and both the main sources to uncertainty and the possible effect on the exposure estimates are presented in the table. A tabular format similar to suggestions from EFSA (EFSA et al., 2018) was used, and the impact of the uncertainty was expressed using symbols defined on a quantitative scale. A dot (•) indicates that the impact of the uncertainty is less than +/- 20%, one plus symbol (+) indicates that the true value could be up to twice as high as the estimate, and two plus symbols (++) indicates that the true value could be 10 times higher. One minus symbol indicates that the true value could be as low as half of the estimate, and two minus symbols (- -) indicates that the true value could be 1/10 of the estimate. Each symbol represents a range of possible values. Pairs of symbols are used when the uncertainty spans a larger range: -/+ indicates that the true exposure is expected to be between half and twice the estimate.

Table 6.2-1. Uncertainties in the external exposure estimates.

Source of uncertainty	Impact on exposure estimate	Direction and effect «realistic» scenario	Direction and effect «high» scenario
BHT concentations in food	Few datapoints for most of the food groups, resulting in uncertain values for all foods and food groups. The variation is likely to be higher than shown in a few samples. However, BHT can be found in many food groups and the overall exposure uncertainty may then be reduced since both too high and too low values will be part of the consumption of the same person.	-/+	-/+
	The lack of BHT data from Europe and USA for the food groups «margarine and butter» and «cheese» may give an underestimation of the «realistic» exposure.	--/●	
	In the «high» scenario the food groups «margarine and butter» and «cheese» are the main contributors to the exposure. Especially the food group «cheese» with only two analyses, are highly uncertain when used for the whole food group «cheese» consumed in Norkost 3 and EuroMix.		●/++
	Scenarios on brand loyal consumers are not included in this assessment, due to lack of specific data.	-/+	-/+
	Each food group has been assigned the mean concentration identified for that food group. This can be an overestimation if not all foods in the food group contain BHT. In the «realistic» exposure scenario, data from Europe/USA were used. In the «high» exposure scenario, all identified concentration data were included. This implies that high concentration data from outside Europe and USA are used, and the uncertainty related to this scenario is larger than in the «realistic» exposure scenario.	+	++
Effect of coocking/processing	The effect of cooking/processing on the BHT concentration in foods was not taken into account. Sampled foods were assumed to represent consumed foods, which could lead to both over- and underestimation of the exposure.	-/+	-/+

Source of uncertainty	Impact on exposure estimate	Direction and effect «realistic» scenario	Direction and effect «high» scenario
BHT available for uptake	The extraction of BHT from chewing gum is set to 100% in this assessment. Several studies have shown that the actual excretion from chewing gum is lower, depending on chewing time. For those who reported using chewing gum this will lead to an overestimation of BHT exposure.	+	•
Classification of concentration data to foods/food groups	Compiling the database for BHT occurrence by expert judgement.	-/+	-/+
Dietary surveys	Two recording days; some foods/food groups have high concentrations of BHT, and the long term consumption of these high occurrence products (e.g. chewing gum, pepperoni) will not be reflected in two days records for one person.	-/+	-/+
	Different dietary assessment methods, with 24-h recalls for Norkost 3 and 2 days weighed record for Euromix. The methods were not interchangable, but the mean energy intake in the two studies indicates that the studies are comparable.	•	•
Concentration of BHT in PCPs	Concentration of BHT in personal care products, and variability in concentrations between brands.	+/-	
	Concentration data for BHT in facial moisturiser and mouthwash were not identified.	-	
Dermal BHT uptake	Original articles on dermal absorption of BHT cited in Lanigan et al. (2002) were not available for the Panel. Thus, it was not possible to evaluate the qualitity of the articles and thereby verify the absorption value of 4% used in the risk assessment.	+/-	+/-
Use: Frequency and amount	Variability in amounts used among individuals	+/- (reducing tails*)	
	Limited number of predefined categories of personal care products leads to not covering all types of PCPs.	-	-

Source of uncertainty	Impact on exposure estimate	Direction and effect «realistic» scenario	Direction and effect «high» scenario
	Decoding individual handwriting in reports.	-/+	-/+
	There is some uncertainty in seasonal use of personal care products.	+/-	
	Products seldom used may be missed on the two study days.	-	
	The retention factors can vary between brands of PCPs and application habits of individuals.	+/- (reducing tails*)	

Pairs of symbols are used where the uncertainty spans a larger range.
++ The true value could be 10 times higher.
+The true value could be up to two times higher than the estimate (> 20%).
-- The true value could be 1/10 of the estimate.
-The true value could be as low as half of the estimate (> 20%).
• The impact of the uncertainty is less than +/– 20%.
* Reducing tails means the factor leads to upper and lower percentiles closer to the mean/median, i.e. underestimating variability among individuals.

6.3 Uncertainties in the exposure modelling

In addition to the uncertainties arising from the data itself, the modelling of exposure (and simulated output from these models) also have inherent uncertainties. To be able to model intakes using formal frameworks we assume that exposures can be treated on a log-scale, i.e. all daily exposures are log-transformed before fitting the statistical model. While this might be the most parsimonious transformation, others have also been suggested (e.g. variation around the Box-Cox transformation implemented in the MCRA software). This also means that we model individual differences (i.e. the random effects) and the day-to-day differences within individuals (the residuals) on a log-scale. Implicitly we are then assuming that an individual with twice the mean exposure is as likely as an individual with half the exposure. Whether day-to-day variability in usage follow such a distributional assumption is hard to assess using the data available.

While Norkost 3 gives a larger data set for estimating and modelling intake of BHT through the diet, our analysis of the EuroMix data shows that there is probably a correlation between intake of BHT through diet and through the use of personal care products.

The different ways to partition variance, either between sexes or with explicit incorporation of covariance (model 1-4), shows that ignoring differences between the sexes in how they vary over days and individuals can be misleading (models 3 and 4 fit the data much better). The Euromix study is rich in detail but not in sample size, and this is still reflected in the difficulty in clearly distinguishing the possible variance/covariance structures.

7 Summary, discussion and conclusion

The aim was to assess whether the exposure of BHT from foods, PCPs and indoor dust constitutes a health risk to the Norwegian population and to compare the contribution from different sources and exposure pathways.

7.1 Hazard identification and characterisation

7.1.1 Literature

To evaluate whether the ADI established by EFSA (2012) needed revision, literature searches, from 2012 to the search date (see Appendix 11 for detailed description) were performed to retrieve articles reporting on adverse health effects related to BHT. Only three original articles were included, namely, two studies on genotoxicity and one on endocrine disruption. The hazard identification and characterisation were therefore based on these three studies and the EFSA opinion of BHT as a food additive.

7.1.2 Toxicological data

The ADI of 0.25 mg/kg bw per day, established by EFSA (2012), based on effects on the litter size and pup body weight was used for the risk characterisation. The ADI was based on a NOAEL of 25 mg/kg bw per day derived from two 2-generation studies in rats, applying an uncertainty factor of 100. No studies retrieved through the systematic literature searches indicated that this ADI needed revision.

7.2 Exposure

7.2.1 BHT concentrations, consumption and absorption

The BHT exposure was estimated using i) data on BHT concentrations in foods, PCPs and indoor dust, ii) data on consumption of foods, frequency of PCP use and generic assumptions on intake of dust, and iii) data on BHT absorption. The exposure was estimated for «realistic» and «high» exposure scenarios (Table 4-2).

Concentration data for BHT analysed in foods, PCPs and indoor dust were identified through literature searches. Articles were screened against the inclusion/exclusion criteria, and the data quality was evaluated and rated to make sure that the quality of the concentration data used for the exposure assessment was satisfactory. No concentration data on indoor air were identified, and BHT reaching the lungs was therefore not included in the exposure estimation. Food consumption data were obtained from EuroMix and Norkost 3. The dietary intake method used in Norkost 3 and EuroMix is well established, and recorded the intake over two days. The same food composition database was used for Norkost 3 and EuroMix, which enabled a direct comparison of these food intake data. Frequency data of PCP use were from EuroMix, whereas the data on dust consumption were derived from EPA's

exposure toolbox (EPA, 2011). Data on PCP amount used per application and data on BHT absorption were obtained from the literature.

In the «realistic» food exposure scenario, the concentration data considered to be the most representative for Norwegian exposure were used. To specify the food consumption estimate, two main food groups were divided into sub-groups, and only concentration data from Europe and USA that fulfilled the quality criteria were applied. A standard exposure factor was used for consumption of indoor dust (EPA, 2011). The 50 percentile for the applied PCPs, as reported in studies from Europe and USA, were used in the «realistic» scenario (Ficheux et al., 2016; Garcia-Hidalgo et al., 2017; Loretz et al., 2006).

In the «high» food exposure scenario, main food groups and all concentration data that fulfilled the quality criteria, regardless of country of origin, were applied. The included foods were divided in broad groups giving a rougher estimate. In the «high» exposure scenario for dust and PCPs, the highest reported BHT concentrations were used. Upper percentile exposure factors (EPA) was applied for consumption of indoor dust. The maximum amounts were included for PCP use. The «high» exposure scenario is a worst-case estimation representing a risk assessment for potentially high consumers.

The number of BHT datapoints included in the «realistic» exposure scenario were 259. Of the 20 food groups with assigned BHT values, 11 had a sample number below ten. The low sample numbers indicate that the whole diet was not covered. There were 412 datapoints in the «high» exposure scenario, which constitute a low number of analyses to cover the whole diet. Of the 21 food groups with an assigned BHT value, 14 had a sample number below ten. The concentration data for the exposure estimation from foods were limited and therefore considered to be the largest source of uncertainty.

The «realistic» scenario do not include concentration data for the food groups «margarine and butter» and «cheese», due to lack of data from Europe and USA. In this scenario, it is assumed 100% excretion of BHT from «chewing gum», and it contributed to about 40% of the BHT exposure (Table 4.2.3-2). However, several studies have shown that the actual excretion from chewing gum is lower than 100%, dependent on chewing time, and the exposure is therefore most likely an overestimate.

In the high scenario, the food groups «margarine and butter» and «cheese» were the main contributors to the exposure (Table 4.2.3-2). Especially the food group «cheese» with only two analyses, are highly uncertain when used for the whole food group «cheese» consumed in Norkost 3 and EuroMix.

The realistic and high concentrations in most PCP categories differed by a factor from two to ten. The data on usage are considered to be the largest source of uncertainty in the estimates; some PCPs are rarely used (or frequently by few individuals) and the data are insufficient to allow for the use of models to strengthen inferences about frequency of use. Amounts of PCPs used per application were obtained from the literature, and the between-individual variability in usage habits was not taken into account. Variability in concentrations between brands and in amounts among individuals as well as infrequently used categories

contribute to the uncertainty in the exposure estimation of PCPs, and is expected to lead to less extreme values in the presented estimates

7.2.2 Results of the exposure estimation

7.2.2.1 External exposure

BHT reaching the physical barriers in the body was defined as external exposure. An overview of the mean oral and mean dermal external exposure is given in Table 7.2.2.1-1.

Table 7.2.2.1-1. Mean oral and dermal external BHT exposure using observed individual means (OIMs).

	Mean oral exposure (µg/kg bw per day)		**Mean dermal exposure (µg/kg bw per day)**	
	«Realistic» exposure scenario	«High» exposure scenario	«Realistic» exposure scenario	«High» exposure scenario
Foods (Norkost 3)	2.5	76	-	-
Foods (EuroMix)	1.7	69	-	-
Personal care products (EuroMix)	1.3	4.1	16	270
Indoor dust (EPA)	0.00076	0.010	-	-

Based on Norkost 3 the mean BHT exposure from foods was 2.5 µg/kg bw per day for the «realistic» exposure scenario and 76 µg/kg bw per day for the «high» exposure scenario. Based on EuroMix, the mean BHT exposure from foods was 1.6 µg/kg bw per day for the «realistic» exposure scenario and 71 µg/kg bw per day for the «high» exposure scenario. The mean dermal BHT from PCP exposure was 16 µg/kg bw per day for the «realistic» exposure scenario and 270 µg/kg bw per day for the «high» exposure scenario. The mean oral BHT exposure from PCPs was 1.3 µg/kg bw per day for the «realistic» exposure scenario and 4.1 µg/kg bw per day for the «high» exposure scenario. The mean BHT exposure from indoor dust was 0.00076 µg/kg bw per day for the «realistic» exposure scenario and 0.010 µg/kg bw per day for the «high» exposure scenario.

The food group «milk, cream, ice cream», followed by «chewing gum» and «fatty fish» were the main contributors to the estimated dietary «realistic» external exposure. Note that the two food groups «cheese» and «margarine and butter» were not included due to lack of concentration data from Europe/USA. The main route of BHT exposure from PCPs (i.e. oral vs dermal) was dermal. The PCP categories «body lotion» and «deodorant» were the two major contributors to the estimated dermal «realistic» external exposure.

EFSA and the VKM Panel had different approaches toward the exposure estimates for foods. EFSA used conservative estimates with maximum reported use levels in foods, whereas VKM used concentration data from the literature. EFSA included only foods where BHT was authorised as a food additive, whereas VKM also included other foods containing BHT. In addition, VKM also included BHT sources other than foods. EFSA (2012) estimated the

average adult BHT exposure from foods to be 10 - 30 µg/kg bw/day and the 95 percentile exposure to be 30 - 170 µg/kg bw perday.

7.2.2.2 Total internal exposure

Absorbed BHT was defined as total internal exposure. The total internal exposure was modelled summing up exposure through the gastrointestinal tract and skin, multiplied by absorption factors of 100% and 4% for gastrointestinal and dermal absorption of BHT, respectively. Using individual data for usage frequency for PCPs and consumption for foods from EuroMix with generic intakes from dust, the total internal exposure was modelled in an attempt to partition the variance in exposure between and within individuals (i.e. between days). Using a generalised linear mixed model, both mean differences between sexes, as well as different structures of variability, were estimated. These model fits were then used to «simulate» chronic exposures through both routes.

The EuroMix study is small and relatively unrepresentative of the general population. However, it can be utilised to directly quantify one of the structural uncertainties when performing exposure estimates with compounds that enter the body through several routes; namely, the common assumption of independence.

Overall, the total internal BHT exposure was predominantly from the oral route and uptake by the gastrointestinal tract. From the total internal exposure modelling, oral exposure constituted approximately 93% for males and 80% for females (median percentage of oral route across 50 000 simulated individuals, assuming the most complex model). Exposure from the diet was the dominant source for males (59%, Euromix OIMs, Table 4.5.4-1), whereas for females diet and oral exposure from PCPs were of similar magnitude (41% and 38%, respectively, Euromix OIMs). Exposure to BHT through the skin contributed less (21% for females and 7.9 % for males), whereas the exposure from dust was even smaller (0.02%).

7.2.3 Modelling

While our modelling approach was performed using the statistical software *R*, the approach is very similar to other models implemented in more standard risk-assessment tools, such as Monte Carlo Risk Assessment (MCRA). However, while MCRA use statistical models to improve exposure estimates, the software still lacks the ability to structure variance in different sub-populations. Males and females differ in their average exposures, but the similar performance of the more complex models indicates that males and females potentially are different in their level of variability in exposure both within and between individuals. Furthermore, across males and females, there are different signs of covariation in exposures, model 4 used in this assessment captures these differences.

Table 4.5.3-2. shows the estimated internal exposure levels for both the observed individual means (OIMs) approach and for multivariate generalised linear mixed models (GLMMs) for realistic exposure parameters (realistic amounts and concentrations of BHT in PCPs, realistic levels of BHT in dust and narrow middle bound concentrations in food). When utilising statistical models to decompose variance between individuals and between days, the internal

exposure estimates for both males and females are estimated to be higher than mean and medians of OIMs estimates (see Table 4.5.3-2). While still being in the same order of magnitude, this suggests that using OIMs can underestimate chronic exposure compared to simulated exposures from GLMMs. However, the difference in numbers is relatively small, and for all «realistic» exposure scenarios, all below the ADI.

While applying GLMMs to daily exposures can increase robustness and uncertainty quantification, there are also several aspects that could be improved in the presented models. For instance, while the models applied estimates of individual level variance for males and females independently (i.e. how much exposure varies among females relative to males), we still assume that the day-to-day variance is similar for both males and females. This assumption is necessecary due to the limitations in the data; EuroMix has very few individuals and only 2 days of exposures, which is not sufficient to allow the day-to-day variability to differ between the sexes. Note that all exposure models treat exposure on a log-scale, so variance is proportional. In other words, male and female exposures vary similarly (days with twice the average exposure exposure is as likely as half the average exposure), and not in absolute terms (days with 0.1 µg less exposure is not as likely as days with 0.1 µg more exposure).

7.3 Conclusions

BHT is characterised by extensive use and multiple exposure sources and routes. Therefore, it is important that these sources and routes are included in the estimations to arrive at the most accurate picture of the population's exposure.

As reference point for BHT toxicity, the Panel used the ADI of 0.25 mg/kg bw per day (EFSA, 2012).

Both estimated «realistic» and «high» total internal BHT exposures were used in the risk characterisation. The «realistic» total internal exposure was estimated to be within 1.4 – 9.6 µg BHT/kg bw per day for females and 0.8 – 9.7 µg BHT/kg bw per day for males. The 50 percentile was estimated to be within 3.5 – 4.2 and 2.2 – 2.8 µg BHT/kg bw per day for females and males, respectively. The high total internal exposure from all routes was estimated to be within 23 – 281 µg BHT/kg bw per day for females and 9 - 319 µg BHT/kg bw per day for males. The 50 percentile was estimated to be within 85 – 111 and 46 – 61 µg BHT/kg bw per day (rounded numbers) for females and males, respectively.

The estimated «realistic» total BHT exposure is below the ADI for both women and men. The 50 percentile of the estimated «high» total exposure is below the ADI, whereas the 95 percentile is above the ADI. Thus, a small fraction of the population may exceed the ADI and be at risk for negative effects on reproductive health. Note that the «high» total internal BHT scenario represents a risk assessment for potentially high consumers.

The Panel concludes that BHT exposure is unlikely to cause adverse health effects in adults.

8 Data gaps

To perform «realistic» exposure estimates, well described concentration data for all food groups are needed. More detailed information on differences between brands and type of products would give better estimates. Especially data on BHT in food groups with no concentration data from Europe/USA, such as «margarine and butter» and «cheese», are needed

To perform realistic exposure estimates for PCPs, data on BHT concentrations in products and amounts used for different products are needed. Brand-loyalty (i.e. that individuals prefer to use the same e.g. deodorant and shampoo) together with variability in BHT concentrations across brands could not be considered, but would impact the variability between individuals in their exposure.

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Yang M.H., Lin H.J., Choong Y.M. (2002) A rapid gas chromatographic method for direct determination of BHA, BHT and TBHQ in edible oils and fats. Food Research International 35:627-633. DOI: Pii S0963-9969(01)00164-8 Doi 10.1016/S0963-9969(01)00164-8.

Yuan M. (2010) Application note. Analysis of Butylated Hydroxytoluene in Food with Headspace Trap-GC/MS, Perkin Elmer, Inc.

10 Appendix - Hazard

10.1 Literature search hazard

The search was performed by Johanne Longva (Norwegian Institute of Public Health, the library) 07.05.2018 and 08.05.2018.
The total result was 936.

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to May 02, 2018>
Result: 270

1	Butylated Hydroxytoluene/	2073
2	("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4-methyl-2" or "4 Methyl 2,6 ditertbutylphenol" or "6-ditertiarybutylphenolor" or "2,6 Di t butyl 4 methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy tolu*" or "butylhydroxytolu*" or "butyloxytolu*" or "dalpac" or "dbpc" or "dibunol" or "dibutyl 4 hydroxytolu*" or "dibutylhydroxytolu*" or "hydroxybutyltolu*" or "impruvol" or "ionol" or "vianol" or "E321" or "CAS 128-37-0").mp.	4944
3	adverse effects.fs.	1573516
4	exp HEMATOLOGIC DISEASES/ or HEMATOLOGY/ or exp Thyroid Neoplasms/ or exp thyroid gland/ or "ALLERGY AND IMMUNOLOGY"/ or Allergens/ or exp Reproduction/	1653197
5	("risk*" or "safety" or "adverse" or "side-effect*1" or "hazard*" or "harm*" or "negative" or "interact*" or "toxicity" or "toxic" or ("health" adj2 "effect?") or ("hemoglobin" or "haematolog*" or "thyroid*" or "tyrosine" or "allerg*" or "reproduct*" or "pregnan*" or "fetal*" or "fertal*" or "pollinat*")).tw.	5996408
6	1 or 2	4944
7	3 or 4 or 5	7701192
8	6 and 7	1252
9	limit 8 to yr="2012 -Current"	270

Database: Embase <1974 to 2018 May 07>
Result: 529

1	butylcresol/	5150
2	("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4 methylphenol" or	6481

	"2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy tolu*" or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or "dibutyl 4 hydroxytolu*" or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321).mp.	
3	exp adverse event/	525854
4	hematology/ or exp hematologic disease/ or exp thyroid gland/ or allergen/ or allergy/ or allergic reaction/ or exp reproduction/	3342682
5	("risk*" or "safety" or "adverse" or "side-effect*1" or "hazard*" or "harm*" or "negative" or "interact*" or "toxicity" or "toxic" or ("health" adj2 "effect?") or ("hemoglobin" or "haematolog*" or "thyroid*" or "tyrosine" or "allerg*" or "reproduct*" or "pregnan*" or "fetal*" or "fertal*" or "pollinat*")).tw.	7813876
6	1 or 2	6481
7	or/3-5	9816411
8	6 and 7	1691
9	limit 8 to yr="2012 -Current"	529

Database: Web of Science - **Indexes:** SCI-EXPANDED, SSCI, A&HCI, ESCI
Result: 218

(((("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4 methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy tolu*" or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or "dibutyl 4 hydroxytolu*" or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321))) *AND* **TOPIC:** ("risk*" or "safety" or "adverse" or "side-effect*1" or "hazard*" or "harm*" or "negative" or "interact*" or "toxicity" or "toxic" or "hemoglobin" or "haematolog*" or "thyroid*" or "tyrosine" or "allerg*" or "reproduct*" or "pregnan*" or "fetal*" or "fertal*" or "pollinat*" or allerg* or ("health" NEAR/2 "effect*"))
Timespan: 2012-2018. **Indexes:** SCI-EXPANDED, SSCI, A&HCI, ESCI.

Database: Cochrane Database of Systematic Reviews

Result: 138 (CDSR: x, DARE: x, Trials: x, Method: x, Tech ass: x, Eco: x)

ID Search Hits
#1 [mh ^"Butylated Hydroxytoluene"] 8
#2 ("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4 methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy

tolu*" or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or "dibutyl 4 hydroxytolu*" or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321):ti,ab 135
#3 ("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4 methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy tolu*" or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or "dibutyl 4 hydroxytolu*" or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321) in Other Reviews, Technology Assessments and Economic Evaluations 2
#4 [mh /AE] 125659
#5 [mh "HEMATOLOGIC DISEASES"] 11620
#6 [mh ^HEMATOLOGY] 32
#7 [mh "Thyroid Neoplasms"] 600
#8 [mh " thyroid gland"] 526
#9 [mh ^"ALLERGY AND IMMUNOLOGY"] 11
#10 [mh ^Allergens] 1755
#11 [mh Reproduction] 8723
#12 ("risk*" or "safety" or "adverse" or "side-effect*1" or "hazard*" or "harm*" or "negative" or "interact*" or "toxicity" or "toxic" or "hemoglobin" or "haematolog*" or "thyroid*" or "tyrosine" or "allerg*" or "reproduct*" or "pregnan*" or "fetal*" or "fertal*" or "pollinat*" or allerg* or ("health" near/2 "effect*")):ti,ab 407093
#13 ("risk*" or "safety" or "adverse" or "side-effect*1" or "hazard*" or "harm*" or "negative" or "interact*" or "toxicity" or "toxic" or "hemoglobin" or "haematolog*" or "thyroid*" or "tyrosine" or "allerg*" or "reproduct*" or "pregnan*" or "fetal*" or "fertal*" or "pollinat*" or allerg* or ("health" near/2 "effect*")) in Other Reviews, Technology Assessments and Economic Evaluations 266
#14 #1 or #2 or #3 138
#15 #4 or #5 or #6 or #7 or 8 or #9 or #10 or #11 or #12 or #13 or #14 651116
#16 #14 and #15 138

Database: Epistemonikos
Result: 2
(title:((title:(("1,3 di tert butyl 2 hydroxy 5 methylbenzene" OR "2,3 di tert butyl 4 methylphenol" OR "2,6 di tert butyl 4 methylphenol" OR "2,6 di tert butyl para cresol" OR "2,6 di(tert butyl) 1,4 cresol" OR "2,6 ditert. butyl 4 methylphenol" OR "2,6 ditert.butyl 4 methylphenol" OR "2,6 ditert.butyl para cresol" OR "3,5 di tert butyl 4 hydroxytolu*" OR "4 methyl 2,6 di(tert butyl)phenol" OR "4 Methyl 2,6 ditertbutylphenol" OR "2,6 Di t butyl 4 methylphenol" OR "2,6 Di tert butyl p cresol" OR butylcresol OR ("butyl hydroxy" AND tolu*) OR ("butylated 4" AND hydroxytolu*) OR (butylated AND hydroxytolu*) OR (butylhydroxy amd tolu*) OR butylhydroxytolu* OR butyloxytolu* OR dalpac OR dbpc OR dibunol OR ("dibutyl 4" AND hydroxytolu*) OR dibutylhydroxytolu* OR hydroxybutyltolu* OR impruvol OR ionol OR vianol OR E321) AND ("risk*" OR "safety" OR "adverse" OR "side-effect*1" OR "hazard*" OR "harm*" OR "negative" OR "interact*" OR "toxicity" OR "toxic" OR "health effect*" OR "hemoglobin" OR "haematolog*" OR "thyroid*" OR "tyrosine" OR "allerg*" OR "reproduct*" OR "pregnan*" OR "fetal*" OR "fertal*" OR "pollinat*")) OR abstract:(("1,3 di tert butyl 2 hydroxy 5 methylbenzene" OR "2,3 di tert butyl 4 methylphenol" OR "2,6 di tert butyl 4 methylphenol" OR "2,6 di tert butyl para cresol" OR "2,6 di(tert butyl) 1,4 cresol" OR "2,6 ditert. butyl 4 methylphenol" OR "2,6 ditert.butyl 4 methylphenol" OR "2,6 ditert.butyl para cresol" OR "3,5 di tert butyl 4 hydroxytolu*" OR "4 methyl 2,6 di(tert butyl)phenol" OR "4 Methyl 2,6 ditertbutylphenol" OR "2,6 Di t butyl 4 methylphenol" OR "2,6 Di tert butyl p cresol" OR butylcresol OR ("butyl hydroxy" AND tolu*) OR ("butylated 4" AND

hydroxytolu*) OR (butylated AND hydroxytolu*) OR (butylhydroxy amd tolu*) OR butylhydroxytolu* OR butyloxytolu* OR dalpac OR dbpc OR dibunol OR ("dibutyl 4" AND hydroxytolu*) OR dibutylhydroxytolu* OR hydroxybutyltolu* OR impruvol OR ionol OR vianol OR E321) AND ("risk*" OR "safety" OR "adverse" OR "side-effect*1" OR "hazard*" OR "harm*" OR "negative" OR "interact*" OR "toxicity" OR "toxic" OR "health effect*" OR "hemoglobin" OR "haematolog*" OR "thyroid*" OR "tyrosine" OR "allerg*" OR "reproduct*" OR "pregnan*" OR "fetal*" OR "fertal*" OR "pollinat*"))) AND (title:(("risk*" OR "safety" OR "adverse" OR "side-effect*1" OR "hazard*" OR "harm*" OR "negative" OR "interact*" OR "toxicity" OR "toxic" OR "hemoglobin" OR "haematolog*" OR "thyroid*" OR "tyrosine" OR "allerg*" OR "reproduct*" OR "pregnan*" OR "fetal*" OR "fertal*" OR "pollinat*" OR allerg* OR "health effect*")) OR abstract:(("risk*" OR "safety" OR "adverse" OR "side-effect*1" OR "hazard*" OR "harm*" OR "negative" OR "interact*" OR "toxicity" OR "toxic" OR "hemoglobin" OR "haematolog*" OR "thyroid*" OR "tyrosine" OR "allerg*" OR "reproduct*" OR "pregnan*" OR "fetal*" OR "fertal*" OR "pollinat*" OR allerg* OR "health effect*")))) OR abstract:((title:(("1,3 di tert butyl 2 hydroxy 5 methylbenzene" OR "2,3 di tert butyl 4 methylphenol" OR "2,6 di tert butyl 4 methylphenol" OR "2,6 di tert butyl para cresol" OR "2,6 di(tert butyl) 1,4 cresol" OR "2,6 ditert. butyl 4 methylphenol" OR "2,6 ditert.butyl 4 methylphenol" OR "2,6 ditert.butyl para cresol" OR "3,5 di tert butyl 4 hydroxytolu*" OR "4 methyl 2,6 di(tert butyl)phenol" OR "4 Methyl 2,6 ditertbutylphenol" OR "2,6 Di t butyl 4 methylphenol" OR "2,6 Di tert butyl p cresol" OR butylcresol OR ("butyl hydroxy" AND tolu*) OR ("butylated 4" AND hydroxytolu*) OR (butylated AND hydroxytolu*) OR (butylhydroxy amd tolu*) OR butylhydroxytolu* OR butyloxytolu* OR dalpac OR dbpc OR dibunol OR ("dibutyl 4" AND hydroxytolu*) OR dibutylhydroxytolu* OR hydroxybutyltolu* OR impruvol OR ionol OR vianol OR E321) AND ("risk*" OR "safety" OR "adverse" OR "side-effect*1" OR "hazard*" OR "harm*" OR "negative" OR "interact*" OR "toxicity" OR "toxic" OR "health effect*" OR "hemoglobin" OR "haematolog*" OR "thyroid*" OR "tyrosine" OR "allerg*" OR "reproduct*" OR "pregnan*" OR "fetal*" OR "fertal*" OR "pollinat*")) OR abstract:(("1,3 di tert butyl 2 hydroxy 5 methylbenzene" OR "2,3 di tert butyl 4 methylphenol" OR "2,6 di tert butyl 4 methylphenol" OR "2,6 di tert butyl para cresol" OR "2,6 di(tert butyl) 1,4 cresol" OR "2,6 ditert. butyl 4 methylphenol" OR "2,6 ditert.butyl 4 methylphenol" OR "2,6 ditert.butyl para cresol" OR "3,5 di tert butyl 4 hydroxytolu*" OR "4 methyl 2,6 di(tert butyl)phenol" OR "4 Methyl 2,6 ditertbutylphenol" OR "2,6 Di t butyl 4 methylphenol" OR "2,6 Di tert butyl p cresol" OR butylcresol OR ("butyl hydroxy" AND tolu*) OR ("butylated 4" AND hydroxytolu*) OR (butylated AND hydroxytolu*) OR (butylhydroxy amd tolu*) OR butylhydroxytolu* OR butyloxytolu* OR dalpac OR dbpc OR dibunol OR ("dibutyl 4" AND hydroxytolu*) OR dibutylhydroxytolu* OR hydroxybutyltolu* OR impruvol OR ionol OR vianol OR E321) AND ("risk*" OR "safety" OR "adverse" OR "side-effect*1" OR "hazard*" OR "harm*" OR "negative" OR "interact*" OR "toxicity" OR "toxic" OR "health effect*" OR "hemoglobin" OR "haematolog*" OR "thyroid*" OR "tyrosine" OR "allerg*" OR "reproduct*" OR "pregnan*" OR "fetal*" OR "fertal*" OR "pollinat*"))) AND (title:(("risk*" OR "safety" OR "adverse" OR "side-effect*1" OR "hazard*" OR "harm*" OR "negative" OR "interact*" OR "toxicity" OR "toxic" OR "hemoglobin" OR "haematolog*" OR "thyroid*" OR "tyrosine" OR "allerg*" OR "reproduct*" OR "pregnan*" OR "fetal*" OR "fertal*" OR "pollinat*" OR allerg* OR "health effect*")) OR abstract:(("risk*" OR "safety" OR "adverse" OR "side-effect*1" OR "hazard*" OR "harm*" OR "negative" OR "interact*" OR "toxicity" OR "toxic" OR "hemoglobin" OR "haematolog*" OR "thyroid*" OR "tyrosine" OR "allerg*" OR "reproduct*" OR "pregnan*" OR "fetal*" OR "fertal*" OR "pollinat*" OR allerg* OR "health effect*")))))
Year: 2012-2018

10.2 Publication selection and data extraction

10.2.1 Publication selection

The aim of this literature search was to retrieve publications on adverse health effects related to BHT. Since EFSA published an opinion on BHT safety in 2012, articles published before 2012 were excluded. The literature search identified 936 articles.

Two persons independently compared the identified articles with the inclusion/exclusion criteria checklist (Table 10.2.1-1 for human studies, 10.2.1-2 for animal studies and 10.2.1-3 for *in vitro* and *in vivo* genotoxicity studies). The first screening, based on analysis of title/abstracts, resulted in 29 articles. The full texts of the articles that passed the primary screening were retrieved for the secondary screening, with application of the very same inclusion/exclusion criteria. The secondary screening resulted in 13 articles; however, only three articles were original studies. An overview of the publication selection is given in Figure 10.2.1-4.

Table 10.2.1-1. Inclusion/exclusion criteria for human studies in the hazard identification and characterisation steps.

Literature screening for data related to the following sub-questions: 1: Is exposure to BHT related to adverse health effects in humans? Identify target organs. 4: What is the nature of any dose–response relationship between BHT and relevant endpoints in the target organs in human studies? 5: What is the ADME* in humans? 6: Is there a difference in ADME between humans and animals?		
Study design	Inclusion	Human studies, including cohort studies, case-control studies (prospective, retrospective and nested), and toxicokinetic biomonitoring studies on any route of exposure
	Exclusion	Animal studies and *in vitro/in silico* studies
Population	Inclusion	Children (>1 - ≤14 years), adolescents (>14-<18 years) and adults (≥18 years)
	Exclusion	Infants
Exposure	Inclusion	All routes of exposure
Outcome of interest	Inclusion	All reported adverse health effects
	Exclusion	Studies reporting exclusively preventive/beneficial effects on the target organs and studies reporting exclusively on the antioxidant properties/activities of BHT
Language of the full text	Inclusion	English, Norwegian, Swedish, Danish, German
Publication type	Inclusion	E.g. primary research studies, systematic reviews, meta-analyses and risk assessments
	Exclusion	Editorials Letters to the editor Book chapters Meeting abstracts and posters

*ADME - absorption, distribution, metabolism, excretion

Table 10.2.1-2 Inclusion/exclusion criteria for animal studies in the hazard identification and characterisation steps.

Literature screening for data related to the following sub-questions: 2: Is BHT exposure related to adverse health effects in animals? Identify target organs. 4: What is the nature of any dose-response relationship between BHT and relevant endpoints in the target organs in animal studies? 5: What is the ADME* in different animal species/strains? 6: Is there a difference in ADME between humans and animals?		
Study design	Inclusion	*In vivo* studies on animals not examining genotoxicity. Toxicokinetic studies (narrative approach)
	Exclusion	Human studies and *in vitro/in silico* studies
Population	Inclusion	All mammalian animals
	Exclusion	Non-mammalian animals
Exposure	Inclusion	All routes of exposure
	Exclusion	Studies where BHT is a part of a mixture and not tested alone
Outcome of interest	Inclusion	All reported adverse health effects excluding genotoxicity
	Exclusion	Studies reporting exclusively on the antioxidant properties/activities of BHT or studies on genotoxicity
Language of the full text	Inclusion	English, Norwegian, Swedish, Danish, German
Publication type	Inclusion	E.g. primary research studies, systematic reviews, meta-analyses and risk assessments
	Exclusion	Editorials Letters to the editor Book chapters Meeting abstracts and posters

*ADME - absorption, distribution, metabolism, excretion

Table 10.2.1-3. Inclusion/exclusion criteria for studies on genotoxicity.

Literature screening for data related to the following sub-question: **3:** Is BHT associated with changes at the molecular level such as mutation and other genotoxicity endpoints?		
Study design / test systems	Inclusion	*In vitro* studies on genotoxicity *In vivo* studies on genotoxicity
	Exclusion	Test systems: *Drosophila melanogaster*, *Vicia faba*, *Allium cepa*, fish Non-genotoxicity studies
Exposure	Inclusion	Route of exposure for animal *in vivo* studies: oral, subcutaneous, intraperitoneal All *in vitro* genotoxicity studies
	Exclusion	Intravenous

Literature screening for data related to the following sub-question: **3:** Is BHT associated with changes at the molecular level such as mutation and other genotoxicity endpoints?		
Outcome of interest	Inclusion	DNA damage (mutations, strand breaks, unscheduled DNA syntehis (UDS)/DNA repair, reactivity towards DNA) and chromosomal damage (chromosomal aberrations, sister chromatid exchange, micronucleus formation, endoreduplication, polyploidy)
Language of the full text	Inclusion	English, Norwegian, Swedish, Danish, German
Publication type	Inclusion	E.g. primary research studies, systematic reviews, meta-analyses and risk assessments
	Exclusion	Editorials Letters to the editor Book chapters Meeting abstracts and posters

10.2.2 Data extraction

Data were extracted from the included original study by Pop et al. (2013), but not for the two original studies on genotoxicity as the approach for studies on genotoxicity was narrative (Table 10.2.2-1).

Table 10.2.2-1. Data extraction. -: Not reported.

	Reference: Pop et al. (2013)
Study ID	Year the study was conducted (start, if available):
	Health outcome category: Endocrine disruptive effects
Funding	Funding source: Support by the POSDRU Project number 6/1.5/S/3 Public/private: -
Type of study and guideline	Good laboratory practice (yes/no): - Guideline studies (if yes, specify): -
	Type of study: -
Animal model	Species/(sub-)strain/line: Wistar rats
	Disease models (e.g. infection, diabetes, allergy, obesity):
Housing condition	Housing condition (including cages, bottles, bedding): Standard conditions of temperature, humidity, day/night cycle, access to food and water *ad libitum* throughout the experiment. Body weight and clinical signs were recorded daily.
	Diet name and source: -
	Background levels of phytoestrogens in the diet (type and levels):
Exposure	BHT provider: -
	Compound purity: -
	Vehicle used: 17-beta estradiol (positive control) at a dose of 20 µg/kg in sun flower oil. Dose regimen (dose level or concentration of BHT per group, and frequency): 75 mg/kg bw

Study ID	**Reference: Pop et al. (2013)**
	Year the study was conducted (start, if available):
	Health outcome category: Endocrine disruptive effects
	Route of administration (diet, drinking water, gavage, subcutaneous, intraperitoneal, dermal, inhalation): Oral suspension. The positive control was given by subcutaneous injection into dorsal surface
	Period of exposure (pre-mating, mating, gestation, lactation, adult):
	Duration of the exposure: BHT was administrated once per day for three consecutive days in the morning between 9-10 a.m. The rats were weighed and sacrificed using diethyl ether at 24 hours after the last treatment
Study design	Sex and age of the initially exposed animals: Female, 17-21 days old
	Number of groups/number of animals per group: 2 control groups; 3 experimental groups; 10 animals in each group
	Randomisation procedures at start of the study: -
	Reducing (culling) of litters and method: -
	Number of pups per litter for next generation and methodology: -
	Number of pups per litter/animals for certain measurements and methodology: -
	Time of measurement/Observation period (premating, mating, gestation, lactation, adult): -
	Endpoints measured: The genital tract (ovaries, oviduct, uterine horns, body, cervix and vagina), the liver, spleen and kidneys were removed and weighed. The endometrial epithelium thickness was measured
	Methods to measure endpoints: Tissue collection, histopathological (H&E staining). Morphometric analysis was performed on midhorn cross sections of both uterine horns for all animals (n = 10 per treatment group) using Olympus Stream Basic image analysis software
	Estimated dietary exposure and method used (validation of the method, measures to avoid contamination of samples, limit of quantification and limit of detection, etc.)
Statistical analysis	Statistical methods: Statistical analysis on all morphometry data were performed using Shapiro-Wilk normality test followed by one way ANOVA and by the two-sample t-test, using R' software
Results	Concentration of the test compound in vehicle (analysed, stated, ambigous):
	Documentation of details for dose conversion when conducted: -
	Level of test compound in tissue or blood: -
	Results per dose or concentration (e.g. mean, median, frequency, measures of precision or variance): -
	No observed adverse effect level, lowest observed adverse effect level, benchmark dose/benchmark dose lower bound, and statistical significance of other dose levels (author's interpretation): Possible endocrine disruptive effects at the dose of 3x NOAEL
	Shape of dose response if reported by the authors: -
Other comments	

11 Appendix - Exposure

11.1 Literature search exposure

11.1.1 First literature search

The search was performed by Marita Heinz (Norwegian Institute of Public Health, the library) October 3 2017. The total result was 3711.

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Result: 1470

1	Butylated Hydroxytoluene/	2155
2	("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4 methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy tolu*" or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or "dibutyl 4 hydroxytolu*" or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321).mp.	3805
3	1 or 2	3805
4	Food Contamination/ or Food Packaging/ or exp Food/ or exp Cosmetics/ or Air Pollution/ or Air/ or Air Pollution, Indoor/ or Dust/	1310497
5	(food? or oil? or migration? or "contact material?" or cosmetic? or "care product?" or sunscreen* or "skin cream?" or "skin lotion?" or "body lotion?" or "dermal cream?" or "skin care" or lipstick? or "lip gloss*" or "lip balm?" or mascara? or eyeliner? or "eye shadow?" or "eyebrow pencil?" or blush* or "face powder?" or foundation* or perfume? or moisturi?er? or "skin cleanser*" or deodourant? or deodorant? or "hair care" or air or dust or housedust).tw.	1061604
6	4 or 5	2152126
7	3 and 6	1530

Database: Embase <1974 to 2017 October 02>

Dato: October 3 2017

Antall treff: 1518

1	butylcresol/	5036
2	("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4	6346

	methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy tolu*" or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or "dibutyl 4 hydroxytolu*" or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321).mp.	
3	1 or 2	6346
4	exp food/ or food packaging/ or food contamination/ or exp cosmetic/ or air pollution/ or air/ or air pollutant/ or indoor air pollution/ or house dust/	1090660
5	(food? or oil? or migration? or contact material? or cosmetic? or "care product?" or sunscreen* or "skin cream?" or "skin lotion?" or "body lotion?" or "dermal cream?" or "skin care" or lipstick? or "lip gloss*" or "lip balm?" or mascara? or eyeliner? or "eye shadow?" or "eyebrow pencil?" or blush* or "face powder?" or foundation* or perfume? or moisturi?er? or "skin cleanser*" or deodourant? or deodorant? or "hair care" or air or dust or housedust).tw.	1362547
6	4 or 5	2120223
7	3 and 6	1918
8	elsevier.cr.	22844501
9	7 and 8	1557

Database: ISI Web of Science
Result: 1349

# 3	**1,349**	#2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 2	**2,214,869**	**TOPIC:** ((food$ or oil$ or migration$ or "contact material$" or cosmetic$ or "care product$" or sunscreen* or "skin cream$" or "skin lotion$" or "body lotion$" or "dermal cream$" or "skin care" or lipstick$ or "lip gloss*" or "lip balm$" or mascara$ or eyeliner$ or "eye shadow$" or "eyebrow pencil$" or blush* or "face powder$" or foundation* or perfume$ or moisturizer$ or moisturiser$ or "skin cleanser*" or deodourant$ or deodorant$ or "hair care" or air or dust or housedust)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 1	**3,794**	**TOPIC:** (("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4 methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy tolu*" or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or "dibutyl 4 hydroxytolu*" or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

Database: Scopus

Result: 1562

19	#9 AND #18	1,562 document results
18	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	3,564,177 document results
17	ABS ((foundation* OR perfume* OR moisturizer* OR moisturiser* OR "skin cleanser*" OR deodourant* OR deodorant* OR "hair care" OR air OR dust OR housedust))	1,557,322 document results
16	TITLE ((foundation* OR perfume* OR moisturizer* OR moisturiser* OR "skin cleanser*" OR deodourant* OR deodorant* OR "hair care" OR air OR dust OR housedust))	365,866 document results
15	ABS ((lipstick* OR "lip gloss*" OR "lip balm*" OR mascara* OR eyeliner* OR "eye shadow*" OR "eyebrow pencil*" OR blush* OR "face powder*"))	3,314 document results
14	TITLE ((lipstick* OR "lip gloss*" OR "lip balm*" OR mascara* OR eyeliner* OR "eye shadow*" OR "eyebrow pencil*" OR blush* OR "face powder*"))	1,214 document results
13	ABS ((cosmetic* OR "care product*" OR sunscreen* OR "skin cream*" OR "skin lotion*" OR "body lotion*" OR "dermal cream*" OR "skin care"))	71,774 document results
12	TITLE ((cosmetic* OR "care product*" OR sunscreen* OR "skin cream*" OR "skin lotion*" OR "body lotion*" OR "dermal cream*" OR "skin care"))	17,064 document results
11	ABS ((food OR food? OR oil OR oil? OR migration OR migration? OR "contact material*"))	1,733,621 document results
10	TITLE ((food OR food? OR oil OR oil? OR migration OR migration? OR "contact material*"))	600,175 document results
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	5,440 document results
8	ABS ((hydroxybutyltolu* OR impruvol OR ionol OR vianol OR e321))	625 document results
7	TITLE ((hydroxybutyltolu* OR impruvol OR ionol OR vianol OR e321))	253 document results
6	ABS ((butylcresol OR "butyl hydroxy tolu*" OR "butylated 4 hydroxytolu*" OR "butylated hydroxytolu*" OR "butylhydroxy tolu*" OR butylhydroxytolu* OR butyloxytolu* OR dalpac OR dbpc OR dibunol OR "dibutyl 4 hydroxytolu*" OR dibutylhydroxytolu*))	3,715 document results
5	TITLE ((butylcresol OR "butyl hydroxy tolu*" OR "butylated 4 hydroxytolu*" OR "butylated hydroxytolu*" OR "butylhydroxy tolu*" OR butylhydroxytolu* OR butyloxytolu* OR dalpac OR dbpc OR dibunol OR "dibutyl 4 hydroxytolu*" OR dibutylhydroxytolu*))	866 document results
4	ABS (("2,6 ditert.butyl 4 methylphenol" OR "2,6 ditert.butyl para cresol" OR "3,5 di tert butyl 4 hydroxytolu*" OR "4 methyl 2,6 di(tert	289 document results

	butyl)phenol" OR "4 Methyl 2,6 ditertbutylphenol" OR "2,6 Di t butyl 4 methylphenol" OR "2,6 Di tert butyl p cresol"))	
3	TITLE (("2,6 ditert.butyl 4 methylphenol" OR "2,6 ditert.butyl para cresol" OR "3,5 di tert butyl 4 hydroxytolu*" OR "4 methyl 2,6 di(tert butyl)phenol" OR "4 Methyl 2,6 ditertbutylphenol" OR "2,6 Di t butyl 4 methylphenol" OR "2,6 Di tert butyl p cresol"))	43 document results
2	ABS (("1,3 di tert butyl 2 hydroxy 5 methylbenzene" OR "2,3 di tert butyl 4 methylphenol" OR "2,6 di tert butyl 4 methylphenol" OR "2,6 di tert butyl para cresol" OR "2,6 di(tert butyl) 1,4 cresol" OR "2,6 ditert. butyl 4 methylphenol"))	431 document results
1	TITLE (("1,3 di tert butyl 2 hydroxy 5 methylbenzene" OR "2,3 di tert butyl 4 methylphenol" OR "2,6 di tert butyl 4 methylphenol" OR "2,6 di tert butyl para cresol" OR "2,6 di(tert butyl) 1,4 cresol" OR "2,6 ditert. butyl 4 methylphenol"))	78 document results

Database: Cochrane Database of Systematic Reviews : Issue 10 of 12, October 2017, Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015, Cochrane Central Register of Controlled Trials : Issue 9 of 12, September 2017, NHS Economic Evaluation Database : Issue 2 of 4, April 2015, Health Technology Assessment Database : Issue 4 of 4, October 2016

Result: 37

ID	Search	Hits
#1	[mh ^"Butylated Hydroxytoluene"]	8
#2	("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4 methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy tolu*" or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or "dibutyl 4 hydroxytolu*" or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321):ti,ab	112
#3	("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4 methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or "butyl hydroxy tolu*" or "butylated 4 hydroxytolu*" or "butylated hydroxytolu*" or "butylhydroxy tolu*" or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or "dibutyl 4 hydroxytolu*" or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321) in Other Reviews, Technology Assessments and Economic Evaluations	2
#4	#1 or #2 or #3	115
#5	[mh ^"Food Contamination"]	62
#6	[mh ^"Food Packaging"]	25

#7	[mh Food]	27607
#8	[mh Cosmetics]	2754
#9	[mh ^"Air Pollution"]	77
#10	[mh ^Air]	520
#11	[mh ^"Air Pollution, Indoor"]	173
#12	[mh ^Dust]	287
#13	(food or food? or oil or oil? or migration or migration? or "contact material*" or cosmetic* or "care product*" or sunscreen* or "skin cream*" or "skin lotion*" or "body lotion*" or "dermal cream*" or "skin care" or lipstick* or "lip gloss*" or "lip balm*" or mascara* or eyeliner* or "eye shadow*" or "eyebrow pencil*" or blush* or "face powder*" or foundation* or perfume* or moisturizer* or moisturiser* or "skin cleanser*" or deodourant* or deodorant* or "hair care" or air or dust or housedust):ti,ab	43564
#14	(food or food? or oil or oil? or migration or migration? or "contact material*" or cosmetic* or "care product*" or sunscreen* or "skin cream*" or "skin lotion*" or "body lotion*" or "dermal cream*" or "skin care" or lipstick* or "lip gloss*" or "lip balm*" or mascara* or eyeliner* or "eye shadow*" or "eyebrow pencil*" or blush* or "face powder*" or foundation* or perfume* or moisturizer* or moisturiser* or "skin cleanser*" or deodourant* or deodorant* or "hair care" or air or dust or housedust) in Other Reviews, Technology Assessments and Economic Evaluations	3692
#15	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	69104
#16	#4 and #15	42

Database: Epistemonikos
Result: 6

("1,3 di tert butyl 2 hydroxy 5 methylbenzene" or "2,3 di tert butyl 4 methylphenol" or "2,6 di tert butyl 4 methylphenol" or "2,6 di tert butyl para cresol" or "2,6 di(tert butyl) 1,4 cresol" or "2,6 ditert. butyl 4 methylphenol" or "2,6 ditert.butyl 4 methylphenol" or "2,6 ditert.butyl para cresol" or "3,5 di tert butyl 4 hydroxytolu*" or "4 methyl 2,6 di(tert butyl)phenol" or "4 Methyl 2,6 ditertbutylphenol" or "2,6 Di t butyl 4 methylphenol" or "2,6 Di tert butyl p cresol" or butylcresol or ("butyl hydroxy" and tolu*) or ("butylated 4" and hydroxytolu*) or (butylated and hydroxytolu*) or (butylhydroxy amd tolu*) or butylhydroxytolu* or butyloxytolu* or dalpac or dbpc or dibunol or ("dibutyl 4" and hydroxytolu*) or dibutylhydroxytolu* or hydroxybutyltolu* or impruvol or ionol or vianol or E321) AND (food or foods or oil or oils or migration or migrations or "contact material" or "contact materials" or cosmetic* or "care product" or "care products" or sunscreen* or "skin cream" or "skin creams" or "skin lotion" or "skin lotions" or "body lotion" or "body lotions" or "dermal cream" or "dermal creams" or "skin care" or lipstick* or "lip gloss" or "lip glosses" or "lip balm" or "lip balms" or mascara* or eyeliner* or "eye shadow" or "eye shadows" or "eyebrow pencil" or "eyebrow pencils" or blush* or "face powder" or "face powders" or foundation* or perfume* or moisturizer* or moisturiser* or "skin cleanser" or "skin cleansers" or deodourant* or deodorant* or "hair care" or air or dust or housedust)

11.1.2 Second literature search

The search was performed by Jens Rohloff January 30th 2018.

Database: SciFinder, American Chemical Society (ACS)

Result: 708

SEARCH METHOD

1. «128-37-0» «food»

- 1137 references received
- remove duplicates (1136 refs)
- Refine search
  - Language: English (563 refs)
  - Reference type: inclusion of *books*, *clinical trials*, *dissertations*, *journal articles*, *reports* and *reviews* (403 refs)

2. «128-37-0» «cosmetic»

- 1470 references received
- remove duplicates (1456 refs)
- Refine search
  - Language: English (700 refs)
  - Reference type: inclusion of *books*, *clinical trials*, *dissertations*, *journal articles*, *reports* and *reviews* (195 refs)

3. «128-37-0» «care»

- 715 references received
- remove duplicates (714 refs)
- Refine search
  - Language: English (387 refs)
  - Reference type: inclusion of *books*, *clinical trials*, *dissertations*, *journal articles*, *reports* and *reviews* (110 refs)

11.2 Publication selection, evaluation of data quality and data extraction

11.2.1 Publication selection

The first literature search, performed by a librarian October 3 2017, identified 3711 articles. Several publications focusing on antioxidant properties/antioxidant activity were identified electronically and were excluded. Titles and abstracts of 411 articles were screened against the inclusion/exclusion criteria checklist (Table 11.2.1-1). Two persons performed this primary screening. Articles that did not meet the inclusion criteria were excluded. The full texts of the 47 articles that passed the primary screening were retrieved for screening against the inclusion/exclusion criteria checklist (Table 11.2.1-1). Two persons performed this screening.

The second literature search was performed by a member of the project group January 30 2018, in SciFinder, and 708 articles were identified. Titles and abstracts were screened against the inclusion/exclusion criteria checklist (Table 11.2.1-1). The full texts of the 32 articles that passed the primary screening were retrieved for screening against the inclusion/exclusion criteria checklist (Table 11.2.1-1). Two persons performed the screening.

Reference lists in some review articles identified in the literature searches were screened, and studies from this manual search were screened against the inclusion/exclusion criteria checklist (Table 11.2.1-1). Seven articles were included.

Table 11.2.1-1. Inclusion/exclusion criteria for the exposure assessment study selection.

Literature screening for concentration data related to the following sub-questions: 1: What is the exposure to BHT from foods? 2: What is the exposure to BHT from PCPs? 3: What is the exposure to BHT from indoor dust? 4: What is the exposure to BHT from indoor air?		
Study design	Inclusion	All publications that address analyses of BHT as concentrations
	Exclusion	Human studies, animal studies, *in vitro* studies
Study characteristics	Inclusion	Studies presenting analytical data and biomonitoring data on BHT
Analytical method	Inclusion	All methods
Sources and outcome of interest	Inclusion	BHT concentrations in foods, PCPs, indoor dust and indoor air
	Exclusion	Studies reporting exclusively on toxicity or preventive/beneficial effects Studies reporting exclusively on the antioxidant properties/activities Studies reporting exclusively on BHT in pharmaceuticals or other sources

Literature screening for concentration data related to the following sub-questions: 1: What is the exposure to BHT from foods? 2: What is the exposure to BHT from PCPs? 3: What is the exposure to BHT from indoor dust? 4: What is the exposure to BHT from indoor air?		
Language of the full text	Inclusion	English, Norwegian, Swedish, Danish, German
Publication type	Inclusion	Primary research articles Risk assessments and reports
	Exclusion	Editorials Letters to the editor Book chapters Meeting abstracts and posters

11.2.2 Result of the evaluation of data quality

An overview of the included articles, all with a total score of 3.5 or higher, is given in Table 11.2.2-1. Articles with a total score of 3.5 or higher, but which were not included is shown in Table 11.2.2-2 (justification is given below the table). An overview of articles excluded due to a total score less than 3.5 is shown in Table 11.2.2-3.

Table 11.2.2-1. An overview of included articles.ACN = acetonitrile; CAN:Pen = acetonitrile:Pentane; DCM = dichloromethane; EtAc = ethyl acetate; EtOH = ethanol; HSSPME = headspace-solid-phase microextraction; HS = headspace; Hx = hexane; MeOH = methanol; SFE = supercritical fluid extraction; SPME = solid-phase microextraction.

Reference	Solvent	How appropriate was the solvent used for the extraction method (diethyl ether = hexane > EtOH > MeOH not H_2O)?	Which instrumental analysis was used (e.g. GC-MS/GC-FID and HPLC-UVD, LC-MS)?	Which validation method has been used, and how were the data presented (LOD/LOQ, internal/external calibration, number of samples, statistical methods)?	Total score (1/5 x sample extraction+1/5 x instrumental analysis+3/5 x validation and data presentation)	Comment method
Liu et al. (2017)	DCM/Hx	4.0	3.5	5.0	4.5	
Cacho et al. (2016)	Hx:ACN	3.0	5.0	4.0	4.0	Potential loss of BHT through 2-phase Hx:ACN extraction
Wang et al. (2016a)	DCM:Hx	4.0	5.0	4.0	4.2	
Myers et al. (2015)	MeOH:ACN	3.5	4.5	4.0	4.0	

Reference	Solvent	How appropriate was the solvent used for the extraction method (diethyl ether = hexane > EtOH > MeOH not H_2O)?	Which instrumental analysis was used (e.g. GC-MS/GC-FID and HPLC-UVD, LC-MS)?	Which validation method has been used, and how were the data presented (LOD/LOQ, internal/external calibration, number of samples, statistical methods)?	Total score (1/5 x sample extraction+1/5 x instrumental analysis+3/5 x validation and data presentation)	Comment method
Alvarez-Rivera et al. (2014b)	SPME/HSSPME	3.5	5.0	4.5	4.4	Test of fibres, solution conc. and a wide range of AOXs; profound and scientifically sound
Celeiro et al. (2014)	EtAc or Hx:Acetone	3.5	4.5	4.0	4.0	
Shasha et al. (2014)	MeOH:ACN	3.0	3.5	4.0	3.7	
Lin et al. (2013)	MeOH	2.0	3.5	4.0	3.5	MeOH too polar for suitable extraction
Akkbik et al. (2011a)	Hx:ACN	3.0	4.0	5.0	4.4	Potential loss of BHT through 2-phase Hx:ACN extraction
Sanchez-Prado et al. (2011)	Hx:Acetone	4.5	4.0	4.5	4.4	
Edin et al. (2010)	ACN + di-tert butylphenol	3.0	4.0	3.5	3.5	

Reference	Solvent	How appropriate was the solvent used for the extraction method (diethyl ether = hexane > EtOH > MeOH not H_2O)?	Which instrumental analysis was used (e.g. GC-MS/GC-FID and HPLC-UVD, LC-MS)?	Which validation method has been used, and how were the data presented (LOD/LOQ, internal/external calibration, number of samples, statistical methods)?	Total score (1/5 x sample extraction+1/5 x instrumental analysis+3/5 x validation and data presentation)	Comment method
Lundebye et al. (2010)	ACN	3.0	4.5	5.0	4.5	
Medeiros et al. (2010)	EtOH	2.5	3.5	4.0	3.6	EtOH too polar for suitable extraction
Sanchez-Prado et al. (2010)	Hx:Acetone	4.0	4.0	4.5	4.3	
Yuan (2010)	HS on-site	3.5	4.0	4.0	3.9	Company article
Garcia-Jimenez et al. (2009)	Hx+MeOH	3.0	4.0	3.5	3.5	
Pattono et al. (2009)	MeOH:Hx	3.0	4.0	3.5	3.5	
Saad et al. (2007)	MeOH:ACN	3.5	3.5	4.0	3.8	
Lee et al. (2006)	MeOH + SFE	4.0	4.5	3.0	3.5	
Lin et al. (2003)	Different solvents	4.0	4.0	3.0	3.5	Relevant data
Yang et al. (2002)	EtAc	3.0	3.5	4.0	3.7	

Reference	Solvent	How appropriate was the solvent used for the extraction method (diethyl ether = hexane > EtOH > MeOH not H_2O)?	Which instrumental analysis was used (e.g. GC-MS/GC-FID and HPLC-UVD, LC-MS)?	Which validation method has been used, and how were the data presented (LOD/LOQ, internal/external calibration, number of samples, statistical methods)?	Total score (1/5 x sample extraction+1/5 x instrumental analysis+3/5 x validation and data presentation)	Comment method
Maziero et al. (2001)	ACN	3.0	3.5	5.0	4.3	Intake data presented
Ni et al. (2000)	MeOH	2.0	3.5	4.0	3.5	MeOH too polar for suitable extraction
Ruiz et al. (1999)	EtAc	3.0	4.0	4.0	3.8	
DeWitt and Finne (1996)	ACN:Hx	3.5	3.0	4.0	3.7	
Boussenadji et al. (1993)	MeOH	2.0	4.0	4.0	3.6	MeOH too polar for suitable extraction

Table 11.2.2-2. An overview of excluded articles, with a total score of 3.5 or higher.

Reference	Solvent	How appropriate was the solvent used for the extraction method (diethyl ether = hexane > EtOH > MeOH not H_2O)?	Which instrumental analysis was used (e.g. GC-MS/GC-FID and HPLC-UVD, LC-MS)?	Which validation method was used, and how was the datapresented (LOD/LOQ, internal/external calibration, number of samples, statistical methods)?	Total score (1/5 x sample extraction+1/5 x instrumental analysis+3/5 x validation and data presentation)	Comment method
Suh et al. (2005)	ACN:Pen	3.5	3.5	4.0	3.8	
Ishiwata et al. (2003)		2.0	3.0	5.0	4.0	Intake from other studies also presented
Tombesi and Freije (2002)	HS-SPME	3.5	3.5	3.5	3.5	

Three reports that got a total score of 3.5 or higher were excluced for other reasons. Suh et al. (2005) was excluded due to lacking LOD/LOQ. Ishiwata et al. (2003) had a large number of analysed samples, but the quality of analysis was not verifiable due to lack of LOD and LOQ values.

The article by Tombesi and Freije (2002) analysed drinking water in Argentina. We decided not to include the measured BHT levels in our exposure estimates, not even in the high concentration dataset, because Argentina was considered to be too distant from Norway to be a source of drinking water.

Table 11.2.2-3. Articles excluded due to a total score less than 3.5.

Reference	How appropriate was the solvent used for the extraction method (diethyl ether = hexane > EtOH > MeOH not H_2O)?	Which instrumental analysis was used (e.g. GC-MS/GC-FID and HPLC-UVD, LC-MS)?	Which validation method was used, and was the data presented (LOD/LOQ, internal/external calibration, number of samples, statistical methods)?	Total score (1/5 x sample extraction+1/5 x instrumental analysis+3/5 x validation and data presentation)
Wang and Liu (2017)	2.5	2.0	2.0	2.1
Sun et al. (2017)	2.0	5.0	1.0	2.0
Haitao et al. (2015)	1.0	3.0	2.0	2.0
Liu et al. (2015)	2.0	4.0	1.0	1.8
Chang et al. (2013)	3.0	4.0	1.0	2.0
Beldi et al. (2012)	5.0	4.0	1.5	2.7
Chen et al. (2012)	1.0	3.0	1.0	1.4
Vaghela et al. (2011)	2.5	4.5	2.0	2.6
Akkbik et al. (2011a)	3.0	4.0	1.0	2.0
Darji et al. (2010)	3.0	3.5	1.0	1.9
Soliman et al. (2007)	4.0	5.0	1.0	2.4
Guan et al. (2006)	2.5	3.5	1.0	1.8
Ding et al. (2006)	2.0	3.5	1.0	1.7
Guan et al. (2005)	2.5	3.5	1.0	1.8
Pinho et al. (2000)	3.0	3.5	1.0	1.9
Riber et al. (2000)	2.0	4.0	1.0	1.8
Sarbach et al. (1996)	3.5	4.0	1.0	2.1
Ceballos and Fernandez (1995)	3.0	2.5	1.0	1.7
Waseem and Kaw (1994)	1.0	3.0	2.0	2.0
Marin and Shlyapnikov (1991)	2.0	2.0	1.0	1.4
Llaurado (1985)	1.0	1.0	1.0	1.0
Buttery and Stuckey (1961)	4.0	3.0	1.0	2.0

11.2.3 Data extraction

An overview of the included studies with data on BHT concentrations in foods, PCPs, air and dust is given in Table 11.2.3-1. Description of the studies follows after the table.

Table 11.2.3-1. Overview of the included studies with data on BHT in foods, PCPs, air and dust.

Source category	Reference	Origin of samples	Sample	Chemical analysis	Rating
Food and drinking water	Cacho et al. (2016)	Spain	Vegetable oils	GC/MS	4.0
	Shasha et al. (2014)	Zimbabwe	Oils, butter, margarine and starch-based snacks	HPLC-UV	3.7
	Lin et al. (2013)	China	Blend vegetable oil	Voltametry, HPLC-DAD	3.5
	Edin et al. (2010)	USA	Chewing gum	GC-MS SIM	3.5
	Lundebye et al. (2010)	Norway	Farmed fish	HPLC-UV	4.5
	Medeiros et al. (2010)	Brazil	Mayonnaise	HPLC-UV + Voltametry	3.6
	Yuan (2010)	USA	Crackers, coffee creamer, instant noodles, sausage and tea leaves	HS-GC/MS	3.9
	Garcia-Jimenez et al. (2009)	Spain	Chewing gum	HPLC/DAD	3.5
	Pattono et al. (2009)	Italy	Milk	GC/MS	3.5
	Saad et al. (2007)	Malaysia	Cooking oil, margarine and butter, and cheese	HPLC-UV	3.8
	Suh et al. (2005)	Korea	Chewing gum, breakfast cereal	GC-FID	3.8
	Ishiwata et al. (2003)	Japan	Fats and oils, dried marine products, chewing gum, confectionary "kashi"	HPLC	4
	Lin et al. (2003)	Taiwan	Chewing gum	GC-FID	3.5
	Tombesi and Freije (2002)	Argentina	Drinking water	GC-MS	3.5
	Yang et al. (2002)	Taiwan	Soybean oil, olive oil, vegetable oil, blended oil, sunflower oil, fish oil, peanut oil, butter, cheese, margarine, mayonnaise and salad dressing	GC-FID	3.7

Source category	Reference	Origin of samples	Sample	Chemical analysis	Rating
	Maziero et al. (2001)	Brazil	Soybean oil, corn oil, hydrogenated vegetable fat, margarine, vegetable cream, halvarina	HPLC-UV	4.3
	Ni et al. (2000)	China	Peanut oil, sesame oil, salad oil, cake, biscuit, milk candy	Voltammetry	3.5
	Ruiz et al. (1999)	Spain	Chewing gum	HPLC-ED	3.8
	DeWitt and Finne (1996)	USA	Pepperoni w/capasaicinoid-oleoresin	HPLC + GC/FID	3.7
	Boussenadji et al. (1993)	France	Chewing gum	HPLC UV+ECD	3.6
PCPs	Myers et al. (2015)	USA	Deodorant, foundation, toothpaste, hand sanitiser, lipstick, hand lotion	LC-MS/MS	4.0
	Alvarez-Rivera (2014)	Spain	Facial cleansing milk, eye make-up remover, deodorant, baby body milk, sunscreen, after shave, baby after sun, make-up, hair conditioner	GC–MS/MS	4.4
	Celeiro 2014	Spain	Shower gel, liquid soap, baby moisturising lotion, sunblock, lipstick, gloss, deodorant	GC-MS SIM or GC-MS/MS	4.0
	Akkbik 2011	Malaysia	Sunscreen cream, milk lotion, hair gel, hair oil	HPLC-UV/Vis	4.4
	Sanchez-Prado 2011	Spain	Hand soaps, liquid soaps, shampoo	GC-MS	4.4
	Sanchez-Prado 2010	Spain	Moisturising cream, moisturising lotion, antiwrinkle cream, hand cream, sunscreen cream, baby moisturising lotion, after-sun cream, shampoo	GC-MS	4.3
	Garcia-Jimenez (2009)	Spain	Body oil	HPLC/DAD	3.5
	Lee (2006)	Taiwan	Lanoline cream, skin milk, cream	LC/MS	3.5
	Boussenadji (1993)	France	Skin care gel	HPLC UV+ECD	3.6
	Liu et al. (2017)	China	Indoor dust (rural and urban)	HPLC-MS/MS	4.5

Source category	Reference	Origin of samples	Sample	Chemical analysis	Rating
Indoor dust	Wang et al. (2016a)	Dust samples from 12 countries	House dust	GC/MS SIM	4.2

Liu et al. (2017) collected 75 dust samples from urban and rural homes in Shandong Province of China. Seven synthetic phenolic antioxidants were detected in most of the samples by HPLC-MS/MS. BHT constituted 74% and 43% of the synthetic phenolic antioxidants found in urban indoor dust and in rural indoor dust, respectively. Three BHT transformation products, 2,6-di-tert-butyl-1,4-benzoquinone (BHT-Q), 2,6-di-tert-butyl-4-hydroxy- 4-methyl-2,5-cyclo-hexadienone (BHT-quinol) and 3,5-di-tert-butyl-4-hydroxybenzal-dehyde (BHT-CHO), were also detected in most of the urban and rural indoor dust samples (>97%).

Study ID	**Reference: Liu et al. (2017)**
	Year the study was conducted/published: -
	Source category: Indoor dust urban and indoor dust rural
Funding	Funding source: The National Natural Science Foundation (21622705, 21577151), the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB14010400), and Youth Innovation Promotion Association CAS projects Public/private: Public
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: DCM/Hx
	Calibration: The linearity of the calibration curve (r^2) was >0.99
	LOD: 10 µg/kg DW
	Recovery data: Average recovery was 89%
	Instrument/detector: HPLC-MS/MS
Results	Number of samples: 55 (urban) and 20 (rural)
	Concentration: In µg/kg dry weight Indoor dust urban: median=1880; min=852; max=18400 Indoor dust rural: median=998; min=163; max=2330
Other comments	

Cacho et al. (2016) determined BHT in several vegetable edible oil samples. The analyses were carried out by gas chromatography–mass spectrometry (GC–MS) using microvial insert large volume injection. The reported mean values, in ng/g, were 1.51 in corn oil, ranged from 0.64 to 5.00 in olive oil, 0.68 in peanut oil and 0.75 in sesame oil. In sunflower oil, BHT ranged from not detected to 12.7. The LOD was 0.04 ng/g, the LOQ was 0.10 ng/g.

Study ID	**Reference: Cacho et al. (2016)**
	Year the study was conducted/published: not specified
	Source category: Food
Funding	Funding source: Financial support of the Comunidad Autónoma de la Región de Murcia (Fundación Séneca 19888/GERM/15 and Project 19462/PI/14). J.I. Cacho also acknowledges a fellowship from the University of Murcia. Public/private: Public
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: Hx:ACN
	Calibration:
	LOD: 0.04 ng/g LOQ: 0.10 ng/g
	Recovery data:
	Instrument/detector: GC/MS
Results	Number of samples: 12
	Concentration: Olive oil – mean=2.68 µg/kg; min=0.64 µg/kg; max=5.00 µg/kg. Sunflower oil – mean=4.89 µg/kg; min=0.0 µg/kg; max=12.7 µg/kg.
Other comments	Spain Potential loss of BHT through 2-phase Hx:ACN extraction

Wang et al. (2016a) determined the concentration of nine synthetic phenolic antioxidants, including BHT, and their metabolites/degradation products in 339 indoor dust samples from homes and microenvironments collected from 12 countries. BHT was analysed using GC/MS SIM. BHT was found in 99.5% of the samples at concentrations that ranged from <LOQ to 118 µg/g in samples from homes and 0.10 to 3460 µg/g in samples from microenvironments. The major BHT derivatives found in dust samples were BHT−CHO, BHT−OH and BHT−Q. The LOD was not reported. The LOQs was 1.2 ng/g for BHT.

Study ID	**Reference: Wang et al. (2016a)**
	Year the study was conducted/published: -
	Source category: Indoor dust
Funding	Funding source: Grant (1U38EH000464-01) from the Centers for Disease Control and Prevention (CDC, Atlanta, GA) to Wadsworth Center, New York State Department of Health Public/private: Public
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: DCM:Hx
	Calibration:
	LOD: - LOQ: 1.2 µg/kg
	Recovery data: Recovery from spiked dust was 106±12%
	Instrument/detector: GC/MS SIM
Results	Number of samples: 339 samples from 12 countries

	Concentration: BHT ranged from 0.01 to 35.1 µg/g. The median ranged from 0.17 to 13.7
Other comments	MeOH too polar for suitable extraction

To determine preservatives, including BHT, in cosmetics and personal care products, an LC-MS/MS method was developed (Myers et al., 2015). Cosmetic and personal care samples were purchased from local stores. The reported BHT concentrations, in %[w/w], was 0.07 in deodorant, 0.00 and 0.01 in foundation, 0.02 in toothpaste, 0.02 in hand sanitiser, 0.06 in lipstick and 0.02 in hand lotion. The LOD was 4.02 µg/mL and the LOQ was 13.4 µg/mL.

Study ID	**Reference: Myers et al. (2015)**
	Year the study was conducted/published: -
	Source category: Cosmetics and health care
Funding	Funding source: The Forensic Science Program in the Chemical and Physical Sciences Department of Cedar Crest College and the 2014 Carol DeForest Research Grant, Northeastern Association of Forensic Scientists Public/private:
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: MeOH:ACN
	Calibration: R^2=0.9943
	LOD: 4.02 µg/mL LOQ: 13.4 µg/mL
	Recovery data: -
	Instrument/detector: LC-MS/MS
Results	Number of samples:
	Concentration: The reported BHT concentrations, in %[w/w], was 0.07 in deodorant, 0.00 and 0.01 in foundation, 0.02 in toothpaste, 0.02 in hand sanitiser, 0.06 in lipstick and 0.02 in hand lotion
Other comments	

BHT in cosmetic products was analysed using a methodology based on solid-phase microextraction followed by GC–MS/MS (Alvarez-Rivera et al., 2014b). The reported concentrations of BHT, in µg per 100g, was 85.2 in facial cleansing milk, 43.9 in eye make-up remover, 53.6 in deodorant, 1830 in baby body milk, 14.1 in sunscreen, 30.6 in after shave, 1990 in baby after sun, 34.5 in make-up and 71.1 in hair conditioner (rinse of product). LOD was 0.04 µg/g, LOQ was 0.13 µg/g.

Study ID	**Reference: Alvarez-Rivera et al. (2014b)**
	Year the study was conducted/published: -
	Source category: Cosmetics
Funding	Funding source: Public/private:
	Analysis: X

Aim of the study	Exposure:
	Migration:
Methods for analysis	Sample extraction: SPME/HSSPME
	Calibration: R^2=0.9999
	LOD: 0.04 µg/g LOQ: 0.13 µg/g
	Recovery data:
	Instrument/detector: GC–MS/MS
Results	Number of samples: 19
	Concentration: BHT concentration in µg/g. BHT in facial cleansing milk 85.2; 43.9 in eye make-up remover; 53.6 in deodorant; 1830 in baby body milk; 14.1 in sun screen; 30.6 in after shave; 1990 in baby after sun; 34.5 in make-up; 71.1 in hair conditioner (rinse of product). In the rest of the samples BHT was below LOQ
Other comments	

BHT in cosmetics was determined using GC-MS SIM or GC-MS/MS (Celeiro et al., 2014). The reported concentrations of BHT, in µm/g, was 0.160 in shower gel, 0.130 in liquid soap, 1057 in baby moisturising lotion, 14.5 in sunblock, 2996 in lipstick, 9.63 in gloss lipstick, 6.23, 174, 13.4 and 29.4 in deodorant. The LOD was 0.006 µg/g and the LOQ was 0.31 µg/g.

Study ID	**Reference: Celeiro et al. (2014)**
	Year the study was conducted/published: -
	Source category: Cosmetics
Funding	Funding source: FEDER funds and projectsCTQ2010-19831 (Ministerio de Ciencia e Innovacion, Spain) andCN 2012/299 (Research group's consolidation program, Xunta deGalicia, Spain) Public/private: Public
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: EtAc or Hx:Acetone
	Calibration: The correlation coefficient was 0.9990
	LOD: 0.006 µg/g LOQ: 0.31 µg/g
	Recovery data:
	Instrument/detector: GC-MS SIM or GC-MS/MS
Results	Number of samples: 17
	Concentration: BHT in µm/g. Concentration in shower gel was 0.160; 0.130 in liquid soap; 1057 in baby moisturising lotion; 14.5 in sunblock; 2996 in lipstick; 9.63 in gloss lipstick; 6.23, 174, 13.4 and 29.4 in deodorant. In the rest of the samples BHT was not detected
Other comments	

Reversed phase HPLC-UV quantification was used to determine BHT in food items sold in supermarkets in Zimbabwe (manufacturing countries were Zimbabwe and South Africa)

(Shasha et al., 2014). The level of BHT in vegetable oils, in mg/kg, ranged from not detected to 67.3. The level of BHT in butter and margarine, in mg/kg, ranged from 7.8 to 158.6. In starch-based snacks the level of BHT, in mg/kg, ranged from 1.8 to 151.3. The LOD was 0.132 mg/kg. The LOQ was not reported.

Study ID	**Reference: Shasha et al. (2014)**
	Year the study was conducted/published: November 2013 to March 2014
	Source category: Food
Funding	Funding source: Not given Public/private: -
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: MeOH:ACN
	Calibration: Calibration curves R^2 were above 0.996 for all standards. Regression equations were y=13245x + 2657 for BHT
	LOD: 0.132 mg/kg
	Recovery data: Percentage recovery ranged from 74.5-89.9%.
	Instrument/detector:
Results	Number of samples: 23
	Concentration: Six cooking oil samples - BHT ranged from 9.8 to 67.3 mg/kg. Seven margarine types - BHT ranged from 10.4 to 158.6 mg/kg. Seven starch based-snacks samples – BHT ranged from 1.8 to 151.3 mg/kg.
Other comments	

Lin et al. (2013) developed a quantitative electroanalytical method for simultaneous determination of the antioxidants BHA, BHT and TBHQ. Using this method, BHT in corn oil, camellia oil, sesame oil, rapeseed oil and blend oil were analysed. BHT concentrations (in µg/g) was 29.1 in corn oil, 28.5 in camellia oil, 27.8 in sesame oil, 27.7 in rapeseed oil and 49.6 in blend oil. The LOD was 0.08 mg/L. The LOQ was not reported.

Study ID	**Reference: Lin et al. (2013)**
	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: The National Natural Science Foundation of China (NSFC-21065007), the State Key Laboratory of Food Science and Technology of Nanchang University (SKLF-MB-201002 and SKLFTS-200919). Public/private: -
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: MeOH
	Calibration: Calibrations was linear in the concentration range 0.20–2.20 µg/mL
	LOD: 0.08 µg/mL
	Recovery data: Recovery ranged from 96.3 to 102.6%

	Instrument/detector: HPLC-DAD
Results	Number of samples: 5
	Concentration: Five edible oil samples – BHT ranged from 28.1 to 50.2 µg/g
Other comments	

Akkbik et al. (2011a) developed an analytical method for evaluation and quality control of BHT by HPLC-UV/Vis in personal care products. Four types of personal care products, sun cream, milk lotion, hair gel and hair oil were purchased from several local supermarkets in Malaysia. For each type of personal care product, three commercial brands were collected. The concentration of BHT in 12 commercial personal care samples ranged from 0.16 to 2.30 mg/g. The LOD was 0.170 mg/L and the LOQ was 0.515 mg/L.

Study ID	**Reference: Akkbik et al. (2011a)**
	Year the study was conducted/published: -
	Source category: Cosmetics
Funding	Funding source: Syrian Ministry of Higher Education (a scholarship) Public/private: Public
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: Hx:ACN
	Calibration: Standards solution of BHT with concentrations of 1, 10, 25, 50, 75, 100, 125 and 250 mg/L were prepared. The calibration curves were obtained by plotting the peak area of chromatograms for BHT against the concentration in four replicates. Correlation coefficients (R^2) were 0.999
	LOD: 0.170 mg/L LOQ: 0.515 mg/L
	Recovery data: The recovery for BHT ranged from 83.2-108.9%
	Instrument/detector: HPLC UV/VIS
Results	Number of samples: 12
	Concentration: The concentration ranged from 0.16 to 2.30 mg/g
Other comments	Potential loss of BHT through 2-phase Hx:ACN extraction

BHT in cosmetics from national and international brands, purchased from local sources, was analysed by GC-MS (Sanchez-Prado et al., 2011). The BHT concentrations, given in % w/w, were 0.00933 and 0.000061 in hand soaps, and 0.000022 and 0.0010 in liquid soaps. The BHT concentration was below LOD in one sample of hand soap, in one sample of shampoo and one sample of liquid soap. The LOD was 0.3 µg/g and the LOQ was 0.99 µg/g.

Study ID	**Reference: Sanchez-Prado et al. (2011)**
	Year the study was conducted/published: -
	Source category: Cosmetics
Funding	Funding source: FEDER funds and project CTQ2010-19831 (Ministerio de Ciencia e Innovacion, Spain). Xunta de Galicia (postdoctoral contracts), Ministerio de Ciencia e

	Innovación (FPI grant) Public/private: -
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: Hx:Acetone
	Calibration: Calibration standards were prepared covering a concentration range from 0.02 to 10 µg/mL. The correlation coefficient (R) was 0.9987
	LOD: 0.3 µg/g LOQ: 0.99 µg/g
	Recovery data: The recovery studies on leave-on and rinse-off cosmetics gave satisfactory values
	Instrument/detector: GC-MS
Results	Number of samples:
	Concentration: BHT concentrationsare given in %, w/w. Hand soaps: 0.00933 and 0.000061; liquid soaps: 0.000022 and 0.0010 in liquid soaps. The BHT concentration was below LOD in one sample of hand soap, in one sample of shampoo and one sample of liquid soap.
Other comments	

BHT in chewing gum was determined using GC-MS SIM (Edin et al., 2010). The reported concentrations of BHT, in µg/g, was 92.3008, 128.4153, 150.2563, 136.0807, 131.8883 and 174.3833. The LOD and the LOQ was not reported.

	Reference: Edin et al. (2010)
Study ID	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: - Public/private: -
Aim of the study	Analysis: X
	Exposure:
	Migration:
Concentration in foods/non-foods	Food: x
	Cosmetics:
	Indoor dust:
	Indoor air:
Methods for analysis	Sample extraction: ACN + di-tert butylphenol
	Calibration:
	LOD: - LOQ: -
	Recovery data: Recovery ranged from 6.2738 to 57.1267
	Instrument/detector: GC-MS SIM
Results	Number of samples: 6
	Concentration: BHT ranged from 92.3008 to 174.3833 µg/g
Other comments	

Lundebye et al. (2010) examined levels of BHT in farmed Atlantic salmon, farmed Atlantic halibut, farmed cod and farmed rainbow trout. The highest BHT level, 7.6 mg/kg, was found in farmed Atlantic salmon fillets. The lowest BHT level, <40 µg/kg, was found in cod fillets. In salmon fillets, the mean BHT concentration was 3.9 mg/kg (n=24). In trout fillets, the mean BHT concentration was 2.6 mg/kg (n=16). In halibut fillets, the mean BHT concentration was 1.7 mg/kg. The LOD was 0.04 mg/kg. The LOQ was not reported.

Study ID	**Reference: Lundebye et al. (2010)**
	Year the study was conducted/published:
	Source category: Food
Funding	Funding source: Research Council of Norway (Project Numbers 143314/130 and 173287 Public/private: Public
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: ACN
	Calibration:
	LOD: 0.04 mg/kg
	Recovery data:
	Instrument/detector: HPLC-UV
Results	Number of samples: Farmed salmon – n=24; farmed trout – n=16; halibout – n=15; cod – n=4
	Concentration: Concentration in wet weight in fillets. Salmon - mean BHT concentration was 3.9 mg/kg (n=24); trout - mean BHT concentration was 2.5 mg/kg (n=16); halibut - mean BHT concentration was 1.7 mg/kg; cod – mean BHT<40
Other comments	

Medeiros 2010 used HPLC-UV + voltammetry to determinate BHT in mayonnaise. Three measurements of four samples were performed, and the BHT concentrations in mayonnaise, in mg/100g, ranged from 1.1 to 1.8. The LOD was 0.4 µmol/L. The LOQ was not reported.

Study ID	**Reference: Medeiros et al. (2010)**
	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: The Brazilian funding agencies FAPESP, CNPq and CAPES Public/private: -
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: EtOH
	Calibration:
	LOD: 0.4 µmol/L
	Recovery data:
	Instrument/detector: HPLC-UV + voltametry

Results	Number of samples: 4
	Concentration: BHT concentration,in mg/100g, ranged from 1.1 to 1.8
Other comments	EtOH too polar for suitable extraction

BHT in cosmetics was analysed using GC-MS (Sanchez-Prado et al., 2010). Different cosmetics from national and global companies were purchased from local stores. They included moisturising and antiwrinkle creams and lotions, hand creams, sunscreen and after-sun creams, and baby lotions. BHT concentrations given in %, w/w, were ranged from below LOD to 0.000027 in moisturising cream, was below LOD and 0.000010 in moisturising lotion, below LOD and 0.002681 in antiwrinkle cream, 0.035424 and 0.000905 in hand cream, 0.000109 in sunscreen cream, 0.034710 and 0.000070 in baby moisturising lotion, 0.000316 in hair conditioning lotion, and below LOD in shampoo and after-sun cream. The LOD was 0.0000041 (%, w/w) and the LOQ was 0.000013 (%, w/w).

Study ID	**Reference: Sanchez-Prado et al. (2010)**
	Year the study was conducted/published:
	Source category: Cosmetics
Funding	Funding source: Public/private:
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: Hx:Acetone
	Calibration:
	LOD: 0.0000041 (%, w/w) LOQ: 0.000013 (%, w/w)
	Recovery data:
	Instrument/detector: GC-MS
Results	Number of samples:
	Concentration: In %, w/w. In moisturising cream 0.000027, 0.000012 and 0.000015; 0.000010 in moisturising lotion; 0.002681 in antiwrinkle cream; 0.035424 and 0.000905 in hand cream; 0.000109 in sunscreen cream; 0.034710 and 0.000070 in baby moisturising lotion; and 0.000316 in hair conditioning lotion. The BHT concentration was below LOD in two samples of moisturizing cream, one sample of moisturising lotion, one sample of antiwrinkle cream, one sample of after-sun cream and one sample of shampoo
Other comments	

BHT in food was determined using HS-GC/MS (Yuan, 2010). The BHT concentration was given as mean value (n=3) in ng/g, and were 0.58 in crackers, 0.69 in coffee creamer, 0.68 in instant noodles, 0.59 in sausage and 0.56 in tea leaves. The LOD was not reported. The LOQ was 1 ng/g.

Study ID	**Reference: Yuan (2010)**
	Year the study was conducted/published:
	Source category: Food
Funding	Funding source: Perkin Elmer Public/private:
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: HS on-site
	Calibration: The instrument calibration included seven calibration levels in the working curve; the response of this calibration curve was linear (Table 2). Additionally, the method is precise throughout the calibration range, as demonstrated by the relative standard deviation of 3.2% at the calibration limit (1 ng, n=5) and 1.9% at 10 ng (n=5)
	LOD: - LOQ: 1 ng/g
	Recovery data:
	Instrument/detector: HS-GC/MS
Results	Number of samples: 5
	Concentration: BHT mean concentration (n=3) in ng/g, were 0.58 in crackers, 0.69 in coffee creamer, 0.68 in instant noodles, 0.59 in sausage and 0.56 in tea leaves
Other comments	

Garcia-Jimenez et al. (2009) used an ultra-short C18 monolithic column combined with flow injection analysis for the determination of BHT inn food and cosmetic samples. BHT values, the mean from three determinations in mg/kg, was 505.0 in body oil, 139.0 in chewing gum and 194.1 in bouillon cube spiked with BT (spiked with 200 mg/kg). The LOD was 0.55 µg/mL and the LOQ was 1.83 µg/mL.

Study ID	**Reference: Garcia-Jimenez et al. (2009)**
	Year the study was conducted/published:
	Source category: Food
Funding	Funding source: The Ministerio de Educación y Cultura, Dirección General de Enseñanza Superior (Spain) (Projects CTQ2005-09060-CO2-01 and CTQ2005-09060-CO2-02) Public/private:
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: Hx+MeOH
	Calibration: To obtain the calibration functions, five different concentration levels and three replicates of each one of the standards were analysed using the peak area as the analytical parameter.
	LOD: 0.55 µg/mL LOQ= 1.83 µg/mL
	Recovery data:
	Instrument/detector: HPLC/DAD

Results	Number of samples: six
	Concentration: BHT mean in chewing gum = 139; in bouillon cube spiked with BT (spiked with 200 mg/kg) = 194.1. BHT was not detected in the rest of the samples
Other comments	

BHT in organic and conventional milk was determined using HPLC (Pattono et al., 2009). Samples of conventional milk (n=11) and samples of organic milk (n=81) were analysed. The BHT concentrations in conventional milk, in µg/100 mL milk, ranged from not detected to 130.4. BHT-CHO was analysed in the same samples, and the concentrations ranged from not detected to 30.4 µg/100 mL. Organic bovine milk, organic goat milk and organic sheep milk were analysed for BHT and BHT-CHO. In bovine milk, the BHT concentrations in µg/100 mL milk, ranged from not detected to 23.0. BHT-CHO was determined in the same samples, and the concentrations, in µg/100 mL milk, ranged from not detected to 24.0. In sheep milk, the BHT concentrations in µg/100 mL milk were 21.9 and 0.9, and in the same samples, the BHT-CHO concentrations were 2.1 and not detected. In goat milk, the BHT concentrations in µg/100 mL milk ranged from 0.5 to 29.0. In the same samples, the BHT-CHO concentrations ranged from not detected to 4.5. BHT and BHT-CHO in organic milk from retail trade was also analysed. The BHT concentrations, in µg/100 mL milk, ranged from not detected to 141.2. The BHT-CHO concentrations ranged from not detected to 11.8. The LOD was 1 µg/kg. The LOQ was not reported.

Study ID	**Reference: Pattono et al. (2009)**
	Year the study was conducted/published:
	Source category: Food
Funding	Funding source: A grant from the Italian Health Ministry. Public/private: Public
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: MeOH:Hx
	Calibration: All standard curves showed good linearity (R2 > 0.99)
	LOD: 1 ppb LOQ: -
	Recovery data: The recoveries at a concentration of 0.25 ppm was 61.5 ± 1.2%, at a concentration of 5 ppm the recoveries was 84.3 ± 7.5%
	Instrument/detector: GC/MS
Results	Number of samples: 11 samples of conventional milk, 81 samples of organic milk
	Concentration: BHT concentrations are given in µg/100 mL milk. BHT in conventional milk ranged from not detected to 130.4. The BHT in organic bovine milk ranged from not detected to 23.0; in organic sheep milk BHT ranged from 0.9 to 21.9; in organic goat milk BHT ranged from 0.5 to 28.4; BHT in organic milk from retail trade ranged from not detected to 141.2.
Other comments	

BHT in Malaysian food items were analysed using HPLC-UV (Saad et al., 2007). BHT concentrations, in mg/kg, ranged from not detected to 88.9 in refined palm olein, from 14.4

to 38.6 in butter, and from 53.5 to 154.2 in margarine. The LOD was 0.5 mg/L. The LOQ was not reported.

Study ID	**Reference: Saad et al. (2007)**
	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: National Science Foundation, Malaysia (a scholarship for one of the participants) Public/private:
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: MeOH:ACN
	Calibration:
	LOD: 0.5 mg/L LOQ:
	Recovery data: Recoveries of the synthetic phenolic antioxidants when spiked to cooking oil, margarine, butter and cheese at 50 and 200 mg/L ranged from 73.9–94.6% for BHT
	Instrument/detector: HPLC-UV
Results	Number of samples: 16 cooking oils, ten margarine, six butter and six cheese samples
	Concentration: BHT concentrations, in mg/kg, ranged from not detected to 88.9 in refined palm olein; ranged from 14.4 to 42 in butter; ranged from 53.3 to 154.2 in margarine
Other comments	

BHT in cosmetic products was determined using LC–MS (Lee et al., 2006). The reported concentrations of BHT, in mg/kg, was 49 in lanoline cream, 86 in skin milk and 56 in cream. The LOD was 87 ng/g. The LOQ was not reported.

Study ID	**Reference: Lee et al. (2006)**
	Year the study was conducted/published: -
	Source category: Cosmetics
Funding	Funding source: The National Science Council of the Republic of China (under contract no. NSC 90-2113-M-005-029) Public/private: Public
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: MeOH + SFE
	Calibration: The correlation coefficient (R^2) was 0.9989
	LOD: 87 ng/g LOQ: -
	Recovery data: -
	Instrument/detector: LC/MS
Results	Number of samples: 3

	Concentration: BHT, in mg/kg, was 49 in lanoline cream, 86 in skin milk and 56 in skin? cream
Other comments	

BHT in foods was determined by GC-FID (Suh et al., 2005). In total, 133 food samples from twelve food categories were analysed for BHT. The samples included soybean oil, corn oil, other vegetable oil, shortening, margarine, seasoned dried fish, dried fish, salted fishery product, frozen fishery product, chewing gum, mayonnaise and breakfast cereal. BHT was detected in margarine and chewing gum. In margarine, BHT was detected in one of seven samples and in chewing gum BHT was detected in three of seven samples. The mean concentration of BHT in margarine and chewing gum were 1.29 and 25.95mg/kg, respectively. The LOD was 3 mg/kg. The LOQ was not reported.

Study ID	**Reference: Suh et al. (2005)**
	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: The article was the part of the project Daily Intake Estimate for Food Additives in Korea, which was supported by the Health Technology Planning and Evaluation Board, Ministry of Health and Welfare in Korea. Public/private: -
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: ACN:Pen
	Calibration:
	LOD: 3 mg/kg
	Recovery data: Oil and butter recovery and CV% for BHT were 94.5% and 3.5, respectively. Solid food recovery and CV% for BHT were 92.6% and 5.8, respectively
	Instrument/detector: GC-FID
Results	Number of samples: 133 food samples among 12 food categories
	Concentration: BHT was detected i two of the twelve food categories. In margarine, BHT ranged from not detected to 9.05 mg/kg; in chewing gum BHT ranged from not detected to 150.88mg/kg
Other comments	

Ishiwata et al. (2003) determined the mean concentration of BHT in foods using HPLC. BHT was not detected in frozen marine products (n=10), salted marine products (n=20) or in butter (n=20). In fats and oils, the mean concentration was 0.002 g/kg. In dried marine products, the mean concentration was 0.0006 g/kg (n=872). In chewing gum, the mean concentration was 0.0525 (n=13). BHT analysis details were not reported.

Study ID	**Reference: Ishiwata et al. (2003)**
	Year the study was conducted/published: 1998
	Source category: Food
Funding	Funding source: Partly supported by the «Health Science Research Grants, 2000 and 2001, from the Ministry of Health, Labour and Welfare». Public/private: -
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction:
	Calibration:
	LOD/LOQ:
	Recovery data:
	Instrument/detector: HPLC
Results	Number of samples: Frozen marine products (n=10), salted marine products (n=20), butter (n=20), dried marine products (n=872), chewing gum (n=13)
	Concentration: BHT was not detected in frozen marine products, salted marine products or in butter. In fats and oils, the mean concentration was 0.002 g/kg. In dried marine products, the mean concentration was 0.0006 g/kg. In chewing gum, the mean concentration was 0.0525
Other comments	Intake from other studies also presented

BHT in chewing gum was determined using GC-FID (Lin et al., 2003). The reported BHT concentrations, in µg/g, ranged from not detected to 295.6. The LOD and the LOQ were not reported.

Study ID	**Reference: Lin et al. (2003)**
	Year the study was conducted/published:
	Source category: Food
Funding	Funding source: TaJen Institute of Technology (No 88012) Public/private: -
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: different? solvents
	Calibration:
	LOD: - LOQ: -
	Recovery data: The recovery of BHT was 99 to 101% (CV: 1.5 to 3.2%)
	Instrument/detector: GC-FID
Results	Number of samples: 15
	Concentration: BHT ranged from 0 to 296 µg/g
Other comments	After chewing for 15 min, 50% BHT was released from the chewing gum

BHT in drinking water in Argentina was analysed using GC-MS (Tombesi and Freije, 2002). Concentrations of BHT were determined in 15 samples of commercial mineral and

mineralszed drinking water. In eight samples, no BHT signal was detected. In one sample, the signal was below the LOD and in another sample, the signal was below the LOQ. In the rest of the samples, the BHT concentrations in µg/L ranged from 21.5 to were 38.0. The LOD was 4.2 µg/L and the LOQ was 13.9 µg/L.

Study ID	**Reference: Tombesi and Freije (2002)**
	Year the study was conducted/published: -
	Source category: Drinking water
Funding	Funding source: - Public/private: -
Aim of the study	Analysis:
	Exposure:
	Migration: X
Methods for analysis	Sample extraction: HS-SPME
	Calibration: The calibration curve was drawn using five points at a concentration range 12.8–64.0 mg/L
	LOD: 4.2 µg/L LOQ: 13.9 µg/L
	Recovery data: Recoveries of BHT from spiked mineral drinking water samples added 25.5, 38.3 and 51.1 µg/L ranged from 84 to 119%
	Instrument/detector: GC-MS
Results	Number of samples: 15
	Concentration: In eight samples, no BHT signal was detected. In the rest of the samples, BHT ranged from below LOD to 38.0 µg/L
Other comments	

BHT in lipid containing food was determined using GC-FID (Yang et al., 2002). The BHT concentrations, given as mean (n=2) in µg/g, was 120.3 and 136.4 in soybean oil, 172.0 in one sample of olive oil, whereas it was not detectable in another sample, 43.5 and 146.4 in vegetable oil, 272 and 135.2 in blended oil, 277.4 and 168.5 in sunflower oil, ranged from 51.9 to 304.4 in fish oil, not detectable in the two peanut oil samples, 319.0 and 251.4 in butter, 56.7 and 87.1 in cheese, 164.2 and 251.6 in margarine, 108.0 and 124.7 in mayonnaise, and 17.0 and 31.5 in salad dressing. The LOD was 0.1 mg/ml. The LOQ was not reported.

Study ID	**Reference: Yang et al. (2002)**
	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: Supported by Project 88016 from Ta-Jen Institute of Technology Public/private: -
Aim of the study	Analysis: x
	Exposure:
	Migration:
	Sample extraction: EtAc
	Calibration: Standard solutions of seven concentrations were prepared and analyzed

Methods for analysis	LOD: 0.1 mg/mL
	Recovery data: The recovery of BHT was 101–104
	Instrument/detector: GC-FID
Results	Number of samples: 27
	Concentration: BHT concentration in µg/g. BHT in soybean oil was 120.3 and 136.4; in olive oil 172.0 and not detected; in vegetable oil 43.5 and 146.4; in blended oil 135.4 and 38.8; in sunflower oil 277.4 and 168.5; in butter 319.9 and 251.4; in cheese 56.7 and 87.1; in margarine 164.2 and 251.6; in mayonnaise 108.0 and 124.7; in salad dressing 17.0 and 31.5. BHT was not detected in peanut oil. BHT in fish oil ranged from 51.9 to 304.4
Other comments	

Maziero et al. (2001) determined the level of BHT in selected food categories in Brazil. The concentrations, in mg/kg, were 81.8 in soybean oil, 18.9 in corn oil, 63.7 in hydrogenated vegetable fat, 33.5 in margarine, 45.5 in vegetable cream and 151.7 in halvarina. The LOD was 2.7 mg/kg. The LOQ was not reported.

Study ID	**Reference: Maziero et al. (2001)**
	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: Financial support from FAPESP (Oric. 1998/13818-0) Public/private:
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: ACN
	Calibration:
	LOD: 2.7 mg/kg
	Recovery data: Mean recovery of BHT in vegetable fat, margarine, vegetable cream and halvarina ranged from 78±4 to 98±2
	Instrument/detector: HPLC-UV
Results	Number of samples: 54
	Concentration: In mg/kg, BHT in soybean oil ranged from 14.1 to 143; in corn oil from not detected to 62; inn hydrogenated vegetable fat from not detected to 125; in margarine from not detected to 69.4; in vegetable cream from from not detected to 109; in halvarina from 71 to 197
Other comments	

Ni et al. (2000) determinated antioxidants, including BHT, in food samples using a chemometric approach. The concentrations of BHT, in mg/g, were 0.009 in peanut oil and 0.057 in sesame oil. BHT was not detected in one sample of peanut oil, two samples of sesame oil, and one sample of cake, biscuit and milk candy. The LOD was 0.15 mg/L. The LOQ was not reported.

Study ID	**Reference: Ni et al. (2000)**
	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: the National Science Foundation of China (NSFC, No. 29765001) and the Natural Science Foundation of Jiangxi Province (NSFJX) Public/private: Public
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: MeOH
	Calibration: Linear calibration graphs were also obtained in the concentration range of 0.5–8.0
	LOD: 0.15 mg/L
	Recovery data: The recovery values were in the range of 80–120%
	Instrument/detector: Voltammetry
Results	Number of samples: 8
	Concentration: Concentrations given in mg/g. BHT in peanut oil were 0.009; in sesame oil 0.057. BHT was not detected in one sample of peanut oil, two samples of sesame oil, and one sample of cake, biscuit and milk candy.
Other comments	MeOH too polar for suitable extraction

BHT in chewing gum samples was analysed by HPLC with amperometric detection (Ruiz et al., 1999). The concentration of BHT was 51 µg/g. The LOD was 30 ng (for a 50 µl volume injected). The LOQ was not reported.

Study ID	**Reference: Ruiz et al. (1999)**
	Year the study was conducted/published:
	Source category: Food
Funding	Funding source: Fundación Universitaria San Pablo C.E.U. (project 12=97) and Subdirección General de formación y promoción del conocimiento (project PB96-0640) Public/private: -
Aim of the study	Analysis: X
	Exposure:
	Migration:
Methods for analysis	Sample extraction: EtAc
	Calibration: BHT was linear in the range 2.0 to 10.0 µg/mL
	LOD: 30 ng
	Recovery data:
	Instrument/detector: HPLC-ED
Results	Number of samples: 1
	Concentration: 51±3 µg/g
Other comments	

A GC method to determine BHT in products containing capsaicinoids was developed by DeWitt and Finne (1996). BHT in pepperoni pizza toppings (14 samples) ranged from <1 to 36.1. The LOD was 1000 µg/kg FW. The LOQ was not reported.

Study ID	**Reference: DeWitt and Finne (1996)**
	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: - Public/private: -
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: ACN:Hx
	Calibration: Standard curves were linear in the range 0.02 to 0.20 mg/mL
	LOD: 1000 µg/kg FW LOQ: -
	Recovery data: Average recovery was 104.3±4.8%
	Instrument/detector: HPLC + GC/FID
Results	Number of samples: 14
	Concentration: BHT concentrations in ppm ranged from <1 to 36.1
Other comments	

Boussenadji et al. (1993) used microbore LC columns coupled to electrochemical detection to analyse BHT in bactericidal cream (1 sample) and chewing gum (2 samples). The reported values, in mg/kg, were 49.7 in bactericidal cream, 164 and 184 in the chewing gums.

Study ID	**Reference: Boussenadji et al. (1993)**
	Year the study was conducted/published: -
	Source category: Food
Funding	Funding source: - Public/private: -
Aim of the study	Analysis: x
	Exposure:
	Migration:
Methods for analysis	Sample extraction: MeOH
	Calibration:
	LOD: - LOQ: -
	Recovery data:
	Instrument/detector: HPLC UV+ECD
Results	Number of samples: 3
	Concentration: Ranged from 121 to 184 mg/kg for the chewing gums
Other comments	MeOH too polar for suitable extraction

11.3 BHT in foods

This appendix provides a comprehensive description of all BHT concentration data available in food and beverages. Data are described for «realistic» and «high» datasets making use of KBS food categories. Table 11.3-1 is identical with Table 4.2.1-1.

Table 11.3-1 BHT content in different foods and food groups, µg/kg wet weight (identical with table 4.2.1-1).

Food group	n	Lower bound	Middle bound	Upper bound
Cereals, bread and cakes[1]	11	2.1	15.8	29.4
Bread and cereals[2]	4		2.6[a]	
Cakes, biscuits[2]	5	2.6	2.9	3.2
Instant noodles[1,2]	1		0.7[a]	
Potatoes[1,2]	4	0.5	0.6	0.8
Vegetables[1,2]	5	0.1	0.3	0.5
Fruit[1,2]	4	1.5	1.5	1.6
Meat, meat products[1,2]	6	0.1	0.3	0.5
Pepperoni[1,2]	14		23586[a]	
Fish and seafood, wild[1]	76	1.5	1.6	1.6
Fish, wild[2]	15	1.6	1.6	1.7
Fish, freshwater[2]	24	0.9	0.9	0.9
Shrimp and mussles[2]	19	0.5	0.5	0.6
Fish liver[2]	18	3.4	3.5	3.5
Fish, farmed[1,2]	60	2644	2645	2646
Egg[1,2]	4	0.3	0.5	0.6
Dairy[1,2]	26		249[a]	
Milk, goat[1,2]	8		147[a]	
Coffee creamer[1,2]	1		0.7[a]	
Vegetable cream[1]	9		45500[a]	
Cheese[1]	2		71900[a]	
Margarine and butter[1]	49		92039[a]	
Various oils[1]	53	43138	43153	43168
Various oils[2]	14	6.2	6.2	6.2
Mayonnaise[1]	6		48117[a]	
Fish oil[1]	5		144140[a]	
Sweets, chocolate[1,2]	4		3.9[a]	
Chewing gum[1]	35		218232[a]	
Chewing gum[2]	10		135132[a]	
Starchy snacks[1]	7		46200[a]	

[1] Used in «high» exposure scenario: all concentration data that fulfilled the quality criteria, regardless of country of origin.
[2] Used in realistic exposure scenario: concentration data from Europe/USA that fulfilled the quality criteria.
[a] All analysed values were above LOQ.
* The number is equal as the middle bound since all analysed values were above LOQ.

Data from all countries were included in the «high» exposure dataset, and the overall number of samples was 359. For the realistic dataset, with samples from Europe and USA, the overall number of samples was 240.

Cereals, bread and cake

Concentration data for «cereals, bread and cake» were available from Livsmedelsverket et al. (2014), Ni et al. (2000) and Yuan et al. (2010), with a total of 11 samples in the «high» exposure scenario. Seven of the samples were of cake and biscuits, and four were of bread and cereals.

The BHT concentrations ranged from non-detected with less than 150 µg/kg (Ni et al. 2000 with a LOD of 150 µg/kg) to 6.75 µg/kg (Livsmedelsverket et al. 2014). When all concentrations were pooled together, the mean concentration (MB) was 15.8 µg/kg.

Two samples (Ni et al. 2000, with a LOD of 150 µg/kg) from China were excluded from the realistic dataset, resulting in nine samples in the realistic dataset.

To be more specific in the coding prosess, cereals and bread were given the pooled concentrations of four samples 2.6 µg/kg (MB), and cakes and biscuits were given the pooled concentration of five samples, 2.9 µg/kg (MB).

Instant noodles

One sample of instant noodles was aviable from Yuan et al. (2010) with a concentration of 0.7 µg/kg.

This concentration from North America was used for instant noodles in both the «realistic» and «high» scenario.

Potatoes

Concentration data for «potatoes» were available from Livsmedelsverket et al. (2014), with a total of four samples. The BHT concentrations ranged from less than 0.5 µg/kg to 1.12 µg/kg. Since the LOD value (1 µg/kg) was higher than several reported sample concentrations, the lowest value of 0.5 µg/kg was used as basis to account for uncertainties of measurements. When the concentrations were pooled together, the mean concentration (MB) was 0.6 µg/kg.

These concentrations were from Sweden, and used both in the «realistic» and «high» scenario.

Vegetables

Concentration data for «vegetables» were available from Livsmedelsverket et al. (2014), with a total of five samples. The BHT concentrations ranged from less than 0.5 µg/kg (LOD of 1 µg/kg) in four samples to 0.68 µg/kg. When the concentrations were pooled together, the mean concentration (MB) was 0.3 µg/kg.

These concentrations were from Sweden, and used both in the «realistic» and «high» scenario.

Fruit
Concentration data for «fruits» were available from Livsmedelsverket et al. (2014), with a total of four samples. The BHT concentrations ranged from less than 0.5 µg/kg (LOD of 1 µg/kg), to 4.72 µg/kg. When the concentrations were pooled together, the mean concentration (MB) was 1.5 µg/kg.

These concentrations were from Sweden, and used both in the «realistic» and «high» scenario.

Meat, and meat products
Concentration data for «meat, and meat products» were available from Livsmedelsverket et al. (2014), and Yuan et al. (2010), with a total of six samples. The BHT concentrations ranged from less than 0.5 µg/kg (LOD of 1 µg/kg) in the five samples from Livsmedelsverket et al. (2014), to 0.59 µg/kg in sausages from Yuan et al. (2010). When the concentrations were pooled together, the mean concentration (MB) was 0.3 µg/kg.

These concentrations were from Sweden and the USA, and used both in the «realistic» and «high» scenario.

Pepperoni
Concentration data for «pepperoni» were available from DeWitt et al. (1996), with a total of 14 samples. The BHT concentrations ranged from 500 µg/kg, to 36100 µg/kg in pepperoni w/capasaicinoid-oleoresin. When the concentrations were pooled together, the mean concentration (MB) was 23586 µg/kg.

These concentrations were from the USA, and used both in the «realistic» and «high» scenario.

Fish, and seafood
Concentration data for «fish and seafood» were available from Livsmedelsverket et al. (2014), Lundeby et al. (2013), Miljødirektoratet (2014), and Overvåkning (2005), with a total of 76 samples. Fifteen of the samples were of «wild fish», 24 of the samples were of «freshwater fish», 19 of the samples were of «shrimp and mussles», and 18 samples were of «fish liver».

The BHT concentrations ranged from less than 0.1 µg/kg (in perch and mussels) to 11.86 µg/kg (in cod liver). When all concentrations were pooled together, the mean concentration (MB) was 1.6 µg/kg.

These concentrations were from Norway and Sweden, and used both in the «realistic» and «high» scenario.

To be more specific in the coding process for the realistic dataset, «wild fish» were given the pooled concentrations of 1.6 µg/kg (MB), «fish, freshwater» were given the pooled concentration of 0.9 µg/kg (MB), «shrimp, and mussles» were given the pooled concentration of 0.5 µg/kg (MB), and «fish liver» were given the pooled concentration of 3.5 µg/kg (MB).

Farmed fish

Concentration data for «farmed fish» were available from Lundby et al. (2010), with a total of 60 samples. The BHT concentrations ranged from 30 µg/kg, to 7560 µg/kg in «farmed fish». When the concentrations were pooled together, the mean concentration (MB) was 2645 µg/kg.

These concentrations were from Norway, and used both in the «realistic» and «high» scenario.

Egg

Concentration data for «egg» were available from Livsmedelsverket et al. (2014), with a total of four samples. The BHT concentrations ranged from less than 0.5 µg/kg (LOD of 1 µg/kg) to 1.05 µg/kg. When the concentrations were pooled together, the mean concentration (MB) was 0.45 µg/kg.

These concentrations were from Sweden, and used both in the «realistic» and «high» scenario.

Dairy

Concentration data for «dairy» were available from Livsmedelsverket et al. (2014), and Pattono et al. (2009), with a total of 26 samples. The BHT concentrations ranged from less than 0.5 µg/kg (LOD of 1 µg/kg), to 1412 µg/kg from Pattono et al. (2009). When the concentrations were pooled together, the mean concentration (MB) was 249 µg/kg.

These concentrations were from Sweden and Italy, and used both in the «realistic» and «high» scenario.

Goat milk

Concentration data for «goat milk» were available from Pattono et al. (2009), with a total of eight samples. The BHT concentrations ranged from 5 µg/kg, to 290 µg/kg in «goat milk». When the concentrations were pooled together, the mean concentration (MB) was 147 µg/kg.

These concentrations were from Italy, and used both in the «realistic» and «high» scenario.

Coffee creamer

One sample of coffee creamer was available from Yuan et al. (2010) with a concentration of 0.7 µg/kg.

This concentration from USA was used for coffee creamer in both the «realistic» and «high» scenario.

Vegetable cream
Concentration data for «vegetable cream» were available from Maziero et al. (2001), with a total of nine samples. The BHT concentrations ranged from less than 2700 µg/kg (LOD), to 109000 µg/kg in «vegetable cream». When the concentrations were pooled together, the mean concentration was 45500 µg/kg.

The concentrations were from Brazil and were excluded from the realistic dataset.

Cheese
Concentration data for «cheese» were available from Yang et al. (2002), with a total of two samples. The BHT concentrations ranged from 56700 µg/kg, to 87100 µg/kg in «cheese». When the concentrations were pooled together, the mean concentration was 71900 µg/kg.

The concentrations were from Taiwan and were excluded from the realistic dataset.

Margarine and butter
Concentration data for «margarine and butter» were available from Yang et al. (2002), Maziero et al. (2001), Saad et al. (2007), and Sasha et al. (2014) with a total of 49 samples. The BHT concentrations ranged from 7800 µg/kg, to 310000 µg/kg in «margarine and butter». When the concentrations were pooled together, the mean concentration was 92039 µg/kg.

The concentrations were from Zimbabwe, Malaysia, Taiwan and Brazil, and were excluded from the realistic dataset.

Various oils
Concentration data for «various oils» were available from Yang et al. (2002), Maziero et al. (2001), Saad et al. (2007), Ni et al. (2000), Cacho et al. (2016), Lin et al. (2013), and Sasha et al. (2014) with a total of 53 samples. The BHT concentrations ranged from less than 0.04 µg/kg (LOD), to 336400 µg/kg in «various oils». When the concentrations were pooled together, the mean concentration was 43153 µg/kg.

Forthy samples from Taiwan, China, Brazil, Zimbabwe, and Malaysia were excluded from the realistic dataset. Fourteen concentrations from Sweden and Spain were included in the realistic dataset. The samples included concentrations form the Swedish foodbasket, and Spanish samples of peanut oil, olive oil, sunflower oil, and sesame oil. When the European concentrations were pooled toghether, the mean concentration was 6.2 µg/kg (MB).

Mayonnaise
Concentration data for «mayonnaise» were available from Medeiros et al. (2010), and Yang et al. (2002), with a total of six samples. The BHT concentrations ranged from 11000 µg/kg,

to 124700 µg/kg in from Yang et al. (2002). When the concentrations were pooled together, the mean concentration (MB) was 48117 µg/kg.

The concentrations were from Brazil and Taiwan, and were excluded from the realistic dataset.

Fish oil
Concentration data for «fish oil» were available from Yang et al. (2002) with a total of five samples. The BHT concentrations ranged from less than 51900µg/kg, to 304400 µg/. When the concentrations were pooled together, the mean concentration (MB) was 144140 µg/kg.

The concentrations were from Taiwan, and were excluded from the realistic dataset.

Sweets and chocolate
Concentration data for «sweets and chocolate» were available from Livsmedelsverket et al. (2014), with a total of 4 samples. The BHT concentrations ranged from 1.53 µg/kg, to 8.32 µg/kg. When the concentrations were pooled together, the mean concentration (MB) was 3.9 µg/kg.

These concentrations were from Sweden, and used both in the »realistic» and «high» scenario.

Chewing gum
Concentration data for «chewing gum» were available from Ruiz et al. (1999), Boussenadji et al. (1993), Edin et al. (2010), Garcia-Jimenez et al. (2009), and Lin et al. (2003) with a total of 35 samples. The BHT concentrations ranged from 25800 µg/kg, to 295600 µg/kg. When the concentrations were pooled together, the mean concentration was 135132 µg/kg.

These concentrations were from Spain, France, and the USA, and were used both in the »realistic» and «high» scenario.

Starchy snacks
Concentration data for «starchy snacks» were available from Sasha et al. (2014), with a total of seven samples. The BHT concentrations ranged from 1800 µg/kg, to 151300. When the concentrations were pooled together, the mean concentration (MB) was 46200 µg/kg.

The concentrations were from Zimbabwe, and were excluded from the realistic dataset.

11.4 BHT in PCPs

Table 11.4-1. BHT concentration data (µg/g) in personal care products (PCP) taken from literature and allocated according to a «realistic» and a «high» exposure scenario.

Product	BHT concentration µg/g «Realistic» exposure approach	BHT concentration µg/g «High» exposure approach
After shave	30.60	30.60

Product	BHT concentration µg/g «Realistic» exposure approach	BHT concentration µg/g «High» exposure approach
After-sun cream	3.16	3.16
Antiwrinkle cream	13.41	26.81
Deodorant	269.79	700.00
Eye make-up remover	43.90	43.90
Facial cleansing milk	85.20	85.20
Foundation	50.00	100.00
Lip gloss & lipstick	1201.88	2996.00
Hair conditioner	71.10	71.10
Hair gel	183.33	220.00
Hair oil	863.33	1540.00
Hand cream	187.76	354.24
Hand sanitizer	200.00	200.00
Hand soaps	31.30	93.30
Liquid soap	2.10	10.00
Make-up	34.50	34.50
Make-up remover	1760.00	1760.00
Moisturizing cream	285.73	2201.00
Shampoo	0.00	4.10
Shower gel	0.16	0.16
Sunscreen	7.42	14.50
Toothpaste	200.00	200.00

Table 11.4-2. Amount of personal care products (PCPs) used (g) per application taken from literature and allocated according to a «realistic» and a «high» exposure approach.

Personal care product (PCP)	P50 amount per application [g] women	P95 amount per application [g] women	P50 amount per application [g] men	P95 amount per application [g] men
Shower gel	8.00	23.20	8.50	26.20
Shampoo	8.10	25.30	5.10	13.90
Conditioner	7.50	27.00	5.20	7.20
Deodorant	0.86	2.55	0.88	2.54
Facial cleanser	2.73	8.04	2.79	6.75
Facial moisturizer	0.68	2.63	1.24	3.63
Body lotion	7.55	23.55	5.10	19.60
Anti-wrinkle cream	0.51	1.90	0.73	0.77
Sunscreen	1.45	7.90	2.35	4.80
Mouth wash	15.10	28.20	15.60	30.40
Toothpaste	1.09	3.00	1.42	2.81
Perfume	0.22	0.59	0.23	0.62
Lip-gloss, lipstick, lip balm	0.01	0.04	0.02	0.05
Foundation	0.09	0.37	0.60	1.20
Intimate soap	2.00	6.50	na	na

Personal care product (PCP)	P50 amount per application [g] women	P95 amount per application [g] women	P50 amount per application [g] men	P95 amount per application [g] men
Hand cream	0.88	2.73	1.39	3.06
Foot cream	2.73	8.37	3.31	8.49
Hair styling products	2.87	8.50	1.93	6.57
Hair styling hair spray	1.35	3.94	na	na
Hair treatment products stay on	0.94	3.15	na	na
Hair treatment products rinse off	10.80	37.70	na	na
Eye-makeup products	0.01	0.02	na	na
Rouge and powder	0.01	0.03	na	na
Make up remover	2.01	5.32	0.30	0.80
Shaving products	7.53	25.37	2.82	10.04
Antibac	0.88	2.73	1.39	3.06
Oils	1.80	4.00	2.10	9.01
Hand soap	1.99	4.90	2.90	7.26

Table 11.4-3. Dermal and oral retention factors (RFs) applied for the estimation of BHT exposure from personal care products (PCPs) in the EuroMix study population.

PCP categories in EuroMix	Application scenario	RF dermal	RF oral
Shower gel	Rinse off skin	0.01	
Shampoo	Rinse off skin	0.01	
Conditioner	Rinse off skin	0.01	
Deodorant	Stay on skin	1	
Facial cleanser	Rinse off skin	0.01	
Facial moisturiser	Stay on skin	1	
Body lotion	Stay on skin	1	
Anti-wrinkle cream	Stay on skin	1	
Sunscreen	Stay on skin	1	
Mouthwash	Brush teeth	0	0.2
Toothpaste	Brush teeth	0	0.2
Perfume	Spray on skin (perfume)	1	
Lip-gloss, lipstick, lip balm	Leave-on skin	0.1	0.9
Foundation	Leave-on skin	1	
Intimate soap	Rinse-off skin	0.01	
Hand cream	Leave-on skin	1	
Foot cream	Stay on skin	1	
Hair styling products	Stay on hair		
Hair treatment products rinse off	Rinse off skin	0.01	
Eye-makeup products	Stay on skin	1	
Rouge and powder	Stay on skin	1	
Make up remover	Stay on skin	0.01	
Shaving products	Rinse off skin	0.01	

PCP categories in EuroMix	Application scenario	RF dermal	RF oral
Antibac	Stay on skin	1	
Oils	Stay on skin	1	
Hand soap	Rinse off skin	0.01	

12 Appendix - Deviations from the protocol

According to the protocol the assessment should include all age groups. It turned out that calculating external and total internal exposure from multiple exposure pathways became tedious, and it was therefore limited to including adults only. It was considered most important to make the exposure calculations thorough for one age group, in order to gain experience with the methodology. In this way, focus could be kept on the differences in methodology used for the exposure assessment

Exposure from indoor air was not estimated as stated in the protocoldue to lack of concentration data on BHT in indoor air.

The total exposure to potential harmful metabolites was not estimated. The BHT metabolism is complex and more than 40 metabolites have been identified. Due to lack of knowledge on the metabolites, the Panel was not able to perform this estimation.

The exposure were calculated both deterministically and probabilistically. The deterministic approach was called OIM in this assessment.