National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

WAGENINGEN UNIVERSITY & RESEARCH

FRONT OFFICE FOOD AND PRODUCT SAFETY

RISK ASSESSMENT OF ETHYLENE OXIDE IN SESAME SEEDS.

Risk assessment requested by:	BuRO
Risk assessment performed by:	RIVM and WFSR
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Nederlandse samenvatting

Risicobeoordeling voor ethyleenoxide in sesamzaad

In partijen sesamzaad werd ethyleenoxide aangetroffen in hoeveelheden tot 86 mg/kg. Deze waarde lijkt een uitbijter in de observaties. Volgens BuRO zijn gehaltes in de range van 1 tot 10 mg/kg meer gebruikelijk. De gehaltes in de opgegeven range liggen een factor 20 tot 1720 boven de Maximale Residu Limiet voor ethyleenoxide in sesamzaad (0,05 mg/kg), die is vastgelegd in de Europese wetgeving. BuRO vraagt het Front Office Voedsel- en Productveiligheid (hierna Front Office) om een toxicologische referentiewaarde af te leiden waarbij blootstelling aan ethyleenoxide nog als veilig kan worden beschouwd. Tevens vraagt BuRO aan het Front Office een schatting te maken van de hoeveelheden van sesamzaad-bevattende levensmiddelen die nog veilig kunnen worden geconsumeerd, rekening houdend met een gebruikelijk aangetroffen range van 1 tot 10 mg/kg ethyleenoxide in het sesamzaad.

Ethyleenoxide is een genotoxische en kankerverwekkende stof. Voor zulke stoffen kunnen geen toxicologische referentiewaarden worden afgeleid, die een veilige blootstelling kunnen weerspiegelen. Risicobeoordeling voor dergelijke stoffen gebeurt op basis van vergelijking van de blootstelling aan de stof met een dosering die (in het algemeen bij dieren) een zekere verhoging van het aantal tumoren opwekt. Voor ethyleenoxide is dat bij opname via de mond een dosis van 0,37 mg/kg lichaamsgewicht (lg) per dag[1], waarbij in 10 van de 100 blootgestelde dieren maagtumoren tot ontwikkeling kunnen komen. Als de blootstelling 10 000 maal lager is dan deze waarde, dan wordt aangenomen dat er sprake is van een laag risico.
De blootstelling van consumenten aan ethyleenoxide is afhankelijk de hoeveelheid sesamzaad in de gegeten levensmiddelen en de hoeveelheden die van die levensmiddelen worden gegeten. Er is gerekend met de hoogste waarde van de gebruikelijke gerapporteerde range (10 mg/kg) ethyleenoxide in sesamzaad en onder de aanname dat alle onderzochte voedingsmiddelen sesamzaad bevatten. De schattingen voor blootstelling aan ethyleenoxide zijn factoren 71 - 695 lager dan 0,37 mg/kg lg per dagen; dus een veel kleinere factor dan de hierboven genoemde factor van 10 000.

[1] Deze waarde is een $BMDL_{10}$. De $BMDL_{10}$ is de blootstelling waarvan met 95% zekerheid gesteld kan worden dat de daadwerkelijke dosis die een 10% effect veroorzaakt (in dit geval dus een toename van 10% in tumor incidentie) daar boven ligt. De daadwerkelijke dosis kan niet exact worden vastgesteld, maar met even grote zekerheid kan uit de beschikbare experimentele gegevens worden afgeleid dat deze lager is dan 1.38 mg/kg lg per dag.

Terugrekenend met hetzelfde gehalte ethyleenoxide in sesamzaad variëren de hoeveelheden brood, crackers of koekjes met sesamzaad die mogelijk veilig te consumeren zijn van 0,26 tot 2,10 gram per persoon per dag. In de praktijk komt dat er op neer dat het nauwelijks tot niet mogelijk is om producten te eten waarin sesamzaad is verwerkt dat ethyleenoxide bevat in een gehalte van 10 mg/kg.

In verband met de erg beperkte data set is de beoordeling is noodzakelijkerwijs erg voorzichtig op een aantal punten:

1) Het is niet helemaal zeker in hoeverre de gevonden maagtumoren bij de dieren van belang zijn voor de mens; er is aangenomen dat dit zo is. De doseringsniveaus voor de berekening van de toxicologische referentiewaarde voor de beoordeling zijn op conservatieve wijze uit de betreffende publicatie afgeleid.
2) Bij gebrek aan precieze gegevens over het aandeel van sesamzaad bevattende levensmiddelen in het voedselpakket is aangenomen dat alle levensmiddelen uit de onderzochte categorieën, sesamzaad bevatten in een gehalte gelijk aan het maximum van de range die gebruikelijk wordt gerapporteerd (10 mg/kg).
3) De analyse van ethyleenoxide in sesamzaad omvat ook het afbraakproduct 2-chloorethanol. De hoeveelheid daarvan is echter niet gespecificeerd in de analyse certificaten. Het is onzeker of 2-chloorethanol net zo giftig is als ethyleenoxide. Gegevens zijn te schaars om dat goed te kunnen beoordelen. Het Front Office is er van uitgegaan dat het in de rapportage alleen om ethyleenoxide gaat en dat dit altijd aanwezig is in het hoogst gerapporteerde gehalte in sesamzaad.
4) Er is van uitgegaan dat er tijdens de voedselbereiding geen daling optreedt van het ethyleenoxide gehalte in sesamzaad. Waarschijnlijk zal een (groot) deel vervluchtigen of weg reageren naar het veel minder giftige ethyleenglycol (De beoordeling heeft hier geen rekening mee gehouden wegens gebrek aan gegevens).

Subject

In India, ethylene oxide is used as a disinfectant on sesame seeds. It is suspected that this has been common practice for several years. At the end of August, Belgium issued a RASFF reporting the presence of ethylene oxide in sesame seeds (30 mg/kg). Additional analysis data from other laboratories also became available early October 2020, showing that sesame seeds may contain high concentrations of ethylene oxide. The highest reported concentration is 86 mg/kg, which exceeds substantially the legal maximum residue limit (MRL) of 0.05 mg/kg in the EU. Commonly, ethylene oxide concentrations are reported that range from 1 to 10 mg/kg (BuRO, 2020).

Question

Does long-time consumption of sesame seeds contaminated with ethylene oxide represent a health risk?

For practical reasons, this question has been reformulated as follows:
1) What is the maximum amount of ethylene oxide that a consumer may ingest before health effects occur.
2) What are amounts of sesame seed-containing foods (e.g. sesame seeds bread) that a person can still safely eat?

Conclusions

1) Ethylene oxide is considered a substance that is genotoxic and carcinogenic. Therefore, it is not justified to derive a Health Based Guidance Value which is associated with absence of risk. The assessment has been carried out using the only available chronic oral toxicity study from which a $BMDL_{10}$ of 0.37 mg/kg body weight per day has been derived for the development of forestomach and stomach tumours.

2) Based on the maximum of the range of ethylene oxide concentrations that is indicated by BuRO to be commonly reported for sesame seeds (10 mg/kg), the consumption of less than 0.26, 1.26, 1.57 or 2.10 g/person per day of biscuits (with 49% of sesame seeds), crackers and rusks (with 10% of sesame seeds), bread (with 8% of sesame seeds) and biscuits (with 6% of sesame seeds), respectively would result in an MOE greater than 10 000. Based on the current methodology in the EU for evaluation of genotoxic and carcinogenic substances in food, consumption of these amounts of food would be of low safety concern. However, in practice this means that these foods cannot be safely consumed in realistic amounts, when they are produced with sesame seeds that contain ethylene oxide at the reported maximum of the indicated commonly found range of ethylene oxide concentrations.

It is noted that due to limited amount of data available, the assessment is very conservative; both with respect to the estimation and relevance of the observed toxicity of ethylene oxide and with respect to the estimation of exposure to ethylene oxide in sesame seeds (for more details; see text).

Introduction

Ethylene oxide is used as a biocide on sesame seeds in countries where this food is produced.
The maximum residue level (MRL) is 0.05 mg/kg. This is equal to the limit of quantification according to Regulation (EC) No 396/2005 (EU, 2020). The MRL has been set at this value because ethylene oxide is not permitted as a pesticide due to its genotoxic and carcinogenic characteristics. The MRL is a sum MRL for ethylene oxide plus 2-chloroethanol; the reaction product of ethylene oxide with chloride. The analytical data available to the Front Office Food and Product Safety (hereafter Front Office) do not distinguish between these two substances.

Ethylene oxide may be used as a biocide and is listed on the ECHA website as PT2 (disinfectant). Permitted uses are:

- in inks, toners and fillers, putties, plasters, and modelling clay;
- indoor use (e.g. machine wash liquids / detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners;
- outdoor use as processing aid.

In Europe, use for disinfection of foodstuffs (e.g. in storage areas) is not permitted. (ECHA, 2020)

Toxicology

The toxicity of ethylene oxide has been extensively studied in relation to inhalatory exposure. The toxicity after oral ingestion has been less well researched. An extensive analysis of the existing data by the US Agency for Toxic Substances and Disease Registry has been published recently (ATSDR, 2020). Effects on many tissues and organ systems have been reported, but the effect of most concern is carcinogenicity, most likely via a genotoxic mechanism.

ATSDR did not derive health based guidance values (HBGVs) for oral exposure, neither for acute nor for short term or for chronic exposure, because the data-base for oral toxicity of ethylene oxide, among which a 3-year oral carcinogenicity study in rats (Dunkelberg, 1982), was considered too limited for this purpose. Based on the available toxicological information, ATSDR considered that "*human oral exposure scenarios resulting in adverse health effects are not likely*", but did not substantiate this with

quantitative estimates of oral exposure. Therefore Front Office cannot further comment on the validity of the ATSDR statement.

In 2000, the Australia New Zealand Food Authority (ANZFA) released an assessment in which an MRL of 20 mg/kg was proposed for the occurrence of ethylene oxide in herbs and spices. This MRL included only ethylene oxide; 2-chloroethanol was not included. It was considered that although the toxicological data on 2-chloroethanol were limited, this substance would not pose an additional cancer risk at the levels found in herbs and spices.
ANZFA set the MRL for ethylene oxide, considering that this MRL would be sufficient to take into account the actual levels found in herbs and spices. It was also considered to be consistent with the policy to maintain residues as low as practically achievable. From the ANZFA opinion it is not clear if this MRL is based on a strategy that takes consideration of Good Manufacturing Practice into account.

Based on the already mentioned study by Dunkelberg (1982) ANZFA used an oral carcinogenicity potency factor of 0.55 per mg/kg body weight (bw) per day[2] for life-time oral exposure to ethylene oxide. This potency factor was used to evaluate the exposure estimates for ethylene oxide in herbs and spices, based on measured concentrations. which were typically below 2 mg/kg (Limit of Detection) and none of them higher than 15 mg/kg. It was not applied to evaluate the safety of the MRL of 20 mg/kg.

Front Office considered the study by Dunkelberg (1982) to be the most appropriate study to evaluate the risk associated with oral exposure to ethylene oxide in sesame seeds, despite its limitations. Dunkelberg (1982) administered ethylene oxide (purity 99.7%) in oil ("salad oil ") by gavage to groups of female rats of 100 days old (50 per group) at two days per week for 150 weeks (i.e. the rest of their life span). Dose levels were 0, 7.5 or 30 mg/kg bw per event. Under the assumption that time-averaging of the exposure is justified, the week-averaged nominal dose levels would correspond to 0, 2.14 and 8.57 mg/kg bw per day, respectively. However, the dosimetry is inconsistently reported, as the authors have also indicated that animals received the substance 214 times (instead of 300) and that the total amounts of substance given were 1186 mg/kg bw and 5112 mg/kg bw for the low and high dose group, respectively, while the total amounts should have been 2250 or 9000 mg/kg bw. The most conservative (i.e. the lowest) estimates of time-averaged dose levels obtained by dividing the reported total amounts administered by the total number of days of the experiment (1050), would be 0, 1.13 and 4.87 mg/kg bw per day. These values will be used further.

Somewhat decreased survival was observed in the high dose group due to tumour development. Observations were limited to histopathology of "pathologically noteworthy organs". The gastro-intestinal tracts were more thoroughly inspected. Observed tumours in the gastro-intestinal tract were most commonly squamous cell carcinomas of the forestomach. Tumours of the glandular stomach and fibrosarcomas were also observed. No such tumours were observed in control animals. Apart from the tumours and histopathological changes in the stomach and forestomach, tumours were also observed in other tissues. However, these occurred at much lower frequencies, except for adenofibromas in the mammary gland, but for these tumours no dose-related trend was seen.

It can be debated whether the tumours in the gastrointestinal tract are relevant for the risk assessment. Often, such tumours are the result from direct tissue irritation,

[2] This means that in a group of 100 persons exposed to ethylene oxide at 1 mg/kg bw per day during their entire life span, 55 would develop cancer.

consequential to high local concentrations following gavage dosing. However, in this study, the incidence of hyperkeratosis did not increase with higher doses, while the gastric tumours did increase with higher doses. This may indicate that the carcinogenicity of ethylene oxide in the stomach is only partially related to local tissue irritation. In addition, considering that ethylene oxide is genotoxic, a direct carcinogenic effect at the site of first contact cannot be excluded. Therefore, the data on stomach and forestomach tumour induction were used in the current risk assessment, although it is acknowledged that this may be a conservative approach.

In line with the EFSA guidance on the risk assessment of substances that are genotoxic and carcinogenic (EFSA, 2005), Front Office decided to apply dose-response modelling. For this the EFSA BMD webtool[3] has been used, following the EFSA Guidance on dose response modelling (EFSA, 2017). The data on squamous cell carcinomas and fibroadenomas were combined. According to the study author, animals were counted only once, even if they had different tumour types. The relevant information from the output of this tool has been presented in Appendix I. A $BMDL_{10}$ of 0.37 mg/kg bw per day was derived upon dose response modelling. This value represents the 95% (single sided) lower confidence limit of the dose associated with a 10% increase in tumour incidence (extra risk).

Exposure
The Dutch food consumption data base contains consumption information on foods with sesame seeds such as tahin, hummus and sesame crackers. Consumption of other foods that can contain sesame seeds (e.g. bread with sesame seeds) is not recorded as such, but is only recorded as their regular counterparts (e.g. regular white bread). Concentration data of ethylene oxide in sesame seeds was also limited. Given the limitations in food consumption data and concentration data, a probabilistic exposure assessment was not carried out and a deterministic approach was followed for each food separately, to estimate chronic exposure. It was assumed that sesame seeds were always present at the percentages indicated in table II.1 (e.g. all consumed bread contained 8% of sesame seeds). This resulted in an overestimation of intake of sesame seeds and consequently in an overestimation of exposure to ethylene oxide.

For bread, crackers and rusks, and biscuits, the intake estimates were averaged over all reporting days included in the food consumption survey (2235 days), including those days on which no consumption was recorded, thus giving a year-average intake estimate. Consumption of sesame seeds, sesame paste / tahin and hummus was only reported incidentally in the survey. Although the estimates may correctly reflect the intake of these foods for a single event ("occasion"), they are not suitable to realistically estimate chronic exposure to ethylene oxide from these foods. Thus, for sesame seeds, sesame paste / tahin and hummus no risk assessment will be carried out; also not for acute effects[4]. Nevertheless, the intake data for sesame seeds from these foods has been reported in appendix II (table II.2).

[3] https://websso-efsa.openanalytics.eu/auth/realms/efsa/protocol/openid-connect/auth?response_type=code&client_id=shiny-efsa&redirect_uri=https%3A%2F%2Fshiny-efsa.openanalytics.eu%2Fsso%2Flogin&state=aae8e02e-1108-4561-99d3-07075d8a02a2&login=true&scope=openid

[4] According to ATSDR (2020) only three acute oral toxicity studies in animals were available, in which only mortality was reported (a NOAEL of 100 mg/kg bw, or 100% mortality at 200 mg/kg in one study and LD_{50}s of approximately 300 mg/kg bw in the two other studies, which is considered too limited to derive a reference point for acute toxicity. Based on an ethylene oxide concentration in sesame seeds of 10 mg/kg, an adult (60 kg bw) should consume about 600 kg of sesame seeds to even come close to the reported NOAEL.

From the food consumption data, the following exposure estimates for ethylene oxide (Table 1) can be calculated based on the maximum of the indicated commonly reported range of ethylene oxide concentrations in sesame seeds (10 mg/kg):

Table 1. Intake data for bread, crackers, rusk and biscuits containing sesame seeds and resulting exposure to ethylene oxide. *These foods were regularly reported in the Food Consumption Survey. A Margin of Exposure (MOE) and the amount of food that would result in an MOE > 10 000 has been calculated.*

Product (% sesame seeds)	**Frequency**	**Intake of food product (g/kg bw per day)**	**Intake of sesame seeds (g/kg bw per day)**	**Exposure to ethylene oxide[a] (mg/kg bw per day)**	**MOE[b]**	**Intake of food[c,d] (g/person per day), that would result in an MOE of 10 000**
Bread (8)	Regular	3.6	0.29	0.0029	128	1.57
Crackers and rusk (10)	Regular	0.5	0.05	0.0005	695	1.26
Biscuits (6)	Regular	1.1	0.06	0.0006	581	2.10
Biscuits (49)			0.52	0.0052	71	0.26

a: calculated on the basis that ethylene oxide in sesame seeds is present at a concentration of 10 mg/kg seeds and based on the assumption that this concentration of ethylene oxide is always present in the sesame seeds. The calculations were for an average body weight of 34 kg for an individual in the age group 1 to 17 years, calculated from the Food Consumption Survey.

b: MOE calculated for the $BMDL_{10}$ of 0.37 mg/kg bw per day.

c: to avoid excessive decimals the numbers in the table have been rounded. However, the calculations have been done with the full numbers, including all decimals.

d: calculated as follows: (MOE/10000) × intake of food product (g/kg bw per day)×(body weight). MOE = $BMDL_{10}$/[intake of food product (g/kg bw) × percentage sesame seeds in food × ethylene oxide content in sesame seed (µg/g) × 1000]

As presented in appendix II, the exposure estimates have been calculated based on the food consumption survey data for the age group 1 to 17 years of age. It is anticipated that in part of this age group the exposure will be on average somewhat higher than in the adult population, since children usually have a higher exposure to substances in food than adolescents and adults, because of their higher food intake per kg bw. In appendix III, the same calculations as done for table 1 above have been presented but for a mean ethylene oxide content (38.8 mg/kg) from 6 analytical reports, available to Front Office and for an ethylene oxide contents of 0.05 mg/kg, corresponding to the MRL for ethylene oxide in sesame seeds.

Additional to the results reported in Table 1, it can be calculated that an MOE of 10 000 will be reached after consumption of 0.126 g sesame seeds /person per day, based on a body weight of 34 kg and the $BMDL_{10}$ of 0.37 mg/kg bw per day,. This is irrespective of the source of food in which these sesame seeds are consumed[5].

[5] Calculated ad follows: amount of sesame seed (g) = 1000 × $BMDL_{10}$ (mg/kg bw per day) × (body weight; kg) / ((ethylene oxide contents; mg/kg) × 10 000)

Risk assessment

Following the EFSA guidance, an exposure to a genotoxic and carcinogenic substance that would correspond to a Margin of Exposure (MOE) larger than 10 000 would be of low concern from a public health point of view, when it is based on a $BMDL_{10}$ from an animal study. Also according to EFSA, in such a case the exposure to that substance might reasonably be considered as a low priority for risk management actions.

In this case of exposure to ethylene oxide in sesame seeds, the MOEs for various foods that are regularly consumed and that may contain these seeds is far below 10 000. For consumers who like these foods and eat them frequently and on a regular basis, an increased risk for the development of gastro-intestinal tumours may be anticipated. It can also be calculated which amounts of foods can be regularly consumed that would result in an MOE for ethylene oxide larger than 10000, assuming that throughout one's life the concentration of ethylene oxide would always be at the maximum of the indicated commonly reported levels (10 mg/kg). These amounts are less than 1.57 or 2.10 g/person per day for bread (with 8% sesame seeds) or biscuits (with 6% sesame seed), respectively. For biscuits (with 49% sesame seeds) and for crackers and rusk (with 10% sesame seeds) these amounts are less than 0.26 or 1.26 g/person per day. This assessment is applicable to the consumption of individual food items; it does not cover the risk of exposure to ethylene oxide from other sources, including all other food sources. Front Office calculated that for sesame seeds that contain 10 mg ethylene oxide/kg a consumption of 0.126 g/person per day would provide a MOE of 10 000. From table III.2 it can be seen that when the concentration of ethylene oxide in sesame seeds is at the level of the MRL, for all four foods considered in this assessment, the MOEs for ethylene oxide would be larger than 10 000 at the amounts in which these foods are consumed.

It is noted that the $BMDL_{10}$ is strictly applicable to pure ethylene oxide. The concentrations measured in sesame seeds always reflect the sum of ethylene oxide and 2-chloroethanol. Data presented in the report from ANZFA (2000) indicate that in herbs and spices the concentrations of ethylene oxide decline rapidly after treatment with ethylene oxide, while concentrations of 2-chloroethanol are much more stable. Consequently, the levels of ethylene oxide in pepper corns and ground pepper were at least 2 orders of magnitude less than the levels of 2-chloroethanol at 2 weeks after fumigation. In addition ANZFA cited studies which indicated that during food processing the levels of ethylene oxide decline further possibly due to evaporation but more significantly due to conversion into ethylene glycol[6] upon heating. ANZFA did not include processing factors in their assessment, and also Front Office did not include such factors, since the concentration data provided by ANZFA were for herbs and spices only and rather limited. ANZFA states that it is not completely clear if 2-chloroethanol is genotoxic. If so, its genotoxic potency may be far less than that of ethylene oxide, based on the outcome of the few summarized genotoxicity tests. The available data-base as cited by ANZFA on genotoxicity of 2-chloroethanol seems to be incomplete, inconsistent and contains obsolete tests. Carcinogenicity data are not available, but if the difference in genotoxic potency does exist and were to reflect a similar difference in carcinogenic potency, the risk would be overestimated. The former EU-scientific committee on food stated in 2002 that 2-chloroethanol is not genotoxic *in vivo*; but did not derive a toxicological reference value (SCF, 2002).

[6] For this substance , together with diethylene glycol, a group-TDI of 0.5 mg/kg bw per day has been derived in 2002 (SCF, 2002).

In addition, it is assumed that the expression of stomach and forestomach tumours is fully relevant to humans. However, if these tumours are predominantly caused by local tissue irritation rather than genotoxicity, this would also result in an overestimation of the risk, since dosing via gavage results in higher concentrations in the (fore)stomach than via dietary exposure. This would increase the chance on development of tissue irritation.

From the critical study (Dunkelberg, 1982), conservative estimates of the dose levels were extracted that were used for dose response modelling and the derivation of the $BMDL_{10}$. Consequently, the resulting $BMDL_{10}$ could be a factor of approximately 2 too low.

Conclusions

1) Ethylene oxide is considered a substance that is genotoxic and carcinogenic. Therefore, it is not justified to derive a Health Based Guidance Value which is associated with absence of risk. The assessment has been carried out using the only available chronic oral toxicity study from which a BMDL10 of 0.37 mg/kg body weight per day has been derived for the development of forestomach and stomach tumours.

2) Based on the maximum of the range of ethylene oxide concentrations that is indicated by BuRO to be commonly reported for sesame seeds (10 mg/kg), the consumption of less than 0.26, 1.26, 1.57 or 2.10 g/person per day of biscuits (with 49% of sesame seeds), crackers and rusks (with 10% of sesame seeds), bread (with 8% of sesame seeds) and biscuits (with 6% of sesame seeds), respectively would result in an MOE greater than 10 000. Based on the current methodology in the EU for evaluation of genotoxic and carcinogenic substances in food, consumption of these amounts of food would be of low safety concern. However, in practice this means that these foods can-not be safely consumed in realistic amounts, when they are produced with sesame seeds that contain ethylene oxide at the reported maximum of the indicated commonly found range of ethylene oxide concentrations.

It is noted that due to limited amount of data available, the assessment is very conservative; both with respect to the estimation and relevance of the observed toxicity of ethylene oxide and with respect to the estimation of exposure to ethylene oxide in sesame seeds.

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Appendix I. Dose-response modelling with the EFSA webtool.

Data used were extracted from Dunkelberg (1982). The effect considered is the development of forestomach and stomach tumours in female rats after life-time exposure to ethylene oxide, administered via gavage.

Data used for analysis:

dose (mg/kg/be per day	N animals responding (Ntum)	N animals per group
0.00	0	50
1.13	8	50
4.87	31	50

Selection of the BMR

The BMR (benchmark response) used is an extra risk of 10% compared to the controls, the default approach following the EFSA Guidance on dose-response modelling (EFSA, 2017). The BMD (benchmark dose) is the dose corresponding with the BMR of interest. A 90% confidence interval around the BMD will be estimated, the lower bound is reported by BMDL and the upper bound by BMDU. The BMDL-BMDU confidence interval has been determined using model averaging (200 bootstrap runs).

Software Used

Results are obtained using the EFSA web-tool for BMD analysis, which uses the R-package PROAST, version 69.0[7].

Results

Response variable: Ntum

Fitted Models

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	conv
null	1	-85.96	173.92		NA	NA	NA	NA
full	3	-55.19	116.38		NA	NA	NA	NA
two.stage	3	-55.19	116.38	yes	0.443	1.25	0.706	yes
log.logist	3	-55.19	116.38	yes	0.365	1.22	0.783	yes
Weibull	3	-55.19	116.38	yes	0.298	1.23	0.736	yes
log.prob	3	-55.19	116.38	yes	0.410	1.21	0.818	yes
gamma	3	-55.19	116.38	yes	0.277	1.23	0.745	yes
logistic	2	-58.44	120.88	no	NA	NA	1.670	yes
probit	2	-58.01	120.02	no	NA	NA	1.520	yes
LVM: Expon. m3-	3	-55.19	116.38	yes	0.301	1.24	0.752	yes
LVM: Hill m3-	3	-55.19	116.38	yes	0.331	1.23	0.798	yes

Weights for Model Averaging

two.stage	log.logist	Weibull	log.prob	gamma	logistic	probit	EXP	HILL
0.14	0.14	0.14	0.14	0.14	0.01	0.02	0.14	0.14

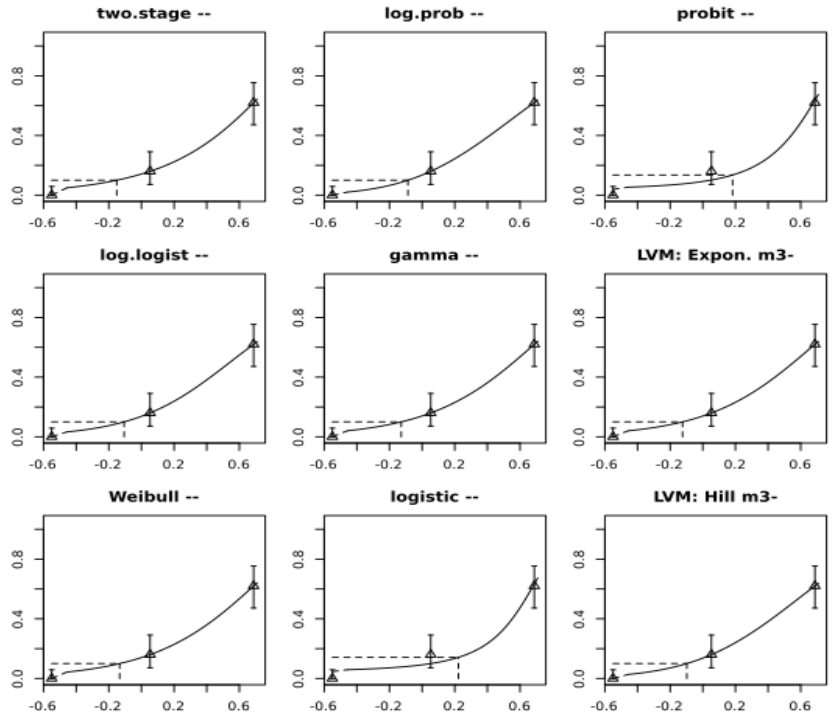
Final BMD Values

subgroup	BMDL	BMDU
all	0.37	1.38

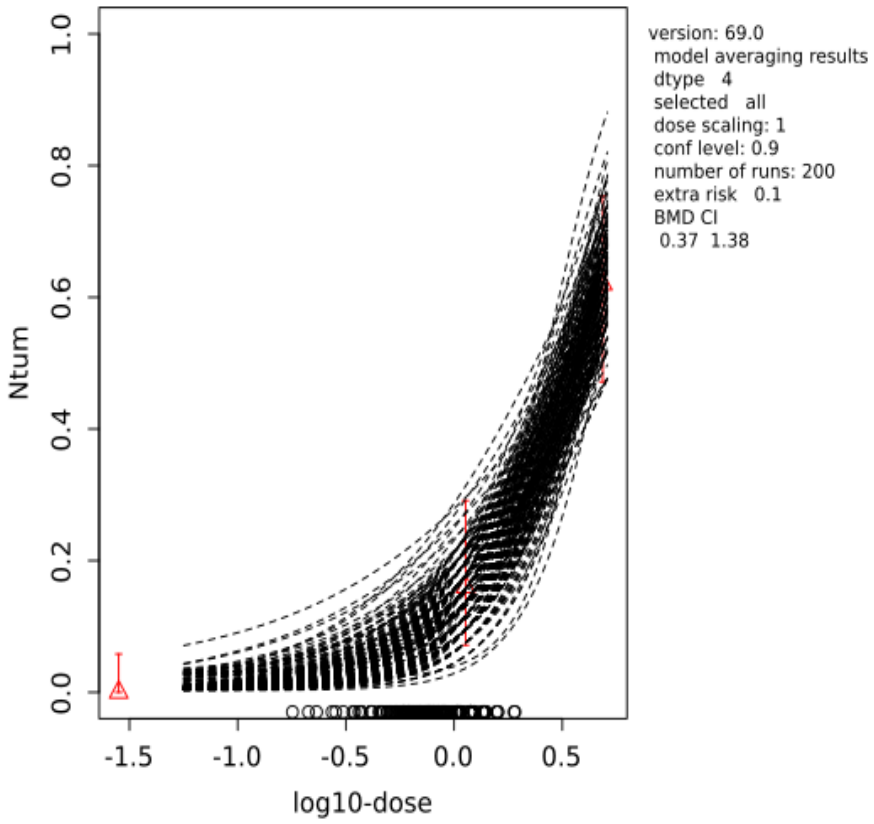
Confidence intervals for the BMD are based on 200 bootstrap data sets.

[7] for more information see: https://www.rivm.nl/en/proast

Graphical presentation of fitted dose-response curves



Graphical representation of bootstrapping curves for model averaging



Appendix II. Intake estimation of sesame seeds for the Dutch population.

The estimation of intake of sesame seeds is based on food consumption monitoring data collected in the Dutch food consumption survey (Van Rossum et al. 2016, 2018). Sesame seed-containing products are not well-recorded in the Dutch national food consumption data-base and the data-base does not contain food composition data that could be used to convert intake of food items into information on the amount of sesame seeds consumed. The assessment of intake of sesame depends on two aspects: the collection of food composition data and based on this the conversion of food consumption data from the food consumption survey into intake estimates for sesame seeds.

Food composition data

To obtain information on the sesame seeds composition of food, the conversion model of Van Dooren et al. (1993) was screened. This conversion model splits food as consumed into mass percentages of their raw ingredients. For example, 100 g of sesame seed-crackers contain 1.7 gram of sesame seeds. The conversion model includes entries for the following sesame seed-containing foods: rusks and crackers, biscuits and cereal bars, hummus, and sesame paste / tahin. Table II.1 lists the range of the percentages of sesame seeds in those foods according to the conversion model. For some sesame seed-containing foods, no entries were found. For those products, the food product data-base LEDA[8], which contains labels of food product on the Dutch market, was searched for declarations of sesame seeds in bread and biscuits with sesame seed. The range of the percentages sesame seeds in those foods obtained from the LEDA is also listed in Table II.1.

Table II.1. Percentage sesame seeds in food products

Product group	**Food product**	**% sesame seeds in food**	**Source**	**Assumed sesame seeds content for food group (%)**
Crackers and rusks	'Knäckebröd'	5-10	Conversion model	10
	Rusks	6	Conversion model	
	Crackers	1.7	Conversion model	
Bread	Bread	0,2-8	LEDA	8
Biscuits and cereal bars	'Sesamzaad-koek'	49	LEDA	49
	biscuits	6	LEDA	6
	Biscuits/bars	0.7-2	Conversion model	
Hummus	Hummus	13	Conversion model	13
Sesame paste / tahin	Sesame paste / tahin	94	Conversion model	94

Food consumption data

Sesame seed-containing products are not well-recorded in the Dutch national food consumption data-base. Although food codes exist for some crackers, rusks, biscuit and cereal bars containing sesame seeds, consumption of those food products can be reported as their regular counterparts not containing sesame seed. Therefore, it was assumed that all bread, crackers and rusk, biscuits and cereal bars consumed and

[8] www.levensmiddelendatabank.nl; not publicly accessible.

reported in the data base contained sesame seed. This is a conservative assumption, leading to overestimation of the intake.

Consumption statistics obtained for crackers and rusk, bread, and biscuits were obtained from RIVM statline[9]. Mean consumption of those foods, was obtained from the Dutch food consumption survey 2012-2016 (van Rossum et al. 2016, 2018). The population aged 1-17 years was selected, because for many foods this age group has the highest food intake. Table II.2 lists the daily mean consumption of the particular foods.

For the calculation of the intake per kg bodyweight (bw), a mean bw of 34 kg was calculated for the participants in the Food Consumption Survey. To calculate the intake of sesame seeds, the highest percentage of sesame seeds in the products was used as listed in Table 1.

Table II.2. Mean consumption[(a)] of grain-based products and sesame seeds via those products for the Dutch population in the age of 1-17 years and 34 kg bw.

Product	**Intake of food product (g per day)**	**Intake of food product (g/kg bw)**	**Intake of sesame seeds (g/kg bw)**
Bread	123	3.6	0.29
Crackers and rusk	18	0.5	0.05
Biscuits (6% sesame seeds)	36	1.1	0.06
Biscuits (49% sesame seeds)			0.52

a: mean, calculated over all reporting days in the food consumption survey (2235)

Consumption of sesame seeds, hummus and sesame paste / tahin, recorded for individuals 1-17 years of age in the Dutch food consumption survey, was occasional rather than frequent. For those food products, the mean consumption is low. For illustration, the consumptions were averaged over the consumption occasions (see table II.3).

- Sesame seed: 3 consumptions days with amounts consumed varying between 2-4 gram per day. Mean intake of sesame seeds per occasion is 3 g per day;
- Tahin: only 1 consumption of 20 g per day was recorded;
- Hummus: 23 consumptions days with amount consumed varying between 4 and 40 gram per day. Mean intake of hummus per occasion is 17 g per day;
- Intake of sesame seeds was calculated according to the percentage sesame seeds in those foods listed in table II.1 and assuming a mean bw of 34 kg

Table II.3. Mean consumption of hummus, tahin per occasion and sesame seeds via those products for the Dutch population in the age of 1-17 years and 34 kg bw.

Product	**Intake of food product (g per day)**	**Intake of food product (g/kg bw)**	**Intake of sesame seeds, consumption days only (g/kg bw)**
Sesame seed	3	0.09	0.09
Hummus	17	0.5	0.07
Tahin	20	0.6	0.56

[9] https://statline.rivm.nl

Appendix III

Table III.1. Intake data for bread, crackers, rusk and biscuits containing sesame seeds at a concentration of 38.8 mg /kg and resulting exposure to ethylene oxide. *These foods were regularly reported in the Food Consumption Survey. A Margin of Exposure (MOE) and the amounts of foods that would result in an MOE > 10 000 have been calculated for foods that contain sesame seeds with ethylene oxide at a concentration of 38.8 mg /kg (average of 6 analytical results available to Front Office; range 2.5 – 86 mg/kg).*

Product (% sesame seeds)	**frequency**	**Intake of food product (g/kg bw per day)**	**Intake of sesame seeds (g/kg bw per day)**	**Exposure to ethylene oxide[a] (mg/kg bw per day)**	**MOE[b]**	**Intake of food[c,d] (g/person per day), that would result in an MOE of 10000**
Bread (8)	Regular	3.6	0.29	0.011	33	0.41
Crackers and rusk (10)	Regular	0.5	0.05	0.002	179	0.32
Biscuits (6)	Regular	1.1	0.06	0.002	150	0.54
Biscuits (49)			0.52	0.020	18	0.07

Table III.2. Intake data for bread, crackers, rusk and biscuits containing sesame seeds at a concentration of 0.05 mg /kg and resulting exposure to ethylene oxide. *These foods were regularly reported in the Food Consumption Survey. A Margin of Exposure (MOE) and the amounts of foods that would result in an MOE > 10 000 have been calculated for foods that contain sesame seeds with ethylene oxide at a concentration of 0.05 mg /kg (EU MRL).*

Product (% sesame seeds)	**frequency**	**Intake of food product (g/kg bw per day)**	**Intake of sesame seeds (g/kg bw per day)**	**Exposure to ethylene oxide[a] (mg/kg bw per day)**	**MOE[b]**	**Intake of food[c,d] (g/person per day), that would result in an MOE of 10000**
Bread (8)	Regular	3.6	0.29	1.44E-05	25653	315
Crackers and rusk (10)	Regular	0.5	0.05	2.66E-06	139006	252
Biscuits (6)	Regular	1.1	0.06	3.19E-06	116159	419
Biscuits (49)			0.52	2.60E-05	14224	51

Footnotes to the tables:
a: calculated on the basis that ethylene oxide in sesame seeds is present at the concentrations mentioned in the table headings (38.8 or 0.05 mg/kg seeds) and based

on the assumption that this concentration of ethylene oxide is always present in the sesame seeds. The calculations were for an average body weight of 34 kg for an individual in the age group 1 to 17 years, calculated from the Food Consumption Survey.
b: MOE calculated for the $BMDL_{10}$ of 0.37 mg/kg bw per day.
c: to avoid excessive decimals the numbers in the table have been rounded. However, the calculations have been done with the full numbers, including all decimals.
d: calculated as follows: (MOE/10 000) × intake of food product (g/kg bw per day)×(body weight). MOE = BMDL10/[intake of food product (g/kg bw) × percentage sesame seeds in food × ethylene oxide content in sesame seed (µg/g) × 1000]