Health Council of the Netherlands

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Flour dust from processed, de-hulled soybeans

Health-based recommendation on occupational exposure limits

2016/07

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Flour dust from processed, de-hulled soybeans*
Uw kenmerk : DGV/BMO/U-932542
Ons kenmerk : U-977709/JR/cn/459-X72
Bijlagen : 1
Datum : 16 juni 2016

Geachte minister,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan meelstof van fijngemalen en gepelde sojabonen.

Het voorliggende advies maakt gebruik van de werkwijze die in 2008 door de Gezondheidsraad is voorgesteld voor het afleiden van gezondheidskundige advieswaarden of voor het vaststellen van op risico gebaseerde referentiewaarden voor allergene stoffen (rapportnr. 2008/03, *Preventie van werkgerelateerde luchtwegallergieën*). De commissie heeft de concentratie soja-eiwit antigenen in de lucht berekend waarbij een werknemer een extra kans van één procent gedurende zijn arbeidszame leven heeft om door beroepsmatige blootstelling gesensibiliseerd te raken ten opzichte van de kans hierop in de niet beroepsmatige blootgestelde algemene bevolking.

De conclusies van het genoemde advies zijn opgesteld door de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad en getoetst door de Beraadsgroep Volksgezondheid.

Ik onderschrijf de aanbevelingen en het advies van de commissie.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van IenM en aan de minister van VWS.

Met vriendelijke groet,

prof. dr. J.L. Severens,
vicevoorzitter

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Flour dust from processed, de-hulled soybeans

Health-based recommendation on occupational exposure limits

Dutch Expert Committee on Occupational Safety,
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2016/07, The Hague, June 16, 2016

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Samenvatting

Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid leidt de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (Commissie GBBS; één van de vaste commissies van de Gezondheidsraad) gezondheidskundige advieswaarden af voor stoffen in lucht waaraan mensen blootgesteld kunnen worden tijdens hun beroepsuitoefening. Deze advieswaarden vormen vervolgens de basis voor grenswaarden waarmee de gezondheid van werknemers beschermd kan worden.

In dit advies bespreekt de commissie de gevolgen van blootstelling aan meelstof van fijngemalen en gepelde sojabonen (kortweg aangeduid als sojameelstof) en probeert zij gezondheidskundige advieswaarden vast te stellen. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór mei 2016 zijn verschenen.

Fysische en biochemische eigenschappen

In dit advies is meelstof geëvalueerd afkomstig van sojabonen (*Glycine hispida* of *Glycine max*) die zijn gepeld en fijngemalen.

Sojameel wordt onder andere toegepast als deegverbeteraar bij de bereiding van bakkerijproducten. Sojameel bevat lipoxygenase dat carotenoïden bleekt. Het bevat daarnaast lecithine dat het deeg doet rijzen. Ook de diervoederindustrie

kent een groot gebruik van sojameel. Sojameel bevat ongeveer 15 allergene glycoproteïnen met een hoge molecuulmassa, waarvan de belangrijkste zijn geïdentificeerd als de opslageiwitten beta-glycinine en glycinine, en trypsineremmers.

Ingeademde stofconcentraties (gemiddeld over een achturige werkdag) in bedrijven waar gewerkt wordt met sojameel, kunnen, over een volledige werkdag, oplopen tot meer dan 35 mg/m^3. Het gehalte aan sojaeiwitantigenen in de lucht kan oplopen tot in de microgrammen per kubieke meter lucht, afhankelijk van de werkzaamheden.

Monitoring

De concentratie van de in lucht aanwezige (vaste) stof van bewerkt sojameel kan op basis van de massa (gravimetrisch) worden bepaald en gemiddeld over een achturige werkdag. In het opgevangen stof kan verder de concentratie van specifieke sojaeiwitantigenen worden vastgesteld. In Nederland is het gebruikelijk de concentratie van de in de lucht aanwezige stof te meten met een gestandaardiseerde techniek (NEN481).

Grenswaarden

In Nederland noch in het buitenland zijn grenswaarden voor sojameelstof vastgesteld.

Kinetiek

Werknemers kunnen aan stof van sojameel worden blootgesteld doordat ze stofdeeltjes inademen op hun werk. Daarbij gedragen deze stofdeeltjes in de lucht zich waarschijnlijk hetzelfde als andere stofdeeltjes. Afhankelijk van de grootte en vorm van de stofdeeltjes, en van de ademhalingsinspanning, komen de deeltjes bij inademing terecht in de neus (grote deeltjes), luchtwegen of longen (kleinste deeltjes). Door trilharen in de luchtwegen, slijmproductie en gespecialiseerde cellen in de longen, worden de stofdeeltjes verwijderd uit de luchtwegen en longen. Hoe dieper een stofdeeltje in de longen terecht komt hoe moeilijker het is het deeltje te verwijderen.

Effecten

Inademing van sojameelstof kan klachten geven als rode en jeukende ogen, hoesten, niezen, opgezette slijmvliezen, verhoogde slijmproductie en benauwdheid

(astma). Dergelijke klachten kunnen wijzen op een neus-/keelontsteking en/of astma. Ze kunnen worden veroorzaakt door irritatie, een ongewenste specifieke reactie van het immuunsysteem (allergische reactie), of door beide mechanismen. Een allergie is een overgevoeligheidsreactie op een lichaamsvreemde stof bij een blootstelling die normaal gesproken wordt getolereerd. Kenmerkend voor allergie is dat het ontstaan van klachten wordt voorafgegaan door een klachtenvrije periode waarin het immuun-systeem door blootstelling in een verhoogde staat van paraatheid wordt gebracht (sensibilisatie). Een onderscheid tussen irritatie en allergie kan worden gemaakt met behulp van speciale tests voor het aantonen van sensibilisatie voor een specifiek allergeen, in dit geval voor allergenen die alleen voorkomen in sojameelstof.

De meeste gegevens over effecten van beroepsmatige blootstelling aan sojameelstof zijn afkomstig van onderzoeken onder medewerkers van (banket)bakkerijen en meelproducerende of -verwerkende bedrijven. Bij een deel van die werknemers is ook aangetoond dat zij gesensibiliseerd zijn voor allergenen in sojameelstof (prevalentie van één tot honderd procent). Ter vergelijking, het aantal gevallen van specifieke sensibilisatie onder niet-blootgestelde controlegroepen lag in die onderzoeken rond de vier à vijf procent en voor de algemene bevolking op twee procent.

Er zijn geen onderzoeken uitgevoerd naar mogelijke andere schadelijke gezondheidseffecten onder werknemers. Ook zijn er geen dierexperimentele studies uitgevoerd.

Evaluatie

Om een gezondheidskundige advieswaarde te kunnen afleiden, zijn kwantitatieve gegevens nodig over de relatie tussen blootstelling en respons, in een zo laag mogelijk blootstellingsgebied. Op één Amerikaans onderzoek na, is in andere onderzoeken een dergelijke relatie niet goed onderzocht. In het Amerikaanse onderzoek zijn de gegevens afkomstig van werknemers die vrijwel alleen blootstonden aan stof van bewerkt sojameel. Als effecteindpunt zijn sensibilisatie en het optreden van (allergische) luchtwegklachten onderzocht; de blootstellingsconcentraties zijn uitgedrukt in ‘totaal ingeademde stof’ of in ‘ingeademde hoeveelheid sojaeiwitantigenen’.

Wat het effecteindpunt betreft hecht de commissie de meeste waarde aan de gegevens over sensibilisatie. Iemand die gesensibiliseerd is, loopt namelijk bij voortdurende blootstelling een grote kans om allergische klachten te krijgen. Aangezien sensibilisatie niet omkeerbaar is, zal deze persoon voor de rest van zijn of haar leven gesensibiliseerd zijn en bij voortzetting van de blootstelling

allergische klachten kunnen krijgen. Daarnaast kan in tests op sensibilisatie bepaald worden door welk allergeen de sensibilisatie is veroorzaakt. Dit is niet mogelijk bij tests op aanwezigheid van luchtwegklachten. Voorts heeft de commissie geen bewijs gevonden dat luchtwegklachten bij een lagere blootstelling optreden dan sensibilisatie. Dit betekent dat een advieswaarde die gebaseerd is op gegevens over sensibilisatie tevens luchtwegklachten zal voorkomen.

Bij het meten van de blootstelling doet zich een vergelijkbare situatie voor. Omdat op de werkplek vaak sprake is van gelijktijdige blootstelling aan verschillende stofbronnen is het meten van 'totaal ingeademde stof' in deze situatie geen goede blootstellingmaat. Daarom geeft de commissie de voorkeur aan het meten van specifieke sojaeiwitantigenen in de lucht, want voor het meten ervan bestaan technieken die onderscheid kunnen maken tussen de antigenen van verschillende bronnen.

Volgens de commissie kan op basis van de beschikbare informatie over sensibilisatie geen drempelwaarde worden aangewezen, omdat in het uitgangsonderzoek geen blootstellingsniveaus zijn gerapporteerd waaronder geen gevallen van sensibilisatie optraden. Dit betekent dat het beste een referentiewaarde kan worden afgeleid. Een referentiewaarde is een concentratie van sojameelstof (allergenen) in de lucht waarbij beroepsmatige blootstelling leidt tot een vooraf bepaalde extra kans op sensibilisatie ten opzichte van het aantal gevallen in de algemene bevolking. Voor allergenen is het extra absoluut risico bepaald op één procent, gebaseerd op bescherming gedurende het gehele arbeidzame leven.

De commissie heeft aan de hand van het voorgaande een referentiewaarde voor sojameelstof berekend met behulp van een lineair regressiemodel. Toepassing van het model leidt tot een referentiewaarde van 0,1 µg sojaeiwitantigeen/m^3 als een tijdgewogen gemiddelde concentratie over een achturige werkdag.

De commissie kon geen referentiewaarde afleiden waarmee sensibilisatie door piekblootstellingen te voorkomen is. Er zijn weliswaar aanwijzingen dat korte hoge blootstelling tijdens het werk ook tot sensibilisatie kan leiden, maar de beschikbare gegevens zijn onvoldoende om daarvoor een betrouwbare referentiewaarde te kunnen afleiden.

Referentiewaarde

De commissie beveelt een referentiewaarde aan voor beroepsmatige blootstelling aan stof afkomstig van fijngemalen en gepelde sojabonen, van 0,1 microgram sojaeiwitantigeen per kubieke meter (0,1 µg/m^3) als een gemiddelde concentratie over een achturige werkdag. Bij deze concentratie hebben werkers ten opzichte

van de algemene bevolking een extra absoluut risico van één procent op sensibilisatie voor allergenen aanwezig in sojameelstof.

De gegevens zijn onvoldoende om een referentiewaarde tegen de effecten van piekblootstellingen af te leiden.

14 Flour dust from processed, de-hulled soybeans

Executive summary

Scope

At the request of the Minister of Social Affairs and Employment, the Dutch expert Committee on Occupational Exposure Safety (DECOS), one of the permanent Committees of experts of the Health Council, proposes health-based recommended occupational exposure limits for chemical substances in the air in the workplace. These recommendations serve as a basis in setting legally binding occupational exposure limits by the minister. In this advisory report, the Committee evaluates the consequences of exposure to dust from processed de-hulled soybean flour (soybean flour dust), and makes an effort in deriving a health-based occupational exposure level or reference value. The Committee's conclusions are based on scientific papers published before May 2016.

Physical and biochemical properties

In this advisory report dust is evaluated from soybeans (*Glycine hispida* or *Glycine max*), which are de-hulled and finely milled.

Soybean flour contains lipoxygenase (bleaches carotenoids) and lecithin (emulsifier). For this reason it is routinely used as dough improver in the preparation of bakery products. Also, the animal food industry is a large user of soybean flour. In soybean flour, there are about 15 allergenic high molecular

weight glycoproteins, the most common of which have been identified as the storage proteins beta-glycinin and glycinin, and trypsin inhibitors.

Average inhalable dust concentrations in companies (average concentrations measured during an eight hour working day) using soybean flour can reach levels of 35 mg/m^3 and more, as measured in the breathing zone during a full-shift.

Monitoring

Exposure to airborne soybean flour dust can be determined gravimetrically in samples of full-shift personal inhalable dust. From the dust samples, the content of soy antigens can be determined. In the Netherlands, it is common practice to measure exposure using a standardized technique for collection of inhalable dust (NEN481).

Limit values

In The Netherlands nor in other countries occupational exposure limits have been set for soybean flour dust.

Kinetics

Exposure to soybean flour dust occurs from dust or aerosols. Most likely, these dust particles behave the same as other types of dust particles. The place of deposition in the airway system is determined by particle size, aerodynamic properties, and the volume of respiration. Macrophages and the mucociliary system in the respiratory tract are responsible for the clearance of dust particles.

Effects

Inhalation of soybean flour dust may elicit immunological and non-immunological responses. Immunological responses, primarily IgE-mediated, lead to sensitisation, which may induce allergic reactions with respiratory symptoms as rhinitis, rhinoconjuctivitis, asthma (i.e., shortness of breathing, cough). These symptoms may also be caused by irritation, a non-immunological response. A distinction between the two types of reactions can be made by testing on sensitisation.

Most data on the effects of occupational exposure to soybean flour dust are retrieved from human studies on employees working in bakeries, and soybean processing and milling companies. Among the employees, symptoms are

described which indicate the presence of rhinitis, rhinoconjuctivitis and asthma-like symptoms. Part of these workers with complaints also showed to be sensitised to allergens present in the soybean flour (prevalence values of one to hundred percent). For comparison, in those studies, the number of cases in non-occupationally exposed control groups averaged around four and five percent, and for the general population at two percent.

No studies are available on other possible adverse health effects of soybean flour dust in humans, nor were there animal studies published.

Evaluation and recommendation

In deriving a health-based occupational exposure limit, quantitative data are needed on exposure-response relationships in as low as possible exposure range. Except for one US study, such a relationship has not well been investigated. In the American study, data were obtained from workers who were unlikely to be co-exposed to other dust sources or substances then soybean flour. Effect endpoints in this study were sensitisation and the occurrence of (allergic) airway symptoms; exposure was expressed as 'total inhalable dust' or 'inhalable soy antigen'.

Regarding the health effects, the Committee considered data on sensitisation as the most relevant. Somebody who is sensitised has a high risk in developing allergic reactions at (continuing) exposure. Because sensitisation is an irreversible effect, the person in question will be sensitised for the rest of his or her life, and at exposure, may show allergic symptoms. In addition, in tests on sensitisation it is possible to assess which allergen was responsible for the positive outcome. Such an assessment cannot be made when examining respiratory symptoms, irrespective the type of response. Moreover, the Committee did not find evidence that respiratory symptoms caused by irritation, occur at lower exposure levels than sensitisation. This means that an occupational exposure limit based on data on sensitisation should prevent also the development of non-specific respiratory symptoms. Workers who are already sensitized may develop allergic respiratory symptoms upon continuing exposure at or perhaps below the OEL for sensitization. However, these workers are considered a vulnerable group, which are not taken into account in setting an OEL, because according to the current policy, an OEL should be set for non-sensitized healthy workers.

A comparable condition arises in assessing exposure levels. Since in most workplaces co-exposure to other dust sources is likely, measuring 'total inhalable dust' is in this situation not a good exposure parameter. Therefore, the

Committee prefers measuring airborne soy antigen levels in the air, because techniques are available that distinguish airborne antigens from different sources.

According to the Committee, based on the available information for the effect 'sensitisation' no threshold level can be assessed, because no exposure levels were reported below which no cases of sensitisation to soybean flour allergens were found. That implies that the setting of reference values is warranted. A reference value is a concentration of soybean flour dust (soy antigens) in the air, at which occupational exposure leads to a predefined accepted level of extra risk of allergic airway sensitisation, compared to the background risk in the general, non-exposed population. In the case of allergens the extra (absolute) risk is set at one percent, based on protection during the 40 years of occupational exposure.

Based on the preceding, the Committee has calculated a reference value for soybean flour dust by using a linear regression model. Using this model, the Committee derived a reference value of 0.1 µg inhalable soy antigen/m^3 (eight-hour time-weighted average concentration).

The Committee has also discussed whether a reference value could be derived to prevent sensitisation due to peak exposure, because it is suggested that short exposure during work to high levels of the allergen could lead to sensitisation. However, the available data are insufficient to derive a reliable short-term reference value.

Reference value

The Committee recommends a reference value for occupational exposure to dust from processed de-hulled soybean flour of 0.1 µg inhalable soy antigen/m^3, as an eight-hour time-weighted average concentration (8-hr TWA). At this concentration workers have an additional sensitisation risk for dust from processed de-hulled soybean flour of one percent compared to the background risk in the general population.

The data are insufficient to derive a short term exposure limit (15-minute TWA).

Chapter 1

Scope

1.1 Background

At request of the minister of Social Affairs and Employment, the Dutch expert Committee on Occupational Safety (DECOS), a Committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of substances that are used in the workplace (Annex A). The purpose of these evaluations is to recommend health-based occupational exposure limits, which specify levels of exposure to airborne substances, at or below which it may be reasonably expected that there is no risk of adverse health effects.

In this advisory report, such an evaluation and recommendation is made for flour dust from processed, de-hulled soybeans (hereafter called soybean flour dust).

1.2 Committee and procedure

The present document contains the assessment of DECOS, hereafter called the Committee, of the health hazard of soybean flour dust. The members of the Committee are listed in Annex B. The submission letter to the Minister can be found in Annex C.

In 2015, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex D. The Committee has taken these comments into account in

deciding on the final version of the report. The received comments, and the replies by the Committee, are publicly available on the website of the Health Council.

1.3 Data

The Committee's recommendations on the health-based occupational exposure limit or reference values of soybean flour dust are based on scientific data, which are publicly available. Published literature was retrieved from the on-line databases Medline and Toxline, supplemented with subject searches in journals and internet sources. The final search was carried out in May 2016.

Chapter 2

Identity, properties and monitoring

2.1 Identity

In this report dust derived from processed, finely-milled and de-hulled soybeans (*Glycine hispida or Glycine max*) is evaluated.

Additives

Dust in bakeries and soybean processing companies may contain a variety of ingredients, other than soybean flour, such as cereal flour, enzymes (e.g. fungal alpha-amylase), and additives (e.g. preservatives, antioxidants, baker's yeast, egg powder). The Committee is aware that these ingredients may contribute to the biological effects of soybean flour dust. For instance, cereal flour dust and fungal alpha-amylase are known to have sensitising properties, as is suggested also for soybean flour dust. However, the present risk evaluation is restricted to soybean flour dust.

2.2 Physical and biochemical properties

About 90% of the whole soybean seed consists of cotyledons and 8% are hulls. Grinding or cracking and pressing of de-hulled soybeans result in soybean grit or flakes.

Soybean flour is obtained by finely grinding de-hulled soybeans. This so-called full-fat soybean flour consists of 46.6% protein, 22.1% fat, 5% moisture, 2.1% fibre, 5.2% ash. The phospholipid fraction is usually called (soy) lecithin. Lecithin is used as a bakery additive because of its emulsifying properties.

Milling of soybean flakes extracted with solvents results in defatted soybean flour, which has nowadays replaced full-fat soybean flour. At least 97% of the particles of soybean flour should be smaller than 150 µm. Defatted soybean flours typically contain 59% protein, 1% fat, 7% moisture, 2.6% fibre and 6.4% ash.

Some proteins present in the soybean flour are potential allergens. Immunoblot analyses using sera of bakery workers showed sensitisation to at least 16 glycoproteins (see Table 1). The most common were soybean storage proteins

Table 1 List of identified allergenic IgE-binding proteins in soybeans.

Nomenclature	Name(s)	Molecular weight
Cotyledon		
Gly m 3[a]	Profilin, actin-binding protein	12-15 kDa
Gly m 4[a]	PR-10 protein, SAM22 (starvation associated message), group 1 Fagales-related protein	16.6 kDa
Gly m 5[a]	Vicilin, alpha subunit of beta-conglycinin	140-180 kDa
Gly m 6[a]	Glycinin, 11S globulin, G1 subunit og glycinin, storage protein	320-360 kDa
Gly m glycinin G1	11S seed storage protein, G1 subunit of glycinin	40 kDa
Gly m glycinin G2	11S seed storage protein, G2 subunit of glycinin	22 kDa
Gly m glycinin G4	11S seed storage protein, G4 subunit of glycinin	61-61 kDa
Gly m 7[a]	Seed biotinylated protein	76 kDa
Gly m 8[a]	Gly m 2S Albumin; 2S albumin, storage protein	28 kDa (dimer)
Gly m Bd 28 k	7S vicilin-like globulin	28 kDa
Gly m Bd 30 k	Thiol protease of the papain family	30-34 kDa
Gly m Bd 60 k	Cupin (7S vicilin like globulin)	63-67 kDa
Gly m TI	Kunitz trypsin inhibitor	20 kDa
Gly m Lectin	Gly m Agglutinin; Lectin, an agglutinin, SBA	14.5 kDa
Gly m IFR	Isoflavone reductase	
Gly m 39 kD	39 kDa protein	39 kDa
Gly m Oleosin	Oleosin, lipid transfer protein	16/24 kDa (monomer) 50 kDa (dimer) 76 kDa (trimer)
Hull		
Gly m 1[a]	Soybean hydrophobic protein, lipid transfer protein	7 kDa (LMW)
Gly m 2[a]	Defensin, storage protein	7.5 kDa (LMW)

[a] Official allergen nomenclature (WHO/International Union of Immunological Societies).
Sources: L'Hocine et al. (2007)[10], Verma et al. (2013)[11], www.allergen.org (May 2016), www.phadia.com (May 2016).
Abbreviations: kDa, kilo Dalton; LMW, low molecular weight.

(beta-conglycinin, glycinin), and soybean trypsin inhibitor (21,000 Dalton). All these proteins (range 10,000-94,000 Dalton) are considered high molecular proteins.[1-5]

In several case studies, allergenic properties have been reported for the phospholipid fraction of soybeans, namely lecithin.[6-9] However, the positive findings upon skin prick testing and serological examination in these studies were probably due to contamination of the lecithin preparations with heat resistant soybean proteins or alpha-amylase.[6,8,9]

2.3 EU classification and labelling

Soybean flour dust has not been evaluated by the European Commission.

2.4 Validated analytical methods

2.4.1 Environmental monitoring

Dust

Flour dust exposure is based on personal inhalable gravimetric dust measurements. In scientific studies, different types of portable pumps, flow rates, filters, and aerosol samplers have been used, depending on the country in which the study was carried out. In the Netherlands, inhalable dust is usually collected with the PAS6 sampling head. The Institute of Occupational Medicine (IOM) in Edinburgh, Scotland, developed the IOM inhalable dust sampling head and cassette to meet the sampling criteria for inhalable particulate mass. Within Europe, size fractions for measurement of airborne particles in workplace atmospheres have been standardized since 1993 (European Standard EN 481:1993). In this standard, three size fractions have been defined (inhalable, thoracic and respirable).[12]

The Committee notes that measuring inhalable total dust in assessing exposure to airborne soybean flour has limited value in most industries because of co-exposure to dust from different sources, except in industries only handling soybean flour. Establishing exposure to inhalable soybean flour in, e.g., bakeries requires the quantization of soybean flour antigens in the airborne dust.

Antigens in airborne soybean flour dust

Immunoassays for the determination of soybean flour antigens (proteins) in airborne dust were developed within the framework of the six-laboratory European research project MOCALEX (Measurement of Occupational Allergen Exposure). The methods involve (stationary) collection of dust, followed by extraction and analysis of airborne soybean flour antigens. Optimization studies for extraction of antigens from airborne (wheat) flour dust were conducted by Bogdanovic et al. (2006).[13] In the study, stationary parallel sampling devices, enabling simultaneous collection of ten identical dust samples, were equipped with PAS-6 sampling heads and modified to capture particles with an aerodynamic diameter of up to 19 µm. Optimal extraction of flour proteins from the filters was achieved using phosphate-buffered saline (pH 7.4) containing 0.05% (v/v) Tween-20.

Using the same method for sampling and extraction, Gómez-Ollés et al. (2007) developed several immunoassays for the measurement of airborne soybean antigens.[14] These included an inhibition enzyme immunoassay (EIA) using human anti-soybean flour protein IgG4, a rabbit soybean flour protein sandwich EIA, and three EIA's aimed at the detection of hull proteins in whole soybeans.

Cummings et al. (2010) modified the inhibition ELISA with soybean hull extract, developed by Gomez-Olles et al. (2007), using an protein extract prepared from de-oiled, de-hulled crushed soybean flakes as reference standard and o-phenylenediamine for generating a colored reaction product.[15] The optical density at 490 nm was compared with the reference standard. The limit of detection was 16 ng inhalable soy antigen/mL.

In order to investigate if soybean trypsin inhibitor or total protein concentrations are viable surrogates for airborne soybean dust concentrations, Spies et al. (2008) conducted an exposure study in two soybean flour producing factories in South-Africa.[16] Data for operator exposure in the early phase (n=13), and in the late phase (n=19) of soybean processing, were analysed separately. Exposure to soybean flour dust occurred exclusively in the late phase. Personal inhalable dust (NIOSH method 0050, 60-80% of full shift) was measured gravimetrically. Total protein content was determined by means of the bicinchoninic acid assay. Trypsin inhibitor content was determined using a polyclonal antibody based inhibition enzyme immunoassay developed for food analysis. There was no significant correlation between personal inhalable dust and soybean trypsin inhibitor concentration. Considering all measurements (early and late phase

combined) in each of the two factories, there was a significant correlation between inhalable dust and protein content (Spearman's $r \geq 0.6$, $p \leq 0.01$), and between protein and trypsin inhibitor contents (Spearman's $r \geq 0.6$, $p < 0.05$). However, for exposure in the late phase (relevant for soybean flour dust), the only significant correlation found was between inhalable dust and protein content in one of the plants. These findings confirm earlier observations, in which dust levels were shown to only partially correlate with the actual allergen concentration.[17]

Soybean flour and wheat or rye flour have few antigens in common, complicating the use of wheat or rye flour antigens as a surrogate for soybean flour exposure.[4,18]

2.4.2 *Biological exposure monitoring*

No publications were found concerning monitoring of soybean flour (allergens) in biological samples.

2.4.3 *Biological effect monitoring*

Tests are available to screen for persons who are sensitised against specific allergens. A useful clinical method to make a rough approximation of the person's sensitivity to an allergen is the skin prick test. In this test, allergens are introduced into the skin, after which the extent of local inflammation (wheal and flare diameter (mm)) is measured, as a result of the pharmacological effects of mediators, such as histamine, on the blood vessels in the skin. Skin prick tests resulting in a wheal diameter of at least 3 mm larger than the negative diluent (saline) control after fifteen minutes are usually considered positive for sensitisation.

Alternatively, analysis of the presence of relevant specific IgE or IgG-antibodies, for instance in blood and nasal secretions, may be carried out. Serum concentration of IgE antibodies to soybean flour can be determined by an enzyme-allergo-sorbent-test (EAST) using allergen-coated disks. In this assay, an anti-IgE-beta-galactosidase conjugate is used for detection.[19] Over the years, several tests for quantifying specific IgE and IgG antibodies to soybean flour allergens in blood have become commercially available, such as a fluorescence enzyme immunoassay (CAP-FEIA/ImmunoCAP 1000, Pharmacia Diagnostics/ Phadia), used in several studies reviewed in this advisory report, and a highly sensitive enzyme-enhanced chemiluminescent enzyme immunoassay (Immulite 2000, Diagnostic Products).[2,15,20,21] The cut-off level for considering a test

positive is usually ≥0.35 kU/L. The discriminating power of the ImmunoCAP and Immulite tests for the presence of soybean specific IgE in serum was almost equal, but precision of the Immulite test was lower.[22]

Specific inhalation challenge (SIC) is performed when occupational asthma is suspected and there is the need for identification of the causal allergen. The test provokes a physical response (rhinitis, asthma), and involves inhalation of a low dose of an allergen. Since there is serious risk of the patient suffering an asthmatic attack during testing, it is important to perform the test in a good clinical setting.

Chapter 3

Sources

3.1 Natural sources

Soybean flour is a product obtained from soybeans. Soybeans are the edible seeds (after cooking) of the soybean plant *Glycine hispida or Glycine max*, which is a species of legumes.

3.2 Man-made sources

3.2.1 Production

According to the Food and Agriculture Organization of the United Nations, the worldwide annual production of edible soybean flours and grits is nowadays more than 2,000,000 tons (mass).

In producing soybean flours, in a first step the whole soybeans are roasted, removing the coat. Grinding or cracking and pressing of de-hulled soybeans result in soybean grit or flakes. Full-fat soybean flour is then obtained by finely grinding de-hulled soybeans grit or flakes. Milling of soybean flakes extracted with solvents results in defatted soybean flour, which has nowadays replaced the full-fat soybean flour.

3.2.2 *Use*

Due to its high protein content it is widely used to produce all kinds of animal food, in particular food for pigs and poultry.

The main use for human consumption being in the soybean processing industry and in the bakery industry.[23] Soybean flour is a common baking additive, routinely added to dough in order to improve its rheology, and for bleaching dough carotenoids (lipoxygenase activity).[24] In general, the soybean flour prepared without heat treatment is added to wheat flour (up to 0.5%) for baking white bread and rolls for its lipoxygenase activity. Enzyme de-activated (heated) soybean flour is used in dough for baking cakes (3-5%).[25] Bread improvers typically contain 30-50% soybean flour.[26,27] Because it is added to baking cereal flour, soybean flour is usually associated with cereal flour dust in bakeries and related facilities. The most common tasks associated with flour exposure involve dust-generating activities such as dispensing, sieving, weighing and mixing.[28]

Sources of occupational exposure to soybean flour dust are inhalable dust in the atmosphere of the bakeries, flour mills, animal food processing factories, and processing factories, and manufacturers of dough improvers.

Chapter 4

Exposure

4.1 General population

A few outbreaks of asthma have been described, which are associated with inhalation of soybean dust, for instance among citizens in the Barcelona area.[3,29,30] However, these asthma outbreaks were considered to be induced by exposure to soybean hull allergens, Gly m 1 and Gly m 2, which are not present in soybean flour dust. In addition, the outbreaks concerned environmental outdoor exposure with low exposure levels, which is a less relevant exposure scenario for the occupational situation.

No studies have been published concerning the non-occupational exposure to airborne processed, de-hulled soybean flour dust or airborne flour dust-associated allergens.

4.2 Working population

4.2.1 Airborne allergen levels

Cummings et al. (2010) reported on airborne soybean antigen (proteins) levels from personal dust samples in workers, which were exposed to soybean flour dust in a soybean processing plant.[15,31] Workers could be divided in three exposure categories. The corresponding mean geometric concentrations (full shift samples) were: 24-804 ng/m^3 (low, n=58); 959-2,297 ng/m^3 (medium,

n=57); and 2,634-25,957 ng/m^3 (high, n=64). Exposure levels of airborne soy flour proteins was determined by an inhibition immunoassay, in which soy flour protein extracts, which were prepared from bulk pre-processed de-hulled soy flakes, served as a standard.[14]

Spies et al. (2008) reported also on total protein levels and soy trypsin inhibitor levels in three soybean processing plants.[16] Median inhalable dust levels ranged between 0.24 and 35.02 mg/m^3 (median 2.58 mg/m^3), whereas total soybean protein ranged between 29.41 and 448.82 µg/m^3 (median 90.09 µg/m^3), and soy trypsin inhibitor between 0.05 and 2.58 µg/m^3 (median 0.07 µg/m^3; sandwich-immunoassay). The investigators did not find a statistically significant correlation between total dust levels and total soybean protein levels or soy trypsin inhibitor.

4.2.2 *Inhalable dust levels*

Inhalable total dust exposure data, taken from studies in which soybean flour effects were determined, are shown in Table 2. Overall in bakeries, it is inevitable that in total dust not only soy flour dust was present, but also dusts from cereal flour and other additives. In none of the studies mentioned in the table, a distinction was made between the different dust sources.

Table 2 Full-shift personal exposure to airborne inhalable dust in various industries.

Type of industry	No. of personal samples	Median (mg/m³)	AM (mg/m³)	GM (mg/m³)	GSD (mg/m³)	Range (mg/m³)	Reference
Soybean processing plants							
3 plants, South-Africa:	64[a]						Spies et al. 2008[16]
• all processes		2.58				0.24-35.02	
• early process		1.86-2.90				0.44-20.82	
• late process		0.58-3.94				0.24-8.83	
• administration		0.25-2.51				0.02-4.78	
1 plant, USA:	178						NIOSH 2009[31]; Cummings et al. 2010[15]
• low				0.17-0.54			
• medium				0.58-0.73			
• high				0.75-1.6			
Bakeries (use of soybean flour as ingredient in bread improver reported, or use of soybean flour likely when based on cases of sensitisation to soybean)							
19 Bread bakeries, UK:							Smith & Wastell Smith 1998[27]
• with LEV	49	2.8-10.1		2.7-8.2	10.3-13.3	0.2-52.6	
• without LEV	141	3.2-9.2		3.3-11.4	19.5-146.7	0.1-770	
3 Cake bakeries, UK, without LEV	44	3.9-30.6		3.8-35.7	4.2-26	0.5-90	Smith & Wastell Smith 1998[27]
18 Small bakeries, Scotland, exposure:							Jeffrey et al. 1999[32]
A: directly	87		6.7	4.9	2.3	0.6-23.7	
B: Indirectly	57		1.5	1.8	2.7	0.1-5.5	
6 Bakeries, Norway:	58[b]						Storaas et al. 2007[33]
• dough making				3.14		0.93-16.56	
• bread forming				1.51		0.26-9.15	
• confectionary				1.35		0.41-5.35	
• oven work				0.54		0.17-1.87	
• packing				0.29		0.02-1.81	
• administration				0.06		0-0.26	

AM: arithmetic mean; GM: geometric mean; LEV, local exhaust ventilation; GSD: geometric standard deviation.

[a] 60-80% of full-shift. Method of analysis in all studies was gravimetric.

[b] Total airborne dust.

Chapter 5

Kinetics

Exposure to soybean flour occurs as dust particles or liquid aerosols. There are no data on absorption, distribution, metabolism, and excretion specifically relating to soybean flour, but they are considered to behave as other particulate matter. Therefore, below the kinetics of particles (with no or very low toxic potential) is summarized.

Upon inhalation, particles are deposited on the mucous membranes of the airways. The place of deposition in the airways is dependent on the size of the particle.[34] Based on the aerodynamic diameter, particles are divided in inhalable, thoracic and respiratory fractions. Inhalable particle (or dust) fractions are defined as fractions in which 50% of the particles have an aerodynamic diameter of 100 µm. These particles are mainly deposited in the nose and nasopharyngeal region of the respiratory tract. In thoracic fractions about 50% of the particles have an aerodynamic diameter of 10 µm, and these can be found the trachea and bronchial region of the respiratory tract. Finally, particles in the respiratory fraction are the smallest, and may reach the lungs (particles with an aerodynamic diameter of 3,5-4 µm or smaller).

The size range of soybean flour particles is from 1 to ~150 µm in diameter. Airborne flour dust particle sizes have been measured in the UK plant bakeries and Swedish bakeries whilst bakers were dough making and forming bread and rolls.[35,36] The majority of the particles was larger than 9 µm, and is therefore

likely to be deposited in the nose, mouth and ciliated airways.[37] In wheat bread bakeries, 75% of the airborne dust particles was 4.7-5.8 µm in diameter.[38]

Dust particles are cleared from the lungs by macrophages and the mucociliary system. However, heavy exposure may lower the ability of macrophages to eliminate particles, which may result in penetration of dust particles into the interstitium. The (anatomic) characteristics of an exposed person are also of importance in the development of disease.[28,39]

Chapter 6

Mechanism of action

Inhalation of soybean flour may induce rhinitis (with frequent sneezing, nasal obstruction and rhinorrhea), conjunctivitis (with itching and inflamed, red eyes), rhinoconjunctivitis, asthma-like symptoms, and flu-like symptoms. Part of these symptoms are allergic in origin and are preceded by sensitisation of the worker (immunological response). However, the other part may be explained by non-specific irritation responses (non-immunological responses). For interpreting the symptoms and its consequences on health, it is important to make a distinction between the non-immunological and immunological responses. In practice, symptoms are associated with irritation if an immunological response is ruled out.

6.1 Immunological responses

Sensitisation is an immunological mechanism (type I hypersensitivity reaction), which may occur at a first exposure, and is characterised by little or no response against the sensitising agent, in this case allergens in soybean flour.[40] However, after a person is sensitised, subsequent exposure may cause intense responses, such as asthma, rhinitis and conjunctivitis. This may occur at low exposure concentrations. The responses may be life threatening and may have an immediate or delayed onset. The key mechanism of sensitisation is the formation of specific IgE-antibodies against allergens present in processed, de-hulled soybean flour. These IgE-antibodies are incorporated at the surface of mast cells.

Following a second encounter with the same allergens, mast cells may overreact when these allergens bind to the antibodies presented at the surface of the mast cells (elicitation). Mast cells are the starting point of a cascade of chemical reactions resulting in clinical symptoms. Specific IgE-antibodies against soybean proteins have been demonstrated in workers who were sensitised after inhalation of dust (see Chapter 7).

6.2 Non-immunological responses

An association between exposure to soybean flour and respiratory symptoms of non-immunological origin has been suggested by a few researchers (see Chapter 7).

As is indicated above (Chapter 5), soybean flour particles are considered to behave as dust particles. In general, exposure to large dust particles, irrespective to its chemical activity properties, may lead to local irritation to the eyes, nose and ears. In addition, inhalable dust particles may lead to irritation and inflammation of the bronchioles, alveolar ducts and alveoli. When dust particles are deposited in the respiratory system, the body tries to clear the material, in which the mucociliary defence system, and/or inflammatory cells, such as macrophages, are involved. Macrophages produce inflammatory mediators, which induce inflammatory responses with symptoms of irritation.

Chapter 7

Effects

In general, all available human data on (single and repeated) occupational exposure to soybean flour dust were mainly restricted to non-specific irritation and allergic reactions in the respiratory tract, eyes, and the skin. No data were available on toxicity in other organs, carcinogenic effects or reproductive toxicity. Also, no animal data were available.

7.1 Irritation

Note: The number of studies in which respiratory irritation can be associated with certainty to exposure to soybean flour dust is limited, because the majority of the studies concern bakeries and other industries, in which co-exposure with other potential sources of dust that also may induce irritation (cereal flour dust, alpha-amylase, and other additives), is inevitable.

Zuskin et al. (1990 and 1994) reported on nineteen workers employed in a mill processing soybeans (mean exposure duration 4 years), and 20 controls from elsewhere, who participated in a study on sensitisation and respiratory changes due to exposure to soybean dust.[9,41] All participants were smokers. The workers were employed in the flaking processing area after extraction of soy oil. Sensitisation was determined using the skin prick test with aqueous extracts of soybean allergens (prepared from dust in soybean processing workrooms), and measuring serum levels of specific IgE. Respiratory symptoms were recorded

using a questionnaire and a lung function test. All workers, and all but one control, showed to be positive for sensitisation to soybean extract when using the skin prick test, but only 3/19 workers had elevated levels of soy-specific IgE. The majority of the workers (13/19) were also positive for allergens in house dust. In general, the number of persons with respiratory symptoms was higher among workers than controls. The authors suggest that because the number of control workers positive in the skin prick test to soybean dust was high, the symptoms were irritative of origin rather than allergic. The authors also reported on high dust exposure levels (mean total dust, 29.5 mg/m^3; respirable fraction, 3.5 mg/m^3). The Committee noted that the authors did not report on potential exposure to other types of dust. Also, the Committee noted that smoking may have influenced the outcome of the study.

Smith et al. (2000) investigated the prevalence of respiratory symptoms and sensitisation (skin prick test) among workers (n=679) in 18 different flour mills, who are daily exposed to wheat flour dust and additives, such as fungal alpha-amylase, rice flour and soybean flour.[42] Prevalence of sensitisation was: 1.2% (wheat flour), 0.9% (fungal alpha-amylase), 0.4% (rice flour), and 0.7% (soybean flour). However, the prevalence of respiratory symptoms was much higher: 22%. The majority of the workers with symptoms (95%) complained of transient occasional symptoms (sneezing, blocked/runny nose, chest tightness, and/or difficulty breathing), which the authors related to non-specific irritation. The flour dust exposure levels (geometric mean, minimum-maximum) were: 6.1 mg/m^3 (0.5-54.7 mg/m^3) for production activities, and 17.6 mg/m^3 (1.1-217 mg/m^3) for hygiene activities.

7.2 Sensitisation

7.2.1 Prevalence and incidence

A number of studies have been published on food allergies in the general population to soybean as a food ingredient. Care should be taken in comparing these data since the general population may also be exposed to potential allergens present in the hull of soybeans, whereas occupational exposure in bakeries and mills mainly concern flour dust from de-hulled soybeans. Also the route of exposure is generally different (oral intake versus inhalation). In at least one Swedish population study with data on 1,397 participants, the prevalence of serum specific IgE for soybean allergens (high molecular allergens present in de-hulled soybeans) was reported to be on average 2%.[43]

Some investigators who reported on the prevalence of sensitisation to soybean flour among bakery workers and millers also reported on reference groups which were not occupationally exposed to soybean flour dust. For instance, Baur et al. (1998) reported on a control group of 43 healthy people who did not work in bakeries. They underwent the same tests as a group of bakers living in the same area.[19] When using the skin prick test none of the controls scored positive for soybean flour, whereas 5% scored positive for serum soybean specific IgE (in bakers 1-11% and 19-21%, respectively). Of the controls, 2% showed respiratory obstruction, and 5% were hyperreactive in the lung function test (in bakers 17-28% and 13-19%, respectively). Also Cummings et al. (2010) included in their study a control group of 50 healthcare workers.[15] The prevalence of serum soybean specific IgE was 4% and the levels for soybean specific IgG was 1.5 mg/L. For soy plant workers the values were 21% and 97.9 mg/L, respectively.

Case reports and patient-based studies

The first who reported on sensitisation to soybean extracts (skin prick test) and allergic respiratory symptoms was Duke in 1934.[44] It concerned five patients with cough and asthma who worked in a soybean mill in the United States. Bush and Cohen (1977) described a case of a previously non-allergic worker in a soybean processing factory who developed immediate and late onset asthma after breathing soybean flour used in the manufacture of food supplements.[45] Skin prick testing to a soybean flour extract showed both an immediate and a late response. Also the bronchial challenge test to a soybean flour extract was positive. Heyer (1983) found a positive response in 6/8 bakers with suspected bronchial disorders upon respiratory challenge testing and skin prick testing to soybean flour extract.[6] Among 202 bakery workers suffering from respiratory disease, Jorde et al. (1986) found 132 (65%) who reacted positively upon skin prick testing with soybean flour extract, and 53 (26%) who were positive upon respiratory challenge testing.[46] Bush et al. (1988) reported on a food processing plant worker who had developed asthma six years after beginning work.[47] The patient reacted positive upon skin prick testing with a soybean flour extract. Serum soybean flour specific IgE was six times higher than in serum of a control.

Quirce et al. (2000) demonstrated (skin prick tests) the presence of sensitisation to high molecular weight soybean proteins (25-55 kDa), and (pure) soybean trypsin inhibitor, in bakers and confectioners (n=4) with work-related asthma.[3] None of these persons were sensitised to allergens typically present in soybean hull (Gly m 1, and Gly m 2). In all four persons asthmatic responses

were elicited when they were challenged with methacholine or soybean flour extracts. Later, the same research group reported on two other bakers with work-related asthma, who were sensitised to soybean trypsin inhibitor (specific IgE), and showed asthmatic responses when challenged to the inhibitor.[48]

Specific sensitisation to storage proteins and to soybean trypsin inhibitor among bakery workers with work-related symptoms, was reported by several other investiga-tors.[1,2,4,15]

Baur et al. (1988) found that of the 140 bakery workers 21% were sensitised to soybean flour (serum specific IgE).[49] The bakers had been employed for at least six months, and were selected on showing workplace-related asthma, rhinitis and/or conjunctivitis. Subsequently, Bauer et al. (1989) reported an incidence of sensitisation of 32% to soybean flour in a group of 260 symptomatic bakery workers.[50] From the same research group, but from another study, 19% of symptomatic bakery workers (6/31) showed to be sensitised (IgE immunoassay) to soybean flour.[8] Of the sensitised workers 58% were sensitised to trypsin inhibitor and 42% to lipoxygenase. Later, Bauer et al. (1996) reported that 86% of a group of symptomatic bakers (12/14) and sensitised to soybean flour, scored positive for serum soybean trypsin inhibitor specific IgE.[1] In addition, Alvarez et al. (1996) described three bakers, a miller and a farmer, who were sensitised to soybean flour (increased serum soybean flour specific IgE levels).[51]

Quirce et al. (2000) examined two bakers and two confectioners who showed asthma symptoms (cough, chest tightness, shortness of breath, and wheeze), on the presence of specific sensitisation to soybean flour extracts, trypsin inhibitor from soybean, and soybean hull extracts.[3] Also (specific) bronchial challenge test were performed. Using the skin prick test, all four patients showed a positive response with soybean flour extracts; two of them were also positive for trypsin inhibitor. Serum soybean-specific IgE levels were elevated in three patients; one patients showed a positive response for soybean hull allergen ‘Gly m 2’, and none for ‘Gly m 1’. In contrast, the authors noted that in a serum pool from patients with soybean epidemic asthma (in the general population) specific IgE against soybean hull allergen (Gly m 1) was strongly positive. The contents of ‘Gly m 1’ in soybean hull and soybean flour extracts were 125 µg/mL and 0.012 µg/mL, respectively. All patients showed hyperresponsiveness with inhalation of metacholine (nonspecific reaction), and soybean flour extract. The investigators suggested that soybean allergens causing asthma outbreaks in the general population were mainly caused by low molecular weight proteins in soybeans (mainly present in hulls), whereas occupational asthma was mainly induced by high molecular weight soybean proteins (both present in hull and flour).

The same research group investigated the presence of specific sensitivity in 24 bakers and pastry makers in the baking industry.[20] All patients had suspected occupational asthma (cough, chest tightness, shortness of breath, and wheezing). They handled routinely cereal flour (wheat and rye), soybean flour and fungal enzymes. Skin prick tests with soybean flour extracts showed that 42% of the patients were positive for soybean flour. In 83% of the patients, the tests revealed sensitivity to more than two occupational allergens (i.e., cereal flour, alpha-amylase). A positive serum soybean flour specific IgE response was observed in 34% of the patients (in comparison, positive responses were also found for wheat flour (75%), rye flour (67%), and alpha-amylase (55%)). Nonspecific bronchial hyperresponsiveness was reported in all but one patient; specific inhalation challenge tests with soybean flour revealed all but one positive response among the 6 patients tested. A positive correlation was found between 'bakery-derived allergens' skin prick testing and early asthmatic reaction (r=0.88, 95% CI 0.77-0.94, $p<0.001$). However, there was a poor correlation between methacholine challenge testing and specific allergen inhalation testing (r=0.30, 95% CI -0.06-0.59, $p=0.07$). No correlation was found between specific serum IgE and allergen-specific inhalation challenge testing. Regarding the correlations, the Committee noted that no correlations were calculated for specifically soybean flour-derived allergens.

Cross-sectional studies

A summary of the studies on the prevalence of soybean flour specific sensitisation is given in Table 3, whereas details of the studies are shown in Annexes E and F.

The Committee is aware that the prevalence values may be influenced by the duration of employment, job tasks, exposure levels, peak exposures and co-exposure to other types of organic dust. Furthermore, in some studies the number of participants was very small, which limits the interpretation of the outcomes. Also potential bias (healthy-worker effect), and the use of different extracts of soybean (flour) for sensitisation testing may have played a role in the variation of the outcomes. Taking these potential influencing factors into account, the Committee concludes that workers who routinely handle soybean flour can get sensitised to allergens present in the soybean flour.

Table 3 Prevalence of soybean flour specific sensitisation in workers exposed to soybean flour dust.

reference	type of industry	n	skin prick test (% positive)	specific serum IgE (% positive)
Soybean milling and processing industry				
• Zuskin et al. 1991[9]		19	100	16
• Roodt and Rees 1995[52]		22	36	36
• Smith et al. 2000[42]		678	0.7	-
• Cummings et al. 2010[15]	soybean processing	135	7	21
• Harris-Roberts et al. 2012[53]	soybean processing	136	-	14
Bakery industry				
• Smith et al. 1997[26]	bakery	383	6	-
• Baur et al. 1998[19]	bakery	88/89	1	19
• Smith & Wastell Smith 1998[27]	bread bakery	392	7	-
• Smith & Wastell Smith 1998[27]	cake bakery	77	1	-
• Jeffrey et al. 1999[32]	bakery	205	-	3
• Storaas et al. 2005[21]	bakery	183	-	2
• Baatjies et al. 2009[54]	supermarket bakery	507/513	8	-
Other industries				
• Zuskin et al. 1992[55]	animal food producer	35	28.6	-

7.2.2 *Exposure-response relationships*

The American National Institute for Occupational Safety and Health (NIOSH) investigated exposure-response relationships between occupational exposure to soybean flour dust and the occurrence of specific sensitisation and respiratory symptoms (NIOSH 2007, Cummings et al. 2010).[15,31] A detailed description of the study design and outcomes are given in Annex F. Briefly, in a US soybean factory de-oiled and de-hulled soybean flakes are processed into soybean powder products. Co-exposure to other organic dust sources was unlikely. The study consisted of 147 workers of the factory, and 50 referents (healthcare workers) who were not exposed. To determine exposure levels, full-shift personal inhalable dust samples were collected; exposure was expressed as inhalable dust and as inhalable soy antigens. Workers were allocated into one of the three exposure groups: low, medium and high. Sensitisation was determined by the skin prick test, and by measuring serum soybean specific IgE and IgG levels. Health information, such as respiratory symptoms, was obtained by interviews using a questionnaire. Also lung function tests and bronchial metacholine challenge tests were performed.

The investigators found prevalence values of soybean-specific sensitisation (IgE levels) of 21% (low exposure), 33% (medium exposure), 6% (high exposure), and 4% (referents). The prevalence values for asthma-like symptoms were: 9% (low), 20% (medium) and 8% (high). No clear relationship was found between exposure levels (expressed as soybean allergen exposure) and serum specific IgE levels or asthma-like symptoms. Most likely this was due to a healthy-worker effect, which would also explain why they found an inverse relation between duration of employment and skin rash (15%, short duration; 13%, medium duration; and, 2%, long duration). There was a positive association between work-related asthmatic symptoms and specific IgE-based sensitisation to soybean flour (OR 5.9; 95% CI, 2.0-17.6). No data on exposure-response relationship were presented for the prevalence of sensitisation by the skin prick test, nor for exposure levels expressed as inhalable dust. Overall, the correlation between personal inhalable dust and soybean flour dust allergen was fair (Spearman's r=0.35; n=178, $p<0.001$).

Furthermore, the authors reported on real-time personal and static peak exposure measurements of inhalable dust in relationship with the occurrence of symptoms. Also for these peak exposures workers were divided in three exposure categories (low, non-production workers; medium, support production workers; and, high, production workers). Prevalence values for asthma-like symptoms were: 2% (low), 15% (medium), and 19% (high). For skin rash the values were: 5% (low), 6% (medium), and 21% (high). The increase in prevalence values for both type of symptoms was statistically significantly associated with increased peak exposure.

The authors did not find an association between work-related asthma and other health outcomes, and several confounding risk factors, such as race/ ethnicity, gender, age, smoking status, soy IgG level, elevated total IgE, and soy IgE positivity. In addition they did not find an association between peanut and storage mite IgE positivity, positive skin response to other extracts (e.g., soybean, house dust mite).

Overall, in the study by Cummings et al., exposure-response relationships were found for peak exposure only, and not for average exposure. The Committee noted several flaws, such as that exposure-response analyses on specific soy IgE levels and exposure levels were carried out without adjustment for potential confounders. In addition, the Committee noted that the analysis on peak exposure shows mainly a difference between non-production and production workers, whereas the difference between production supporting work and production work is small.

7.2.3 *Cross-reactivity*

A cross-reaction involves a specific antibody, which binds an allergen other than the target allergen.[40] It usually involves allergens that are structurally very similar, but not always. The phenomenon may indicate that sensitisation of an allergen in for instance cereal flour may also lead to sensitisation of a comparable allergen in soybean flour without previous exposure to dust of soybean flour. Overall, only a few data are available on the possible cross-reactivity regarding soybean flour. At least it appears that soybean flour and cereal flour have some allergens in common. For instance, Sandiford et al. (1995) reported on a major common protein of soybean and wheat flour with a molecular weight of 21 kDalton (trypsin inhibitor), which would suggest that they have common enzyme inhibitors.[4] However, the same authors reported on a poor correlation between several other allergens present in cereal flour and allergens present in soybean flour. This would indicate that a large number of potentially cross-reacting proteins in cereal flour are absent in soybean flour. In addition, Smith and Wastell Smith (1998) concluded from their study among bakery workers that fungal alpha-amylase does not cross-react with wheat and soybean allergens.[27]

Regarding food allergy in the general population, a number of studies has investigated the potential of cross-reactivity among legumes, because they have structurally homologous proteins and share common epitopes.[11,56,57] Like peanuts, lentils and lupins, also soybeans are legumes. All these legumes are known to have allergenic potential. However, only low frequencies of cross-reactivity in humans have been reported between for instance peanut and soybean.[10,11] In addition, Mittag et al. (2004) showed a high degree of cross-reactivity between the soybean allergen ‘Gly m 4’ and birch pollen allergen in an inhibition immunoassay.[58]

7.3 Other symptoms

Reports are available on flu-like symptoms among workers in the soy processing industry. For instance, Harris-Roberts et al. (2012) associated flu-like illness (fever, aching, tiredness after work) with off-loading of whole soybeans among workers in South Africa (n=25/114), of which 7/57 (12.3%) were nor currently exposed to dust during soybean off-loading, and 18/57 (31.6%) were currently exposed (OR 2.7, 95% CI 1.0-7.2).[53] However, the etiology of these flu-like symptoms was unclear, and the authors could not exclude that the presence of

high concentrations of endotoxin (in the hulls) may have been the cause, and/or the antigens in the hull of the soybeans.

In 2013, Cummings et al. reported on flu-like symptoms (fever, aching, pain, chills, and night sweats during the past 12 months) in their study (see Section 7.2.2).[59] In this case, workers were mainly exposed during the processing of de-hulled soy beans. Of the 147 participants, 55 (37%) reported flu-like illness, and 20 (14%) work-related flu-like illness (flu-like illness that was better away from work). Production workers had a higher odds ratio for work-related flu-like illness than non production workers (OR 4.4; 95% CI 0.9-21.0). However, the work-related flu-like illness could not be associated with soy specific IgE (OR 1.6; 95% CI 0.5-4.9), soy-specific IgG, or with exposure categories (inhalable dust, inhalable soy antigen, peak dust). The latter was most likely due to immune tolerance of a health-worker effect. Since workers were not exposed to the hulls of whole soybeans, also the concentrations of endotoxin in the samples were low.

7.4 Summary

Data on the adverse health effects of occupational exposure to soybean flour dust are mainly restricted to respiratory symptoms in humans. No animal data have been presented nor data on carcinogenicity and reproductive toxicity.

Respiratory symptoms (cough, dyspnea, wheezing, chest tightness, shortness of breath) are associated with rhinitis, rhinoconjunctivitis and asthma. The etiology of these symptoms may be (non-specific) irritation or allergic reactions, or a combination of both. A way to discriminate between the two mechanisms is determining specific immune responses (sensitisation) against allergens present in soybean flour.

A number of case reports, hospital-based studies, and cross-sectional studies report on workers in bakeries, soybean mills and processing factories, who are sensitised specifically to allergens present in soybean flour, indicating that allergic responses do occur. Part of these workers also showed respiratory symptoms. However, prevalence values on soybean specific sensitisation vary widly among the cross-sectional studies. This is partly explained by variations in job history and exposure circumstances, and by variations in test systems used to determine sensitisation. In one cross-sectional study among workers in a soybean processing factory, also exposure-response relationships were investigated. However, no clear correlation was found between levels of exposure (airborne soy antigens) and the prevalence value of sensitisation. This was probably due to a healthy-worker effect. In contrary, a statistically significant positive

correlations was found between levels of peak exposure (inhalable dust), and asthma-like symptoms and skin rash.

It is inevitable that most of the workers who participated in the epidemiological studies are exposed simultaneously to organic dust from other sources than soybean flour, such as cereal flour dusts, and fungal alpha-amylase in bakeries. All these sources may have induced respiratory symptoms by themselves, and thus may have influenced the outcomes of the studies on soybean flour dust exposure. In soybean processing and manufacturing plants, co-exposure with dust from other sources than soybeans is less likely. There are some indications that cross-reactivity with allergens that are present in cereal flour dust and fungal alpha-amylase, does not play a role in sensitisation to allergens that are present in processed soybean flour.

Chapter 8

Existing guidelines, standards and evaluation

8.1 General population

Not available.

8.2 Occupational population

In the Netherlands and in other countries no occupational exposure limits have been set specifically for soybean flour dust.

Chapter 9

Hazard assessment

The Committee specified soybean flour dust as dust from processed, de-hulled soybeans.

9.1 Hazard identification

Available studies have shown that the main health effects of inhalation to soybean flour dust are symptoms in the respiratory tract and eyes, such as rhinitis, rhinoconjunctivitis, asthma (baker's asthma), and flu-like symptoms. Upon contact with the skin also rash is recorded. Part of the symptoms has been shown to be of allergic origin, mediated by immunoglobulin E (IgE) antibodies to proteins present in soybean flour. This is a concern to the Committee, because once allergic, the person in question may express allergic symptoms for the rest of his or her life upon exposure to soybean flour dust. However, the symptoms may also be explained by non-allergic irritation responses, as is shown in a few studies among bakery workers, and flour milling and processing workers.

No relevant human and animal data were available on other adverse health effects, nor were there data presented on the carcinogenic potential and reproductive toxicity.

In the bakery and animal food industry where soybean flour is handled, it is inevitable that workers are simultaneously exposed to organic dust from other sources, such as dust from whole soybeans, cereal flour dusts, fungal alpha-

amylase, and additives that improve bread baking. Part of these sources are known for their allergic and irritation potential, which may induce the same symptoms as described for soybean flour. This makes it difficult to distinguish the symptoms caused by soybean flour dust from other dust sources. Therefore, co-exposure hampers the use of data on symptoms in deriving a health-based occupational exposure level. The same applies for using dust (inhalable or respirable) levels as exposure parameter, since dust present in the air in those types of workplaces may contain particles from different sources. The problem may be overcome by using specific sensitisation (see below) and airborne antigen levels as effect and exposure parameter, respectively. Co-exposure in the processing and manufacturing industry, in which only soybeans are used is less likely.

Regarding allergic symptoms, these are preceded by and coincide with sensitisation. Sensitisation is an immunologic response to a specific allergen. Soybean flour, and also cereal flour and fungal alpha-amylase, contains proteins that may induce IgE mediated immune responses. In contrast to recording symptoms, tests like the skin prick test and determination of serum specific IgE levels can distinguish sensitisation caused by soybean flour allergens from sensitisation caused by allergens from other sources. In addition, the available data indicate that there is no or only a low frequency of cross-reactivity. For these reasons, in assessing a health-based occupational exposure limit, the Committee is of the opinion that data on sensitisation to dust from processed soybean flour can be used as critical effect endpoint. Furthermore, since sensitisation often precedes the onset of allergic symptoms, by preventing sensitisation also allergic symptoms will be prevented.[40]

The available data clearly show that occupational exposure to soybean flour dust is associated with an increased risk for developing sensitisation and allergic symptoms. However, there is a considerable heterogeneity in the prevalence estimates of sensitisation to soybean flour dust among soybean flour handling workers (see Section 7.2.1). The heterogeneity may be explained by differences in job history, job tasks, working conditions, the use of different extracts of soybean flour for testing sensitisation, the use of different tests, potential bias, such as the healthy-worker effect, and personal factors (smoking habits, atopy). The highest prevalence estimates are made in the soybean milling and processing industry (16-36%; see Table 3). The prevalence for serum soy-specific IgE in the general population is 2 percent.[43]

9.2 Selection of study suitable for quantitative risk estimation

In many studies no exposure levels were assessed, but when it was done, mainly levels of inhalable dust were reported. So far two studies have been published with data on airborne soybean flour antigens. In the study by Spies et al. (2008) exposure levels on soybean antigens were reported (Spies et al. 2008).[16] A few years later, in the same soybean processing plants also investigations on health effects were performed (Harris-Roberts et al. 2012). However, no exposure-response relationships were assessed.[53] This leaves one study in which an exposure-response analysis was performed with the preferred exposure and effect parameters (Cummings et al. 2010, NIOSH 2009).[15,31] In this cross-sectional study, data were obtained from workers in a soybean processing factory. The plant processed de-oiled, de-hulled soybean flakes into soybean powder products. Combined exposure to other organic dust sources was unlikely, and although the Committee focuses on airborne allergen levels and specific sensitisation, in this particular study also inhalable dust levels and airway symptoms were recorded. Study details and results are shown in Annex F. The participants (n=135) showed a significantly higher prevalence of serum soy-specific IgE than controls (21% versus 4%; PR 52; 95% confidence interval 1.3-21.0). Also, the participants with a positive soy-specific IgE outcome showed significantly more symptoms of asthma than participants with a negative outcome. The Committee examined the possibility of using the data from this study for its quantitative risk analysis.

9.2.1 Reference value (8-hour TWA)

Suitability of the study

Regarding full shift exposure measurements, the investigators did not find a significant association between inhalable soy antigen exposure and soy-specific sensitisation (see Table 4). In particular participants in the highest exposure group showed the lowest prevalence of soy-specific sensitisation. According to the investigators this may be due to the healthy-worker effect, in which workers with a positive score on the soy-specific IgE test may have left the workplace to avoid further exposure before this study started. This would explain the bell-shaped exposure-response relationship (see Figure 1). Theoretically, it may also be explained by the occurrence of tolerance, i.e, with continued exposure the soy-specific IgE levels decrease over time. Furthermore, the authors noticed the

Table 4 Exposure-response analysis based on full shift inhalable soy antigen exposure.[15,31]

	Exposure level (ng/m³)		Prevalence of sensitisation (serum specific IgE levels)	Prevalence ratio
	Range	Median		
Control	0	0	4%	No statistically significant positive association
Low	24-804	400	21%	
Medium	959-2,297	1,628	33%	
High	2,635-25,958	4,296	6%	

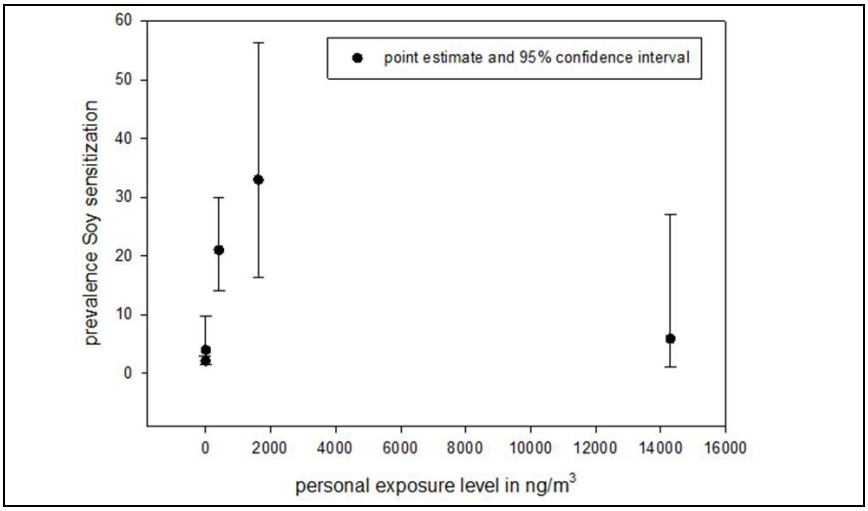

Figure 1 Association between soy exposure in ng/m³ and soy sensitisation (in percentages). Reference sensitisation level from Björnsson et al. (1996)[43]; point estimates from the exposure categories as given by Cummings et al. (2010).[15]

small number of participants in the groups, which may have limited the ability to detect associations. Including the large differences in exposure levels within the groups, the Committee confirms that these points may have considerably limited the power of the study. In addition, the Committee has noticed that in the lowest exposure group, the prevalence for soy-specific IgE is relatively high compared to the control group (21% versus 4%). This may indicate that in the lowest exposure group the exposure to soybean dust allergens was already rather high.

Overall, despite these limiting factors, the Committee is of the opinion that the data in the study can be used in assessing a health-based occupational exposure level, since: data concerns exposure to soybean flour dust only (no interference due to co-exposure); measurements are performed on specific endpoints (antigens in soybean flour, specific sensitisation); the prevalence on

sensitisation is rather high; and, in the lower exposure range a steep exposure-response relationship is observed. The lower exposure range is the most relevant range in assessing an occupational exposure limit.

Linear Poisson regression analysis

The Committee did not observe a level below which no additional cases of sensitisation to soybean flour allergens were found. This means that an exposure level, at which sensitisation to airborne soybean flour allergens will not occur, cannot be identified; thus no threshold-based occupational exposure level can be attained. Earlier, the Health Council reported on this issue.[40] The Council concluded that in theory a threshold level exists for allergic sensitisation by inhaled allergens. This implies that a health-based recommended occupational exposure limit can be calculated, using the same procedures and methods as for other non-carcinogenic substances. However, the Council emphasized that for most allergens, in practice it will not be possible to calculate a reliable health-based recommended occupational exposure limit. The reason being that the threshold level will be too low to discern using the techniques presently available. For those allergens, the Health Council proposed an alternative approach, involving determination of reference values, i.e., concentration levels that correspond to predefined accepted levels of extra risk of allergic sensitisation.

The risk analysis method used in the Cummings/NIOSH-study is very sophisticated. To cope with the bell-shaped relationship, data on the highest exposure group could be omitted in the analysis. However, the other limiting factors are still remaining. Alternatively, several robust risk analysis methods are available that have been used for many years. For example, the approach using a No-Observed-Adverse-Effect-Level (NOAEL) or the Lowest-Observed-Adverse-Effect-Level (LOAEL) as starting point. Also, a straightforward linear relationship can be assumed, making use of more data points instead of one as with the NOAEL/LOAEL-approach. The Committee emphasises that none of these methods cope with the limitations of the data set, rather they indicate approximately the level of an exposure limit. Alternatively, another (less preferential) effect endpoint may be chosen. However, using work-related symptoms as an effect endpoint instead of specific sensitisation, is obstructed by missing data on the control group, number of persons per group, and missing data on prevalence for symptoms other than work-related asthma-like symptoms (see Annex F).

Overlooking the alternatives, the Committee proposes to estimate a health-based occupational exposure limit by assuming a linear exposure-response relationship.

The data from all exposure groups were combined. The Committee estimated the average exposure level by taking the midpoint (median) of the exposure range per group, and weighting this midpoint with the number of participants in the concerning groups. This leads to a weighted average exposure level of 2,324 ng inhalable soy antigen/m^3.

Regarding setting a reference value, the Ministry of Social Affairs and Employment has requested the council to base a reference value on an additional absolute sensitisation risk to an allergen of 1 percent due to occupational exposure, compared to the background risk in the general population.

The reference value was estimated by using a simple linear Poisson regression model and by fitting the line through the intercept (zero). The slope coefficient of the regression model is calculated to be 0.0039 (p=0.041). This resulted in the equation:

$$RR = 1 + 0.0039 \times \text{exposure concentration}$$

in which RR is the relative risk, '1' is the relative risk at the baseline, and exposure concentration is expressed in ng inhalable soy antigen/m^3. The background risk (risk level of the non-exposed population) is set at 2 percent.[43] An additional absolute risk of 1% corresponds to an RR of (2 +1)/2 = 1.5. Using the formula, this results in a reference value of 0.1 µg inhalable soy antigen/m^3 (128 ng inhalable soy antigen /m^3, rounded-off).

The Committee discussed whether the estimated exposure concentrations should be adjusted for inter-individual differences in vulnerability among humans. In case of developing allergies, a group of vulnerable people are the atopics. Since atopics were included in the study populations, no adjustments are needed.

The available literature does not suggest that non-allergic symptoms occur at lower exposure levels than allergic symptoms. Therefore, the Committee is of the opinion that a risk assessment based on sensitisation not only protects against allergic symptoms, but most likely against the development of non-allergic symptoms as well.

9.2.2 *Health-based short-term exposure limit (STEL; 15-minutes TWA)*

When peak exposure to total inhalable dust was taken into account, positive correlations were found for asthma-like symptoms, airway obstruction, and rash or other skin problems (see Table 5). According to Cummings et al. (2010), this means that prevention of peak exposure will most likely lower the risk for development of specific sensitisation and symptoms.

Since peak exposure is a risk factor in developing work-related respiratory allergies, the Committee evaluated whether it is possible to derive a STEL. In the study by Cummings et al. (2010; NIOSH 2009) effect data on peak exposure were reported. Statistically significantly positive correlations were found for work-related asthma-like symptoms, airway obstruction, and rash or skin problems (see Table 5 and Annex F). The strongest correlations were found for asthma-like symptoms.

However, the Committee noted also incomplete reporting of peak exposure data that are needed in deriving a STEL. For instance, data on the non-exposed control group are missing, and no data are presented as to how many persons per exposure group were included. In addition, no data are given on the prevalence of sensitisation, the most sensitive effect parameter in assessing the risk on allergy development. Overall, the Committee is of the opinion that data on peak exposure are too limited to be useful in deriving a STEL.

Table 5 Exposure-response analysis based on *peak* total inhalable dust exposure measurements.[15,31]

Effect parameter	Exposure levels	Prevalence	Prevalence ratio
Work-related asthma-like symptoms	Low: <1 mg/m^3	2%	1.0
	Medium: 1-10 mg/m^3	15%	6.96 (1.22-131)
	High: ≥10 mg/m^3	19%	9.37 (1.61-178)
Airway obstruction (spirometry)	Low: <1 mg/m^3	-	1.0
	Medium: 1-10 mg/m^3	-	4.9 (0.79-94.5)
	High: ≥10 mg/m^3	-	8.49 (1.41-163)
Rash or skin problems	Low: <1 mg/m^3	-	1.0
	Medium: 1-10 mg/m^3	-	1.38 (0.26-10.3)
	High: ≥10 mg/m^3	-	5.29 (1.26-36.3)

Correlation expressed as odds ratio (95% confidence interval). No data on control group reported.

9.3 Conclusion and recommendation

The Committee recommends a reference value for occupational exposure to dehulled soybean flour dust allergens of 0.1 µg inhalable soy antigen/m^3, as an eight-hour time-weighted average concentration (TWA). At this concentration

workers have an additional absolute sensitisation risk for allergens in soybean flour dust of 1 percent compared to the background risk in the general (not exposed) population.

Data are insufficient to derive a short term exposure limit (15-minute TWA).

9.4 Groups at extra risk

Some people are more likely to develop allergies, as a result of genetic susceptibility, or other factors such as atopy.[40] As stated by the World Allergy Organization atopy is "a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis".[60-62] Atopy is not considered an illness, but a predisposition. It is estimated that up to 45% of the general population can show any form of atopic sensitisation to a panel of aeroallergens, which means that they are sensitised to one or more 'every day' common allergen. In an earlier report by the Health Council on work-related respiratory allergies, the council stated that "atopy is not seen as a good predictor of specific sensitisation or of the development of allergic symptoms, because a high proportion of atopic people are not sensitised by exposure to work-related allergens and do not develop allergic symptoms".[40,63]

Workers with pre-existing asthma or those with more general respiratory symptoms may have an increased risk to develop symptoms (i.e., work-aggravated asthma). Also, it is possible that workers who are already sensitized to soybean allergens may experience allergic symptoms with continuing exposure at very low exposure levels.

References

1 Baur X, Pau M, Czuppon A, Fruhmann G. Characterization of soybean allergens causing sensitization of occupationally exposed bakers. Allergy 1996; 51(5): 326-330.

2 Green BJ, Cummings KJ, Rittenour WR, Hettick JM, Bledsoe TA, Blachere FM et al. Occupational sensitization to soy allergens in workers at a processing facility. Clinical & Experimental Allergy 2011; 41(7): 1022-1030.

3 Quirce S, Polo F, Figueredo E, Gonzalez R, Sastre J. Occupational asthma caused by soybean flour in bakers--differences with soybean-induced epidemic asthma. Clin Exp Allergy 2000; 30(6): 839-846.

4 Sandiford CP, Tee RD, Newman-Taylor AJ. Identification of crossreacting wheat, rye, barley and soya flour allergens using sera from individuals with wheat-induced asthma. Clinical & Experimental Allergy 1995; 25(4): 340-349.

5 Smith TA, Lumley KPS. Work-related asthma in a population exposed to grain, flour and other ingredient dusts. Occupational Medicine 1996; 46(1): 37-40.

6 Heyer N. Backmittel als berufsbedingte Inhalationsallergene bei mehlverarbeitenden Berufen. Allergologie 1983; 6(10): 389-292.

7 Lavaud F, Perdu D, Prevost A, Vallerand H, Cossart C, Passemard F. Baker's Asthma Related to Soybean Lecithin Exposure. Allergy 1994; 49(3): 159-162.

8 Wüthrich B, Baur X. Backmittel, insbesondere alpha-Amylase, als berufliche Inhalationsallergene in der Backwarenindustrie. Schweiz Med Wochenschr 1990; 120(13): 446-450.

9 Zuskin E, Kanceljak B, Schachter EN, Witek TJ, Marom Z, Goswami S et al. Immunological and respiratory changes in soy bean workers. International Archives of Occupational and Environmental Health 1991; 63(1): 15-20.

10 L'Hocine L, Boye JI. Allergenicity of soybean: new developments in identification of allergenic proteins, cross-reactivities and hypoallergenization technologies. Crit Rev Food Sci Nutr 2007; 47(2): 127-143.
11 Verma AK, Kumar S, Das M, Dwivedi PD. A comprehensive review of legume allergy. Clin Rev Allergy Immunol 2013; 45(1): 30-46.
12 CEN. EN 481:1993, Workplace atmospheres - Size fraction definitions for measurement of airborne particles. Brussels: Comité Européen de Normalisation; 1993.
13 Bogdanovic J, Wouters IM, Sander I, Zahradnik E, Harris-Roberts J, Rodrigo MJ et al. Airborne exposure to wheat allergens: optimised elution for airborne dust samples. J Environ Monit 2006; 8(10): 1043-1048.
14 Goméz-Ollés S, Cruz MJ, Bogdanovic J, Wouters IM, Doekes G, Sander I et al. Assessment of soy aeroallergen levels in different work environments. Clin Exp Allergy 2007; 37(12): 1863-1872.
15 Cummings KJ, Gaughan DM, Kullman GJ, Beezhold DH, Green BJ, Blachere FM et al. Adverse respiratory outcomes associated with occupational exposures at a soy processing plant. Eur Respir J 2010; 36(5): 1007-1015.
16 Spies A, Rees D, Fourie AM, Wilson KS, Harris-Roberts J, Robinson E. Inhalable dust and protein exposure in soybean processing plants. Int J Occup Environ Health 2008; 14(3): 225-230.
17 Heederik D, Doekes G, Nieuwenhuijsen MJ. Exposure assessment of high molecular weight sensitisers: contribution to occupational epidemiology and disease prevention. Occup Environ Med 1999; 56(11): 735-741.
18 Sandiford CP, Nieuwenhuijsen MJ, Tee RD, Taylor AJ. Measurement of airborne proteins involved in Bakers' asthma. Clin Exp Allergy 1994; 24(5): 450-456.
19 Baur X, Degens PO, Sander I. Baker's asthma: still among the most frequent occupational respiratory disorders. J Allergy Clin Immunol 1998; 102(6 Pt 1): 984-997.
20 Quirce S, Fernández-Nieto M, Escudero C, Cuesta J, De Las Heras M, Sastre J. Bronchial responsiveness to bakery-derived allergens is strongly dependent on specific skin sensitivity. Allergy 2006; 61(10): 1202-1208.
21 Storaas T, Steinsvag SK, Florvaag E, Irgens A, Aasen TB. Occupational rhinitis: diagnostic criteria, relation to lower airway symptoms and IgE sensitization in bakery workers. Acta Otolaryngol 2005; 125(11): 1211-1217.
22 Wood RA, Segall N, Ahlstedt S, Williams PB. Accuracy of IgE antibody laboratory results. Ann Allergy Asthma Immunol 2007; 99(1): 34-41.
23 FAO. Oilseeds, oils and meals. Monthly soybean supply & demand round-up. http://www fao org/ fileadmin/templates/est/COMM_MARKETS_MONITORING/Oilcrops/Documents/MSSDR/ MSSDR_Aug__12 pdf 2012; consulted November 2015.
24 Singh P, Kumar R, Sabapathy SN, Bawa AS. Functional and Edible Uses of Soy Protein Products. Comprehensive Reviews in Food Science and Food Safety 2008; 7(1): 14-28.
25 Berk Z. Technology and production of edible flours and protein products from soybeans. FAO Agricultural Services Bulletin 1992; 97.

26 Smith TA, Lumley KPS, Hui EHK. Allergy to flour and fungal amylase in bakery workers. Occupational Medicine (London) 1997; 47(1): 21-24.

27 Smith TA, Wastell Smith P. Respiratory symptoms and sensitization in bread and cake bakers. Occupational Medicine 1998; 48(5): 321-328.

28 Health Council of the Netherlands. Wheat and other cereal flour dusts. An approach for evaluating health effects from occupational exposure. The Hague: Health Council of The Netherlands, 2004; publication no. 2004/02OSH.

29 Antó JM, Sunyer J, Rodriguez-Roisin R, Suarez-Cervera M, Vazquez L. Community outbreaks of asthma associated with inhalation of soybean dust. Toxicoepidemiological Committee. N Engl J Med 1989; 320(17): 1097-1102.

30 Rodrigo MJ, Cruz MJ, García MD, Antó JM, Genover T, Morell F. Epidemic asthma in Barcelona: an evaluation of new strategies for the control of soybean dust emission. Int Arch Allergy Immunol 2004; 134(2): 158-164.

31 NIOSH. Health Hazard Evaluation Report: Report on an investigation of asthma and respiratpry symptoms among workers at a soy processing plant, Memphis, Tennessee, Cincinnati, OH. 2009: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA No. 2007-0073-3089.

32 Jeffrey P, Griffin P, Gibson M, Curran AD. Small bakeries--a cross-sectional study of respiratory symptoms, sensitization and dust exposure. Occup Med (Lond) 1999; 49(4): 237-241.

33 Storaas T, Ardal L, Van Do T, Florvaag E, Steinsvag SK, Irgens A et al. Nasal indices of eosinophilic and exudative inflammation in bakery-workers. Clin Physiol Funct Imaging 2007; 27(1): 23-29.

34 Brisman J. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 111. Industrial Enzymes. Arbete och Hälsa 1994; 28: 1-25.

35 Burdorf A, Lillienberg L, Brisman J. Characterization of exposure to inhalable flour dust in Swedish bakeries. Annals of Occupational Hygiene 1994; 38(1): 67-78.

36 Sandiford CP, Nieuwenhuijsen MJ, Tee RD, Newman Taylor AJ. Determination of the size of airborne flour particles. Allergy 1994; 49(10): 891-893.

37 HSE. EH71/11 Flour dust: Risk assessment document. Health and Safety Executive; 1999.

38 Houba R, van Run P, Doekes G, Heederik D, Spithoven J. Airborne levels of alpha-amylase allergens in bakeries. Journal of Allergy and Clinical Immunology 1997; 99(3): 286-292.

39 Health Council of the Netherlands. Grain dust. Health-based recommended occupational exposure limit. The Hague: Health Council of The Netherlands, 2011; publication no. 2011/13.

40 Health Council of the Netherlands. Prevention of work-related respiratory allergies. Recommended occupational exposure limits and periodic screening. The Hague: Health Council of The Netherlands, 2008; publication no. 2008/03E.

41 Zuskin E, Schachter EN, Kanceljak B, Mustajbegovic J, Witek TJ. Immunological and respiratory reactions in workers exposed to organic dusts. Int Arch Occup Environ Health 1994; 66(5): 317-324.

42 Smith TA, Parker G, Hussain T. Respiratory symptoms and wheat flour exposure: a study of flour millers. Occupational Medicine 2000; 50(1): 25-29.
43 Bjornsson E, Janson C, Plaschke P, Norrman E, Sjoberg O. Prevalence of sensitization to food allergens in adult Swedes. Ann Allergy Asthma Immunol 1996; 77(4): 327-332.
44 Duke WW. Soy bean as a possible important source of allergy. Journal of Allergy 1934; 5(3): 300-302.
45 Bush RK, Cohen M. Immediate and late onset asthma from occupational exposure to soybean dust. Clin Allergy 1977; 7(4): 369-373.
46 Jorde W, Heyer N, Schata M. Bäckereistoffe als berufsspezifische Allergene. Allergologie 1986; 9(12): 522-524.
47 Bush RK, Schroeckenstein D, Meier-Davis S, Balmes J, Rempel D. Soybean flour asthma: detection of allergens by immunoblotting. J Allergy Clin Immunol 1988; 82(2): 251-255.
48 Quirce S, Fernández-Nieto M, Polo F, Sastre J. Soybean trypsin inhibitor is an occupational inhalant allergen. J Allergy Clin Immunol 2002; 109(1): 178.
49 Baur X, Sauer W, Weiss W. Baking additives as new allergens in baker's asthma. Respiration 1988; 54(1): 70-72.
50 Baur X, Sauer W, Weiss W, Fruhmann G. Inhalant allergens in modern baking industry. Immunol Allergy Pract 1989; 11: 13-15.
51 Alvarez MJ, Tabar AI, Quirce S, Olaguibel JM, Lizaso MT, Echechipia S et al. Diversity of allergens causing occupational asthma among cereal workers as demonstrated by exposure procedures. Clinical & Experimental Allergy 1996; 26(2): 147-153.
52 Roodt L, Rees D. Tests for sensitisation in occupational medicine practice--the soy bean example. S Afr Med J 1995; 85(6): 522-525.
53 Harris-Roberts J, Robinson E, Fishwick D, Fourie A, Rees D, Spies A et al. Sensitization and symptoms associated with soybean exposure in processing plants in South Africa. Am J Ind Med 2012; 55(5): 458-464.
54 Baatjies R, Lopata AL, Sander I, Raulf-Heimsoth M, Bateman ED, Meijster T et al. Determinants of asthma phenotypes in supermarket bakery workers. Eur Respir J 2009; 34(4): 825-833.
55 Zuskin E, Kanceljak B, Schachter EN, Witek TJ, Maayani S, Goswami S et al. Immunological and respiratory changes in animal food processing workers. Am J Ind Med 1992; 21(2): 177-191.
56 Lehrer SB, Reese G, Malo JL, Lahoud C, Leong-Kee S, Goldberg B et al. Corn allergens: IgE antibody reactivity and cross-reactivity with rice, soy, and peanut. Int Arch Allergy Immunol 1999; 118(2-4): 298-299.
57 Vinje NE, Namork E, Lovik M. Cross-allergic reactions to legumes in lupin and fenugreek-sensitized mice. Scand J Immunol 2012; 76(4): 387-397.
58 Mittag D, Vieths S, Vogel L, Becker WM, Rihs HP, Helbling A et al. Soybean allergy in patients allergic to birch pollen: clinical investigation and molecular characterization of allergens. J Allergy Clin Immunol 2004; 113(1): 148-154.

59 Cummings KJ, Gaughan DM, Green BJ, Beezhold DH. Flu-like illness among workers at a soy processing plant. Am J Ind Med 2013; 56(5): 520-521.

60 Gerth van Wijk R, van Cauwenberge PB, Johansson SG. [Revised terminology for allergies and related conditions]. Ned Tijdschr Geneeskd 2002; 146(48): 2289-2293.

61 Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001; 56(9): 813-824.

62 Johansson SG, Bieber T, Dahl R, Friedman PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: report of the nomenclature review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004; 113: 832-836.

63 Meijer E, Heederik D, Grobbee DE. Diagnostiek en preventie van allergische beroepsziekten als gevolg van blootstelling aan hoogmoleculaire allergenen. Een handleiding ten behoeve van de bedrijfsgeneeskundige praktijk. Institute for Risk Assessment Sciences, Division Environmental and Occupational Health, Universiteit Utrecht, en Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde, UMC, Universiteit Utrecht. Evertwijn Meijer (ed), PrintPartners Ipskamp BV, Enschede; 2002.

64 Storaas T, Irgens A, Florvaag E, Steinsvag SK, Ardal L, Van Do T et al. Bronchial responsiveness in bakery workers: relation to airway symptoms, IgE sensitization, nasal indices of inflammation, flour dust exposure and smoking. Clin Physiol Funct Imaging 2007; 27(5): 327-334.

65 Baatjies R, Meijster T, Lopata A, Sander I, Raulf-Heimsoth M, Heederik D et al. Exposure to flour dust in South African supermarket bakeries: modeling of baseline measurements of an intervention study. Ann Occup Hyg 2010; 54(3): 309-318.

A	Request for advice
B	The Committee
C	The submission letter (in English)
D	Comments on the public review draft
E	Prevalence of sensitisation to soybean flour allergens and respiratory symptoms
F	Exposure-response relationships

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in Annex B.

Annex **B**

The Committee

- R.A. Woutersen, *chairman*
  toxicologic pathologist, TNO Innovation for Life, Zeist; professor of translational toxicology, Wageningen University and Research Centre
- P.J. Boogaard
  toxicologist, Shell International BV, The Hague
- D.J.J. Heederik
  professor of risk assessment in occupational epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R. Houba
  occupational hygienist, Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht
- H. van Loveren
  professor of immunotoxicology, Maastricht University, Maastricht
- I.M.C.M. Rietjens
  professor of toxicology, Wageningen University and Research Centre, Wageningen
- G.B.G.J. van Rooy
  occupational medicin specialist, ArboUnie Expert Centre for Chemical Risk Management, Utrecht; Outpatient Clinic for Occupational Clinical Toxicology, Radboud University Medical Centre, Nijmegen

- F.G.M. Russel
  professor of pharmacology and toxicology, Radboud University Medical Centre, Nijmegen
- R.C.H. Vermeulen
  epidemiologist, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- A.H. Piersma, *structurally consulted expert*
  professor of reproductive toxicology, Utrecht University, Utrecht; National Institute for Public Health and the Environment, Bilthoven
- B.P.F.D. Hendrikx, *observer*
  Social and Economic Council, The Hague
- H. Stigter, *observer*
  Labour Inspectorate, Utrecht
- J.M. Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, persons are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the Health Council to assess whether or not someone can become a member. An expert who has no financial but another clearly definable interest, can become a member under the restriction that he will not be involved in the debate on the subject to which his interest relates. If a person's interest is not clearly definable, he can sometimes be consulted as an expert. Experts working for a ministry or governmental organisation can be structurally consulted. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

The submission letter (in English)

Subject	: Submission of the advisory report *Flour dust from processed, de-hulled soybeans*
Your reference	: DGV/BMO/U-932542
Our reference	: U-977709/JR/cn/459-X72
Enclosure(s)	: 1
Date	: June 16, 2016

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to flour dust from processed, de-hulled soybeans.

The present advisory report makes use of the method, which is proposed by the Health Council to derive health-based occupational exposure limits, or on risk-based reference values for allergenic substances (report No. 2008/03E, *Prevention of work-related airway allergies*). The Health Council has calculated the concentration of soybean protein antigens in the air, at which occupational exposure leads to an additional sensitisation risk of 1%, compared to the background risk in the non-exposed, general population.

The conclusions in the advisory report were drawn by the Health Council's Dutch Expert Committee on Occupational Safety (DECOS), and included the reviews by the Health Council's Standing Committee on Public Health.

I confirm the recommendations made by the Committee.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,
(signed)
Professor J.L. Severens
Vice President

Annex **D**

Comments on the public review draft

A draft of the present report was released in 2015 for public review. The following persons and organisations have commented on the draft review:

- Lentz, Green and Cummings, National Institute for Occupational Safety and Health, Cincinnatti OH, USA
- Passchier, Georganiseerd Overleg van werkgevers- en werknemers-organisaties in het bakkersbedrijf, Gouda
- Flipsen, Nederlandse Vereniging Diervoederindustrie (Nevedi), Rijswijk.

The comments received, and the reply by the committee can be found on the website of the Health Council.

Annex **E**

Prevalence of sensitisation to soybean flour allergens and respiratory symptoms

Study design and population information	Exposure information	Health information	Results	Reference
Studies with exposure data on total inhalable dust levels				
Cross-sectional design; 19 workers in a soybean processing mill, Yugoslavia. Study included 20/31 controls (transport workers not exposed to industrial dust or fumes).	Mean environmental dust levels (full-shift): • total inhalable: 29.5 mg/m^3 • respirable: 3.5 mg/m^3. Mean exposure duration was 4 years (1-6 years). Cracking of soybean produces soy flakes from which oil is extracted. The remaining material is dried and ground into flour, then packed and store. Workers who participated in the study worked in the soy flake processing areas.	Questionnaire on respiratory symptoms; lung function tests; skin prick test with extracts of soybean dust, soybean after separation of oil, soy lecithin and soil oil; serum soybean specific IgE levels.	Prevalence of sensitisation, skin prick test (soybean workers vs control group (n=20)): • soybean dust: 100% vs 95% • soybean after separation of oil: 94.7% vs 100% • soy lecithin: 15.8% vs 0% • soy oil: 5.3% vs 0% • house dust: 68.4% vs 20%. Prevalence of sensitisation, specific IgE (soybean workers versus control group (n=20)): 15.8% vs 5%. Respiratory symptoms, workers versus control group (n=31)): • chronic cough: 36.8% vs 19.4% • chronic phlegm: 31.6% vs 16.1% • chronic bronchitis: 21.1% vs 16.1% • asthma: 10.5% vs 0% • dyspnea: 47.4% vs 9.7% • nasal catarrh: 15.8% vs 6.5% • sinusitis: 10.5% vs 6.5%. Only for dyspnea the difference between the two groups was statistically significant.	Zuskin et al. 1991[9], 1994[41]

			Authors suggest that the irritant effect of soy dust may have played a role.	
Cross-sectional design: 35 workers in an animal food processing factory, Yugoslavia. Study included 30/39 controls (clerical office workers, not occupationally exposed to animal food components).	Environmental dust measurements (full-shift; range): • total dust: 0.77-10.62 mg/m^3 • respirable dust: 0.34-2.94 mg/m^3. Food for pigs and chickens was prepared with different components including soybeans and wheats. Workers were exposed to food aerosols during grinding, weighing, mixing, and packaging.	Questionnaire on respiratory symptoms; lung function tests; skin prick test with extracts of soybean; serum soybean specific IgE levels.	Prevalence of sensitisation, skin prick test, all workers: • soybean: 28.6% • fish flour: 82.9% • carotene: 77.1% • corn dust: 65.7%. Prevalence of sensitisation, IgE assay, all workers: • total IgE: 40% • IgE soybean: 2.8% (1/35) Prevalence of sensitisation, IgE assay, control group: • total IgE: 2.6% (1/39). Respiratory symptoms, workers versus control group (n=36)): • chronic cough: 54.3% vs 26.7% • chronic phlegm: 51.4% vs 23.3% • chronic bronchitis: 42.9% vs 23.3.1% • asthma: 5.7% vs 0% • dyspnea: 31.4% vs 6.7% • chest tightness: 48.6% vs 6.7% • rhinitis: 25.7% vs 6.7%. For chronic cough, chronic phlegem, dyspnea, and chest tightness, the difference between the two groups was statistically significant.	Zuskin et al. 1992[55], 1994[41]
Cross-sectional design; 392 employees from 19 bread bakeries, and 77 workers from 3 cake bakeries, the UK.	Exposure includes wheat flour dust and fungal alpha-amylase. The use of soybean flour was not specified. Personal sampling of respirable dust at various times between 1990 and 1996. Soybean flour allergen content of dust was not determined. No data presented on the use of soybean flour. The 1990-1996 dust exposure measurements were collated (no local exhaust ventilation, 8-h TWA GM±SD and range): *Bread bakeries*: • sieving (n=35): 11.4±73.1 mg/m^3 (range, 0.9-349.5)	Structured interview (3 occupational physicians with prior agreed criteria for diagnosis); skin prick tests to common and work-related allergens (wheat, soybean and rice flour, and fungal alpha-amylase). Extract of soybean flour for skin prick test was not specified. Workers were allocated to 4 categories: • occupational asthma • occupational rhinitis	Prevalence of sensitisation to soybean flour: • bread baking: 7% (26/392) • ake baking: 1% (1/77) (difference marginally significant, p=0.045). Prevalence of sensitisation to other bakery allergens: *Wheat flour*: • bread baking: 6% • cake baking: 3%. *Rice flour*: • bread baking: 4% • cake baking: 1%. *Fungal alpha-amylase*: • bread baking: 16% • cake baking: 1%. Prevalence of work-related respiratory symptoms: • bread baking: 20.4% (80/392, occupational asthma, occupational rhinitis or respiratory irritation); • cake baking:10.4% (8/77, only respiratory irritation).	Smith and Wastell Smith 1998[27]

	• weighing (n=26): 8.2±146.7 mg/m^3 (range, 1.0-770) • dough making (n=80): 3.3±19.5 mg/m^3 (range, 0.1-142.2) *Cake bakeries*: • sieving (n=12): 35.7±26 mg/m^3 (15.9-90) • weighing (n=8): 19.2±20.7 mg/m^3 (7.4-68.5) • mixing (n=24): 3.8±4.2 mg/m^3 (0.5-16.3).	• respiratory irritation • asymptomatic	No effect data presented based on type of activity.	
Cross-sectional design; 224 workers in 18 small bakeries (<50 employees), Scotland.	Use of soybean flour not specified. Exposure includes wheat flour dust and fungal alpha-amylase. Job-based exposure categories: A - workers handling flour directly (dough break/roll machine, cleaning, bag collection, weighing and mixing, dividing and moulding, cake mixing); B - workers exposed from general contamination of spaces. Full-shift personal inhalable dust (geometric mean ± standard deviation): A: 4.9±2.3 mg/m^3 (range 0.6-23.7 mg/m^3) B: 1.0±2.7 mg/m^3 (range 0.1-5.5 mg/m^3).	Physician-administered questionnaire on work-related symptoms, past medical history, smoking status and occupational history (n=224); serum IgE to common and bakery allergens, including an extract of soybean flour (IgE measured by RAST; threshold for positive sera was defined as mean plus 2.5 standard deviations of the background level, established in workers in an electronic factory).	Prevalence of sensitisation: Soybean flour: 3% (6/205) Wheat flour: 24% (49/205) Rye flour: 16% (33/205) Barley flour: 16% (32/205) Amylase: 15% (71/205) Oat flour: 4% (9/205). The authors did not present job-title specific sensitisation prevalence rates for soybean flour. Work-related symptoms: *Chronic bronchitis* A: 9.3% (10/108) B: 4.3% (5/116) *Asthma* A: 25% (27/108) B: 17.4% (20/116) *Nasal/eye* A: 33.3% (36/108) B: 20.8% (24/116) *Specific IgE to wheat flour* A: 30% (31/103) B: 18% (72/400).	Jeffrey et al. 1999[32]
Cross-sectional design; 679 employees of 18 flour mills, the UK; workers were regularly exposed to flour dust (workers involved in milling, production or packing activities)	Milling of wheat. Authors report on use of fungal alpha-amylase. Use of soybean flour not specified, but in some mills bread improvers are added to the flour for bread baking. Potential of exposure to grain dust present. Full-shift personal total inhalable dust measurements between	Screening by occupational physician, using structured interview on type, time of onset and duration of work-related respiratory symptoms; skin prick testing to common allergens, and to typical bakery allergens, such as present in	Prevalence of sensitisation: Soybean flour: 0.7% (5/678) Wheat flour: 1.2% (8/679) Amylase: 0.9% (6/679) Rice flour: 0.4% (3/679) Atopy: 37% (248/678). Work-related respiratory symptoms were reported by 147/679 workers (22%), mostly occasional and transient, which were classified as non-specific irritation. Allergic respiratory symptoms were reported by 8/679 workers (1%, 4 rhinitis and 4 asthma).	Smith et al. 2000[42]

	1990 and 1998. Exposure by job category (geometric mean and range): • -production (n=78): 6.1 mg/m^3 (0.5-54.7) • -hygiene (n=38): 17.6 mg/m^3 (1.1-217). Exposure to inhalable dust (median, 8-h TWA, all workplaces): 8.1 mg/m^3 (range, 0.5-217).	wheat flour, soybean and rice flour and to fungal alpha-amylase. Mean duration of employment: 12.5 years (2 months - 47 years).	Authors did not present effect data based on job categories.	
Cross-sectional design; 197 employees of 6 bakeries, Norway.	Exposure includes wheat and rye flour dust, and fungal alpha-amylase. No data on the use of soybean flour. Breathing zone personal total inhalable dust samplers (n=58). Four exposure groups: • <1.0 mg/m^3 (packers, oven workers, administration) • 1.0-1.9 mg/m^3 (mainly confectionary workers, bread formers) • 2.0-3.9 mg/m^3 (mainly dough makers) • >3.9 mg/m^3 (mainly dough makers).	Interview focusing on occupational rhinitis (n=181) and self-administered questionnaire on work tasks, family history, occupational symptoms, smoking habits and prevalence of allergy and atopic dermatitis/eczema (n=180). Specific serum IgE for occupational and common allergens (n=183). Spirometry, bronchial provocation test with methacholine, nasal challenge and lavage. Categorisation of workers in job titles: • dough makers • bread formers • oven staff • packers • confectionary workers • administration and cleaning workers.	Prevalence of sensitisation: Soybean flour: 2% (3/183) Wheat flour: 11% (20/183) Rye flour: 10% (18/183) Barley flour: 8% (14/183) Oats: 5% (9/183) Amylase: 2% (4/183). Occupational rhinitis, preceded lower airway symptoms and was associated with asthma symptoms. Bronchial hyperresponsi-veness (BHR), determined by methacholine challenge, was associated with smoking and work-related asthma. BHR, corrected for baseline lung function, was not associated with occupational IgE sensitisation (defined as positive to wheat, alpha-amylase, oats, barley, rye, soybean, storage mites, mold or cockroach). It is concluded that IgE sensitisation is not the main causative factor for airway hyperresponsive-ness and occupational rhinitis in bakery workers. BHR was not associated with current flour dust exposure level, with number of working hours in a bakery, or with a history of dough-making. No effect data presented based on exposure categories.	Storaas et al. 2005[21], 2007[33], 2007[64]

Cross-sectional design; 517 employees of 31 supermarket bakeries, South-Africa.	Exposure includes wheat and rye flour dust, and fungal alpha-amylase. No data on the use of soybean flour. Full-shift personal airborne dust was sampled (PAS6) in 18 bakeries on 2 days (n=211). Inhalable dust in each job category (GM±GSD): • bread baker (n=112): 1.33±2.25 mg/m^3 • confectioner (n=38): 0.65±2.08 mg/m^3 • supervisor (n=13): 0.56±2.05 mg/m^3 • manager (n=13): 0.51±2.34 mg/m^3 • counterhand (serving customers, n=35): 0.28±1.89 mg/m^3.	Self-administered questionnaire on respiratory symptoms, employment history and job title, degrees of exposure to flour dust, baking activities at home and smoking habits. Skin prick tests to common and work-related allergens, including soybean flour. Pulmonary function testing (spirometry and metha-choline challenge). Average duration of employment in a bakery: 6±5 years.	Prevalence of sensitisation *Soybean flour* all: 8% (42/507) atopics: 15% (32/213) nonatopics: 3% (10/294) *Wheat flour* All: 16% (79/507) atopics: 24% (52/213) nonatopics: 9% (270/294) *Fungal alpha-amylase* All: 3% (17/507) atopics: 6% (13/213) nonatopics: 1% (4/294) *Atopy:* 42% (whole population). The authors did not present job-title (or exposure) specific sensitisation prevalences. Work-related symptoms (all workers, n=517): Asthma diagnosed: 13% Tight chest, wheeze or cough: 13% Chest symptoms: 17% Upper airway symptoms, ocular-nasal: 31%.	Baatjies et al. 2009[54], 2010[65]
Studies without exposure information				
Cross-sectional design; 22 day-shift workers in a soybean mill, South Africa	Low-exposure: clerical and maintenance workers (n=10); high-exposure: millers and packers (n=12). Exposure category based on job activities. Study included 20 control Exposure to full-fat and defatted soybean powder.	Questionnaire on clinical work-related symptoms; test for sensitisation (skin prick test and serum specific IgE levels; extracts from full fat and defatted soybean powder). Also smoking status and soybean consumption was recorded.	Sensitisation, specific IgE: • all workers: 36% (8/22) • high exposure: 25% (3/12) • low exposure: 50% (5/10) • control group: 5% (1/20) Sensitisation, skin prick test: • all workers:36% (8/22) • high exposure: 25% (3/12) • low exposure: 50% (5/10) • control group: 0% (0/20). Authors reported that the prevalence of work-related cough and breathlessness was higher in the exposed groups than in controls. However, this differences was not statistically significantly different. The Committee noted the low number of participants.	Roodt and Rees 1995[52]
Cross-sectional design; 383 workers in 19 bakeries, the UK.	Workers currently exposed to dust from bread improver, wheat flour and other ingredients, such as fungal alpha-amylase, on a regular basis. Exposure to soybean flour possible by the use of	Interview on work-related symptoms by physician; skin prick tests to common and work-related allergens, including soybean flour (source of extract and	Prevalence of sensitisation to soybean flour: • all workers: 6% (24/383) • atopics: 11% (15/132) • non-atopics: 4% (9/257) Diagnostic categories: • asthma: 50% (1/2) • rhinitis: 80% (8/10) • respiratory irritation: 14% (9/66) • asymptomatic: 2% (6/305).	Smith et al. 1997[26]

	bread improver. Normal content of bread improver: • soybean flour: 40-50% • wheat flour: up to 20% • fungal amylase: maximum of 0.1%.	composition not specified). Workers were allocated to the following groups: • occupational asthma (alone or in combination with rhinitis); • occupational rhinitis; • respiratory irritation (non-specific); • asymptomatic (= no work-related symptoms).	Prevalence of sensitisation to other allergens (all workers): • wheat flour: 6% • rice flour: 4% • fungal alpha-amylase: 16%. The authors explain the low prevalence of asthmatics by healthy worker effect.	
Cross-sectional design; 89 bakery workers, 104 persons with bakers' asthma, and 43 control subjects (not working in a bakery), Germany.	Exposure includes wheat flour dust and fungal alpha-amylase. No data on the use of soybean flour. No data on job activities.	Skin prick tests to common and bakery allergens, including soybean flour (extract used not specified); Measurement of specific IgE antibodies (EAST - enzyme-allergo-sorbent-test); lung function tests.	Prevalence of sensitisation to soybean flour *Skin prick test*: bakery workers: 1% (1/88) asthmatics: 11% (11/103) control subjects: 0% (0/43) *Specific IgE*: bakery workers: 19% (17/89) asthmatics: 21% (22/104) control subjects: 5% (2/41). Authors reported also on sensitisation to other bakery allergens, such as wheat flour, rye flour, and fungal alpha-amylase. Lung function tests: *Obstructive*: bakery workers: 17% (13/76) asthmatics: 28% (26/94) control subjects: 2% (1/39) *Hyperreactive*: bakery workers: 13% (10/76) asthmatics: 19% (18/94) control subjects: 8% (3/39) *Normal*: bakery workers: 70% (1/76) asthmatics: 53% (11/94) control subjects: 90% (0/39).	Baur et al. 1998[19]

Annex **F**

Exposure-response relationships

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Cross-sectional study by Cummings et al. (2010)[15] and NIOSH (2009)[31].

Study design and population information	Exposure information	Health information	Results
147 workers of a soybean processing plant, USA. Study included referents (n=50, healthcare workers) not occupationally exposed to soybean flour.	Plant receives de-oiled, de-hulled crushed soy flakes for further processing. Flakes are processed into soybean powder. Full-shift personal inhalable dust (n=178, IOM samplers and gravimetric analysis) and total soy antigen (protein) concentrations measured (inhibition immunoassay). Real-time photometric measurements of personal (n=23) and area (n=47) peak airborne dust levels. Job-title categories: inhalable soy antigen (geometric mean±standard deviation): • production support (n=39 workers): 2,991±15 ng/m^3 • production (n=66 workers): 2,782±5.4 ng/m^3 • non-production (n=42 workers): 235±9.1 ng/m^3.	Interviewer-administered questionnaire (n=147) on work-related respiratory and dermatological symptoms, physician-diagnosed asthma and eczema, smoking history and employment and demographic information; lung function (n=140) and methacholine challenge tests. Skin prick tests (n=132) to commercially available extracts of soybean food, and common allergens (positive if wheal diameter at 15 min reading ≥3 mm larger than negative control and ≥25% of positive control). Analysis of soybean-specific IgG and IgE in blood (n=135) ImmunoCAP, positive if specific IgE >0.35 kU/L) n=135).	See separate Table at the end of this Annex for exposure-response analysis Prevalence of sensitisation: *All workers*: • skin prick test: 7% (9/132) • specific IgE: 21% (28/135) Referents: • specific IgE: 4% (2/50). Prevalence of sensitisation to soybean flour dust (specific IgE): *By job category*: • production: 20% • production support: 24% • non-production: 18%. Authors did not find an association between sensitisation (IgE) and the level of inhalable soybean antigens or job categories. This was possible due to a healthy worker effect. The suggestion is strengthened by the inverse relation between duration of

Job-title categories by inhalable soy antigen exposure:
- low: 24-804 ng/m^3
- medium: 959-2,297 ng/m^3
- high: 2,635-25,958 ng/m^3

(*low*, autopack assistants, maintenance workers, office staff, warehouse workers; *medium*, autopack operators, feed dryer operators, spray dryer operators, laboratory technicians; *high*, curd operators, production leads, sanitation operators, unloading operators).

Job-title categories: inhalable dust (geometric mean ± standard deviation):
- non-production: 0.29±2.6 mg/m^3
- production support: 0.60±3.2 mg/m^3
- production: 0.77±2.9 mg/m^3.

Peak dust exposure categories (maximum concentration during real-time sampling, 23 personal and 47 area samples):
- low: <1 mg/m^3
- medium: 1-10 mg/m^3
- high: ≥10 mg/m^3

(*low*, non-production workers - laboratory technicians, office staff and warehouse workers; *medium*, curd operators, production leads, spray dryer operators, maintenance workers; *high*, autopack operators, autopack assistants, feed dryer operators, sanitation operators, unloading operators).

employment and skin rash:
- short: 15% (OR 1.0; 95% CI -)
- medium: 13% (OR 0.9; 95% CI 0.3-2.7)
- long: 2% (OR 0.1; 95% CI 0.01-0.7).

Detection of soybean-specific IgG levels (all workers had detectable IgG to soybean):
- low: 60 mg/L
- medium: 46 mg/L
- high: 219 mg/L
- referents: 1.5 mg/L

Work-related asthma symptoms, outcome (OR; 95% CI):
IgE to soy
- negative: 7% (1.0; -)
- positive: 32% (5.9; 2.0-17.6)

Current work classification
- non-production: 2% (1.0; -)
- prod. support: 13% (6.0; 0.9-118)
- production: 18% (9.1; 1.7-169).

Work-related nasal allergies, outcome (OR; 95% CI):
Current work area
- non-production: 2% (1.0; -)
- prod. support: 15% (7.5; 1.2-144)
- production: 8% (3.4; 0.5-65.6).

The Committee noted that in the analysis of the data, no corrections were made for confounding, and that the results on peak exposure mainly show a difference between the production and non-production workers (the difference between the two production groups is small).

Exposure-response analysis (data from Cummings et al. and NIOSH).

Effect parameter	Exposure levels	Prevalence	Correlation (Odds ratios)
Exposure parameter: Inhalable soy antigen (full shift)			
Sensitisation (serum specific IgE)	Low: 24-804 ng/m^3	21%	No significant positive correlation
	Medium: 959-2,297 ng/m^3	33%	
	High: 2,635-25,958 ng/m^3	6%	
	Control: not exposed	4%	
Work-related asthma like symptoms	Low: 24-804 ng/m^3	9%	No significant positive correlation
	Medium: 959-2,297 ng/m^3	20%	
	High: 2,635-25,958 ng/m^3	8%	
Cough	Low: 24-804 ng/m^3	-	1.0
	Medium: 959-2,297 ng/m^3	-	3.13 (1.09-9.80)
	High: 2,635-25,958 ng/m^3	-	2.18 (0.67-7.33)
Sinusitis or sinus problems	Low: 24-804 ng/m^3	-	1.0
	Medium: 959-2,297 ng/m^3	-	0.99 (0.46-2.17)
	High: 2,635-25,958 ng/m^3	-	1.40 (0.62-3.29)
Nasal allergies	Low: 24-804 ng/m^3	-	1.0
	Medium: 959-2,297 ng/m^3	-	0.34 (0.14-0.79)
	High: 2,635-25,958 ng/m^3	-	0.43 (0.17-1.01)
Rash or skin problems	Low: 24-804 ng/m^3	-	1.0
	Medium: 959-2,297 ng/m^3	-	1.58 (0.63-3.96)
	High: 2,635-25,958 ng/m^3	-	1.34 (0.50-3.56)
Exposure parameter: total inhalable dust (peak exposure, maximum level measured)			
Work-related asthma like symptoms	Low: <1 mg/m^3	2%	1.0
	Medium: 1-10 mg/m^3	15%	6.96 (1.22-131)
	High: ≥10 mg/m^3	19%	9.37 (1.61-178)
Airway obstruction (spirometry)	Low: <1 mg/m^3	-	1.0
	Medium: 1-10 mg/m^3	-	4.9 (0.79-94.5)
	High: ≥10 mg/m^3	-	8.49 (1.41-163)
Sinusitis or sinus problems	Low: <1 mg/m^3	-	1.0
	Medium: 1-10 mg/m^3	-	2.16 (0.75-7.17)
	High: ≥10 mg/m^3	-	2.86 (0.95-9.83)
Nasal allergies	Low: <1 mg/m^3	-	1.0
	Medium: 1-10 mg/m^3	-	0.64 (0.09-2.94)
	High: ≥10 mg/m^3	-	1.08 (0.26-4.01)
Rash or skin problems	Low: <1 mg/m^3	-	1.0
	Medium: 1-10 mg/m^3	-	1.38 (0.26-10.3)
	High: ≥10 mg/m^3	-	5.29 (1.26-36.3)

Correlation expressed as odds ratio (95% confidence interval).

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory opinions that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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