Wheat and other cereal flour dusts

Health-based recommendation on occupational exposure limits

To: the Minister of Social Affairs and Employment
No. 2017/10, The Hague, July 20, 2017

Health Council of the Netherlands

contents

samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) actualiseert de Gezondheidsraad het advies over de beroeps- matige blootstelling aan tarwemeelstof. Eerder leidde de Gezondheidsraad een gezond- heidskundige advieswaarde af van 0,12 milli- gram (mg) inhaleerbaar tarwemeelstof per kubieke meter (m^3) lucht (gemiddeld over een 8-urige werkdag). In het huidige advies stelt de Gezondheidsraad de advieswaarde bij tot 0,2 mg inhaleerbaar tarwemeelstof per m^3 lucht. Dit advies is tot stand gekomen in de commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) – een vaste commissie van de Gezondheidsraad.

De Gezondheidsraad heeft een vaste rol bij de bescherming van werknemers tegen mogelijke schadelijke effecten van stoffen waar zij tijdens hun werk mee in aanraking kunnen komen. Meer informatie over die rol staat op www.gezondheidsraad.nl.

Tarwemeelstof: gezondheidsrisico's voor bakkers

Blootstelling aan meelstof afkomstig van tarwe en aan tarwe verwante graansoorten waaronder haver, gerst en rogge (hierna aangeduid als tarwemeelstof) kan leiden tot aandoeningen zoals:

- astma;
- ontsteking van het neusslijmvlies;
- ontsteking van het oogslijmvlies.

Deze kunnen het gevolg zijn van een allergische reactie. Vooral mensen die werken in bakkerijen en de meelverwerkende industrie krijgen hiermee te maken.

Advieswaarde op basis van 1% extra risico op sensibilisatie

Aan een allergische reactie op een stof gaat *sensibilisatie* vooraf: het moment waarop het immuunsysteem in verhoogde staat van paraat- heid raakt, maar er nog geen of nauwelijks klachten optreden. De Gezondheidsraad hanteert bij advieswaarden voor allergenen het uitgangspunt dat niet alleen de allergische klachten, maar ook de sensibilisatie voorkomen moet worden, zo ook voor tarwemeelstof. Voor allergenen die mensen inademen is het in het algemeen niet mogelijk een concentratie vast te stellen waaronder sensibilisatie *niet* optreedt. In die gevallen schat de Gezond- heidsraad een concentratie waarbij het extra risico op sensibilisatie door blootstelling op de werkvloer *beperkt* is tot 1%.

In de algemene bevolking raken 2 op de 100 mensen (2%) gesensibiliseerd voor tarwemeel- stof. Een extra risico van 1% betekent dat er in een werkomgeving waar mensen worden bloot- gesteld aan tarwemeelstof niet 2, maar 3 op 100 mensen gesensibiliseerd raken. Die '1% extra' geldt sinds 2009 als een uitgangspunt voor het Nederlandse grens-waardenstelsel.

Nieuwe berekening op basis van meer gegevens

In het vorige advies van de Gezondheidsraad heeft de commissie een onderzoek gebruikt over risico's op sensibilisatie door blootstelling aan tarwemeelstof bij Nederlandse bakkers. Op basis van dit onderzoek is er een advieswaarde van 0,12 mg per m^3 lucht berekend, overeenkomend met een extra risico op sensibilisatie van 1%. Sindsdien zijn er twee nieuwe publicaties verschenen die zich lenen voor het afleiden van een advieswaarde. Het ene onderzoek is uitgevoerd bij bakkers in Zuid-Afrika, het andere bij bakkers in Nederland – net als het onderzoek dat voor het eerdere advies is gebruikt.

Op basis van het onderzoek bij Zuid-Afrikaanse bakkers schat de commissie voor een extra risico van 1% een blootstelling van 0,04 mg per m^3 lucht. Dit suggereert dat Zuid-Afrikaanse bakkers al bij een lagere blootstelling een bepaald risico lopen.

De commissie acht het waarschijnlijk dat het verschil in risico tussen Nederlandse en Zuid-Afrikaanse bakkers het gevolg is van een relatief groot aantal personen met een aanleg voor het ontwikkelen van een allergie (atopie) in de Zuid-Afrikaanse populatie. Ook wijst de commissie erop dat de werkomstandigheden in Zuid-Afrika verschillen van die in Nederland. De commissie is daarom van mening dat het onderzoek bij Zuid-Afrikaanse bakkers niet representatief is voor de Nederlandse werknemers en dat het risico het meest betrouwbaar kan worden geschat op basis van de onderzoeken bij Nederlandse bakkers.

Uitgaande van de twee Nederlandse onderzoeken komt de commissie tot een advieswaarde van 0,2 mg inhaleerbaar tarwemeelstof per m^3 lucht. Dit is een hogere concentratie dan de aanbeveling uit een eerder advies (0,12 mg/m^3). Het verschil wordt verklaard doordat de commissie de nieuwe gegevens heeft toegevoegd aan de oude gegevens (waarop het eerdere advies was gebaseerd), wat de betrouwbaarheid vergroot.

Advies aan de minister

Voor de beroepsmatige blootstelling aan tarwemeelstof komt de commissie tot een gezondheidskundige advieswaarde van 0,2 mg inhaleerbaar tarwemeelstof per m^3 lucht, als een gemiddelde concentratie over een 8-urige werkdag. Bij deze concentratie hebben werkenden ten opzichte van de algemene bevolking 1% extra risico op sensibilisatie voor tarwemeelstof.

executive summary

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 the Health Council, has updated its recommendation on occupational exposure to wheat flour dust and the risk of sensitisation. Previously, the Health Council derived a health-based recommended occupational exposure limit of 0.12 milligram (mg) inhalable wheat flour dust per cubic metre (m^3) air (8-h mean for a working day). In the current report, the Health Council adjusts its advisory value to 0.2 mg inhalable wheat flour dust per m^3 air.

Wheat flour dust: health risks for bakers

Exposure to flour dust from wheat and the related cereal grains rye, barley and oats (hereafter referred to as wheat flour dust) can lead to diseases, including:

- asthma;
- inflammation of the nasal mucous membrane;
- inflammation of the conjunctiva.

These can be the result of an allergic reaction. In particular, the health effects concern people who work in bakeries and the flour processing industry.

Recommendation based on 1% extra risk of sensitisation

A chemical-induced allergic reaction is preceded by sensitisation: the situation at which the immune system is triggered, but no (significant) complaints have yet occured. For recommendations on allergens, including wheat flour dust, the Health Council applies the principle that not only the allergic complaints, but also the sensitisation should be prevented. For inhalatory allergens, it is generally not possible to derive a concentration below which no sensitisation occurs. In those cases, the Health Council calculates the concentration at which the extra risk of sensitisation by occupational exposure is *limited* to 1%.

In the general population – independently from occupational exposure – 2 out of 100 people (2%) are sensitised for wheat flour dust. An extra risk of 1% means that in a workplace where people are exposed to wheat flour dust not 2, but 3 out of 100 people are sensitised. For allergens, this '1% extra' is the starting point for the Dutch OEL-system.

New calculation based on additional information

In the previous advice of the Health Council, the Committee has used a study in Dutch bakery workers and the risk of sensitisation to wheat flour dust. On the basis of this study an advisory value was derived of 0.12 mg per m^3 air, corresponding with a 1% extra risk of sensitisation. Since then, two new studies have been published that can be used to derive an advisory value. One study was done in bakery workers in South Africa, the other in Dutch

bakery workers – similar to the study used for the previous recommendation.

On basis of the study in South-African bakery workers, the Committee calculates an exposure level of 0.04 mg/m^3, corresponding to an extra risk of 1%. This suggests that at lower exposure levels South-African bakery workers are already at a certain risk.

The Committee considers it likely that the differences in sensitisation risk between Dutch and South-African bakery workers is the result of a relatively large number of people predisposed to allergies (atopy) in the South-African population. The Committee also notes that working conditions in South-Africa differ from those in the Netherlands. The Committee therefore considers the study in South-African bakery workers not representative for the Dutch workers and concludes that the most reliable estimation of sensitisation risk can be made on basis of the studies in Dutch bakery workers. Based on the two Dutch studies, the Committee derives an advisory value of 0.2 mg inhalable wheat flour dust per m^3 air. This concentration is higher than the previous recommendation (0.12 mg/m^3). The difference can be explained by the fact that the Committee has combined new data and data used previously, which increases the reliability of the estimation.

Recommendation to the minister

For occupational exposure to wheat flour dust, the Committee derives a health-based recommended exposure level of 0,2 mg inhalable dust per m^3 air, as a mean concentration over a 8-h working day. At this concentration, workers have a 1% extra risk of wheat flour dust sensitisation compared to the general population.

01 scope

1.1 Background

At request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Exposure Safety (DECOS), one of the permanent committees of the Health Council, proposes health-based recommended occupational exposure limits for chemical substances in the air at the workplace. These recommendations serve as basis in setting legally binding occupational exposure limits by the minister.

Workers in bakeries and flour mills may be exposed to wheat and cereal flour dusts. The Committee has previously evaluated the consequences of exposure to these dusts (2004).[1] The recommendation of the Committee then, has not been implemented in the Dutch occupational exposure limit system. In 2008, the Scientific Committee on Occupational Exposure Limits (SCOEL) also published a report on wheat flour dust, and the related cereal grains rye, barley and oats.[2]

In the current evaluation, the Committee updates its quantitative hazard assessment of specific sensitisation by exposure to wheat and other cereal flour dusts. For additional information, the Committee refers to its previous report.

1.2 Committee and procedure

The present document contains the evaluation of the DECOS, hereafter called the Committee.

The Committee has taken into account the published literature until November 2016. In January 2017, DECOS released a draft version of the report for public review. The individuals and organisations that commented, the received comments, and the subsequent replies by the Committee are publicly available on the website of the Health Council.

1.3 Data

The Committee's recommendations are based on scientific data, which are publicly available. Published literature was retrieved from Pubmed using key words 'wheat' and 'allerg*'. The final search was carried out in November 2016.

02 previous evaluations

2.1 DECOS (2004)

DECOS has evaluated the consequences of occupational exposure to wheat and other cereal flour dusts, previously.[1] In this Chapter, the Committee summarises the critical considerations and conclusions of this evaluation. For details, the Committee refers to the original report from 2004.

Definition

'Wheat flour dust' is specified as finely ground particles of taxonomically related cereal grains of the subfamily *Festucoideae* and the tribes *Triticeae* and *Aveneae*, such as wheat (*Triticum sp.*), rye (*Secale cereale*), barley (*Hordeum sp.*) and oats (*Avenea sativa*) produced by subjecting these grains to milling or some other form of processing. This specification includes these flour dusts as due to cross-reactivity[a], exposure to one of these cereal flour dusts could result in sensitisation towards another.

Monitoring

For sampling the inhalable flour dust fraction, gravimetric techniques are used. In the Netherlands, monitoring inhalable dust is usually done with the Dutch 'PAS6' sampling head; international equivalents are also available.

The allergen content of the dust can be evaluated by the use of immunoassays. Most of these techniques, however, have not yet been standardised for routine monitoring.

Effects

Exposure to allergens from these flour dusts can lead to allergenic respiratory effects, such as cough, rhinitis, conjunctivitis and asthma.

[a] Data on cross-reactivity mainly consist of data on wheat and rye. Since co-exposure to other barley and oats is common and (some degree of) cross-reactivity highly likely, these cereal grains are also included as subject for recommendation.

These complaints can also be caused by irritation. Typically, development of allergy involves an initial exposure by which the immune system is sensitised, usually without the occurrence of symptoms. At subsequent exposures, sensitised individuals can suffer from allergenic respiratory effects.

Risk calculation and recommendation

The Committee concluded that it was not possible to determine a threshold for sensitisation by allergens in (wheat) flour dust. To enable some protection for the large group of potentially exposed workers, the Committee calculated exposure levels corresponding with predefined risks on sensitisation induced by wheat and other cereal flour dusts. The Committee considered the study published by Heederik et al. (2001)[3] most suitable for quantitative hazard assessment, as it includes a good quality data set on both exposure and response (i.e. data on amounts of inhalable dust and allergens, on cases of sensitisation and prevalence of atopy), and extensive statistical analyses were performed. Importantly, of all good quality studies, Heederik et al. measured concentrations in the lowest exposure range. In line with the current Dutch regulations, the Committee calculated the exposure level that corresponds to an extra risk of sensitisation of 1% (i.e. a risk of 1%, in addition to the background risk). For this calculation, the Committee used the exposure metric (mg dust/m^{3}) since this metric, in contrast to the amount of airborne allergens, can be measured by standardised and validated methods.

The Committee determined the best fit of the exposure-response relationship in the lower exposure range using linear regression, which was described by the function:

$$AR = D/0.124 \text{ (lineair model)}$$

where AR is the additional risk (%) and D is the estimated mean concentration inhalable dust (in mg/m^3).

In this model, an uncertainty factor of 2 was included for taking into account the variation in amounts of allergens in inhalable dust. The model was considered only valid for exposure concentrations up to 3 mg inhalable/m^3, as only below this value the exposure-response relationship is linear.

On the basis of this model, the Committee derived a concentration of 0.12 mg/m^3 for inhalable dust, corresponding with an extra risk of sensitisation of 1% due to occupational exposure, in addition to the risk of 4% in the general population of already being sensitised to allergens in wheat flour dusts and other cereal flour dusts. This represents a mean concentration for 8 hours a day, 5 days a week, for life, under normal working conditions.

2.2   SCOEL (2008)

The European Scientific Committee on Occupational Exposure Limits (SCOEL) published a report on flour dust in 2008.[2]

SCOEL reasoned that the symptoms induced by cereal flour exposure that should be prevented are related to disorders of the respiratory tract and the eyes, such as rhinitis, conjunctivitis and, especially, asthma. According to SCOEL, these symptoms are persistent when induced immunologically (primarily IgE-mediated), and reversible when caused by irritation. SCOEL defined sensitisation as the development of specific IgE antibodies to any of several wheat flour dust allergens, and considered sensitisation as a sentinel event since it causes an increased risk of developing respiratory symptoms.

SCOEL concluded that the available literature does not demonstrate a trustworthy threshold for any of the wheat flour dust-induced effects. Exposure levels exceeding 1 mg/m^3 and 3 mg/m^3 inhalable wheat flour dust were considered as levels at which the risk increased of nasal symptoms and asthma, respectively. Reference was made to studies on dose-response relationships that according to SCOEL, indicated that symptoms (especially related to the lower respiratory tract, asthma, as well as sensitisation) are rare in the exposure range of 0.5-1.0 mg/m^3. Although SCOEL generally does not recommend health-based OELs for sensitisers, it recommended one for wheat flour dust in view of the large number of workers exposed and the relatively large data base. SCOEL recognized that the majority of exposed workers would not develop onset of disease at exposures ≤ 1 mg/m^3 of inhalable flour dust and that the envisaged symptoms would be mild. However, SCOEL also noted that concentrations below 1 mg/m^3 may trigger symptoms in already sensitised workers.

03 update quantitative hazard assessment

3.1 Literature published since 2004

Since the previous report of the Health Council[1], several new studies on the exposure to wheat flour dust and the induction of allergy have been published (see Annex B). The selection has been limited to publications involving both exposure measurements and effect assessment. Some of these studies are particularly relevant for the calculation of risk of sensitisation by wheat flour dust exposure, since these studies have addressed an exposure-response relationship. All studies involve cross-sectional studies, for which confounding by a healthy worker effect cannot be excluded.

The relevant studies for quantitative risk assessment are summarised below and in Annex B.

Baatjies et al. (2015) derived exposure-response relationships for wheat flour dust exposure and the occurrence of asthma in a cross-sectional study, involving 466 supermarket bakery workers from 31 bakeries.[4] The exposure-response relationships were derived using questionnaires, specific serum-specific IgE and IgG4 measurements, methacholine challenge testing, and exposure models developed previously[5] to predict average personal exposure to wheat allergens. A linear exposure-response

relationship between average exposure and sensitisation was obtained. However, the relationship between allergic symptoms and probable occupational asthma followed a bell-shaped curve increasing up to 10-15 $\mu g/m^3$ wheat allergen concentration, which levelled off and decreased at higher exposure concentrations. This relationship was modified by atopic status and IgG4 levels were strongly related to exposure.

The authors also separately analysed bakers with and without atopy. The relationship exhibited a bell-shaped curve, i.e. with increasing exposures the number of cases with allergy increased, but leveled off at the highest exposures. This was most prominent for atopic bakers. Bell-shaped shaped curves are suggestive for a healthy worker effect. The Committee notes a relatively high atopy prevalence of 42% – a major risk factor for occupational sensitisation – in the population studied by Baatjies. For further analysis, the Committee obtained the data set of this study (see Section 2.4). Interestingly, the atopy prevalence was particularly high in the low exposure group, i.e. 48% compared to less than 40% in the high exposure group.

In a study by Page et al. (2009 and 2010) performed in the US, 161 workers from bakeries were divided in a low and a high exposure group, with mean inhalable wheat flour dust levels of 0.24 and 3 mg/m³, respectively.[6,7] The fraction of cases with specific sensitisation for wheat flour dust allergens (based on IgE levels measured in serum) in the low exposure group was 24% and in the high exposure group 42%.

Harris-Roberts et al. (2009) reported on an investigation in 225 bakery workers in the UK.[8] Based on measurements derived by Elms et al. (2005;[9] in the same bakeries) these authors divided workers in 4 exposure categories: low, middle, middle-high and high (with mean inhalable exposure levels of 2.1 mg/m^3, 3.6 mg/m^3, 4.4 mg/m^3 en 5.2 mg/m^3, respectively).The fraction of cases of specific sensitisation (determined by serum IgE) was 9.7%, 5%, 0% and 11.1%, respectively. The fact that in the middle-high group no cases were observed can be explained by the small group size (only 2 workers).

In another British study, Brant et al. (2005) found one case of specific sensitisation (specific IgE measured) in a group of 53 confectioners exposed to 0.3 mg inhalable dust/m^3 (geometric mean), and 18 cases in a group of 71 bakers exposed to 1.2 mg inhalable dust/m^3.[10] The Committee considers it likely that the wheat-allergen levels in the inhalable dust differed between confectioners and bakers, since these groups use different products. Usually, confectioners will be exposed to lower levels of wheat flour dust compared to bakers and therefore hardly any sensitisation has been observed among confectioners. With respect to the bakers, the number of cases of sensitisation was clearly increased compared to an unexposed control group.

Jacobs et al. (2008) reported on a Dutch study with 860 bakers, in which an extensive exposure-response relationship analysis was based on allergen concentration instead of dust concentration, and specific sensitisation.[18] In this study, atopic bakers were distinguished from non-atopic bakers and an increase was found in cases of sensitisation at increasing exposure levels in both groups. In the group of atopics however, this increase leveled off at higher concentrations, probably due to the healthy worker effect.

Other studies, included in Annex A, do not allow the calculation of a health-based recommended occupational exposure level. In the publication of Droste et al. (2005) for instance, the cumulative exposure was not measured and therefore the actual exposure in the study is not completely clear.[11] Storaas et al. (2005; 2007) has addressed other effects (i.e. chronic inflammation), at higher exposure levels.[13-15] In the South-African studies of Baatjies et al. (2009; 2010) exposure categories were distinguished based on tasks, but no exposure-response relationship can be derived since the prevalence for each category was not given.[5,16]

3.2 Existing guidelines and standards

Current occupational exposure limits of several countries are presented in Table 1. In the Netherlands, no legally binding OEL has been set up to now.

Table 1. Occupational exposure limits applied word-wide. (source: Health Council 2004, unless specified otherwise)

Country (organisation)	Concentration (mg/m³)	TWA	Type of OEL	Note
The Netherlands[a]	-			
European Union	-			
Belgium[b]	0.5			
Canada[c]	3			Total dust
Germany (DFG)	-			Sa; wheat and rye flour dusts
The United Kingdom (HSE)	10	8-h	MEL	Sen; flour dust
	30	15 min	MEL	
Spain[d]	4			
Sweden	3	8-h	LLV	S
USA (ACGIH)	0.5	8-h	TLV	Sen; inhalable dust fraction

<p>a   https://www.ser.nl/en/grenswaarden/meelstof.aspx</p>
<p>b   http://www.werk.belgie.be/WorkArea/DownloadAsset.aspx?id=23914</p>
<p>c   http://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx</p>
<p>d   http://www.insht.es/</p>

3.3 Quantitative assessment of risk of sensitisation

3.3.1 Assessment of relevant studies

The Committee concludes that most studies published since 2004, do not provide a reliable basis to calculate the risk of sensitisation due to exposure to wheat flour dust. The reason for this conclusion is that in most studies, the measured exposure levels were relatively high.[6-8,10] As a consequence, these studies do not provide specific information on exposure levels that are associated with risk levels around 1%. Extrapolation far outside the exposure range under study would therefore be necessary, introducing a large uncertainty for the estimate. Noteworthy, although the study of Harris-Roberts et al. (2009)[8] is not an appropriate starting point due to the high exposure levels involved, the observed cases of sensitisation are, however, consistent with the exposure-response relationship derived previously by the Committee. Furthermore, these studies have additional limitations. The study by Page et al. (2009; 2010)[6,7] is based on a small number of subjects, with only two exposure categories and a high response in the low exposure group, which hampers a reliable exposure-response assessment. The report by Brant et al. (2005)[10] also provides very limited information on a concentration-response relationship, since only the mean exposure was specified based on a limited number of bakery workers.

The Committee considers the study by Baatjies et al.(2015)[4] of interest for quantitative risk assessment purposes. This study is of high methodological quality (i.e. a large population; reliable measurement methods) and the endpoints studied are robust and clinically relevant (i.e. presence of non-specific bronchial hyper-responsiveness and sensitisation). The Committee notes that a relatively high prevalence of workers with an atopic status were included, which is a risk factor for the development of sensitisation, is observed (in particular in the low exposure group, i.e. 48%). The Committee considers it likely that this high prevalence of atopy is related to the atopic constitution since the prevalence of atopic dermatitis, which could result in a higher risk for

allergic disease, is high in a population of African origin.[17] The Committee therefore considers the workers studied by Baatjies et al. not representative for the Dutch working population. Furthermore, the Committee considers the paper by Jacobs et al. (2008)[18] suitable for quantitative risk assessment. This is a well-performed study which provides detailed information on the exposure-response relationship of wheat flour dust in a Dutch worker population.

3.3.2 Risk calculations

The Committee performed risk calculations on the data from the studies by Jacobs et al. (2008)[18] and, for comparison, Baatjies et al. (2015).[4] For the risk calculation of the previous report, a linear regression analysis was done on the dataset used by Heederik et al.[3] (which involved data from Houba et al.[19]) The Committee acknowledges that presently, more appropriate methodological approaches are applied for risk assessments using rates (e.g. Poisson regression instead of linear regression). Therefore, the Committee also did a re-calculation of the exposure-risk estimate based on the data of Houba et al. (1998)[20], according to the current scientific standards and using an updated sensitisation baseline rate (for details, see Annex B).

The calculated exposures that correspond to an extra risk of 1% are 0.18 mg inhalable wheat flour dust/m^3 (Jacobs et al. (2008)[18]), 0.04 mg/m^3 (Baatjies et al. (2015)[4]), and 0.20 mg/m^3 (Houba et al. (1998)[20]). As mentioned previously, the Committee considers the dataset of Baatjies et al. (2015)[4] not representative for the Dutch working population. The Committee is of the opinion that the most reliable risk estimate is obtained by combining the data derived by Jacobs et al. (2008)[18] and Houba et al. (1998).[20] The calculation based on both data sets results in an exposure level of 0.2 mg inhalable wheat flour dust/m^3, corresponding to an 1% extra risk of sensitisation by occupational exposure to wheat flour dust.

3.4 Comparison with SCOEL

Both the DECOS and SCOEL have concluded that no threshold can be determined below which no adverse health effects due to exposure to wheat flour dust are expected to occur. In those cases, in analogy with stochastic genotoxic carcinogens, the Committee applies a risk-based approach.[21] This approach has been supported by the Social and Economic Council[a] and adopted by the Ministry of Social Affairs and Employment that is responsible for the Dutch OEL-system. In this approach, the Committee uses sensitisation as primary endpoint and calculates the exposure level that results in an extra risk of 1%. In contrast, SCOEL mainly focuses on allergic complaints after exposure. The SCOEL approach does not involve calculations of exposure concentrations that correspond to specific risks of developing health effects, but provides an exposure level based on an expert opinion without applying a specified guideline.

---

[a] SER: Aanpak inhaleerbare allergene stoffen op de werkplek; Den Haag, 2008 (in Dutch).

3.5 Groups at risk

In the previous report, the Committee identified three groups of workers that have an increased risk of developing allergic respiratory symptoms after exposure to wheat flour dust: 1) workers already sensitised; 2) workers with an atopic status or an allergic constitution; and 3) workers with pre-existing asthma.[1] In addition, the Committee notes that the prevalence of an atopic status differs between ethnic subgroups (for instance, the prevalence of atopic dermatitis is particularly high in people of African descent).[17] This suggests that the risk of sensitisation varies between these populations correspondingly.

3.6 Conclusions and recommendation

The Committee recommends a health-based occupational exposure level of 0.2 mg inhalable wheat flour dust/m^3 (8h time-weighted average). This exposure concentration corresponds to an extra sensitisation risk of 1%, compared to the general population, against wheat and other cereal flour dusts.

references

1   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.

2   Scientific Committee on Occupational Exposure Limits. *Recommendation from the Scientific Committee on Occupational Exposure Limits for flour dust.* 2008; SCOEL/SUM/123.

3   Heederik D, Houba R. *An exploratory quantitative risk assessment for high molecular weight sensitizers: wheat flour.* Ann Occup Hyg 2001; 45(3): 175-85.

4   Baatjies R, Meijster T, Heederik D, Jeebhay MF. *Exposure-response relationships for inhalant wheat allergen exposure and asthma.* Occup Environ Med 2015; 72(3): 200-7.

5   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): 309-18.

6   Page EH, Dowell CH, Mueller CA, Biagini RE. *Exposure to flour dust and sensitization among bakery employees.* Washington, DC 200910, 2009; Health Hazard Evaluation Report: HETA-2005-0248-3077, Sara Lee Bakery, Sacramento, California.

7   Page EH, Dowell CH, Mueller CA, Biagini RE, Heederik D. *Exposure to flour dust and sensitization among bakery employees.* Am J Ind Med 2010; 53(12): 1225-32.

8   Harris-Roberts J, Robinson E, Waterhouse JC, Billings CG, Proctor AR, Stocks-Greaves M, et al. *Sensitization to wheat flour and enzymes and associated respiratory symptoms in British bakers.* Am J Ind Med 2009;

52(2): 133-40.

9   Elms J, Robinson E, Rahman S, Garrod A. *Exposure to flour dust in UK bakeries: current use of control measures*. Ann Occup Hyg 2005; 49(1): 85-91.

10 Brant A, Berriman J, Sharp C, Welch J, Zekveld C, Nieuwenhuijsen M, et al. *The changing distribution of occupational asthma: a survey of supermarket bakery workers*. Eur Respir J 2005; 25(2): 203-8.

11 Droste J, Vermeire P, van SM, Bulat P, Braeckman L, Myny K, et al. *Occupational exposure among bakery workers: impact on the occurrence of work-related symptoms as compared with allergic characteristics*. J Occup Environ Med 2005; 47(5): 458-65.

12 Meijster T, Tielemans E, de PN, Heederik D. *Modelling exposure in flour processing sectors in the Netherlands: a baseline measurement in the context of an intervention program*. Ann Occup Hyg 2007; 51(3): 293-304.

13 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): 1211-7.

14 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): 327-34.

15 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): 23-9.

16 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): 825-33.

17 Silverberg IJ. *Racial and ethnic disparities in atopic dermatitis*. Curr Derm Rep 2015; 4: 44-8.

18 Jacobs JH, Meijster T, Meijer E, Suarthana E, Heederik D. *Wheat allergen exposure and the prevalence of work-related sensitization and allergy in bakery workers*. Allergy 2008; 63(12): 1597-604.

19 Houba R, van Run P, Heederik D, Doekes G. *Wheat antigen exposure assessment for epidemiological studies in bakeries using personal dust sampling and inhibition ELISA*. Clin Exp Allergy 1996; 26(2): 154-63.

20 Houba R, Heederik D, Doekes G. *Wheat sensitization and work-related symptoms in the baking industry are preventable. An epidemiologic study*. Am J Respir Crit Care Med 1998; 158(5 Pt 1): 1499-503.

21 Health Council of the Netherlands. *Prevention of work-related respiratory allergies. Recommended occupational exposure limits and periodic screening*. The Hague, 2008; 2008/03E.

22 Khodadadi I, Abdi M, Aliabadi M, Mirmoeini ES. *Exposure to respirable flour dust and gliadin in wheat flour mills*. J Occup Health 2011; 53(6): 417-22.

23 Ijadunola KT, Erhabor GE, Onayade AA, Ijadunola MY, Fatusi AO,

Asuzu MC. *Pulmonary functions of wheat flour mill workers and controls in Ibadan, Nigeria*. Am J Ind Med 2005; 48(4): 308-17.

24 Wagh ND, Pachpande BG, Patel VS, Attarde SB, Ingle ST. *The influence of workplace environment on lung function of flour mill workers in Jalgaon urban center*. J Occup Health 2006; 48(5): 396-401.

25 Health Council of the Netherlands. *Fungal alpha-amylase (derived from the fungus Aspergillus oryzae) - Health-based recommended occupational exposure limit.* The Hague: Health Council of the Netherlands, 2014; publication no. 2014/25.

26 Health Council of the Netherlands. *Flour dust from processed, de-hulled soybeans. Health-based recommendation on occupational exposure limits*. The Hague: Health Council of the Netherlands, 2016; publication no. 2016/07.

27 Gautrin D, Infante-Rivard C, Dao TV, Magnan-Larose M, Desjardins D, Malo JL. *Specific IgE-dependent sensitization, atopy, and bronchial hyperresponsiveness in apprentices starting exposure to protein-derived agents*. Am J Respir Crit Care Med 1997; 155(6): 1841-7.

28 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): 327-32.

annexes

A   epidemiological data published since 2004

Overview of studies with data on the relationship between exposure to wheat flour dust and the prevalence of sensitisation

Study design and population information	Exposure information	Health information	Results sensitisation
Cross-sectional: 1 US bakery (n=186) Page et al., 2009[6]; Page et al., 2010[7]	Two categories: lower-exposure (not handling dough, e.g. office, transportation, oven areas) and higher-exposure (handling raw materials and/or dough: e.g. bread & bun production, distribution) Full-shift air sampling (IOM sampler with Teflon filter, pore size 1 µm): personal breathing zone (n=83) and general area (n=19) **Inhalable flour dust** lower-exposure: 0.235 mg/m^3 (ND-1.4) higher-exposure: 3.01 mg/m^3 (trace-65) Wheat allergen concentration lower-exposure: 0.433 µg/m^3 (0.14-3.6) higher-exposure: 12.6 µg/m^3 (0.18-900)	Self-administered questionnaire on job history and work-related symptoms and smoking habits (n=161) Specific serum IgE antibodies to flour and wheat, and common allergens to assess atopy (n=96). The method was a highly sensitive enzyme-enhanced chemilumine-scent enzyme immune-assay, Immulite 2000. Traditionally, IgE levels ≥0.35 kU/L serum are considered positive for sensitisation. The threshold for this assay is 0.10 kU/L There was no difference in prevalence of atopy between the two exposure groups	Prevalence of **sensitisation** (Usually, specific IgE levels ≥ 0.35 kU/L are considered to indicate sensitisation. For the method used in this study, the cut-off value for a positive test is 0.10 kU/L (FDA-approved)): **flour dust exposure** 0.235 mg/m^3: 24% (12/51) 3.01 mg/m^3: 42% (19/45) PR 1.79 (95% CI 0.98-3.27) wheat allergen exposure 0.433 µg/m^3: 24% (12/51) 12.6 µg/m^3: 36% (16/45) PR 1.51 (95% CI 0.80-2.84) A number of employees working in lower-exposure group reported past work in higher exposure group; prevalence if these employees were included in the high-exposure group: **flour dust exposure** lower: 15% (5/33); current & past higher: 41% (26/63) PR 2.72 (95% CI 1.15-6.43) wheat allergen exposure lower: 15% (5/33); higher & past higher: 37% (23/63) PR 2.41 (95% CI 1.01-5.75) Prevalence of **sensitisation** (positive if IgE ≥ 0.35 kU/L): **flour dust exposure** lower: 6% (2/33); current & past higher: 21% (13/63) PR 3.40 (95% CI 0.82-14.20) wheat allergen exposure lower: 6% (2/33); higher & past higher: 27% (17/63) PR 4.45 (95% CI 1.09-18.12) Atopics were significantly more likely to be sensitised to wheat and flour at both cut-off values (*p*<0.01)

Cross-sectional: bakers (n=227) from 74 Belgian bakeries. Number of workers in industrial packers n=34; industrial bakers n=49; traditional pastry bakers n=37; traditional bread baker n=23; traditional bread+pastry n=84 Droste et al., 2005[11]	Personal inhalable dust and wheat allergen concentrations measured (PAS-6, during shift 5-7 h). Job/exposure categories (GM±GSD): low (industrial packers), medium (industrial bakers and traditional pastry bakers) and high (traditional bread bakers and traditional bread+pastry bakers) **Inhalable dust exposure** (GM±SEM) low: 0.53±1.14 mg/mL medium: 1.05±1.15 mg/mL high: 2.09±1.07 mg/mL Wheat allergen exposure (GM±SEM) low: 2.81±1.15 ng/mL medium: 8.13±1.23 ng/mL high: 16.34±1.14 ng/mL	Self-administered questionnaire on respiratory, asthma and allergy-related symptoms, supplemented with questions on smoking habits Skin prick testing on common and bakery-specific antigens (wheat flour, rye flour, fungal alpha-amylase) Lung function tests	Prevalence of **sensitisation**: wheat allergen exposure 2.81 ng/m³: 9.1% 8.13 ng/m³: 10.5% 16.34 ng/m³: 16.5% Intergroup difference not statistically significant: medium vs. low OR 1.4 (95% CI 0.3-5.7); high vs. low OR 1.9 (95% CI 0.5-7.5) Sensitisation to bakers' allergens (OR 5.9-95% CI 2.3-15.1) and atopy (OR 2.6-95% CI 1.2-5.5) were shown to be the best predictors of work-related symptoms; current dust exposure levels (medium exposure OR 4.7-95% CI 0.9-24.6; high exposure OR 9.4-95% CI 1.8-49.1) add only little to their prediction
Cross-sectional: UK bakers (n=225) from 22 bakeries: 140 general bakers, 31 mixer/siever/weigher, 7 cleaner and 47 other jobs Harris-Roberts et al., 2009[8]; Elms et al., 2005[9]	Job categories for flour dust exposure were based on the job group median concentrations from personal breathing zone dust exposure measurements (IOM samplers) in 208 workers from 55 bakeries in a previous study (Elms et al., 2005) **high exposure** (flour mixers/weighers/sievers, n=59): 5.2 mg/m³ (ND-30.6) cleaners (n=6): 4.4 mg/m³ (0.4-14.3) **medium exposure** (general bakers, n=108): 3.6 mg/m³ (ND-47.0) **low exposure** (others, n=35): 2.1 mg/m³ (ND-30.8)	Interviewer-led questionnaire on work-related respiratory symptoms, demographic details, work history and smoking habits; lung function assessment (n=225) Specific serum IgE (RAST assay) to wheat flour, enzymes and common allergens (n=160). Workers were categorized in 4 groups: not sensitised, sensitised to wheat flour only, sensitised to enzymes only, sensitised to wheat flour and any enzyme	Prevalence (%) of wheat flour specific **sensitisation** **low** (others, 2.1 mg/m³): 9.7% (3/31) **medium** (general bakers, 3.6 mg/m³): 5.0% (5/100); **high** (cleaners, 4.4 mg/m³): 0% (0/2); **high** (flour mixer/weigher/sievers, 5.2 mg/m³): 11.1% (3/27) Work-related **upper respiratory symptoms** were more common in atopic workers (OR 2.8, 95% CI 1.4-5.4) and in those sensitised to both wheat and enzyme (OR 13.9, 1.7-114.6) but not to wheat (OR 1.45, 0.42-4.99) or enzyme only Atopy was the most important risk factor for sensitisation to workplace allergens (OR 18.4, 5.3-64.3). Correction for atopy was not feasible. Among atopic workers smoking was a strong predictor of sensitisation to wheat or enzymes, corrected for duration of employment and current exposure category (OR 4.7, 1.1-20.8) *Comment*: The date of study conduct was not reported. Exposures were determined in 2002-2003 and may not be representative for later years
Cross-sectional: 197 employees of bakeries in Norway (n=6) Storaas et al., 2005[13]; Storaas et al., 2007[14]; Storaas et al., 2007[15]	Breathing zone personal dust samplers (n=58). Four exposure groups: <1.0 mg/m³ (packers, oven workers, administration); 1.0-1.9 mg/m³ (mainly confectionary workers, bread formers); 2.0-3.9 mg/m³ (mainly dough makers); >3.9 mg/m³ (mainly dough makers)	Interview focusing on occupational rhinitis (n=181) and self-administered question-naire on work tasks, family history, occupation-al symptoms, smoking habits and prevalence of allergy and atopic dermatitis/eczema (n=180)	Prevalence of **sensitisation** to cereal allergens (skin prick test / specific serum IgE): wheat: 4% / 11% rye: 1% / 10% barley: 3% / 8% oats: 1% / 5% Prevalence of sensitisation to storage mites was 20% (37/183)

	Allergy tests for occupational and common allergens (skin prick, total and specific IgE and histamine release, n=183)	Occupational rhinitis, IgE and non-IgE mediated, preceded lower airway symptoms and was associated with asthma symptoms. Storage mite sensitisation was related to occupational rhinitis and exposure
	Spirometry, bronchial provocation test with metacholine, nasal challenge and lavage	**Bronchial hyperresponsiveness** (BHR) was associated with smoking and work-related asthma. BHR, corrected for baseline lung function, was not associated with occupation-al IgE sensitisation (defined as positive to wheat, alpha-amylase, oats, barley, rye, soybean, storage mites, mold or cockroach). It is con-cluded that IgE sensitisation is not the main causative factor for airway hyperresponsiveness and occu-pational rhinitis in bakery workers.
	Categorisation of workers in job titles: dough makers, bread formers, oven staff, packers, confectionary workers, administration and cleaning 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
		A healthy worker effect cannot be excluded

Overview of studies with data on the relationship between exposure to wheat flour dust (expressed as concentration allergen) and the prevalence of sensitisation and respiratory symptoms

Study design and population information	Exposure information	Health information	Results sensitisation
Cross-sectional: Dutch bakers (n=860) from 341 traditional and 28 industrial bakeries Jacobs et al., 2008[18]; Meijster et al., 2007[12]	A dataset of personal breathing zone exposure assessments (full-shift, PAS-6 sampler) between 2000 and 2005 (details in Meijster et al., 2007) was used for estimating average and cumulative exposure to dust and wheat allergens (GM and range) avg. dust exposure (GM): 1.8 ± 1.7 mg/m^3 (range 0.3-7.3) cum. dust exposure: 30.5 mg/m^3 x yr (range 0.8-278) **avg. wheat allergen exposure** (GM): 12.8 ± 3.5 µg/m^3 (range 0.3-95.6) **cum. wheat allergen exposure**: 318.5 µg/m^3 x yr (range 1.0-4492)	Self-administered questionnaire on job history, history of respiratory, allergic, and work-related symptoms, symptoms suggesting bronchial hyper-responsiveness, medication use and smoking habits Specific serum IgE antibodies to wheat and common allergens to assess atopy	Prevalence (%) of **sensitisation** wheat allergen exposure (GM) 12.8 ± 3.5 µg/m^3 overall: 12% (107/859) nonatopics: 7% (38/572) atopics: 24% (69/288) Analyses included wheat allergen exposure only since the correlation between dust and wheat allergen exposure was very high Prevalence (%) of work-related symptoms and asthma in non-sensitised/sensitised persons: **Upper respiratory symptoms:** overall: 20/50; nonatopics: 16/42; atopics: 29/55. **Lower respiratory symptoms:** overall: 6/32; nonatopics: 5/26; atopics: 9/35. **Asthma**: overall: 6/35; nonatopics: 4/21; atopics: 11/42 Wheat sensitisation was strongest associated with lower respiratory symptoms and asthma (3.8-5.8 times more sensitised individuals reported these symptoms; 1.9-2.6 for lower respiratory symptoms). Atopics reported more frequently respiratory health symptoms (factor 1.3-2.8), but the association with sensitisation to wheat allergens was stronger than atopy

			Model calculations showed that in atopic workers, exposure to wheat allergens was associated with a higher frequency of wheat sensitisation and respiratory symptoms, increasing linearly up to an average wheat allergen concentration of 25-30 $\mu g/m^3$. At higher exposure levels, the exposure-response relation flattened and decreased (bell-shaped curve). This decrease, which has been explained as the "healthy worker effect", was not observed in non-atopic workers, who showed a very weak and not statistically significant exposure-effect relation. The exposure-response relation was strongest for the cumulative exposure, indicating that duration of exposure is also an important determinant
Cross-sectional (baseline measurements): 517 employees of 31 supermarket bakeries in South-Africa Baatjies et al., 2009[16], 2010[5], 2015[4]	Full-shift personal airborne dust was sampled (PAS6) in 18 bakeries on 2 days (n=211). Analysis for total mass and wheat and rye allergens by polyclonal AB-EIA Inhalable dust in each job category (GM±GSD): bread baker (n=112): .33±2.25 mg/m³; confectioner (n=38): 0.65±2.08 mg/m³; supervisor (n=13): 0.56±2.05 mg/m³; manager (n=13): 0.51±2.34 mg/m³; counterhand (serving customers, n=35): 0.28±1.89 mg/m³ **Wheat allergen** in each job category (GM±GSD): bread baker (n=112): 13.66±2.66 µg/m³; confectioner (n=38): 5.82±2.25 µg/m³; supervisor (n=13): 4.99±1.93 µg/m³; manager (n=13): 3.41±4.01 µg/m³; counterhand (serving customers, n=35): 1.16±4.81 µg/m³ **Rye allergen** in each job category (GM±GSD): bread baker (n=112): 5.14±2.89 µg/m³; confectioner (n=38): 2.04±2.41 µg/m³; supervisor (n=13): 1.74±1.97 µg/m³; manager (n=13): 1.99±4.06 µg/m³; counterhand (serving customers, n=35): 0.39±4.57 µg/m³ Note: inhalable dust concentrations were strongly correlated with wheat and rye allergen concentrations (Pearson r=0.84 and 0.86, respectively, p<0.001)	Self-administered questionnaire (n=517) on respiratory symptoms, employment history and job title, degrees of exposure to flour dust, baking activities at home and smoking habits Skin prick tests (n=507) to common and work-related allergens, including cereal flour allergens Wheat and rye specific serum IgE was measured by fluorescence EIA (n=513). A result >0.35 kU/L was considered positive Pulmonary function testing (spirometry and methacholine challenge, n=517). FEV_1/FVC and PD20 metacholine dose (≥20% decrease of FEV_1 during challenge test) were determined	Prevalence of **sensitisation** to wheat flour allergen (IgE-positive): all: 26% (134/513) atopics: 42% (90/213) nonatopics: 15% (44/294) atopic/nonatopic significant Prevalence of **sensitisation** to rye flour allergen (IgE-positive): all: 24% (123/513) atopics: 38% (81/213) nonatopics: 14% (42/294) atopic/nonatopic significant The authors did not present job-title specific prevalences for sensitisation. Exposure-response relations can therefore not be established. Relevant in this respect is that exposure assessment was done in 18 of the 31 bakeries Atopy prevalence was 42%, comparable with Brant et al., 2005[10] Correlation between long function and sensitisation to wheat flour (IgE-positive) was not very strong: PD20: Spearman r=-0.30 (p<0.001), independent of atopy status FEV_1/FVC: r: r=-0.15 (p=0.001) FEV_1: r=-0.07 (p=0.090) The prevalence of probable occupational asthma (defined as bronchial hyperresponsiveness and sensitisation to bakery dust allergens) was 13% (60/457). Among atopics and nonatopics, the prevalence was 22% and 7%, respectively. By including ex-bakers, the healthy worker effect was partially avoided in this study

In the 2015 paper, Baatjies et al. was submitted on the exposure-response relationships for average current wheat allergen exposure, specific sensitisation and respiratory symptoms. The authors found a bell-shaped relationship for symptoms, which they explained mainly to a healthy-worker effect. The prevalence reached a maximum up to 10 to 15 µg/m³, after which it levelled-off and decreased at higher exposure levels. Atopy modified the relationship, in that atopic workers showed highest effects

Overview of studies with data on the relationship between exposure to wheat flour dust (expressed as concentration dust) and the prevalence of sensitisation and respiratory symptoms

Study design and population information	Exposure information	Health information	Results sensitisation
Cross-sectional: 239 employees of in-store bakeries in UK super-markets (n=20) Brant et al., 2005[10]	Whole-shift personal inhalable dust exposure measurement (10 stores): bakers (GM): 1.2 mg/m³ (n=27); managers (GM): 0.5 mg/m³ (n=8); confectioners (GM): 0.3 mg/m³ (n=21); assistants (GM): 0.3 mg/m³ (n=33); total (GM): 0.5 mg/m³ (n=89) (Instead of a range of measured exposures, 2GSD values are reported) Job title was used as a surrogate for flour and amylase exposure in exposure-response analyses	Self-administered questionnaire on employment history and work-related respiratory symptoms (n=239) Skin prick tests to common allergens (n=233) and RAST assay for determining specific serum IgE to wheat flour and alpha-amylase (n=210) Atopy was evenly spread across the work groups.	Prevalence of wheat flour specific **sensitisation**: bakers (1.2 mg/m³): 27% (18/66) managers (0.5 mg/m³): 7% (2/28) confectioners (0.3 mg/m³): 2% (1/45) assistants (0.3 mg/m³): 4% (3/71) total (0.5 mg/m³): 11% (24/210) Prevalence of atopy was 41%, comparable with Baatjies et al., 2009[23]
Cross-sectional/case-control: workers (n=95) and unexposed office workers (n=95) from 8 wheat flour mills in Iran. Excluded were: smokers, workers employed less than 1 year, and subjects with previous lung and/or immune-deficiency disease history Khodadadi et al., 2011[22]	Breathing zone personal samplers for 8-h sampling of respirable dust (n=64) flour packing: 3.50±1.80 mg/m³ (n=26); husk packing: 2.53±1.18 mg/m³ (n=19); flour production: 1.72±0.92 mg/m³ (n=9); wheat unloading: 2.33±1.00 mg/m³ (n=10)	Total serum IgE and anti-gliadin-specific IgA and IgG. The report does not contain health information of the workers	Total serum IgE: exposed workers (n=95): 146.26±132.46 IU/mL; control subjects (n=95): 67.49±81.92 IU/mL
Cross-sectional/case control: production workers at 3 flour mills in Nigeria (n=91), other employees (internal control, n=30) and external control subjects (n=121), all males. Excluded were subjects with a history of chronic respiratory problems before current employment. Controls	Static breathing zone area samplers for total floor dust at two locations: shop-floor (production unit): 2.4±2.0 mg/m³ (range 0.6-4.7) maintenance workshop (internal controls): 0.4±0.3 mg/m³ (range 0.1-0.6)	Interviewer-administered questionnaire and lung function assessment (spirometer)	Prevalence (%) of long function abnormalities (FEV_1, FVC, FEV_1/FVC) non-smokers): production (n=75): 20%, 9%, 20% internal control (n=19): 0%, 0%, 11% external control (n=109): 7%, 2%, 2%

were of a similar socio-economic class and were matched for age, length and weight Ijadunola et al., 2005[23]			ex-smokers: production (n=12): 25%, 8%, 17% internal control (n=7): 14%, 0%, 14% external control (n=10): 20%, 10%, 10% Only the differences between non-smoking production workers and external control subjects were statistically significant
Cross-sectional: Indian flour mill workers (n=59) and a non-employee control group (n=54). All non-smoking Wagh et al., 2006[24]	Personal dust samplers (8-h PM10 sampling): 624±190 µg/m^3 (430-814)	Recording (undefined) of general characteristics (age, length, weight) and respiratory symptoms. Pulmonary function testing	Prevalence of respiratory symptoms controls (n=54): 5-16% flour mill workers (n=59): 19-42% (RR 2.3-3.6, AR 0.11-0.24) Prevalence (%) of long function abnormalities (FEV$_1$, FVC, FEV$_1$/FVC) control (n=54): 20%, 16%, 17% flour mill workers (n=59): 43%, 40%, 68%

Abbreviations: PD20: the administered dose of a substance in the inhaled aerosol which causes the FEV1 to fall by 20%; PR: prevalence ration; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity.

B   risk calculations

Additional analysis by the Netherlands Health Council DECOS, based on the papers by Houba et al. (1998)[20], Jacobs et al. (2008)[18] and Baatjies et al. (2015)[4]

The Health Council previously[1] used exposure-response relationships based on sensitisation and dust exposure from a study by Houba et al. (1998).[20] Since the publication of this study, two new studies were published which describe exposure-response relations. Exposure-response analyses are presented here and compared with updated analysis of Houba et al.[20]

Analysis using data from Houba et al. (1998)[20]

The data of Houba et al. has previously been used by the Committee for estimation of the risk of sensitisation by wheat flour dust. The Committee applied linear regression for that analysis. Here, the Committee reanalyzed the data using Poisson regression. In this study exposure-response relations were calculated for cumulative exposure, and based on duration of exposure recalculated to average exposure in the different exposure groups. The number of sensitised individuals per exposure group was estimated based on calculated prevalence ratio, in combination with the total number of participants in the study (n=246) and "equal group size" as reported by Heederik et al. (2001).[3]

Data used for Poisson regression analysis

Number of subjects	Sensitised	Estimated average dust exposure mg/m³
68	4 (5.9%)	0.13
69	5 (7.2%)	0.46
70	5 (7.1%)	1.03
69	10 (14.5%)	2.50
69	12 (17.4	7

Analysis using data from Baatjies et al. (2015)[4]

The paper describes exposure-response analyses for supermarket bakery workers of wheat allergen levels and different endpoints (wheat sensitisation, allergic chest symptoms, probable occupational asthma, etc.). For the purpose of this analysis the dataset from Baatjies was obtained with permission of the authors. Exposure response analyses were evaluated for estimated average exposure in each exposure category. The average exposure was measured on the job title level and average job title levels were assigned to all individuals in the study.

Data used for Poisson regression analysis

Number of subjects	Sensitised	Estimated average dust exposure mg/m³
43	4 (9.3%)	0.23
106	19 (17.9%)	0.33
111	33 (29.7%)	0.66
203	59 (29.1%)	1.41

Analysis using data from Jacobs et al. (2008)[18]

The study by Jacobs was undertaken as part of a health surveillance programme in the Dutch baking industry. A large population survey was included as a validation of the surveillance approach. For this population, information on sensitisation, atopy and respiratory symptoms were available. In addition, exposure assessment surveys were conducted which made it possible to characterize dust and allergen exposure of participants. For this analysis, results from the study by Jacobs et al. were produced by the first author with information on dust exposure instead of wheat allergen exposure (as used in the original publication). Exposure levels in this study at the low end of the distribution are higher than for the Houba study because of the inclusion of a higher number of traditional bakery workers.

Data used for Poisson regression analysis

Number of subjects	Sensitised	Estimated average dust exposure mg/m³
207	23 (11%)	1.2
210	23 (11%)	1.5
210	28 (13%)	1.8
209	33 (16%)	2.6

Comparison of risk estimates

The information from the tables above was analyzed by the Committee, as done earlier for other allergens,[25,26] in a Poisson regression analysis (see Figure 1). A baseline rate of 2.8% has been used[a], based on the studies by Houba et al. (1996)[19], Gautrin et al. (1997)[27], and Björnsson et al. (1996)[28] with in total 2,239 controls without known occupational wheat flour dust exposure of whom 62 were sensitised to wheat allergens.

---

[a] In 2004, the Committee used a background prevalence of 4%.

Of these exposure-response relationships, the slope estimates were obtained and subsequently used to calculate the exposure that corresponds to an extra risk of sensitisation of 1% using the formula:
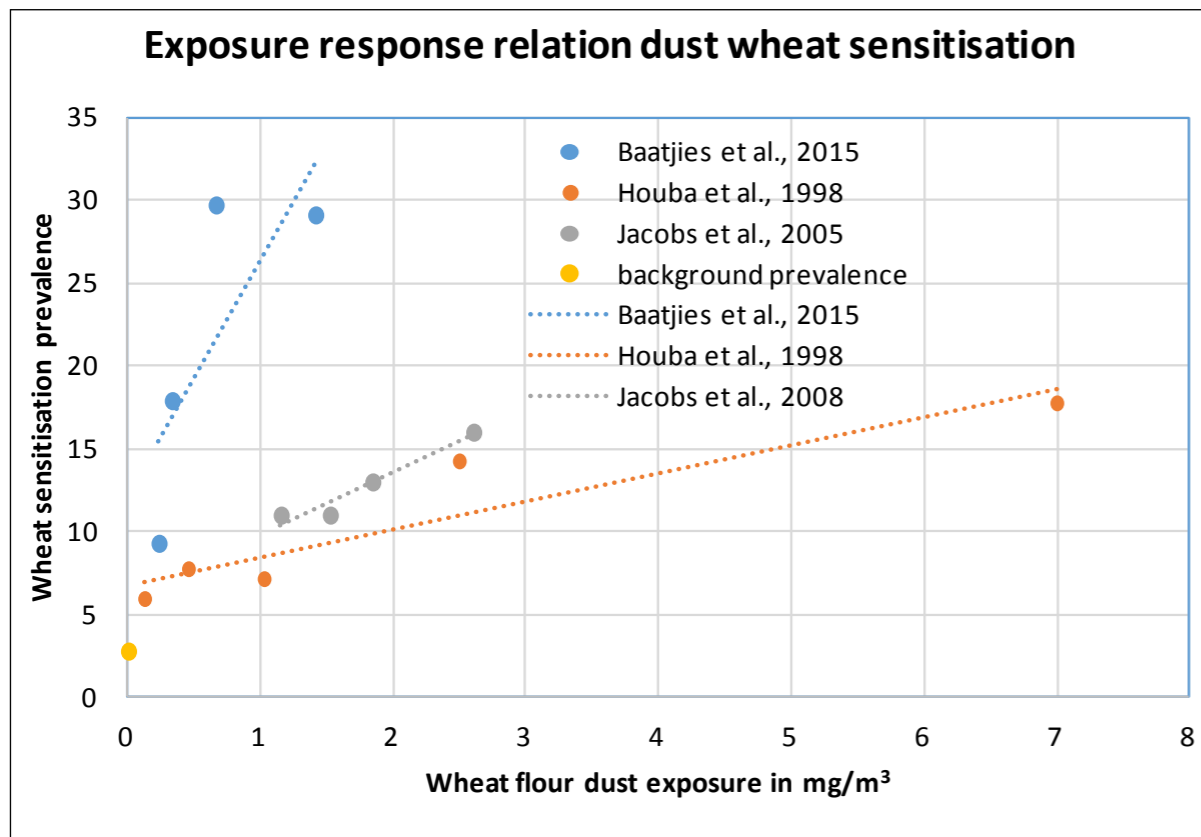
$$RR = 1 + [slope \times average\ exposure]$$

	Slope estimate	Standard error	p-value	1% excess risk
All three studies	3	0.24	<0.0001	0.12
Houba & Jacobs	1.97	0.22	<0.0001	0.18
Baatjies	8.9	0.95	0.0007	0.04
Houba	1.8	0.42	0.0077	0.20
Jacobs	2.03	0.25	0.0013	0.18

The steeper exposure-response slope of the Baatjies study could be explained by the high proportion of atopics in the study relative to the other two studies. Atopy is known to be more common in westernised native African and Asian communities. Because exposure-response relations are not linear in these studies, particularly in atopics (bell shape, see original papers), and not fully comparable (probably because of differences in the local context (healthy worker effect, job mobility)), a detailed comparison of exposure response relationships in atopics is not possible. However, in all three populations, the sensitisation risk is higher in atopics and ranges from 20-30%, dependent on the exposure level.

Exposure response relation dust wheat sensitisation

Legend:
- Baatjies et al., 2015
- Houba et al., 1998
- Jacobs et al., 2005
- background prevalence
- Baatjies et al., 2015
- Houba et al., 1998
- Jacobs et al., 2008

Y-axis: Wheat sensitisation prevalence
X-axis: Wheat flour dust exposure in mg/m³

Figure 1 Derived exposure-response relationships for wheat sensitisation, based on the studies by Houba et al. (1998)[20], Baatjies et al. (2015)[4] and Jacobs et al. (2008)[18]

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and the Environment, Social Affairs and Employment, and Economic Affairs. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.