Wheat and other cereal flour dusts

An approach for evaluating health effects from occupational exposure

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid
Postbus 90801
2509 LV Den Haag

Onderwerp : Aanbieding advies (tarwe)meelstof
Uw kenmerk : DGV/MBO/U-932542
Ons kenmerk : U 949/JR/459-R42
Bijlagen : 1
Datum : 10 augustus 2004

Mijnheer de staatssecretaris,

Bij brief van 3 december 1993, nr DGV/BMO/U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

In dat kader bied ik u hierbij een advies aan over meelstof, afkomstig van tarwe en aan tarwe verwante graansoorten. Dit advies is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Daarbij wil ik u het volgende laten weten.

Beroepsmatige blootstelling aan meelstof veroorzaakt onder andere specifieke overgevoeligheid (sensibilisatie) voor allergenen aanwezig in meelstof. De kans is groot dat personen die overgevoelig zijn bij voortdurende blootstelling allergische klachten ontwikkelen, zoals astma. Daarom heeft de Commissie WGD geprobeerd een advieswaarde af te leiden om het optreden van overgevoeligheid te voorkomen. De commissie heeft echter geen concentratie kunnen vaststellen waaronder *geen* overgevoeligheid optreedt. Dit betekent dat een gezondheidskundige advieswaarde in de gebruikelijke betekenis van de term niet kan worden afgeleid. Wel heeft zij gemeend het verband te kunnen afleiden tussen de kans dat een persoon overgevoelig zal worden voor meelstof en de concentratie van meelstof in de lucht op de werkplek. Dit de eerste keer dat voor sensibiliserende stoffen zo'n verband is gekwantificeerd.

Met behulp van deze afleiding kunnen voor verschillende kansen de bijbehorende luchtconcentraties worden berekend. Of en in welke mate de blootstelling in de bakkerij en

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 6631
E-mail: jolanda.rijnkels

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23
www.gr.nl

Gezondheidsraad
Health Council of the Netherlands

meelverwerkende industrie moet worden verlaagd, wordt bepaald door de als nog acceptabel te beschouwen kans op het ontwikkelen van overgevoeligheid. Het is niet aan de Gezondheidsraad om daarover een uitspraak te doen.

Wel wil ik u, op voorspraak van de Commissie WGD, in dit verband nog op het volgende attenderen. Naast klachten van immunologische aard (allergie) als gevolg van het optreden van overgevoeligheid, kunnen ook luchtwegklachten optreden van niet-immunologische aard (irritatie). Voor dit laatste type klachten zou in principe een gezondheidskundige advieswaarde kunnen worden afgeleid. Met de huidige beschikbare gegevens is dit echter niet mogelijk, omdat in het onderzoek vaak geen onderscheid is gemaakt tussen de immunologische en de niet-immunologische klachten. Uit diezelfde gegevens valt echter wel op te maken dat de luchtwegklachten, ongeacht de aard ervan, al optreden bij een blootstellingsniveau dat in de orde van grootte ligt van concentraties waarbij naar schatting 10 procent kans bestaat dat personen overgevoelig raken.

De bijzondere manier van risicoschatting heeft tot vele reacties geleid tijdens de openbare conceptfase. Daardoor heeft de afhandeling de nodige tijd gevergd. Daar tegenover staat dat dit advies een opstap kan vormen naar het nog voor te bereiden advies over de beoordeling van de risico's van sensibiliserende stoffen in het algemeen.

Ik heb dit advies vandaag ter kennisname toegezonden aan de Minister van Volksgezondheid, Welzijn en Sport en de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

Prof. dr JA Knottnerus

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 6631
email: jolanda.rijnkels

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23

Wheat and other cereal flour dusts

An approach for evaluating health effects from occupational exposure

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

to:

the minister and State Secretary of Social Affairs and Employment

No. 2004/02OSH, The Hague, August 10, 2004

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..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. 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.

This report can be downloaded from www.healthcouncil.nl.

Preferred citation:
Health Council of the Netherlands. Dutch Expert Committee on Occupational Standards. Wheat and other cereal flour dusts. The Hague: Health Council of the Netherlands, 2004; publication no. 2004/02OSH.

all rights reserved

ISBN: 90-5549-5219-8

Contents

Samenvatting *11*

Executive summary *19*

1 Scope *25*
1.1 Background *25*
1.2 Committee and procedure *25*
1.3 Data *26*

2 Identification, properties and monitoring *27*
2.1 Identification *27*
2.2 Physical and biochemical properties *28*
2.3 Validated analytical methods *30*

3 Exposure *33*
3.1 General population *33*
3.2 Working population *33*

4 Kinetics *41*

5 Effects *43*
5.1 Observations in man *43*
5.2 Animal experiments *62*

5.3 Other relevant studies *62*
5.4 Summary and evaluation *62*

6 Existing guidelines and standards *65*
6.1 General population *65*
6.2 Working population *65*

7 Hazard assessment *69*
7.1 Assessment of health hazard *69*
7.2 Groups at extra risk *74*
7.3 Health-based estimated additional sensitisation risk *74*

References *77*

Annexes *87*
A Request for advice *89*
B The committee *91*
C Comments on the public review draft *93*
D Background information on sensitisation *95*
E Selection of epidemiological studies suitable for risk estimation *97*
F Calculation of the estimated additional sensitisation risk *99*
G Abbreviations *103*
H DECOS-documents *107*

Samenvatting

Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in de lucht waaraan mensen beroe psmatig blootgesteld kunnen worden. Deze aanbevelingen vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grens-waarden, aangeduid als maximaal aanvaarde concentraties (MAC-waarden).

In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan meelstof afkomstig van tarwe en aan tarwe verwante graansoorten en presenteert zij luchtconcentraties die verbonden zijn aan de risico's van blootstelling. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór mei 2004 zijn verschenen.

Fysische en chemische eigenschappen

De commissie heeft meelstof gedefinieerd als meelstof van tarwe en aan tarwe verwante graansoorten (familie *Poaceae*, subfamilie *Festucoideae*), waaronder haver, gerst en rogge, welke ontstaat als gevolg van het malen of anderszins verwerken van dit graan. De aan tarwe verwante graansoorten zijn bij de risico-evaluatie betrokken, omdat zij kruisreacties kunnen vertonen, dat wil zeggen dat overgevoeligheid voor één soort meel-stof ook overgevoeligheid voor een ander soort meelstof geeft.

Buiten de definitie vallen andere graansoorten (o.a. boekweit), niet-graansoorten (o.a. sojabonen), en alle andere ingrediënten die aan meel kunnen worden toegevoegd (o.a. α-amylase (broodverbeteraar)). Een aantal van deze ingrediënten kunnen overigens dezelfde gezondheidseffecten veroorzaken als meelstof afkomstig van tarwe en aan tarwe verwante graansoorten.

Monitoring

De luchtbemonstering moet plaatsvinden gedurende de hele werkdag, zodat de persoonlijke hoeveelheid inhaleerbare stof over een achturige werkdag kan worden vastgesteld. In Nederland is het gebruikelijk de stofbelasting te meten met meetapparatuur bestaande uit een zogenaamde PAS6 monsternamekop, ten behoeve van het bepalen van inhaleerbaar stof, die eventueel gekoppeld kan worden aan een draagbare pomp.

Grenswaarden

In Nederland en Duitsland zijn geen grenswaarden voor meelstof vastgesteld of aanbevolen. In Zweden is een 'Level Limit Value' van 3 mg/m^3 (tijdgewogen gemiddelde (tgg) 8 uur) vastgesteld, en in het Verenigd Koninkrijk een 'Maximum Exposure Limit' van 10 mg/m^3 (tgg 8 uur) en van 30 mg/m^3 (tgg 15 minuten). De 'American Conference of Governmental Industrial Hygienists' heeft een 'Threshold Limit Value' voor inhaleerbaar (meel)stof van 0,5 mg/m^3 (tgg 8 uur) aanbevolen.

In alle bovenstaande landen, behalve in Nederland, is meelstof aangemerkt als een sensibiliserende stof.

Kinetiek

De kinetiek van meelstofdeeltjes in de longen wordt goed beschreven door depositiemodellen voor stofvormige luchtverontreiniging. Dit betekent dat de depositie van meelstof in de luchtwegen wordt bepaald door de grootte, dichtheid, vorm, en aërodynamische eigenschappen van deze deeltjes en door de ademhalingsinspanning. Voor de verwijdering van meelstofdeeltjes uit de longen zijn macrofagen en het mucociliaire systeem verantwoordelijk.

Effecten

Uit epidemiologisch onderzoek blijkt dat blootstelling aan meelstof kan leiden tot luchtwegaandoeningen, zoals rhinitis en astma, en oogaandoeningen, zoals conjunctivitis. Astma is een ernstige aandoening, die soms levensbedreigend is. Al deze effecten zijn

beschreven bij blootstellingen tussen de 2 en 5 mg/m^3 inhaleerbaar (meel)stof. Ook zijn er aanwijzingen uit de literatuur dat de effecten bij een lagere blootstelling kunnen optreden. Verder zijn er geen betrouwbare epidemiologische gegevens die kunnen bevestigen dat blootstelling aan meelstof tot neus- en longkanker zou kunnen leiden. Dit geldt ook voor de in de literatuur beschreven huidaandoeningen.

De hierboven beschreven luchtweg- en oogklachten kunnen zowel van immunologische (allergie) als van niet-immunologische (aspecifieke irritatie) aard zijn. De symptomen van allergie en irritatie lijken erg op elkaar, waardoor ze moeilijk van elkaar zijn te onderscheiden. Uitsluitsel kan worden verkregen door laboratoriumtesten, zoals het testen op de aanwezigheid van antistoffen gericht tegen meelstofallergenen in het bloed bij allergie. De gegevens van dergelijke laboratoriumtesten afkomstig van epidemiologisch onderzoek tonen aan dat een groot deel van de genoemde luchtweg- en oogklachten door allergie wordt veroorzaakt. Allergie ontstaat doordat na herhaalde blootstelling aan een allergeen, in dit geval één of meerdere eiwitten in meelstof, het immunologische afweersysteem overgevoelig wordt voor deze allergenen (sensibilisatie). Overgevoeligheid in deze betekenis verloopt zonder klachten; de betreffende persoon merkt er dus niets van, hoewel in het bloed meer antistoffen tegen meelstof (immunoglobuline E (IgE) antistoffen) aanwezig zijn dan normaal. Bij verdere blootstelling is de kans groot dat bij overgevoeligheid zoveel antistoffen worden geproduceerd, dat die immuunreacties uitlokken die klinische zichtbare luchtweg- en oogklachten geven, zoals rhinitis, conjunctivitis en astma. Er is dan sprake van allergie, die in tegenstelling tot overgevoeligheid wel met zichtbare klachten gepaard gaat. Personen die eenmaal overgevoelig zijn geraakt voor meelstofallergenen blijven dat in principe voor de rest van hun leven. Geschat wordt dat tot 28 procent van de mensen die werken in bakkerijen en aanverwante industrieën overgevoelig zijn voor allergenen in meelstof. In de algehele bevolking is dat getal 2 tot 4 procent.

In de afgelopen jaren is veel onderzoek verricht naar de relatie tussen blootstelling aan meelstof en het optreden van overgevoeligheid en allergie. De gegevens uit de verschillende onderzoeken zijn echter niet makkelijk onderling te vergelijken. Dit komt omdat de opzet van de onderzoeken zeer verschillend was. Zo zijn bijvoorbeeld niet alleen verschillende meetmethoden gebruikt, maar ook verschillende blootstellingsmaten (inhaleerbaar of respirabel stof, meelstof-allergenen in de lucht), en zijn verschillende effecten onderzocht (allergische en andere symptomen, specifieke overgevoeligheid). Verder kunnen de gegevens beïnvloed zijn doordat persoonsgebonden factoren, zoals atopie, niet afzonderlijk zijn onderzocht. Atopie is een erfelijke aanleg voor het ontwikkelen van allergie. Ook kunnen de gegevens beïnvloed zijn door het ‘healthy worker’ effect, dat wil zeggen dat werknemers met klachten ander werk zoeken. Dit laatste zou kunnen verklaren waarom in verschillende epidemiologische onderzoeken bij toename van de blootstelling het optreden van de klachten stabiliseerde of

zelfs afnam. Rekening houdend met deze verschillen en beïnvloedende factoren tonen de gegevens naar het oordeel van de commissie aan dat met toenemende stofblootstelling de frequentie van de klinische symptomen en overgevoeligheid voor meelstof toeneemt. Beneden inhaleerbare stofconcentraties van 3 mg/m^3 gedraagt de relatie zich praktisch lineair.

Uit meetgegevens blijkt verder dat blootstelling vaak een piekpatroon volgt, dat sterk gerelateerd is aan de taken die de werknemer uitvoert. Piekblootstelling kan een belangrijke rol spelen bij het ontstaan van overgevoeligheid, irritatie en allergie: preventie ervan zou het aantal klachten kunnen doen verminderen. Echter op dit moment is er nauwelijks wetenschappelijke documentatie over de invloed van de hoogte en frequentie van dergelijke piekblootstellingen in relatie tot het ontstaan van klachten in kwantitatieve zin.

Evaluatie en advies

Klachten veroorzaakt door irritatie verdwijnen als de blootstelling wordt verlaagd of stopgezet. Omdat dit niet het geval is bij allergie beschouwt de commissie allergie het kritische effect waarvoor mensen die beroepsmatig zijn blootgesteld aan meelstof beschermd dienen te worden. Omdat verder geen aanwijzingen in de literatuur bestaan dat (aspecifieke) irritatie optreedt bij lagere blootstelling dan allergie, baseert de commissie de risico-evaluatie van meelstof op het voorkomen van allergische symptomen van de luchtwegen, zoals allergische rhinitis en astma. Daarbij acht zij het van belang te voorkomen dat werknemers overgevoelig (gesensibiliseerd) raken voor meelstofallergenen, omdat overgevoeligheid een voorloper is van allergie, ook al krijgt niet iedereen die overgevoelig is daadwerkelijk allergische klachten. Een gezondheidskundige advieswaarde zou dan ook gebaseerd moeten zijn op het voorkomen van specifieke overgevoeligheid voor meelstofallergenen.

In zijn algemeenheid geldt dat een gezondheidskundige advieswaarde alleen kan worden afgeleid als uit de beschikbare gegevens een veilige drempelwaarde waaronder geen gezondheidsschade (meer) optreedt – het geen-waargenomen-nadelig-effect-niveau (NOAEL) – kan worden afgeleid. Voor meelstofovergevoeligheid lijkt dat niet het geval te zijn. De commissie heeft namelijk geen literatuurgegevens gevonden die erop wijzen dat onder een bepaalde drempelwaarde overgevoeligheid voor meelstof niet optreedt of althans niet wordt waargenomen. Dit betekent niet alleen dat de commissie geen gezondheidskundige advieswaarde kan afleiden, zoals gebruikelijk, maar ook dat volgens de commissie een volledige bescherming tegen het optreden van overgevoeligheid voor meelstofallergenen en dus tegen allergische symptomen niet mogelijk is. Wel meent ze concentratieniveaus te kunnen afleiden die een indicatie geven van een bepaalde extra kans op het overgevoelig worden voor meelstofallergenen. Uitgangspunt

hierbij is dat die kans evenredig is met de hoogte van de blootstelling aan meelstof, dat wil zeggen dat een hogere blootstelling een grotere kans op overgevoeligheid geeft. Verder spreekt de commissie van een extra kans, omdat deze kansen komen bovenop de kans van 2 tot 4 procent die iemand van nature heeft om overgevoelig te raken voor meelstof. Door deze benadering hoopt de commissie de betrokkenen een handreiking te geven voor adequate maatregelen om werknemers te beschermen tegen de gezondheidseffecten bij beroepsmatige blootstelling van meelstof in de lucht. Het is de eerste keer dat een dergelijke benadering wordt toegepast voor sensibiliserende stoffen.

Voor de afleiding van deze concentratieniveaus heeft de commissie een Nederlands onderzoek als uitgangspunt genomen. Dit onderzoek heeft gegevens opgeleverd over het verband tussen concentraties van tarwe-allergenen en inhaleerbaar stof in de lucht, en het optreden van overgevoeligheid voor tarwe-allergenen (IgE antistoffen in bloed) en gezondheidsklachten bij mensen werkzaam in bakkerijen. Bij toenemende blootstelling werd een toename van het aantal mensen met overgevoeligheid voor tarwe-allergenen geconstateerd. Verder bleek de relatie tussen overgevoeligheid en blootstelling in goede benadering lineair te zijn tot concentraties van tarwe-allergenen van ongeveer 10 $\mu g/m^3$, overeenkomend met concentraties van inhaleerbaar stof van ongeveer 3 mg/m^3.

Voor de afleiding van de beoogde concentratieniveaus heeft de commissie inhaleerbaar-stofconcentraties als blootstellingsmaat gekozen, omdat de meetmethoden voor inhaleerbaar stof gestandaardiseerd zijn en eenvoudig te gebruiken op de werkplek, in tegenstelling tot de niet-gestandaardiseerde meetmethoden voor allergeenconcentraties in de lucht.

Uit de onderzoeksgegevens leidt de commissie het volgende verband af: de geschatte kans op overgevoeligheid voor tarwe-allergenen (*AR*), uitgedrukt in procenten, is gelijk aan de inhaleerbare stofblootstelling (*D*), uitgedrukt in mg/m^3, gedeeld door 0,248 ($AR = D/0{,}248$). Dit verband is geldig voor het lineaire deel van de relatie, dat wil zeggen voor inhaleerbaar-stofconcentraties oplopend tot 3 mg/m^3. De commissie acht het verder nodig de inhaleerbaar-stofconcentratie te corrigeren met een factor van 2 voor de onzekerheid van het tarwe-allergeengehalte in inhaleerbaar stof. Daardoor ontstaat het volgende verband: $AR = D/0{,}124$. De commissie leidt hieruit af dat de concentratieniveaus voor inhaleerbaar stof bij beroepsmatige blootstelling gelijk zijn aan:

- 0,012 mg/m^3 bij een extra kans van 0,1% op overgevoeligheid voor tarwe-allergenen;
- 0,12 mg/m^3 bij een extra kans van 1% op overgevoeligheid voor tarwe-allergenen;
- 1,2 mg/m^3 bij een extra kans van 10% op overgevoeligheid voor tarwe-allergenen.

Deze inhaleerbaar-stofconcentraties zijn gemiddelde concentraties geldig onder normale werkomstandigheden van acht uur per dag en vijf dagen per week, gedurende een langere tot zelfs arbeidsleven omvattende periode.

Bovenstaande getallen geven aan dat iemand die voor het eerst beroepsmatig blootstaat aan tarwemeelstof, naar schatting een kans heeft van niet meer dan 1 procent om *ooit* overgevoelig te raken voor tarwemeelstof als gemiddeld de blootstelling 0,12 mg/m^3 inhaleerbaar stof is. Ze komt bovenop de kans van 2 tot 4 procent die iemand van nature loopt om overgevoelig te raken voor meelstofallergenen.

De wetenschappelijke literatuur bevat aanwijzingen dat het optreden van overgevoeligheid (en dus de kans) in de eerste jaren van beroepsmatige blootstelling hoger is dan in de latere jaren. Dit betekent waarschijnlijk dat door gebruik te maken van de hierboven gegeven getallen het risico voor (klachtenvrije) werknemers die al jaren in de werkomgeving aan tarwemeelstof zijn blootgesteld, enigszins wordt overschat en voor nieuwkomers onderschat. De beschikbare gegevens laten het echter niet toe om een betrouwbare kwantitatieve relatie tussen duur van blootstelling en het optreden van overgevoeligheid te bepalen.

Bovenstaande afleiding is gebaseerd op gegevens over overgevoeligheid voor tarwemeelstof. Tarwemeel is de meest gebruikte meelsoort in de Nederlandse bakkerijen en meelverwerkende industrie. Blootstelling aan meelstof van andere graansoorten komt veel minder voor. Uit de literatuur blijkt dat de allergenen in deze aan tarwe verwante meelsoorten onderling kruisreacties vertonen, dat wil zeggen dat overgevoeligheid voor één soort meelstof overgevoeligheid voor andere soorten meelstof kan veroorzaken. Daardoor is de commissie van mening dat de afleiding voor tarwemeelstof ook geldig is voor meelstof van aan tarwe verwante graansoorten.

Extra kans op overgevoeligheid

De Commissie WGD schat de extra kans op overgevoeligheid voor meelstof afkomstig van tarwe en andere verwante graansoorten op

- 0,1% bij een beroepsmatige blootstelling van 0,012 mg/m^3 inhaleerbaar stof;
- 1% bij een beroepsmatige blootstelling van 0,12 mg/m^3 inhaleerbaar stof;
- 10% bij een beroepsmatige blootstelling van 1,2 mg/m^3 inhaleerbaar stof.

Deze gemiddelde inhaleerbaar-stofconcentraties zijn concentraties geldig onder normale werkomstandigheden van acht uur per dag en vijf dagen per week, gedurende een langere tot zelfs arbeidsleven omvattende periode. De geschatte extra kansen komen bovenop de kans van 2 tot 4 procent die iemand van nature heeft om overgevoelig te raken voor meelstof.

De hoogten van deze kansen dienen als voorbeeld. Andere waarden kunnen daarvoor worden ingevuld. De bijbehorende concentraties inhaleerbaar stof kunnen simpel wor-

den berekend door gebruik te maken van de formule: $AR = D/0{,}124$. Deze formule is geldig voor inhaleerbaar-stofconcentraties oplopend tot 3 mg/m^3.

Tenslotte, naast klachten van immunologische aard (allergie) als gevolg van het optreden van overgevoeligheid, kunnen ook luchtwegklachten optreden van niet-immunologische aard (irritatie). Voor dit laatste type klachten zou in principe een gezondheidskundige advieswaarde kunnen worden afgeleid. Met de huidige beschikbare gegevens is dit echter niet mogelijk, omdat in het onderzoek vaak geen onderscheid is gemaakt tussen de immunologische en de niet-immunologische klachten. Uit diezelfde gegevens valt echter wel op te maken dat de luchtwegklachten, ongeacht de aard ervan, al optreden bij een blootstellingsniveau dat in de orde van grootte ligt van concentraties waarbij naar schatting 10 procent kans bestaat dat personen overgevoelig raken.

Executive summary

Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands sets Health-Based Recommended Occupational Exposure Limits (HBR-OEL) for chemical substances in the air in the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure, which leads to legally binding limit values.

In this report, the committee discusses the consequences of occupational exposure to wheat and other cereal flour dusts. The committee's conclusions are made on scientific papers published before May 2004.

Physical and chemical properties

The committee specified ‘flour dust’ 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 flour dusts from all of the above cereal grains, because they contain allergens that may cross-react. Therefore, exposure to one of these cereal flour dusts could result in allergic reactions, which are initiated by other cereal flour dusts.

Not included in this specification are flour dusts from other sources or grains, such as soybeans or buckwheat, and additives, such as fungal α-amylase, although the committee is aware that these compounds may cause the same kind of health effects as flour dust.

Monitoring

For assessing individual occupational dust exposure levels, air monitoring should take place during the whole working period (8 h TWA). In the Netherlands, monitoring inhalable dust is usually done with the Dutch 'PAS6' sampling head.

Limit values

The Netherlands and Germany have no specific limit value for flour dust. Sweden has recommended a Level Limit Value of 3 mg/m^3 (8-h TWA), and the United Kingdom a Maximum Exposure Level of 10 mg/m^3 (8-h TWA) and of 30 mg/m^3 (15-min TWA). The American Conference of Governmental Industrial Hygienists has recommended a Threshold Limit Value for inhalable flour dust of 0.5 mg/m^3 (8-h TWA).

All of the above countries, with the single exception of the Netherlands, have classified flour dust as a sensitising compound.

Kinetics

Overall, the kinetics of flour dust particles in the lungs follows the pattern of other solid aerosols of similar particle type. The deposition of particles in the lungs is determined by the particles' size, density, shape, aerodynamic properties, as well as by the volume of respiration. Macrophages and the mucociliary system of the lung are responsible for the clearance of flour dust particles.

Effects

A lot of epidemiological studies have shown that the main health effects of flour dust exposure are symptoms observed in the respiratory tract and the eyes, such as rhinitis, asthma (baker's asthma), and conjunctivitis. These effects have been demonstrated in bakery workers exposed to flour dust levels between 2 and 5 mg/m^3, but available data do indicate that these effects may occur at even lower levels. Some investigators related lung and nasal cancer to flour dust exposure. However, there is insufficient evidence that supports the view that exposure to flour dust could cause cancer. For the same reason, it is not clear whether flour dust exposure may cause dermatitis.

A main part of the work-related asthma and rhinitis have repeatedly and convincingly been shown to be of allergic origin, mediated by immunoglobulin E (IgE) antibodies to flour dust antigens. Up to 28% of the workers in the bakery and flour milling industry are sensitised against one or more of these flour dust allergens, whereas the background sensitisation incidence of the general population is estimated to be between 2 and 4%. Concerning non-IgE-mediated respiratory symptoms, these are probably caused by non-specific irritation responses.

In recent years, a lot of investigations have been performed on the dose-response relationships between airborne flour dust exposure and sensitisation or symptoms associated with sensitisation. However, different studies used different variables, which makes it difficult to compare their results. For example, some studies used inhalable or respirable dust as an exposure parameter, while others used airborne flour dust allergens. In some cases the effect parameter was allergic and/or non-allergic symptoms, in others it was specific sensitisation to wheat allergens. Furthermore, sometimes sources of bias were not taken into account, such as the presence of atopics, lack of knowledge of job history or healthy worker effect. The latter bias could explain why in several epidemiological studies the dose-response relationships levelled off at higher exposure levels, resulting in a lower relative risk at higher exposure levels. Despite these variations and the presence of confounding factors, most of these data showed an increased incidence of respiratory symptoms and specific sensitisation with increasing exposure levels. Below inhaled dust concentrations of 3 mg/m^3, this relationship appears to be linear.

Frequently, peak exposures have been observed, which are related to work activities. These peak exposures may play an important role in inducing work-related adverse health effects. This means that prevention of peak exposure might lower specific sensitisation, and allergic and other symptoms. However, at this moment, insufficient data are available to the committee on the influence of the height and frequency of these peaks on the dose-response relationship.

Evaluation

Based on the epidemiological data, the committee concludes that the symptoms observed in the respiratory tract and eyes are the health effects to be prevented. These symptoms may be caused by allergy or by (non-specific) irritation. The latter symptom is transitory, whereas allergy is not. Therefore, the committee considers the allergenic potential of flour dust as the critical effect of flour dust exposure. In addition, in the literature no indications are given that irritation is induced at lower exposure levels than allergy. For this reason, the committee based the risk evaluation on preventing allergic symptoms in the respiratory tract. With this respect, of particular importance is prevention of sensitisation to flour dust - although sensitisation per se is not an illness - because

sensitisation often precedes the onset of allergic symptoms. Moreover, because specific sensitisation to several flour dust allergens seems to be dose related, the committee is of the opinion that assessing a health risk based on sensitisation is justified. The committee is also of the opinion that a risk assessment based on sensitisation protects against other respiratory symptoms than the allergic ones.

In general, evaluations made by the committee should lead to a health-based recommended exposure limit for the concentration of substances in air. However, such an exposure limit cannot be derived if the toxic action does not show a threshold. The latter seems to be the case for flour dust. The committee did not find any indications in the literature for the existence of a threshold for flour dust sensitisation. This implies that complete protection against sensitisation to airborne flour dust allergens at low exposure levels cannot be achieved. However, the committee strongly believes that work-related sensitisation and clinical symptoms caused by flour dust exposure are important to control. Therefore, it used a 'non-threshold' approach, which is based on estimating additional risks for sensitisation associated with occupational exposure to flour dust. It is the first time that such an approach is used for sensitising substances.

A Dutch cross-sectional study is used as a starting point. In that study, data were presented on airborne wheat allergen concentrations, inhalable dust concentrations, specific wheat flour sensitisation (specific IgE plus total serum IgE ≥ 100 kU/L) and work-related symptoms. Both conventional categorical analyses and smoothed non-parametric exposure-response curves clearly showed an increased incidence with increasing exposure, which was linear till it levelled off at around 10 $\mu g/m^3$ airborne wheat allergen or 3 mg/m^3 inhalable dust. Concerning exposure data, the committee uses inhalable dust exposure levels in contrast to airborne allergen measurements, because dust measurements are standardised, validated and applicable for frequent measurements in the workplace.

From the Dutch data, the committee used a linear extrapolation method to propose a simple model to estimate additional sensitisation risk at lower exposure levels: the estimated additional risk to specific sensitisation (*AR*), expressed in percentages, equals to the inhalable dust exposure concentration (*D*), expressed in mg/m^3, divided by 0.248 ($AR = D/0.248$). This formula is only valid for exposure concentrations up to 3 mg/m^3, because only below this level the relationship showed to be linear. Furthermore, the estimated inhalable dust concentrations are corrected with a factor of 2 for the variable amounts of airborne flour allergens in dust. As a result, the final derivation becomes $AR = D/0.124$.

The estimated additional sensitisation risk for wheat flour dust is presented as the concentration inhalable dust with excess sensitisation risk of 1 per 1,000 (0.1%), 1 per 100 (1%) and 1 per 10 (10%) persons, as a result of occupational exposure, and amounts to:

- 0.1% for an occupational exposure to 0.012 mg/m^3 inhalable dust;
- 1.0% for an occupational exposure to 0.12 mg/m^3 inhalable dust;
- 10.0% for an occupational exposure to 1.2 mg/m^3 inhalable dust,

as a time-weighted average concentration under normal working conditions of eight hours a day and five days a week, during a life-long employment exposure.

These risk estimates suggest that a person, who starts working in the bakery or flour milling industry for the first time, has a chance of 1% for *ever* becoming sensitised to flour dust, if occupationally exposed to an average of 0.12 mg/m^3 inhalable dust. Furthermore, the estimated additional risk values are independent of the general background sensitisation incidence of 2 to 4 percent.

The committee likes to add that the available data do suggest that the risk to becoming sensitised is not equal during the lifetime working period. The risk is higher in the first years and becomes much lower in later years. However, a time-related exposure-response relationship cannot be defined, because data on the relationship between the time of exposure and the appearance of sensitisation are lacking.

The additional sensitisation risk is based on specific sensitisation to airborne wheat flour allergens. This is important, because in the Netherlands wheat is the most often used cereal in the bakery industry. Therefore, sensitisation to wheat flour is more prominent than sensitisation to other cereal flours. However, data from the literature suggest that allergens from other cereal flours may also cause allergy in the respiratory tract and eyes, and produce frequent cross-sensitisation. The committee did not find evidence of a different risk of these cereal flour dusts compared to wheat flour dust. Therefore, it is of the opinion that the estimated additional sensitisation risks for wheat flour dust may be generalised to other cereal flour dusts.

Additional sensitisation risk

The Dutch Expert Committee on Occupational Standards estimates that the additional sensitisation risk for wheat and other cereal flour dusts amounts to:

- 0.1% for an occupational exposure to 0.012 mg/m^3 inhalable dust;
- 1% for an occupational exposure to 0.12 mg/m^3 inhalable dust;
- 10% for an occupational exposure to 1.2 mg/m^3 inhalable dust,

as a time-weighted average concentration under normal working conditions of eight hours a day and five days a week, during a life-long employment exposure. The general population incidence of flour dust sensitivity of 2 to 4 percent is not included in these risk values.

The additional risk values used in the previous section serve as examples. Other excess sensitisation risk values may be used. The inhalable dust levels are simply calculated by using the formula: $AR = D/0.124$, which is valid for inhalable dust concentrations up to 3 mg/m^3.

Finally, the committee points out that due to flour dust exposure, not only immunological symptoms (allergy), but also non-immunological symptoms may occur. In principle, for the latter type of symptoms a health-based recommended occupational exposure limit could be derived. However, this is not possible, because most epidemiological studies did not make a distinction between immunological and non-immunological symptoms. However, the data from the epidemiological studies do indicate that symptoms, irrespective of their nature, do occur at exposure levels in the order of magnitude of concentrations, at which there is about 10 percent chance on getting sensitised.

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, at the request of the Minister of Social Affairs and Employment (Annex A). The purpose of the committee's evaluation is to set a health-based recommended exposure limit for the atmospheric concentration of the substance, provided the database allows derivation of such a value.

In the next phase of the three-step procedure the Social and Economic Council advises the Minister on the feasibility of using the health-based limit as a regulatory Occupational Exposure Limit (OEL) or recommends a different OEL. In the final step of the procedure, the Minister of Social Affairs and Employment sets the legally binding OEL.

1.2 Committee and procedure

This document contains the assessment of DECOS, hereafter called the committee, of the health hazard of wheat and other cereal flour dusts. The members of DECOS are listed in Annex B. The first draft of this report was prepared by D Heederik, R Houba and G Doekes, of the Wageningen University in the Netherlands.

In 2001, the President of the Health Council released a draft of the report for public review. In 2002 an update of the draft was released. The individuals and organisations that commented on the second draft are listed in Annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The committee's recommendations on the health-based occupational exposure limit of wheat and other cereal flours have been based on scientific data, which are publicly available. Data were obtained from the online databases Toxline and Medline.

The final search has been carried out in May 2004.

Finally, in annex G a list of abbreviations and symbols is given.

Chapter 2

Identification, properties and monitoring

2.1 Identification

2.1.1 Flour dust

In this report, the term ‘flour dust’ means dust coming from finely milled or otherwise processed cereal grains and is distinguished from grain dust, which is coming from unmilled flour and has other health properties.

Flour dusts from various cereal grains have been shown to induce allergic reactions (see chapter 5). Also they are known causes of allergic diseases in flour millers and bakery workers. Because the committee is of the opinion that sensitisation and allergic reactions are the critical effects to be prevented, the present evaluation includes only: those cereals known to induce sensitisation/allergy in humans; and, which are taxonomically related to the Poaceae family, specifically to the Festucoideae subfamily and Triticeae or Aveneae tribes. The common names for these cereals are wheat (*Triticum sp.*), rye (*Secale cereale*), barley (*Hordeum sp.*) and oats (*Avenea sativa*). Allergens present in these cereals have been shown to cross-react with each other, causing allergic sensitisation against each other (see below).

Flour from corn or maize (*Zea mays*) is not included in this report, because maize flour seems to show less cross-sensitisation with other cereal grain flours (Hei96; Kal78; Bal80). Furthermore, in studies in which workers were exposed to maize flour dust, only low allergenic potencies of the maize flour were found (Par98; Cri97).

A variety of flour dusts from non-cereal grains, such as soy (*Glycine hispida*) and buckwheat (*Fagopyrum escalentum*) are also identified as causes of allergy in the upper and lower airways. However, flour dust from these grains is not taken into account in this report, because they are not taxonomically related to cereal grains.

2.1.2 Additives

The dust in the bakery industry may contain several other ingredients used in the bakery process than dust from cereal flour, such as enzymes (*e.g*. fungal α-amylase, malt enzymes), chemical ingredients (*e.g*. preservatives, bleaching agents, antioxidants), flavourings and spices, and other additives (*e.g*. baker's yeast, egg powder, sugar) (Tik96). The committee is aware that these ingredients could contribute to the biological effects of cereal flour dust. For instance, fungal α-amylase is known to have sensitising properties (Bau86, Hou96). However, the present risk evaluation is restricted to flour dust from wheat and other cereals, because data were obtained from specific cereal flour dust sensitisation.

2.2 Physical and biochemical properties

Wheat is the primary cereal grain used in bread making in the Netherlands. Seeds are composed of endosperm (85%), husk (13%) and a germ (2%). The milling process separates the endosperm from husk and germ and reduces the particle size of the endosperm. From the endosperm wheat flour is made. This wheat flour contains starch and four different groups of proteins (water soluble albumin's, globulin's, prolamins (gliadin), and glutelins (glutenin)). Both gliadins and glutenins form viscous complexes, called gluten, which determine the structure and texture of bread to a great extent.

The proteins present in flour dust are potential allergens. The strongest allergic potency has been observed with water-soluble albumin fractions *in vitro* (Bal78; Pri85), but the allergic potency of gliadin, globulin and glutenin protein fractions should not be ruled out (Wal85). Overall, the number of potent dust flour allergens from these four protein fractions is large. In one study, 40 different allergens were identified by Crossed-Immuno-Electrophoresis (Bla76). Sander *et al*. (San01) reported that each patient in study showed an individual IgE-binding pattern with 4 to 50 different protein spots in the immunoblots. Furthermore, the authors found a big interindividual variation of IgE-binding patterns of wheat flour proteins. In addition, in sera of most sensitised bakers, IgE-antibodies were found which reacted with several of these flour allergens, although individual reaction profiles showed large variability (Sut84).

Attempts were made to identify the flour dust allergens. In general, most sera from sensitised workers reacted with allergens having a protein mass of 12-17 kDa (Góm90;

Pfe90; San90; San95). The mayor types of allergens of 12-15 kDa belong to the α-amylase/trypsin inhibitor family (Boi83; Frä94; Pos95; San94b; Wei97). Purified enzymes of this enzyme inhibitor family have been shown to be allergenic, both *in vitro* (San92; Frä94) as well as *in vivo* (Arm93), and this was irrespective of the cereal species used (Gar87; Men92; Ada95; Gar96). For instance, García-Casado *et al*. (Gar95) isolated a rye flour protein of about 13.5 kDa, as well as its barley homologue. The rye component was recognized *in vitro* by IgE of allergic patients and provoked positive responses in 15 out of 21 baker's asthma patients (71%) when skin prick tests were performed. Its barley homologue showed no detectable *in vitro* reactivity and caused positive responses in only one-third of patients. Moreover, a 14.5 kDa protein of barley, also belonging to this enzyme inhibitor family, has been associated with baker's asthma (Bar89). Allergens with a higher mass are also identified and have been characterised as homologous of cereal enzymes, such as acyl-CoA-oxidase (26 kDa), fructose-bisphosphate aldolase (28 kDa) and acyl-CoA oxidase, respectively (35 kDa) (Bau98a, Wei97, Pos95).

Some allergens from different cereals are chemically and functionally so closely related, that cross-reactivity occurs. For instance, Block *et al*. (Blo84) showed the existence of cross-antigenicity between different cereal grains, by using radioallergosorbent (RAST) inhibition tests. The degree of cross-reactivity closely paralleled their taxonomic relationship and appeared to be in the following order of decreasing closeness: wheat, triticale, rye, barley, oat, rice and corn. The allergenic activity in the rye and wheat extracts was found to be distributed among various fractions of different molecular weights.

Using the same RAST assay, Baldo *et al*. (Bal80) showed that the sera from subjects sensitised to wheat and rye flour reacted with seed extracts of 12 different cereals, for instance wheat, rye, barley, and oats. Wheat and its close relatives generally gave higher RAST figures than did other cereals. Fränken *et al*. (Frä91) described cross-reactivities between the low molecular weight allergens of wheat flour with a molecular weight of 15- and 17-kD and a main allergen of rye flour. Using *in vitro* test systems, Sanchez-Monge *et al*. (San92) suggested that members of the alpha-amylase/trypsin inhibitor family will also be shown to be allergens in rye flour as described for other cereal flours.

Sandiford *et al*. (San95) conducted RAST assays and gel electrophoresis using sera from patients with wheat-induced asthma to investigate the immunological relationship between wheat, rye, barley and soya, and to identify common proteins between these flours. RAST showed strong associations between the levels of specific IgE to wheat flour and those of rye and barley flour. Furthermore, wheat, rye, barley and soya flours contained cross-reacting proteins, in decreasing concentrations. Wheat, rye and barley flours had similar protein profiles on gel electrophoresis. The majority of cross-reacting allergens identified between the different flours have molecular weights similar to those of known flour enzymes or enzyme inhibitors.

Houba *et al*. (Hou96a) determined the specificity of wheat flour extracts by ELISA inhibition tests with other ingredients, which are frequently used in the bakeries. Extracts from closely related grain species showed some inhibition, suggesting cross-reactivity with wheat antigens. As judged from the protein concentrations required for 50% inhibition, the inhibitory capacities of barley, rye and oats extracts were approximately 10, 500 and 2000 times less than that of the wheat flour extracts, respectively. Extracts of baker's yeast, egg, and fungal alpha-amylase gave no inhibition.

Airborne flour dust particle sizes have been measured by several investigators. Lillienberg and Brisman (Lil94) showed a biomodal distribution of aerodynamic diameters of flour dust, using an IOM dust spectrometer. The smallest particles were around 5 μm, and the bigger ones around 15-30 μm. Over 50% of the particles had an aerodynamic diameter over 15 μm.

Using the IOM personal inspirable aerosol spectrometer, Burdorf *et al*. (Bur94) estimated that the thoracic fraction contributed 39% to the total mass of inhalable dust. The respirable fraction amounted to 19%.

Sandiford *et al*. (San94c) measured that approximately 9%, 52% and 20% of the airborne flour proteins were borne on particles ≤ 6 μm diameter in the bakery dough-brake, bakery roll-production and in the flour mill-packing areas, respectively. The investigators conclude that in dusty areas up to 20% of the airborne flour particles are of a diameter likely to allow them to be deposited in the bronchial airways and alveoli.

Sometimes malt flour, a dough improver, is added to dough. Malt flours contain potent allergens, which are probably related to cereal amylases (Hey83; Jor86; Wüt90).

2.3 Validated analytical methods

2.3.1 Environmental 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 to measure the inhalable dust fraction (Ken96). For determining the aerodynamic particle size of flour dust, personal air samplers can be used. 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. Most commonly, the particle size of flour dust ranges between less than 1 μm up to 200 μm in diameter (Hos86).

The allergen content of the dust can be evaluated by recently developed immunoassays (San94a, Hou96a, Wil97, Bur98), in which allergens bind to specific antibodies. In

short, Sandiford *et al*. (San94a) developed a method for measuring airborne wheat flour allergens in bakeries and flour mills, using polyclonal rabbit IgG-antibodies in a Radio-Allergo-Sorbent-Test (RAST). Houba *et al.* (Hou96a) developed a similar technique using an anti-wheat IgG_4 serum pool from bakery workers in an Enzyme Linked ImmunoSorbent Assay (ELISA). Both methods measure the total spectrum of allergens in wheat flour using the specificity of the reaction between antibodies and allergens. More recently, a method was developed which is more specific for one of the major allergens in wheat flour, the 15 kDa alpha-amylase inhibitor protein, using monoclonal antibodies (Wil97).

Although these techniques are extremely useful, the techniques are not yet standardised for routine monitoring, because until now different standard allergen preparations, antibody sources and different filters and solutions were used.

2.3.2 Biological monitoring

No validated methods for the determination of the amount of flour dust or allergens in biological samples were found.

Chapter 3

Exposure

3.1 General population

No studies have been published concerning exposure to flour dust in non-occupational settings.

3.2 Working population

3.2.1 Number of workers

Flours from cereal grains are used for human and animal consumption. Depending on the products made, exposure to cereal flour dust occurs in the flour milling and baking industry and sometimes in the animal food industry (Val88).

Table 3.1 shows an overview of the flour milling and baking industry in the Netherlands. Four main categories can be distinguished: flour milling, factories of bakery requisites (*e.g.* bread improvers), bakeries for bread production, and bakeries making other products (*e.g.* confectioneries). The table shows that in 1994, in these industries approximately 50,000 people were employed. However, these numbers also include administrative and commercial jobs. Assuming that in the Netherlands in the large facilities about 50% of all employees are involved in production work, and in the small facilities (<20 employees) about 75%, the population potentially exposed to flour and flour related products approximates 32,000.

Table 3.1 Types of industry and number of workers in the Netherlands.

type of industry	number of facilities	number of workers in industry
flour milling[a]	12	1,450
factories of bakery requisites[b]	14	1,200
cake, biscuit and rusk industry[c]	103	7,900
bread industry		
facilities ≥ 20 employees[d]	189	12,050
facilities < 20 employees	2,951	28,300
total	3,269	50,900

[a] Only facilities with ≥ 20 employees (CBS94a).
[b] Only facilities with ≥ 20 employees (CBS93).
[c] Only facilities with ≥ 20 employees (CBS94b).
[d] CBS94b.

3.2.2 *Dust levels*

Some early reports have presented stationary dust measurements (Ber76; Ber76; Wal80), but usually these measurements have not been considered very reliable for quantitative exposure assessment in occupational environments. The first measurements of personal samples from bakeries have been described by Hartmann (Har86), and since then several other studies have presented personal exposure levels (for a summary see Tables 3.2 and 3.3).

Summarised, bakers working in the dough making area (dough making and bread forming) usually were exposed to the highest dust concentrations with mean levels varying from 2.3 - 8.6 mg/m^3. Mean flour dust exposure levels of oven workers varied from 1.1 - 3.2 mg/m^3. Bakery workers involved in slicing and packing of the bread or other products usually were exposed to levels less than 1 mg/m^3. The committee noted that the sampling strategy and sampling equipment used varied from study to study. Sometimes essential information was not reported, such as information on sampled dust fraction and duration of sampling.

Two studies examined the variability in full-shift inhalable dust exposure levels more closely. In both studies, the type of occupation was considered as the most important determinant of dust exposure and the best way to categorize bakery workers into exposure groups for studying dose-response relationships (Nie95a; Hou97). In these studies, job title explained 43-50% of the variability in dust exposure levels. No important differences in dust exposure levels were found between the bakeries in both studies. In a Canadian study, however, a statistically significant association between the type of product manufactured and geometric means of full-shift inhalable dust as well as allergen exposure was found (Bur97, Bur98).

Few studies describe exposure levels in flour milling industry. Two studies, a German and a French one reported extremely high dust exposure levels. These have not been included in the table, because measurement techniques, sampled fraction nor sampling times were specified. The German study involved exposure data from 14 small mills and reported dust levels between 9 and 201 mg/m^3 (Ber79). Similarly high levels were reported in the study from France (Tay88). Furthermore, in a study from Sudan extremely high respirable dust levels between 20 and 160 mg/m^3 (n=14) were reported

Table 3.2 Levels of total (flour) dust in the workplace in the baking industry.

reference	sampling time (hr)	type of samplers	dust fraction	N	n	job title	concentration of dust (mg/m^3)		
							GM±GSM	AM±SD	range
Har86	3	-	-	31	-	all	-	-	0.2-19.8
Mas88	full-shift	PVC filters	total dust	56	49	all	1.7	-	0.1-8.0
Mus89	full-shift	Casella/Millipore	total dust	79	10	dough makers	2.7	-	0.6-14.1
					16	oven staff	1.7	-	0.0-37.6
Jef92	full-shift	7-hole ore Casella	inhalable and total dust	68	3	weighing/mixing	8.6±2.3	-	3.3-15.8
					16	dividing/moulding	4.7±2.0	-	1.6-19.1
Jau93	4-7	3-piece cassettes	total dust	20	13	making of dough	-	4.6±3.6	0.9-14.7
					7	making of bread	-	2.3±0.9	1.5-3.5
Kol94	full-shift	-	inhalable flour dust	1	38	all	-	4.9±9.1	-
Boh94	4	Millipore	total dust	21	14	general baker	-	3.4±3.7	0.7-8.7
					6	oven handler	-	1.1±0.9	0.5-2.7
Lil94	full-shift	IOM sampler	inhalable dust	29	6	dough mixing	7.5±5.4	-	-
					10	dough forming	2.5±0.8	-	-
					3	oven control	3.2±1.7	-	-
Bur94	1-7	IOM sampler	inhalable dust	129	34	dough makers	5.5±2.1[a]	-	1.2-16.9
					62	bread formers	2.7±2.01[a]	-	0.6-14.2
					10	oven workers	1.2±2.4[a]	-	0.2-4.0
Nie94	full-shift	7-hole	inhalable	352	24	dispense/	5.0±2.5	-	1.4-86.0
					32	mixing roll production	2.4±2.5	-	0.4-21.1
Hou96a	full-shift	PAS-6	inhalable	546	105	dough makers	3.0	-	0.4-37.7
					81	oven staff	0.6	-	0.1-5.1
Van96	full-shift[b]	Millipore		30	7	dough making	-	8.4	3.0-18.8
			total dust		10	bread making	-	3.2	1.2-5.5
Bur97	full-shift	7-hole	inhalable	96	-	bakers	2.1±5.1	-	0.1-110
Tal02	> 4	-	total dust	-	11	mixing and roll	2.1	-	0.5-6.6
					48	ovens area	0.6	-	0.1-1.6
					9	bread wrapping	2.3	-	0.2-12.6

- Not reported. Abbreviations: N = Total number of personal samples; n = number of samples in occupational title; AM±SD = -arithmetical mean ± standard deviation; GM±GSD = geometrical mean ± standard deviation. [a] GM and GSD could be biased, because of large variations in sampling time. [b] Sampling time varied between 2-4 hours, but several consecutive personal samples were taken to cover the whole working shift.

Table 3.3 Levels of total (flour) dust in the workplace in the milling industry.

reference	sampling time (hr)	type of samplers	dust fraction	N	n	job title	concentration of dust (mg/m^3)		
							GM±GSM	AM±SD	range
Awa86	4-8	horizontal two stage sampler Hexlett	total dust	-	-	plansifters room	-	3.6±1.6	-
						sacks room	-	3.5±1.6	-
						wheat cleaning	-	2.7±1.3	-
						rollers room	-	2.2±1.0	-
						packing area	-	1.6±0.8	-
						wheat store	-	1.4±0.1	-
Bac91	full-shift	37 mm cassettes	-	50	-	shovel/pack grain	-	17.6	0.8-96
						millers/silo, packing	-	1.3	0.4-2.4
Fak92	-	Bendix super sampler	respirable dust	7	237	several occupational titles	-	-	20-160
Kol94	full-shift	-	inhalable flour dust	11	121	all	-	10.1±12.7?	-45
Mas95	5-7	37-mm cassettes 11/min	approximates inhalable dust	83	-	reception work	27	-	8-58
						wheat crushing	4.8	-	1.2-27
						saking	14.3	-	1-76
						polyvalent	13.8	-	2.2-79
Tal02	> 4	-	total dust	-	11	unloading area	1.1	-	0.1-6.9
					6	grain cleaning	1.0	-	0.3-5.8
					6	flour mill	0.2	-	0.3-0.4
					15	packing area	2.2	-	0.1-8.7

- Not reported. Abbreviations: N = Total number of personal samples; n = number of samples in occupational title; AM±SD = arithmetical mean ± standard deviation; GM±GSD = geometrical mean ± standard deviation.

(Fak92). More detailed information comes from a South African study (Bac91). Average total dust levels ranged from 0.5 mg/m^3 (office workers) up to 1.4 mg/m^3 (millers), 3.5 mg/m^3 (cleaners and sweepers and bag handlers), and 17.6 mg/m^3 (shovel workers, grain packers). The study was based on a measurement series of 50 samples. Similar patterns of exposure were observed in a recently conducted French study (Mas95).

Overall, exposure levels seem higher in flour milling operations than in the baking industry.

3.2.3 *Airborne (wheat) flour allergen levels*

Nieuwenhuijsen *et al*. (Nie95c) reported on relationships between various measures of exposure in a longitudinal study of bakery workers and flour millers. Allergen content from air samples was measured using a competitive immunoassay with whole meal flour extracts and polyclonal rabbit IgG antibodies. Characteristics of the measures of exposure are given in Table 3.4.

Table 3.4 Characteristics of the measures of exposure (Nie95c).

measures of exposure	median	minimum	maximum
exposure duration (month)	26.0	1.0	70.0
average dust level (mg/m^3)	1.6	0.4	16.9
average allergen level (μg/m^3)	169.8	45.5	1,899.0
cumulative dust level (mg*month/m^3)	40.2	0.9	2,119.0
cumulative allergen level (μg*month/m^3)	5,307.0	170.5	169,937.0
peak dust level (mg/m^3)	8.6	0.5	97.2
peak allergen level (μg/m^3)	163.1	18.6	3,808.0

The investigators found no correlations between the duration of the exposure and peak and average exposure levels of dust and allergens. Moderate to good correlations existed between the various measures of exposures both for dust and for airborne flour allergens. Also, good correlations were found between exposure levels of dust and of airborne flour allergens.

Houba *et al*. (Hou96a) measured personal airborne dust (n=546) and personal wheat flour antigen (n=449) exposure in employees working in 21 different bakeries, during full-shift periods of 6 to 8 hours. Airborne wheat flour allergens were extracted from the filters of personal air samples. The concentrations of these allergens in the extracts were measured using an ELISA inhibition immunoassay and an anti-wheat IgG_4 serum pool. Characteristics of all personal dust measurements and its wheat antigen content are summarized in Table 3.5. Overall, in bakeries, large differences in personal airborne flour levels were found between occupational titles. The relation between dust exposure and wheat antigen exposure varied considerably, depending on the job title, the size of the bakery, and the type of product produced by the bakery.

Pater *et al*. (Pat02) took personal air samples to examine flour dust and flour allergen exposures during a full-shift period of at least 6 hours in a large Dutch study on the health effects of flour dust exposure in the bakery industry. The airborne wheat flour allergen content in the samples was determined by the same assay as in the study by Houba *et al*. (Hou96a). A summary of the measurement results is given in Table 3.6.

Furthermore, continuous registration of exposure levels showed that during the work shift peak exposures occurred frequently, whereas between those peak exposures almost no exposure took place. These peak exposures were related to work activities.

Overall, as for wheat flour dust exposure, the type of job appeared to be the most important determinant of exposure, in that higher exposure levels of allergen were measured among workers involved in milling and handling flour, emptying flour bags, mixing dough and cleaning. Workers involved in slicing and packing bread usually had lower wheat allergen exposures.

Table 3.5 Characteristics of all personal dust measurements and its wheat allergen content (Hou96a).

job category	personal dust exposure (mg/m^3)			personal wheat allergen exposure ($\mu g/m^3$)			mean ratio allergen/ dust[f]
	n	GM	range	n	GM	range	($\mu g/mg$)
total	546	1.0	0.1-37.7	449	0.7	0.03-252	1.5
large bakeries							
dough makers	105	3.0[a]	0.4-37.7	76	5.3[a]	0.03-252	2.9[a]
all-round staff	66	0.9[b]	0.1-26.8	54	0.9[c]	0.03-68	1.6[c]
oven staff	81	0.6	0.1-5.1	71	0.3	0.03-28	1.2
slicers and packers	132	0.4[a]	0.1-2.8	109	0.8[a]	0.03-8	0.4[a]
production managers	20	0.6	0.1-4.9	17	0.5	0.03-74.6	2.1[d]
maintenance and cleaning workers	27	0.7	0.3-5.5	20	0.2	0.03-2.5	0.6
small bakeries							
bread baker	36	3.3[a]	1.2-8.8	31	6.0[a]	1.3-53.3	2.0[e]
mixed baker	57	2.0[a]	0.3-14.2	55	2.7[a]	0.3-44.2	1.6
confectioner	22	0.7[a]	0.1-3.7	16	0.6[a]	0.03-3.8	1.6

n = number of measurements; GM = geometric mean. [a] Significantly different from all other job categories in large and small bakeries ($p<0.05$). [b] Significantly different from oven staff ($p<0.05$). [c] Significantly different from oven staff and maintenance and cleaning workers ($p<0.05$). [d] Significantly different from maintenance and cleaning workers ($p<0.05$). [e] Significantly different from confectioner's ($p<0.05$). [f] dust = inhalable total dust.

Table 3.6 Characteristics of all inhalable dust and wheat allergen measurements (Pat02).

type of industry	inhalable flour dust exposure (mg/m^3)			wheat allergen exposure ($\mu g/m^3$)			mean ratio allergen/ dust ($\mu g/mg$)[a]
	n	GM	range	n	GM	range	
traditional bakeries (n=55)	162	1.5	0.2-318	134	5.5	0.1-5,365	5.7
large industrial bakeries (n=16)	186	1.0	0.1-292	175	2.2	0.0-7,571	2.1
flour mills (n=6)	156	3.2	0.1-1,837	140	11.7	0.0-3,874	5.7
'raw material' industry (n=7)	128	2.0	0.0-627	114	4.0	0.1-1,517	2.6

n = number of measurements; GM = geometric mean. [a] dust = inhalable total dust; regression coefficients of 0.06 (R^2=99.6%), 0.04 (R^2=98.9%), 0.05 (R^2=59.5%), 0.12 (R^2=8.7%) for the small bakeries, large bakeries, flour mills and 'raw material' industry, respectively, all $p<0.001$.

The results of the airborne allergen measurements in the flour milling and baking industry should be interpreted with care for several reasons. Currently, not all wheat flour antigens are characterised and therefore some could be missed in the assays. Only recently more sophisticated immunoassays have become available (see chapter 2, section 2.3.1), which enable investigators to screen for a broad variety of wheat allergens. But most of these techniques still need to be standardised and validated. For this reason the measurement results of the study by Nieuwenhuijsen *et al.* (Nie95c) are difficult to compare with the results of Houba *et al*. (Hou96a) and Pater *et al*. (Pat02). Therefore, at this moment, the committee considers airborne allergen measurements inadequate for assessing a health risk of wheat flour dust exposure.

3.2.4 Relationship between inhalable dust and airborne flour allergen levels

In a few studies, the correlations between airborne wheat allergen and personal inhalable dust levels were evaluated. The correlations differed from one type of industry to another. For instance, the correlations obtained for traditional and industrial bakeries were 0.69 (Nie94), 0.85 (Bur99) and 0.99 (Pat02). In flour mills and 'raw materials' industry correlations of 0.77 and 0.33 were found, respectively (Pat02). Correlations were also shown to be dependent on job title (see variation in mean allergen/dust ratios in Tables 3.5 and 3.6). The differences in correlation and ratios are mainly explained by the presence of other additional dust sources than flour dust, as is the case in the 'raw materials' industry. These additional dust sources result in lower correlations. Furthermore, the committee observed that the correlations between the two Dutch studies (Hou96a and Pat02), in which the same monitoring and analysis methods were used, varied by no more than a factor of 2 to 4, and that the correlation of the Canadian study (Bur99) was within this range.

Chapter 4

Kinetics

Data on the kinetics of the dust particles described below are retrieved from Parkes (Par94) and partly quoted from Tikkainen *et al*. (Tik96).

The location where flour dust particles will most likely deposit is influenced by several factors. The particles' size, density, shape, aerodynamic properties, as well as the volume of respiration determine the deposition of the particles in the lung. In general, particles having an aerodynamic diameter of 5 to 30 μm are deposited in the nasopharyngeal region. Particles with lower aerodynamic diameters are deposited in the trachea, bronchial and bronchiolar region or in the alveolar region (≤ 1 μm). The American Conference of Governmental Industrial Hygienists uses the terms inhalable (≥ 10 μm, 100 μm cut-point), thoracic (4 -10 μm) and respirable (≤ 4 μm) particulate mass for Threshold Limit Values for particulates that may be hazardous when inhaled. Substantial amounts of flour dust particles are over 10 μm in diameter and, therefore, they remain in the upper respiratory tract. In dusty areas up to 20% of the airborne flour particles are of a diameter likely to allow them to be deposited in the bronchial airways and alveoli (San94c).

Macrophages and the mucociliary system are responsible for the clearance of flour particles from the lungs. However, heavy exposure may lower the ability of macrophages to eliminate particles, which may result in penetration of the dust particles into the interstitium. The individual characteristics of an exposed person are also of big importance in the development of disease.

Chapter 5

Effects

5.1 Observations in man

5.1.1 Irritation and sensitisation

Different types of cereal flour dust may evoke respiratory, dermal or conjunctival reactions in workers exposed to these agents. The most severe reaction is asthma, known as baker's asthma. However, other clinical symptoms have been described as well, such as rhinitis (with frequent sneezing, nasal obstruction and rhinorrhea) and conjunctivitis (with itching and inflamed, red eyes). Most of these symptoms are allergic in origin and are preceded by sensitisation of the worker (for a detailed discussion see annex D and section 5.1.4). The other part may be explained by (non-specific) irritation responses.

Concerning irritation, the symptoms of this non-immunological effect are similar to allergic reactions. Therefore, for interpreting the symptoms it is important to make a distinction between the non-immunological and immunological responses. In practice, symptoms are associated with irritation if immunological responses are ruled out, as shown in the studies described below.

Zuskin *et al*. (Zus94b) showed that most respiratory symptoms in a group of confectionery workers (n=71; mean exposure 11 years) were caused by irritation of the respiratory tract. In all these workers, skin prick tests were performed with food extracts (*e.g*. flour, wheat and rye, milk, cacao) and respiratory symptoms and smoking histories were recorded. Furthermore, blood samples were taken to determine the presence of total IgE. There was a high prevalence of acute symptoms (*e.g*. coughing, dyspnea, throat irrita-

tion) during the work shift, but no significant association with immunological tests was found. In another study, involving 344 workers from bakeries and mills, it was suggested that respiratory symptoms, measured by skin tests using wheat flour and α-amylase, might have resulted from direct irritation (Cul94). In both studies, these conclusions were made, because the authors could not correlate the results with immunological responses.

In a study performed in the Netherlands, 393 bakery workers were surveyed of which 23% reported work-related rhinitis and/or chest tightness, but in only 30% of this group (7% of all bakery workers) an immunological response to wheat flour or fungal α-amylase could be demonstrated (Hou96). Although the authors noted that the sensitivity of the immunological test (IgE-test) was not perfect and that there are also other potential bakery allergens that have not been tested, they consider a non-specific reaction to the dusty environment in the bakeries as one of the likely explanations for this finding. Most workers with work-related symptoms, but without an immunologic response (sensitisation) to wheat flour or fungal amylase, had IgE antibodies to non-occupational allergens (58%), had a history of allergic symptoms to common allergens (27%), or reported chronic respiratory symptoms outside the job environment (55%).

Smith and Lumley (Smi96) screened 3,450 bakery workers with a questionnaire. An overall prevalence of work-related asthmatic symptoms of 4.4% was found. After a closer examination by a physician, only 9% of this group had occupational asthma. The majority was thought to arise from irritation or aggravation of pre-existing asthma.

In a group of workers (n=679) from 18 different UK flour mills, the prevalence of respiratory symptoms and their relationship to sensitisation to wheat flour allergens and fungal amylases has been determined. Of the examined workers, 20.5% described upper respiratory tract symptoms of an occasional nature, which the investigators related to short-term exposures to high levels of dust. Only three individuals were identified as having symptoms due to wheat flour allergy. Of the workers, 1.2% was sensitised to wheat flour allergens (positive skin prick test). Furthermore, total inhalable dust exposure was measured for personnel exposed to flour dust at 10 different sites (116 samples). Median levels of 6.2 mg/m^3 were measured (range 1-10 mg/m^3; TWA 8 h) for production personnel and a median of 18.7 mg/m^3 for hygiene operatives. Overall, 43% of the samples taken exceeded 10 mg/m^3 (TWA 8 h). The authors concluded that the principal causation of symptoms experienced by the workforce were non-specific irritant effects related to short-term exposures to high levels of total inhalable dust (Smi00).

Brisman *et al*. (Bri98) examined 12 currently flour-exposed bakers in a cross-sectional study. They were tested for nasal symptoms, and their current and cumulative exposure to inhalable flour dust was estimated after exposure measurements. Personal inhalable dust measurements among bakers working as a dough maker or bread former ranged from 1.0 to 3.8 mg/m^3. Of the 12 bakers, 10 reported at least 1 nasal symptom, a

proportion significantly higher than that of the controls (office workers without occupational exposure to dust or any other known nasal irritant or sensitiser). Two bakers were sensitised to wheat. Closer examination of the nasal symptoms revealed mucosal inflammation. Furthermore, the investigators proposed that the inflammation might be non-allergic, characterized by the release of myeloperoxidase from neutrophils and of hyaluronic acid from fibroblasts and subsequent lymphatic oedema. The conclusion that exposure to inhalable flour dust may cause nasal inflammation, must be interpreted with caution, because the population studied was small and the observed relationship was considered to being influenced by the strong responses of the two sensitised bakers.

Overall, the present literature does not suggest that these 'irritant' effects occur at exposure levels below which an immunological response may be triggered.

5.1.2 Toxicity due to acute and short-term exposure

No relevant data are available about acute or short-term toxicity after occupational exposure to (wheat) flour dust.

5.1.3 Case reports

No case reports relevant for the present evaluation have been published.

5.1.4 Epidemiological studies

Prevalence of sensitisation against (wheat) flour allergens

Studies on the percentage of workers who are sensitised after exposure to (wheat) flour dust are listed in Table 5.1. As indicated in the Table, the prevalence rates for sensitisation varies between 5 and 28% among bakery workers. Similar or even higher prevalence rates have been reported for workers from flour mills (Fak92; Ber79).

Pavlovic *et al*. (Pav01) evaluated the prevalence of bronchial hyperreactivity in bakers, and correlated bronchial hyperreactivity with positive skin tests and atopy. One hundred workers (54 males and 46 females) employed in the former Yugoslav baking industry had to fill in questionnaires on their health and living conditions. They were also challenged with methacholine and flour by the bronchial challenge test and had to undergo a skin prick test with various work-related and environmental allergens. Eleven percent of the bakers scored positive in the bronchial challenge test with methacholine and 2% scored positive with wheat flour. The skin prick test was positive in 15% of the bakers. The prevalence of atopy was 18%.

Table 5.1 Sensitisation rates in bakery workers exposed to wheat flour (cross-sectional studies).

reference	n	skin prick test (% positive)	specific IgE test (% positive)	skin prick test used (extract concentration: criteria for positive test)
Her67	895	18%	-	Information not available
Thi80	29	21%	28%	Intracutaneous (0.1% wt/v; cut-off not known
Pri84	176	15%	-	Prick test (1mg/mL: 3mm)
Har85	292	6%	-	Intracutaneous (no details available). Bakers evaluated were non-symptomatic
Bau86	91	-	9%	
Mus89	259	5%	-	Prick test (-; 2 mm)
Jef92	205	-	24%	
Boh94	44	11%	-	Prick test (10 mg/mL: 1/2 pos. control
Cul94	344	5%	-	Prick test (10 mg/mL; 3 mm)
DeZ94	226	12%	-	Prick test (1 mg/mL; 3 mm)
Zus94b	71	12%	-	Prick test (0.05% wt/v; 3 mm)
Hou96	393	-	10%	
Smi97	383	6%	-	Prick test (1 mg/mL; 3 mm)
Hou98	169	8%	5%	Prick test (5 mg/mL; 3mm)

- Not reported. n = number of workers in the study.

In one recent study, the frequency of work-related symptoms and the clinical relevance of sensitisation to allergens in bakers have been investigated. In this study, three groups participated: a group (n=43) comprising subjects not working in bakeries; a group A (n=89) comprising bakery workers; and, a group B (n=104) comprising bakery workers filing a claim for compensation of baker's asthma. For sensitisation, a skin prick test with wheat, rye and other allergens was carried out, as well as blood analyses to the presence of specific IgE antibodies against wheat and rye. The test revealed that 0% (control), 16% (group A) and 47% (group B) scored positive for the skin prick test (wheal > 3mm) against wheat allergens, and 5%, 11% and 37% against rye allergens, respectively. In addition, 15% (control), 53% (group A) and 62% (group B) scored positive concerning the presence of IgE antibodies (> 0.35 IU/mL) against wheat allergens, whereas in respectively 10%, 34% and 50% of the subjects IgE antibodies were found against rye (Bau98b). Furthermore, the authors made a distinction between asymptomatic (n=45) and symptomatic (n=142) bakers, selected from group A and B. Bakery-associated symptoms included eczema, conjunctivitis, rhinitis and dyspnea. Of the asymptomatic bakers nobody responded positive on the skin prick test (wheat and rye), whereas 44% and 34% of the symptomatic bakers scored positive for wheat and rye allergens, respectively. Concerning IgE antibodies, 14% and 13% of the asymptomatic

bakers and 65% and 52% of the symptomatic bakers scored positive against wheat and rye allergens, respectively. The different outcomes between symptomatic and asymptomatic bakers differed significantly ($p \leq 0.0001$) on all the parameters measured (Bau98b).

Armentia *et al*. (Arm90) investigated the prevalence of bakers' asthma and sensitisation to various work-related allergens in the Northwest region of Spain. The total number of workers evaluated was 1,395, distributed among 454 factories (bakeries, pastry factories, animal feed). Of these, 139 workers showed symptoms of rhinoconjunctivitis and/or asthma, of which 35 showed allergic sensitisation to wheat flour. The major percentage of sensitisation (demonstrated by the skin prick test and specific IgE) was to wheat flour (100%), and in decreasing order to barley flour (48.6%), grass pollen (45.7%) and mites (28.6%). The investigators did not find positive reactions to gluten, alpha gliadin and alpha amylase. The average time of exposure for the onset of symptoms was 12.8 ± 9.6 years. In 57.1% of the population studied, onset of symptoms occurred after less than 10 years exposure to wheat flour.

Two studies give some idea whether workers in bakeries or mills have higher prevalence rates than the non-occupational exposed population. In one, Houba *et al.* (Hou96b) reported positive reactions in skin prick tests with a wheat extract in 2.1% of the 416 tested laboratory animal workers. The number of IgE positive workers in the population has been estimated to be approximately 6% (serum concentration of specific IgE against wheat flour allergen, >0.35 IU/mL) (Hee01). In the other study, Gautrin *et al*. (Gau97) found in a cohort of 769 apprentices starting career programs, that 1.2% and 4.1% of apprentices in animal health and dental hygiene, respectively, were sensitised to wheat flour compared to 5% of baker's apprentices.

These studies suggest that there is at least some background level of sensitisation in the general population. This background level may be explained by cross-reactivity among other (related) allergens, such as pollen (Gau97), in atopics, or by a lack of standardised methods for testing specific sensitisation.

Overall, the committee noted that the origin and concentration of the extracts used for skin prick testing differed among the studies. This could be explained by the absence of standardised extracts for flour dust allergens. This and the fact that for the skin prick tests various methods and cut-off time points were used, hamper a valid comparison of the study results. In spite of these differences, the available studies clearly show that immunological sensitisation to wheat flour is common in bakery and flour milling workers.

Prevalence of respiratory symptoms

In several epidemiological studies prevalence rates of respiratory symptoms were investigated in bakery workers occupationally exposed to (wheat) flour dust. The available data show that occupational-related respiratory symptoms are common (see Table 5.2).

Zuskin *et al*. (Zus98) investigated the respiratory function and immunological status in 53 flour-processing workers in a Croatian confectionary industry and in 65 unexposed control workers in the same industry. A high prevalence of chronic respiratory symptoms was recorded varying from 5.7% (occupational asthma) to 28.3% (chronic coughing) in flour workers (control workers, 0.0% and 6.2%, respectively). There was also a high prevalence of acute symptoms that developed during the work shift in flour workers, being highest for coughing (50.9%) and eye irritation (54.7%) (data on controls not presented). The prevalence of positive skin prick test with flour extracts in exposed workers was significantly higher in flour workers than in control workers (25.8% versus 12.3%; $p<0.01$). Increased total serum IgE levels were found in 18.7% of the flour workers (0.0%, control workers). In the flour processing area, the mean total dust was 12.3 mg/m^3 (range: 2.4-17.1 mg/m^3) and the respirable fraction was 1.9 mg/m^3 (range: 0.5-2.7 mg/m^3). These dust samples were taken over the entire work shift of 8 hours.

Concerning flour millers, investigators of two smaller studies, involving 63 exposed workers in an industrial flour mill (Tay88) and 25 asymptomatic flour miller workers (Kap89), reported no statistical differences in lung function compared to matched controls not working in the flour mill, although exposure related changes in bronchial hyperresponsiveness and lung function had been observed in flour millers by several other investigators (Bac91, Mas95).

Gimenez *et al*. (Gim95) compared the prevalence of respiratory symptoms, ventilatory impairment and variations in pulmonary function over a work shift, in a group of mill workers (n=142) exposed to wheat flour and in unexposed workers (n=37; controls). Concentrations of the inhalable fraction of airborne flour dust (11 samples at seven work stations) ranged from 5 mg/m^3 (bagging flour) to 54 mg/m^3 (cleaning sifters). The duration of sampling differed by operation: for bagging flour it was 157 minutes and for cleaning sifters is was 96 minutes. The concentration of respirable particles (aerodynamic diameter < 5 μm) was low and sometimes below the detection limit. Of the lung function values measured, only the peak expiratory flow rate and the forced expiratory flow rate at 75% of the forced vital capacity was significantly lower ($p<0.05$) in exposed workers compared to controls, both before and after the work shift. Workers with asthma (n=6) showed significant differences in lung function across the work shift. The prevalence of respiratory symptoms was significantly higher ($p<0.05$) in exposed workers compared to controls: any respiratory symptoms (56.3% versus 27.0%), usual

coughing (14.8% versus 0.0%), morning phlegm (12.7% versus 0.0%), usual phlegm (13.4% versus 0.0%). The authors cannot exclude a healthy worker effect.

Table 5.2 Prevalence of respiratory symptoms in occupationally exposed bakery workers.

ref.	country	type of bakery	n	participation rate	method used	prevalence of symptoms	remarks
Baa33	DK	22 SB	66	-	-	N 12%	Mill-workers excluded
Dis39	NL	LB, SB, C	152	100%	-	N 26%	
Lin47	SF	LB, SB, C	328	100%	-	N 18%, A 8%	
Pes55	S	5 LB, MB	159	-	-	N 26%, A 4%	
Gad56	DK	-	1,316	78%	-	N 15%, A 7%	Sensitised workers with symptoms
Ber76	Croatia	-	130	-	Q	N 30%, A 3%	Non-smokers
Jär79	SF	1 LB (b)	234	-	Q	N 23%, A 9%	Not necessarily work-related
Wal79	D	B	354	-	Q, CI	R 60%, A 35%, Br 30%	
		FM	25	-	Q, CI	R 40%, A 25%, Br 60%	
		grinding	58	-	Q, CI	R 20%, A 8%, Br 60%	
Thi80	BRD	-	29	-	-	N 21%, A 10%	Not necessarily work-related
Cha84	F	-	154	91%	Q	N 22%, A 5%	Not necessarily work-related
Pri84	AU	18 B	176	-	Q	N 19%, A 5%	Physician administered questionnaire
Har85	S	1 LB	314	-	Q	N 7%	No further definition symptoms given
Thi87	BRD	-	242	-	-	N 14%, A 7%	
Mus89	UK	1 LB	279	88%	Q	N 13-19%, A 7%	Self administered questionnaire
Ros91	F	B, 7 C	2088	-	Q	N or A 6%	
Jef92	UK	B	224	-	Q	N 21%, R27%	Physician administered questionnaire
Boh94	F	1 B	44	85%	Q	N 18%, A2%	Not necessarily work-related
DeZ94	I	105 SB	226	82%	Q	N 14%, A5%	
Cul94	UK	3 LB, 3FM	344	86%	Q	N 14-29%	
Zus94a	Croatia	1 C	78	85%	Q	N 14-41%, A 4%	Symptoms of flour exposed workers; confirmed by medical records
Zus94b	Croatia	1 C	71	-	Q	N 24-48%	Exposure to various agents
Sha95	S-Africa	-	63	-	Q	N 54%	
Hou96	NL	C, RB, L/SB	178	75%	Q	N 5-15%	Self administered questionnaire

Hou96	NL	C, RB, L/SB	393	75%	Q	N 7-21%	Self administered questionnaire
Smi96	UK	1 FM	3,45	-	Q	N 7%, A 4%	
Van96	SF	4 B, 1 CB	303	90%	Q	R and N: 14-17%	
Smi97	UK	19 B	385	99%	CI	N 3-17%, A 0.5%	
Bau98b	D	B	104	100%	CI	R 39%, D 37% (plus eczema 11%, conjuctivitis 20%)	lung functions tests, inhalative and methacholine challenge test

- Not reported. *Abbreviations:* A, asthma; B, bakery; Br, bronchitis; C, confectionery; CB, crisp bread bakery; CI, clinical investigation; D, dyspnea; FM, flour mill; LB, large bakery; MD, medium size bakery; N, nasal symptoms and non-specified symptoms; Q = questionnaire; R, rhinitis; RB, rusk bakery; SB, small bakery.

Most of the studies evaluated on the previous pages, have limitations, which hamper a good interpretation of the study results. Such limitations were, for instance, lack of information on used screening methods, type of questionnaire, the use of various definitions for symptoms, and no clear distinction between atopic and non-atopic status. Furthermore, it is well possible that results are underestimated, because it is likely that workers having clinical symptoms by flour dust exposure left the bakery trade at an earlier time and are thus missed (healthy worker bias). This source of bias may have influenced the results of the study by Talini *et al*. (Tal02), who stated that the prevalence of occupational asthma in their study (3%) was most likely an underestimation, not only because of the high drop-out rate in their selection steps (the specific bronchial challenge test with flour dust is carried out on a part of the selected subjects only), but also because the healthy-worker effect could not be excluded.

More reliable results on the prevalence rates of sensitisation and allergic symptoms are obtained from epidemiological studies with a cohort design. In such kind of studies, data are received by following subjects during a certain time period.

In 1956, such a cohort study has been carried out, in which 487 randomly chosen Danish bakers in Copenhagen were re-examined 5-6 years later (Gad56). Nineteen of them had developed wheat flour sensitisation and 7 had developed a wheat flour induced respiratory allergy. This suggests an incidence rate for wheat flour sensitisation of about 10 per 1,000 workers per year. For respiratory allergic symptoms, an incidence rate of 3-4 per 1,000 per year was found.

In another study, 880 bakers' apprentices were followed for 5 years (Her73). The percentage sensitised persons increased by year: 12% (2^{nd} yr), 19% (3^{rd} yr), 27% (4^{th} yr) and 30% (5^{th} yr), using skin prick tests for sensitivity testing. Symptom rates “compatible to allergic rhinitis or asthma” rose as well from 0.2% to 7% (3^{rd} yr), but then dropped to 4.8% (5^{th} yr). These data may have been influenced by the large drop-out, due to the fact that after having finished their apprenticeship, many young men left the workplace

and could not be traced anymore (start, 100%; 1st year, 74%; 2nd yr, 48%; 3rd yr, 33%; 4th yr, 11%; 5th yr, 4.2%).

A Swedish retrospective cohort study, carried out in 1959 and 1989, involved 2,226 persons trained as baker, and two external reference groups. One group comprised persons, who went to the same trade schools as the bakers, but followed another program in the trade schools (I; n=1,258). The second group comprised persons selected at random from the Swedish population register (II; n=1,258) (Bri95). Asthmatic bakers had changed work significantly more than referents (2.5% versus 1.1% (both reference groups), $p<0.05$). Incidence rates of asthma for men during employment as a baker was 3.0 cases per 1,000 person-years, compared to 1.1 and 1.9 cases for reference groups I and II, respectively. This indicates that the incidence of asthma attributable to being a baker was 1-2 cases per 1,000 person-years. The relative risk of asthma for male bakers during employment compared to referents was 2.7 (95% confidence interval 1.3-6.0; reference I) or 1.6 (95% confidence interval 0.82-3.1; reference II). When all reference groups were combined and compared to employed bakers, the relative risk to asthma was 1.8 (95% confidence interval 1.3-2.6). For female bakers, no differences were found compared to their respective referents. The authors estimated that male bakers have an approximately double risk to develop asthma.

Time of onset between exposure, appearance of specific sensitisation and allergic symptoms

Several studies among bakery students showed that sensitisation could occur within a few months after exposure to flour dust started. The prevalence rates in these populations varied from 3 to 8 % for wheat flour sensitisation and from 0 to 0.7 % for sensitisation to α-amylase (Gau97; Her67; Thi80). In one study, in which 144 trainee bakers and 81 students of a graphic artist course co-operated, positive skin prick tests to wheat flour (3.5%) and rye flour (0.7%) were found in bakers and not in the other students (DeZ95). In another study, the prevalence of positive wheat flour specific IgE tests in bakery students (after 4 to 20 weeks of exposure) was even 17% (total baker's apprentices was 258) (Pop94).

Cullinan *et al*. (Cul01) investigated the incidence of specific IgE sensitisation and allergic respiratory symptoms among 300 new UK bakery and flour mill workers, without previous occupational exposure to flour, during a follow-up for a median (range) of 40 (1-91) months. The accumulation of cases (*i.e.* positive skin prick test to flour or alpha-amylase, chest symptoms, eye symptoms and skin symptoms) by time since first employment was highest during the first 12 months of employment, and approximated 50% of the incident symptoms and positive skin tests. A total of 106 workers showed work-related symptoms: eye/nose symptoms (n=86, incidence 11.8 cases per 100 person

years (py), chest symptoms (n=36, 4.1 cases per 100 py) or skin symptoms (n=31, 3.5 cases per 100 py). Twenty-one employees were positive for the skin prick test to flour (2.2 cases per 100 py), and 24 to alpha-amylase (2.5 cases per 100 py).

Other studies have estimated the latency period for the development of respiratory symptoms by asking asthmatic bakers for the time since first exposure and the onset of first symptoms. The mean latency period for each study population varied from 4 to 13 years (Die55; Pop70; Jär79; Har85; Bri95; Smi96), and on individual levels this varied even more (months to >30 years). Some investigators suggested that the risk of baker's allergy is in particular high during the first couple of years of exposure, although this was not always confirmed by others (Bri95). In a British study, in which 264 bakery workers participated, the median duration of employment before onset of chest symptoms was 1 year (1 month - 4.2 year), and of eye and nose symptoms 0.5 year (1 month - 3.3 year) (Cul94). However, the results may have been underestimated, because bakers working in the trade longer than 4 years had been excluded.

De Zotti and Bovenzi (DeZ00) investigated work-related respiratory symptoms among 125 trainee bakers. A questionnaire plus skin prick test with wheat flour and α-amylase allergens was performed at the first day and then after 6, 18 and 30 months. The cumulative incidence of work-related respiratory symptoms increased from 3.2% (first day), 3.4% (6 mo), 4.8% (18 mo) to 9.0% (30 mo). The work-related symptoms were significantly associated with a personal history of allergic diseases (odds ratio 5.8 (1.8-18.2)) and skin sensitisation to wheat flour or α-amylase (odds ratio 4.3 (1.2-14.9)).

Overall, the study results illustrate that there is still little understanding of the relationship between length and intensity of exposure to flour dust and the development of sensitisation or respiratory symptoms. But, the available studies do suggest that sensitisation may occur soon after start of exposure, whereas it can take several years for symptoms to develop.

Dose-response relationships

Several studies investigated the relationship between the dose of flour dust or airborne allergen levels, and sensitisation, symptoms or both in bakery workers.

Musk *et al*. (Mus89) performed a cross-sectional survey of 279 bakery workers in a modern British bakery. Employment was categorized by perceived dustiness and ranked from 0 (no exposure) to 10 (highest exposure). In general, the ranking correlated well with the concentrations of inhalable dust obtained from personal air measurements, although there was residual variation within some exposure ranks (*e.g.* geometric means: rank 6 (staff attending ovens or in cooking areas), 1.7 mg/m^3 (range, 0.00-37.57); rank 10 (flour room staff, scone production staff), 6.6 mg/m^3 (range, 1.84-13.03)). All participants completed a self administered questionnaire on respiratory

symptoms. Furthermore, lung function (spirometry) and skin prick tests were performed. Fourteen participants had a positive skin test to mixed flour. Logistic regression analysis of a positive skin test to one or more bakery allergens was significantly associated with atopy (odds ratio, 16.3), a history of exposure in rank 6 or higher (odds ratio, 3.0 (range, 1.4-6.3 (95% CI)), and the number of years worked in the bakery (10-yr period: odds ratio, 1.8 (range, 1.5-2.8)). Of the participants, 13% reported work-related chest symptoms and 19% work-related nasal symptoms. The committee noted that statistical analyses were not made separately for each allergen from the work environment. Furthermore, possible associations between respiratory symptoms and exposure ranking or scores of the skin prick test were not presented.

Cullinan and his colleagues (Cul94) presented an initial cross sectional phase of a cohort study in three modern British bakeries. The survey included 264 workers from bakeries and flour mills, without a previous flour exposure. The participants were divided into three flour dust (<1 mg/m^3, 1-5 mg/m^3, >5 mg/m^3) or three wheat flour allergen (<101 μg/m^3, 101-225 μg/m^3, >225 μg/m^3) exposure categories according to job title. The prevalence of sensitisation to wheat flour extracts (skin prick test), tended to increase with intensity of dust exposure (low (2%), intermediate (6%) and high (5%) dust exposure (test for trend p=0.28), which was slightly clearer with wheat allergen exposure (1, 5, and 6%, respectively; test for trend p=0.099). In distinguishing atopics from non-atopics, non-atopics were only sensitised if exposed to the highest dose levels, whereas several atopics were sensitised at lower dose levels. Furthermore, atopics were more often sensitised to work-related allergens than non-atopics. The authors did not test for statistical significance, but multiple regression analyses (correcting for age, gender, smoking and atopy) did not reveal an independent effect of allergen exposure, probably because of lack of sufficient power (data not presented). The committee noted that no average exposure was given for the three exposure categories, and that relationships between exposure and symptoms were not stratified for atopic status or work-related sensitisation.

In 2001, Cullinan and his colleagues (Cul01) described a (nested) case-control analysis of the longitudinal phase of the same cohort. A total of 300 workers, who had never previously worked in this industry, were included in this analysis. Health information was obtained by a questionnaire. Furthermore, skin prick tests were performed using a prepared extract of five Canadian and British wheat flours. As in the previous study, participants were divided into three exposure categories (inhalable dust (geometric means in mg/m^3): 0.58 (low), 1.17 (medium), 4.37 (high); flour allergen (geometric means in μg/m^3): 65 (low), 144 (medium), 296 (high)). Mutually adjusted odds ratios and 95% confidence intervals derived from logistic regression analysis showed a clear increase in chest, eye/nose and skin symptoms by increased exposure. Furthermore, skin prick tests with extracts of wheat flour revealed an increase in positive scores by increasing expo-

sure (total dust exposure (OR, 95% CI): 1 (-, low), 5.0 (0.4-58, medium), 21 (1.2-363, high); flour allergen exposure (OR, 95% CI): 1 (-, low), 6.1 (0.5-71.0, medium), 14.0 (1-199, high)). The committee noted that the authors used the lowest exposure group as reference, and that these references were exposed to relative high concentrations.

Houba *et al*. (Hou98) conducted a cross-sectional study among 393 bakery workers from 21 bakeries to study the relationship between wheat allergen exposure and wheat sensitisation and work-related allergic symptoms. All workers completed a short self-administered questionnaire. From 346 workers, venous blood was taken and analysed for total IgE and specific IgE antibodies to common allergens and to wheat flour. Personal inhalable total dust samples were collected in the worker's breathing zone during full-shift periods of 6 to 8 hours. Wheat allergen exposure varied considerably among bakery workers, depending on the type of job and on the type of bakery (see Table 3.5 (Hou96a)).

For assessing a dose-response relationship, three wheat allergen exposure groups were formed according to job title, i) low (n=151, mean 0.2 μg/m^3, range 0.03-7.7 μg/m^3), ii) intermediate (n=120, mean 3.5 μg/m^3, range 0.03-74.6 μg/m^3), and iii) high (n=178, mean 11.0 μg/m^3, range 0.03-252.4 μg/m^3); the geometric mean total inhalable dust exposure levels for the three groups were, i) 0.46 mg/m^3 (low), ii) 0.78 mg/m^3 (intermediate), and iii) 2.37 mg/m^3 (high). The prevalence of wheat flour sensitisation (specific IgE plus total serum IgE ≥ 100 kU/L) in the three exposure categories increased from 4.4% (low exposed category), 7.8% (intermediate exposed category) to 14.1% (high exposed category). This category-related increase was steeper if only atopics were taken into account (25% (87/346) of the persons in study were atopic): from low to high exposed category: 4.6%, 11.8% and 22.9%, respectively. The prevalence of work-related symptoms (rhinitis and/or chest tightness) in relation to wheat allergen exposure increased from 15.4% (low exposed category), 23.4% (intermediate exposed category) to 28.7% (high exposed category). In the group of workers, who were sensitised to wheat flour (36/346), the prevalence ranged from 14.3% (1/7), 40.0% (4/10) and 52.6% (10/19), respectively.

Heederik *et al*. (Hee01) used the data of the previous study by Houba *et al*. (Hou98) to evaluate the presence of an exposure threshold using advanced statistical tools (non-parametric generalized additive modelling) and smoothed plots. Because from a statistical point of view it was better to use cumulative exposure levels than current or past exposure levels, categories of cumulative exposure were made. Cumulative inhalable dust and wheat allergen exposure was calculated as the sum of the products of job (arithmetic exposures) and duration of the exposure in that particular job title; the bakery workers had on average worked 11.7 years in the baking industry. For assessing a dose-response relationship five cumulative exposure groups were formed, of which the corresponding prevalence ratios of wheat allergen sensitisation are shown in Table 5.3.

Table 5.3 Dose-response relation between cumulative wheat allergen or inhalable dust exposure and prevalence of specific wheat allergen sensitisation in the whole population in study (n=346) (Hee01).

exposure group	cumulative wheat allergen exposure		cumulative inhalable dust exposure	
	average (SD) ((μg/m^3)×yr)	prevalence ratio (confidence interval)	average (SD) ((mg/m^3)×yr)	prevalence ratio (confidence interval)
1. low	0.7 (0.5)	1.0 (-)	1.5 (0.8)	1.0 (-)
2.	5.3 (3.0)	1.6 (0.4–14.0)	5.4 (1.7)	1.3 (0.3-4.7)
3.	22.4 (8.0)	1.7 (0.4-7.1)	12.0 (3.0)	1.2 (0.3-4.5)
4.	70.6 (2.4)	3.7 (1.0-13.3)	29.3 (8.2)	2.4 (0.8-7.7)
5. high	224.0 (109.0)	3.9 (1.1-13.9)	81.9 (39.3)	3.0 (1.0-9.2)
2 log likelihood		411.9		414.2

SD = standard deviation.

The sensitisation rates in the lowest cumulative wheat allergen and inhalable dust exposure categories were 4.4% (3/69) and 5.9% (4/68), respectively. These values can be considered as the lowest base-line sensitisation rates in the studied population. As was shown in the study by Houba *et al.* (Hou98), the prevalence ratios of wheat allergen sensitisation increased at increasing exposure levels and this increase was steeper for atopics than for non-atopics. However, differences between atopics and non-atopics were small, in particular at lower exposure levels. Furthermore, smoothed plots clearly levelled off at higher exposure levels resulting in a less steep dose-response relationship (Figure 5.1), and even in a reduction of the dose-response relationship for atopics and sensitised persons with apparent clinical symptoms, resulting in a decreased risk at higher exposure levels (Figure 5.2).

The authors suggested that this decrease in risk might be caused by the healthy worker effect, in which symptomatically sensitised workers change to jobs with no or low exposure risks. Furthermore, the authors concluded that the more advanced analysis models and the smoothed plots did not show any evidence of the existence of an exposure threshold.

The statistical analysis methods applied in the study by Heederik *et al*. (Hee01) suggest that atopics have an increased sensitisation risk of a factor of 2 ($e^{0.70}$=2; 0.70 is the coefficient of the model used to calculate the extra risk). Age and gender were not associated with wheat sensitisation risk.

In a large Dutch study, Oostenbrink *et al*. (Oos01) investigated in the bakery industry the prevalence of respiratory tract symptoms (rhinitis, asthma) and sensitisation to various work-related flour dust allergens. Participants underwent lung function tests and blood analysis, and completed a questionnaire. Of the 391 participants, 154 worked in traditional bakeries, 85 in large industrial bakeries, 83 in flour mills and 69 in the 'raw material' industry. In 11.5% of the workers, work-related asthma was found (disturbed

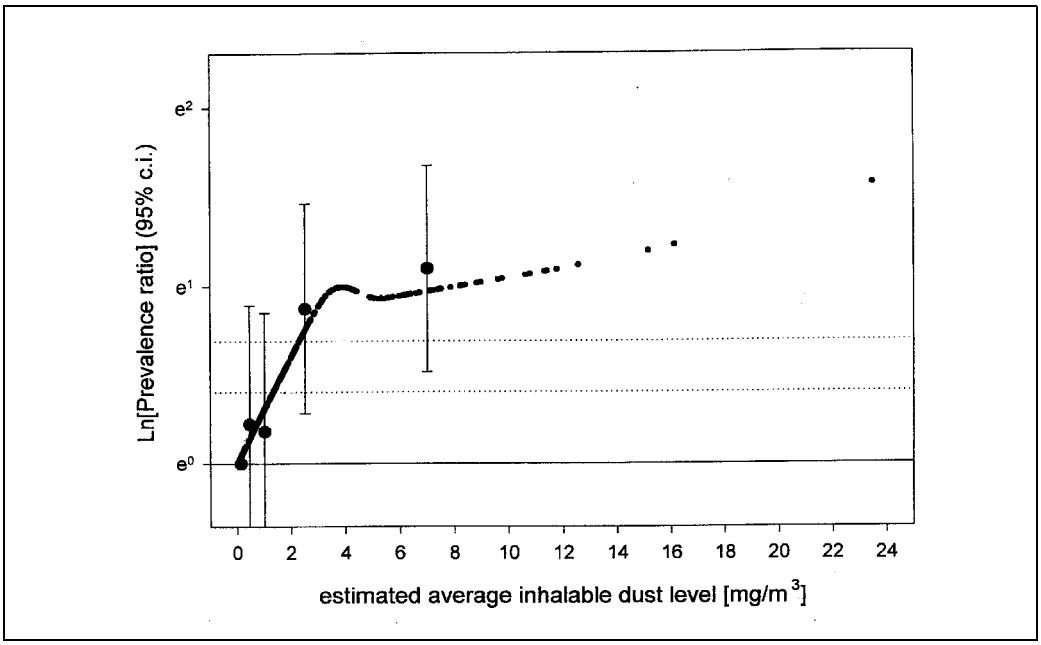

Figure 5.1 Dose-response relationship for estimated inhalable dust exposure with wheat specific sensitisation for the whole studied population (n=346). Adapted from Hee01.

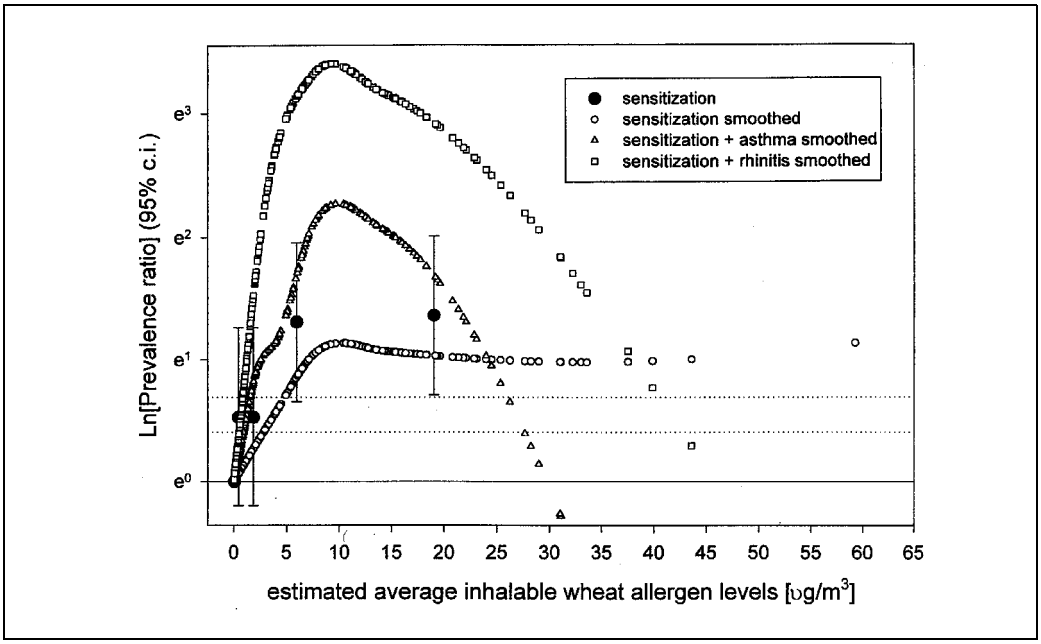

Figure 5.2 Dose-response relationship for estimated average inhalable wheat allergen exposure with wheat specific sensitisation (●,○) for the whole studies population (n=346) and for sensitisation accompanied by rhinitis (□) or asthmatic (△) symptoms. Adapted from Hee01.

lung function with or without medication/ rhino-conjunctivitis), and 8.2% of the workers suffered from work-related rhinoconjunctivitis (nasal or eye symptoms, normal lung function, no lung medication). Sensitisation to flour wheat allergens was found in more than 25% of the workers. Of these sensitised workers 52.3% had asthma, 33.7% rhinitis (without asthma) and 14.0% had no clinical symptoms. More details on the health effects of wheat flour exposure is given in Table 5.4.

Furthermore, the investigators categorised all workers in five exposure categories, from low to high exposure, to study exposure-response relationships for the whole study population (see Table 5.5). A significant relationship between exposure to wheat flour dust and sensitisation to wheat flour allergens (IgE class 1 or higher) was found. This relationship had a bell-shaped form, indicating that less workers were sensitised when exposed to high concentrations. Concerning symptoms, no association was found between the level of exposure and the presence of clinical visible symptoms.

Using the crude data of the previous study, Peretz *et al.* (Per03) analysed in more detail the relationship between exposure and specific sensitisation. For this, she and her colleagues used a 2-stage modelling approach (semi-parametric generalized additive modelling and a parametric logistic model), and combined actual measured exposure data with variance weighted estimates to reduce the effect of exposure measurement errors. With their analysis the authors confirmed that the overall exposure-response relationship seemed to be quadratic (bell-shaped). Overall, the risk for sensitisation increased with increasing exposure until about 2.7 mg/m^3 (inhalable dust) or about 25.7 µgEQ/m^3 (wheat allergens). However, when looking more closely to the data, the investigators found some heterogenic outcomes among the four sectors of industry. The quadratic relationship was strongly driven by data from flour mills, whereas in the other three industries the relationship was best described in between a linear or quadratic one

Table 5.4 Current exposure, work-related symptoms and sensitisation in bakery industry (Oos01, Pat02).

	Total	Traditional bakeries	Large industrial bakeries	Flour mills	'Raw material' industry
No. of workers	391 (100%)	154 (39.4%)	85 (21.7%)	83 (21.2%)	69 (17.6%)
Air exposure[b] (GM, range)					
- inhalable dust (mg/m^3)	2.7 (0.1-98.4)	1.5 (0.2-318)	1.0 (0.1-292)	3.2 (0.1-1,837)	2.0 (0.0-627)
- wheat allergen (µg/m^3)	30.0 (0.1-1,269)	5.5 (0.1-5,365)	2.2 (0.0-7,571)	12 (0.0-3,874)	4.0 (0.1-1,517)
Work-related symptoms					
- No symptoms (%)	80.3	16[c]	13[c]	2.5[c]	10[c]
- Asthma (%)	11.5	2[c]	21[c]	6.0[c]	16[c]
- Rhinoconjunctivitis (%)	8.2	18[c]	14[c]	2.3[c]	15[c]
Specific Sensitisation[a]					
- wheat flour allergens (%)	25.3%	18.8 (n=29)	38.8 (n=3)	16.9 (n=14)	33.3 (n=23)

[a] IgE class 1 or higher; [b] See also Pat02, GM, geometric mean;
[c] Data obtained from a graph, no absolute values given in original publication.

Table 5.5 Relationship between flour dust, wheat allergen exposure and the risk for sensitisation and work-related symptoms: all 4 sectors taken together (Oos01).

	No. of workers	IgE to wheat flour[a]		Symptoms (%)[b]		
		Positive (%)[b]	Odds ratio	Asthma	Rhinitis	Conjuncitivitis
Inhalable dust						
- < 1.6 mg/m^3 (low)	54	29	-	12	20	15
- 1.6 – 2.0 mg/m^3	102	31	1.04 (p=0.92)	16	23	19
- 2.1 – 3.5 mg/m^3	73	23	0.72 (p=0.42)	7	13	9
- 3.6 – 10.0 mg/m^3	51	26	0.81 (p=0.64)	14	19	13
- > 10.1 mg/m^3 (high)	111	20	0.59 (p=0.16)	10	16	8
Wheat allergen in air						
- < 13.4 µg/m^3 (low)	80	24	-	7	12	8
- 13.4 – 16.0 µg/m^3	84	32	1.52 (p=0.23)	17	23	19
- 16.1 – 36.0 µg/m^3	71	19	0.79 (p=0.55)	4	15	11
- 36.1 – 106.0 µg/m^3	50	36	1.81 (p=0.55)	18	24	16
- > 106.1 µg/m^3	106	20	0.79 (p=0.52)	8	15	8

[a] IgE class 1 or higher; [b] Data obtained from a graph, no absolute values given in original document.

(see Figure 5.3). Concerning the flour mill sector, the authors noted that the population characteristics in this sector differed from the other sectors; workers in this sector were exposed to the highest flour dust concentrations (see Table 5.4), whereas the number of atopics and sensitised workers was the lowest (atopy: traditional bakeries, 64%; industrialised bakeries, 55.0%; bakery ingredients industry, 50.3%; flour mills, 26.3%).

According to the authors, the quadratic relationship suggest that selection bias (healthy worker effect) or immunological tolerance could have occurred. However, the committee thinks that selection bias played a more important role, because a lowered risk at higher exposure was not observed in the other three sectors at the same exposure range. In addition, the population characteristics in the flour mill differed from the other three sectors.

Beside the previous findings, analysis of the data revealed also that being atopic was a strong determinant for sensitisation (50.6% (atopics) *versus* 16.1% (non-atopics)).

In a Swedish retrospective cohort study, Brisman *et al*. (Bri00) investigated the exposure-response relationship between estimates of inhalable dust exposure and the incidence rates of asthma and rhinitis, among 2,226 bakers and two control groups (n=931 school controls; n=930 population controls). Information on the diseases and the exposure was obtained from a postal questionnaire. From a previous study performed by the same authors and experiences from working conditions in bakeries, Brisman *et al*. distinguished three current estimated exposure categories, namely 1, 3 and 6 mg/m^3 inhalable dust for the different combinations of the reported job-tasks. Also three different

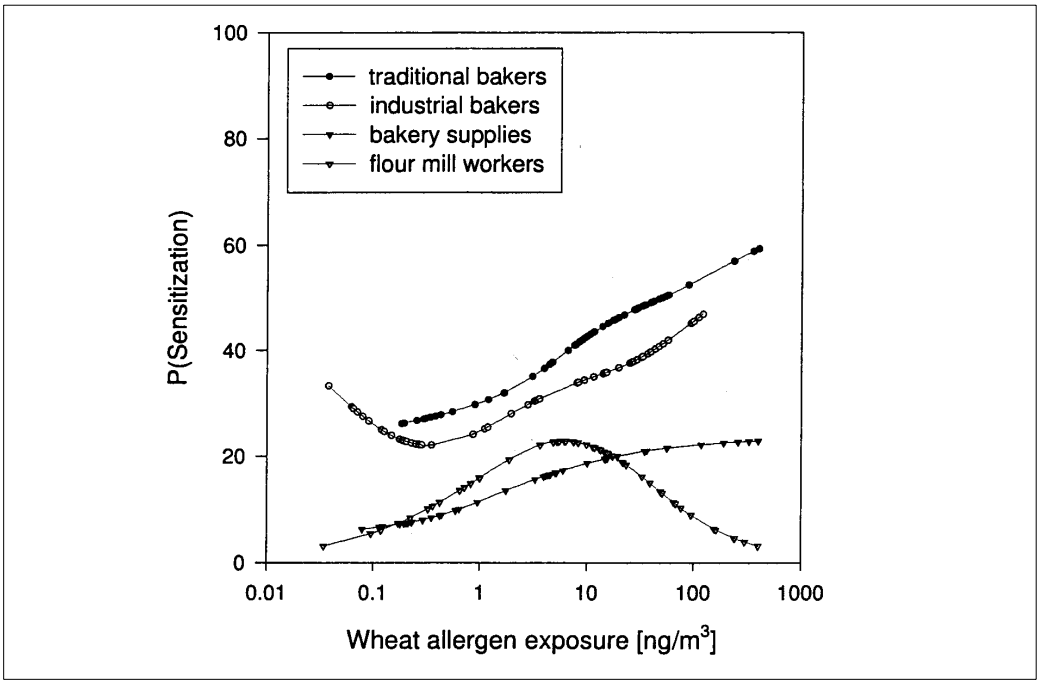

Figure 5.3 Probability for sensitisation (P) as function of exposure to wheat allergens (logged µgEQ/m^3). Results for dust exposure were similar (not shown). Figure attained from Per03.

cumulative exposure groups were established: 1-9, 10-29, and ≥ 30 mg/m^3 years. The incidence rate of asthma in men increased by current exposure at time of onset from 0.5 to 7.3/1000 person-years in men (*p* for trend 0.001). No significant increase was observed in women (*p*=0.60). The incidence rate of asthma increased non-significantly by cumulative dose from 2.3 to 4.8 cases/1000 persons-years in men (*p* for trend 0.15) and from 2.0 to 5.5/1000 persons-years in women (*p* for trend 0.82). The incidence rate for rhinitis increased by current exposure at time of onset from 18.8 to 43.4 cases/1000 person-years in men (*p* for trend 0.0004) and from 29.6 to 38.5 cases/1000 person-years in women (*p* for trend 0.65). No significant increases were observed by cumulative dose, either in men (*p* for trend 0.09) or in women (*p* for trend 0.48). The authors concluded that "the risk for asthma and rhinitis was increased by current exposure to dust at the onset of disease. This indicates that mean concentrations of inhalable dust should be < 1 mg/m^3 to prevent rhinitis and < 3 mg/m^3 if only asthma is considered".

Controlled clinical studies

A few studies have been performed in which volunteers were exposed to flour dust under controlled laboratory conditions. One has been carried out to investigate the relationship between specific bronchial reactivity and respective non-specific bronchial and

immunological reactivity (Cho99). Patients (n=21; all males except one; all reported work-related symptoms of asthma) were challenged to 3.0±0.2 mg/m^3 wheat flour in an inhalation chamber for several periods. The duration of the nine inhalation periods was increased in a step-wise manner (15 s, 30 s, 1 - 2 - 5 - 15 - 20 - 30 and 30 min; cumulative duration 104 min). Each period was separated from the following period by an interval of 10 min. FEV_1, FVC and PEF were measured 1 to 10 min after each inhalation period. The test was stopped if FEV_1 decreased by 20% or after 104 min of exposure. Furthermore, the patients were given a peak flow meter or an electronic device that recorded PEF and FEV_1 for 24 h following the last exposure period. Three groups of patients were identified according to specific bronchial reactivity: a high reactivity group (n=9; >20% decrease in FEV_1), an intermediate reactivity group (n=5; <20% decrease in FEV_1, but still above base-line value) and a negative group (n=7).

In another study, the results have been collected of 160 specific inhalation challenges (SIC) with wheat flour, performed in six Italian laboratories. Patients with suspected baker's asthma were exposed in an exposure chamber for a maximum of 30 min or stopped earlier if the FEV_1 decreased by at least 20% with respect to the base-line value. After the end of exposure, FEV_1 was monitored for at least 8 h. The SIC test was positive for early asthma in 42 subjects and for late/dual asthma in 19 subjects. Positive outcome to SIC was significantly associated with non-specific bronchial hyper-responsiveness and skin sensitisation to wheat flour, measured by skin prick tests. Exposure levels to wheat flour were less than or equal to 10 mg/m^3 in 12% of the individuals (n=8/12 were SIC positive), ranged between 11-30 mg/m^3 in 43% (n=33/69 were SIC positive) and exceeded 30 mg/m^3 in 45% (n=19/72 were SIC positive) of the patients (DeZ99).

5.1.5 Other studies

Cancer in the respiratory tract

Some reports have been published suggesting that workers in bakeries had higher risks for developing nasal or other respiratory tract cancers. Other reports, however, did not show any relationship between bakery workers and increased risk of cancer.

Increased risks of uncertain significance of nasal cancer among bakers and pastry cooks were reported in a case-control study (period 1963-1967) (Ach81). In another case-control study, in which 207 cases and 409 controls were included, significant excesses in risk of squamous nasal cell cancer were noted for bakers, pastry cooks and grain millers (OR=3.9, 95% confidence interval=1.2-12.8) (Luc92).

Using the Swedish Cancer Environment Registry, which links cancer incidence with employment data, Malker *et al*. (Mal86) observed more nasal cancers for bakers and

pastry makers than expected on the basis of the age and sex-specific nasal cancer incidence rates of the Swedish population (6 times that of the population as a whole).

Significantly increased mortality rates for cancer of the respiratory tract for bakery workers in small plants (standardised mortality ratio of 136, 95% confidence interval limits 110-164, p=0.0033%) were found compared to all skilled workers (all economically active men) in a Danish death registry cohort study (Tüc86). However, exposure data were not available and the increased risk could not be attributed to any specific agent in the work environment.

No increased mortality risk from respiratory cancers (nasal cancer or lung cancer) was found for bakery workers in a retrospective cohort study among 327 male millers and bakers in England and Wales (Ald87).

Furthermore, no statistically significant association between hypopharyngeal and laryngeal cancer was found in a French study, in which 'never' and 'ever' flour dust exposed male patients were questioned. Odds ratios were 1.92 (95% CI 0.82 to 4.50) for hypopharyngeal cancer (n=21) and 1.52 (95% CI 0.69 to 3.34) for laryngeal cancer (n=22). These odds ratios were adjusted for age, smoking and alcohol habits (Laf00).

Asthma mortality

Asthma mortality rates for bakery workers have been reported in a study performed in the US. Among the 184 death certificates examined (persons aged 20-35 years), with at least asthma contributing to the cause of death, were closer examined. Bakers appeared to have markedly higher mortality rates than expected, with almost nine times the age and race adjusted rates for the city of Chicago and 41 times the national rate (DeM94). The committee noted that raw data were not presented and the results should be interpreted with care, also because of the small size of the study. The authors concluded that these bakers might suffer from early mortality because of chronic exposure.

Only one case of baker's asthma with fatal outcome has been described, but special social circumstances were an important factor in this particular case (Ehr94).

Effects on skin

Allergic contact dermatitis among bakery workers has been reported from the beginning of this century (Gro51; Bon58; Hey70; Tel27), but the contact dermatitis was later attributed to ammonium and potassium persulphate, two dough improvers (For68; Hey70; You74). Still, occupational skin diseases are reported and may be a serious problem in the bakery occupation, with prevalence rates varying from 5 to 8% (Jär79; Har86; Cul94). In Finland, 101 new cases with dermatosis among grain and flour dust workers were registered between 1980 and 1989; the annual incidence for dermatosis was esti-

mated to be 0.6 per 10,000 workers (Tos94). However, various agents have been identified as potential dermal sensitisers, such as cereal flours (Pig87), cellulase, xylanase enzymes (Tar91), fungal α-amylase (Sch87; Mor93), baker's yeast (Kor94), cinnamon oil/cinnamic aldehyde (Fis75; Net89), benzoyl peroxide (Bai45; Fis89), chromium compounds (Hei80), certain emulsifiers (Foodmuls E 3137; Vin95) and antioxidants (propyl gallate; Boj87)).

5.2 Animal experiments

Currently, two animal experiments have been carried out concerning flour dust exposure and health effects. The group of Kolopp-Sarda *et al.* developed a mouse model to study effects of flour dust exposure on immunological responses (Kol96, Kol97). In both studies, Swiss male mice (n=5/group; n=10, controls) were exposed to 27±8 mg/m^3 wheat flour dust for 3, 6 or 10 consecutive days (6h/day). In one study they showed a rapid kinetics of immune response in Peyer's patches (Kol96). Peyer's patches play a major role in the initiation of mucosal immune responses in the gastro-intestinal tract. In the other study, analysis of T- and B-lymphocytes, macrophages and immunoglobulin A in plasma cells in the lungs of the animals suggested that the lung could be a sensitive target for inhaled xenobiotics, which might generate rapid local immune modifications that result in maintenance of homeostasis.

5.3 Other relevant studies

No other relevant studies were found.

5.4 Summary and evaluation

Most data on the effects of occupational exposure to flour dust are retrieved from human studies on bakery workers and flour millers. Hazardous effects are mainly described on the upper airways and lungs, such as asthma (baker's asthma), rhinitis, and on the eyes, such as conjunctivitis. These effects have been demonstrated in bakery workers exposed to flour dust levels between 2 and 5 mg/m^3, but available data do indicate that these effects may occur at even lower levels. Part of the symptoms are explained by (non-specific) irritation responses, whereas another part of the symptoms are allergic responses. These allergic reactions are hyperactive IgE mediated immune responses against allergens present in flour dust. They always are preceded by sensitisation of the workers, who are at that moment free of symptoms. The available studies suggest that sensitisation may occur soon after start of exposure (months), but it can take several years to develop symptoms.

In spite of the large variations and limitations in study design, the available studies show that sensitisation to wheat flour is common among bakery and flour mill workers (prevalence, 5-28%). In the non-occupational exposed population, the prevalence of sensitisation against allergens of wheat flour ranges between 2 and 4%.

A number of epidemiological studies put effort in quantifying the dose of (wheat) flour dust and the occurrence of work-related sensitisation against specific (wheat) flour allergens or clinical symptoms, such as asthma, rhinitis and conjunctivitis. However, different studies used different variables, which make it difficult to compare their results. For example, some studies used inhalable dust as an exposure parameter, while others used respirable dust or airborne flour dust allergens. In some cases the effect parameter was allergic or non-allergic symptoms, in others it was specific sensitisation. Furthermore, the presence of atopics, a lack of knowledge of job history, or the existence of a healthy worker effect, in which symptomatically sensitised workers change to jobs with no or low exposure risks, may have been sources of bias. The latter could explain why in several epidemiological studies the risk for sensitisation levelled off at higher exposure levels.

Overall, the committee did not find any epidemiological or clinical study, in which evidence of the existence of an exposure threshold at low exposure levels was found, *i.e.* an exposure level below which no sensitisation or clinical symptoms is observed. Despite the variations in measurements and the presence of confounding factors, most data showed an increased incidence of respiratory symptoms and specific sensitisation with increasing exposure levels, although not always statistically significant. However, the exposure-response curves differed somewhat between different industries. For instance, in two different Dutch studies, at relatively low exposure concentrations in the traditional bakery, industrialised bakery and in the bakery supply industries, the relationship between inhalable dust/wheat allergen exposure and sensitisation (IgE class 1 or higher) was linear or near linear; however, data obtained from the flour mill industry in one of these two Dutch studies revealed a bell-shaped (quadratic) relationship. The latter is most probably due to selection bias.

Frequently, peak exposures have been observed, which are related to work activities. However, to the committee no data were available in which peak exposure and the risk for sensitisation or work-related symptoms was quantitatively assessed. This makes it very difficult to assess their respective contributions to the observed health effects.

Some investigators correlated higher mortality rates among bakery workers to flour dust exposure. The causes of death were asthma and nasal cancer. Also (contact) dermatitis is correlated to flour dust exposure. Evidence for these correlations, however, is very weak or absent, because of limitations in study design and because in practice workers are simultaneously exposed to several other agents than to flour dust.

Chapter 6

Existing guidelines and standards

6.1 General population

Not available.

6.2 Working population

Current occupational exposure limits of some countries are presented in Table 6.1.

Table 6.1 Occupational exposure limits in several countries.

country (organisation)	concentration (mg/m^3)	TWA plus type of exposure limit		note[a]	ref.
The Netherlands	-	-	-	-	-
Germany (DFG)	-	-	-	Sa; wheat and rye flour dusts	DFG02
The United Kingdom (HSE)	10	8-h	MEL	Sen; flour dust	HSE02
	30	15-min	MEL	Sen	HSE02
Sweden	3	8-h	LLV	S	Hyg00
USA (ACGIH)	0.5	8-h	TLV	Sen; inhalable dust fraction	ACG02

[a] Sa, Sen and S: classified as a sensitizing compound.

The Netherlands

In the Netherlands no standards are published for occupational exposure to wheat or other cereal flour dust.

Germany

The Deutsche Forschungsgemeinschaft (DFG, Germany) has designated wheat and rye flour dust with a Sa. 'Sa' is used to designate substances, which can cause symptoms of the airways and also of the conjunctiva (substances causing airway sensitisation) (DFG00).

The United Kingdom

The Health and Safety Executive (HSE) specified that "flour dust is taken to be the finely ground particles of cereals or pulses (including contaminants) which result from any grinding process and from any subsequent handling and use of that 'flour'. Included in this definition are any additives added to the final product mix".

The HSE stated that the main risk from occupational exposure to flour dust relates to the risk of developing respiratory diseases, of which developing asthma is the main cause of concern, and of which some diseases may be related to irritancy. Furthermore, according to the HSE, "existing data do not allow the clear characterisation of dose-response relationships, nor do they permit thresholds for the induction of a hypersensitive state or provocation of an asthmatic response to be defined" (HSE00).

Scandinavian countries

The Nordic Expert Group for criteria documentation of health risks from chemicals of the Nordic Council of Ministers has published a criteria document on flour dust. It summarized that "Current data indicate that existing occupational exposure levels for flour dust (total/organic dust) which are in the range of 3-15 mg/m^3 will allow high prevalences of sensitisation, symptoms and allergic diseases as well as disorders caused by non-immunological mechanisms". Furthermore, it concluded that "Based on the current knowledge it appears unrealistic and not sufficiently founded to suggest an OEL to prevent sensitisation ...", and "Existing data on exposure response relationships do not allow the identification of a NOAEL for flour dust. Due to the nature of allergy it is unlikely that setting of a NOAEL for flour dust will be practicable even in the future." (Tik96).

Currently, in Finland flour dust is evaluated for its respiratory sensitising effects (Sos00).

ACGIH (USA)

The American Conference of Governmental Industrial Hygienists has recently reviewed flour dust. Flour dust is listed as Notice of Intended Changes as 0.5 mg/m^3 inhalable dust (TLV, 8-hour TWA), based on the allergenic properties of wheat, rye, millet, barley, oats or corn flour dust, with a sensitiser notation (ACG99).

Chapter 7

Hazard assessment

7.1 Assessment of health hazard

7.1.1 Hazard identification

The committee specified wheat and other cereal flour dusts as airborne dust of finely ground particles of cereal (*e.g.* wheat, rye, barley and oats). Ingredients added to flour, such as the dough improver fungal α-amylase, which is known to have sensitising properties, are not included.

Several epidemiological studies have shown that the main health effects of flour dust exposure are symptoms observed in the respiratory tract and the eyes, such as rhinitis, asthma (baker's asthma), and conjunctivitis. Occasionally also dermatitis is recorded. However, there is insufficient evidence that wheat flour alone may cause skin disorders. Also mortality due to asthma and nasal cancer is reported. Yet, in the literature no evidence is presented that wheat flour alone is the cause of these mortalities.

Most of the work-related asthma and rhinitis have repeatedly and convincingly been shown to be of allergenic in origin, mediated by immunoglobulin E (IgE) antibodies to flour dust antigens. However, flour dust-induced asthma and rhinitis may also be explained by non-allergic, irritation responses.

Concerning allergenic responses, in recent years, data have been collected on the dose-response relationships between airborne flour dust exposure and symptoms associated with sensitisation (Bri00, Cul94/Cul01, Hou98/Hee01, Mus89, Oos01/Per03). However, different studies used different variables, which make it difficult to compare

their results. For example, some studies used inhalable or respirable dust as an exposure parameter, while others used airborne flour dust allergens. In some cases the effect parameter was allergic and/or non-allergic symptoms, in others it was specific sensitisation. Furthermore, sometimes sources of bias were not taken into account, such as the presence of atopics, lack of knowledge of job history or healthy worker effect. The latter bias could explain why in the two Dutch studies (Hou98/Hee01, Oos01/Per03) the dose-response relationships levelled off at higher exposure levels, resulting in a lower relative risk at higher exposure levels. Despite these variations and the presence of bias, at the lower exposure range most of these data showed an increased incidence of respiratory symptoms and specific sensitisation with increasing exposure levels.

Frequently, peak exposures have been observed, which are strongly related to work activities (*e.g.* Nie95c, Pat02). These peak exposures may play an important role in inducing work-related health effects. This means that prevention of peak exposure will most likely lower specific sensitisation and symptoms. However, at this moment, insufficient data are available to the committee on the influence of the height and frequency of these peaks on the dose-response relationship. Consequently, the committee is not able to use data on the presence of peak exposures in its quantitative risk assessment. Yet, it expresses its concern about these observations and strongly advices to take preventive measures against those peak exposures.

Based on the epidemiological data, the committee concludes that the symptoms observed in the respiratory tract and eyes are the health effects to be prevented. These symptoms may have an allergenic and/or an irritative origin. However, the main concern to the committee is the allergenic potential. Once allergic, the person in question will express allergic symptoms for the rest of his or her life at exposure concentrations far below which irritation does occur. For this reason the committee is of the opinion that an OEL should be based on prevention of allergic symptoms due to wheat flour dust exposure. With this respect, of particular importance is prevention of sensitisation to allergens present in flour dust, although sensitisation per se is not an illness. Concerning sensitisation (*i.e*. the development of specific IgE antibodies to flour dust allergens), it often precedes the onset of allergic symptoms.

Because the available literature does not suggest that non-allergic symptoms occur at similar or even lower exposure levels than allergic symptoms, the committee is of the opinion that a risk assessment based on sensitisation not only protects against allergic symptoms, but most likely against non-allergic symptoms as well. Furthermore, because the committee observed that specific sensitisation to several flour dust allergens seems to be dose related (measured by the skin prick tests with flour extracts and/or specific IgE tests), it is of the opinion that assessing an occupational exposure risk based on sensitisation is justified.

7.1.2 *Occupational exposure risk for sensitisation*

The committee did not find evidence in the literature for the existence of a threshold level for sensitisation against flour dusts, which is needed to identify a no-observed adverse effect level (NOAEL). This implies that complete protection against sensitisation to airborne flour dust allergens at low exposure levels cannot be achieved. However, the committee strongly believes that work-related sensitisation and clinical symptoms caused by flour dust exposure are important to control. For this reason, the committee has chosen a 'non-threshold' approach, which is based on estimating additional risks for sensitisation associated with occupational exposure to flour dust, so that most of the exposed workers will be protected. This approach is based on linear exposure-response relationships. It is the first time that such an approach is used for sensitising substances.

7.1.3 *Selection of study suitable for risk estimation*

The committee has thoroughly evaluated epidemiological studies, which could serve as a starting point in estimating risk values for specific sensitisation against wheat flour allergens. Details of these studies are shown in annex E. A few of these studies were considered not suitable. These included: the study by Musk *et al*. (Mus89), because data were not specified for wheat flour allergen exposure; and, the two studies performed by Cullinan and his colleagues (Cul94, Cul01), because exposure was only expressed in categories (Cul94), or because of the relatively high exposure in the reference group (Cul01). This left two studies of interest. These are two Dutch studies (Hou98/Hee01, Oos01/Per03), which are independently performed of each other. They both assessed wheat allergen and inhalable dust exposure in the bakery and related industries in relation to the risk for sensitisation using sophisticated statistical models (Hee01, Per03). Furthermore, they had similar study designs. In both studies, the increase per unit risk was comparable (except for the flour mill industry, see Per03). Because of the similarities, the committee investigated the possibility to pool the data. However, closer examination revealed that there were also differences. These included different assays used to assess specific sensitisation and differences in the prevalence of atopy among the different industries (in particular in the flour mill industry (Per03)). As a result, the reliability could become an issue when pooling data. Consequently, the committee decided not to do this.

The final decision was made on the basis of exposure measurements. In the study by Heederik and Houba (Hee01) lower exposures were measured than in the study of Peretz *et al*. (Per03). Since for risk estimation in particular the lower exposure range is

of importance, the committee, therefore, concluded that the study by Heederik and Houba (Hee01) could best serve as starting point in estimating risk values for specific sensitisation against wheat flour allergens.

7.1.4 *Calculation of the additional sensitisation risk for flour dust*

In the study of Heederik *et al*. (Hee01), data were presented on airborne wheat allergen concentrations, inhalable dust concentrations, specific sensitisation (specific IgE plus total serum IgE ≥ 100 kU/L) and work-related symptoms. Both conventional categorical analyses (Table 5.3) and smoothed non-parametric exposure-response curves (Figure 5.1 and 5.2) clearly showed an increased incidence with increasing exposure. The committee observed that this relationship was linear till it levelled off at around 10 μg/m^3 airborne wheat allergen or 3 mg/m^3 inhalable dust.

From a theoretical point of view, because sensitisation is the most critical effect, a dose-response relationship with airborne allergen exposure levels would be preferred, because sensitisation only occurs by exposure to allergens. Nevertheless, for practical reasons, the committee prefers to use inhalable dust exposure levels, because dust measurements are standardised, validated and applicable for frequent measurements in the workplace, in contrast to airborne allergen measurements.

Assuming a linear relationship between inhalable dust exposure and flour dust sensitisation at lower exposure levels, the committee proposes a simple model, based on linear regression, to enable the calculation of an additional sensitisation risk. The committee points out that these additional sensitisation risks refer to an *excess* sensitisation as a result of occupational exposure. The background sensitisation incidence of the general population of 2 to 4 percent is not included.

A detailed description on the calculation of the linear relationship between the estimated average dust exposure levels and sensitisation to wheat dust allergens is given in Annex F. The final expression is calculated as $AR = D/0.248$, in which D is the estimated average dust exposure level, expressed in mg/m^3, and AR is the additional risk, expressed in % of the exposed working population. This formula is only valid for exposure concentrations up to 3 mg/m^3, because only below this level the relationship showed to be linear.

With respect to inhalable dust measurements, a point of concern is that dust may contain varying amounts of airborne flour dust allergens, which is partly attributed to the presence of other dust sources than flour dust in the workplace. Because this problem is difficult to overcome, the committee finds it necessary to compensate for this uncertainty. Evaluation of the available exposure data about this subject revealed that the allergen content varies at least with a factor of 2 and at most with a factor of 4 (see section 3.2.4). However, despite the differences in methodology and design among epide-

miological studies (annex E), the dose-response relationships are comparable. Furthermore, differences in the slope of the relationships are relatively small within the lower exposure range. Lastly, in the study that served as starting point for estimating risk values variability of allergen content is taken into account. Since the relationships are based on a large amount of data, the committee is of the opinion that an uncertainty factor of 2 for the variability of allergen content is justified. As a result, the final derivation becomes

$$AR = D/0.124$$

The estimated additional sensitisation risk for wheat flour dust is presented as the concentration inhalable dust with excess sensitisation risk of 1 per 10 (10%), 1 per 100 (1%) and 1 per 1,000 (0.1%) persons, as a result of occupational exposure, and amounts to:

- 0.1% for an occupational exposure to 0.012 mg/m^3 inhalable dust;
- 1.0% for an occupational exposure to 0.12 mg/m^3 inhalable dust;
- 10.0% for an occupational exposure to 1.2 mg/m^3 inhalable dust,

as a time-weighted average concentration under normal working conditions of eight hours a day and five days a week, during a life-long employment exposure.

These risk estimates suggest that a person, who starts working in the bakery industry for the first time in his or her life, has a chance of 1% for *ever* becoming sensitised to flour dust, if occupationally exposed to an average of 0.12 mg/m^3 inhalable dust. Furthermore, the estimated additional risk values are independent of the general background sensitisation incidence of 2 to 4 percent.

The committee calculated inhalable dust concentrations as average values, valid for the whole employment period. In practice, however, the available data suggest that the risk of becoming sensitised is also time-related, in that sensitisation develops within an exposure period of one to a few years of employment. Therefore, the estimated risk values are most likely overestimated for non-sensitised workers with long employment duration and underestimated for newcomers, who were never exposed earlier. Nevertheless, the committee decided to average exposure duration in estimating additional risk values, because the set of data on time-response relationships was too limited. Furthermore, from the data that were available, the committee judged that the under- and overestimation stays within acceptable limits.

The data used for the risk estimation concern specific sensitisation to airborne wheat flour allergens. This is important, because in the Netherlands wheat is the most often used cereal in the bakery industry, and thus sensitisation to wheat flour is more prominent than sensitisation to other cereal flours. However, data from the literature suggest that allergens from other cereal flours may also cause allergy in the respiratory tract and

eyes. Moreover, allergens in wheat flour and other cereal flours, such as rye flour, produce frequent cross-sensitisation. Because, the committee did not find evidence of a different risk between these cereal flour dusts and wheat flour dust, it is of the opinion that the estimated additional sensitisation risks for wheat flour dust may be generalized to other cereal flour dusts.

7.2 Groups at extra risk

Three groups of workers have or may have an increased risk when exposed to cereal flour dust. First, workers with a flour sensitisation will most certainly develop symptoms after repeated exposure to low levels of flour dust. Second, workers with an atopic status or an allergic constitution may have an increased risk to develop work-related allergic sensitisation and subsequently respiratory symptoms and lung function changes. Third, workers with pre-existing asthma or those with more general respiratory symptoms may also have an increased risk to develop symptoms most likely because of non-specific irritation.

7.3 Health-based estimated additional sensitisation risk

The Dutch Expert Committee on Occupational Standards estimated that an additional sensitisation risk for wheat and other cereal flours amount to:

- 0.1% for an occupational exposure to 0.012 mg/m^3 inhalable dust;
- 1.0% for an occupational exposure to 0.12 mg/m^3 inhalable dust;
- 10.0% for an occupational exposure to 1.2 mg/m^3 inhalable dust,

as a time-weighted average concentration under normal working conditions of eight hours a day and for 5 days a week during a life-long employment exposure. The estimated additional risk values are independent of the general background sensitisation incidence of 2 to 4 percent.

The additional risk values used in the previous section serve as examples. Other excess sensitisation risk values may be used. The inhalable dust levels are simply calculated by using the formula: $AR = D/0.124$, which is valid for inhalable dust concentrations up to 3 mg/m^3.

Finally, the committee points out that due to flour dust exposure, not only immunological symptoms (allergy), but also non-immunological symptoms may occur. In principle, for the latter type of symptoms a health-based recommended occupational exposure limit could be derived. However, this is not possible, because most epidemiological studies did not make a distinction between immunological and non-immunological symptoms. However, the data from the epidemiological studies do indicate that

symptoms, irrespective of their nature, do occur at exposure levels in the order of magnitude of concentrations, at which there is about 10 percent chance on getting sensitised.

References

ACG99 American Conference of Governmental Industrial Hygienists. Document on Flour Dust. ACGIH, Cincinnati, 1999.

ACG02 American Conference of Governmental Industrial Hygienists. Guide to occupational exposure values 2002. ACGIH, Cincinnati, 2002.

Ach81 Acheson ED, Cowdell RH, Rang EH. Nasal cancer in England and Wales: an occupational survey. Br J Ind Med 1981; 38:218-224.

Ada95 Adachi T, Alvarez AM, Aoki N, Nakamura R, Garcia VV, Matsuda T. Screening of rice strains deficient in 16-kDa allergenic protein. Biosci Biotech Biochem 1995; 59:1377-1378.

Ald87 Alderson MR. Mortality of millers and bakers. Br J Cancer 1987; 55:695-696.

Arm90 Armentia A, martin-Santos MJ, Quintero A, Fernandez A *et al*. Baker's asthma: prevalence and evaluation of immunotherapy with wheat flour extract. Annals of Allergy 1990; 65: 265-272.

Arm93 Armentia A, Sanchez-Monge R, Gomez L, Barber D, Salcedo G. *In vivo* allergenic activities of eleven purified members of a major allergen family from wheat and barley flour. Clin Exp Allergy 1993; 23:410-415.

Awa86 Awad El Karim, MA, Gad El Rab MO, Omer AA and El Haimi YAA. Respiratory and Allergic Disorders in workers exposed to grain and flour dusts. Arch Environ Health 1986; 41: 297-301.

Baa33 Baagöe KH. Mehlidiosynkrasie als Ursache vasomotorischer Rhinitis und Asthma. Acta Med Scand 1993a; 80:310-322.

Bac91 Bachmann M, Myers JE. Grain dust and respiratory health in South African milling workers. Br J Ind Med 1991; 48: 656-662.

Bai45 Baird KA. Allergy to chemicals in flour. J Allergy 1945; 16:195-198.

Bal78 Baldo BA, Wrigley CW. IgE antibodies to wheat flour components. Clin Allergy 1978; 8:109-124.

Bal80 Baldo BA, Krilis S, Wrigley CW. Hypersensitivity to inhaled flour allergens - comparison between cereals. Allergy 1980; 35:45-56.

Bar89 Barber D, Sánchez-Monge R, Gómez L, Carpizo J, Armentia A, López-Otín C, Juan F, Salcedo G. A barley flour inhibitor of insect alpha-amylase is a major allergen associated with baker's asthma disease. FEBS Letters 1989; 248:119-122.

Bau86 Baur X, Fruhmann G, Haug B, Rasche B, Reiher W, Weiss W. Role of aspergillus amylase in baker's asthma. The Lancet 1986; 1:43.

Bau98a Baur X and Posch A. Characterized allergens causing baker's asthma. Allergy 1998; 53: 562-566.

Bau98b Baur X, Degens PO and Sander I. Baker's asthma: still among the most frequent occupational respiratory disorders. J Allergy Clin Immunol 1998; 102-984-997.

Ber76 Beritic-Stahuljak D, Valic F, Cigula M, Butkovic D. Simultaneous exposure to airborne flour particles and thermal load as cause of respiratory impairment. Int Arch Occup Environ Health 1976; 37:193-203.

Ber76 Bergmann I, Rebohle E, Wallenstein G, Gemeinhardt H, Thürmer H. Häufigkeit und Bedeutung von Schimmelpilzsensibilisierungen bei Werktätigen in der Backwarenindustrie. Allergie und Immunologie 1976; 22:297-301. [in German]

Ber79 Bergmann I, Wallenstein G, Rebohle E, Schneider WD. Berufsbedingte allergische und irritative Atemerkrankungen bei Müllern. Z ges Hyg 1997; 25: 287-290.

Bla76 Blands J, Diamant B, Kallós P, Kallós-Deffner L, Løwenstein H. Flour Allergy in Bakers - Identification of Allergenic Fractions in Flour and Comparison of Diagnostic Methods. Int Archs Allergy Appl Immun 1976; 52:392-406.

Blo83 Block G, Tse KS, Kijek K, Chan H, Chan-Yeung M. Baker's asthma - clinical and immunological studies. Clin Allergy 1983; 13:359-370.

Blo84 Block G, Tse KS, Kijek K, Chan H, Chan-Yeung M. Baker's asthma - studies of the cross-antigenicity between different cereal grains. Clin Allergy 1984; 14:177-185.

Boh94 Bohadana AB, Massin N, Wild P, Kolopp MN, Toamain JP. Respiratory symptoms and airway responsiveness in apparently healthy workers exposed to flour dust. Eur Respir J 1994; 7:1070-1076.

Boi83 Boisen S. Comparative physico-chemical studies on purified trypsin inhibitors from the endosperm of barley, rye, and wheat. Z Lebensm Unters Forsch 1983; 176:434-439.

Boj87 Bojs G, Nicklasson B & Svensson Å. Allergic contact dermatitis to propyl gallate. Contact Dermatitis 1987; 17:294-298.

Bon58 Bonnevie P. Occupational allergy in bakery. In: Occupational allergy - lectures held during a course on occupational allergy, Stenfert Kroese NV, Leiden, The Netherlands, 1958.

Bri95 Brisman J, Järvholm BG. Occurrence of self-reported asthma among Swedish bakers. Scand J Work Environ Health 1995; 21:487-493.

Bri98 Brisman J, Torén K, Lillienberg L, Karlsson G and Ahlstedt S. Nasal symptoms and indices of nasal inflammation in flour-dust exposed bakers. Int Arch Occup Environ Health 1998; 71: 525-532.

Bri00 Brisman J, Järvholm B and Lillienberg L. Exposure-response relations for self reported asthma and rhinitis in bakers. Occup Environ Med 2000; 57: 335-340.

Bur94 Burdorf A, Lillienberg L, Brisman J. Characterization of exposure to inhalable flour dust in Swedish bakeries. Ann Occup Hyg 1994; 38:67-78.

Bur97 Burstyn I, Teschke K, Kennedy SM. Exposure levels and determinants of inhalable dust exposure in bakeries. Ann Occup Hyg 1997a; 41: 609 - 624.

Bur98 Burstyn I, Teschke K, Barlett K, Kennedy SM. Determinants of wheat antigen and fungal α-amylase exposure in bakeries. Am Ind Hyg Assoc J 1997b; 55: 313-320.

Bur99 Burstyn I, Heederik D, Bartlett K, Doekes G, houba R *et al*. Wheat antigen content of inhalable dust in bakeries: modeling and inter-study comparison. Appl Occup Environ Hyg 1999; 14: 791-798.

CBS93 CBS. Produktiestatistieken Industrie. K-195: Bakkerijgrondstoffenfabrieken 1991. Centraal Bureau voor de Statistiek, Voorburg/Heerlen, The Netherlands, 1993. [in Dutch]

CBS94a CBS. Produktiestatistieken Industrie. K-35: Meelindustrie 1992. Centraal Bureau voor de Statistiek, Voorburg/Heerlen, The Netherlands, 1994a. [in Dutch]

CBS94b CBS. Produktiestatistieken Industrie. K-129: Brood-, banket-, biscuit-, beschuit- en koekfabrieken 1992. Centraal Bureau voor de Statistiek, Voorburg/Heerlen, The Netherlands, 1994b. [in Dutch]

Cha84 Charpin D, Court E, Kleisbauer JP. Enquête épidémiologique chez les boulangers. Arch maladis prof 1984; 45:381-382. [in French]

Cho99 Choudat D, Fabriès JF, Martin JC, Villette C, Tabka F, Dessanges JF, Dall Ava J and Conso F. Quantification of the dose of inhaled flour: relation with nonspecific bronchial and immunological reactivities. Eur Respir J 1999; 14: 328-334.

Cri97 Crippa M, and Pasolini G. Allergic reactions due to glove-lubricant-powder in health-care workers. Int Arch Occup Environ Health 1997; 70: 399-402.

Cul94 Cullinan P, Lowson D, Nieuwenhuijsen MJ, Sandiford C, Tee RD, Venables KM, McDonald JC, Newman Taylor AJ. Work related symptoms, sensitisation, and estimated exposure in workers not previously exposed to flour. Occup Environ Med 1994; 51:579-583.

Cul95 Cullinan P, Lowson D, Nieuwenhuijsen M, Sandiford C, Tee RD, Venables KM, McDonald JC, Newman Taylor AJ. Work-related symptoms, specific sensitisation and exposure in a cohort of flour workers. Eur Resp J 1995; 8 (Suppl) 19:272s.

Cul01 Cullinan P, Cook A, Nieuwenhuijsen MJ, Sandiford C, Tee RD, *et al*. Allergen and dust exposure as determinants of work-related symptoms ans sensitization in a cohort of flour-exposed workers; a case-control analysis. Ann Occup Hyg 2001; 45: 97-103.

DeM94 DeMers MP, Orris P. Occupational exposure and asthma mortality. JAMA 1994; 272:1575.

DeZ94 De Zotti R, Larese F, Bovenzi M, Negro C, Molinari S. Allergic airway disease in Italian bakers and pastry makers. Occup Environ Med 1994; 51:548-552.

DeZ95 De Zotti R, Molinari S, Larese F, Bovenzi M. Pre-employment screening among trainee bakers. Occup Environ Med 1995; 52:279-283.

DeZ99 De Zotti R, Bovenzi M, Negro C, Cirla A, *et al*. Specific inhalation challenge with wheat flour in workers with suspected baker's asthma. Int Arch Occup Environ Health 1999; 72: 335-337.

DeZ00 De Zotti R and Bovenzi M. Prospective study of work related respiratory symptoms in trainee bakers. Occup Environ Med 2000; 57: 58-61.

DFG02 Deutsche Forschungsgemeinschaft. List of MAK and BAT values 2002. Commission for the investigation of Health Hazards of Chemical Compounds in the Work Area. 2002; Report no. 38.

Die55 Diederich W, Lübbers P. Das Mehlasthma als Berufskrankheit. Zentralblatt für Arbeitsmedizin und Arbeitsschutz 1995; 5:189-197. [in german]

Dis39 Dishoeck HAE van, Roux DJ. Sensitisation to flour and flour illnesses amongst flour workers. J Hygiene 1939; 39:674-679.

Ehr94 Ehrlich RI. Fatal asthma in a baker: a case report. Am J Ind Med 1994; 26:799-802.

Fak92 Fakhri ZI. Causes of hypersensitivity reactions in flour mill workers in Sudan. Occup Med 1992; 49: 149-154.

Fis75 Fisher AA. Dermatitis due to cinnamon and cinnamic aldehyde. Cutis 1975; 16:383-388.

Fis89 Hisher AA. Allergic baker's dermatitis due to benzoyl peroxide. Cutis 1989; 43:128-129.

For68 Forck G. Vorkommen und Persistenz von Persulfatallergien. Berufsdermatosen 1968; 16:84-92. [in German]

Frä91 Fränken J, Stephan U, Neuber K, Bujanowski-Weber J, Ulmer WT, König W. Characterization of allergenic components of rye and wheat flour (Secale, Triticum vulgaris) by western blot with sera of bakers: their effects on CD23 expression. Int Arch Allergy Appl Immunol 1991; 96:76-83.

Frä94 Fränken J, Stephan U, Meyer HE, König W. Identification of alpha-amylase inhibitor as a major allergen of wheat flour. Int Arch Allergy Immunol 1994; 104:171-174.

Gad56 Gadborg E. Allergy to flour. Thesis. 1956. Copenhagen. (as quoted by: Bonnevie P. Occupational allergy in bakery, 1958; and in: Thiel H & Kallweit C. Das Bäckerasthma - eine klassische allergische Berufskrankheit, 1984).

Gar95 García-Casado G, Armentia A, Sánchez-Monge R, Sánchez LM, Lopez-Otín C, Salcedo G. A major baker's asthma allergen from rye flour is considerably more active than its barley counterpart. FEBS letters 1995; 364: 36-40.

Gar96 García-Casado G, Armentia A, Sánchez-Monge R, Malpica JM, Salcedo G. Rye flour allergens associated with baker's asthma. Correlation between *in vivo* and *in vitro* activities and comparison with their wheat and barley homologues. Clin Exp Allergy 1996; 26: 428-435.

Gar87 Garcia-Olmedo F, Salcedo G, Sanchez-Monge R, Gomez L, Royo J, Carbonero P. Plant proteinaceous inhibitors of proteinases and -amylases. Oxford Surveys Plant Mol Cell Biol 1987; 4: 275-334.

Gau97 Gautrin D, Infante-Rivard C, Dao TV, Magnan-Larose M, Desjardins D, Malo JM. Specific IgE-dependent sensitisation, atopy, and bronchial hyperresponsiveness in apprentices starting exposure to protein-derived agents. Am J Respir Crit Care Med 1997; 155: 1841-1847.

Gim95 Gimenez C, Fouad K, Choudat D, Laureillard J, Bouscaillou P and Leib E. Chronic and acute respiratory effects among grain mill workers. Int Arch Occup Environ Health 1995; 67: 311-315.

Góm90 Gómez L, Martin E, Hernández D, Sánchez-Monge R, Barber D, del Pozo V, *et al*. Members of the -amylase inhibitors family from wheat endosperm are major allergens associated with baker's asthma. FEBS letters 1990; 261: 85-88.

Gro51 Grosfeld JCM. Onderzoekingen over het ontstaan van eczeem bij bakkers. Thesis. Amsterdam, 1951. [in Dutch]

Har85 Hartmann AL, Wüthrich B, Deflorin-Stolz R, Helfenstein U, Hewitt B, Guérin B. Atopie-Screening: Prick-Multitest, Gesamt-IgE oder RAST? Schweiz med Wschr 1985; 115: 466-475. [in German]

Har86 Hartmann AL. "Berufsallergien bei Bäckern - Epidemiologie; Diagnose, Therapie und Prophylaxe; Versicherungsrecht." München-Deisenhofen, Germany: Dustri-Verlag Dr. Karl Feistle, 1986. [in German]

Hee01 Heederik D, R Houba. An explorative quantitative risk assessment for high molecular weight sensitizers: wheat flour. Ann of Occup Hyg 2001; 45: 175-185.

Hei80 Heine A and Fox G. Bäckerekzem durch Chromverbindung in Mehlen. Dermatosen 1980; 28: 113-115. [in German]

Hei96 Heiss S, S Flicker, DA Hamilton, D Kraft, JP Mascarenhas and R Valenta. Expression of Zm13, a pollen specific maize protein, in *Escherichia coli* reveals IgE-binding capacity and allergenic potential. FEBS letters 1996; 381: 217-221.

Her67 Herxheimer H. Skin sensitivity to flour in bakers' apprentices. The Lancet 1967; 1: 83-84.

Her73 Herxheimer H. The skin sensitivity fo flour of bakers' apprentices. Acta Allergologica 1973; 28: 42-49.

Hey83 Heyer N. Backmittel als berufsbedingte Inhalationsallergene bei mehlverarbeitenden Berufen. Allergologie 1983; 6: 389-392. [in German]

Hey70 Heyl U. Das Bäckerekzem. Therapeutische Umschau 1970; 27: 521-524. [in German]

Hos86 Hoseney RC. Dry milling of cereals: In Hoseney RC, ed. Principles of cereal Science and Technology. St. Paul Minnesota, the USA: Am Association of Cereal Chemists Inc., 1986; p133-152.

Hou96 Houba R. "Occupational respiratory allergy in bakery workers - relationships with wheat and fungal a-amylase aeroallergen exposure." Thesis. Wageningen, The Netherlands: Agricultural University Wageningen, Department of Occupational and Environmental Health, Wageningen, 1996.

Hou96a Houba R, van Run P, Heederik D, Doekes G. Wheat antigen exposure assessment for epidemiologic studies in bakeries using personal dust sampling and inhibition ELISA. Clin Exp Allergy 1996a; 26: 154-163.

Hou96b Houba R, Heederik DJJ, Doekes G, van Run PEM. Exposure-sensitisation relationship for a-amylase allergens in the baking industry. Am J Respir Crit Care Med 1996b; 154: 130-136.

Hou97 Houba R, Heederik D, Kromhout K. Grouping strategies for exposure to inhalable dust, wheat allergens and -amylase allergens in bakeries. Ann Occup Hyg 1997b; 41: 287-296.

Hou98 Houba R, D Heederik, G Doekes. Wheat sensitisation and work related symptoms in the baking industry are preventable: an epidemiological study. Am J Resp Crit Care Med 1998; 158: 1499-1503.

HSE00 Health and Safety Executive. Flour dust. Risk assessment document EH72/11. HSE books, Suffolk, UK, reprinted 2000.

HSE02 Health and Safety Executive. Occupational exposure limits 2002. HSE, Caerphilly, UK, EH40/2002.

Hyg00 Arbetarskyddsstyrelsen. Hygiensiska gränsvärden och åtgärder mot luftföroreningar. Stockholm, 2000. [in Swedish]

Jär79 Järvinen KAJ, Pirilä V, Björksten F, Keskinen H, Lehtinen M, Stubb S. Unsuitability of bakery work for a person with atopy: a study of 234 bakery workers. Ann of Allergy 1979; 42: 192-195.

Jau93 Jauhiainen A, Louhelainen K, Linnainmaa M. Exposure to Dust and a-Amylase in Bakeries. Appl Occup Environ Hyg 1993; 8: 721-725.

Jef92 Jeffrey PM. "Respiratory problems in workers in small bakeries." Glasgow, Great Brittain: Dissertation for membership of the Faculty of Occupational Medicine of the Royal College of Physicians, 1992.

Jor86 Jorde W, Heyer N, Schata M. Bäckereirohstoffe als berufsspezifische Allergene. Allergologie 1986; s552-s524. [in German]

Kal78 Kalveram KJ and G Forck. Cross-reactivity between grass and corn pollen antigens. Int Arch Allergy Appl Immunol 1978; 549-553.

Kap89 Kapoor R, Mahajan KK, Marya RK. Ventilatory and diffusion studies in smoker and non-smoker flour-mill workers. Ind J Physiol Pharmacol 1989; 33: 211-215.

Ken96 Kenny LC. Developments in workplace aerosol sampling. A review. Analyst 1969; 121: 1233-1239.

Kol94 Kolopp-Sarda MN, Massin N, Gobert B, Wild P, Moulin JJ, Béné MC, Faure GC. Humoral immune responses of workers occupationally exposed to wheat flour. Am J Ind Med 1994; 26: 671-679.

Kol96 Kolopp-Sarda MN, Bene MC, Martin P, Faure GC. Kinetics of local immune responses in mouse Peyer's patches after respiratory exposure to flour. Immunopharmacol 1996; 34: 125-130.

Kol97 Kolopp-Sarda MN, Bene MC, Martin P, Faure GC. Mouse lung immune response after acute exposure to flour dust. Arch Environ Health 1997; 52: 304-308.

Kor94 Kortekangas-Savolainen O, Savolainen J, Lantto R & Kalimo K. Immediate hypersensitivity to bakery, brewery and wine products in yeast-sensitive atopic dermatitis patients. Clin Exp Allergy 1994; 24: 836-842.

Laf00 Laforest L, Luce D, Goldberg P, *et al*. Laryngeal and pharyngeal cancers and occupational exposure to formaldehyde and various dusts: a case-control study in France. Occup Environ Med 2000; 57: 767-773.

Lil94 Lillienberg L, Brisman J. Flour dust in bakeries - a comparison between methods. Ann Occup Hyg 1994; 38 (1) Suppl: 571-575.

Lin47 Linko E. On allergic rhinitis and bronchial asthma in bakers. Ann Med Intern Fenn 1947; 36: 98-111.

Luc92 Luce D, Leclerc A, Morcet JF, Casal-Lareo A, Gérin M, Brugère J, Haguenoer JM, Goldberg M. Occupational risk factors for sinonasal cancer: a case-control study in France. Am J Ind Med 1992; 21: 163-175.

Mal86 Malker HSR, McLaughlin JK, Blott WJ, Weiner JA, Malker BK, Ericcson JLE & Stone BJ. Nasal cancer and occupation in Sweden, 1961-1979. Am J Ind Med 1986; 9: 477-485.

Mas88 Masalin KE, Degerth RK and Murtomaa HT. Airborne sugar and flour dust in the finnish confectionary industry. Appl Ind Hyg 1988; 3: 231-235.

Mas95 Massin N, Bohadana AB, Wild P, Kolopp-Sarda MN, Toamain JP. Airway responsiveness to metacholine, respiratory symptoms, and dust exposure levels in grain and flour mill workers in eastern France. Am J Ind Med 1995; 27: 859-869.

Men92 Mena M, Sanchez-Monge R, Gomez L, Salcedo G, Carbonero P. A major barley allergen associated with baker's asthma disease is a glycosylated monomeric inhibitor of insect a-amylase: cDNA cloning and chromosomal location of the gene. Plant Molecular Biology 1992; 20: 451-458.

Mor93 Morren MA, Janssens V, Dooms-Goossens A, van Hoeyveld E, Cornelis A, de Wolf-Peeters C, Heremans A. a-Amylase, a flour additive: an important cause of protein contact dermatitis in bakers. J Am Acad Dermatol 1993; 29: 723-728.

Mus89 Musk AW, Venables KM, Crook B, Nunn AJ, Hawkins R, Crook GD, *et al*. Respiratory symptoms, lung function, and sensitisation to flour in a British bakery. Br J Ind Med 1989; 46: 636-642.

Nak96 NBS94 NBS. De structuur van het bakkersbedrijf in Nederland. Nederlandse Bakkerij Stichting, Den Haag, The Netherlands, 1994. [in Dutch]

Net89 Nethercott JR & Holness DL. Occupational dermatitis in food handlers and bakers. J Am Acad Dermatol 1989; 21: 485-490.

Nie94 Nieuwenhuijsen MJ, Sandiford CP, Lowson D, Tee RD, Venables KM, McDonald JC, Newman Taylor AJ. Dust and flour aeroallergen exposure in flour mills and bakeries. Occ Environ Med 1994; 51: 584-588.

Nie95a Nieuwenhuijsen MJ, Lowson D, Venables KM, Newman Taylor AJ. Flour dust exposure variability in flour mills and bakeries. Ann Occup Hyg 1995a; 39: 299-305.

Nie95b Nieuwenhuijsen MJ, Sandiford CP, Lowson D, Tee RD, Venables KM, Newman Taylor AJ. Peak exposure concentrations of dust and flour aeroallergen in flour mills and bakeries. Ann Occup Hyg 1995b; 39: 193-201.

Nie95c Nieuwenhuijsen MJ, Lowson D, Venables M and Newman Taylor AJ. Correlation between different measures of exposure in a cohort of bakery workers in flour millers. Ann Occup Hyg, 1995; 3: 291-298.

Oos01 Oostenbrink JH, Tomee JFC, Heide van der S, Steketee I, Kerkhof M and Monchy de JGR. Aard en omvang van beroepsgebonden klachten bij werknemers in bakkerijen, meelfabrieken en grondstoffenindustrie. Resultaten Fase II onderzoek. Verslag Onderzoeksprogramma Grondstofallergie van het Productschap Granen, Zaden en Peulvruchten, december 2001. [in Dutch]

Par98 Park HS, Nahm DH, Kim HY, Suh CH, and Kim KS. Role of specific IgE, IgG and IgG4 antibodies to corn dust in exposed workers. Korean J Intern Med 1998; 13: 88-94.

Pat02 Pater de N, Doekes G, Miedema E, Goede H, Hemmen van J and Heederick D. Expositie aan stof, tarwe-allergenen en schimmel alfa-amylase en stand der techniek in ambachtelijke bakkerijen, meelmaalderijen en bakkerijgrondstoffen leveranciers. Verslag onderzoeksprogramma Grondstofallergie van het Productschap Granen, Zaden en Peulvruchten. TNO Voeding (Zeist), maart 2002. [in Dutch]

Pav01 Pavlovic M, Spasojevic M, Tasic Z and Tacevic S. Bronchial hyperreactivity in bakers and its relation to atopy and skin reactivity. Science of the Total Environ 2001; 270: 71-75.

Per03 Peretz C, Pater de N, Monchy de J, Oostenbrink J and Heederik D. Assessment of Exposure to wheat flour and the shape of its relationship with specific sensitization. Chapter 6. In thesis: Repeated measurement data for exposure assessment, Utrecht University, the Netherlands, 2003. Submitted for publication.

Pes55 Pestalozzi C, Schnyder UW. Zur Frage der Bäckerrhinitis und des Bäckerasthmas. Schweiz med Wschr 1955; 21: 496-501. [in German]

Pfe90 Pfeil T, Schwabl U, Ulmer WT, König W. Western Blot Analysis of Water-Soluble Wheat Flour (Triticum vulgaris) Allergens. Int Arch Allergy Appl Immunol 1990; 91: 224-231.

Pig87 Pigatto PD, Polenghi MM & Altomare GF. Occupational dermatitis in bakers: a clue for atopic contact dermatitis. Contact Dermatitis 1987; 16: 263-271.

Pop70 Popa V, Al-George S, Gavanescu O. Occupational and non occupational respiratory allergy in bakers. Acta Allergologica 1970; 25: 159-177.

Pop94 Popp W, Wagner C, Kiss D, Zwick H, Sertl K. Prediction of sensitisation to flour allergens. Allergy 1994; 49: 376-379.

Pos95 Posch A, Weiss W, Wheeler C, Dunn MJ, Görg A. Sequence analysis of wheat grain allergens separated by two-dimensional electrophoresis with immobilized pH gradients. Electrophoresis 1995; 16: 1115-1119.

Pri84 Prichard MG, Ryan G, Musk AW. Wheat flour sensitisation and airways disease in urban bakers. Br J Ind Med 1984; 41: 450-454.

Pri85 Prichard MG, Ryan G, Walsh BJ, Musk AW. Skin test and RAST responses to wheat and common allergens and respiratory disease in bakers. Clin Allergy 1985; 15: 203-210.

Ros91 Rosenberg N, Rameix F, Demangeat G, Philippon JJ, Rigault MH, Schlacther T, Sandret N. Prévalence de l'allergie respiratoire dans la boulangerie-pâtisserie parisienne en 1987. Arch Mal Prof 1991; 52: 33-36. [in French]

San92 Sanchez-Monge R, Gomez L, Barber D, Lopez-Otin C, Armentia A, Salcedo G. Wheat and barley allergens associated with baker's asthma - glycosylated subunits of the -amylase-inhibitor family have enhanced IgE-binding capacity. Biochem J 1992; 281: 401-405.

San01 Sander I, Flagge A, Mergret R, Halder TM, Meyer HE and Baur X. Identification of wheat flout allergens by means of 2-dimensional immunoblotting. Allergy Clin Immunol 2001; 107: 907-913.

San90 Sandiford CP, Tee RD, Newman Taylor AJ. Identification of major allergenic flour proteins in order to develop assays to measure flour aeroallergen. Clin Exp Allergy 1990; 20 Suppl 1: 3.

San94a Sandiford CP, Nieuwenhuijsen MJ, Tee RD, Newman Taylor AJ. Measurement of airborne proteins involved in Bakers' asthma. Clin Exp Allergy 1994; 24: 450-456.

San94b Sandiford CP, Tee RD, Newman Taylor AJ. The role of cereal and fungal amylases in cereal flour hypersensitivity. Clin Exp Allergy 1994; 24: 549-557.

San94c Sandiford CP, Nieuwenhuijsen MJ, Tee RD, Newman Taylor AJ. Determination of the size of airborne flour particles. Allergy 1994; 49: 891-893.

San95 Sandiford CP, Tee RD, Newman Taylor AJ. Identification of cross-reacting wheat, rye, barley and soya flour allergens using sera from individuals with wheat-induced asthma. Clin Exp Allergy 1995; 25: 340-349.

Sch87 Schirmer RH, Kalveram KJ, Kalveram CM, Siebert J & Kunze J. Chronisch lichenoide Dermatitis bei Sensibilisierung gegen Alpha-Amylase bei einem Bäcker. Z Hautkr 1987; 62: 792-797. [in German]

Sha95 Shamssain MH. Respiratory symptoms and pulmonary function in flour processing workers in the baking industry. Am J Ind Med 1995; 27: 359-365.

Smi96 Smith TA, Lumley KPS. Work-related asthma in a population exposed to grain, flour and other ingredient dusts. Occup Med 1996; 46: 37-40.

Smi97 Smith TA, Lumley KPS, Hui EHK. Allergy to flour and fungal amylase in bakery workers. Occup Med 1997; 47: 21-24.

Smi00 Smith TA, Parker G and Hussain T. Respiratory symptoms and wheat flour exposure: a study of flour millers. Occup Med 2000; 50: 25-29.

Sos00 Sosiaali-ja Terveysministeriö Työsuojeluosasto. HTP-arvot 2000. Tampere, 2000. [in Finnish]

Sut84 Sutton R, Skerritt JH, Baldo BA, Wrigley CW. The diversity of allergens involved in bakers' asthma. Clin Allergy 1984; 14: 93-07.

Tal02 Talini D, Benvenuti A, Carrara M, Vaghetti E, Bianchi Martini L, Paggiaro PL. Diagnosis of flour-induced occupational asthma in a cross-sectional study. Respiratory Medicine 2002; 96: 236-243.

Tar91 Tarvainen K, Kanerva L, Tupasela O, Grenquist-Nordén B, Jolanki R, Estlander T, Keskinen H. Allergy from cellulase and xylanase enzymes. Clin Exp Allergy 1991a; 21: 609-615.

Tay88 Taytard A, Tessier JF, J Vergeret, Pellet F, Faugere JG, Gachie JP, *et al.* Respiratory function in flour mill workers. Eur J Epidemiol 1988; 4: 104-09.

Tel27 Teleky L. Bäckerekzem. Zbl Haut Geschl Kr 1927; 21: 682-683. [in German]

Thi80 Thiel H, Ulmer WT. Bakers' Asthma: Development and Possibility for Treatment. Chest 1980; 78: 400-405.

Thi87 Thiel H. Probleme der berufsbedingten Inhalations-Allergien am Beispiel des Bäcker-Asthmas. Dermatosen 1987; 35: 81-91. [in German]

Tik96 Tikkainen U, Louhelainen K and Nordman H. 120. Flour dust. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. Nordic Council of Ministers. Arbete och Hälsa 1996; 27: 1-45.

Tos94 Tossaveinen A, Jaakkola J. Occupational exposure to chemical agents in Finland. Appl. Occup Environ Hyg 1994; 9: 28-31.

Tüc86 Tüchsen F, Nordholm L. Respiratory cancer in Danish bakers: a 10 year cohort study. Br J Ind Med 1986; 43: 516-521.

Val88 Valdivieso R, Pola J, Zapata C. Farm animal feeders: another group affected by cereal flour asthma. Allergy 1988; 43: 406-410.

Van96 Vanhanen M, Tuomi T, Hokkanen H, Tupasela O, Tuomainen A, *et al*. Enzyme exposure and enzyme sensitisation in the baking industry. Occup Environ Med 1996; 53: 670-676.

Vin95 Vincenzi C, Stinchi C, Ricci C & Tosti A. Contact dermatitis due to an emulsifying agent in a baker. Contact Dermatitis 1995; 32: 57.

Wal79 Wallenstein von G, Rebohle E and Bergmann I. Allergischen Atemtrakterkrankungen bei Bäckern und Müllern. Dt Gesundh-Wessen 1979; 34: 2577-2580. [in German]

Wal80 Wallenstein von G, Bergmann I, Rebohle E, Gemeinhardt H, Thürmer H. Berufliche Atemtrakterkrankungen durch Schimmelpilze bei Getreidemüllern und Bäckern. Z Erkrank Atm Org 1980; 154: 229-233. [in German]

Wal85 Walsh BJ, Wrigley CW, Musk AW, Baldo BA. A comparison of the binding of IgE in the sera of patients with bakers' asthma to soluble and insoluble wheat-grain proteins. J Allergy Clin Immunol 1985; 76: 23-28.

Wei97 Weiss W, Huber G, Engel KH, Pethran A, Dunn MJ, Gooley AA, Görg A. Identification and characterization of wheat grain albumine/globulin allergens. Electrophoresis 1997; 18: 826-833.

Wil97 Wiley K. Development of an assay for wheat allergens. International Occupational Hygiene Association Meeting, Switserland, September 1997.

Wüt90 Wüthrich B, Baur X. Backmittel, insbesondere -Amylase, als berufliche Inhalationsallergene in der Backwarenindustrie. Schweiz med Wschr 1990; 120: 446-450. [in German]

You74 Young E. Allergic reactions among bakers. Dermatologica 1974; 148: 39-42.

Zus94a Zuskin E, Mustajbegovic J, Schachter EN, Kern J. Respiratory symptoms and ventilatory function in confectionery workers. Occup Environ Med 1994a; 51: 435-439.

Zus94b Zuskin E, Kanceljak B, Mustajbegovic J, Schachter EN. Immunologic findings in confectionary workers. Ann Allergy 1994b; 73: 521-526.

Zus98 Zuskin E, Kanceljak B, Schachter En *et al*. Respiratory function and immunological status on cocoa and flour processing workers. Am J Ind Med 1998; 33: 24-32.

A	Request for advice
B	The committee
C	Comments on the public review draft
D	Background information on sensitisation
E	Selection of epidemiological studies suitable for risk estimation
F	Calculation of the estimated additional sensitisation risk
G	Abbreviations
H	DECOS-documents

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 in the workplace.

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 in the workplace. 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

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Boogaard
  toxicologist; Shell International B.V., The Hague
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- LJNGM Bloemen
- epidemiologist; Dow Benelux BV, Terneuzen
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- A Mulder, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- TM Pal
  occupational physician; Dutch Centre for Occupational Diseases, Amsterdam
- IM Rietjens
  professor in Toxicology; Wageningen University, Wageningen.
- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague

- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- RA Woutersen
  toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

D Heederik, R Houba and G Doekes, Wageningen University, Wageningen, the Netherlands, prepared the first draft of the present report by contract with the Ministry of Social Affairs and Employment. Furthermore, D Heederik advised the committee on this subject.

Secretarial assistance: A Aksel-Gauri and F Smith.
Lay-out: J van Kan.

Annex C

Comments on the public review draft

A draft of the present report was released in December 2002 for public review (a former draft was released in 2001). The following organisations and persons have commented on the second draft document:

- Mr ThL Volkeri, Nederlandse Brood- en Banketbakkers Ondernemers Vereniging, the Netherlands
- Mr P Rijnhout, Vereniging van Nederlandse Fabrikanten van Bakkerijgrondstoffen, the Netherlands
- Mr JG van de Kolk, Nederlandse Vereniging voor de Bakkerij, the Netherlands
- Mr J de Keijzer, Nederlandse Vereniging van Meelfabrikanten, the Netherlands
- Mr T Scheffers, the Netherlands
- Ms E Ball, Health & Safety Executive, the United Kingdom
- Mr R Zumwalde, National Institute for Occupational Safety and Health, the USA

Annex **D**

Background information on sensitisation

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 flour dust. 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 flour dust. 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. Mast cells form the starting point of a cascade of chemical reactions resulting in clinical symptoms. Specific IgE-antibodies against extracts from cereal flours have been demonstrated in workers who were sensitised after inhalation, by *in vivo* and *in vitro* tests (Blo83; Pri85; Sut84). Workers who have become sensitised to a particular agent may also exhibit cross-reactivity to other agents with similar chemical structures.

A special group among the population are the atopics, that are persons with a family history of similar clinical symptoms or persons who are allergic to common allergens. In general, atopic individuals may be slightly more prone to sensitisation to flour dust allergens than non-atopic individuals. In the human population it is estimated that 5.1 to 20.8% are atopic. Most investigators found that atopic workers were 2.7 to 11.7 times more vulnerable for getting work-related respiratory symptoms than non-atopic workers. In addition to being atopic, other factors may increase the risk of getting sensitised

to work-related allergens, such as the level of airborne allergens and smoking habits (Mus89; Cul94), although others did not always confirm this. Age and gender are so far known not related.

Tests are available to screen for sensitised persons against specific allergens. A useful clinical method for determining 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. Alternatively, nasal provocation tests or analysis of the presence of relevant specific IgE-antibodies, for instance in blood and nasal secretions, may be carried out.

Annex **E**

Selection of epidemiological studies suitable for risk estimation

Study design and population information	Exposure information	Health information	Results sensitisation	Ref.
Nested case-control study, within a prospective cohort study (baseline described in Cul94); UK bakery and flour mill workers, n=300; matched controls (exposed, but not having work-related symptoms or being sensitised) obtained from the same cohort.	Exposure (geometric mean, 95% CI) in categories: ***Low (L)***: 65 (57-74) g/m^3 flour allergen, 0.58 (0.5-0.7) mg/m^3 inhalable dust; ***Medium (M)***: 144 (124-167) µg/m^3 flour allergen, 1.17 (1.0-1.4) mg/m^3 inhalable dust. ***High (H)***: 296.1 (257-340) µg/m^3 flour allergen, 4.37 (3.8-5.1) mg/m^3 inhalable dust. Approximately equal-sized categories.	Survey: questionnaire recording presence and date of onset respiratory and skin symptoms. Skin prick tests with common inhalant allergens and extract of five Canadian and British wheat flours. Employees were tested for atopy.	Prevalence (%) positive for skin prick test (flour): L: 14% cases, 43% contr M: 33 % cases, 30% contr M: 52% cases, 27% contr Mutually adjusted odds ratios: ***Allergen exposure***: L: 1.0 (95% CI, -) M: 5.0 (95% CI, 0.4-58) H: 21.0 (95% CI, 1.2-363) ***Inhalable dust exposure (IOM sampler)***: L: 1.0 (95% CI, -) M: 6.1 (95% CI, 0.5-71 H: 14.0 (95% CI, 1-199)	Cul01
Baseline (cross-sectional) analysis of cohort ; UK bakery and flour mill workers, n=344 (n=264 without previous exposure); previous exposure, median 40 months (range: 1-91 months).	Exposure categories (geometric means): ***Low (L)***: < 101 µg/m^3 flour allergen, < 1mg/m^3 inhalable dust; ***Medium (M)***: 101-215 µg/m^3 flour allergen, 1-5 mg/m^3 inhalable dust. ***High (H)***: >227 µg/m^3 flour allergen, >5 mg/m^3 inhalable dust.	Survey: questionnaire recording presence and date of onset respiratory and skin symptoms. Skin prick tests with common inhalant allergens and extract of five Canadian and British wheat flours. Employees were tested for atopy.	Prevalence (%) of sensitisation. ***Allergen exposure***: L: 1 %, M: 5%, H: 6% test for trend p=0.28 ***Inhalable dust exposure (IOM sampler)***: L: 2%, M: 6%, H: 5% test for trend p=0.099 Not adjusted for atopy and smoking habits.	Cul94

Cross-sectional: 1 modern British bakery; n=279.	Job ranking from 0 to 10 by perceived dustiness: - rank 6 (oven staff): median 1.7 (range, 0-37.4) mg/m^3 total dust; - rank 10 (flour room staff): median 6.6 (1.8-13.0) mg/m^3 total dust.	A self-administered questionnaire on symptoms related to work; lung function tests; skin prick test with common allergens and allergens likely to be found in bakery dust, including mites and moulds.	Positive skin test to one or more bakery allergens for rank 6 or higher: ever *v* never Odds ratio, 3.0 (95% CI, 1.4-6.3). Of the 259 workers who scored positive for skin prick test, 14 were positive for mixed flour allergens. Statistical analyses were not performed for each allergen form the work environment.	Mus89
Cross-sectional study; Dutch bakers (n=270) from different industries. Number of workers in traditional bakeries, n=70; industrialized bakeries, n=72; flour-mills, n=73; and, bakery-ingredient industry, n=55.	Personal inhalable dust and wheat allergen concentrations measured. Categories inhalable dust exposure: 0.01-0.59, 0.59-1.14, 1.14-2.06, 2.06-4.70 and 4.70-100.00 mg/m^3. Categories wheat allergen exposure: 0.03-0.34, 0.34-4.84, 4.84-15.18, 15.18-47.39, and 47.39-400 µgeq/m^3. Number of workers per group = 54.	Test for wheat specific sensitisation by blood analyses of specific IgE-antibodies. Also tested for presence of atopy.	Prevalence (%) of sensitisation. ***Inhalable dust exposure (PAS6 sampler)***: 0.01-0.59: 18.5% 0.59-1.14: 33.3% 1.14-2.06: 29.6% 2.06-4.70: 27.7% 4.70-100.00: 20.4% Test for trend significant described by smoothing. ***Wheat allergen exposure:*** 0.03-0.34: 10.6% 0.34-4.84: 25.5% 4.84-15.18: 34.0% 15.18-47.39: 29.8% 47.39-400: 27.1% Test for trend significant (described by smoothing) Based on actual measured exposure levels, the relationship was found to be monotonic up to a value of ~2.7 mg/m^3 inhalable dust or ~25.7 µgeq/m^3 wheat allergen. ***By sector***: traditional b: 37.1% industrial. b: 34.7% ingredients ind.: 16.4% flour mills: 13.7% Exposure-response relationship all sectors (except flour mills): between linear and quadratic relationship. Flour mill sector, quadratic relationship (bell shaped). Atopy was a significant modifier in exposure-response relationship.	Per03 Oos01
Cross-sectional; Dutch bakers (n=393) from small (traditional) and large industrial bakeries	Personal inhalable dust and wheat allergen concentrations measured. Categories cumulative inhalable dust exposure: 1.5±0.8, 5.4±1.7, 12.0±3.0, 29.3±8.2 and 81.9±39.3 mg/m^3-yr. Categories cumulative wheat allergen exposure: 0.7±0.5, 5.3±3.0, 22.4±8.0, 70.6±2.4 and 224.0±109.0 µg/m^3-yr. Average exposure duration 11.7 years.	A self-administered questionnaire on respiratory symptoms. Specific IgE antibodies to wheat flour in blood. Also tested for presence of atopy.	Prevalence (%) ratios. ***Cumulative dust exposure***: 1.5±0.8: 1.0 (95% CI, -) 5.4±1.7: 1.3 (CI, 0.3-4.7) 12.0±3.0: 1.2 (CI, 0.3-4.5) 29.3±8.2: 2.4 (CI, 0.8-7.7) 81.9±39.3: 3.0 (CI, 1.0-9.2) 2 log likelihood 414.2 ***Cumulative wheat allergen exposure***: 0.7±0.5: 1.0 (95% CI, -) 5.3±3.0: 1.6 (CI, 0.4-14.0) 22.4±8.0: 1.7 (CI, 0.4-7.1) 70.6±2.4: 3.7 (CI, 1.0-13.3) 224±109: 3.9 (CI,1.1-13.9) 2 log likelihood 411.9	Hee01 Hou98

Annex **F**

Calculation of the estimated additional sensitisation risk

The estimated additional sensitisation risk to wheat and other cereal flour dusts is calculated by linear extrapolation from the dose-response relationship between the estimated average dust exposure and the prevalence ratio of sensitisation to flour dust allergens. As a starting point the data presented by Heederik *et al*. (Hee01) are used. In general, the committee compares data of occupationally exposed persons with data of non-exposed workers or the general population. Heederik *et al*. did not present such data in their study, but others did (Hou96b; Gau97; DeZ00). From these studies, the committee has chosen a prevalence value of 4% for sensitisation against flour dust for the general population*. The committee adjusted the data of Heederik *et al*. for this 'background' prevalence, as shown in the table below.

* The committee has chosen a 'background' prevalence of 4%, based on the findings of Gautrin *et al*. (Gau97), because of the high reliability and quality of the study. However, other studies do indicate 'background' prevalence values of as low as 2%. According to the committee, the use of 2% instead of 4% would have resulted in only a minor difference in outcome. For instance, the concentration of inhalable dust with an excess sensitisation risk of 1% and a 'background' prevalence of 4% amounts to 0.06 mg/m^3, whereas with a 'background' prevalence of 2% it would be 0.05 mg/m^3.

Group	*cumulative dust* exposure (SD) ((mg/m^3)×yr)	prevalence ratio for sensitisation[a]
1. low	1.5 (0.8)	1.48 (5.9/4.0)
2.	5.4 (1.7)	1.92 (7.7/4.0)
3.	12.0 (3.0)	1.77 (7.1/4.0)
4.	29.3 (8.2)	3.54 (14.2/4.0)
5. high	81.9 (39.3)	4.43 (17.7/4.0)

[a] Prevalence ratio = prevalence of 5 exposure categories divided by the prevalence of the general population, which is 4% according to the committee. Adapted from Hee01.

For estimating the *average* dust exposure levels, *cumulative* dust exposure levels should be corrected for the average duration of employment in the baking industry, which was 11.7 years (Hee01):

Group	*estimated average* dust exposure (mg/m^3) (= *D*)	prevalence ratio for sensitisation (=*PR*)
1. low	0.13	1.48
2.	0.46	1.92
3.	1.03	1.77
4.	2.50	3.54
5. high	7.00	4.43

Furthermore, Figure 5.1 shows that at approximately 3 mg/m^3 the relationship between dust exposure level and sensitisation is levelled off and becomes less steep. For this reason, the committee used only data below this 'levelling off' point for the linear extrapolation. This means that the highest dose group (no. 5) was not taken into account. Taking this into consideration, the linear relation is expressed as

$$1.01 \times D = PR - 1 \ (R^2 = 0.844)$$

in which

- *D* is the estimated average inhalable dust exposure level in mg/m^3
- *PR* is the prevalence ratio for sensitisation in %
- (-)1 is the intercept at a relative risk of 1.0 and exposure at 0 mg/m^3.

For calculating the additional sensitisation risk, the prevalence ratio should be read as

$$PR = \frac{\text{('background' prevalence + additional sensitisation risk)}}{\text{'background' prevalence}}$$

in which

- the committee set the 'background' prevalence at 4%
- the additional sensitisation risk (*AR*) is the excess sensitisation risk in %

so that

$$PR = (4.0 + AR)/4.0$$

and the final expression becomes

$$1.01 \times D = ((4.0 + AR)/4.0) - 1 \quad \rightarrow \quad AR = D/0.248$$

in which

- *D* is the estimated average inhalable dust exposure level in mg/m^3
- *AR* is the additional sensitisation risk to wheat and other cereal flour dusts in %.

Annex **G**

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at which inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LOAEL	lowest observed adverse effect level
LLV	level limit value
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration
MEL	maximum exposure level
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit

ppb	parts per billion (v/v)10^{-9}
ppm	parts per million (v/v)10^{-6}
RD_{50}	concentration at which a 50% decrease in respiratory rate is observed
REL	recommended exposure limit
STEL	short term exposure limit
tgg	tijd gewogen gemiddelde
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice per day)
bw	body weight
CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds complete adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)

GPMT	guinea pig maximisation test
GSH	glutathione
HliA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAC	minimal alveolar concentration
MFO	mixed function oxidase
NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

CI	Confidence interval
GM	geometric mean
OR	odds ratio
RR	relative risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
ELISA	enzyme linked immunosorbent assay
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography
GLC	gas liquid chromatography

GSC	gas solid chromatography
HPLC	high performance liquid chromatography
IR	infrared
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Additional abbreviations in the present report

IgE	Immunoglobulin E
FVC	Forced vital capacity
PEF	Peak expiratory flow

Annex **H**

DECOS-documents

Aanpassing van grenswaarden bij flexibele werktijden	2001/06OSH
Acetone cyanohydrin	1995/05WGD
p-Aramid fibres	1997/07WGD
Azathioprine	1999/04OSH
Aziridine (ethyl imine)	2000/13OSH
Azobisisobutyronitril	2002/01OSH
1,2,3-Benzotriazole	2000/14OSH
Bisphenol A and its diglycidylether	1996/02WGD
Bromoethane	1998/10WGD
1,2-and t-Butanol	1994/10WGD
n-, iso-, sec-, tert-Butylacetaten	2001/03OSH
β-Butyrolactone	1999/05OSH
Cadmium and inorganic cadmium compounds	1995/04WGD
Calculating cancer risk	1995/06WGD
Carbadox	1999/06OSH
Carbon disulphide	1994/08
Chlorine dioxide	1995/07WGD
p-Chloroaniline	1998/09WGD
4-Chloro-o-toluidine	1998/08WGD
Chlorotrimethylilane	2001/05OSH
Chromium and its inorganic compounds	1998/01WGD
Chromium VI and its compounds	2001/01OSH
Cresols	1998/15WGD

Copper sulphate	1999/01OSH
1996-1997 WGD-rapporten/1996-1997 DECOS reports	1999/01WGD
1,2-Dibromoethane	1999/07OSH
1,2-Dichloroethane	1997/01WGD
Diethylsulphate	1999/08OSH
Diglycidyl resorcinol ether	1999/09OSH
Diphenylamine	1997/05WGD
Endotoxins	1998/03WGD
Epichlorohydrin (1-Chloro-2,3-epoxypropane)	2000/10OSH
1,2-Epoxybutane	1998/11WGD
1,2-Ethanediamine	1996/03WGD
Ethyleneglycol ethers	1996/01WGD
Ethylene oxide	2001/11OSH
Ethylene thiourea	1999/03OSH
Formaldehyde	2003/02OSH
Formamide and dimethylformamide	1995/08WGD
Halothane	2002/14OSH
Hydrazinoethanol, phenylhydrazine, isoniazid, maleic hydrazide	1997/03WGD
Hydrogen cyanide, sodium cyanide, and potassium cyanide	2002/15OSH
Isopropyl acetate	1997/04WGD
Lactate esters	2001/04OSH
Lindane	2001/07OSH
Man made mineral fibers	1995/02WGD
Manganese and its compounds	2001/02OSH
2-Methylaziridine (propylene imine)	1999/10OSH
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/11
Methyl-t-butylether	1994/23
Methyl chloride	1995/01WGD
4,4'-Methylene bis (2-Chloroaniline)	2000/09OSH
4,4'-Methylene dianiline	2000/11OSH
Metronidazole	1999/11OSH
Nitrogen dioxide	2004/01OSH
2-Nitropropane	1999/13OSH
N-Nitrosodimethylamine (NDMA)	1999/12OSH
2-Nitrotoluene	1998/12WGD
Pentaerythritol	1997/06WGD
Phenol	1996/04WGD
o-Phenylenediamine	1998/06WGD
Piperidine	1997/08WGD
Procarbazine hydrochloride	1999/14OSH

1- and 2-Propanol	1994/24
Propylene oxide	1997/02WGD
Ronidazole	1998/05WGD
Styrene	1998/07WGD
Styrene	2001/08OSH
Sulphur dioxide	2003/08OSH
Tetrachloroethylene (PER)	2003/01OSH
Quartz	1998/02WGD
Toluene	2001/09OSH
1,1,1-Trichloroethane	1995/03WGD
1,2,3-Trichloropropane	1994/25
1,2,3-Trichloropropane	1998/14WGD
Urethane (ethyl carbamate)	2000/12OSH
Vinylbromide	1999/15OSH
Xylene	2001/10OSH
Wood dust	1998/13WGD