Health Council of the Netherlands

Grain dust

Health-based recommended occupational exposure limit

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Grain dust*
Uw kenmerk : DGV/MBO/U-932342
Ons kenmerk : U 6629/HS/fs/459-Y65
Bijlagen : 1
Datum : 22 juli 2011

Geachte staatssecretaris,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan graanstof.

Dit advies maakt deel uit van een uitgebreide reeks, waarin gezondheidskundige adieswaarden worden afgeleid voor concentraties van stoffen op de werkplek. Het genoemde advies is opgesteld door de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. L.J. Gunning-Schepers,
voorzitter

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Health-based recommended occupational exposure limit

Dutch Expert Committee on Occupational Safety
A Committee of the Health Council of The Netherlands

to:

the State Secretary of Social Affairs and Employment

No. 2011/13, The Hague, July 22, 2011

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

ISBN: 978-90-5549-846-8

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Samenvatting

Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid leidt de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad gezondheidskundige advieswaarden af voor de beroepsmatige blootstelling aan stoffen in de lucht op de werkplek.

In het voorliggende rapport bespreekt de commissie de gevolgen die blootstelling aan graanstof heeft op de gezondheid van werknemers in de graanverwerkende en diervoederindustrie. Vervolgens presenteert zij een gezondheidskundige advieswaarde voor deze stof. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór september 2010 zijn verschenen.

Fysische en chemische eigenschappen

De commissie definieert graanstof als stofdeeltjes afkomstig van ondermeer tarwe (*Triticum sp.*), haver (*Avena sativa*), gerst (*Hordeum vulgare*), rogge (*Secale cereale*), mais (*Zea mays*), rijst (*Oryza sativa*), peulvruchten – waaronder erwten (*Pisum sativum)* en soja (*Glycine hispida*) – en diverse oliezaden. Buiten deze definitie valt stof afkomstig van gemalen tarwe en rogge (meelstof), zoals dat aanwezig is in meelfabrieken en bakkerijen. Endotoxinen vormen een variabele en belangrijke component van graanstof.

Monitoring

Blootstelling aan graanstof in de lucht moet worden gemeten als de persoonlijke hoeveelheid inhaleerbare stof over een achturige werkdag. In Nederland is het gebruikelijk de stofbelasting te meten met een gestandaardiseerde techniek voor het verzamelen van inhaleerbaar stof.

Grenswaarden

In Nederland bestaat geen specifieke grenswaarde voor de blootstelling aan graanstof. De American Conference of Governmental Industrial Hygienists hanteert sinds 1988 een Threshold Limit Value (TLV) voor totaal graanstof van 4 milligram per kubieke meter lucht (4 mg/m^3), gemiddeld over een achturige werkdag. De Britse Health and Safety Executive heeft een Workplace Exposure Limit van 10 mg/m^3 voor graanstof, gemiddeld over een achturige werkdag (tijd gewogen gemiddelde over 8 uur).

Effecten

Blootstelling aan graanstof kan leiden tot een scala van klinische syndromen die voornamelijk te maken hebben met longen en luchtwegen, maar ook met huid en slijmvliezen. Hoesten, slijmproductie, piepen, kortademigheid en longfunctieveranderingen komen vaak voor na inademing van graanstof en wijzen op chronische bronchitis en astma. Ook ‘graankoorts’ is een bekend ziektebeeld bij graanwerkers. Extrinsieke allergische alveolitis wordt zelden waargenomen. De schadelijke effecten van inademing van graanstof zijn voornamelijk immunologisch van aard en endotoxinen in het graanstof spelen een belangrijke rol bij het tot stand komen van de effecten. Blootstelling aan graanstof lijkt ook te kunnen leiden tot niet-respiratoire effecten zoals huidaandoeningen; de diervoederindustrie wordt vanwege toevoeging van diverse stoffen regelmatig genoemd als industrie met verhoogd risico voor het ontstaan van allergische huidaandoeningen. Daarnaast zijn er bij graanwerkers aanwijzingen gevonden voor verhoogde morbiditeit en mortaliteit ten gevolge van kanker.

Evaluatie en advies

De commissie realiseert zich dat endotoxinen in graanstof een zeer belangrijke rol spelen bij het tot stand komen van de gezondheidseffecten. Zij wijst er op dat

de endotoxine inhoud per mg graanstof sterk kan variëren en dat daardoor de handhaving van de bestaande gezondheidskundige advieswaarde voor endotoxine (90 Endotoxine Units met kubieke meter lucht (90 EU/m^3)) wel in de meeste, maar niet in alle, gevallen bescherming biedt tegen gezondheidseffecten van graanstof. Dit houdt in dat een gezondheidskundige advieswaarde voor graanstof zelf noodzakelijk blijft.

De commissie beschouwt vermindering van longfunctie en met name vermindering van FEV_1 (Forced Expiratory Volume in 1 second, de hoeveelheid lucht die in 1 seconde geforceerd kan worden uitgeademd), als het meest kritische effect van blootstelling aan graanstof.

De basis voor het afleiden van een advieswaarde wordt gevormd door een een tweetal studies naar effecten van graanstof op graanwerkers na acute en korte termijn blootstelling (Corey *et al.* 1982[32], DoPico *et al.* 1983[50]). Bovendien wordt gebruik gemaakt van een dwarsdoorsnede-onderzoek (en een follow-up studie na 5 jaar) naar effecten op de longfunctie van werknemers in de mengvoederindustrie (Smid *et al.* 1992[141], Post *et al.* 1998[125]) na chronische blootstelling.

Uit het epidemiologisch materiaal van de studies van Corey *et al.*[32] en Dopico *et al.*[50] leidt de commissie een LOAEL (lowest observed adverse effect level) af van 4 mg/m^3 inhaleerbaar graanstof op grond van longfunctie. De commissie acht het gebruik van een standaard veiligheidsfactor 3 voldoende om hieruit vervolgens een no observed adverse effect level (NOAEL) van ca 1,5 mg/m^3 af te leiden. Bovendien komt uit de studie van Dopico *et al.*[50] een blootstellingswaarde voor graanstof voort waarbij acute symptomen afwezig zijn. Deze waarde bedraagt eveneens 1,5 mg/m^3, en wordt door de commissie gezien als een NOAEL voor acute symptomen. De commissie acht de groep graanwerkers die door Corey *et al.*[32] en Dopico *et al.*[50] bestudeerd is voldoende representatief voor de totale populatie van graanwerkers. Derhalve is commissie van mening dat een extra veiligheidsfactor om te corrigeren voor verschillen in individuele gevoeligheid niet nodig is en dat 1,5 mg/m^3 kan worden beschouwd als een gezondheidskundige advieswaarde (gemiddeld over een 8-urige werkdag) die voldoende bescherming biedt tegen acute en korte termijn blootstelling.

De commissie gaat vervolgens na of deze waarde van 1,5 mg/m^3 ook bescherming biedt tegen chronische blootstelling. Op grond van de berekende relatie tussen blootstelling aan graanstof en longfunctie (Smid *et al.* 1992[141], Post *et al.* 1998[125]) blijkt dat bij een chronische blootstelling van 1,5 mg/m^3, over een achturige werkdag gedurende 40 jaar, rekening moet worden gehouden met een extra daling van het FEV_1 met 45 ml. De normale afname van FEV_1 in

40 jaar bij gezonde individuen bedraagt ongeveer 1 l. De commissie is van mening dat een extra verlaging van FEV_1 met 45 ml niet is geassocieerd met een toename van het aantal individuen met verminderde longfunctie en met verhoogde cardiovasculaire mortaliteit.

Uitgaande van deze gegevens acht de commissie een gezondheidskundige advieswaarde van 1,5 mg/m^3 inhaleerbaar graanstof, gemiddeld over een achturige werkdag voldoende laag om bescherming te bieden aan de werknemer bij acute, kortdurende en chronische blootstelling.

Gezondheidskundige advieswaarde

De commissie adviseert om een gezondheidskundige advieswaarde van 1,5 milligram per kubieke meter lucht (1,5 mg/m^3) inhaleerbaar graanstof, gemiddeld over een achturige werkdag aan te houden.

De gegevens geven geen aanleiding om een aparte grenswaarde voor blootstelling aan graanstof over kortere tijdsperioden vast te stellen. Er is ook geen aanleiding om een huidnotatie vast te stellen.

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 (HBROEL) for existing substances in the air in the workplace. These recommendations are prepared by the Council's Dutch Expert Committee on Occupational Safety (DECOS).

In this report, the Committee discusses the health consequences of occupational exposure to grain dust for employees in the grain and animal feed industries. Subsequently, the Committee recommends a health-based occupational exposure limit. The Committee's conclusions are based on scientific papers published before September 2010.

Physical and chemical properties

The Committee defines grain dust as fine particulate matter originating from several grains, such as wheat (*Triticum sp.*), oats (*Avena sativa*), barley (*Hordeum vulgare*), rye (*Secale cereale*), sorghum (*Panicum miliaceum*), and including maize (*Zea mays*), rice (*Oryza sativa*), pulses – such as soy beans (*Glycine hispida*) and peas (*Pisum sativum*) – and various oil seeds. Flour dusts, originating from milled wheat and rye, and present in flour mills and bakeries are

not included in the definition of grain dust. Endotoxins are a variable and important component of grain dust.

Monitoring

Grain dust levels should be monitored as 8-hour time-weighted averages of personal gravimetric inhalable dust. In the Netherlands, it is common practice to measure exposure using a standardized technique for collection of inhalable dust.

Limit values

There is no specific limit value for grain dust in the Netherlands. In 2001, the American Conference of Governmental Industrial Hygienists (ACGIH) has re-established a TLV (threshold limit value for 8-hours time-weighted average) of 4 mg/m^3 total grain dust (wheat, oats, barley). The Health and Safety Executive in Great Britain has established a Workplace Exposure Limit (WEL) for grain dust of 10 mg/m^3 (8-hour time-weighted average).

Effects

Exposure to grain dust may lead to a spectrum of clinical syndromes mainly affecting lungs and airways, but also skin and mucous membranes. Cough, sputum, wheeze and dyspnoea as well as lung function changes that indicate chronic bronchitis and asthma are frequently found after grain dust inhalation. Also grain fever is a well known disease in grain workers. Extrinsic allergic alveolitis is rarely reported. The predominant mechanism of respiratory toxicity is related to immunologic factors and endotoxins in grain dust play an important role in the development of the effects. Exposure to grain dust may lead to non-respiratory effects such as skin disorders; the animal feed industry is, frequently mentioned as an industry with an increased risk for allergic skin disorders, due to the extensive use of additives. Moreover, an increased cancer incidence and mortality may occur among grain workers.

Evaluation and recommendation

The Committee is aware that endotoxins in grain dust contribute significantly to the development of the health effects of grain dust. It points out that the actual endotoxin content in grain dust, expressed as EU per mg dust is extremely variable and that the implementation of a HBROEL for endotoxin (90 EU/m^3)

will protect in most, but not in all, situations against health effects of grain dust. Therefore, a HBROEL for grain dust itself is still necessary.

The Committee considers decrease of lung function and especially decrease of forced expiratory volume in 1 second (FEV_1) as critical effect of grain dust exposure.

Two acute and short term exposure studies on grain workers were selected as critical studies for the derivation of a health-based recommended occupational exposure limit (HBROEL) (Corey *et al.* 1982[32], Dopico *et al.* 1983[50]). In addition, a cross sectional study and its 5-year follow-up on effects on lung function of employees in the animal feed industry after chronic exposure were selected as critical studies (Smid *et al.* 1992[141], Post *et al.* 1998[125]).

Using the data from the studies of Corey *et al*. 1982[32] and Dopico *et al.* 1983[50] the Committee establishes a LOAEL (lowest observed adverse effect level) of 4 mg/m^3 inhalable grain dust based on lung function. The Committee considers the use of a standard safety factor 3 sufficient for the calculation of a no observed adverse effect level (NOAEL) of 1.5 mg/m^3. Moreover, Dopico *et al.*[50] report a grain dust exposure level in grain workers with no acute respiratory symptoms. This level is, again, 1.5 mg/m^3 inhalable dust, and is considered as a NOAEL for acute symptoms.

The Committee judges that these study populations are a representative sample of the working force. Therefore, the Committee is of the opinion that an additional safety factor to compensate for interindividual differences is unnecessary and that a level of 1.5 mg/m^3 (8-hour time-weighted average) can be considered as a HBROEL offering sufficient protection against health effects of acute and short term exposure.

Next, the Committee verifies whether the proposed HBROEL of 1.5 mg/m^3 protects against the health effects of chronic exposure to grain dust. Calculated dose-response relationships between grain dust and lung function (Smid *et al.* 1992[141], Post *et al.* 1998[125]) show that chronic grain dust exposure of 1.5 mg/m^3 for 8 h a day (time weighted average) during a working lifetime exposure (40 years) leads to an additional loss of FEV_1 with 45 mL. The normal loss of FEV_1 in 40 years in healthy individuals is approximately 1 L. The Committee is of the opinion that an additional average decrease of FEV_1 of 45 mL is not associated with an increase in the number of individuals with abnormal lung function and with increased cardiovascular mortality.

From these data the Committee expects that a health-based recommended occupational exposure limit (HBROEL) for inhalable grain dust of 1.5 mg/m^3 as 8-hour time-weighted average offers sufficient protection to the employee at acute, short term and chronic exposure.

Health-based recommended occupational exposure limit

The Committee recommends a health-based occupational exposure limit (HBROEL) for inhalable grain dust of 1.5 mg/m^3 as 8-hour time-weighted average.

The Committee does not recommend a separate short-term exposure limit for inhalable grain dust (STEL), or a skin notation.

Chapter 1

Scope

1.1 Background

At the request of the Minister of Social Affairs and Employment (Annex A), the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of existing substances that are used in the workplace. The purpose of these evaluations is to recommend health-based occupational exposure limits for concentrations of substances in the air, provided that the database allows the derivation of such values. In the Netherlands, these recommendations serve as the basis in setting public occupational exposure limits by the Minister.

1.2 Committee and procedure

The present document contains the assessment of DECOS, hereafter called the Committee, of the health hazard of grain dust. The members of the Committee are listed in Annex B.

In October 2010, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex 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 grain dust are based on scientific data, which are publicly available. The initial search was carried out in December 1995 in the databases MEDLINE and NIOSHTIC, starting from 1980. In April 2004, an additional literature search covering the period 1996-2004 was performed in Chemical Abstracts, MEDLINE and TOXLINE. A final search was carried out in MEDLINE and TOXLINE covering the literature up to September 2010, and included the search terms grain dust, animal feed, occupational exposure, adverse health effects.

A list of abbreviations used in this report is given in Annex D.

Chapter 2

Identity, properties and monitoring

2.1 Identity

Grain dust is the dust produced during the harvesting and handling of grain, excluding milling. In this advisory report, however, grain dust has a broader meaning: it includes the dust produced in the animal feed industry during the processing of animal feed. This broad meaning of grain dust is derived from the epidemiological studies on respiratory impairment by occupational exposure to grain and animal feed dust. Most of this research was initiated in workers in American and Canadian grain elevators, In these grain elevators various grain products are stored, handled, and sometimes dried, mixed and cleaned. In the Netherlands and in other European countries, similar mixed exposures have been found in the animal feed industry where raw materials for animal feed are mixed, cut or otherwise processed, and subsequently pelleted. These raw materials include pulses, various oil seeds, tapioca, and waste products of the human food industry.

Consequently, grain dust in the broad meaning used in this report may contain dry plant particles as well as bacteria, fungi, insects, sand, and residues of pesticides, and it may originate from various grains and animal feed sources: the cereal grains wheat (*Triticum sp.*), oat (*Avena sativa*), barley (*Hordeum vulgare*), rye (*Secale cereale*), sorghum (*Panicum miliaceum*), maize (*Zea mays*), rice (*Oryza sativa*), but also pulses (the edible seeds of legumes such as soy

beans (*Glycine hispida*) and peas (*Pisum sativum*)), various oil seeds and other animal feed.[12,45,122]

Grain dust is distinguished from flour dust produced during the milling of various cereal grains. Flour dust has different health effects and is therefore not dealt with in this advisory report. The adverse health properties of flour dust have been described and evaluated in a separate report of the Health Council of the Netherlands.[79]

2.2 Physical and chemical properties

As other organic dusts, grain dust has a heterogeneous composition. The main part consists of husk and pericarp fragments generated by the abrasion of kernels when grain is handled. Pollen and fragmented outer cells of pollen walls may also be present. Small husk fragments and 'trichome-like' objects are common. In addition, a variety of other components may be found:

- non-grain plant matter[12,45,165]
- fungal spores, hyphae and fragments derived from a diverse spectrum of phyloplane fungi belonging to the fungal genera *Fusarium*, *Aspergillus Cladosporium* and *Alternaria* species, and in humid grain thermophilic *Actinomycetes spp*.[35,45,64,69,70,93,115,117,165]
- mycotoxins, such as aflatoxins, fusariotoxin, zearalenone, vomitoxin, ochratoxin, and toxin T2[39,93,94,116,117,138,144,145,152]
- bacteria and their chemical components and excretions, such as endotoxins and proteolytic enzymes[42,43,58,115,124]
- mites, such as *Glycophagus destructor* and *Tyroglyphus farinae*, and other insects as the grain weevil[12,36,168]
- other animal matter, including parts of insects, rodents, birds, and their excreta[12,168]
- pesticides, fumigating agents, herbicides, and fertilizers[12,40,41,118,127]
- inorganic matter such as soil, sand, silica, and quartz.[64,168]

The physical and biochemical properties of grain dust have been reviewed by Chan-Yeung and co-workers.[25] Each type of grain dust consists of a distinct assortment of particles of variable form and structure and with particle sizes varying from 10-200 µm. Most grains contain water (10%), proteins (10%) and carbohydrates (80%) in complex peptide- and saccharide-containing molecular structures.

2.3 EU Classification and labelling

Grain dust has not been evaluated by the European Union.

2.4 Validated analytical methods

Grain dust exposure is based on personal inhalable gravimetric dust measurements. In scientific studies, different types of portable pumps, flow rates, filters, and aerosol samplers have been used, depending on the country in which the study was carried out. An overview of personal dust sampling equipment has been given by Boleij *et al.* (1995).[16] In the Netherlands, inhalable dust is usually collected with the PAS6 sampling head.[143] Within Europe, size fractions for measurement of airborne particles in workplace atmospheres have been standardized since 1993.[63] In this standard three size fractions have been defined (inhalable, thoracic and respirable). In the Netherlands measurements of personal inhalable dust exposure on the workfloor are performed in agreement with this standard.[105]

2.4.1 Environmental monitoring

In most epidemiological studies, measured grain dust represents the inhalable dust fraction. In some early studies, a 'total dust' fraction has been measured. In most cases, total dust overestimates the amount of inhalable dust, and the degree of overestimation depends on the method used for the measurements.

Consequently, the Committee recommends to measure the inhalable dust level, constituting the mass fraction of total airborne particles which is inhaled through the nose and mouth (aerodynamic diameter at 50% w/w deposition, 30 µm).

Since endotoxin may be considered as one of the principal components of graindust responsible for the development of acute inflammation and obstruction of the airways, the Committee recommends that environmental monitoring should be extended by endotoxin measurements.[132,159]

2.4.2 Biological monitoring

No methods have been described in the literature for biological monitoring of grain dust.

2.4.3 Biological effect monitoring

The Committee recommends that lung function parameters FEV_1 and FVC should be monitored in employees on a regular time basis.

Chapter 3

Sources

Grain dust is present in the ambient air of facilities in which a significant part of the working activities involves the production, processing and/or use of grains, pulses or oil seeds. Therefore, exposure to grain dust is common in the farming industry (during the production of grain and the use of animal feed), in the animal feed production industry, in grain elevators, and in elevators for raw materials of animal feed, as well as in several other processes in which grain dust is generated.[35,99,131,160,162,164]

This report will primarily focus on adverse health effects in the grain processing industry. The literature that deals with farming environments will not be discussed extensively. The reason for this is that the literature on exposure in the farming industry contains little information on levels of grain dust exposure. Besides, most exposures are combined exposures to grain dust and other substances as well (*e.g.*, pesticides). Nevertheless, the effects described in this report are also relevant for workers exposed to grain dust in farming environments.

Chapter 4

Exposure

4.1 General population

Almost no studies have been published concerning exposure levels to grain dust in non-occupational settings. Only in the Barcelona asthma epidemic study[4,5,150], airborne exposure levels to soybean allergens have been measured before and after installation of filters on top of a soybean silo. Aerosol samples were collected with high-volume suction pumps located in the urban area, where most cases were reported during asthma epidemics. Concentration of airborne soybean allergens on days when soybeans were unloaded decreased from 324 units/m^3 to 25 units/m^3 ($p<0.001$) after installation of filters. Airborne dust levels were not reported.

4.2 Working population

Characteristic exposure data for grain dust are available for a number of industrial activities in the Netherlands such as the animal feed industry[90,143,146], a grain mill[84], three grain elevators[81,146,166], a wheat starch producing facility[110], and two traditional grain wind mills.[140] The results of personal measurements (Table 1) show exposures similar to those found in studies from other countries.[32,85] Except for one seaport elevator, all measurements were carried out with the PAS6 air sampling head[154] which collects the inhalable dust fraction.[16,24,86]

Workers in the animal feed industry may also be exposed to additives like antioxidants (ethoxiquin[23,101,157]), antibiotics (tylosin[106], virginiamycine[153]), growth promoters (furazolidone[38], quinoxaline dioxide[37]), other agents (ethylenediamine dihydroiodide[65]), and trace elements (cobalt[98]). Phytase, a phosphatase derived from *Aspergillus niger* that enhances phosphate bioavailability, is increasingly used as animal feed enzyme additive.[8,44] Bacterial single cell protein, which contains all constituents of dried bacteria including proteins and bacterial cell wall fragments, is used as protein enrichment in animal feed and constitutes a significant source of exposure.[137]

In addition, workers in both the grain and animal feed industry will be exposed to a rich diversity of bacteria and fungi and their components such as bacterial endotoxins, fungal spores, hyphae and mycotoxins.[59,74,96,132]

Table 1 Personal exposure (full-shift, 8 hours) to dust in the Dutch grain industry.

type of industry	number of personal samples	AM (mg/m^3)	GM (mg/m^3)	GSD	range (mg/m^3)	reference
animal feed	530	9.8	2.4	4.7	0.2 - 450	143
animal feed	54	1.8 - 36[a]	1.4 - 13.1[a]	-[b]	0.4 - 199	90
Animal feed	20	-[b]	1.1	3.7	<0.1-7.5	146 c
wheat starch mill	43	20.8	7.4	4.2	-[b]	110
grain mill	98	-[b]	6.8	4.5	-[b]	84
traditional wind mill	16	-[b]	-[b]		>10	140
grain elevator	200	39.9	0.9 - 57.2[a]	-[b]	0.2 - >500	81
grain elevator	92	-[b]	4.4 - 540[a]	-[b]	0.2 - >550	166
grain transshipment	19	-[b]	6.7	5.1	0.8-99	146 c

AM: arithmetic mean; GM: geometric mean; GSD: geometric standard deviation

[a] No overall AM and/or GM was presented in the original publication, but only for each occupational title; the means presented are the lowest and highest AM and GM for the occupational titles.

[b] This information could not be obtained from the original publication.

[c] Endotoxin measurements available.

Chapter 5

Kinetics

No information has been found regarding the uptake and disposition of grain dust in the human lung. No animal studies have been identified addressing this issue.

Chapter 6

Mechanism of action

Exposure to grain dust may lead to a spectrum of clinical syndromes mainly affecting lungs and airways (including organic dust toxic syndrome (grain fever), hypersensitivity pneumonitis (extrinsic allergic alveolitis), asthma, asthma-like syndrome, bronchitis, progressive irreversible airway obstruction), but also skin and mucous membranes (rash and pruritus). (see Chapter 7).[25,132]

No uniform mechanism has been established underlying and completely explaining these effects. Grain dust exposure apparently triggers a variety of mechanisms in the respiratory tract.[19,132] It is very likely that each of the heterogeneous components *(i.e.* mycotoxins, tannins, lectins, lymphocyte mitogens, endotoxin, β1,3-D-glucan, allergens) of the grain dust contributes to, or modifies, a certain type of mechanism.[94]

Non-specific inflammatory reactions are frequently observed after grain dust inhalation.

In addition, a variety of specific immune responses (allergic reactions) may follow grain dust exposure. These immune responses may be either IgE-mediated or not IgE-mediated.

The IgE-mediated immune response may be the most frequently observed response following grain dust exposure. Elevated IgE levels are seen in grain dust induced sensitization (see Section 7.1.1) while the IgE-mediated type I hypersensitivity reaction (the immediate type) is seen in grain dust induced rhinitis, asthma and asthma-like reactions (see Section 7.1.3: Immunological effects).

However, the non-IgE mediated type III (involving other antibodies such as IgG, and immune complexes) and type IV hypersensitivity reactions (the delayed type, involving T-lymphocytes mediation) may be the underlying mechanism of the extrinsic allergic alveolitis.[97] (see Section 7.1.3: Immunological effect).

6.1 Human studies

In early studies, specific antibodies have not been found in sera of patients with an asthmatic response on inhalation challenge.[18,28] Chan-Yeung *et al.* (1979)[28] studied 22 grain workers with respiratory symptoms and/or lung function abnormalities and compared them with 11 asymptomatic grain workers with normal lung function as the controls. Six of the 22 developed asthmatic responses after inhalation challenge with crude grain dust extract. Moreover, the responders had significantly higher peripheral blood eosinophil counts than those who had no such response. None of the controls had a positive skin reaction to the crude grain dust extract. Broder *et al.* (1983)[18] found that grain elevator workers having possible work-related respiratory problems showed no response to inhalation challenge with grain dust extract. In addition, the grain workers exhibited neither an increase in positive serum precipitin tests with fungal antigens, nor abnormal serum levels of complement components C3 and C4 or C-reactive protein.

However, in more recent studies increased cytokine levels and decreased lung function parameters were detected in exposed workers. Zuskin *et al.* (1992)[171] reported immunological reactions to several constituents of animal feed dust among Yugoslavian animal feed mill workers. These immunological reactions did not correlate with respiratory findings.

Becker *et al.* (1999)[10] showed in humans 6 hr after inhalation of corn dust extract that the inflammatory response may be compartmentalized. Bronchial epithelial cells appear to contribute to airway inflammation by producing IL-8, alveolar macrophages are responsible for most of the IL-1β and IL-6 production in the alveolar region, whereas both alveolar macrophages and polymorphonuclear cells both produce IL-1 receptor antagonist. No spirometric parameters were analyzed in this study.

Three experimental studies in volunteers (Blaski *et al* 1996[15], Schwarz 1996[132], Jagielo *et al.* 1996[88]) described effects of grain dust in comparison with the effects of bacterial endotoxin (lipopolysaccharide, LPS) (see Table 2).

Table 2 Biological effects of inhalation of endotoxin from grain dust on respiratory function.

exposure		effects	measured after	n	ref.
endotoxin (μg)	grain dust				
30	Nebulised extract (single dose)	FEV_1↓, FVC↓ in BAL fluid: TNF-α, IL-1β, IL-6, IL-8, histamine↑; total cells, neutrophils, and eosinophils↑	10-24 h 24 h	20[a]	15
Not reported	Corn dust extract (single dose)	in BAL fluid: TNF-α, IL-1β, IL-6, IL-8, and neutrophils↑ FEV_1↓	4 h	14 volunteers (cross-over design)	132
	LPS (single dose)	in BAL fluid: TNF-α, IL-1β, IL-6, IL-8, and neutrophils↑ FEV_1↓			
Not reported	Corn dust extract (single dose)	in BAL fluid: TNF-α, IL-1RA, IL-1β, IL-6, IL-8, and neutrophils↑; FEV_1↓	4 h	15 grain workers (cross-over design)	
	Buffered saline (single dose)	no effect on FEV_1			
36	Corn dust extract (single dose)	in BAL fluid: total cells, neutrophils, TNF-α, IL-1β, IL-6, IL-8↑↑ FEV_1↓	4-24 h	12-14	88
36	LPS (single dose)	in BAL fluid: total cells, neutrophils, TNF-α, IL-1β, IL-6, IL-8↑↑; FEV_1↓			
5.4	Corn dust extract (single dose)	in BAL fluid: total cells, neutrophils, TNF-α, IL-1β, IL-6, IL-8↑; FEV_1↓			
5.4	LPS (single dose)	in BAL fluid: total cells, neutrophils, TNF-α, IL-1β, IL-6, IL-8↑; FEV_1↓			

IL: interleukine; BAL: broncho-alveolar lavage; TNF-α: tumor necrosis factor alfa; FEV_1: forced expiratory volume in 1 second; LPS: lipopolysaccharides (carbohydrates of the outer membrane of gram negative bacteria responsible for the majority of the biological effects of endotoxins).

[a] Including 10 atopic subjects.

Schwarz *et al.* (1996)[132] studied lung function in 14 healthy volunteers and in 15 grain workers in cross over studies. The 14 volunteers were exposed to corn dust extract and three weeks later to lipopolysaccharide (LPS). The 15 grain workers were exposed to saline and three weeks later to corn dust extract. In the healthy volunteers the decline in airflow (FEV_1, FVC) following exposure to LPS was equivalent to the decline after corn dust exposure. This decline was also similar to that in grain workers after corn dust exposure. Marked increases in the concentrations of interleukine (IL)-β, IL-6, IL-8 and tumor necrosis factor (TNF)-α) were observed in the bronchoalveolar lavage fluid of grain workers

and healthy volunteers after inhalation of corn dust extract and after inhalation of LPS in volunteers.

Fourteen volunteers were exposed by Jagielo *et al.* (1996)[88] to a series of inhalation challenges to corn dust extract or LPS each containing a high (6 µg/mL) or low (0.9 µg/mL) endotoxin concentration. Similar symptoms (chest tightness, cough, dyspnea and sputum production) were experienced after both LPS and corn dust extract exposure with similar frequency. No significant differences were observed after corn dust extract challenge and LPS challenge when measuring total cell and cytokine concentrations (tumor necrosis factor (TNF)-α, interleukin (IL)-β, IL-6, IL-8) in lung lavage fluids. Spirometric declines (FEV_1, FVC) were similar both for corn dust and LPS.

Blaski *et al.* (1996)[15] investigated whether atopy influenced the inflammatory response to corn dust extract (containing 0.4 µg of endotoxin/kg body weight) using spirometric measures of airflow (FEV_1, FVC) and broncheoalveolar lavage measures (TNF-α, IL-β, IL-6, IL-8) between demographically similar non atopic (n=10) and atopic study subjects (n=10). No significant differences between atopic and non atopic subjects was found.

All three abovementioned studies[15,88,132] suggested that endotoxin might be a principal component of grain dust responsible for the development of acute inflammation and obstruction of the airways. Furthermore, atopy was not considered a significant factor in the development of the *acute* lower airway response to grain dust.[15]

In some studies, specific allergens in grain dust against the grain mite *'Glycophagus destructor'*[36], (storage) mites[7,161] or durum wheat extract[49] were discovered. In addition, a broad variety of fungal allergens relating to spores and hyphae may contribute to exposure and health effects of grain dust.[74]

6.2 Studies in animals

The relationship between the physiological and inflammatory response to grain dust and endotoxin was experimentally investigated in animals.

Jagielo *et al.* (1998)[87] investigated in mice whether pre-treatment with penta-acylated diphosphoryl lipid A (RsDPLA from *Rhodiobacter sphaeroides*, an endotoxin inhibitor) was capable of inhibiting corn-dust induced inflammatory response. Mice (20/treatment) were exposed to nebulised corn dust (containing 0.2 and 5.4 µg/m^3 endotoxin) during 4 hours after intratracheal pre-treatment with RsDPLA or Hank's balance salt solution (HBSS). After exposure animals were killed and lung lavage and analyses for cytokines were performed (ELISA). After pretreatment with RsDPLA and at the low dose level of corn dust the total

cell numbers, neutrophil cells, TNF-α and MIP-2 (macrophage inflammatory protein-2) were significantly reduced compared to HBSS treated controls.[87] At the high dose level of corn dust the pre-treatment with RsDPLA led again to significant reductions of total cells, neutrophil cells, but also to significant reduction of IL-1β and IL-6 These results support the role of endotoxin as an important agent in the development of airway inflammation.

George *et al.* (2001)[71] performed an 8-week inhalation study (4 hours/day, 5 days/week) with aerosolized grain dust with mass median aerodynamic diameter of 1.4 µm in endotoxin-sensitive mice and in mice hypo-respondent to endotoxin (3 times 20 mice per exposed group). The mice were evaluated before exposure to grain dust, and immediately after and 4 weeks after 8 weeks of exposure. A control group was also included. During the study, airway resistance was measured (enhanced pause pressure), inflammatory response was determined in bronchial alveolar lavage (BAL) fluid by measurements of cells, IL-6, TNF-α and MIP-2, and airway stereology was examined. Airway resistance did not differ between both groups of exposed animals and controls during the study. However, after the recovery period (4 weeks) endotoxin-sensitive animals continued to show airway hypersensitivity. At base line and after the recovery period, cells and cytokines in the lavage fluid did not differ between groups. After 8 weeks, endotoxin-sensitive mice demonstrated a profound inflammatory response (increased levels of neutrophil cells, TNF-α, IL-6 and MIP-2) in the lavage fluid) compared to non-sensitive and control animals. Thickened airway walls, specifically in the airway sub-mucosa, were reported in endotoxin sensitive mice, but not in animals of the other groups. The findings demonstrate that endotoxin has a role in the development of airway disease after exposure to grain dust. Sub-epithelial inflammatory responses appear to be important in the development of *chronic* airway disease. The results of this study are comparable to those of an earlier study of Schwartz (1996)[132] who showed a reduced inflammatory response to grain dust in mice with genetic or acquired hypo-responsiveness to endotoxin.

Gao (1998)[68] investigated the mechanism underlying the nasal effects reported with grain dust exposure (nasal irritation consisting of nasal congestion, rhinorrhea and postnasal drip) was investigated. Macromolecular flux (70-kDa fluorescein isothiocyanate-labelled dextran, FITC-dextran) was used to establish whether grain sorghum dust induces tachykinins (substance P) to elicit a neurogenic inflammation. The model used was *in situ* hamster nasal mucosa, which was suffused with grain dust extract. Grain dust increased FITC-flux. This flux was inhibited by pre-treatment with substance P-receptor antagonists. This

finding supports the hypothesis that grain sorghum dust elicits neurogenic plasma exudation from the *in situ* nasal mucosa.

6.3 *In vitro* studies

Park *et al.* (1999)[121] exposed cells of a bronchial epithelial cell line (Beas-2B), for 24 hours to 1-200 µg/ml grain dust in the presence and in absence of peripheral blood mononuclear cells (producing pro-inflammatory cytokines like TNF-α and γ-IFN) The IL-8 production, as measured by ELISA, was increased in a concentration dependent way. The presence of peripheral blood mononuclear cells enhanced IL-8 production from bronchial epithelial cells. The presence of the glucocorticoid dexamethasone was shown to inhibit IL-8 production. IL-8 production from broncho-epithelial cells may contribute to neutrophil recruitment occurring in grain dust induced airway inflammation.

Redente and Massengale (2006)[128] determined the inflammatory response to various organic dusts and LPS (0-1,000 µg/L) by measuring IL-8 production from transformed respiratory epithelial cells (A549) after dust exposure during 24 hours. The results indicated that all dust types (corn, wheat and poultry) and LPS induced significantly higher levels of IL-8 than control. Corn dust exposure induced IL-8 levels that increased with increasing dust concentrations and correlated with increasing amounts of LPS in the corn dust samples. IL-8 production in response to wheat dust was inversely related to LPS concentration suggesting that other factors besides LPS are present that are responsible for IL-8 production.

Fragments from grain contaminating fungi have been shown to modulate the expression of cytokines in this cell line (A549).[170]

6.4 Conclusion

The physiologic response to graindust exposure is both inflammatory and allergic. The discussion continues on the actual mechanism of the processes involved. Endotoxin probably plays a significant role in the development of grain dust-induced airway disease. However, it is very likely that other agents present in grain dust (*i.e.*, mycotoxins, tannins, lectins, lymphocyte mitogens and β1,3-D-glucan) contribute to, or modify, the inflammatory response.[88] Both in humans and animals the inflammatory response after grain dust inhalation is characterised by neutrophilic alveolitis.This effect is associated with increased neutrophil response and cytokine stimulation (IL-8 in humans only). Although

these effects could be related to changes in respiratory function in the challenge studies, a dose-response relationship was not always clear.

Chapter 7

Effects

Exposure to grain dust may lead to a spectrum of clinical syndromes mainly affecting lungs and airways, but also skin and mucous membranes.[25,132] A wide variety of adverse effects is reported in numerous studies (*i.e.*, organic dust toxic syndrome (grain fever), hypersensitivity pneumonitis (extrinsic allergic alveolitis), asthma, asthma-like syndrome, bronchitis, progressive irreversible airway obstruction, rash and pruritus).[25, 132] Some observations even suggest that grain workers may develop emphysema or diffuse interstitial fibrosis. However, these findings are based on a limited number of case studies[31,57,80], and valid epidemiologic data are lacking. Symptoms that have been reported in epidemiological studies point to an underlying chronic bronchitis, but asthmatic components have also been detected.[46,47,51,53,85,135,141,142]

An important complication in evaluating the available literature, is the occurrence of a healthy-worker effect in observational epidemiological research. In a study in Canadian west coast grain elevators, a lower prevalence of atopy compared to controls was found in grain workers.[26] A repeated study after three years revealed that workers who had left the industry had a lower methacholine threshold in bronchial challenge tests than those who remained in the industry.[62] In another Canadian study, grain workers were found to show less serum precipitin reactions against grain dust extract than a control group.[20] In the follow-up study, Broder *et al.* (1985)[17] compared changes in the respiratory symptoms and pulmonary function of 441 grain elevator workers and a control group of 180 civic workers during a three-year period. They found that workers

who remained in the industry had less prevalence of cough and shortness of breath at base line than those who left. This difference was not found in civic workers. Zejda and co-workers (1992)[169] performed a prospective study of 164 young men from the start of employment in grain elevators. Many workers dropped out of industry during the four-year follow up. The average decline in lung function over the first year appeared to be associated with duration of follow up and the lung function decline was largest in leavers. This clearly shows the healthy-worker effect and implies that restriction of analysis to survivors may underestimate the relation between exposure and respiratory impairment.

7.1 Observations in humans

7.1.1 Irritation and sensitisation

An epidemiological study of Hogan *et al.* (1986)[83] in Canadian grain elevators showed prevalence rates of pruritus of over 50% in two populations. Exposure to barley and oats was reported to provoke the greatest number of complaints.

In an Italian study among 204 workers of 15 animal feed mills, the prevalence of clinically verified occupational contact dermatitis was 13.7%. Duration of employment was positively associated with the rate of contact dermatitis. From these, 7.8% was diagnosed as an irritant contact dermatitis, while 5.8% had an allergic origin (IgE-mediated).[98] A large variety of clinical reports support the authors' conclusion that additives, rather than the feed itself, are a cause of sensitization in animal feed workers and farmers. Among the many additives mentioned in the literature are antioxidants (ethoxiquin[23,101,157]), antibiotics (tylosin[106], virginiamycine[153]), growth promoters (furazolidone[38], quinoxaline dioxide[37]), other agents (ethylenediamine dihydroiodide[65]), and trace elements (cobalt[98]). Although there is consensus on the dominant role of additives as a cause of allergic contact dermatitis[23,98], some grains such as barley are reported to lead to IgE-mediated sensitizing reactions.[34]

Armentia *et al*. (1997)[7] evaluated a population of 4,379 persons residing in an area of cereal industries for IgE-mediated allergy to stored grain pests. Of these individuals 1,395 were cereal workers. In a clinical survey a questionnaire was filled out and IgE studies using skin prick tests and RASTests were performed. Of the 4,379 individuals, 19% (n=791) presented IgE positive to mites (including house mites and storage mites) in the skin prick test and RAST. Among these 791 mite-sensitive individuals, 12% was specifically sensitised to storage mites. However, no relationship with grain dust exposure could be

established. Part of the workers was exposed to flour dust only. Therefore, no conclusions can be drawn.

7.1.2 *Acute and short-term exposure*

Grain fever

Grain fever has been referred to as “organic dust toxic syndrome” (ODTS). Symptoms include malaise, chills, fever, dyspnoea, and leucocytosis, and indicate a systemic reaction. These symptoms may occur during or up to 4-8 hours after short-term exposure to high concentrations of grain dust (>100 mg/m^3), or at working days after prolonged absence from exposure.[46,48,66,103] The mechanism that causes grain fever is different from the mechanism that causes extrinsic allergic alveolitis (see also Section 7.1.3, Immunological effects) which has similar symptoms. In grain fever, there is no immunological mechanism and precipitating antibodies are not found. Symptoms only develop after very high exposures, in the large majority of the exposed people. No chronic characteristics are found after repeated occurrence of grain fever.[46,48,66,104] The number of workers that reported to have experienced grain fever symptoms, ranged from none to 33% in foreign studies. No data on the Dutch situation are available.

Lung function changes

Research on acute reversible lung function changes (spirometric measurements) has been conducted as observational and intervention studies. A common observation in all these studies[19,21,26,27,29,32, 49,50, 89,100,129,151] is that parameters as FEV_1 and FVC are generally reduced upon exposure to grain dust, however, only a few of the of the available studies provide a quantitative exposure-effect relationships (see Table 3).

The first field studies were conducted about 25 years ago. Broder *et al*. (1980)[21] studied 77 grain elevator workers in a 7-month period of less activity in a grain elevator. Half of the workers were laid off for several months in this period. In this group, respiratory symptoms decreased during layoff, and increased after rehiring. All workers showed an increase in flow variables during the period of low activity, and a decrease after restoration of the full elevator activity. The results of this study indicate that lung function abnormalities due to exposure to grain dust can at least be partly reversible.

Table 3 Acute and short term effects of grain dust exposure on lung function.

exposure to	objective (to study)	participants (type/number)	effect level (mg/m^3)	effect	reference
grain dust	changes in respiratory variables during layoff and after rehire in a 7 m period	grain elevator workers (n=77)	not reported	increase of symptoms during employment/ decrease during layoff	21
grain dust	changes in respiratory symptoms and lung function before hiring and after 2½ m employment	new grain elevator workers (n=27)/ civic controls (n=14)	not reported	FVC↓	19
grain dust	changes in respiratory symptoms and lung function before and toward the end of grain harvest (18 d)	seasonal grain handlers (n=119)	not reported	FEV↓	89
grain dust	changes in pulmonary function at the beginning and end of a work shift (1 w)	grain handlers (n=47)/ civic controls (n=15)	1 mg/m^3 (respirable dust)	FEV↓ FVC↓	32 a
grain dust	changes in pulmonary function befor and after 8-h work shift	grain handlers (n=248)/ city services workers as controls (n=192)	3.3 ± 7.0 mg/m^3 (total dust)	ΔFVC = - 46 mL	50 a
extracts of durum wheat (a constituent of grain dust) experimental	changes in lung function after inhalation provocation tests	grain elevator workers (volunteers, n=11)	100.000 PNU/mL	FEV_1↓	49
grain dust	prevalence of respiratory abnormalities and pulmonary function changes during 1 w	grain elevator workers (n=485)//Sawmill workers (n=65) as controls	10.2-13.5 mg/m^3	FEV↓ FVC↓	26
grain dust	(follow-up of Chan-Yeung 1980) after 2½ y pulmonary function changes during 1 w	grain elevator workers (n=396)/Civic workers (n=111)	3.6-17.2 mg/m^3	FEV↓ FVC↓ positive correlation between the annual decline in lung function and the acute decline during the course of 1 work week	27
grain dust	(follow-up of Chan Yeung 1980 after 6 y) pulmonary function changes during 1 w	grain elevator workers (n=267)	not reported	FEV↓ FVC↓ positive correlation between the annual decline in lung function and the acute decline during the course of 1 work week	151
barley dust	lung function changes over 2 d	dock workers (n=6)/controls (n=4)	31 mg/m^3	FEV↓ FVC↓	29
barley dust	lung function changes during 2 d	dock workers (n=6)/control (n=5)	not reported	FEV↓ FVC↓	100

animal feed dust	lung function changes and respiratory symptoms before and after workshift	animal feed workers (n=265)/controls (n=175)	1 -10.1 mg/m^3	FEV↓ FVC↓	142 a
				ΔMMEF = -4 -40 mL/s ΔMEF_{50} = -7.4-75 mL/s	
			for endotoxin 2.7-29.3 ng/m^3	ΔMMEF = -2.7-79 mL/s ΔMEF_{50} = -4.1-120 mL/s	
wheat	lung function changes and respiratory symptoms before and after workshift	wheat harvest workers (n=98)	0.09-15.33 mg/m^3 (total dust)	FEV↓, FVC↓	159 a
			for endotoxin 4.4-744.4 EU/ m^3		

[a] These studies provide exposure-effect relationships.

In a second study among newly hired grain workers, a small decrease in FVC was found in the initial months of employment, as well as an increase in respiratory symptoms.[19] In both studies, exposure levels were not assessed.

In an Australian study, 119 newly hired seasonal grain handlers (mean age 23 year) were assessed for respiratory symptoms before and towards the end of grain harvest (mean work period 18 days).[89] The eighteen percent of workers that experienced wheeze, breathlessness, or chest tightness at work also had a significantly greater decline in FEV_1 ($p< 0.05$) than workers without these symptoms. Symptoms were not associated with changes in bronchial reactivity.

Corey *et al*. (1982)[32] studied 47 grain workers during one week. Mean exposure levels were approximately 1 mg/m^3 respirable dust and 6 mg/m^3 non-respirable dust (dust collected in cyclones during the collection of respirable dust on filters). Compared to a control group of outside labourers, FEV_1 and FVC decreased during the week (from Monday morning to Friday morning). A correlation between exposure and cross-shift decreases of MEF_{50} and MEF_{25} was found.

Another observational study was carried out by DoPico *et al*. (1983)[50] who studied 248 grain handlers before and after an 8-hour work shift, and compared them to 192 city service workers as the controls. Grain workers were exposed to a mean personal total dust concentration of 3.3 mg/m^3. Upon correction for effects of age, height, and smoking habits, the increase of total dust concentration correlated significantly ($p< 0.05$) with the decrease in FVC, MEF_{50} and MEF_{75}, and the increase in leukocyte count.

Moreover, in the same study it is reported that grain workers with one or more respiratory symptoms (cough, expectoration, wheezing, or dyspnea) during the daily work shift (n=122) were on the average, exposed to a higher total dust

concentration (4.1 ± 8.1 mg/m^3) when compared with grain workers (n=87) with no respiratory symptoms (2.1 ± 4.5 mg/m^3).

Chan-Yeung *et al.* (1980)[26] studied 485 grain workers in the port of Vancouver and found statistically significant cross-shift decreases on Mondays, and decreases during the week, for both FVC and FEV_1. A group of 65 sawmill workers taken as a control group showed statistically significant increases for the variables mentioned, as expected due to circadian rhythm.

After 2.5 years, the study had a follow-up among the same workers (n=396). The mean annual decrease of lung function variables was computed by comparing the Friday afternoon measurements. The authors reported a statistically significant correlation (p=0.037) between the annual decline in lung function and the acute decline in lung function (during one work shift or one work week) at the initial health survey. It is, however, not clear which lung function variables are concerned.[27]

In the second follow-up after six years in 267 workers, significant correlations between the annual decline and the cross-week changes in the base-line study were found for FVC, FEV_1 and MMEF.[151]

A Danish study among 132 grain elevators was aimed at identifying diurnal variation in peak expiratory flow rate (PEFR). The difference between the highest and lowest PEFR was related to respiratory symptoms, and weakly related to grain dust exposure.[129]

Cockcroft and co-workers (1983;1985)[29,100] found considerable changes in FEV_1 and FVC in six people – without previous exposure – who spent two hours in a barley silo. The dust concentration was extremely high: the environmental total dust concentration was approximately 580 mg/m^3 and the respirable dust level was 31 mg/m^3.

DoPico *et al*. (1982)[49] found a greater than 20% decrease in FEV_1 in 5 out of 11 grain workers after bronchial challenge with durum wheat extract. In four of the five responders the reactions did not appear immediately, but only after a few hours. In the fifth responder, the reaction was immediate and he was the only subject that reacted on the durum wheat dust itself. No reactions were found after challenge with extracts of mites and insects.

Cross-shift lung function changes (FVC, FEV_1, MEF_{50}, MEF_{75}) were found during exposure to soy bean dust.[172]

Smid *et al.* 1994 [142] compared respiratory symptoms in 265 exposed animal feed workers with those in 175 controls. Symptoms indicating respiratory and nasal irritation were significantly increased in the animal feed workers. In 119 workers of these 265 cross shift spirometric lung function changes were measured. Almost all lung function parameters (including FEV_1 and FVC) were

decreased. Moreover, a dose response trend was established between dust exposure and MMEF and MMF_{50} . A stronger and more significant dose response was observed between endotoxin exposure and MMEF and MMF_{50}.

Viet *et al.* 2001[159] studied 98 wheat harvest workers exposed to 0.09 to 15.33 mg/m^3 dust and 4.4 to 744.4 EU/m^3 endotoxin. Sixty percent of the workers experienced a cross-shift change in at least one respiratory symptom (a.o. shortness of breath, chest wheezing). The authors developed a respiratory index which was defined as the sum of the cross-shift changes in the eight acute respiratory symptoms. They observed a significant correlation between the respiratory index and both total dust and endotoxin exposure. On the other hand, cross-shift changes were also observed in the spirometric variables (FEV_1, FVC etc.) but these were not clearly associated with dust or endotoxin exposure.

7.1.3 Long-term toxicity

Many cross sectional and a few longitudinal studies were conducted to detect chronic effects in populations of grain workers. Most of these studies did not include detailed exposure assessment. Studies that included exposure assessment and that focused on the exposure-response relationship will be described first and their relevance discussed.[32,33,52,54, 61,81,85,90,123,125,126,133,136,141,142,166] In these studies, the quality of lung function measurements is high and meets the requirements of the American Thoracic Society (ATS) or the European Community for Coal and Steel (ECCS). Furthermore, all of these studies had a high response rate of participants, and in most studies the analyses of exposure-response relationships were controlled for potential confounders (such as smoking habits). Also, the quality of exposure measurements in these studies was high. Unfortunately, most of these studies have a cross-sectional design. Until now, the number of well designed (prospective) cohort studies among grain workers is limited.

A few studies have indicated a relationship between current grain dust exposure and lung function impairment.[32,33,52,54,90] Other studies showed a relationship between duration of employment and lung function.[111,112,136,166] A few showed that lung function impairment is related to cumulative grain dust exposure as well as to the duration of exposure.[85,141] In a literature survey, Chan-Yeung *et al.* (1992)[25] mentioned three studies in support of an exposure-response relationship. The first study, by Corey *et al.* (1982)[32], identified an inverse relationship in grain handlers who did not wear a mask, between present respirable dust concentration and baseline FEV_1, MEF_{50}, and MEF_{25}.

Paradoxically, however, FEV_1 and FVC were found to increase with longer employment duration. Furthermore, lung function levels were not related to non-respirable dust levels.

Table 4 summarizes the effects found in a number of chronic epidemiological studies.

Table 4 Chronic effects of grain dust exposure on lung function (FEV1, FVC) found in epidemiological studies.

type of study	exposure to	objective (to study)	participants (type/ number)	effect level (mg dust/m^3)	effect	reference
longitudinal, nested case-control	grain dust	respiratory parameters over 6 y	grain elevator workers (n=27)	5 mg/m^3	$FEV_1\downarrow$ (100 mL/y)	61
longitudinal	grain dust	dose-response between grain dust exposure and respiratory abnormalities over 15 y	grain elevator workers (n=454)/Civic workers (n=55)	4-9 mg/m^3	FVC↓(4.0%) and FEV_1(3.2%)	85
longitudinal	'agricultural dust'	decline in lung function over 2 y	swine confinement operators (n=168)/ Farmer controls (n=127)	6.4 mg/m^3	$FEV_1\downarrow$ and FVC↓	133
cross-sectional	animal feed dust	relationship between organic dust and respiratory symptoms and chronic lung function changes	animal feed workers (n=315)	5 mg/m^3	FVC↓(64 mL) and $FEV_1\downarrow$ (70 mL) at 8.6 mg/m^3	141
	animal feed dust	changes in prevalence of respiratory symptoms and lung function (follow up of Smid *et al.* 1992 after 5 y)	animal feed workers (n=140)	4-10 mg/m^3 >10 mg/m^3)	$FEV_1\downarrow$ 12.8 mL $FEV_1\downarrow$ 22.4 mL	125,126
cross- sectional	animal feed dust/endotoxin	relate respiratory symptoms to lung function measurements	animal feed workers (n=194)	0-4 mg/ m^3	Chronic bronchitis, wheezing, FEV_1(6.9%)	90
meta-analysis of 4 studies including Huy *et al.* 1992 and Smid *et al.* 1992	grain dust/ animal feed dust	compare exposure-response relationships between exposure to grain dust and respiratory health	dutch and Canadian grain elevator worker & Dutch animal feed workers (n= approx 1200)	7.9 (Dutch animal feed) 44.6 (Dutch grain elevator workers) 3.5 (Canadian grain elevator workers)	$FEV_1\downarrow$ 71 mL $FEV_1\downarrow$ 87 mL $FEV_1\downarrow$28 mlL	123

In a 6-year longitudinal study, Enarson *et al.* (1985)[61] used a nested case-control design to study lung function in grain handlers. Cases (n=27) were identified as persons belonging to the 10% of workers with the worst trend of FEV_1 during the study. Cases were matched with two control subjects identified as the workers in the cohort (with the same age and smoking habit) who had the best trend in FEV_1 over the study period. Cases showed a rapid decline in FEV_1, averaging 100 mL per year (2.6% of mean group FEV_1 in 1975), and a mean decline of 682 mL (17.9% of group mean FEV_1 in 1975) after six years. No decline in lung function was observed in the control group. The authors compared the distribution of cases and controls in the various job categories with varying exposures and found that the higher the dust concentration, the higher the likelihood of being a case. The mean dust level at which no increased risk was observed (odds ratio equal to one) was obtained by interpolation and appeared to be about 5 mg/m^3. This value is valid for 'cases' as defined and which constituted the most severely affected workers (average FEV_1 decline of 100 mL/year). An exposure limit of 5 mg/m^3 would, therefore, prevent only the most severe respiratory damage. From this study, no conclusions can be drawn about respiratory effects at grain dust levels below 5 mg/m^3.

A more extensive analysis of the same cohort, by Huy *et al*. (1991)[85], showed that workers with an 'average' exposure between 4 and 9 mg/m^3 were found to have lower values for FVC and FEV_1 when compared to grain workers exposed to < 4 mg/m^3 (4.0% and 3.2%, respectively) and when compared to a reference population of civil workers (6.7% and 7.4%, respectively). Annual declines in FEV_1 of 10.4 mL, 20.7 mL and 34.1 mL at respective exposure levels < 4 mg/m^3; 4-9 mg/m^3; and > 9 mg/m^3 were found. In this analysis, the group exposed to 'average' grain dust levels less than 4 mg/m^3 reported significantly more phlegm production and had a significantly lower FVC compared to the office workers. A major problem when interpreting the results of this analysis is that average dust exposure was expressed as the geometric mean by job title. When computing retrospective individual average exposures, however, the arithmetic mean of yearly geometric job title means was used. The arbitrary use of one year periods does not have physiological plausibility, since it presumes that for periods of up to one year the effects are related logarithmically to the total body burden, whereas for time segments of one year, effects are linearly related to exposure. A reanalysis of this study showed the exposure-response slope for FEV_1 to be moderately in agreement with the slopes found in Dutch industries.[123]

Schwartz *et al.* (1995) reported on determinants of longitudinal changes in lung function in 168 swine confinement operators and 127 farmers (controls).[133] Follow-up time was about 2 years (range 56-1900 days). Groups were controlled

for age, gender, racial background, smoking and atopy status. Environmental dust concentrations were measured as total dust, showing a higher exposure in swine confinement operators than in farmers (6.4 mg/m^3 versus 2.3 mg/m^3). Farmers tended to have a greater decline in FEV_1 and FVC than swine confinement operators over the follow-up period, but the swine confinement operators showed greater declines during shift (also for FEF_{25-75}). For every percentage decrease in lung function during shift, one could anticipate longitudinally a decline of 100 mL in FEV_1, 30 mL in FVC and 20 mL/s in FEF_{25-75}. The authors concluded that longitudinal declines of lung function were independently associated with cross-shift declines of lung function and with higher concentrations of endotoxin in the aerosol.

In the Netherlands, large-scale studies focusing on exposure-response relationships were carried out in animal feed workers and grain elevator workers.[81,90,123,125,141,142] Unexposed controls were included in the study by Jorna *et al.* (1994)[88] and in the study by Smid *et al.* (1992).[141]

Smid and co-workers (1992)[141] carried out a cross-sectional study of 315 animal feed workers. The analysis of reported symptoms indicated frequent cough to be more often reported in the exposed group than in the control group. Other respiratory symptoms were not consistently related to current dust levels. Selection bias (*i.e.*, a healthy-worker effect) was apparent, and for this reason, exposure analysis was carried out with exposed workers and internal control subjects only. Exposure related lung function decreases were found for most flow variables studied (*i.e.*, FVC, FEV_1, MMEF, PEF, MEF_{75}, MEF_{50}, and MEF_{25}). FVC decline was not significantly related to retrospective exposure and MMEF decline not significantly related to present exposure. The estimated lung function losses at the overall mean current dust level of 8.6 mg/m^3 were 64 mL for FVC ($p<0.05$), 70 mL for FEV_1 ($p<0.01$), 63 mL/s for MMEF (not significant), 568 mL/s for PEF ($p<0.01$), 370 mL/s for MEF_{75} ($p<0.01$), and 138 mL/s for MEF_{50} ($p<0.05$). At the mean cumulative dust exposure of 111 mg/m^3 • years (estimated from current dust levels, assuming current and historic dust levels to be similar), FVC decreased with 51 mL (not significant), FEV_1 decreased with 82 mL ($p<0.01$), MMEF with 114 mL/s ($p<0.05$), PEF with 670 mL/s ($p<0.01$), MEF_{75} with 502 mL/s ($p<0.01$), and MEF_{50} with 216 ml/s ($p<0.01$).[141] In other words, the FEV_1 decline was 82/111=0.74 mL per year per mg/m^3 grain dust, or 30 mL per 40 years per mg/m^3 *i.e.* 120 mL per 40 years at 4 mg/m^3. In addition to these results, the study also showed that both respiratory symptoms and lung function were more clearly related to present and historic endotoxin exposure than to inhalable dust exposure.

Post *et al.* (1996, 1998)[125,126] studied 140 of the 315 workers of the Smid *et al.* (1992)[141] cohort at five-year follow-up. The prevalence of respiratory complaints was again low among workers and not related to the exposure level. In contrast, FVC (though not statistically significant), FEV_1 and MMEF decreased with increasing exposure. The excess annual declines in FEV_1 were 12.8 mL and 22.4 mL for workers in the intermediate (4-10 mg/m^3) and high (>10 mg/m^3) dust exposure level category, compared to the (<4 mg/m^3) low exposure group and corrected for age, standing height, and smoking. For a 40-year working life, the excess FEV_1 declines were estimated to be 512 mL and 896 mL (95% CI, 65-1,727 mL) at the intermediate and high exposure levels, respectively. For FEV_1 and MMEF, the largest decline was found in workers remaining highly exposed during the follow-up or going from high/intermediate-exposure jobs to low-exposure jobs. When cumulative exposure to 5 mg/m^3 was assumed during a working life of 40 years, FEV_1 (corrected for age, standing height, and smoking) would decrease with 157 mL (95% CI, 13-300 mL) and MMEF with 473 mL/s (95% CI, 127-820 mL/s), which is in agreement with the findings of Smid *et al.* (1992).[141]

In another study among 194 animal feed workers, lung function and respiratory symptoms were associated with dust exposure levels.[90] Exposure categorisation was by arithmetic mean, as in the analysis of Huy and co-workers (1991)[85]: not exposed; 0 to 4 mg/m^3; 4-9 mg/m^3; and >9 mg/m^3. Exposure-related lung function changes were found for all lung function variables studied, except for FVC, and these were already significantly different from controls at exposure levels below 4 mg/m^3. The decrease at 0-4 mg/m^3 was 6.9% for FEV_1 and 14.6% for MMEF. An exposure-response relationship was found for chronic bronchitis and 'ever wheezing'. In the group exposed to 0-4 mg/m^3, 14% of the workers had complaints of chronic bronchitis, and this was significantly elevated compared to the 7% of non-exposed workers with complaints.

A qualification of the magnitude of the respiratory disorders in these studies is difficult because the constituents and, therefore, the toxicity of grain dusts may vary depending on the source. In addition, methods of analysing exposure-response relationships differ across studies. To overcome this, data from 4 previously conducted studies[81,85,141] of grain-dust exposed workers in the Netherlands and in Canada were combined, and analysed for relationships between grain dust exposure and respiratory health (comparisons were made for FEV_1 and respiratory symptoms).[123] The study showed that despite existing exposure misclassification, healthy-worker effects, and differences in exposure levels, exposure characteristics, and sampling devices, there was a moderate similarity in the slopes of the exposure-response relationships for FEV_1 in the

four different grain industries in the two countries. Only the slope for the Dutch transfer industry differed significantly from the control group slope. This was explained by misclassification of exposure and the healthy-worker effect. The estimated FEV_1 lung function losses for the overall mean dust level per industry were 71 mL for the animal feed workers (mean current exposure 7.9 mg/m^3), 87 mL for the Dutch grain elevator workers (mean current exposure 44.6 mg/m^3), and 28 mL for the Canadian terminal workers (mean current exposure 3.5 mg/m^3).

The following studies focus on measurement of spirometric effects but lack a sufficiently detailed exposure assessment. However, in some studies indirect measures of exposure such as years of employment in the industry are available.

In a twelve-year follow up study among workers in the vicinity of Paris, exposure to grain dust was reported to be related to FEV_1 decreases.[91] Chan-Yeung *et al.* (1980)[26] found a lower FVC and FEV_1 in 600 grain elevator workers on the Canadian West coast compared to a control group of office and saw mill workers. The incidence of respiratory symptoms and eye and nose irritation was elevated. In a follow up after 2.5 years, the results were reproduced.[27] The largest decreases in FEV_1 and MMEF were found in older workers, compared to a control group. In a second follow up after six years, it was found that the 10% of workers who showed the largest decreases in FEV_1 compared to the 10% who had the best trend were exposed to significantly larger exposures during the base-line study.[60]

Corey *et al.* (1982)[32] found an inverse relationship between the mean personal respirable dust exposure and the baseline FEV_1, MEF_{50}, and MEF_{25} in 17 grain workers who did not use respiratory protection.

In a longitudinal Canadian study among 441 grain workers in Thunder Bay, no differences from the control group were found.[17] In South Africa, differences in respiratory symptoms were detected between 582 non-white grain workers and 153 controls. No differences in lung function were found. However, cross-week changes differed between groups for FVC, FEV_1 and MMEF.[167] In a study in Scotland, lung function variables did not differ between 75 grain workers and 48 controls.[122] In an Amsterdam grain elevator, differences in FEV_1, MMEF, MEF_{50}, MEF_{25} and respiratory symptoms were found between workers and control in a group of 71 subjects.[166]

A Canadian research group reported a number of longitudinal studies on the same population of grain workers.[108,111-114] They used a database containing data form a large scale grain dust medical surveillance program. The database included follow-up over many years of pulmonary function measurements and pulmonary symptoms among Canadian grain workers in the primary and

terminal grain elevators in Canada. The investigators selected different subpopulations for their evaluation of long term effects (see Table 5).

To evaluate the relationship between the long term effects of grain dust and decline in lung function, grain elevator workers in Saskatchewan were studied over a 15-year period (1978 to 1993). The number of years employed in the grain industry was used as a surrogate measure of exposure. Data on respiratory symptoms and pulmonary function tests (FEV_1, FVC) were collected once every three years; each three-year interval was called a 'cycle'.[55,56,111,112] There were 203 grain workers who participated in all five cycles, 259 in four cycles, 497 in three cycles, 739 in two cycles and 2,394 in one cycle. Over a period of three years, a change of FVC and FEV_1 was found between exposed workers and controls.[55] Mean annual loss of FEV_1 (and FVC) increased with increasing

Table 5 Longitudinal studies[a] based on material from the Labor Canada Grain Dust Medical Surveillance Program (GDMSP),

Type of study	exposure (to)	objective (to study)	participants (type/number)	main findings	ref.
longitudinal	grain dust/years in industry	longitudinal changes in lung function over 6 y	grain elevator workers (n=3,196)/non-smokers/ current smokers/ ex-smokers	annual decline in FEV_1 and FVC	111
longitudinal	grain dust/years in industry	longitudinal changes in lung function over 15 y	grain elevator workers (n=4,092) /non-smokers/ current smokers/ ex-smokers	annual decline in FEV_1 and FVC increased with length of time in grain industry/dust control measures were effective	112
longitudinal	grain dust/years in industry	longitudinal changes in prevalence of respiratory symptoms	grain elevator workers (n=20,831) / non-smokers/current smokers/ex-smokers	prevalence of symptoms (wheeze, dyspnoe, sputum, cough) increased with years in industry/dust control measures were effective	114
longitudinal	grain dust/years in industry	longitudinal changes in lung function in new grain workers (initial years of employment)	new grain elevator workers(n=299)/'old' grain elevator workers (n=2,184) /non-smokers / ever smokers/	non smoking new grain workers had the greatest annual decline in FEV_1 and FVC, while non smoking grain workers with more years in the industry had the least annual decline in FEV_1 and FVC	108
longitudinal	grain dust/years in industry	longitudinal changes in lung function before and after dust control measures	grain elevator workers (n=14,906 before and n=5825 after)/ non-smokers/ ex-smokers/current smokers	grain dust control was effective in reducing decline in the lung function measurements (FEV_1, FVC) in all exposure categories mean annual loss of FEV_1 was greatest among current smoking grain workers followed by ex-smokers and non smokers	113

[a] No detailed exposure assessment was reported.

exposure time for non-smokers, smokers and ex-smokers (FEV_1 9.2-52.6 mL/y, FVC 21-61 mL/y). Initially, the decline was greater with (ex-) smokers, but with an estimated exposure duration of > 20 years of employment this effect disappeared.[111] A transitional model was developed to predict the annual decline in FEV_1 and FVC. Significant predictors of FEV_1 decline were previous FEV_1, base height, weight, years in the grain industry, current smoking status, cycle II, cycle III and cycle V. Significant predictors of FVC were previous FVC, base height, weight, years in the grain industry, cycle II, cycle III and cycle IV.[112] Over the whole period a healthy-worker effect became apparent.

In a longitudinal study monitoring individuals from the same grain elevator worker population[108] as in the abovementioned study[111,112] a comparison was made between lung function changes in workers in their initial years in the industry (n=299) and workers with a longer employment history (n=2,184). It was observed that 'new' grain workers had the greatest annual decline in FEV_1 and FVC, while grain workers with more years in the industry had the least annual decline in FEV_1 and FVC thus confirming the healthy worker effect in the older employees population.

The effectiveness of the preventive measures taken in the grain industry could also be assessed from this Canadian cohort using the data from the same database. Apparently, remediation measures were implemented after cycle II and before cycle III (from 1987), keeping the dust exposure below 10 mg/m^3. The lung function[113] of the same population of grain elevator workers and the symptoms[114] were monitored before and after these specific remediation measures. The decline in lung function during the first three cycles was much faster compared to the decline in cycles IV and V. This suggests that grain dust control was effective in reducing the decline in the lung function measurements FEV_1 and FVCC.[113] Moreover, a reduction in the prevalence of chronic respiratory symptoms (wheeze, dyspnea, sputum, and cough) was observed in all employees during these cycles IV and V, as compared to cycles I, II and III.[114]

Carcinogenicity

Several mortality and cancer incidence studies mainly published in the eighties of last century were aimed at evaluating risks of occupational exposure in the grain industry.

The actual proof that grain dust is a causal factor in cancer development is not strong in most of these studies. This is mostly due to the variable composition of the grain dust. Therefore, relevance of these findings for occupational health is not representative for every type of grain dust.

Two cancer incidence studies, one among grain millers in Sweden[1] and one from the animal feed industry in Denmark[109], indicate an increased incidence of primary liver cancer. In these Scandinavian reports, exposure to aflatoxin, which is of fungal origin, was hypothesised as a plausible cause of the liver cancer. Evidence from a Dutch mortality study in a vegetable oil pressing facility with exposure to aflatoxin[75,158] showed that an increased mortality from non-malignant liver disease and (respiratory) cancer is possible at low exposure levels. The study cohort (71 exposed workers and 67 controls) was too small to detect differences in mortality from liver cancer. The increased mortality from respiratory cancer was not confirmed in the Scandinavian incidence studies mentioned before. Since no adjustment for smoking habits was made, the smoking behaviour of the Dutch vegetable oil press workers may have been a confounding factor. Among others, carcinogenic mycotoxins such as aflatoxin, sterigmatocystine, and zearalenone are hypothesised as causes.

Lymphatic and haemopoietic malignancies were reported from two proportionate mortality ratio studies in the USA, one in the corn-wet milling industry[155], and one in the grain industry.[2] Both studies identified a relationship between lymphatic malignancies and occupation. Alavanja *et al.* (1987)[2] found elevated proportionate mortality ratios in grain industry workers. However, no increased mortality rates for Hodgkin's disease were found.. In the corn-wet milling industry, elevated proportionate mortality ratios for lymphatic malignancies were also found but an increase of Hodgkin's disease was not reported.[155] However, the actual causal factor could not be indicated.

Bladder cancer mortality was reported in the US corn-wet milling industry mentioned above.[155] An Ohio case control mortality study also identified working in grain mills as a risk factor for bladder cancer.[147]

Parent *et al.* (1998)[119] performed a case-control study with approximately 2,300 cancer patients (no lung or oesophagus cancer) and 533 healthy controls in the region of Montreal. There was some indication of an excess risk of stomach cancer among workers exposed to grain dust. However, it should be kept in mind that confounding exposures may have occurred in this group (fertilizers, pesticides, fuels, engine exhausts, and organic and inorganic dust). The authors concluded that due to the paucity of data, the overall result is a weak association.

Two non-occupational studies on the relationship between cancer mortality and the proximity of the grain industry were performed.[72,134] A cluster of Hodgkin's disease was found in a small town in Michigan. The incidence in a twenty-year period was 10 cases in the 1,250 inhabitants' town, while 0.74 cases were expected. The only industrial facility in the town was a grain elevator, and most of the cases resided near the elevator. The authors speculated chronic

immune stimulation by mitogenic substances (especially, phytohaemagglutinin in navy beans) to be a predisposing factor for the development of Hodgkin's disease.[134] Although the increased incidence rate is clearly significant, the causal link to dust exposure is highly speculative.

In a case-control study in Louisiana, slightly elevated relative risk estimates of lung cancer were found for over ten years of residence near grain industry. The authors hypothesised particulates as causal factors but also stated that no conclusions were warranted because of the small number of cases.[72]

Exposure to organic dusts, including grain dust, and its relation to incidence of respiratory cancers was studied in a large cohort of Finns (born between 1906 and 1945, 667,121 men and 513,110 women). Cumulative exposure was calculated as a product of prevalence, level and estimated duration of exposure, using data from the population census records (1970). Combining these with data from the Finnish Cancer Registry allowed to study the relationship between exposure and cancer incidence. For laryngeal cancer men exposed to plant dust (mainly grain millers) had a raised standard incidence ratio (SIR 3.55, CI, 1.30-7.72) in the high inhalatory exposure class (> 40 mg/m^3 y).[95]

Reproduction toxicity (fertility and development)

No data available.

Immunological effects

Extrinsic allergic alveolitis

Extrinsic allergic alveolitis has been observed in individuals working with mouldy hay, straw, and grain. Extrinsic allergic alveolitis has been incidentally described among grain workers following grain dust inhalation. Respiratory and systemic symptoms appear some hours after exposure and include chills, fever, cough and dyspnoea.[97,102] Precipitating antibodies (IgG) are present.[97] The alveolitis seems to be the result of hypersensitivity immune reactions to repeated inhalation of various grain dust antigens. These reactions are thought to be immunocomplex mediated processes (type III hypersensitivity) but cell-mediated immunity (type IV hypersensitivity) may be involved as well.

Grain dust may induce asthma or asthma like reactions both by an IgE and a non IgE mediated mechanism.[9,107]

Occupational asthma in grain handlers has been observed in several studies. In 1974, Warren and co-workers[163] investigated 15 grain workers with respiratory symptoms and compared the results to those of 5 controls without such symptoms. Inhalation challenge tests with extracts of grain dust showed that eight out of 15 grain workers developed asthmatic responses after challenge; 7 out of 8 had a positive immediate skin test to crude grain dust extract. Immediate, late, and dual asthmatic responses were described.

Chan-Yeung and co-workers (1979)[28] studied 22 grain workers with respiratory symptoms and/or lung function abnormalities. Six of the 22 grain workers developed immediate asthmatic responses after inhalation challenge to crude grain dust; three of them in addition developed a late asthmatic (dual) reaction occurring four to six hours after challenge with recovery within 24 hours. None in the comparison group developed any reaction (see Paragraph 6.1 for further details).

Occupational asthma and IgE sensitization to grain dust was investigated in 43 male workers exposed to grain dust in the animal feed industry and compared to 27 control subjects (Park *et al*. 1998)[120]. Symptomatic workers were identified as persons with experience of lower respiratory symptoms or with positive skin prick test using grain dust extract (A/H ratio ≥ 2+). In the exposed group, 8/43 persons were positive in the skin prick test; increased total IgE was found in 24/43 exposed workers; and 15/43 complained of respiratory symptoms (7 of these 15 showed significant broncho-constriction after inhalation of ≤ 25 mg/mL methacholine). Challenge of these 15 workers with nebulised grain dust extract gave 5 immediate asthmatic responses and one dual asthmatic response. The increased IgE levels may be indicative of involvement of mast cells which release IL-4 and induce IgE synthesis. In both controls and exposed groups, the incidence of increased specific IgE antibody was higher in symptomatic subjects (40%) than in asymptomatic subjects (11%). Next to smoking, atopy was significantly associated with specific IgE antibodies to grain dust. These results suggested that atopy could be a predisposing factor in the development of grain dust-induced asthma.[120] However, this contrasts with the results of Blaski *et al.* (1996)[15] who found similar airway obstruction and lower-airway inflammation in atopic (n=10) and non-atopic (n=10) healthy non-smoking volunteers after acute inhalation of a corn dust extract.

A study was conducted in Barcelona (the Barcelona asthma epidemic study, see also Paragraph 4.1) after frequent outbreaks of asthma. All 13 epidemics that were registered in a two-year period coincided with the unloading of soybeans in the harbour, as well as with meteorological conditions that favoured transportation of dust from the harbour to the city. The likelihood of a causal relationship was increased by a serological case-control study in which the IgE levels against extracts of soybean from Barcelona harbour were found to be highly significantly (OR unquantifiable high, 95% lower confidence limit 11.7) raised in patients.[5,150]

In 321 grain workers, immunological parameters (IgE and IgG) were measured and related to clinically assessed work related symptoms. Workers showed long-term (up to 3 years) decline in lung function and increase of IgE and IgG to grain dust allergens (the grain itself, storage mites, bacteria and fungi not specified). There was no easily defined dose-response relationship; only a small proportion of the decline in FEV_1 or work-related symptoms could be related to immunological effects.[73]

In a case-control study in 321 asthmatic subjects and 1,459 controls from a Swedish city, the correlation between prevalence of asthma and exposure to grain dust was assessed. Self-reported grain dust exposure was linked to asthma in 7 cases (OR 4.2; 95% CI, 1.6-10.7). The asthma was also linked to time of exposure (when leaving out the time of exposure, the OR decreased to 1.9; 95% CI, 1.0-3.5). Both over-reporting and underreporting of symptoms may have been possible due to the study design. Exposure levels were not reported.[156]

In a case-control study in Argentina the prevalence of sensitization to soya bean hulls in subjects with asthma or allergic rhinitis was studied in 365 subjects and compared with 50 healthy individuals. All subjects were classified according to the estimated degree of soya bean dust inhalation. Skin reactivity tests with a soybean hull extract and with common allergen were performed in all subjects and specific IgE and IgG4 to soyabean hull antigen were measured in sera. Fifty six subjects (15.3%) from the exposed group and no subjects from the control group reacted positive for soyabean hull extract. In the exposed group 39.2% and 27.4% was positive for IgE and IgG4 respectively, while in the control group these amounted to 10 and 12%. The study demonstrated that in subjects with asthma or allergic rhinitis the degree of exposure between soya bean dust inhalation correlates with the skin test reactivity and levels of specific IgE and IgG4 to soybean aeroallergens and with the severity of the asthma symptoms.[30]

No adequately quantified dose-response between exposure to grain dust and asthmatic response is reported. Most studies on asthma did not include detailed

exposure assessment and are therefore not suitable for a risk assessment analysis of grain dust exposure.

Neurological effects

No data available.

Miscellaneous

No data available.

7.2 Animal studies

There is no animal testing system, which satisfactorily mimics asthma, chronic bronchitis or pulmonary emphysema. However, the animal studies on mechanisms of toxicity gave results similar to those obtained in human studies (see Paragraph 6.2).

Animal studies on the effects of grain dust exposure have been reviewed by Chan-Yeung and co-workers (1992).[25] According to this review, Stepanov [148] showed protracted bronchitis and pneumonitis with granulomata formation and fibrosis in rats exposed to grain dust with high silica concentration (8 to 18%) over a period of 9 months. Friborsky and co-workers (1972)[67] found changes of macrophage activation and evidence of emphysema in rats exposed for 4 weeks. Armanious and co-workers (1982)[6] exposed mice to very high concentrations of grain dust (> 1,000 mg/m^3, 5 days/week, 16 weeks; or for three 8-hour periods/day for 2 to 28 days). These animals consistently showed lesions assessed as minimal at 5 days; obvious at 10, 20, and 28 days; and maximal at 80 days. Alveolar sacs and alveoli showed clusters of eosinophilic macrophages and a few polymorphonuclear cells. There were no consistent changes in the bronchi and no evidence of interstitial lung damage. Stepner *et al.* (1986)[149] exposed rabbits to grain dust at a concentration of 20 mg/m^3 for 7 hours/day 5 days/week for as long as 6 months. The lungs of these rabbits demonstrated a granulomatous interstitial pneumonitis associated with exudation of mononuclear cells into the alveoli and conducting airways. These changes appeared within 5 days after the onset of exposure, reached a peak at 3 weeks and were still present after 6 months. There was no evidence of lung fibrosis after 6 months of exposure. The experimentally induced changes in these rabbits histologically resembled a Type 4 reaction or hypersensitivity pneumonitis. Discussing the results of these studies, Chan-Yeung and co-workers[25] concluded that the available studies show

contradictory findings, probably due to differences in species of animals used, duration of exposure, dust concentrations used, and silica content of dust.

7.3 Summary

Acute effects of grain dust exposure mainly involve the respiratory tract (cough, sputum, wheeze and dyspnoea and effects on lung function), although systemic effects (grain fever) and skin effects (contact dermatitis) are also reported. Only a few acute and short term studies report a reliable assessment of the exposure concentrations.

Epidemiological data from acute, short term and chronic exposure studies have clearly shown an inverse relation between grain dust exposure and lung function, and an increasing prevalence of respiratory symptoms with increasing grain dust exposure (Tables 3 and 4).

The main effects on lung function measured by spirometry are on FVC (due to current exposure) and FEV_1 (due to cumulative exposure). In a collaborative study, the estimated FEV_1 lung function losses for the overall mean dust level per industry (cumulative exposure, 111-644 mg/m^3 • years) were 28-87 mL/y.[123]

In most studies, clear effects on the respiratory system are reported at grain dust levels exceeding 4-5 mg/m^3. The effects are related to an evoked immune response, leading to inflammation and airway obstruction. It can not be excluded that effects occur in groups of workers exposed to lower grain dust levels. Especially acute and short term exposure studies indicate that work-related symptoms and cross-shift decrease of lung function may occur at levels at and below 4 mg/m^3.

Most studies on mortality and cancer did not include detailed exposure assessment and are therefore not suitable for the risk assessment of grain dust exposure.

Few studies have been carried out on the effects of grain dust exposure in animals. Varying results have been found reflecting differences in exposure duration, dust concentration levels, type of dust, and silica content of dust.[25] The available studies show that grain dust exposure is able to induce hypersensitivity pneumonitis, macrophage stimulation, and emphysema in animals. These studies also show that endotoxin is involved in the inflammatory response to grain dust inhalation and that endotoxin may have a significant role in the development of chronic airway disease.[71]

In addition, other exposures such as fungal contaminants in the dust may also exacerbate an inflammatory response.[170] However, since data are limited, further

research needs to be undertaken to understand the contribution of these other contaminants.

Chapter 8

Existing guidelines, standards and evaluations

8.1 General population

No information available.

8.2 Occupational population

The available standards for occupational exposure to grain dust are summarised in Table 6.

The American Conference of Governmental Industrial Hygienists (ACGIH) has established a TLV (threshold limit value for 8-hour time-weighted average) of 4 mg/m^3 total grain dust (wheat, oats, barley) since 1988.[3]

A criteria document for occupational standards from the Swedish NIOH and the United States NIOSH, prepared in the late eighties, states that 'it is presently impossible to recommend an exposure concentration at which all workers would be protected from adverse health effects', because the lack of quantitative exposure information at that time.[22]

An *ad-hoc* Committee on grain dust of the Canadian Thoracic Society Standards Committee reviewed the evidence on health effects caused by grain dust.[13,14] In 1978, Labour Canada classified grain dust as a nuisance dust and set a permissible level at 10 mg/m^3 (total dust). However, the Committee notes that, since it has been convincingly shown that grain dust has biological and clinical effects on the lungs, it is not just a nuisance dust.[11,13] Dosman and McDuffie[56]

have reviewed the results of the Labour Canada environmental and medical surveillance program of workers in the grain industry in Canada. Despite the drawbacks of the data yielded in this program, they offered the conclusion that ill health effects of grain dust exposure were detectable to a level of 5 mg/m^3. The *ad-hoc* Committee on grain dust of the Canadian Thoracic Society Standards Committee based their judgement largely on this document. Although this Committee did not recommend a personal exposure limit (PEL), a PEL of 5 mg/m^3 was considered advisable to control short term effects even if these effects are transient.[13,14]

In 1992, the Health and Safety Executive in Great Britain established a new Maximum Exposure Limit (MEL) for grain dust of 10 mg/m^3 (8-hour time weighted average). In this limit, grain dust is taken to be dust arising from the harvesting, drying, handling, storage or processing of barley, wheat, oats, maize and rye, including contaminants. Since 2005, setting occupational exposure limits as MELs and OESs has been discontinued and has been replaced by setting limits as Workplace Exposure Limits (WELs).[76]

Table 6 Occupational exposure limits for grain dust in various countries.

country	occupational exposure limit (mg/m^3)	time-weighted average	type of limit	note	reference
Canada	5	8h	PEL		[11,13,14]
Great Britain					
- HSE[a]	10	8h	WEL	Sen	[76,77]
USA					
- ACGIH[b]	4	8h	TLV		[3]
- NIOSH[b]	4	10h	REL		[3]
- OSHA[b]	10	8h	PEL		[3]

[a] oat, wheat, barley, maize, and rye including contaminants; Sen(sitizer notation), capable of causing occupational asthma.

[b] oat, wheat, barley.

Chapter 9

Hazard assessment

9.1 Assessment of the health hazard

Grain dust is produced during the harvesting and handling of grain, excluding milling. In this advisory report grain dust also includes the dust produced during the processing of animal feed. Grain dust has a heterogeneous composition and includes not only components of plants but also components of microbial origin such as endotoxins. Acute, short term and chronic exposure to grain dust on the work floor can lead to a variety of health effects.

Role of Endotoxin: Is a HBROEL for grain dust necessary?

The main effects of occupational exposure to grain dust are on the respiratory tract and the lungs. The Committee realizes that simultaneous exposure to endotoxin contributes significantly to the effects of grain dust. However, it probably does not fully explain all grain dust effects. Moreover, the actual endotoxin content in grain dust, expressed as EU per mg dust is extremely variable and large differences are found both within and between the individual studies (see Table 7). The average endotoxin content (EU) per mg grain dust ranges from 30 to 450. The individual samples range between 2 and 13,000 EU/mg grain dust.

Table 7 Endotoxin content of grain dust.

exposure to	dust (mg/m^3) mean (range)	endotoxin (EU/m^3) mean (range)	endotoxin/dust (EU/mg)	reference
animal feed	8.2 (0.2-150)	250 (2-4,700)	30.5	[141]
animal feed	7.6 (1.7-20.3)	278 (36-990)	36.6	[125]
grain dust	0.83 (0.09-15.33)	54.2 (4.4-744)	65.3	[159]
animal feed and grain dust	1.1 (<0.1-7.5) 6.7 (0.8-99)	470 (24-4,930) 2150 (113-13,140)	427.3 320.9	[146]

When the existing HBROEL for endotoxin (90 EU/m^3)[78] is applied on the workfloor, this will lead, depending on the ratio between endotoxin and dust, in most situations to inhalable grain dust levels below 4 mg/m^3. Even lower dust levels (< 1 mg//m^3) will be achieved when the endotoxin contents per mg dust is above 90 EU/m^3. In special situations however, *e.g.* when grain dust contains very low endotoxin levels, application of the HBROEL for endotoxin will not automatically lead to sufficient protection against grain dust exposure. This implies that the HBROEL for endotoxin cannot fully protect against all grain dust effects and that a HBROEL for dust itself is necessary.

The Committee chooses a stepwise derivation of the health-based recommended occupational exposure limit (HBROEL) for grain dust in close comparison with the previously defined HBROEL for endotoxin (90 EU/m^3).[78]

Critical effect of grain dust

Several epidemiologic studies on grain dust are available. The Committee observes in these studies an inverse relation between grain dust exposure and lung function, and an increase in prevalence of respiratory symptoms with increasing grain dust exposure (Tables 3 and 4). This observation is made in acute, short term and long-term exposure studies.

However, only few studies have tried to identify quantitative dose-response relationships or no-effect levels for acute, short term and chronic lung function changes. The Committee notes that dose-response relationships are more consistently seen in chronic exposure studies than in acute and short-term exposure studies. Forced expiratory volume in one second (FEV_1) is the parameter which is most consistently affected by grain dust exposure, especially in chronic studies. FEV_1 was previously also used as the critical parameter for the derivation of the HBROEL for endotoxin.[78]

It has been shown that small decrements in FEV_1 are sensitive indicators of respiratory impairment. Moreover several studies indicate that a lowered FEV_1 is

not only a predictor of respiratory morbidity and mortality[82], but also of all cause mortality and cardiovascular mortality.[130,139] The average FEV_1 decline during 40 years is approximately 1 liter in the general non-smoking population, this corresponds to approximately 25-30 mL per year.[92]

9.2 Quantitative Hazard Assessment

Acute and short-term exposure

The Committee selects the studies of Corey *et al.*[32] and Dopico *et al.*[50] on acute and short term effects in grain elevator workers to estimate a lowest observed adverse effect level (LOAEL). These studies monitor grain workers across the workshift (8 h, one week) and report data on the relation between dust exposure levels and lung function quantified by spirometric measurements including FEV_1. Dopico *et al.*[50] also reports a quantitative relation between dust exposure and acute respiratory symptoms. Using the spirometric data from the studies of Corey *et al.*[32] and Dopico *et al.*[50] the Committee estimates that 4 mg/m^3 inhalable dust exposure can be considered as a LOAEL for acute and short term exposure. Extrapolation from LOAEL to a NOAEL using a standard safety factor 3 results in a value of approximately 1.5 mg/m^3.

This NOAEL, based on effects on lung function, is strongly supported by the observations of Dopico *et al.* 1983[50] on the relation between dust exposure levels and respiratory symptoms. Dopico *et al.*[50] compares exposure levels in grain workers showing no respiratory symptoms (n=87) with levels in grain workers showing one or more respiratory symptom(s) (cough, expectoration, wheezing, or dyspnea)(n=122) during the daily work shift. The grain workers with no respiratory symptoms are exposed to approximately 1.5 mg/m^3 inhalable dust. This level is considered as a NOAEL for respiratory symptoms.

The populations studied by Corey *et al.* (1982)[32] and DoPico *et al.* (1983)[50] include over 250 individuals. Although it may not be ruled out that the results have been influenced by a healthy worker effect, the Committee is of the opinion that these populations are a representative sample of the working force and considers that an additional safety factor to compensate for interindividual differences is unnecessary.

Therefore, a HBROEL of 1.5 mg/m^3 (8-hour time-weighted average) is proposed by the Committee and considered sufficient to protect the employee against health effects of acute and short term exposure to graindust.

Chronic exposure

Next, the Committee verifies whether the proposed HBROEL of 1.5 mg/m^3 protects against health effects of chronic exposure to grain dust. The epidemiologic material for chronic studies does not allow a derivation of a grain dust level at which the loss of FEV_1 is zero after 40 years. However, an exposure level can be estimated for which the loss of FEV_1 is not associated with adverse health effects. To make this estimate the Committee selects a Dutch cross-sectional study by Smid *et al.*[141] and its follow-up by Post *et al.*[125] on workers in the animal feed industry after chronic exposure to grain dust, which provide exposure data on both endotoxin and dust. The data from these two studies were previously used to derive the HBROEL (90 EU/m^3) for endotoxin.[78] The data allow the prediction of additional loss of FEV_1 in time. The Committee calculates from these data that exposure to the proposed HBROEL of 1.5 mg/m^3 inhalable grain dust for 40 years on an 8-hour time-weighted average basis, leads to an additional loss in FEV_1 of 45 mL.[141]

The Committee decides that this additional average loss of FEV_1 of 45 mL should not be considered as an adverse effect. To support this decision, the Committee refers to the study of Sin *et al.* (2005)[139] which suggests that a mean FEV_1 decline of 120 mL is not statistically significantly associated with cardiovascular mortality.

Therefore, the Committee judges that a HBROEL of 1.5 mg/m^3 (8-hour time-weighted average) also offers sufficient protection to the employee against health effects of chronic exposure to grain dust.

Groups at extra risk

Workers with an atopic status or an allergic constitution and workers with existing respiratory symptoms due to asthma or COPD may be at increased risk to develop respiratory symptoms and lung function changes. Workers with existing respiratory symptoms may have an increased risk, especially when immunologic mechanisms are involved.

Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards (DECOS) recommends a Health-based recommended occupational exposure limit (HBROEL) for inhalable grain dust of 1.5 mg/m^3, as an 8-hour time-weighted average.

The Committee does not recommend a short-term exposure limit or a skin notation.

Chapter 10

Recommendations for research

No recommendations for research are made.

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A Request for advice

B The Committee

C Comments on the public review draft

D Abbreviations

Annexes

Annex **A**

Request for advice

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

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

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

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

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

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

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

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

Annex **B**

The Committee

- G.J. Mulder, *chairman*
  Emeritus Professor of Toxicology, Leiden University, Leiden
- P.J. Boogaard
  Toxicologist, Shell International BV, The Hague
- J.J.A.M. Brokamp, *advisor*
  Social and Economic Council, The Hague
- D.J.J. Heederik
  Professor of Risk Assessment in Occupational Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R. Houba
  Occupational Hygienist, The Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht
- H. van Loveren
  Professor of Immunotoxicology, Maastricht University, Maastricht; National Institute for Public Health and the Environment, Bilthoven
- T.M. Pal
  Occupational Physician, Netherlands Center for Occupational Diseases, Amsterdam
- A.H. Piersma
  Professor of Reproductive Toxicology, Utrecht University, Utrecht; National Institute for Public Health and the Environment, Bilthoven

- H.P.J. te Riele
  Professor of Molecular Biology, Free University Amsterdam
- I.M.C.M. Rietjens
  Professor of Toxicology, Wageningen University and Research Centre, Wageningen
- G.M.H. Swaen
  Epidemiologist, Dow Benelux N.V., Terneuzen
- R.C.H. Vermeulen
  Epidemiologist/environmental hygienist, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R.A. Woutersen
  Professor of Translational Toxicology, Wageningen University, Wageningen; TNO Innovation for Life, Zeist
- P.B. Wulp
  Occupational Physician, Labour Inspectorate, Groningen
- G.B. van der Voet, *scientific secretary*
  Toxicologist, Health Council of the Netherlands, The Hague

The first draft of the present report was prepared in 1997 by R. Houba and D.J.J. Heederik from the Department of Environmental Sciences, Environmental and Occupational Health Group of the Agricultural University, Wageningen, the Netherlands. An update was prepared in 2004 by W.M.L.G. Gubbels-van Hal from NOTOX BV, 's-Hertogenbosch, the Netherlands.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are

discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public draft

A draft of the present report was released in October 2010 for public review. The following organisations and persons have commented on the draft report:

- National Institute for Occupational Safety and Health (NIOSH), Cincinnati, USA
- Comité van Graanhandelaren, Rotterdam
- Nederlandse Vereniging Diervoederindustrie (NEVEDI), Rotterdam
- Plantum NL (branchevereniging voor bedrijven uit de sector plantaardig uitgangsmateriaal), Gouda
- Vereniging voor de Aardappelverwerkende Industrie, Rijswijk
- Nederlandse Vereniging van Meelfabrikanten, Den Haag

Annex **D**

Abbreviations

A/H ratio	area ratio of the wheal size caused by the antigen to the wheal size caused by histamine
AM	arithmetic mean
BAL	bronchial alveolar lavage
CI	confidence interval
EU	Endotoxin Unit
FEF_{25}	forced expiratory flow at 25% of the expired vital capacity
FEF_{75}	forced expiratory flow at 75% of the expired vital capacity
FEV	forced expiratory volume
FEV_1	forced expiratory volume in 1 second
ΔFEV	(across-shift) change in FEV over an exposure period of several hours
FVC	forced vital capacity
GM	geometric mean
GSD	geometric standard deviation
HBROEL	health-based recommended occupational exposure limit
IgE	immunoglobulin E
IL	interleukine
LPS	lipopolysaccharide
LOAEL	lowest observed adverse effect
MEF	maximum expiratory flow

MEF_{50}	maximum expiratory flow at 50% of the expired vital capacity
MEF_{75}	maximum expiratory flow at 75% of the expired vital capacity
ΔMEF	(across-shift) change in MEF over an exposure period of several hours
MMEF	maximum mid-expiratory flow (average flow over middle half of FVC)
$\Delta MMEF$	(across-shift) change in MMEF over an exposure period of several hours
NOAEL	no observed adverse effect level
OR	odds ratio
PAS	personal air sampler
PEL	personal exposure limit
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
REL	recommended exposure limit
RAST	radioallergosorbent test
RR	relative risk
SD	standard deviation
SEM	standard error of the mean
SMR	standard mortality ratio
STEL	short term exposure limit
Tgg	tijdgewogen gemiddelde
TLV	threshold limit value
TNF-α	tumour necrosis factor alpha
TWA	time-weighted average
WEL	workplace exposure limit

units

d	day
h	hour
w	week
y	year

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
DECOS	Dutch Expert Committee on Occupational Safety
HSE	Health and Safety Executive (UK)
NIOSH	National Institute for Occupational Safety and health (USA)
OSHA	Occupational Safety and Health Administration (USA)