
HSC
Health & Safety
Commission

**Control of Substances Hazardous to Health Regulations
2002**

Proposals for New Maximum Exposure Limits

This consultative document is issued by the Health and Safety Commission in compliance with its duty to consult, under sections 16(2) and 50(3) of the Health and Safety at Work etc. Act 1974.

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to reach him no later than ??? 2003.

The Commission tries to make its consultation procedure as thorough and open as possible. Responses to this consultative document will be lodged with the Health and Safety Executive's Information Centres after the close of the consultation period where they can be inspected by members of the public or be copied to them on payment of the appropriate fee to cover costs.

Responses to this consultative document are invited on the basis that anyone submitting them agrees to their being dealt with in this way. Responses, or part of them, will be withheld from the Information Centres only at the express request of the person making them. In such cases, a note will be put in the index to the responses identifying those who have commented and have asked that their views, or part of them, be treated as confidential.

Many business e-mail systems now automatically append a paragraph stating the message is confidential. If you are responding to this CD by e-mail and you are content for your responses to be made publicly available, please make clear in the body of your response that you do not wish any standard confidentiality statement to apply.

**CONSULTATIVE
DOCUMENT**

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Control of Substances Hazardous to Health Regulations 1999
Proposal for a New Maximum Exposure Limits for Refractory Ceramic Fibres

CONSULTATIVE DOCUMENT

Contents	Page
SUMMARY	1
WHAT ARE EXPOSURE LIMITS – CURRENT SYSTEM	2
HOW ARE OELS SET?	2
PROPOSED NEW SYSTEM OF OCCUPATIONAL EXPOSURE LIMITS	3
REGULATORY IMPACT/COST BENEFITS ASSESSMENTS	4
PROPOSALS FOR CHANGES TO THE LIST OF MAXIMUM EXPOSURE LIMITS	5
Proposal for refractory ceramic fibres	5
Proposal for subtilisins	6
INVITATION TO COMMENT	7
Annexes	
Annex 1	9
Annex 2	17
Annex 3	19
Annex 4	20
Annex 5	23

SUMMARY

The Health and Safety Commission (HSC) would like your comments on proposals for occupational exposure limits (OELs) for chemical substances. A form is included at the back of this booklet to help you do this. It repeats the questions set out at appropriate points in the text below.

This consultative document contains proposals for new Maximum Exposure Limits (MELs) for Refractory Ceramic Fibres and Subtilisins.

A panel of scientific experts has already discussed these proposals but you may have views or further information of which they were not aware. For example, you may have data relating to whether a limit can reasonably be achieved in the workplace. Please do take a few minutes to fill in the response form at the back of this booklet.

The Health and Safety Commission seeks to inform its decision-making by consulting a wide range of interested bodies. In the light of your comments, the Health and Safety Commission will approve the new limits as appropriate. The agreed limits will then come into force on the publication of the 2004 issue of HSE's publication '*EH40 - Occupational Exposure Limits*'.

Please feel free to copy this consultative document more widely. Further copies are available from the address on the back cover and on the Internet on the HSE home page at:

<http://www.hse.gov.uk/condocs/live.htm>

BACKGROUND - WHAT ARE EXPOSURE LIMITS ?

1. Substances that may cause harm to health are subject to the Control of Substances Hazardous to Health Regulations 2002 (COSHH). These Regulations require employers to prevent, or if this is not reasonably practicable, adequately control, employees' exposure to hazardous substances. To help protect workers against ill-health HSE has set **occupational exposure limits** (OELs).

CURRENT SYSTEM

2. There are currently two types of occupational exposure limit - **Maximum Exposure Limits** (MELs) and **Occupational Exposure Standards** (OESs). These are expressed as concentrations of a hazardous substance in the air, averaged over a specified period of time referred to as a time weighted average (TWA). Two time periods are used: 8-hour (based on an average shift); and 15 minute short-term exposure limits (STELs) which are set to help prevent effects, such as eye irritation, which may occur after just a few minutes' exposure.

3. MELs and OESs are legally binding as they are approved by the Health and Safety Commission. Both types of limit are defined in COSHH and retain their legal status when published in EH40.

4. A **MEL** is set for substances which may cause the most serious health effects, such as cancer and occupational asthma: health effects for which no 'safe' levels of exposure can be determined or for which safe levels may exist but at a concentration that is not yet routinely achievable in the workplace. To comply with COSHH, exposure should be reduced as far below the MEL as is reasonably practicable and should not exceed the MEL when averaged over the specified reference period. For substances given a short term MEL (15 minute reference period), the level of exposure should never be exceeded.

5. For more information on employers' duties under COSHH, see HSE's leaflet *COSHH - a brief guide to the regulations* (INDG136 (rev2)).

HOW ARE OELS SET ?

6. MELs and OESs are set on the recommendations of the Health and Safety Commission's (HSC) Advisory Committee on Toxic Substances (ACTS). Information on

ACTS, and the agendas and summaries of its meetings are available on the Internet on the HSE home page at:

<http://www.hse.gov.uk/aboutus/hsc/iacs/acts/index.htm>

ACTS papers are also available from HSE's public information points (see back cover).

7. ACTS has been advised on scientific issues by its Working Group on the Assessment of Toxic Chemicals (WATCH). WATCH, an independent committee consisting of toxicologists, occupational hygienists and other scientific experts made a thorough and critical assessment of the available information on the human health hazards for specific substances, on the extent of occupational exposure to these substances and on the risks associated with their use in workplaces. Using this information WATCH determined whether an OES or a MEL would be more appropriate for an individual substance. WATCH's recommendations were then passed to ACTS for discussion.

8. ACTS is an independent tripartite committee which advises the Commission on matters relating to the prevention, control and management of hazards and risks to the health and safety of persons arising from the supply or use of toxic substances at work. In setting a MEL, ACTS will also take socio-economic factors into account. A short description of this process is included in paragraphs 11-13 and in Annex 2 for information.

9. Summaries of the much more extensive and detailed risk assessment considered by WATCH, and the criteria used by WATCH and ACTS when proposing an occupational exposure limit are published in HSE's ***EH64: Summary criteria for occupational exposure limits*** (available from HSE Books). This consultative document includes a copy of the proposed summary criteria for the three proposed maximum exposure limits to help you understand the reason why the limits are being proposed (Annex 1). A copy of the full WATCH documentation for the substances under consultation is available through HSE public information centres (see back cover).

PROPOSED NEW SYSTEM OF OCCUPATIONAL EXPOSURE LIMITS

10. In autumn 2003, the Health and Safety Commission will consult on formal proposals for a change in the system of establishing OELs. The HSC will propose that MELs which are well-founded are transferred directly into the proposed new framework without amendment..

The MELs for refractory ceramic fibres and for subtilisins that are approved by the HSC as a result of the responses to this consultative document will be treated in the same way.

REGULATORY IMPACT/COST BENEFIT ASSESSMENTS

11. Before any new piece of legislation can be introduced, the Health and Safety Commission carries out an assessment of the costs that it would impose on industry and the benefits that it is expected to bring. Since October 1998, this assessment has been included in the Regulatory Impact Assessment (RIA). Annex 2 of this document gives a description of the methodology behind the formulation of cost benefit assessments (CBAs) for RIAs and a general statement on their application.

12. HSE has examined what costs and benefits will result from these proposals. It is anticipated that some increased costs to industry will occur as a result of having to introduce controls on exposure to refractory ceramic fibres and subtilisins. These are summarised in Annex 3.

13. Copies of the detailed RIAs for these substances are available free of charge from Richard Pedersen at **Health Directorate, Health and Safety Executive, 7th Floor, Rose Court, 2 Southwark Bridge Road, London, SE1 9HS**. If you have any comments on these RIAs we would welcome them also.

PROPOSALS FOR CHANGES TO THE LIST OF MAXIMUM EXPOSURE LIMITS

14. Summary criteria documents explaining the rationale behind the proposed maximum exposure limits for refractory ceramic fibres and subtilisins are enclosed at Annex 1. To help you a response form (Annex 5) is included at the back of this booklet repeating the questions set out in bold in the text below and giving space for your comments.

15. It is proposed that the following two substances be added to the list of MELs.

(1) New MEL proposal for refractory ceramic fibres

<u>Substance</u>	<u>CAS Number</u>	<u>Notes</u>	<u>Reference Periods</u>			
			Long-term exposure limit (8-hour TWA reference period)		Short-term exposure limit (15 minute reference period)	
			<u>f/ml</u>	<u>mg.m⁻³</u>	<u>f/ml</u>	<u>mg.m⁻³</u>
Refractory Ceramic Fibres		-	1 or 0.5	5 (unchanged)	-	-

16. Refractory Ceramic Fibres (RCFs) are currently grouped together for OEL purposes with mineral wools and special purpose fibres (SPFs) within the MEL for machine-made mineral fibres (MMMFs). These are also commonly-known as “man-made mineral fibres”. They are classified as skin irritants and as Category 2 carcinogens under the European Commission Directive 97/69/EC.

17. In March 2002, ACTS was asked to consider the feasibility of setting a separate MEL for RCFs because of their carcinogenic potential and HSE produced an RIA for MEL proposals of 1 fibre/millilitre (f/ml) and 0.5f/ml (summary attached at Annex 3). Recommendations for these proposals were considered by ACTS at its meetings in March and November 2002, and in November 2002 the Committee agreed that consultation should take place on a MEL set at either 1 or 0.5 f/ml (8-hour TWA) (airborne fibre limit).

18. The Health and Safety Commission is particularly interested in the views of small and medium-sized firms as to whether they could comply with the MEL set at 0.5 f/ml without accruing substantial additional costs.

19. There are no proposals to remove or amend the existing gravimetric limit of 5 mg.m⁻³. The Health and Safety Commission recognises that the relevance of gravimetric limits for

modern fibres is questionable, and that a gravimetric limit for RCFs would be of limited value because, except for the coarsest of fibres, the airborne fibre limit would be exceeded first. Nevertheless, in kiln-wrecking very high dust levels are generated which can cause upper respiratory tract irritancy. In these circumstances alone the gravimetric limit might prove a useful back-up to the airborne fibre limit. The Health and Safety Commissions would be interested in the views of consultees as to whether, in the longer term, the gravimetric limit for RCFs should be removed or amended.

20. Further details are given in the ‘Basis for the limit’ section of the summary criteria document at Annex 1. The References section of this document lists all the inhalation studies which were considered by WATCH in its recommendation for a separate, more stringent MEL for RCFs.

Question 1: Do you agree that a MEL should be set for RCFs?

Question 2: At what level should this limit be set; 0.5 f/ml or 1 f/ml?

If you disagree with the setting of a MEL or with the level of the limit please explain why.

Question 3: Do you think that the gravimetric limit for RCFs should eventually be removed or amended ?

(2) New MEL proposal for subtilisins

<u>Substance</u>	<u>CAS Number</u>	<u>Notes</u>	<u>Reference Periods</u>				
			Long-term exposure limit (8-hour TWA reference period)	ppm	mg.m ⁻³	Short-term exposure limit (15 minute reference period)	ppm
Subtilisins	57-24-9	Sen	-		0.00004 (40ng.m ⁻³)	-	0.00004 (40ng.m ⁻³)

21. WATCH considered subtilisins in September 2000 and concluded that they met the criteria for establishment of a MEL. In common with its general position on asthmagens, WATCH considered that it would be appropriate for both 8-hour TWA and STEL MELs to be established. On the basis of the potential of subtilisins to cause occupational asthma and allergic rhinitis, and the inability to establish exposure response relationships for the

induction of these conditions, WATCH recommended that the existing OES of 60 ng.m⁻³ should be withdrawn.

22. ACTS considered these recommendations at its meeting in March 2001 and agreed that HSE should pursue the development of a MEL. As a result, a CHAN was issued in June 2001 (see Annex 4) and HSC withdrew the existing OES following public consultation (CD182). At its meeting in March 2003, ACTS agreed to a public consultation on the basis of a MEL set at 40 ng.m⁻³, measured using personal monitoring rather than, as previously, static sampling.

23. Further details are given in the ‘Basis for the limit’ section of the summary criteria document at Annex 1.

**Question 4: Do you agree with the 8-hour TWA MEL proposal for subtilisins?
If you disagree, please explain why.**

**Question 5: Do you agree with the STEL MEL proposal for subtilisins ?
If you disagree, please explain why.**

INVITATION TO COMMENT

24. The Health and Safety Commission would welcome comments on proposals set out in this consultative document. For convenience, all the questions are repeated in a form (Annex 5) set out at the back of the document which you may find helpful to use for your reply. We will acknowledge receipt of all comments sent to us and will give careful consideration to all comments received in developing our proposals. We may contact you, for example, if we have a query.

25. If you reply to this consultative document in a personal capacity, rather than as a postholder of an organisation, you should be aware that information you provide may constitute “personal data” in the terms of the Data Protection Act 1998. For the purposes of this Act, HSE is the “data controller” and will process the data for health and safety and environmental purposes. HSE may disclose these data to any person or organisation for the purposes for which it was collected, or where the Act allows disclosure. You have the right to

ask for a copy of the data and to ask for inaccurate data to be corrected. Please note all replies will be made public unless you specifically state you wish yours to be made confidential.

26. The Health and Safety Commission/Executive would also like to know what you think about this consultation, both the content and layout. Your views may help to improve further consultations. If you are not satisfied with the way in which this consultation exercise has been conducted you can complain by contacting:

Ms C Sullivan
Health and Safety Executive
7th Floor, North Wing
Rose Court
2 Southwark Bridge Road
London
SE1 9HS.

ANNEX 1

Summary criteria for occupational exposure limits

REFRACTORY CERAMIC FIBRES

Maximum Exposure Limit

1/0.5 f/ml
(subject to consultation)
5 mg.m⁻³

IDENTITY AND PROPERTIES

Index: 650-017-00-8

Refractory Ceramic Fibres and Special Purpose Fibres. These are machine-made (or as given in Directive 97/69/EC, man-made) vitreous (silicate) fibres with random orientation with alkaline oxide and alkaline earth oxide (Na₂O + K₂O + CaO + MgO + BaO) content less or equal to 18% by weight.

These fibres are classified under the CHIP Regulations (2002) as carcinogenic (category 2) and are labelled as:

Carc Cat2:R49 *May cause cancer by inhalation.*

Xi: R38 *Irritating to the skin.*

OCCURRENCE AND USE

These fibres are made either by blowing an air stream on the molten material flowing from an orifice at the bottom of a melting furnace (blowing process) or by directing the molten material onto a series of spinning wheels (spinning process). They are used mainly as insulation material in high temperature applications in the ceramic, steel and metal treatment industries. The largest single use is for furnace linings and related applications.

EXPOSURE

There are approximately 25,000 workers in Europe exposed to RCFs. Within the UK, the exposed workforce is approximately 5,000 strong. The highest exposures are encountered during kiln or furnace wrecking, where 8-hour TWAs can range up to 12 f/ml. RPE is used in more than 80% of sites. Finishing and assembly work may produce 8-hour TWAs of up to 6 f/ml.

MEASUREMENT

(to be added)

DEPOSITION AND CLEARANCE

The key factor determining the extent of pulmonary deposition of inhaled fibres is their aerodynamic diameter¹. Properties such as fibre length and aspect ratio are of lesser importance in this respect. There is approximately a 3:1 ratio between the values of the aerodynamic and absolute diameters of mineral fibres such as RCFs. Thus, a fibre of 1 µm absolute diameter would have a corresponding aerodynamic diameter of about 3 µm. In humans, fibres with an aerodynamic diameter of 1-2 µm are in the optimum size range for deposition in the lungs; fibres with an aerodynamic diameter of 9 µm have an extremely small probability of depositing in the lungs such that RCFs with absolute diameters of >3 µm would be essentially non-respirable.

Following deposition in the respiratory tract, no absorption and systemic distribution of intact RCFs would be anticipated. There are two mechanisms for the clearance of RCFs from the alveolar regions of the lung. The main mechanism involves macrophage-mediated phagocytosis which is effective for short fibres (<5 µm) but becomes increasingly difficult with increasing fibre length, such that clearance by this mechanism will be negligible for RCFs >16 µm in length. Macrophage-mediated clearance mechanisms result in transport by the muco-ciliary escalator to the pharynx and subsequent swallowing. Clearance from the lungs for RCFs that are too long to be phagocytosed by macrophages may occur by dissolution. Dissolution rates are likely to vary with different RCF products but current information suggests that the dissolution rates of RCFs are likely to be an order of magnitude greater than for crocidolite asbestos². Mathematical modelling based on the airborne fibre-size distribution of RCFs likely to occur in the workplace, suggests that the clearance half-time for RCFs from the human lung would be around 3 years³.

HEALTH EFFECTS

Studies in animals

The health effects of RCFs of most relevance to occupational exposure relate to the consequences of repeated inhalation, and so this section summarises only the results of long-term inhalation studies.

In a study by Davis et al (1984)⁴ a group of 48 rats was exposed to an RCF preparation for 7 hours/day, 5 days a week for 12 months at 95 fibres/ml (>5 µm in length). The respirable mass concentration was 10 mg.m⁻³. Groups of 4 rats were killed immediately and at 6 months after exposure, the remaining rats were allowed to live out their lifespan or were killed at 32 months. Pathological examinations at 12 and 18 months revealed large areas of alveolar proteinosis in the lungs, and small areas of interstitial fibrosis. At the end of the study, one benign pulmonary adenoma was found, and 3 rats had bronchial carcinomas (two squamous cell and one a mixed squamous and adenocarcinomatous type) and one rat had developed a peritoneal mesothelioma. In addition to these tumours, it appears that four rats had pulmonary tumours that were described as malignant histiocytomas, comprised of large masses occupying most of one or more lung lobes. No pulmonary neoplasms were found in a concurrent group of 40 untreated control rats. The incidence of non-pulmonary tumours was similar in control and RCF-exposed rats.

As part of a larger study by Smith et al⁴, groups of rats (n=55) and hamsters (n=70) were exposed to RCF for 24 months at a concentration of 200 fibres/ml (with 88 fibres/ml >10 µm in length with diameters < 1µm). Positive and negative control groups were exposed to crocidolite asbestos (3000 fibres/ml with 90 fibres/ml >10 µm in length) and clean air respectively. Following exposure animals were allowed to live out their lifespan. The results showed that no RCF-exposed rats developed pulmonary or mesothelial tumours. One RCF-exposed hamster that died at 10 months developed a pleural mesothelioma. Among the crocidolite-exposed rats, 2/57 developed lung tumours and 1/57 developed a pleural mesothelioma. There were no pulmonary or mesothelial tumours in the crocidolite exposed hamsters. One air-exposed control hamster developed a secretory broncho-alveolar tumour.

Two-year inhalation exposure studies were conducted with 4 different types of RCF in rats (Mast et al 1995a)⁶. Groups of 140 rats were exposed to approximately 220 fibres/ml (30 mg.m⁻³) of RCF1 (manufactured from kaolin); RCF2 (manufactured from zirconia); RCF3 (high purity kaolin fibres); and RCF4 (a heat treated kaolin fibre designed to simulate an “after service” fibre). The mean lengths and diameters of the RCFs were 20 and 1 µm respectively. Negative and positive control groups were exposed to clean air or chrysotile (10,600 fibres/ml, 10 mg.m⁻³) respectively. The tumour findings are shown in Table 1 below.

In a further study in the same laboratory (Mast et al 1995b)⁷, groups of 140 rats were exposed to 36, 91 or 162 fibres/ml of RCF1 (3, 6, or 16 mg.m⁻³) for 24 months. A control group was exposed to clean air. Pulmonary interstitial fibrosis had developed by 12 months in rats from the 2 highest exposure groups, but not in the lowest exposure group at any time point. Minimal focal pleural fibrosis also developed in rats in the two top exposure groups by 12 months, which progressed in severity by the end of the study (30 months). A single pleural mesothelioma developed in one rat in the intermediate exposure group (91 fibres/ml). There were no RCF exposure-related increases in lung tumours in this study.

A study was also carried out in this laboratory in hamsters (McConnell et al 1995)⁸. Groups of 140 hamsters were exposed for 18 months to RCF1 (220 fibres/ml, 30 mg.m⁻³), or to clean air. A group of 80 hamsters was exposed to 10,500 fibres/ml of chrysotile. Animals were killed at the 20% survival time (20 months). In the RCF1 exposed hamsters, interstitial pulmonary fibrosis and focal pleural fibrosis were observed by 6 months. A greater severity of pulmonary fibrosis was observed in the chrysotile exposed hamsters at this time. No pulmonary tumours developed in the RCF1, chrysotile or air-exposed groups. No mesotheliomas developed in the chrysotile or air exposed groups. Forty-two of 102 hamsters developed pleural mesotheliomas. Twenty four of the mesotheliomas were detected by gross observation. The rest were detected only with the aid of a dissecting microscope.

Studies in humans

A cross-sectional study of pulmonary function and respiratory symptoms was carried out in workers at 5 US RCF manufacturing facilities (Lemasters et al 1998)⁹. Investigations took place between 1987-1989. Of 753 eligible current employees, 742 completed the symptoms questionnaire and 736 performed the pulmonary function tests. The results showed a 2- to 5-fold increase in the prevalence of symptoms in the production workers compared to the non-production workers, which the authors felt was typical for workers in dusty trades. No employment-related effects on pulmonary function were found in male non-smokers, but there was a pattern of a decline in FVC and FEV1, over and above that due to age and smoking, that related to years of employment in RCF production in male smokers.

A longitudinal investigation of pulmonary function was conducted in RCF manufacturing workers (Lockey et al 1998)¹⁰. Between 1987 and 1994 pulmonary function was assessed on an

approximately annual basis in 361 male workers. The initial findings suggested a decline in FVC in workers employed in production jobs for more than 7 years prior to the initial test (i.e. in workers employed prior to 1980). However, longitudinal analysis of the data from between 1980-1994 showed no effect of RCF exposure on pulmonary function, possibly reflecting a decrease in airborne exposures to RCF after 1980.

The prevalence of pleural changes was investigated in current and former RCF production workers at a number of US plants (Lockey et al 1996)¹¹. Chest radiographs were obtained for 652 workers. Pleural changes were detected in 20 (3.1%) workers; these comprised 19 with pleural plaques and 1 with diffuse pleural thickening. 9 of 72 workers (12.5%) with > 20 years since first exposure showed pleural plaques, and 5 of 19 (26%) workers with >20 years in RCF production had plaques. There were positive statistical associations between the presence of pleural plaques and time since first RCF exposure, duration of exposure, and also cumulative exposure to RCF. These associations were still positive after adjusting for known asbestos exposure. The results showed pleural plaque rates of 0.3% (n=1), 5.3% (n=8), 6.4% (n=8) and 7.8% (n=4) for cumulative exposures of >0-15, >15-45, >45-135 and >135 fibre.month/ml respectively.

A cross-sectional study was carried out to investigate respiratory symptoms, pulmonary function and chest radiography in 628 workers from seven European RCF manufacturing plants (Trethowan et al 1995)¹². Contemporary measurements (full-shift personal sampling) were made for exposures to RCFs. The mean duration of employment was 10.2 years and the mean (range) of cumulative exposure was 3.84 (0.22 – 9.4 fibre.ml⁻¹.years). This implies a mean current exposure of about 0.38 fibre/ml, although the distribution of exposure was described as heavily skewed. Eye and skin symptoms were frequent in all plants, as were symptoms of breathlessness and wheeze, and the frequency of these symptoms increased with increasing current exposure. For illustration, 41% complained of eye irritation, 18% of wheeze. Multiple linear regression analysis of the pulmonary function results, taking into account age, height and smoking status etc, showed statistically significant cumulative exposure-related declines in FEV1 that were restricted to current and ex-smokers. For current smokers, cumulative exposure to 1 fibre.ml⁻¹.year was predicted to cause a decline in FEV1 of 32 ml per year compared to an age related annual decline of 28 ml. The prevalence of workers with small opacities as detected by chest X-ray was 13% but did not show a relationship with cumulative exposure. There

were 16 films with pleural abnormalities (not described further), two of which were known to have had previous exposure to asbestos. The pleural abnormalities were said not to be independently related to cumulative exposure to RCF.

A further cross-sectional study was conducted in 1995 on workers from six of the European plants included in the above study (Cowie et al 2001)¹³. The study population comprised 774 workers (90% of eligible current workers and 37% of leavers from the earlier 1987 study). Mean current exposures to RCFs varied across the 6 plants and across different occupational groups with a range of 0.03-1.249 fibre/ml. Pulmonary function testing showed an inverse relationship between FEV1, FVC and cumulative exposure to respirable RCFs. The estimated loss of FEV1 in male smokers was 100 ml for a cumulative exposure of 5 fibre.ml⁻¹.years. There were only 82 women in the study but again there was a decline in FEV1 and to a lesser extent in FVC that related to cumulative exposure to RCF. Symptoms of skin and eye irritation were not investigated in this study. The prevalences of respiratory symptoms were generally low. There were only 25 workers reporting chronic bronchitis and this appeared to be related (but not statistically significantly) to cumulative exposure. The frequency of self-reported recurrent chest illness (28 cases) was more strongly related to cumulative exposure (Odds ratio 1.48 [1.11-to 1.96]). The profusion of small opacities as measured using ILO criteria was 51% with 0/1+ and 8% with 1/0+. Profusion with 1/0+ was not related to cumulative exposure, and profusion with 0/1+ was only weakly and inconsistently related to cumulative exposure. Pleural changes of any kind were identified in 78 (11%) and pleural plaques in 40 (5 %). The corresponding prevalences in those with no known past exposure to asbestos (n = 355) came down to 9% and 3%. Statistical analyses showed a relationship between the prevalence of pleural changes and pleural plaques with time since first exposure to RCF.

There are no published studies that have investigated the potential carcinogenicity of RCFs in humans.

BASIS FOR THE LIMIT

Studies of the respiratory health of workers engaged in the production of RCFs have been conducted in the US and Europe. The evidence from these studies suggests the potential for skin and eye irritation, for a decline in pulmonary function, for an increase in respiratory symptoms, and for the development of pleural plaques in RCF exposed workers. The potential carcinogenicity of

RCFs have not been investigated in epidemiological studies. Long-term inhalation studies have shown the potential for pleural mesothelioma in rats and hamsters, and for pulmonary fibrosis and lung cancer in rats. The evidence in rats for lung cancer is of uncertain relevance to human health; compared to other laboratory animals, the rat appears to be particularly susceptible to the development of dust-related tumours at high lung burdens of dust that result in overload of macrophage clearance mechanisms. However, concern for carcinogenicity in humans remains in view of the evidence for mesothelioma in the rat and hamster. WATCH agreed that the animal evidence on RCFs supported classification as a Category 2 carcinogen. Overall, from the evidence available, a clear threshold level of exposure to RCFs below which there would be no risks of respiratory effects or carcinogenicity cannot be identified with confidence.

(to be completed after consultation and final ACTS deliberations).

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TABLE 1 Results from a study by Mast et al. (1995a)

Exposure group	No of rats "at risk"	Lung adenoma	Lung carcinoma	Combined lung tumour incidence	Mesothelioma
RCF1	123	8	8	16 (13%)	2
RCF2	121	4	5	9 (7.4%)	3
RCF3	121	10	9	19 (15.7%)	2
RCF4	118	2	2	4 (3.4%)	1
Chrysotile	69	7	6	13 (18.8%)	1
Air	120	2	0	2 (1.5%)	0

SUBTILISINS

(As active enzyme)

Maximum Exposure Limit

8-hour TWA: 40 ng.m⁻³

15 minute STEL: 40 ng.m⁻³

Notation: Sen

(subject to consultation)

IDENTITY AND PROPERTIES

CAS No: 1395-21-7 (*Bacillus subtilis* BPN)

9014-01-1 (*Bacillus subtilis* Carlsberg)

Enzyme Commission No: EC.3.4.21.62

Synonyms and Trade names: Subtilisin Carlsberg, Subtilisin A, Subtilopeptidase A, Subtilisin BPN, Subtilisin B, Subtilopeptidase B, Subtilopeptidase C, Alcalase, Savinase, Maxatase, Esperase, Biozym, Milezyme, Opticlean

Molecular weight: Approx. 28,000

Subtilisin (9014-01-1) is classified in the 7th edition of the Approved Supply List under the Chemicals (Hazard Information and Packaging for Supply) Regulations 2002 (CHIP 3) and is labelled with the following risk (R) phrases to indicate its toxicological hazards:

R37/38: *Irritating to the respiratory system and skin*

R41: *Risk of serious damage to the eyes*

R42: *May cause sensitisation by inhalation*

OCCURRENCE AND USE

Subtilisins are not manufactured in Great Britain but are imported by a few major suppliers. It is estimated that, annually, up to 100 tonnes of the enzyme is imported contained in up to 5,000 tonnes of granulated powder, wheat substrate or liquid formulation with a concentration of total subtilisin up to 10%. Subtilisins are used in the manufacture of detergents and animal feeds; also for food and leather processing.

EXPOSURE AND CONTROL

Subtilisins for soap detergent use are imported as granulates, liquids or slurries. The dustiness of the dry product is controlled by “encapsulating” the enzyme in a coarse granule (>150µ) of phosphate base using a tacky non-ionic detergent. The enzyme is also supplied in the form of “prills” which are beads containing enzyme embedded in a non-dusty matrix. The result is non-dusty solid beads containing up to 5 % total enzyme.

Liquid formulations of subtilisins for all uses are stabilised with an additive which decreases the vapour pressure.

Work practices in the soap detergent industry include a high degree of automation, containment, engineering control and use of PPE to control residual risks. The potential for inhalation and dermal exposure is likely to arise during the handling and tipping of dry and liquid concentrated enzyme formulations and the packing of dry product. However, the liquid-handling processes are unlikely to generate aerosol. The dustiness of solid formulate is low. About 100 people are potentially exposed to subtilisin in the soap detergent industry, with exposure generally kept below 15 ng/m³ active enzyme.

In the preparation of animal feeds, the potential for inhalation and dermal exposure to subtilisins occurs in filling the liquid reservoir, weighing and addition of dry enzyme concentrate formulations, plant operation, QA sampling and lorry loading. However, the liquid processes are unlikely to generate aerosol, and the dustiness of materials will be low; three-quarters of the final product will be in pelletised form. It is estimated that up to 1,000 people may be potentially exposed to the 0.5% subtilisins concentrate during weighing and/or tipping, and up to 15,000 exposed to the “downstream” animal feed containing subtilisins at about 0.0005%.

Subtilisins are used in food processing to hydrolyse soya bean, gelatin and yeast. Up to 25 tonnes of the enzyme is used annually for these applications with concentrations of up to 10% total enzyme. The potential for inhalation and dermal exposure to subtilisin will occur at the point of dispensing the enzyme and adding to the broth. However, these processes are unlikely to generate aerosol; and the dustiness of the materials will be low. It is estimated that fewer than 50 people may be potentially exposed to the enzyme during food processing.

Within leather processing, the potential for exposure to subtilisin will occur at the point of weighing the enzyme concentrate formulation and addition to the drum. However, the dustiness of the substances will be low. It has been estimated that fewer than 40 workers are exposed to subtilisin during leather processing.

MEASUREMENT

Workplace personal monitoring

[To be added]

Biological Monitoring

There are no published methods available for the biological monitoring of exposure to subtilisins.

TOXICOKINETICS

No toxicokinetics studies are available. However, the following aspects of toxicokinetic behaviour can be predicted. The subtilisins are high molecular weight water-soluble proteins that may be present in the workplace either as a dry powder or in a liquid preparation. If inhaled, the large molecular size of these enzymes would minimise the potential for absorption directly across the respiratory tract epithelium. However, their proteolytic activity may enable these enzymes to damage the epithelial barrier in the lung thus increasing their potential for direct absorption. If deposition in the alveolar lung occurred then it is likely that the subtilisins will be phagocytosed by macrophages and broken into smaller peptides by proteolytic enzymes within lysosomes. Orally administered subtilisins will be subject to the same digestive processes as any other protein. In relation to dermal exposure, it is considered that absorption across intact skin would be precluded by the large molecular size of the molecule.

HEALTH EFFECTS

Studies in animals

Single exposure inhalation studies in animals indicate that subtilisins are toxic via the inhalation route, causing direct effects on the lungs, haemorrhage, congestion and oedema, probably reflecting the proteolytic activity of these enzymes. Guinea pigs appeared to be more sensitive than rats or rabbits, with mild microscopic changes reported in the lungs at 0.1 mg.m⁻³ enzyme. However, no changes were observed in rats or rabbits at this concentration. Four-hour LC₅₀ values of 130 or 229 mg.m⁻³ were obtained in the rat for two other subtilisin preparations. Subtilisins are of low oral toxicity on single exposures. The systemic effects

of single dermal exposures have not been studied but given the predicted lack of dermal absorption, systemic toxicity would not be anticipated by this route.

Mild erythema and oedema was observed in skin irritation tests with concentrated subtilisin preparations and there is clear evidence to show that subtilisin enzyme preparations are irritant to the eye. There is no evidence to suggest that subtilisins have sensory irritant properties.

In relation to skin sensitisation, very little testing has been conducted in animals; an apparently positive result was obtained in a single study in guinea pigs. However, there are doubts about whether the skin reactions observed were irritant or allergic in nature and this "positive" finding has not been confirmed in other animal studies. There is no useful information concerning the effects of repeated inhalation exposure to subtilisins in animals. However, results from single exposure studies suggest that on repeated inhalation exposure, chronic inflammatory damage could occur, caused by the localised proteolytic activity of these enzymes. Oral dosing studies in rats suggest that with repeated high doses, local gastrointestinal disturbances can occur, but this has no obvious relevance to occupational exposure conditions. The only predicted effects of repeated dermal exposure would be for local skin irritation.

Negative results were obtained in Ames tests with two subtilisin preparations, and *in vivo* tests in somatic and germ cells were negative for one preparation. The results support the conclusion that subtilisins are not genotoxic. No studies have been conducted to investigate carcinogenic potential but this would not be predicted for this class of substance. No studies have been conducted to investigate reproductive toxicity. Reproductive effects would not be anticipated, as systemic distribution to the reproductive organs is not likely to occur via occupational routes of exposure.

Studies in humans

There are no human data on the systemic effects of single exposures to subtilisins.

In human volunteer studies aqueous solutions containing up to 20% of a concentrated subtilisin preparation were not irritant to intact skin but were irritant to damaged skin. Workers directly handling concentrated enzyme preparations reported skin problems mainly on the fingertips, wrist and neck but the role of subtilisins in causing these problems have not been adequately explored.

Extensive patch testing in large-scale human volunteer studies has shown no evidence for the ability of subtilisins to induce skin sensitisation. Negative results have also been obtained in patch tests in subtilisin-exposed workers. Furthermore, no confirmed cases of skin sensitisation caused by subtilisins have been identified in workers engaged in the manufacture/use of these enzymes. Overall, human evidence suggests that subtilisins should not be regarded as skin sensitisers.

Evidence from bronchial and nasal challenge studies in detergent workers shows that subtilisins can cause occupational asthma and allergic rhinitis. When subtilisins were first introduced into the detergents manufacturing process there were a large number of cases of occupational asthma attributed to these enzymes each year (7-39 before 1975). It is likely that all of these cases were due to subtilisins as these were the only enzymes used in detergent manufacture over that time period. Since then, hygiene conditions have improved, and there has been a corresponding drop in the number of cases of detergent enzyme-related asthma per year (0-4 since 1980). No personal exposure data are available and there is no information concerning the exposure-response relationships for subtilisin-induced asthma/allergic rhinitis. Other than occupational asthma and allergic rhinitis, a large body of health surveillance data in detergent workers reveals no evidence for other adverse health effects relating to the use of subtilisin preparations.

BASIS FOR THE LIMIT

The key health concerns for subtilisins are their potential to cause occupational asthma and allergic rhinitis. The available data do not allow a threshold for the induction of these conditions by subtilisins to be identified nor is it possible to determine what the exposure-response relationship might be. On this basis WATCH consider that subtilisins do not meet the criteria for the establishment of an OES. In view of the potentially serious nature of occupational asthma, subtilisins meet the criteria for the establishment of MEL(s). Since both long-term repeated exposures and short-term peak exposures may be of relevance to the induction of occupational asthma and allergic rhinitis, both 8-hour TWA and STEL MELs should be established.

In relation to other risk management measures, given that there is clear evidence that subtilisins are a cause of occupational asthma, an OEL for subtilisins should be accompanied by a "Sen" notation. As dermal absorption is not an issue, a "Sk" notation is not warranted. Subtilisins do not meet the criteria for establishing a BMGV because the lack of dermal absorption indicates that an airborne limit will be sufficient to control exposure, and no suitable methods are available for biological monitoring of exposure to subtilisins.

REFERENCES

The use of NN-dimethylcasein in the determination of proteolytic enzymes in washing products and airborne dust samples, *Analyst* 96, 159-163

Fulwiler, R.D., Abbot, J.C., and Darcy, F.J. (1972) Evaluation of detergent enzymes in air, *Am Ind Hyg Ass J* 33, 231-236

Health and Safety Executive (1997) General methods for the gravimetric determination of respirable and total inhalable dust, HMSO, UK MDHS 14/2

Soap and Detergent Industry Association (1991) The Standing Committee on Enzyme Washing Products. Revised Operating Guidelines.

Fifth report Soap and Detergent Industry Association, UK

OTHER USEFUL PUBLICATIONS

Subtilisins: Risk Assessment Document EH72/x. Due to be published in 2003.

ANNEX 2

EXPLANATORY NOTE - COST BENEFIT ASSESSMENT METHODOLOGY FOR REGULATORY IMPACT ASSESSMENT AND APPLICATION TO OCCUPATIONAL EXPOSURE LIMITS: AN OVERVIEW

1. It is Government policy that the costs of all new or revised regulation must be assessed. Since 1982 the Health and Safety Commission (HSC) has required **cost benefit assessments** (CBAs) to be undertaken for all major proposals for health and safety regulations unless the costs resulting from their introduction are negligible. This approach has also been extended to the consultation period for Occupational Exposure Limits (OELs). Since October 1998, costs and benefits are discussed in the **regulatory impact assessment** (RIA) framework.

2. The complexities of applying CBA/RIA methodology to occupational ill-health issues as opposed to accident prevention mean that the results need to be considered with particular caution. The uncertainties resulting from imperfect information on the cost of controls, and validation of exposure compliance data can be more pronounced in relation to health issues, so that estimates of the costs often need to be viewed as rough estimates. The extent of uncertainty will vary according to each substance and the availability of accurate information.

3. On the other side of the scale, quantifying the benefits of an OEL also poses some particular problems. Quantification is normally based upon how far the OEL reduces the risk to employees exposed using dose-effect information. However, for substances such as carcinogens the dose-effect relationship is commonly not established, and alternative ways of deriving a monetary value to represent the benefits of setting OELs have been developed.

4. In addition, there are a number of underlying benefits that can accrue from the introduction of an OEL and lead to more general improvements in worker protection but cannot easily be quantified. Such benefits are often less tangible, longer term, or relate to the general principles of introducing an OEL rather than to its specific level. They may also lead to consequential improvements in productivity, reduction in product loss and improvements in employee recruitment and retention, some of which are difficult to quantify. These potential benefits include factors such as:

- Defining a level playing field for all users.

- Defining adequate control.
- Providing clearer guidance on the level considered to be reasonably practicable.
- Providing a standard for new users.
- Reducing/ limiting scope of 'discretion' by enforcing authority.
- Providing consistency with international developments.
- Reinforcing/ improving good practice.
- Encouraging/ stimulating proper reporting of ill-health.
- Promoting more effective health surveillance.
- Reducing ambient air contamination generally.

5. The Health and Safety Commission's Advisory Committee on Toxic Substances (ACTS) takes such uncertainties and potential benefits into consideration when discussing and agreeing proposals for OELs. It fully recognises that CBA is an aid to decision-making. During the process of deciding on the proposal for an OEL, ACTS will consider the CBA/RIA and the existence of the potential benefits, and will make a recommendation in the context of its responsibilities for employee health protection, and the provision of help to industry in risk management. The CBA/RIA provides a tool which enables HSC to make decisions based on a knowledge of available factors including the socio-economic impact of the proposed OEL. It is not, however, the over-riding determining factor.

ANNEX 3

MEL PROPOSALS: SUMMARY COMPARISON OF COSTS AND BENEFITS

Substance	Summary of RIA
Refractory Ceramic Fibres	<p>Around 5,000 people in the UK are estimated to be potentially exposed to RCFs. Health benefits arising from the MEL would be a reduction in the risk of contracting pulmonary fibrosis, pleural plaques, lung cancer and mesothelioma. These benefits cannot be quantified, as there is no conclusive evidence regarding dose and effects. The total cost of a MEL set at 1 f/ml is expected to be in the range of £2,700,000 to £2,800,000 in present value terms over a ten-year period. The total cost of a MEL set at 0.5 f/ml is expected to be between £4,400,000 and £4,500,000 over the same period. In some cases small companies may have disproportionately large costs per worker.</p>
Subtilisins	<p>Around 16,000 people are potentially exposed to subtilisins in the workplace, although only around 100 people are exposed to subtilisins during the handling of dry concentrate and dry detergent product where the concentration is highest. Subtilisins are known to a causative agent of occupational asthma. No attempts have been made to estimate the health benefits of introducing a MEL. Total compliance costs to industry have been estimated as being £120,000 in the first year of compliance with ten-year discounted costs of between £542,000 and £593,000. The bulk of these costs will be met by the millers of animal feeds (approximately 100 businesses).</p>

ANNEX 4



CHEMICAL HAZARD ALERT NOTICE

SUBTILISINS

This guidance provides information on the health effects associated with exposure to subtilisins at work. It also gives advice on good practice, which employers, users and suppliers may find helpful in considering what they need to do.

Why issue a chemical hazard alert notice?

Currently, subtilisins have Occupational Exposure Standards (OESs) of 0.00006 mg.m⁻³ (60 ng.m⁻³) for both, long-term exposure of 8-hour time-weighted average and 15-minute short term exposure limit. Subtilisins have been reviewed by an independent committee of scientific experts in occupational health¹. Because of the information on the health effects of subtilisin, the committee could not identify an exposure level which is both safe and practicably achievable. The Health and Safety Commission (HSC) will therefore be consulting on the withdrawal of the current OESs from 2003.

Because no safe exposure limit for subtilisins could be identified, HSC's Advisory Committee on Toxic Substances (ACTS) will consider, in due course, setting a Maximum Exposure Limit (MEL). A MEL places a duty on the employer to reduce exposure to as low as is reasonably practicable, and in any case below the MEL. Once any MEL is set, the Control of Substances Hazardous to Health (COSHH) Regulations will clearly identify responsibilities. It can take some time to set a MEL and **this guidance provides interim advice and information to suppliers, employers and users.**

What are subtilisins? - Subtilisins are proteolytic enzymes of bacterial origin, light coloured, free-flowing powders. They are readily soluble in water. They are derived

This guidance is issued by the Health and Safety Executive. Following the guidance is not compulsory and you are free to take other action. But if you do follow the guidance you will normally be doing enough to comply with the law.

¹Health and Safety Commission's Working Group on the Assessment of Toxic Chemicals

by a fermentation process from *Bacillus subtilis*. Subtilisins are not manufactured in Great Britain. It is estimated that annually up to 100 tonnes of the enzyme are imported, contained in up to 5,000 tonnes of granulated powder, spray-dried on a wheat substrate or liquid formulation with a concentration of subtilisin of 0.5 to 10%.

Where are they used? - Subtilisins are used in the manufacture of detergents and animal feeds; also for food and leather processing.

What are the key health hazards? - The key health concerns for subtilisins are their potential to cause occupational asthma and allergic rhinitis. They are toxic via the inhalation route, causing direct effects on the lungs, haemorrhage, congestion and oedema. There is clear evidence to show that subtilisin enzyme preparations are irritant to the eye.

How do they get into the body? - Subtilisins can enter the body when breathed in but are unlikely to cross intact skin.

What should suppliers do? -

- ◆ You should ensure that the information contained in this notice is passed on to your customers as required by the Chemicals (Hazard Information and Packaging for Supply) Regulations 1994, as amended. You should take steps to review your safety data sheets to reflect the new findings.

What should employers do? -

- ◆ You should give priority to preventing your employees being exposed to subtilisin by any route (i.e. inhalation, absorption through skin or contact with the skin), as required by the COSHH Regulations 1999.

- ◆ Where preventing exposure to subtilisin is not reasonably practicable (e.g. by using a different substance), then you should adequately control exposure by a combination of engineering and process control measures. **HSE recommends that, although the legal obligation is to reduce exposure to the OESs while they remain in force, it would be prudent for you to control exposure to as low a level as is reasonably practicable below the OESs.**

- ◆ Once the OESs are withdrawn, your legal obligation under COSHH remains to achieve adequate control. Since a safe level of exposure cannot be determined it remains our recommendation that you should control exposure to as low a level as is reasonably practicable.

- ◆ In dealing with exposure, whether before or after the OESs are withdrawn, you should try to reduce the number of people exposed and the length of time each is exposed as required by good hygiene practice.

- ◆ You must give all your employees who are, or who may be exposed to subtilisin, sufficient information, instruction and training to understand the potential problems and the precautions they need to take.

- ◆ You should make sure that safety representatives, employees or representatives of employee safety are aware of this information and consult on any action that you propose to take as a result.

What should employees do?

- ◆ You must co-operate with your employer in using the control provided and reporting any defects found in the control measures.
- ◆ You may wish to seek the advice of your safety representative or representative of employee safety.

Further information is contained in the next issue of EH64 (available from HSE Books)

Further help: Contact HSE's InfoLine: Tel 08701 545500

ANNEX 5

RESPONSE FORM

**Control of Substances Hazardous to Health Regulations 2002
Proposals for Maximum Exposure Limits,
and Biological Monitoring Guidance Value**

We would like you to tell us what you think about the proposals set out in this consultative document. The proposals are summarised below in this reply form which you may wish to copy or tear out and use. Please add extra sheets if you wish.

Name of organisation or company	
Name of individual	
Address
Telephone number	

Question	Comment
<p>1. Do agree that a MEL should be set for RCFs?</p> <p>2. At what level should this limit be set, 0.5 f/ml or 1f/ml?</p> <p>If you disagree with the setting of a MEL or with the level of the limit , please explain why.</p> <p>3. Do you think that the gravimetric limit for RCFs should eventually be removed or amended?</p>	

<p>4. Do you agree with the 8-hour TWA MEL proposal for subtilisins? If you disagree, please explain why.</p> <p>5. Do you agree with the STEL MEL proposal for subtilisins? If you disagree, please explain why.</p>	
<p>6. In your view how well does this consultation document represent the different policy issues involved in this matter? [Tick one box]</p>	<p><input type="checkbox"/> Very Well <input type="checkbox"/> Well <input type="checkbox"/> Not Well <input type="checkbox"/> Poorly</p>
<p>7. Is there anything you particularly liked or disliked about this consultation? (Please add extra sheets if you wish)</p>	

Please return to:

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Please note: All views will be placed in HSE Information Centres unless you specifically state that this response, or a part of it, should be treated as confidential.