MANUFACTURE, PROCESSING AND USE OF STAINLESS STEEL: A REVIEW OF THE HEALTH EFFECTS

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PREAMBLE

This review comprises a critical evaluation of available data concerning the health effects associated with stainless steels, from manufacture through to processing and end-use.

The review has been divided into the following three sections to reflect the qualitative variations in exposure which occur:

- metallic stainless steel
- stainless steel manufacture
- stainless steel processing

The information contained in this review is intended to provide the basis of an assessment of the hazards associated with metallic stainless steel and those substances which occur during the manufacture and the processing of stainless steel.

Currently, stainless steels are classified in the European Union according to the Preparations Directive (88/379/EEC). Consequently, by using the conventional method specified in the Directive, stainless steels which contain nickel at a concentration of 1% or more are classified as category 3 carcinogens (R40) and skin sensitisers (R43). In this review, identifiable hazards associated with metallic stainless steel are evaluated against the criteria for classification, as contained in Annex VI of European Council Directive 92/32/EEC, amending Directive 67/548/EEC. The purpose of this evaluation is to establish how, based on currently available data, metallic stainless steels would be classified if they were substances.

Identifiable hazards associated with the materials occurring during the processing of stainless steel, for example welding fume or grinding dust, are also evaluated against the same classification criteria. The purpose of this evaluation is to determine how the toxicological properties of the materials concerned correlate with the classification criteria for substances, and thus enable an objective judgement of whether the materials should be considered hazardous.

The review is also intended to provide the basis of a risk assessment for those hazards which have been identified.

The final part of each section focuses on "future research needs". Gaps in the database, which have been identified during the preparation of this document, are reviewed and suggestions are put forward regarding future research needs where it is thought appropriate.

Within the review, each section is divided into the following sub-sections: general information; information on exposure; toxicokinetics; toxicity; hazard assessment; risk assessment; gaps in knowledge. The review was prepared using primary sources of data. In each toxicity sub-section, the review of the epidemiological literature relating to occupational cancers is limited to original publications of cohort studies. Population-based case-control studies were considered to be too problematic to include reliable analyses of detailed occupational exposures and were not evaluated.

Literature search strategy

Primary sources of published data used in this review were identified using TOXLINE, NIOSHTIC, CISDOC, MEDLINE, HSELINE and the Science Citation Index databases for the period 1970 to 1996 (project start date). Key words used in the searches were “stainless steel”, “chromium-nickel alloys”, and “nickel alloys”.

References were selected from the search results using a two-stage approach. Firstly, reference abstracts were scanned for relevance to the project and selected references were then acquired. Secondly, acquired references were read in full before being selected for inclusion in the review. References included in the review are listed in the "Bibliography"; those not included are given in the "Reference List".

References published subsequent to the start of the project, that is for the period 1996 to early 1998, were identified by conducting updated searches using the above databases. Further articles were identified from bibliographies of references used during the course of the project and by scanning scientific journals.

EXECUTIVE SUMMARY

This document comprises a critical review of the literature relating to health effects associated with stainless steels, from manufacture through to processing and end-use. The purpose of the review is to provide an assessment of the hazards associated with metallic stainless steel, stainless steel manufacture and stainless steel processing, and an evaluation of these hazards against the EU classification criteria[1]. The review also provides assessments of the associated risks to health and recommendations for further research.

Metallic stainless steel

Stainless steels are defined, according to the European Standard EN 10088, as iron-based alloys containing at least 10.5% chromium and a maximum of 1.2% carbon. Stainless steels may contain nickel as another major alloying element, with a content of up to 38%, plus other alloying elements and stabilisers. The chromium content renders stainless steels corrosion resistant. Metallic stainless steel is produced mainly in the massive form (>99%); the remainder is produced in powdered form.

In spite of the absence of data from animal experiments and of human data on acute toxicity, the corrosion resistant properties of stainless steels, together with evidence of negligible nickel release in leaching studies and lack of activity in human patch-testing studies, suggest that no acute toxicity would be anticipated. This view is supported by the absence of any reports of acute toxicity associated with exposure to metallic stainless steel despite the extremely large number of individuals who are exposed to stainless steels on a regular basis.

Patch-testing studies, in conjunction with investigations of nickel release, show that prolonged skin contact with most stainless steel grades is unlikely to elicit a skin response in nickel-sensitised individuals. However, prolonged skin contact with AISI 303, a resulfurised grade of stainless steel produced specifically for machining purposes, may evoke skin reactions in nickel-sensitised subjects.

The small quantity of experimental data for unsensitised subjects provides no evidence that skin contact with stainless steel **induces** skin sensitisation. Further, there is an extremely large population exposed to stainless steels, with either prolonged or intermittent skin contact, or as a result of stainless steel surgical implants, and there are very few reports of suspected allergic reactions available in the literature.

Investigations of prolonged exposure to implanted metallic stainless steel in animals and case-reports of effects of prolonged exposure to stainless steel prosthetic implants in humans provide no evidence of specific reactions to stainless steel over and above non-specific response such as seen with any inert implanted material.

[1] Annex VI of European Council Directive 67/548/EEC, as amended.

Results from a single intra-muscular carcinogenicity study provide no evidence for the carcinogenicity in animals of metallic stainless steel.

When data concerning the hazardous properties of metallic stainless steels are evaluated against the current EU classification criteria, there appears to be no basis for classifying stainless steels for any of the toxicological end-points.

There are gaps in the database for metallic stainless steels for acute toxicity, carcinogenicity, mutagenicity and reproductive effects. However, based on the physical properties of the material and the negligible bioavailability of stainless steel constituents, further testing using internationally agreed protocols would not be expected to generate much useful information. Alternative approaches could be considered in order to further examine the carcinogenic potential of stainless steels.

Stainless steel manufacture

Within this review, the manufacture of stainless steel is considered to include the stages of stainless steel production from melting through to finishing. Stainless steel production gives rise to a mixture of airborne dusts and fumes, and thus presents the potential for inhalation exposure in the occupational setting. The airborne dusts and fumes may contain various metal oxides and other metal compounds. Chromium predominantly occurs in the trivalent state, although hexavalent chromium may occur. Polycyclic aromatic hydrocarbons (PAHs) are only likely to occur if casting is performed using moulds containing binders and other additives. There are few qualitative and quantitative exposure data available for this industry.

With regard to long-term effects on health among workers engaged in the manufacture of stainless steel, only a few investigations have been conducted. Morbidity studies show no evidence of adverse effects on respiratory health in workers engaged in the melting stages of stainless steel production which might be associated with chromium exposure, although the available data preclude wider conclusions being drawn regarding the health of workers in the stainless steel manufacturing industry. Epidemiological studies do not provide convincing evidence of elevated lung cancer risk in workers involved in stainless steel manufacture. One epidemiological study provided some evidence of excess lung cancer risk in stainless steel foundry workers; an occupation which nowadays employs very few workers in Europe.

Identified research needs include the collection of qualitative and quantitative data on exposure for the stainless steel manufacturing industry, and further investigation of morbidity among workers in the industry.

Processing of stainless steel

Processing of stainless steel includes activities such as welding, grinding, cutting, polishing and forming.

Welding of stainless steel

Welding fumes are complex mixtures of particles and gases, the composition and concentration of which vary according to several parameters including the welding method used and the consumable. The particulate fraction is mostly respirable and therefore welding operations present the potential for inhalation exposure in the occupational setting.

Information concerning the acute toxicity of fume from the welding of stainless steel is available only from animal data. Inhalation of high concentrations of welding fume was associated with inflammatory changes in the lungs of rats, but a no observed adverse effect level *(*NOAEL) was not identified for this effect.

The database concerning the effects of repeated exposure in animals is limited to a few studies. Pulmonary toxicity has been reported in rats in inhalation studies following exposure to high concentrations of MIG/SS or MMA/SS welding fume; again a NOAEL was not identified.

Investigations of the effects of repeated exposure in humans have focused on renal toxicity and effects on respiratory health. Although investigations of renal toxicity are deficient in several respects, overall the results provide little evidence of an appreciable risk of renal disease at exposure levels likely to occur in modern industry. With regard to respiratory effects excluding cancer, although "welding fume" has been extensively studied, few data relate exclusively to stainless steel welders. Overall, the available data suggest that welding in general may be associated with an increased risk of reporting respiratory symptoms, but provide no convincing evidence of any increased risk of developing lung function abnormalities or of any specific association with stainless steel.

The particulate fraction of MMA/SS fume, and to a lesser extent that of MIG/SS fume, has generated positive results in several *in vitro* genotoxicity assays. The results indicate that certain constituents of the particulate fraction of welding fume from stainless steel, probably water-soluble constituents, are mutagenic *in vitro*. Results from a single *in vivo* assay indicate that water-soluble components of MMA/SS fume particulate may be mutagenic to somatic cells *in vivo*. Investigations of genetic damage in lymphocytes from stainless steel welders have generated generally inconclusive results.

Data from non-standard carcinogenicity bioassays provide no evidence for the carcinogenicity in animals of fume from stainless steel welding.

A number of investigations into cancer risks in workers engaged in the welding of stainless steel have been performed. Whilst the lung cancer findings from these

studies are often based on small numbers and interpretation is also hindered by the absence of reliable exposure histories, these studies provide no consistent pattern of excess lung cancer risk attributable to the welding of stainless steel. These findings are in agreement with the conclusion of a meta-analysis of lung cancer in welders, namely that the elevated lung cancer rates in welders *"cannot be explained by hexavalent chromium and nickel exposures among stainless steel welders"*.

Several studies have investigated the effect of stainless steel welding in males on fertility and developmental toxicity, although variation in study design and deficiencies in methodology make summarising the information from these investigations difficult. Investigations of the effect on fertility provide equivocal evidence of an effect on semen quality, although there is no evidence to suggest any significant implications in terms of fertility. Investigations of developmental toxicity provide no evidence to suggest that welding of stainless steel as an occupation in males has an effect on developmental toxicity.

When data concerning the hazards associated with fume from welding of stainless steel are evaluated against the current EU classification criteria, no stainless-steel-specific concern would appear to be raised in relation to any of the toxicological end-points. Welding of any type of steel appears to be associated with a possible increase in the risk of lung cancer, but there is no further increased risk associated specifically with stainless steel welding.

As some of the substances which occur in fume from welding are known to be carcinogenic, the potential for cancer is the most serious health concern. This and other potential health effects may be controlled by the use of occupational exposure limits for welding fume and for individual components of welding fume[2]. If exposure limits are maintained or, in the case of hexavalent chromium, reduced as far below the exposure limit as is reasonably practicable, then risks are considered to be negligible.

Investigation of non-cancer respiratory health among welders of stainless steel is proposed as an area requiring further research. Such investigations should involve collection of exposure data and characterisation of welding fume for metal species present. With regard to the carcinogenicity of welding fume, it is suggested that the genotoxic activity of fume from stainless steel welding should be investigated in *in vivo* studies.

[2] In the UK, the occupational exposure limit for welding fume as a total particulate mixture is 5 mg/m^3 and for hexavalent chromium is 0.05 mg/m^3.

Grinding of stainless steel

Airborne dust from grinding of stainless steel is made up of spinels and therefore has a different chemical composition and metallurgical structure to that of metallic stainless steel. A proportion of the airborne dust particles are respirable and therefore grinding operations present the potential for inhalation exposure in the occupational setting. Grinding activities frequently accompany welding operations and also occur during the later stages of stainless steel manufacture.

Data on the acute toxicity of grinding dust from stainless steel are limited to a single animal intratracheal (i.t.) instillation study which simply showed that a suspension of grinding dust (up to 112 mg/kg) was non-lethal in hamsters.

Animal data on the effects of repeated exposure are limited to a single study. Effects on body weight occurred with repeated i.t. instillation of up to 9 mg dust (total of 12 doses administered at 14-day intervals); information regarding other effects was not available and it was not possible to identify a NOAEL. No human data are available concerning the effects of repeated exposure to grinding dust.

Data from two i.t.-dosing carcinogenicity bioassays provide no evidence for the carcinogenicity of grinding dust from stainless steel, with two austenitic grades and one ferritic grade failing to induce lung tumours.

Two available studies of cancer risks in grinders of stainless steel do not indicate that such work leads to excess risks of lung cancer. One study reported cancer findings under broad headings rather than for individual cancer sites. Nevertheless, it provided no support for the hypothesis of an effect on cancers of the colon and rectum suggested by the other study.

When data concerning the hazards of grinding dust from stainless steel are evaluated against the current EU classification criteria, no concern would appear to be raised in relation to any of the toxicological end-points.

According to the available data, there appears to be no identifiable hazard associated specifically with grinding dust from stainless steel. Nevertheless, as some of the airborne dust is respirable and thus presents the potential for inhalation exposure, it appears appropriate to treat grinding dust as any other kind of dust and to control exposure to the appropriate exposure limit[3].

Although there are gaps in the toxicological database for grinding dust, there appear to be no major concerns for health and therefore no further testing is warranted.

Cutting of stainless steel

Cutting of stainless steel may be performed using mechanical, laser or plasma cutting methods. Plasma cutting performed in the open atmosphere appears to be the only method which presents the potential for inhalation exposure in the workplace.

[3] In the UK, the occupational exposure limit for dust is 10 mg/m^3 (total inhalable dust) or 4 mg/m^3 (respirable dust).

The toxicological database for fume from the cutting of stainless steel is very small. The only study which has specifically investigated workers engaged in this activity, which focused on effects on kidney function, reported no evidence of renal toxicity in a small group of workers.

The toxicological database for fume from the cutting of stainless steel precludes the identification of any hazards associated with this operation.

Other processes

No data were available concerning the health effects associated with polishing or forming of stainless steel, or relating to exposure.

ABBREVIATIONS

AIBI	β-aminoisobutyric acid
AISI	American Iron and Steel Institute
AOD	argon oxygen decarburization
AWS	American Welding Society
B-Cr	blood chromium concentration
BHK	Baby Hamster Kidney
BSI	British Standards Institution
CHO	Chinese Hamster Ovary
CI	confidence interval
DMG	dimethylglyoxime test
DMSO	dimethlysulphoxide
DNA	deoxyribonucleic acid
EAF	electric arc furnace
EC	European Community
EU	European Union
FCAW	flux metal arc welding
FCW	flux cored electrode welding
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GMAW	gas metal arc welding
GTAW	gas tungsten arc welding
HGPRT	hypoxanthine guanine phosphoribosyl transferase
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer
ICDRG	International Contact Dermatitis Research Group
IgE	immunoglobulin E
IgG	immunoglobulin G
i.m.	intramuscular
i.p.	intraperitoneal
i.t.	intratracheal
i.v.	intravenous
LEV	local exhaust ventilation
LOD	limit of detection
LTT	lymphocytic transformation test
MAG	metal active gas
MEF	maximum expiratory flow
MIG	metal inert gas
MIG/SS	metal inert gas/stainless steel
MMA	manual metal arc
MMA/SS	manual metal arc/stainless steel
NAG	*N*-acetyl-β-D-glucosaminidase
n.d.	not detectable
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OR	odds ratio
PAH	polycyclic aromatic hydrocarbons
PAW	plasma arc welding

PEFR	peak expiratory flow rate
PSD	particle size distribution
PTFE	polytetrafluoroethylene
RAST	radioallergoimmunosorbent test
RBC	red blood cells
RNA	ribonucleic acid
RR	relative risk
s.c.	sub-cutaneous
SCE	sister chromatid exchange
SMAW	shielded metal arc welding
SMR	standardised mortality ratio
$t_{1/2}$	half-life
TIG	tungsten inert gas
TWA	time-weighted average
U-Cr	urinary chromium
U-Ni	urinary nickel
UDS	unscheduled DNA synthesis
VC	vital capacity

1 METALLIC STAINLESS STEEL

This section is concerned with metallic stainless steel, which is supplied either in the massive form (long products or flat products) or in the powdered form. The purpose of this section is to review available data concerning the health effects of metallic stainless steel and, on the basis of this, to assess the hazards and ensuing risks.

1.1 Metallic stainless steel: massive

1.1.1 General information

Stainless steels are defined according to the European Standard EN 10088 as iron-based alloys containing at least 10.5% chromium and a maximum of 1.2% carbon (British Standards Institution 1995). Stainless steels may contain nickel as another major alloying element, with a content of up to 38%. Other alloying elements may be present including molybdenum (0-8%), manganese (0-11%), silicon and copper (0-3% each). Titanium and niobium may be present as stabilisers.

One of the most important properties of stainless steels is resistance to corrosion. Corrosion resistance in stainless steels is provided by a passive surface film which acts as a barrier between the alloy and the surrounding medium. The passive film is a continuous, non-porous and insoluble film which, if broken under normal conditions, is self-healing. Of all the constituent elements of stainless steel, chromium plays the most important role in the formation and stabilisation of the passive film; raising the chromium content of stainless steel above the minimum content of 10.5% increases the stability of the passive film. Other elements may also contribute to the passive film: molybdenum plays a role in its stabilisation; nickel plays a role in promoting repassivation.

Stainless steels are sub-divided into a number of categories according to their metallurgical structure: ferritic steels; martensitic steels; austenitic steels; austenitic-ferritic steels; and precipitation-hardening steels. A description of each stainless steel family is presented in *Table 1.1*, together with information on physical properties, elemental composition and examples of some applications.

Table 1.1 **Identity of stainless steels**

Stainless steel family	Description	Composition (examples)	Typical applications
Martensitic group	Stainless steels of 400 series; capable of being heat treated to wide range of hardness and strength levels.	Type AISI 410: carbon 0.11% chromium 12%	Bolts, nuts, screws, cutlery, scissors, knife blades, surgical equipment, springs, beater bars for paper mills.
Ferritic group	Stainless steels in 400 series; used for corrosion resistance and resistance to sealing at high temperatures, rather than for high strength; non-hardenable by heat treating; always magnetic.	Type AISI 430: carbon 0.05% chromium 16.5%	Vehicle mufflers and catalytic converters, containers, vehicle trim, kitchen trim and equipment, drums and tubs for washing machines, drums for dryers, heat exchangers, oil burner parts, interior architectural trim.
Austenitic group	All stainless steels in the 200 and 300 series; have excellent formability and corrosion resistance; non-hardenable by heat treating; non-magnetic in annealed condition and depending on composition; become slightly magnetic when cold worked.	Type AISI 304: carbon 0.04% chromium 18.2% nickel 8.7%	Architectural trim, vehicle wheel cover, railroad car bodies, chemical processing equipment, food processing and handling equipment, hospital equipment, dairy equipment, beverage equipment, pharmaceutical equipment, petrol refining equipment.
Duplex alloys group	Austenitic-ferritic stainless steels; based on 2205 alloy; have a mixture of austenitic and ferrite in their structure; nitrogen added to improve corrosion resistance and strength.	Alloy AISI 2205: carbon 0.02% chromium 22% nickel 5.5% molybdenum 3% nitrogen 0.14%	Pipe and tube applications, petro-chemical equipment, pulp and paper processing machinery and equipment.

Stainless steel family	Description	Composition (examples)	Typical applications
Precipitation hardening (PH) alloys group	Sub-divided into semi-austenitic and martensitic alloys; develop high strength and hardness through heat treatment; usual form is as flat rolled material.	17-7 PH (semi-austenitic): carbon 0.08% chromium 17% nickel 7% aluminium 1% 17-4 PH (martensitic): carbon 0.05% chromium 16% nickel 4.5% copper 3.5% niobium 0.3%	Springs, clips, pressure tanks.

Source: PJ Cunat (personal communication); Cross *et al.* (1997)

There are several different systems currently in existence for designating stainless steels. Common designations include the AISI system, used in the USA, and the European Standard, adopted for use in the European Union (BSI 1995). Other national designations are also used. Under the AISI system, austenitic grades are in the 300 series; martensitic and ferritic grades are in the 400 series. Most of the sources of data reviewed in this document have used the AISI designation of stainless steels. Examples of stainless steel grades, with corresponding AISI and European Standard designations are presented in the following table:

Stainless steel family	AISI designation	European Standard designation	
		Name	Number
Austenitic	301	X10CrNi18-8	1.4310
	301L	X2CrNiN18-7	1.4318
	304	X5CrNi18-10	1.4301
	304L	X2CrNi18-9	1.4307
	305	X4CrNi18-12	1.4303
	316	X5CrNi Mo17-12-2	1.4401
	316L	X2CrNiMo17-12-2	1.4404
	321	X6CrNiTi18-10	1.4541
Martensitic	410	X12Cr13	1.4006
	420	X30Cr13	1.4028
Ferritic	430	X6Cr17	1.4016
	409	X2CrTi12	1.4512
	434	X6CrMo17-1	1.4113
	441	X2CrTiNb18	1.4509
	436	X6CrMoNb17-1	1.4526

Source: BSI (1995); Bourgain and Giauque (1993)

The austenitic grades account for about 75% of stainless steel production, much of this represented by AISI 304. Ferritic grades of stainless steel account for much of the remaining 25% of stainless steel production.

AISI 303, a unique high sulphur austenitic grade which figures later in this section, is a free-machining stainless steel supplied in the form of long products. AISI 303 is not widely used and in Europe represents <4% of austenitic production and <3% of total stainless steel production.

Stainless steel prosthetic devices are generally made using AISI 316. Production of AISI 316 for this purpose involves a vacuum-based process which eliminates the formation of small surface defects on the stainless steel.

1.1.2 Information on exposure

Occupational exposure

Stainless steels are used in the production of a wide range of appliances and other articles; some of these are listed in *Table 1.1*. The wide use of stainless steel products results in an extremely large number of workers experiencing some exposure to stainless steels during their work. In the occupational setting, skin contact with stainless steels is a common occurrence, although the pattern of exposure is likely to be intermittent rather than prolonged.

Consumer exposure

The wide use of stainless steels in a variety of domestic, surgical and other applications means that an extremely large number of consumers are likely to experience exposure to stainless steels. With regard to skin exposure in consumers, this may be may be prolonged or intermittent. Prolonged skin contact is associated with stainless steel articles such as watches, jewellery and fasteners on clothing. Intermittent skin exposure to numerous stainless steel articles or appliances is also to be expected for consumers.

Ingestion of metal ions released from stainless steel may represent a potential route of exposure for consumers. Chromium or nickel ions may be released in small quantities from stainless steel cooking utensils during the preparation of food.

Information regarding exposure to metallic stainless steel comes from studies that have investigated the release of nickel and, in some cases, other elements from stainless steel. These investigations have by and large been prompted by concerns about nickel and its involvement in skin sensitisation, and are divided into two types. Firstly, there are studies investigating nickel release into synthetic sweat and other biological fluids; these data are relevant to consumers because of possible prolonged skin contact with stainless steel articles. Secondly, there are studies investigating the release of elements from stainless steel cooking utensils; the data from these studies are also relevant to consumers because of the wide use of stainless steels in domestic cooking equipment.

"Jewellery Directive"

The European Parliament and Council Directive 94/27/EC, which was adopted in 1994, contains provisions that are intended to prevent the development of nickel allergy (EC 1994; see *Appendix I*). The Directive states that products may not be used *"…. if the rate of nickel release from the parts of these products coming into direct and prolonged contact with the skin is greater than 0.5 µg/cm^2/week"*. Further, the Directive states that such products should not be placed on the market. A reference test method for determining nickel release is under development (prEN 1811) which, when formally adopted by the European Committee for Standardisation (CEN), will form part of the Directive. The then most recent drafts of the CEN prEN 1811

method have been used in some of the studies reviewed in this section. Fundamental changes to the method are not anticipated.

Investigations of nickel release into synthetic sweat and other biological fluids

Several studies have been conducted which have investigated the release of nickel from stainless steel into synthetic sweat[4]. The most informative of these investigations are a study by Haudrechy *et al.* (1994) and a related unpublished study conducted at Ugine Savoie Centre de Recherches (Haudrechy and Pedarre 1997).

Haudrechy *et al.* (1994) examined nickel release from four different stainless steels into artificial sweat and saline solution. Three austenitic stainless steels were tested (AISI 303, AISI 304 and AISI 316L) and one ferritic stainless steel (AISI 430). Nickel release was determined according to the draft CEN prEN 1811 method. Samples of the stainless steels were immersed in synthetic sweat (pH 4.5 or 6.6) for one week at room temperature, after which the nickel content of the leaching solution was determined. Information on the elemental composition of the stainless steels tested and corresponding nickel release rates are presented in the following table:

Stainless steel	**Elemental composition (% by weight)**				**Ni release (µg/cm^2/week)**	
	Cr	**Ni**	**Mo**	**S**	**pH 4.5**	**pH 6.6**
AISI 303	17.3	8.46	0.26	0.280	1.0	0.3
AISI 304	18.2	8.65	0.26	0.007	0.03	0.1
AISI 316L	17.9	11.30	2.15	0.002	0.02	-
AISI 430	16.6	0.11	0.11	0.001	0.01	-

Similar results were obtained when 0.05M saline (pH 4.5) was used as the leaching solution. Lowering the pH of the leaching solution to 3.0, or increasing the chloride ion concentration caused nickel release to increase. Nickel release from pure nickel or nickel-plated steel, which was investigated in the same experiment, was markedly higher than that of any of the stainless steels tested (approximately 100 µg/cm^2/week). This study shows that for three of the stainless steels tested (AISI 304, 316L and 430), nickel release into synthetic sweat or saline solution was negligible. However, the extent of nickel release from AISI 303 was somewhat higher. At pH 4.5 (the lowest value for biological sweat reported in the literature), the nickel release rate for AISI 303 was 1.0 µg/cm^2/week. This value exceeded the 0.5 µg/cm^2/week limit specified in the EC Jewellery Directive (94/27/EC). AISI 303 is a high sulphur grade of stainless steel, developed for its free machinability. The relatively poor resistance of this grade to pitting corrosion results from its sulphur content, which, in combination with manganese, initiates pitting corrosion sites. The nickel release result indicates that AISI 303 should not be used where prolonged skin contact might occur, in accordance with the Jewellery Directive, to avoid the risk of eliciting skin reactions in nickel-sensitised persons.

[4] Synthetic sweat is an artificially created sweat containing sodium chloride (0.3-0.5%), lactic acid (0.1-0.2%), urea (0.1-0.2%) and, in some studies, sodium sulphate (0.1%), all dissolved in deionised water. The pH of synthetic sweat used in studies reported in this review ranged from 4.5 to 6.6.

As part of the same study, all four stainless steels were investigated for free nickel using the dimethylglyoxime (DMG) test and gave negative results; however, this test may be inappropriate for stainless steels[5]. The results of patch tests, which were conducted as part of this study, are reported in Section *1.1.4.*

In an unpublished study by Haudrechy and Pedarre (1997), nickel release into synthetic sweat was investigated using a more extensive range of stainless steels. The study involved six austenitic grades of stainless steel and one ferritic grade. Nickel release rates were determined according to the then latest version of the CEN prEN 1811 method. The pH of the synthetic sweat was 6.5. Elemental composition of the stainless steels tested and corresponding nickel release rates are presented in the following table:

Stainless steel	**Elemental composition (% by weight)**				**Nickel release ($\mu g/cm^2$/week)[a]**
	Cr	**Ni**	**Mo**	**S**	
303	17.21	8.61	0.300	0.313	1.308
304	18.48	8.71	0.192	0.0045	0.002
304L	18.27	9.05	0.241	0.0252	0.004
316	17.09	10.55	2.196	0.0011	0.004
316L	16.84	11.04	2.017	0.0258	0.006
310S	24.75	19.55	0.056	0.0007	0.006
430	16.39	0.16	0.032	0.0015	0.005

a. Mean values from three experiments; values were adjusted by a correction factor of 0.4, according to results from an interlaboratory trial; Ni release was determined in accordance with the draft CEN method of March 1997.

The results of this study show that, of the stainless steels tested, the highest nickel release rate occurred with the AISI 303 grade. The nickel release rate from this grade of stainless steel, under the conditions of this experiment, exceeded the 0.5 $\mu g/cm^2$/week limit recommended in the EC Jewellery Directive. This finding, in agreement with the previous study, indicates that AISI 303 stainless steel should not be used where prolonged skin contact may occur to avoid the risk of eliciting skin reactions in nickel-sensitised subjects. This study also demonstrated that, under the conditions of this experiment, nickel release rates for the remaining stainless steels tested were negligible and therefore prolonged skin contact with these grades of stainless steel is unlikely to result in skin reactions in nickel-sensitised subjects.

An earlier study measured nickel release from several different nickel alloys, including stainless steel, into synthetic sweat (Menné *et al.* 1987). One stainless steel

[5] The DMG test is used to detect the presence of nickel in alloys. The colorimetric test is based on the reaction of nickel ions with DMG, in the presence of ammonia solution, to form Ni^{2+} compounds that have a pink colour. The test, however, appears to be limited by poor sensitivity and false negatives have been reported (Haudrechy *et al.* 1993). The poor sensitivity may be overcome by etching the material, although with stainless steels etching destroys the passive film and thus provides a misleading indicator of nickel release from the alloy surface. The test is further limited by lack of specificity. DMG also reacts with iron, and coloured Fe-DMG complexes interfere with the detection of Ni-DMG complexes, generating false positives.

grade was tested, an austenitic stainless steel (elemental composition: 9% nickel, 18% chromium, 70% iron). Discs of the stainless steel were immersed in synthetic sweat (pH 6.5) for six weeks at 30°C. The amount of nickel released during the first week was approximately 0.04 µg/cm^2/week; this decreased during the six-week period. Discs made of the same type of stainless steel were also investigated in nickel-sensitised subjects in a human patch-testing study (see *Section 1.1.4).* The extent of nickel release reported in this study is similar to the values reported for some of the austenitic stainless steels by Haudrechy *et al.* (1994).

Ten items of stainless steel ear jewellery were investigated for release of nickel into synthetic sweat (Fischer *et al.* 1984). The items were stored in synthetic sweat (pH 6.4) at room temperature for one week, after which the nickel content of the sweat was determined. With eight items of jewellery, 0.05 - 3.0 µg Ni was released; with the two other items of jewellery, 15 and 19 µg Ni was released. No details were available regarding chemical composition of the stainless steel(s), nor the weight or surface area of the items tested. This study therefore contributes little useful information to this review of metallic stainless steel.

Nickel release into synthetic sweat from items of stainless steel jewellery was quantified by Kanerva *et al.* (1994). Ten different *"metal"* items were investigated, although only two of the items, two rivets, were reported to be made of stainless steel. Each item was immersed in synthetic sweat (pH 6.5) at 30°C. Nickel content of the sweat was determined after 1, 3 and 6 weeks using atomic absorption spectrometry. Nickel release from the rivets ranged from <0.1 to 65 µg/cm^2/week. No clear explanation was provided for the marked variability in the nickel release rates. The study was further weakened by the lack of information regarding the 'stainless steel'; this latter issue is important as the fairly high nickel release rates reported may have been associated with some other material. The findings of this study are therefore of limited value for this review. A case-report of hypersensitivity to nickel was presented in this study (reviewed in *Section 1.1.4*).

Samitz and Katz (1975) examined nickel release from stainless steel prostheses and other surgical accessories into various biological fluids. The objects (surface area 2 - 5 cm^2) were immersed in physiological saline, sweat, whole blood or plasma for one week at room temperature. The lowest concentrations of nickel were measured in plasma (range n.d. - 1.0 ppm) and the highest concentrations in sweat (range n.d. - 99 ppm). Nickel levels in saline ranged from n.d. to 9.8 ppm; and in whole blood n.d. to 17.4 ppm. The detection limit was 1.0 µg. With some items tested, the type of stainless steel was reported (AISI 302, 303 or 316L). This study shows that, under the conditions of this experiment, detectable amounts of nickel are released into biological fluids from stainless steel. However, there was insufficient information to allow the differences in nickel release from individual items to be explored or the variation between different biological fluids. Further, as stainless steel prostheses are generally made of AISI 316, data relating to other grades may not be relevant to this application. Overall, this study contributes limited information to this review of metallic stainless steel.

Barrett *et al.* (1993) investigated nickel and chromium release from stainless steel orthodontic appliances. Ten sets of appliances, each made from AISI 305, 316, 303

and 304 stainless steels, were immersed in artificial saliva (pH 6.75). Nickel and chromium release into fresh solution was measured at different time-points, up to 28 days. This study demonstrated nickel and chromium release from the appliances tested, although the available data did not allow the release rates to be quantified.

In vitro studies of nickel release from stainless steel have shown that the amount of nickel released can be affected by several factors which should be considered when extrapolating the information to *in vivo* conditions. Grimsdottir *et al.* (1992), for example, showed that the presence of solder on stainless steel orthodontic appliances caused an increase in nickel release. Soldering of alloys can cause galavanic coupling to occur, facilitating the release of nickel and other metals from the alloy. Kerosuo *et al.* (1995) demonstrated increased nickel release from stainless steel orthodontic appliances into saline when the experiment was conducted under dynamic conditions, simulating the oral environment, compared to when static conditions were used.

Investigations of nickel release from cooking utensils

Several studies have been conducted which have investigated the release of nickel, and in some cases other elements, from stainless steel cooking utensils. These studies have been prompted largely by concerns about the possible effects of ingested nickel in nickel-sensitive individuals.

Nickel and chromium levels were measured in a range of meals cooked in pans made from stainless steel (Accominotti *et al.* 1997). The pans were made from either AISI 436 stainless steel (17% Cr, 0.95% Mo) or AISI 304 (18% Cr, 9% Ni). Glass pans were used for reference values. The pH of the meals ranged from 7.0 to 8.7. Slightly increased levels of nickel and chromium were measured in several of the meals prepared in stainless steel pans. The increase levels of nickel appeared to be associated with particular meals. However, the increases in nickel and chromium levels were small relative to the nickel and chromium content of the meals. The resulting increased nickel intake would therefore make a negligible contribution to an individual's daily intake of nickel[6]. This study provides evidence that some nickel and chromium are released from stainless steel cooking utensils, but the relative contribution to the diet is small.

Release of nickel and chromium from stainless steel into a range of food preparations was investigated in a well-reported study by Flint and Packirisamy (1997). Five different foods were cooked in new pans made from AISI 304 stainless steel. The cooking operation was repeated on up to 20 occasions. The foods tested were selected on the basis that they would provide media aggressive to stainless steel (rhubarb, apricots, lemon marmalade, green tomato chutney and potatoes). The pH values of the foods after cooking ranged from 2.8 to 5.9. The highest release of nickel and chromium (referred to as *"pick-up"*) occurred when new pans were used for the first time; this was particularly evident with rhubarb and, to a lesser extent, apricots. However, this pick-up of nickel and chromium fell off to negligible levels with repeated use of the pans. With other foodstuffs tested, the pick-up of nickel and chromium was negligible at all times. The authors suggest that the initially "high"

[6] Current intake of nickel is reported to be approximately 150 µg/day (UK Department of Health 1991).

pick-up of nickel and chromium when using pans for the first time may be due to residue remaining on the pan surface which comes from the final polishing operation. This seems a plausible explanation. Overall, the findings of this study show that using stainless steel cooking utensils in the preparation of food contributes negligible quantities of nickel or chromium to the diet compared to background or normal levels.

Kumar *et al.* (1994) investigated the release of nickel and chromium from stainless steel utensils into several food materials following storage in stainless steel containers for several hours. Leaching into acidic and alkaline solutions was also measured. In a number of the food materials there was evidence of the release of nickel and chromium. However, the quantities of nickel and chromium measured in the foods tested would have a negligible effect on the daily intake of these elements.

Several other investigations have focused on nickel and chromium release into acidic solutions. Kuligowski and Halerin (1992), for example, demonstrated nickel and chromium release into 5% acetic acid (pH 2.4) which was boiled for five minutes. Brun (1979), in a briefly reported study, reported nickel release into natural acids (citric, malic and oxalic) and some foods (spinach, lemons, tomatoes, and apricots) after cooking in stainless steel pans for one hour.

Summary of information on exposure to metallic stainless steel

Information on exposure to metallic stainless steel comes from investigations of nickel release into synthetic sweat and other biological fluids, and from experiments where the release of elements from stainless steel cooking utensils has been determined. In either case, the information has most relevance for consumers rather than for the occupational setting.

In many of the studies of nickel release into synthetic sweat and other biological fluids, the items of stainless steel tested are poorly characterised in terms of grade, elemental composition, size or surface area. Therefore, although nickel release has been demonstrated under the conditions of the experiment, the results are difficult to interpret and thus contribute limited useful information to this review of metallic stainless steel.

The most reliable data on nickel release from stainless steel come from two studies that investigated a number of well-characterised stainless steels. Both studies showed that nickel release into synthetic sweat under the conditions of the experiment varied according to the grade of stainless steel. Of the stainless steels tested, the only grade of stainless steel for which nickel release rates were close to or exceeded the 0.5 $\mu g/cm^2$/week limit specified in the EC Jewellery Directive was AISI 303. Nickel release rates for this grade of stainless steel were reported as 1.0 $\mu g/cm^2$/week (pH 4.5), 0.3 $\mu g/cm^2$/week (pH 6.6) and 1.3 $\mu g/cm^2$/week (pH 6.5). In accordance with the Jewellery Directive, these findings indicate that AISI 303 stainless steel should not be used where prolonged skin contact may occur to avoid the risk of eliciting skin reactions in nickel-sensitised subjects. All other grades of stainless steel investigated, which included five austenitic grades and one ferrititic grade, demonstrated negligible nickel release in these tests, in all cases less than 0.03 $\mu g/cm^2$/week. These stainless

steel grades are therefore unlikely to evoke skin responses in nickel-sensitised subjects. In comparison, nickel release from pure nickel or from nickel-plated steel, under the same conditions was ~100 µg/cm^2/week. The association between nickel release from these materials and skin reactions were investigated in patch testing experiments; these are reported later in this section.

Several studies have investigated the release of nickel and other elements from stainless steel cooking utensils. The most relevant of these studies, which involve measuring release into food materials during cooking, have shown that the quantities of nickel and chromium released from stainless steel are negligible relative to natural nickel and chromium content of the foods. The studies provide no evidence that cooking food in stainless steel pans would lead to current recommended daily intakes for nickel or chromium being exceeded.

1.1.3 Toxicokinetics

No studies appear to have been conducted which have specifically investigated the absorption, distribution, metabolism or excretion of metallic stainless steel. However, in view of the passive surface film, which provides a barrier between stainless steel and the surrounding medium, and the negligible nickel release that has been demonstrated for a number of stainless steels, the bioavailability of potentially harmful constituents of most grades of stainless steel is anticipated to be negligible.

1.1.4 Toxicity

Acute toxicity, skin and eye irritation

No studies have been conducted in animals or humans which have specifically investigated the acute toxicity of metallic stainless steel, or the potential of stainless steels to cause skin or eye irritation. However, given the resistance of stainless steels to corrosion due to the presence of the passive film, the findings of leaching studies and the lack of positive results in human patch testing studies, none of these effects would be expected to occur.

Sensitisation

Animal data

No information is available regarding the ability of metallic stainless steel to induce skin sensitisation in animals as a consequence of dermal exposure.

Human data

Patch-testing studies

Several studies are available which have investigated the potential for involvement of stainless steel in allergic skin responses using patch-testing methods. Patch-testing is a standard technique used to detect delayed hypersensitivity (type IV) reactions in humans. The following test procedure is recommended by the International Contact Dermatitis Research Group (ICDRG). The subject's skin is exposed to a small quantity of the test substance or material under occlusion on the upper back for 48 hours. The skin response is assessed on day 2, after removal of the test material, and again on day 4-6; alternatively a single reading is made on day 3. A positive response is indicated by skin redness (erythema), oedema and/or vesicle formation. The response of each subject is graded. When testing for previous nickel sensitivity, 5% nickel sulphate is generally used as the test substance.

Four different grades of stainless steel (AISI 303, AISI 304, AISI 316L and AISI 430) were included in a patch-testing study involving 50 subjects with previous nickel sensitisation (Haudrechy *et al.* 1994). Elemental composition of each stainless steel tested and the rates of nickel release into synthetic sweat have previously been reported in *Section 1.1.2.* Patch-testing was conducted according to the ICDRG method. Circular samples of each stainless steel (1.5 cm diameter) were applied to the back of each subject and the skin response was assessed after two or three days. Negative results were obtained with AISI 430, 304 and 316L in all 50 subjects. With the high-sulphur, free-machining, stainless steel (AISI 303), 7/50 subjects (14%) gave a positive response. Pure nickel and nickel-plated steel were also tested; positive responses were recorded for 100% and 96% of subjects, respectively. This study showed that of the four stainless steels tested, only the high-sulphur grade AISI 303 appeared to release sufficient nickel to elicit skin reactions in some individuals with previous nickel sensitivity; this grade of stainless steel was also associated with the highest rate of nickel release into synthetic sweat. However, the number of positive responses with AISI 303 was substantially less than with either pure nickel or nickel-plated steel. This study showed no evidence that the other grades of stainless steel tested, all of which demonstrated negligible nickel release, had the potential to elicit a skin response in nickel-sensitised individuals.

Subjects with known nickel sensitivity were tested in a patch-testing study using discs of stainless steel (elemental composition 9% nickel, 18% chromium, 70% iron) (Menné *et al.* 1987). Nickel release from the stainless steel into synthetic sweat was found to be <0.05 μg/cm^2/week (see *Section 1.1.2*). Subjects were exposed to the discs for 48 hours and the skin response assessed after 48 and/or 72 hours. The strength of the response reported was dependent on the proportion of subjects giving a positive skin reaction. Two out of 66 subjects (3%) gave a positive reaction to the stainless steel, which was considered to be a weak response. Results from this study indicate that the stainless steel tested elicits a weak skin response among subjects with prior nickel sensitivity. Nickel release and patch-test results from other nickel alloys, including stainless steel, investigated in the same study showed the following general pattern: alloys with nickel release >1.0 μg/cm^2/week elicited a strong response (>50%

of subjects gave a positive skin reaction); alloys with nickel release <0.5 μg/cm^2/week elicited a weak response; in most cases <30% of subjects gave a positive skin reaction.

A range of nickel-containing alloys, including stainless steel, were investigated in a series of patch testing experiments which were simultaneously conducted in three different laboratories (Lidén *et al.* 1996). The study involved 100 nickel-sensitised subjects; 20 non-nickel-sensitised subjects acted as controls. Three stainless steels were tested in each subject using the recommended ICDRG method. Samples were applied to the upper back for 48 hours; the skin response was assessed on day 3. The stainless steels tested were: surgical grade (ISO 5832), 13-15% nickel [AISI 317]; 18/8 grade (ISO 683 XIII), 6.5-9.5% nickel [AISI 304]; stainless steel 142382, <0.5% nickel[7]. The three stainless steels were negative in all nickel-sensitised subjects. Gold-plated stainless steel 18/8 grade was also tested; 4/100 positive responses occurred with this material, although the result was not statistically significant when compared with results from non-nickel-sensitised controls. When the stainless steels were tested in the non-nickel-sensitised subjects, no positive responses occurred. The three stainless steels were further investigated in 20 of the nickel-sensitised subjects, using the ear-lobe as the exposure site and a seven-day exposure period; no positive responses occurred with any of the stainless steels tested. The results of this study showed that none of the three stainless steels tested elicited positive skin reactions in nickel-sensitised subjects, either with a two-day or a seven-day exposure period. The small number of positive responses that occurred with the gold-plated stainless steel may be explained by increased nickel release from the alloy caused by galvanic corrosion.

Räsänen *et al.* (1993) investigated nickel sensitivity in a group of nine volunteers who had their ears pierced using stainless steel ear-piercing kits. The subjects, all females, had no reported history of nickel sensitivity, although crucially none were patch-tested at the start of the study to confirm their non-sensitised status. The subjects were monitored for symptoms of sensitisation after ear piecing and were investigated in patch tests. Six of the subjects developed local symptoms (itching, swelling or discharge) within one to three weeks of ear piercing. All symptomatic subjects gave positive responses to nickel in patch tests. Nickel release from the nine ear-piercing kits was investigated using plasma and distilled water as the leaching fluids. The highest nickel release occurred with plasma, although the values showed wide variability (0.03 - 104.59 μg/cm^2/week). Nickel release into distilled water was up to a maximum of 1.39 μg/cm^2/week. In a subsequent communication, it was reported that the ear-piercing kits were all made of 18/8 stainless steel; four of these were plated with gold with a layer of nickel underneath the gold (Fisher 1994). Three of the subjects receiving the gold-plated ear-piercing kits developed local symptoms and patch-tested positive to nickel. This investigation is deficient in several respects. The immunological status of the subjects with respect to nickel was not ascertained prior to starting the experiment. Further, the exact chemical composition of the ear-piercing kits tested is unclear. Although all items were reported to be made of 18/8 stainless steel, some were also plated with gold and nickel. Consequently, this study

[7] Although the precise identity of this stainless steel is uncertain, the low nickel content indicates that it is probably either a martensitic or a ferrititic stainless steel.

does not allow any conclusions to be drawn regarding the potential of stainless steel to induce skin sensitisation.

Three cases of nickel sensitisation were reported among 300 workers at an electronics plant (Widström *et al.* 1986). Workers at the plant wore stainless steel wrist straps in order to dissipate static electricity. Nine workers developed contact dermatitis under the straps; three of these gave a positive response to nickel sulphate in a patch test. No information was presented regarding whether the three subjects had been previously sensitised to nickel. The wrist straps were reported to be made of stainless steel, although no information was provided regarding the identity of the stainless steel. In a leaching study, nickel release from two components of the wrist strap into synthetic sweat was measured over a 24-hour period at room temperature. Nickel release from the plate was 0.02 $\mu g/cm^2$ (a weekly rate of 0.14 $\mu g/cm^2$/week may therefore be calculated). Nickel release from the rivet was higher (0.20 $\mu g/cm^2$ over 24 hours), although it may not have been made of stainless steel which could account for this higher value. The findings of this study are weakened by the lack of information regarding the immunological status of the subjects with respect to nickel, together with uncertainties about the composition of the wrist strap components. These limitations therefore preclude any conclusions being drawn regarding the potential of stainless steel to induce skin sensitisation in these subjects, or regarding the potential of the stainless steel component to evoke skin responses in subjects previously sensitised to nickel.

Kanerva *et al.* (1994) briefly described a case of hypersensitivity to nickel in which a subject developed contact dermatitis a few days after first wearing a stainless steel watchstrap. The subject gave a positive patch-test response to nickel. The stainless steel watchstrap had apparently elicited the skin response in the previously sensitised subject. The identity of the stainless steel used in the watchstrap was not reported. Induction of nickel sensitisation was ascribed to nickel contained in metal spectacle frames that had formerly been worn by the subject, although no supportive evidence was provided.

Reactions to prosthetic devices

A number of case-reports have been published which have reported health effects in individuals who have received surgical or dental prosthetic devices made of stainless steel. These case-reports are reviewed here, although it is recognised that generally such reports do not provide much useful information.

Three cases were described of local dermatitis that appeared to be associated with stainless steel prosthetic devices used for fixing fractures of the tibia (Cramers and Lucht 1977). No infection was involved and the skin reactions subsided on removal of the implants. The implants were made of AISI 316L stainless steel. In patch-testing experiments, one of the subjects gave a positive response to nickel; the other two subjects gave positive responses to chromium and cobalt. Information regarding the immunological status of the subjects was not provided. It is therefore uncertain whether the skin response reported in the one subject represented induction of skin sensitisation by nickel from the stainless steel, or the eliciting of a response in

a previously sensitised individual. In a separate leaching experiment, 316L stainless steel was immersed in Ringers solution (37.5°C) for 35 days. Detectable amounts of nickel, manganese and iron were found in the solution, but no chromium. However, no quantitative information was provided for this leaching study.

Fisher *et al.* (1982) reported a single case in which asthmatic symptoms together with skin sensitisation appeared to be associated with internal surgical clips made of stainless steel. One month after a routine cholecystectomy which involved the use of surgical clips, the subject experienced wheezing and abdominal pain, with oedematous changes affecting the face and hands. Previous sensitivity to jewellery was reported. In patch-tests, the subject gave a positive skin response to nickel sulphate and also developed respiratory effects. Direct skin contact with stainless steel items caused the subject to develop local swelling and respiratory effects, including wheezing and a reduction in FEV_1 values. Respiratory symptoms subsided on removal of the surgical clips. The stainless steel clips used were reported to contain 12-14% nickel, although no further details regarding its identity were provided. A DMG test on the surgical clips failed to show evidence of any free nickel as discussed earlier, although this test may not be a reliable indicator of nickel release from stainless steel (see *Section 1.1.2*). This single case study provides some evidence of an association between stainless steel implants and the expression of skin responses and asthmatic symptoms in a nickel-sensitised individual. However, in view of the wide use of such stainless steel 'implants', this would seem to be an idiosyncratic reaction.

Possible hypersensitivity reactions associated with stainless steel sternal wires were described in two similar case-reports (Fine *et al.* 1990; Ancalmo *et al.* 1993). Both cases were those of women who experienced persistent chest pains after cardiovascular surgical procedures which involved the use of stainless steel sternal wires. In the first case, the stainless steel wires contained 8% nickel. In the second case, the sternal wires were made of 316L stainless with an elemental composition of 18% chromium, 12% nickel, 3% molybdenum and 67% iron. Both subjects had a history of skin sensitivity to jewellery and patch-tested positive to nickel. In both cases, chest pain subsided following removal of the sternal wires. Whilst the two case-reports indicate a possible hypersensitivity reaction to stainless steel implants, chest discomfort is a likely sequel of such a severe surgical procedure. Therefore these two reports provide no conclusive evidence that stainless steel implants elicit a hypersensitive response.

Local tissue response to stainless steel implants was investigated in seven subjects with no history of nickel or other sensitivity (Torgensen *et al.* 1995). Following removal of the stainless steel osteosynthesis devices, samples of local soft tissue and bone tissue underwent histological examination using immunohistochemical techniques. Local tissue response to the implants consisted of fibrous changes in the soft tissue and cellular infiltrates (lymphocytes and macrophages), indicative of a mild inflammatory reaction. Changes in local bone tissue were less marked. The results of this study indicate that local tissue response to the stainless steel implants was limited to a mild inflammatory response, but indicated no evidence of a hypersensitivity response.

Schriver *et al.* (1976) reported a case of a female with a possible allergic reaction to a stainless steel dental prosthesis. Hypermobility of the temporomandibular joint region and secondary arthritis were reported which appeared to be associated with a stainless steel wire prosthesis. Subsidence of symptoms coincided with removal of the prosthesis. The stainless steel had an elemental composition of 17% Cr and 16% Ni. Nickel sensitisation was indicated by a positive result to nickel in a skin patch-test, although no details of the test were provided. However, as there was no information about whether the subject had been previously sensitised to nickel, it is uncertain whether this case represents induction of nickel sensitisation by the stainless steel prosthesis or exacerbation of a pre-existing condition. Alternatively, the symptoms may have been a non-specific local response to implanted foreign material.

Olerud *et al.* (1984) reported the case of a woman, with previous nickel sensitivity, who developed a skin hypersensitivity reaction after being treated with nickel-contaminated dialysis fluid. The subject had a history of jewellery dermatitis and gave a positive patch-test response to nickel sulphate. Skin rashes developed after receiving dialysis fluid that had apparently been contaminated with nickel from a 316 stainless steel fitting used to deliver acid to the dialysis system. The stainless steel fitting was removed for further dialysis, and the rash subsided. An *in vitro* experiment demonstrated the ability of nickel to diffuse from dialysate into blood, mostly binding to plasma proteins. It was noted that, in the case-report, the site of the skin rash was distal from the site of injection of the dialysis fluid; the reason for this seems uncertain. This case-report presented no clear evidence to link the nickel contaminant of the dialysis fluid with the stainless steel fitting, or regarding the conditions which might have lead to this occurring. This case-report therefore provides only weak, indirect evidence of an association between exposure to nickel arising from stainless steel and a possible allergic skin response.

In vitro studies

Torgensen *et al.* (1993) used an *in vitro* test called the lymphocytic transformation test (LTT) as an indicator of nickel sensitivity in patients undergoing osteosynthesis with stainless steel plates following mandibular fracture. The LTT involved incubating peripheral lymphocytes with different concentrations of nickel sulphate. After four days, cell cultures were assessed for lymphocytic transformation. Increased lymphocytic transformation at non-toxic concentrations of nickel sulphate reflects an increased immunological response and is therefore considered to provide an indicator of nickel sensitisation. The study involved fifteen subjects undergoing osteosynthesis. The subjects were reported as having *"no metal hypersensitivity or allergic diseases"*, although no details were provided as to how this was established. Blood samples were collected before the operation and after removal of the plates. Lymphocytes collected from subjects *after* removal of the plates had significantly increased transformation rates following exposure to nickel compared with lymphocytes collected *before* the operation. This finding suggests an altered immunological response to nickel in subjects who had received stainless steel implants, although, significantly, none of the subjects displayed clinical signs of skin sensitisation. The results from the post-operative subjects were compared with several control groups. Lymphocytes from a group of nickel-sensitised controls showed more marked

lymphocytic transformation, indicating that the effect in the post-operative group was relatively weak. Lymphocytes from a group of controls with titanium implants showed similar transformation rates to the post-operative group, indicating that the altered immunological response observed could be a non-specific reaction to a foreign body. Overall, the findings of this study indicate an altered immunological response to nickel in previously unsensitised subjects which appeared to be associated with stainless steel implants, but which may have been a non-specific response to foreign material. The changed immunological response was only demonstrated *in vitro* and did not result in clinical signs of skin sensitivity in affected subjects. The relevance of these *in vitro* data to the *in vivo* situation is at present uncertain.

Summary of studies investigating sensitisation

No animal studies are available which have investigated the potential of stainless steels to induce sensitisation by skin contact. Animal investigations of local tissue response to implanted stainless steel contribute little to our understanding of the sensitising potential of stainless steels.

Several studies are available which have investigated the potential for involvement of stainless steels in allergic skin responses in humans. These studies fall into two categories: investigations of the potential of stainless steel to **elicit** skin responses in subjects previously sensitised to nickel; and investigations of the potential of stainless steel to **induce** hypersensitivity in non-sensitised subjects.

Several patch-testing studies are available which have investigated the potential of stainless steel to elicit skin responses in nickel-sensitised subjects. Results from these studies, which were conducted according to ICDRG guidelines, show that the stainless steel grades AISI 304, AISI 316L, AISI 317 and AISI 430 are unlikely to elicit skin responses in nickel-sensitised individuals. In contrast, stainless steel AISI 303 evoked skin responses in patch tests in a small proportion (14%) of nickel-sensitised subjects.

This grade of stainless steel also demonstrated the highest nickel release of all the grades tested, reported earlier in this review. AISI 303 may therefore have the potential to elicit skin reactions in nickel-sensitised subjects if there is prolonged skin contact with the material. However, the response rate with AISI 303 is far less than with pure nickel or nickel-plated material which gave positive response rates of 100% and 96%, respectively.

Regarding the potential of stainless steels to induce hypersensitivity, little information is available. In a single patch testing study, uniformly negative reactions were reported in a small group of non-nickel-sensitised subjects exposed to three stainless steels (AISI 317, AISI 304 and an unidentified grade).

Other studies reviewed in this section include case-reports involving skin exposure to stainless steel articles or exposure to stainless steel prosthetic devices. Overall these studies provide no reliable information on which to base an assessment of the potential of stainless steel to elicit responses or induce sensitisation. However, given the extremely large population that is exposed to stainless steels, either by prolonged or intermittent skin contact, or as a result of stainless steel surgical implants, it is notable that so few case-reports are available.

Effects of prolonged exposure

Animal data

Due to the wide use of stainless steel in dental and surgical prostheses, a number of animal studies have been conducted to investigate local tissue responses to implanted stainless steel. No studies appear to have been conducted which have investigated the effects of prolonged exposure to stainless steel by other routes of exposure.

Local tissue reaction sub-cutaneous (s.c.) implants of stainless steel wire was investigated in rabbits (Gjerdet *et al.* 1987). Orthodontic stainless steel wire ("Tru-Chrome"; 1.05 mm diameter, 16 mm length; elemental composition 68% Fe, 19% Cr, 13% Ni) was implanted into s.c. tissue of the flank in 12 rabbits. Polytetrafluoroethylene (PTFE) tubing, implanted into s.c. tissue in the same animals, served as the control material. Surrounding tissue underwent histopathological examination 31 days after implantation. The only local response observed, which occurred with both the stainless steel wire and the PTFE implants, was the presence of a surrounding collagen capsule containing fibroblasts and fibrocytes. Previous sensitisation of some of the animals to nickel appeared to have no effect on local tissue response to the implanted materials.

Stainless steel orthopaedic implants were investigated for their potential to elicit a local response in animals previously sensitised to nickel or chromium (Lewin *et al.* 1982, 1987). In the more recent and more extensive study, male guinea pigs were sensitised to nickel or chromium using $NiSO_4.6H_20$ or $K_2Cr_2O_7$, respectively, administered by intramuscular (i.m.) and s.c. injections and topical application. Stainless steel screws (ASTM F55, F138-189; 2.7 mm diameter) were inserted into the distal femur and proximal tibia of animals with confirmed allergic responses (9 Cr-sensitised and 8 Ni-sensitised animals) and groups of unsensitised control animals (8 or 9 in each group).

Four months after treatment, animals were killed and the effect of the implants on bone tissue examined. Mechanical strength of fixation of the screws in the bone tissue was determined and changes in bone density were assessed, the latter parameter by measuring the amount of bone ash. Histopathological examination of bone tissue was also conducted. In none of these parameters was there found to be any difference between the sensitised animals and non-sensitised animals. Eczematous changes on the skin of sensitised animals were reported. This study provided no evidence of bone

tissue involvement in allergic responses to stainless steel orthopedic implants in sensitised animals.

Reaction of skeletal muscle to implanted stainless steel wire was investigated in mice (McGeachie *et al.* 1992). Surgical grade stainless steel wire (0.5 x 5 mm) was implanted into the leg muscle of mice and the time-course of local tissue response examined at 3 days to 12 weeks after implantation. No information was provided about the identity or chemical composition of the stainless steel. Four animals were examined at each time-point (36 mice in total). Histopathological examination of leg muscle demonstrated initial inflammatory response, formation and consolidation of a collagen capsule, and evidence of muscle regeneration (3 days to 2 weeks post-implant); from 3 weeks onwards little change was reported. Autoradiograpy, which was performed on an additional eight animals, confirmed that the stainless steel implant had no inhibitory effect on myogenesis. Titanium implants, which were investigated in the same study, induced a similar tissue reaction to that of stainless steel. The local tissue response to stainless steel implants therefore appeared to be a typical non-specific local response to foreign material.

316L stainless steel was used as the control material in an investigation of local tissue reaction to a range of materials following i.m. implantation (Escales *et al.* 1976). Six months after a stainless steel rod (approximately 5 x 220 mm) was implanted in the paravertebral muscle in rabbits, histopathological examination showed a mild tissue response in surrounding tissue, with some fibrosis and minimal inflammation. These changes appear to represent a fairly typical non-specific local response to foreign material.

Two studies which investigated local tissue response in the brain to implants of stainless steel reported negligible tissue damage in rats 35 or 63 days after treatment (Babb and Kupfer 1984) or in cats two months after treatment (Dymond *et al.* 1970). The relevance of this study to the effects of using surgical implants in humans is uncertain.

Human data

Human data on the effect of prolonged exposure to stainless steel consist of a number of case-reports of subjects with stainless steel implants. These case-reports have been reviewed in the *'Sensitisation'* sub-section.

Summary of effects of prolonged exposure

Information on the effect of prolonged exposure to metallic stainless steel comes from a number of animal implantation studies, where implantation of stainless steel items into muscle or sub-cutaneous tissue resulted in a local response characterised by inflammatory and fibrotic changes. These changes are considered to be a typical, non-specific local response to foreign material. No studies appear to have been conducted which have investigated the effects of prolonged exposure to stainless steel by other routes of exposure.

Human data on the effects of prolonged exposure to metallic stainless steel are limited to a few case-reports in which local and/or distal effects have been reported in subjects who have received prosthetic implants made from stainless steel. However, these reports provided no conclusive evidence of an association between stainless steel and the reported changes. Further, given the wide use of stainless steel in prosthetic devices, surgical and dental, it is significant that only a small number of case-reports have been reported.

Mutagenicity

No data are available relating to the mutagenicity of metallic stainless steel, although this is not unexpected given the difficulties that would be encountered in conducting tests using currently available methods.

Carcinogenicity

Data relating to the potential carcinogenicity of metallic stainless steel are limited to a single study which investigated the local tumour development in animals following i.m. implantation of stainless steel rods.

The study by Takamura *et al*. (1994) investigated a number of alloys including stainless steel in C57BL/6N mice. In the stainless steel treatment group, cylindrical rods of 316L stainless steel (1 x 5mm) were implanted in the left thigh muscle of animals (25 females and 25 males). The elemental composition of the stainless steel was 12.51% nickel, 17.84% chromium, 2.34% molybdenum, 1.82% manganese, <1% each of carbon, phosphorus, silicon, and the balance as iron. A control group comprised 25 female and 25 male sham-operated animals. Tumour development at the implantation site was examined 24 months after the operation. Survival in the stainless steel treatment group was similar to the control group. No implantation-site sarcomas occurred in the stainless steel treated animals or in the control group. Lymphomas near the implantation site occurred in three of the stainless steel treated animals. No lymphomas occurred in sham-operated control group. Lymphomas also occurred in other treatment groups and it is highly probable that the lymphomas may be associated with a local inflammatory response. Haematology and assessment of organ weights revealed no significant differences between treated and control animals, with the exception of blood levels of glutamate oxaloacetate transmitase which were significantly reduced in male animals treated with stainless steel. The toxicological significance of this one biochemical parameter is uncertain.

Summary of investigations of carcinogenicity

The only data relating to the carcinogenicity of metallic stainless steel comes from a single animal study in which i.m. implantation of stainless steel rods failed to increase tumour development in mice. No standard animal carcinogenicity studies have been conducted with metallic stainless steel using recommended protocols, although this is not surprising given the problems that would be faced exposing animals to the test material.

There are no data available regarding the carcinogenicity of metallic stainless steels in humans.

Effects on reproduction

No studies are available which have investigated the effect of metallic stainless steel on reproduction, either in animals or in humans.

1.2 Metallic stainless steel: powder

There is no relevant published information available on metallic stainless steel in the powdered form. The chemical structure of stainless steel powder is anticipated to be the same as for metallic stainless steel in the massive form. According to the European Powder Metallurgy Association (EPMA), there are three main particle size ranges for stainless steel powders:

Powder type/application	**Particle diameter (µm)**	
	Median	**Range**
Pressing and sintering	70	20-150
Metal injection moulding	15	5-40
Filtration	from 20µm upwards	

Source: EPMA (personal communication)

With the three main powder types, at least some of the particles fall within the inhalable[8] range. With metal injection moulding powders, some of the particles are also likely to be within the respirable range.

Currently, stainless steel powder production represents a small section of metallic stainless steel production. In the EU, annual production of stainless steel powder intended for sintering is estimated to be less than 5000 tonnes; this represents less than 0.1% of total stainless steel production for the EU.

[8] 'Inhalable' dust is the fraction of airborne material which enters the nose and mouth during breathing and is therefore available for deposition in the respiratory tract; 'respirable' dust is the fraction of airborne material which penetrates to the gas exchange region of the lung (Health and Safety Executive 1997). As an approximation, particle diameter for inhalable particles is generally $\leq$100µm and for respirable particles $\leq$10µm.

Exposure to stainless steel powder may occur during the manufacturing process and during use in plasma spraying operations. As some powders are inhalable, and some may also be respirable, stainless steel powders present the potential for inhalation exposure in the occupational setting. No exposure data are available.

The intrinsic toxicological properties of stainless steel in the powdered form are considered to be the same as for stainless steel in the massive form. Consequently, there is unlikely to be any identifiable hazard specifically associated with this form of metallic stainless steel.

1.3 Hazard assessment

This section contains a summary of data on the health effects of metallic stainless steel, reviewed in the preceding sections. Data relating to each toxicological end-point are then evaluated against the criteria contained in Annex VI of Directive 92/32/EEC, amending Directive 67/548/EEC. The purpose of this evaluation is to establish how, based on currently available data, metallic stainless steels would be classified if they were substances.

Currently, stainless steels are classified in the EU according to the Preparations Directive (88/379/EEC). According to the conventional method contained within the Preparations Directive, stainless steels which contain nickel at a concentration of 1% or more are classified as category 3 carcinogens (R40) and skin sensitisers (R43).

Acute toxicity

No studies have been conducted in animals or humans which have investigated the acute toxicity of metallic stainless steels, or the potential of stainless steels to cause skin or eye irritation. However, given the resistance of stainless steels to corrosion due to the presence of the passive film, the findings of leaching studies and the lack of positive results in human patch-testing studies, none of these effects would be expected to occur. This view is supported by the absence of any reports of acute toxicity associated with exposure to metallic stainless steel. The absence of such data is even more notable given the extremely large number of individuals who are exposed to stainless steel on a regular basis, for example in cooking utensils, other domestic appliances, wristwatches, clothes fasteners and prosthetic devices.

Consideration against classification criteria: No studies have been conducted in animals to provide any evidence concerning the acute toxicity of metallic stainless steel, or regarding irritancy to the skin or eyes. Further, there are no human data available. However, in view of the widespread human exposure to metallic stainless steel, human experience provides no reasonable basis for classifying metallic stainless steel for acute toxicity, or for irritancy to the skin or eyes.

Sensitisation

No animal studies are available.

Investigations of the involvement of stainless steel in allergic skin responses in humans fall into two categories: investigations of the potential of stainless steel to **elicit** skin responses in subjects previously sensitised to nickel; and investigations of the potential of stainless steel to **induce** hypersensitivity in non-sensitised subjects. Induction of hypersensitivity is the only toxicological property considered when deciding whether a substance or preparation should be classified as a skin sensitiser.

Patch-testing studies have been conducted which have investigated the potential of stainless steels to elicit skin responses in subjects previously sensitised to nickel. The findings of these studies, in conjunction with results from nickel-release experiments, indicate that the ability of stainless steels to elicit skin responses in nickel-sensitised individuals depends upon the bioavailability of nickel. The results show that prolonged skin contact with stainless steel grades AISI 304, AISI 316L, AISI 317 and AISI 430 is unlikely to elicit skin responses in nickel-sensitised individuals. In contrast, the high-sulphur grade AISI 303 may, with prolonged skin contact, have the potential to elicit skin responses in nickel-sensitised subjects.

With regard to the **induction** of hypersensitivity, there are few data are available for stainless steels. In one small study, stainless steel grades AISI 317, AISI 304 and one unspecified martensitic or ferritic grade failed to induce hypersensitivity in non-nickel-sensitised subjects as a result of skin contact. No information is available concerning the potential of AISI 303 to induce hypersensitivity as a result of skin contact.

Given the extremely large population that is exposed to stainless steels, either by prolonged or intermittent skin contact, or as a result of stainless steel surgical implants, it is highly notable that so few reports of suspected sensitisation reactions are available.

*Consideration against classification criteria: The classification criteria for skin sensitisation are concerned with the **induction** of hypersensitivity as result of skin contact, not the potential to elicit a skin response in previously sensitised subjects. No animal studies are available. Data from a single human study provide no evidence to indicate that the three stainless steels tested induce hypersensitivity as result of skin contact. There is no toxicological basis for classifying stainless steels as sensitising by skin contact.*

Prolonged exposure

Information on the effects of prolonged exposure to metallic stainless steel come from a number of animal implantation studies, where implantation of stainless steel items into muscle or sub-cutaneous tissue has resulted in a local response, characterised by inflammatory and fibrotic changes. These changes are considered to be a typical, non-specific local response to foreign material.

Human data on the effects of prolonged exposure to metallic stainless steel are limited to a few case-reports in which local and/or distal effects have been reported in subjects who have received prosthetic implants made from stainless steel. However, these reports have not provided consistent evidence of an association between stainless steel and the reported changes over and above a non-specific response to implanted materials. Further, given the wide use of stainless steel in prosthetic devices, surgical and dental, it is highly significant that only a small number of cases have been reported.

Consideration against classification criteria: Only limited animal and human data are available. These provide no evidence that prolonged exposure to metallic stainless steels has any serious detrimental effect on health. There is no basis for classifying metallic stainless steels for effects arising from repeated or prolonged exposure.

Carcinogenicity

The only data relating to the carcinogenicity of metallic stainless steel comes from a single animal study in which i.m. implantation of stainless steel rods failed to increase tumour development in mice. No standard animal carcinogenicity studies have been conducted with metallic stainless steel using recommended protocols, although this is not surprising given the problems that would be faced exposing animals to the test material.

There are no data available regarding the carcinogenicity of metallic stainless steels in humans.

Consideration against classification criteria: The available data provide no basis for classifying metallic stainless steels for carcinogenicity.

Mutagenicity

No data are available relating to the mutagenicity of metallic stainless steel, although this is not unexpected given the difficulties that would be encountered in conducting tests using currently available methods.

Consideration against classification criteria: In the absence of any data, there is no basis for classifying metallic stainless steels for mutagenicity.

Effects on reproduction

No studies are available which have investigated the effect of metallic stainless steels on reproduction, either in animals or in humans.

Consideration against classification criteria: In the absence of any data, there is no basis for classifying metallic stainless steels for effects on reproduction.

1.4 Risk assessment

Data concerning the health effects of metallic stainless steel, reported in the hazard assessment, meet none of the criteria for classification. Consequently, most of the metallic stainless steels concerned are considered as presenting negligible risk to human health.

In view of the skin reactions that have occurred under experimental conditions with AISI 303, it is considered that the health effects associated with this stainless steel grade should be evaluated as part of a risk assessment with the aim of clarifying any associated risk. The results of patch-testing studies in humans, in conjunction with investigations of nickel release, indicate that prolonged skin contact with stainless steel AISI 303 may elicit skin reactions in nickel-sensitised subjects. The available data indicate that AISI 303 is not widely used and that its production represents a very small proportion of stainless steel production as a whole. Nevertheless, should AISI 303 be used in applications in which prolonged skin contact occurs, there may be a risk of it eliciting skin responses in a small proportion of nickel-sensitised subjects.

In the absence of any toxicological data to indicate otherwise, there appears to be no identifiable hazard specifically associated with metallic stainless steel in the powdered form. As stainless steel powders present the potential for inhalation exposure in the occupational setting, it is deemed appropriate to treat stainless steel powders as for any dusts and to control exposure by the appropriate exposure limits where these exist. In the UK, dusts are controlled by a limit of 10 mg/m^3 (total inhalable dust) or 4 mg/m^3 (respirable dust). If exposure levels are controlled according to these limits, then the risk to health is considered to be negligible.

1.5 Future research needs

The available information on metallic stainless steel in the massive form indicates that there are gaps in the database for many of the toxicological end-points. No data have been published relating to acute toxicity, skin and eye irritancy, mutagenicity, and effects on reproduction. For several other end-points, such as carcinogenicity, effects of prolonged exposure and induction of skin sensitisation, the data are very limited.

In view of the chemical/physical properties of stainless steels and the associated nickel-release data, there appears to be little reason based on bioavailability for suggesting that further testing of metallic stainless steel in the massive form is warranted. However, issues raised by the current classification of some stainless steels as skin sensitisers and carcinogens, on the basis of nickel content, indicate the need for some additional testing to explore the appropriateness of such classification. With regard to skin sensitisation, animal tests using a modified Buehler test method may generate some useful information for those stainless steel grades with the highest associated nickel release.

None of the standard animal carcinogenicity tests currently available are considered likely to generate useful information, due to practical difficulties associated with dosing procedures. The carcinogenicity issue may be partly explored by examining the fate of any nickel or chromium released from stainless steel within biological systems (e.g. *in vitro* studies of cellular uptake, *in vivo* distribution studies), with a view to establishing whether nickel or chromium has potential to reach the target molecule (DNA).

2 STAINLESS STEEL MANUFACTURE

This section is concerned with the manufacture of stainless steel which, for the purpose of this review, is considered to include the stages of melting through to finishing. The purpose of this section is to present a review of available data on the health effects associated with stainless steel manufacture and, on the basis of this review, to provide an assessment of the hazards and any ensuing risk.

2.1 General information

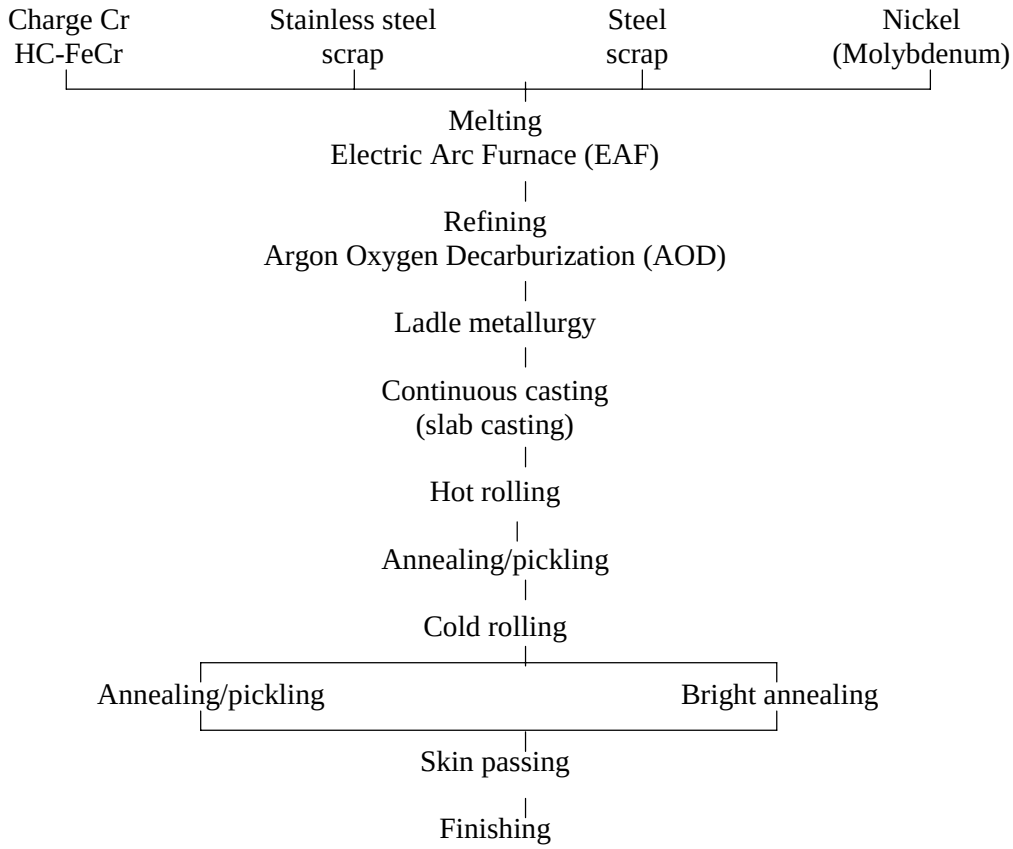
Stainless steels are currently produced by melting a charge, containing high-carbon ferro-chromium alloy, stainless steel scrap, steel scrap and nickel and sometimes molybdenum, in an electric arc furnace. The molten metal is then refined using argon/oxygen decarburization (AOD), during which the carbon content is reduced to the desired level and a reduction mix, containing silicon, aluminium and lime, is added. The molten metal then undergoes various metallurgical operations in the ladle, involving addition of, for example, titanium or niobium, and deoxidation treatments, followed by continuous casting (slab or bloom casting) and hot processing. The hot processing stage is followed by cold processing, typically involving annealing, pickling and cold rolling, and finally finishing.

The production processes currently used for stainless steels flat products and long products are summarised in *Figure 2.1*.

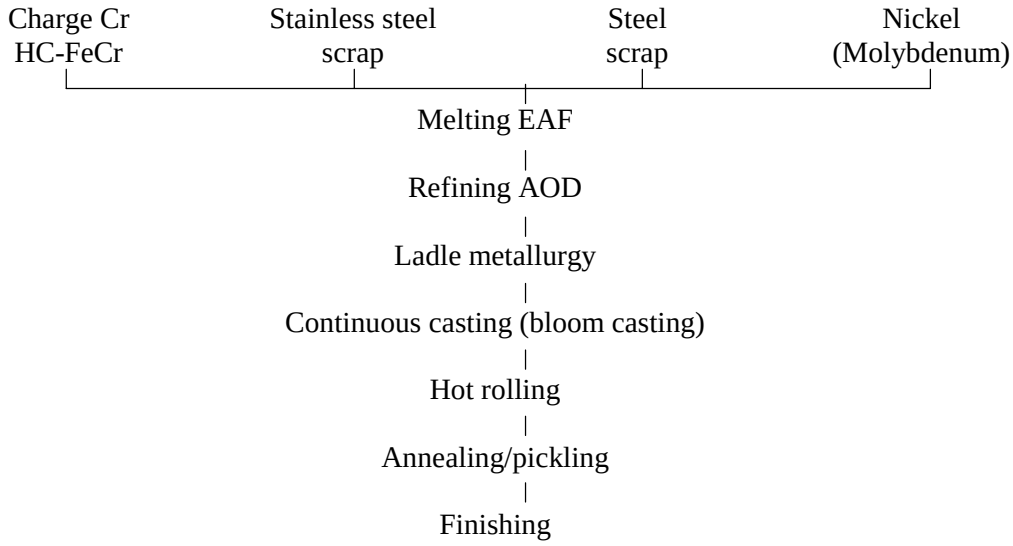
With regard to stainless steel powders, no information appears to have been published which provides a description of the production process or provides qualitative or quantitative information on exposure during production.

Figure 2.1

Production of stainless steel flat products



Production of stainless steel long products



Source: PJ Cunat *(personal communication)*

2.2 Information on exposure

The manufacture of stainless steels gives rise to airborne dusts and fumes and thus presents the potential for inhalation exposure in the occupational setting. The components of the airborne dusts and fumes are likely to vary according to the type of production process, the stage of the process and also according to the grade of stainless steel under production. Airborne substances may arise from the metal constituents used to produce the stainless steel, such as oxides of chromium, nickel, iron, molybdenum and manganese. Available information indicates that airborne dust contains chromium predominantly as Cr^{III}, although Cr^{VI} compounds do occur (Huvinen *et al.* 1993; Koponen *et al.* 1981a). Other substances present in the atmosphere may contain the following elements: silicon, calcium, aluminium, magnesium and sodium (Koponen *et al.* 1981a). From the available data, it is difficult to characterise the type of exposure that occurs at each stage of the manufacturing process more precisely.

With regard to polycyclic aromatic hydrocarbons (PAHs), former methods of stainless steel manufacture involved the use of electrodes which may have given rise to airborne PAHs during the melting stage. Modern methods of manufacturing stainless steel use electrodes which do not release PAHs during melting, and thus there is no exposure to PAHs during this stage of the production process. PAHs may occur during the casting stage if molds are used which contain binders and additives, airborne PAHs arising as decomposition products of these materials. However, currently most stainless steel is cast using the continuous casting process; this process involves water-cooled copper molds and PAH exposure is therefore not anticipated.

Although there is the potential for inhalation exposure in the stainless manufacturing industry, the quantitative data on exposure are limited. Two reports have been published; both studies are based on the same company in Finland. The results from these studies are summarised in *Table 2.1*. The UK Health and Safety Executive (HSE) were unable to provide any additional exposure data relating to the manufacture of stainless steel.

Table 2.1 **Manufacture of stainless steel - summary of exposure data in published literature**

(a) From: Koponen *et al.* (1981a)

Production stage[a]	Sampling strategy (no. of samples)	Analytical method(s)	Mean dust conc'n (mg/m^3)	Chemical composition (%)									
				Fe	Cr	Ni	Mo	Mn	Mg	Al	Si	Ca	Na
FeCr melting	2-hr sampling period; uncertain whether personal/ static samples (6)	Elemental: OES Cr/Ni: AAS Cr^{VI}: colorimetric	1.4 ± 0.6	5-20	6-15[b]	<0.1[c]	<0.1	0.2-0.6	5-10	5-10	10-20	1-3	1.5-2
St/steel melting	" " " " (11)		2.3 ± 1.3	3-6	1.5-5[b]	0.2-0.7[c]	<0.1	0.5-1	2-8	1-3	3-10	10-50	0.5-1
St/steel casting	" " " " (18)		4.3 ± 2.7	1.4-2.4	0.2-0.3	0.2-0.4	<0.1	0.2-1					

a. FeCr melting - this stage involved production of FeCr from chromite ore; St/steel melting - molten FeCr, stainless steel scrap and other materials were heated in an electric arc furnace; St/steel casting - stainless steel was continuously cast through a water-cooled mould.
b. Six samples each from the FeCr melting and st/steel melting stages were used for determination of total Cr, acid-soluble Cr and water-soluble Cr; values were 14.5%, 2.9% and <0.02% (FeCr melting), and 2.5%, 0.5% and <0.02% (st/steel melting), respectively. All values are expressed as a % of the total dust.
c. The same samples were used for determination of total Ni, acid-soluble Ni and water-soluble Ni; values were 0.07%, 0.06%, and <0.02% (FeCr melting), and 0.4%, 0.3% and <0.02% (st/steel melting), respectively. All values are expressed as a % of the total dust.

Table 2.1 **Manufacture of stainless steel - summary of exposure data in published literature, cont'd.**

(b) From: Huvinen *et al.* (1993)

Production stage[a]	Total dust concentration (mg/m^3)	No. of samples	Total Cr concentration ($\mu g/m^3$)	No. of samples	Cr^{VI} concentration ($\mu g/m^3$)	No. of samples
Steel smelting shop[b]	1.8 (18)	153	30 (432)	82	0.5 (6.6)	72
Steel smelting shop[c]	0.8 (5.5)	10	66 (459)	4	<0.5 (0.6)	5
Cold rolling mill[d]	0.5 (1.8)	82	<10 (180)	50	<0.5 (6.6)	29
Cold rolling mill[e]	0.3 (1.1)	49	<10 (33)	40	<0.5 (<0.5)	12

The exposure data reported were determined from personal samples collected over two 4-hour periods or one 8-hour period on four or five consecutive days; median values are reported with maximum values are in parentheses.

a. exposure measurements were taken in the smelting shop and in the cold rolling mill;
b. area with no exposure to grinding dust;
c. area with exposure to grinding dust;
d. activities included annealing pickling, neutralisation and acid regeneration;
e. activities excluded annealing pickling, neutralisation and acid regeneration.

In this study, the *"smelting shop"* was where melting of ferrochromium alloy and addition of stainless steel scrap took place; this appears to correspond to the *"melting"* stage referred to in Section 2.2.

2.3 Toxicokinetics

Toxicokinetics is concerned with the absorption, distribution, metabolism and excretion of substances. Human toxicokinetic data relating to stainless steel manufacture are limited to two studies by the same research group based on workers at an integrated stainless steel production plant (Huvinen *et al.* 1993; 1997).

In the first study, chromium levels were measured in urine and blood samples from workers engaged in stainless steel manufacture: smelting shop workers[9] and workers in the cold rolling mill (Huvinen *et al.* 1993). Slightly elevated urinary chromium levels in pre- and post-shift samples indicated that some chromium absorption had occurred. Mean U-Cr levels adjusted for specific gravity for four groups of workers ranged from 0.02 to 0.04 µmol/l (1.04–2.08 µg/l)[10]. Levels of chromium in whole blood samples (B-Cr) were also reported to be slightly elevated; mean levels of 0.01 µmol/l were reported, although these are at the upper limit of unexposed reference values used by clinical laboratories in the UK. This study, which focused on exposure to chromium, provided evidence that some absorption of chromium occurs in stainless steel production workers.

The second study investigated the retention of dust in the lungs of stainless steel production workers in the same plant (Huvinen *et al.* 1997). The study employed a technique called magnetopneumography, a non-invasive technique which indirectly measures the lung load of magnetic particles. Of the two groups of stainless steel production workers investigated, smelting shop workers had a slightly elevated lung load of magnetic material compared to controls; workers in the cold rolling mill showed no increase. However, as subjects were selected partly on the basis of *"documented higher dust exposure levels"*, these results may not be very representative. Further, the study provided no details of the control group. This study therefore contributes limited information to the subject of 'Toxicokinetics'.

2.4 Toxicity

Acute toxicity, skin/eye irritation, and sensitisation

No studies are available which have investigated acute toxicity, skin or eye irritation, or sensitisation resulting from exposure during the manufacture of stainless steels.

Effects of repeated exposure in humans

Only one study is available which has investigated long-term effects on health among workers engaged in the manufacture of stainless steel: in a unique facility comprising an integrated chromite mine, stainless steel smelter and rolling mill, respiratory

[9] The term *"smelting shop"* was used in this study. The smelting shop is where melting of ferrochromium alloy and addition of stainless steel scrap took place; this appears to correspond to the *"melting"* stage referred to in Section 2.2 of this review.

[10] U-Cr levels in unexposed subjects have been reported as 0.125 µg/l (Kiilunen *et al.* 1987) and 0.18-1.60 µg/l (Angerer *et al.* 1987).

morbidity was investigated in a cross-sectional study by Huvinen *et al.* (1996). All workers who had been working for eight years or more in the same department at the site were invited to participate, representing 222 from a total of 892 at the plant, and 221 of these agreed to participate. In addition, 95 of 132 workers from a cold rolling mill were included as controls. Exposure data came from a survey which was conducted during one year. This survey, which was separately reported in Huvinen *et al.* (1993), involved the collection of 162 personal air samples and 72 static samples in different parts of the plant. The samples were analysed for total dust, total chromium and Cr^{VI}. Data reported here represent personal sampling data only and are 8-hour TWA values.

Median total dust levels in different parts of the plant were 0.9 mg/m^3 (chromite mine), 1.5 mg/m^3 (furnace department of ferrochromium plant), 2.4 mg/m^3 (sintering and crushing area of ferrochromium plant) and 1.8 mg/m^3 (steel smelting shop[11]). Lower levels occurred in the cold rolling mill, which represented the "control" area; median total dust levels for two parts of this area were 0.3 mg/m^3 and 0.5 mg/m^3.

Measurable levels of total chromium occurred in all areas, with the exception of the cold rolling area; median values were 22 $\mu g/m^3$ (chromite mine), 143 $\mu g/m^3$ (furnace department of ferrochromium plant), 248 $\mu g/m^3$ (sintering and crushing area of ferrochromium plant) and 30 $\mu g/m^3$ (steel smelting shop), respectively. In contrast, median levels of Cr^{VI} were below the limit of detection (<0.5 $\mu g/m^3$) in most areas of the plant, with the exception of the steel smelting shop where the median value was 0.5 $\mu g/m^3$ (maximum value 6.6 $\mu g/m^3$).

Information on respiratory symptoms, smoking habits, and medical and occupational history was determined by questionnaire and, in most subjects, clinical examination was performed. In order to compare effects on respiratory health, subjects were grouped on the basis of exposure data (Cr^{III} or Cr^{VI}) as follows: chromite miners (n=36); workers in furnace department of FeCr plant and steel smelting shop (n=109); workers in sintering and crushing department of the FeCr plant (n=76); cold rolling mill workers (controls; n=95). There were few differences in the prevalence of respiratory symptoms between the groups, and these were attributed to differences in age, smoking status and pre-existing allergic diseases (presumably a marker for atopy) in a multivariate logistic regression. Lung function tests suggested that the chromite miners had significantly lower forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and gas diffusing capacity than all the other groups. The lower gas diffusing capacity may however have been in part attributable to the lower FVC as, when corrected for alveolar volume, this difference was no longer significant. The group containing ferrochromium furnace workers and workers from the stainless steel smelting shop showed no evidence of impaired lung function compared to the control group.

The study had focused on the relationship between respiratory health and exposure to chromium (total, Cr^{III} and Cr^{VI}) and the authors concluded that, at the levels of exposure and duration of exposure (mean 18 years) of subjects included in this

[11] The term *"smelting shop"* was used in this study. This is where melting of ferrochromium alloy and addition of stainless steel scrap took place, and appears to correspond to the *"melting"* stage referred to in Section 2.2 of this review.

survey, there was no evidence of any adverse effect on respiratory health attributable to chromium. They further suggested that the effects on lung function seen in the chromite workers might be attributable to fibrous materials in the rock being mined rather than to the total chromium content.

This study was conducted at a plant where, in addition to stainless steel manufacture as described in *Section 2.1*, chromite mining and ferrochromium production also took place. Further, the study focused on respiratory health and chromium exposure, and consequently subjects were grouped according to chromium exposure. Workers in the stainless steel smelting shop were therefore grouped with workers in ferrochromium plant, and workers in the cold rolling mill represented the "unexposed" control group. Thus, it is difficult to dissect out the results for workers solely engaged in stainless steel manufacture and subjects in the 'unexposed' group are not truly unexposed to any respiratory hazard. The findings of this study show no evidence of adverse effects on respiratory health in stainless steel smelting workers that might be associated with chromium exposure. However, it is difficult to draw any conclusions regarding respiratory health of workers engaged in stainless steel production and the role of exposures other than chromium, or regarding other adverse effects on health.

Summary of effects of repeated exposure during the manufacture of stainless steel

Only one study is available which has investigated long-term effects on health in workers engaged in the manufacture of stainless steel. The findings of the study, which focused on respiratory health and chromium exposure, show no evidence of adverse effects on respiratory health in stainless steel smelting workers which might be associated with chromium exposure. However, the design of this study prevents wider conclusions being drawn regarding the health of workers in the stainless steel manufacturing industry and the association with exposures other than chromium. It is considered that this is an area which would benefit from further investigation.

Carcinogenicity

Several epidemiological studies are available which have investigated cancer mortality among workers engaged in the manufacture of stainless steels.

Cornell 1984

A proportional mortality analysis was performed on 4487 deaths of white males who had been employed at one of twelve facilities owned by seven US companies (Cornell 1984). These facilities produced stainless and low nickel alloy steels. The majority of the deaths occurred in the period 1973-77, but an unspecified percentage occurred in earlier years. The paper did not supply any information as to how these deaths were identified; the impression was given that death details were limited to those available from company personnel and pension records. The proportion of deaths from specified causes was compared with that expected on the basis of age-specific deaths for all US white males in the year 1974. This comparison was made for all deaths in the study sample, and then separately for those decedents with and without potential exposure to nickel. Any operation in which nickel-bearing steel or nickel alloys were processed or handled was considered to be an operation which could

produce potential nickel exposures. Furthermore, if an employee worked at any time in such operations, he was considered to have potential nickel exposure. This general style of classification led to all decedents from four of the plants being classified as potentially exposed to nickel. The proportional mortality ratio (PMR) for lung cancer in the study sample was 92 (based on 280 deaths). Corresponding PMRs for employees with and without potential exposure to nickel were 97 (based on 218 deaths) and 80 (based on 62 deaths), respectively. There were no deaths from nasal cancer and findings were not supplied for cancers of the stomach, colon or rectum.

The study did not provide any evidence of occupational lung cancers having occurred in plant employees. The study was limited in a number of ways: relevant deaths had probably not all been identified, no quantitative exposure data were supplied, and exposure classification was simplistic.

Moulin et al. 1990

Mortality was investigated in workers at a French plant producing ferrochromium and stainless steel (Moulin *et al.* 1990). The plant started production in 1952. The study population comprised 2269 males first employed in the period 1952-82 who were employed for a minimum period of twelve months. Mortality was investigated for the period 1952-82. Observed deaths were compared with expectations based on national mortality rates, after adjusting for sex, age-group and calendar period. For the whole cohort, mortality from all causes was significantly lower than expected (Observed 137, Expected 166.9, SMR 82, 95% confidence interval (95% CI) 69 to 97). There was a non-significant excess for lung cancer (Observed 12, Expected 8.6, SMR 140, 95% CI 72 to 245). For stomach cancer, four deaths were observed with an expectation of 2.5. There were no observed deaths for either cancer of the colon (Expected 2.0) or cancer of the rectum (Expected 1.1).

The cohort comprised two sub-cohorts, 1718 "exposed" workers (employed for at least one year in workshops producing ferrochromium or stainless steel), and 551 "non-exposed" workers (remainder of study cohort). Overall mortality was similar in the two groups (exposed workers: Observed 94 Expected 109.4, SMR 86, 95% CI 69 to 105; non-exposed workers: Observed 43, Expected 57.6, SMR 75, 95% CI 54 to 101). A lung cancer excess was only apparent in the exposed group (exposed workers: Observed 11 Expected 5.4, SMR 204, 95% CI 102 to 364; non-exposed workers: Observed 1, Expected 3.2, SMR 32, 95% CI 1 to 177). Smoking habits were available in medical records for some 67% of the cohort; these data did not offer any satisfactory explanation for the differences in lung cancer mortality between the exposed and non-exposed workforce. All four deaths from stomach cancer occurred in the exposed group (Observed 4, Expected 1.46, SMR 275, 95% CI 75 to 701).

Mortality from lung cancer was investigated by duration of exposure (length of employment in ferrochromium or stainless steel workshops) and separately by period from first exposure. No clear trends were shown (duration of exposure: P-value for trend 0.11; period from first exposure: P-value for trend 0.71). These trend statistics were not available in the published paper and have been calculated by the current reviewers from data supplied in Table 5 of the published paper.

The "exposure" variable used by the authors was not capable of distinguishing between employment in the ferrochromium production workshop and employment in the stainless steel production workshop. PAH exposures were only found in the ferrochromium workshops; the working environments of the two sets of workshops would, presumably, also have been different in other ways. In an attempt to obtain more specific findings the authors carried out a nested case-control study. Detailed job histories were sought both for the twelve workers who had died from lung cancer (the cases) and for randomly-selected workers with the same year of birth as the cases (maximum of five controls per case) who were still alive at the time of the case death. Three broad categories were defined - definitely exposed to PAH and to chromium compounds, possibly or intermittently exposed to PAH and chromium compounds, and exposed to chromium (or nickel) compounds in the absence of PAH exposures. The largest odds ratio was found for exposure to both PAHs and chromium compounds (OR 14.86, 95% CI 3.04 to 72.52); the odds ratio for chromium compounds was much lower (OR 2.75, 95% CI 0.29 to 26.30). However, these findings presented in Table 7 of the published paper are difficult to interpret partly because the table presents a mixture of matched odds ratios and *inappropriate* un-matched odds ratios, and partly because rather than treating the "possible" exposure category as a separate category, it is combined first with the non-exposed category and then with the exposed category.

Taken together, the above findings suggest that occupational lung cancers had occurred in this cohort; the excess seemed to be associated with employment in the ferrochromium plant rather than with employment in the stainless steel production plant. A number of limitations and caveats are to be attached to the findings. The lung cancer findings were based on relatively small numbers of deaths and no quantitative exposure data were available. The authors noted the non-availability of the cause of death as stated on the death certificate. Because of French confidentiality arrangements, information on causes of death had to be obtained from hospital and GP records. The authors indicate that in their analysis workers enter the person-years-at-risk on the date of first employment. This is incorrect, and workers should have been so entered twelve months later, at the end of the minimum period of employment, because, *by definition*, all employees were alive on this date. This would mean that the person-years-at-risk available for study have been inflated by some 7% (2269/33945). More importantly, if this rather naive mistake has been made, the somewhat complex calculations required to obtain person-years-at-risk by duration of exposure may not have been performed correctly; no information was supplied in the paper to enable this concern to be assessed.

Moulin et al. 1993a

The same research group investigated mortality in another stainless steel production plant (Moulin *et al.* 1993a). The study population involved workers with at least three years of employment during the period 1968-1984, followed through to 1986. The total cohort comprised 4227 workers. The subjects were categorised according to the workshops where they were employed (ferroalloy, stainless steel melting and casting,

hot rolling mills, stainless steel foundry[12], and maintenance). Expected numbers of deaths were based on national mortality rates, adjusted for sex, age and calendar period. Overall mortality was close to expectation (Observed 452, Expected 434.7, SMR 104, 95% CI 95 to 114). There were no significant mortality excesses for any cancer site. For lung cancer mortality, there was a non-significant increase (Observed 39, Expected 29.6, SMR 132, 95% CI 94 to 180). When lung cancer mortality data were analysed according to the workshop where subjects were employed, the only significant increase was in workers employed in the stainless steel foundry (Observed 11, Expected 4.8, SMR 229, 95% CI 114 to 409). In this group of workers, the greatest excess lung cancer mortality occurred in workers with at least 30 years since first employment (SMR 324, 95% CI 119 to 705). Lung cancer mortality among ferroalloy production workers was less than expected (Observed 2, Expected 3.0, SMR 68, 95% CI 80 to 245), among workers from the stainless steel melting and casting workshops was close to expectation (Observed 7, Expected 6.7, SMR 104, 95% CI 42 to 215), and in the hot rolling mills workshops showed a non-significant increase (Observed 17, Expected 11.3, SMR 151, 95% CI 88 to 242). For all workshops combined, lung cancer mortality did not show any relationship with either time since first exposure or duration of employment. No exposure data were provided in this study. It was reported, however, that in some of the workshops, including the stainless steel foundry, exposure to PAHs may occur, originating from moulds and cores, in addition to exposure to metal fumes.

Overall, in this study, no elevated lung cancer risk was apparent for workers involved in the stainless steel production (melting shop) process. The study provides some evidence of increased lung cancer risk in workers in a stainless steel foundry which was integrated into a stainless steel production plant, but provides little indication as to causative agent(s). It should be noted that “iron and steel founding” is considered by IARC to be a Group 1 carcinogenic activity (IARC, 1984 & 1987). There is no definitive identification of the carcinogenic agents by IARC. PAHs, silica, phenol, isocyanates, various amines and formaldehyde (apparently arising from the materials added to the foundry sand, including organic binders) and "metal fumes" are suggested as possibilities. The carcinogenic agents are not apparently specific to the metals being cast. It should also be noted that, in Europe, only a very small number of people is now employed as stainless steel foundry workers.

Summary of epidemiological investigations

Epidemiological studies of cancer mortality among stainless steel production workers are summarised in *Table 2.2*. These studies do not provide convincing evidence of elevated lung cancer risk in workers involved in stainless steel manufacture. In one of the studies, information was provided on excess lung cancer risk in stainless steel foundry workers.

[12] In this study, foundry operations were integrated into the stainless steel production process and the foundry was located in the same plant. Foundry operations are not strictly part of the production process and, in the modern industry, it would be more appropriate to consider them under "stainless steel processing".

Table 2.2 **Epidemiological studies of workers engaged in the manufacture of stainless steel**

Reference	Study population	Reference population	Cancers of respiratory tract		Cancers of other sites		Other information
			Site (no.)	SMR	Site (no.)	SMR	
Cornell 1984	4487 deaths of white males who had been employed in 12 US factories. Most deaths occurred in the period 1973-1977	US white males	Lung (280)	92[a]			Little detail supplied on how the study was carried out.
Moulin *et al*. 1990	1 French plant; males employed ≥1 year after 1952; follow-up to 1982 (a) whole cohort 2269 males (b) 1718 males employed in work-shops producing ferro-chromium or stainless steel	French male population	(a) Lung (12) (b) Lung (11)	(a) 140 *ns* (b) 204 *s*	(a) Colon (0) Rectum (0)	0 0	Excess associated with ferrochromium plant rather than stainless steel plant – possible association with PAH exposure.
Moulin *et al*. 1993a	Different French plant; males employed ≥3 years during 1968-1984; follow-up to 1986; 4227 males	French male population	Lung (39)	132 *ns*	Colon (6) Rectum (3)	88 *ns* 81 *ns*	Lung cancer mortality for whole cohort showed no association with time since first exposure or duration of employment. Highest lung cancer risk in stainless steel foundry workers. No excess risk for stainless steel melting and casting.

a: proportional mortality ratio (PMR); ***s***: statistically significant; ***ns***: not significant;

Effects on reproduction

There have been no investigations of the effect of employment in stainless steel manufacture on reproductive health.

2.5 Hazard assessment

The manufacture of stainless steels gives rise to airborne dusts and fumes. Qualitative information on exposure indicates that workers in this industry may be exposed to various substances, including metal oxides, and compounds containing silicon, aluminium and calcium. Chromium, which predominantly occurs in the trivalent oxidation state (Cr^{III}), may, during some parts of the process, become oxidised to hexavalent chromium (Cr^{VI}). According to modern methods of production, PAHs are only likely to occur during the casting stage and then only if moulds are used which contain binders and additives.

The available exposure data for this industry are limited and, with the exception of a few substances, it is difficult to identify all of those which exist. Some of the identified substances have known or suspected toxicological properties including sensitisation and carcinogenicity.

Hazard assessments are made below for the end-points reviewed in the preceding sections of this chapter. The summarised data are evaluated against the classification criteria contained in Annex VI of Directive 92/32/EEC, amending Directive 67/548/EEC, with a view to assessing the hazards against objective criteria so that a risk assessment can be conducted.

Acute toxicity

No studies are available which have investigated acute toxicity, skin or eye irritation, or sensitisation resulting from exposure during the manufacture of stainless steels.

Consideration against classification criteria: There are no data relating to acute toxicity, skin or eye irritation, or sensitisation which can be considered against the classification criteria.

Effects of repeated exposure

Only one study is available which has investigated long-term effects on health in workers engaged in the manufacture of stainless steel. The findings of the study, which focused on respiratory health and chromium exposure, show no evidence of adverse effects on respiratory health in stainless steel smelting workers which might be associated with chromium exposure. However, the design of this study precludes wider conclusions being drawn regarding the health of workers in the stainless steel manufacturing industry.

Consideration against classification criteria: From the limited quantity of data available, repeated exposure during the manufacture of stainless steel does not appear to present any serious risk to health.

Carcinogenicity

Three epidemiological studies are available which have investigated cancer mortality among workers engaged in the manufacture of stainless steels. These studies do not provide convincing evidence of elevated lung cancer risk in workers involved in stainless steel manufacture. In one of the studies information was provided on excess lung cancer risk in stainless steel foundry workers.

Consideration against classification criteria: The available data for humans engaged in stainless steel production (melting shop) do not indicate that there is concern in relationship to carcinogenicity. The data on stainless steel foundry workers are too limited to form a judgement on possible carcinogenicity specifically associated with stainless steel.

Effects on reproduction

No studies appear to have been conducted which have investigated the effect of employment in stainless steel manufacture on reproductive health.

Consideration against classification criteria: There are no data on effects on reproduction which can be considered against the classification criteria.

2.6 Risk assessment

The manufacture of stainless steels gives rise to a complex mixture of airborne dusts and fumes, and thus presents the potential for inhalation exposure in the occupational setting. There are some uncertainties regarding the identity of many of the substances which may occur in this industry and also regarding the conquences of any interactions. The known toxicological properties of some of the constituents, although well-documented, tend to be associated with very high levels of exposure and may have little relevance at exposures expected in this industry. As some of the substances which have been identified are known to be carcinogenic, clearly the potential for cancer is the most serious health concern.

Health effects, including the possibility of cancer, are controlled by the use of occupational exposure limits. In the UK, there are occupational exposure limits for the following substances which may occur in the production of stainless steel: Cr^{VI} compounds (0.05 mg/m^3), Cr^{III} compounds (0.5 mg/m^3); inorganic nickel compounds (0.5 mg/m^3); iron oxide fume (5 mg/m^3); dust (total:10 mg/m^3; respirable: 4 mg/m^3). For those substances presenting the most serious health effect, cancer, if exposures are controlled as far below the exposure limit as is reasonably practicable, then the risks are considered to be negligible if present at all.

The limited data on exposure in this industry, presented in *Section 2.2*, indicates that personal exposure levels for Cr^{VI} compounds, the only specific substances measured, are generally below 0.05 mg/m^3.

2.7 Future research needs

The database on exposure in the stainless steel manufacturing industry is limited. Information concerning the identity of substances that occur at each stage of the process, together with personal sampling data, would benefit the risk assessment process.

There is a limited quantity of data available relating to the health of workers currently engaged in the manufacture of stainless steel. In view of the potential for inhalation exposure in this industry, investigation of morbidity among stainless steel manufacturing workers is considered to be area which would benefit from further study. Such investigations should include the collection of exposure data for the different stages of the manufacturing process, so that the association between any effect and exposure can be examined.

3 STAINLESS STEEL PROCESSING

This section focuses on the processing of stainless steels and comprises a review of the health effects associated with such processes. Processing of stainless steel includes welding, grinding, cutting, polishing and forming.

3.1 Welding of stainless steel

3.1.1 General information

Welding is a joining operation that ensures the continuity of the metallic state between the two work pieces. The operation involves establishing a controlled electrical discharge between the electrode and the work piece through a gaseous conductive medium, called an arc plasma. Metal from the consumable electrode is transfered through the arc into a weld pool which joins the two work pieces.

A number of different methods are used for welding of stainless steel. These are listed below; a brief outline of each method is presented later in this section:

AWS[a] term	**Term used in some EU member states**
Gas tungsten arc welding (GTAW)	Tungsten inert gas (TIG)
Gas metal arc welding (GMAW)	Metal inert gas (MIG)
Shielded metal arc welding (SMAW)	Manual metal arc (MMA)
Plasma arc welding (PAW)	- (PAW)
Flux cored arc welding (FCAW)	Flux cored electrode welding (FCW)
Submerged arc welding (SAW)	- (SAW)

[a] AWS American Welding Society; the AWS terms are the recognised "international" terms

Welding fume

Welding fumes are complex mixtures of particles and gases. The particulate fraction is formed during metal transfer in the arc through complex vaporisation-condensation (oxidation) or (oxidation) vaporisation-condensation processes. The temperature in the arc is very high (~7000°C) and droplets of metal are superheated at a temperature above the boiling point of stainless steel (2500°C). When the vapour condenses in the vicinity of the arc, small particles are generated (diameter 0.001-0.1µm) which can form agglomerates of up to 0.250 µm in diameter. Welding fume particles are mainly of a respirable size.

The composition of the fume and the concentrations of its components will depend largely on the welding process employed and the welding consumable used. The consumable electrode, not the base metal, is the major source of fume.

The rate of fume formation during welding of stainless steel depends on several factors:

- welding process
- type of consumable
- welding current
- arc voltage or arc length
- type of metal transfer
- shielding gas

Welding process

Fume generation rate (quantity of fume generated per weight of metal deposited) is highest for methods using covered electrodes and flux cored wires (SMAW, FCAW), compared to methods using solid wire electrodes (GMAW, SAW). Of all the methods used for welding of stainless steel, SAW consistently produces the least quantity of fume as a result of the fume being captured by the flux and slag cover.

Type of consumable

For a specific process, the fume rate depends on the composition of the welding consumables. Some components of covered and flux-cored electrodes are designed to decompose and form protective gases during welding. Some typical welding consumables used for welding of stainless steel are as follows:

	Welding consumable [a] (welding method)		
Base metal (AISI)	**Covered electrode (SMAW)**	**Solid wire (GTAW, PAW, GMAW, SAW)**	**Flux-cored wire (FCAW)**
Ferritic 409	E 309 L-15 (16)	ER 309 L	E 309 LT-X
430	E 430-15 (16)	ER 430	E 309 LT-X
430 Ti	E 309 L-15 (16)	ER 309 L	E 309 LT-X
444	E 309 MoL-15 (16)	ER 309 MoL	E 309 MoLT-X
Austenitic 304	E 308-15 (16)	ER 308	E 308-T-X
316	E 316-15 (16)	ER 316	E 316 T-X
309	E 309-15 (16)	ER 309	E 309 T-X
310	E 310-15 (16)	ER 310	E 310 T-X

a. L = low carbon; 15 = lime type; 16 = titania type; X= shielding gas; Mo = molybdenum

Welding current

In general, the rate of fume generation increases with welding current. The increase varies according to the process and the electrode type. With covered electrodes, fume generation rate is proportional to the welding current. However with some flux-cored and solid wire electrodes, the relationship between the fume generation rate and current is more complex. In this case the current level affects the type of metal droplet transfer, which can be either globular transfer or spray transfer (*see below*).

Arc voltage or arc length

Arc voltage and arc length are directly related; they depend on the electrode type, the welding process and the power supply. In general, increasing arc voltage, and thus arc length, results in increased fume generation.

Type of metal transfer

In GMAW using a solid wire electrode, the type of metal transfer during welding depends on the current and the voltage. At low current and voltage, short circuiting transfer occurs (i.e. metal droplets are deposited during short circuits between the electrode and the weld pool). At high currents, spray transfer occurs when fine metal droplets are propelled across the arc. Spray transfer of metal is associated with greater generation of welding fume than short circuiting transfer.

For other welding processes, the type of metal transfer does not change substantially with current or voltage.

Methods for welding of stainless steel

Gas tungsten arc welding (GTAW)

The GTAW process involves the use of a tungsten electrode that carries the current between the electrode and the workpiece. In this welding process the electrode is not consumed. Filler metal may be added either manually, using 900mm lengths of bare rod, or it may be automatically fed from spools of wire. Gases (argon, helium, and/or hydrogen) are used to prevent oxidation of the electrode and to shield the welding zones.

Gas metal arc welding (GMAW)

GMAW is an arc welding process that involves automatic feeding of a continuous, consumable electrode. An externally supplied gas provides shielding. GMAW involves two main types of metal transfer – short circuiting and spray transfer (described in the earlier part of this section).

Shielded metal arc welding (SMAW)

SMAW employs a covered (coated) electrode. The weld is produced by fusion of metal from the electrode core with edges of the joint. The coating of the electrode provides a molten mineral substance, called slag, which forms over the fused weld, protecting the weld during solidification and controlling the contour of the weld bead. The electrode coating also provides shielding gases, and metallic ingredients, some of which act as supplementary alloying ingredients for the weld metal. The composition of the electrode coating is complex, containing many different substances. A typical electrode coating would contain the following substances:

- slag formers (titania, silica flour, fluospar, feldspar)
- gas-forming material (carbonates, limestone)
- deoxidisers (ferrosilicon, ferromanganese)
- binding agents (sodium silicate, potassium silicate, or lithium silicate)
- slipping agents (kaolin clay, talc, bentonite clay)

Electrode coatings fall into two types: (i) lime type (containing large amounts of limestone and fluospar and producing globular transfer of metal); (ii) titania type (containing rutile (titania), medium amounts of limestone and limited quantities of fluospar, and producing spray-like transfer of metal).

Sodium or potassium silicates, which are commonly used as binding agents in the electrode coating, are the main source of alkali ions and can lead to the formation of soluble hexavalent chromium compounds (sodium or potassium dichromate) in SMAW fume. Some electrodes have been developed using lithium silicate as an alternative binding agent; such electrodes have been shown to generate fume with a lower hexavalent chromium content than those containing sodium or potassium silicate binders (Soudure Autogéne Francaise 1997).

Flux-cored arc welding (FCAW)

FCAW is an arc welding process that uses an arc between a continuous filler electrode and the weld pool. Shielding gas is provided by flux contained within the tubular electrode; additional shielding may be provided by an external supply. The flux contains deoxidisers, slag formers, arc stabilisers and alloying materials. Small diameter flux-cored wires using an argon-based shielding gas can involve either short circuit metal transfer or spray transfer.

Submerged arc welding (SAW)

The SAW process is completely shielded by a layer of loose granules of flux. Fluxes used in this process generally contain a mixture of slag-forming, deoxidising and alloying ingredients, bonded together by a silicate binder. The process uses a consumable solid wire electrode which is continuously fed from a spool.

Plasma arc welding (PAW)

The PAW process uses an open, unrestricted gas tungsten arc that is squeezed through a copper nozzle, resulting in an arc that is longer, thinner and more focused. The tungsten electrode is non-consumable. Two gases are supplied by the welding torch, a shielding gas that shields the weld and a plasma or orifice gas that controls the arc characteristics and shields the electrode. Shielding may also be supplemented by an external gas supply.

3.1.2 Information on exposure

Welding of stainless steel results in the formation of fume containing particles and gases. As the particulate is mostly respirable, welding operations present the potential for inhalation exposure in the occupational setting.

Published exposure data for the welding of stainless steel come from field studies and laboratory-based studies. The data from these studies are summarised in *Table 3.1*. Information on the elemental composition of MMA/SS and MIG/SS welding fume is presented in *Table 3.2.*

Only a few studies are available which have investigated workplace exposure to stainless steel welding fumes using well-designed sampling strategies. In a number of studies, the use and effectiveness of controls have not been assessed and relatively small sample sizes have been used. Overall, the published data on exposure indicate that daily personal TWA concentrations for total fume are in the range 0.1-40 mg/m^3 (range of mean values 1.3-3.1 mg/m^3). In confined spaces, mean personal exposure levels up to 37.2 mg/m^3 have been reported. Comparison of total fume concentrations for the different welding methods shows that the highest levels occur with MMA welding compared to MIG or TIG welding. Fume concentrations measured in static samples constitute about one tenth of those found in personal samples.

Laboratory-based studies on welding of stainless steel have provided useful data on the composition of fume associated with the different welding methods, the effect of welding parameters on fume composition, and the physical and chemical properties of welding fume. The available data show that MIG/SS welding produces higher total chromium concentrations than MMA/SS welding, although only a negligible proportion of this occurs as Cr^{VI} (see *Table 3.1*). In contrast, MMA/SS welding generates a higher concentration of Cr^{VI} in the fume compared to MIG and TIG welding; this is due to the presence of alkaline metals in the flux coating. Cr^{VI} in MMA/SS welding fume occurs as sodium or potassium dichromate. The percentage of total chromium which exists as Cr^{VI} in MMA/SS welding fume has been reported to range from 30 to 100% (*see Table 3.1*), and Cr^{VI} concentrations of up to 1.5 mg/m^3 have been reported with MMA/SS welding operations (van der Wal 1985). The nickel content of fume from welding of stainless steel has been reported to be between 0.2 and 4.9% of the total fume. Nickel in welding fume occurs as oxides, predominantly in the insoluble form.

Table 3.1 **Stainless steel welding - summary of exposure data from published literature**

Reference	Welding method [a,b]	Base metal (stainless steel grade)[c]	Consumable[d]	Total fume concentration (mg/m^3) [e]	Total Cr concentration (% of total fume or µg/m^3)	Cr^{VI} (% of total Cr or µg/m^3)	Total Ni (% of total fume or µg/m^3)	Analytical method[f]
Lautner *et al.* (1978)	MMA (Possibly)	Type 304: Cr 18-20% Ni 8-12%	Type 308: Cr 19.8% Ni 10%	(a)1016 µg/filter (b) 996 µg/filter (c) 999 µg/filter	- 95.6 µg/filter 58.0 µg/filter	73% - 74%	N/R	(a) ESCA (b) NAA (c) Col./AA
Bohgard *et al.* (1979)	MMA	Cr 18% Ni 8% Ni	(i) B (ii) R (iii) RB		3.4% 2.9% 4.0%	57% 52% 73%	0.22% 0.38% 0.31%	PIXE, Col, ESCA
Eichhorn & Oldenburg (1986)	MMA	N/R	N/R	N/R	3.0-5.3%	36-60%	0.3-1.3%	N/R
Wilson *et al.* (1981)	MMA + MIG P (7) MMA + MIG P, CS (23)	AISI 316 + 'Inconel' AISI 316 + 'Inconel'	F-316-15 rods F-316-15 rods	3.3 37.2	49 µg/m^3 804 µg/m^3	2 µg/m^3 116 µg/m^3	313 µg/ m^3 1624 µg/ m^3	Col./AA
Moreton *et al.* (1985)	MMA MIG	E316L-16 E316L-Si	Cr 18% Ni 10% Mo 3%	N/R N/R	5.0% 13.4%	82% 1.5%	0.4% 4.9%	XRF/Col.
Ulfvarson (1981)	TIG P (N/R) MMA P (N/R)	Cr –12-22% Ni - 1-19%	Coated electrode	1.0-2.0 5.0	200 µg/m^3 N/R	N/R	N/R	PIXE,AAS, & Col.

Reference	Welding method [a,b]	Base metal (stainless steel grade)[c]	Consumable[d]	Total fume concentration (mg/m^3) [e]	Total Cr concentration (% of total fume or µg/m^3)	Cr^{VI} (% of total Cr or µg/m^3)	Total Ni (% of total fume or µg/m^3)	Analytical method[f]
Akesson & Skerfving (1985)	MMA	N/R	N/R	N/R	101 µg/m^3 (range 26-220)	N/R	440 µg/ m^3 (range 70-970)	N/R
Froats & Mason (1986)	MIG P (5) (area 1)	N/R	308 wire	0.33-2.25	N/R	0.1-0.6 µg/m^3	N/R	AAS
	MIG S (10)		308 wire	0.190-1.05	N/R	0.1-0.4 µg/m^3		
	MIG P (6) (area 2)		308 wire	0.67-8.32	8.1-37.7 µg/m^3	1.0-3.4 µg/m^3		
Van der Wal (1985)	MMA P (15)	Cr –16-20% Ni.-8.5-14%	As for base metal	2.0-40	30-1600 µg/m^3 (0.5-2.7%)	25-1500 µg/m^3 (50-90%)	10-210 µg/ m^3	AAS / Col.
	MIG P (2)			1.5-3.0	60 µg/m^3	<1.0 µg/m^3	30.0 µg/ m^3	
	TIG P (48)			0.8-4.2	10-55 µg/m^3	<1.0 µg/m^3	10-40 µg/ m^3	
Matczak and Chmielnicka (1993)	MMA P (160)	N/R	Cr 13-22% Ni 8-27%	0.2-23.4	5-991 µg/m^3 (1.4-3.4%)	5.0-842 µg/m^3 (36-100%)	0.5%	AAS Col.

Reference	Welding method [a,b]	Base metal (stainless steel grade)[c]	Consumable[d]	Total fume concentration (mg/m^3) [e]	Total Cr concentration (% of total fume or µg/m^3)	Cr^{VI} (% of total Cr or µg/m^3)	Total Ni (% of total fume or µg/m^3)	Analytical method[f]
Van der Wal (1986)	PC P (13)	AISI 304, 316 & 410	N/R	1.0-7.5	30-440 µg/m^3	<1.0-40 µg/m^3	<10-260 µg/ m^3	AAS/ Col.
	PW P (2)	AISI 304		1.0-1.1	20 µg/m^3	<1.0 µg m^3	1-20 µg/ m^3	
	PC S (9)	AISI 304, 316 & 410		0.6-4.0	12-140 µg/m^3	<1.0-4.0 µg/m^3	<10-170 µg/ m^3	
	PW S (2)	AISI 304		0.5-0.9	4.0 µg/m^3	1.0 µg/m^3	3.0 µg/ m^3	
Emmerling *et al.* (1989)	MMA	Unspecified SS	N/R	2.7 (range 1.4-9.2)	59 µg m^3 (range 15-228)	17.5 µg/m^3 (30%)	24.0 µg/ m^3	N/R
	MIG			5.34 (range 1.6-8.2)	180 µg/m^3 (range 42-630)	8.0 µg/m^3 (4%)	68.6 µg/ m^3	
	TIG			1.50 (range 0.7-2.4)	13 µg/m^3 (range 3-31)	1.5 µg/m^3 (12%)	8.0 µg/ m^3	

a. P - personal sample (number of samples); S - static sample; CS - sampling in confined spaces.
b. MIG - metal inert gas; MMA - manual metal arc; TIG - Tungsten inert gas; PC - plasma cutting; PW- plasma welding.
c. AISI304 (18-20% Cr, 8-11% Ni); AISI 316 (16-18% Cr, 10-14% Ni); AISI 410 (11.5-13.5 Cr)
d. B - basic electrode; R - high yield rutile electrode; RB - rutile basic electrode
e. TWA, mean value
f. AAS - Atomic absorption spectroscopy; NAA - Neutron activation analysis; PIXE - Particle induced X-ray fluorescence
ESCA - Electron spectroscopy for chemical analysis; XRF - X-ray fluorescence; Col. - Colorimetry
N/R - Not reported

Table 3.2

Elemental composition of fume from MIG and MMA welding of stainless steel

Elemental composition	MMA welding (% by weight)	MIG welding (% by weight)
Cr	3.0 - 5.0	10 - 13.4
Ni	0.22 - 0.4	4.5 - 4.9
Fe	3.3 - 5.1	28 - 33.3
Mn	2.4 – 14	4.8 - 12.6
Si	10	1.7
F	14.9 - 24.0	ND
K	18 – 22	ND - <0.1
Ca	0.4 – 10	ND - 0.2
Ti	0.62 - 2.3	ND - 0.1
Cu	ND - 0.01	0.06 - 0.6
Zn	0.01 - 0.25	0.17 - 0.18

Sources: Moreton *et al.* (1985); Malmqvist *et al.* (1981).

3.1.3 Toxicokinetics

Animal data

Animal studies have been conducted which have examined the lung clearance and deposition of fume particles generated from the welding of stainless steel, following exposure by inhalation or by i.t. instillation.

Lung clearance of welding fume particles was investigated in rats following single and repeated exposure by inhalation to MIG/SS welding fume (Hicks *et al.* 1983). The welding fume was generated using a mild steel workpiece and stainless steel electrode wire (Borstrand 61). Chemical composition of the fume, which was reported to originate mainly from the stainless steel electrode, was approximately 50% as Fe_3O_4, and 20% as mixed-metal oxides ($NiCr_2O_4$, $NiFe_2O_4$, $FeCrO_4$) with a cubic spinel structure. Elemental analysis of the particulate fraction, which was collected onto a glass-fibre filter, demonstrated the following main constituents: Cr 11%, Fe 60.9%, K 4.0%, Mg 5.4%, Ni 5.6%. No analysis of Cr^{VI} was performed in this study, although in a subsequent study using similar welding conditions Cr^{VI} content was reported to be 3.5% of total chromium. Particle size distribution data were as follows: median diameter 0.064 µm (geometric standard deviation 2.34); mass median aerodynamic diameter 1.1 µm. Animals were exposed to the fume by the head only for a single period of 184 min (400 mg particulate/m^3) or 173 min (580 mg/m^3). Animals were also exposed repeatedly for 30 min/day for 6 days, followed by 40 days without exposure, followed by 30 min/day for 8 days (mean chamber concentration during exposure 380 mg particulate/m^3). At varying intervals after exposure, lung clearance of fume particulate was monitored by measuring lung tissue levels of Fe and Cr. Unexposed animals served as controls. In animals exposed for a single period, tissue levels of both elements decreased over the seven-day period after

exposure, indicating lung clearance, although histological examination demonstrated small deposits in the alveoli 180-450 days after exposure. In animals repeatedly exposed to the fume, elevated tissue levels of Fe and Cr were sustained throughout the 56-day period after exposure; histological examination demonstrated large persistent deposits of particles in the alveolar and peribronchial areas of the lung. This study demonstrated the persistence of welding fume particles in the lungs of rats following single or repeated exposure by inhalation to high concentrations of welding fume. However, the high exposure levels used in this study, which are well above levels currently reported in the occupational setting, may have interfered with normal clearance mechanisms in the lung. The relevance of such findings is therefore uncertain.

Slow lung clearance of chromium was demonstrated in rats, repeatedly exposed by the nose only to MMA/SS welding fumes (43 mg/m^3) for 2 hr/day for up to 5 days or up to 4 weeks (Kalliomäki *et al.* 1982a). The total chromium content of the fume was 3.6%. The Cr^{VI} content of the fume was not reported. Chromium levels in the lungs increased linearly with each exposure and, following cessation of exposure, decreased ($t_{1/2}$ 40 days). B-Cr levels remained constant throughout the exposure period and then decreased rapidly ($t_{1/2}$ of six days). Chromium levels in the liver increased only after two weeks of exposure, reached maximum levels two to four weeks after the end of exposure, and returned to control levels within two months. Chromium content of the kidney increased during the first week of exposure, then plateaued and subsequently returned to control levels within one month of ending exposure. In the spleen, chromium levels increased with increasing exposure duration and reached maximum levels two months after exposure, reflecting sequestration of RBCs. This study, which focused on tissue levels of chromium, demonstrated fairly slow clearance of chromium from the body in rats following repeated exposure by inhalation to welding fume.

Particle deposition and lung clearance of MIG/SS welding fume in rats following intratracheal (i.t.) instillation were briefly reported by Hicks *et al.* (1983). A description of the welding fume is presented earlier in this section. Male rats were treated with a single dose of fume particulate in suspension (0.4 ml volume) containing either 10 mg particulate or 50 mg particulate. Vehicle-only animals served as controls. Histological examination of lung tissue over the 450-day observation period after exposure showed that large quantities of particulate were retained in the lungs, although there was reported to be evidence of *"substantial lung clearance"*. This study involved i.t. instillation of fairly high concentrations of welding fume particulate and therefore contributes little to our understanding of the toxicokinetics of inhaled welding fume at exposure levels likely to occur in the workplace.

Distribution and excretion of ^{51}Cr was studied in male rats following i.t. instillation of radiolabelled MMA/SS welding fume in suspension (Kalliomäki *et al.* 1986). Total chromium content of the fume was 3.7%, 77% of which existed as water-soluble Cr^{VI}, largely potassium chromate. Each animal received 74 µg Cr. Chromium content of the lungs, which accounted for 64% of the administered chromium one hour after dosing, decreased with a $t_{1/2}$ of 53 days. 14% of the dose remained in the lungs 103 days after treatment. Chromium was readily absorbed from the lungs, with maximum levels occurring in blood (mainly RBCs), liver and kidney one hour after dosing.

These levels decreased, although chromium was still detectable in the liver and kidneys after 103 days. Chromium content of the spleen increased with time after treatment, reaching maximum levels after 60 days. Gastro-intestinal tract levels of chromium, thought to result from ingestion of administered material, were highest one hour post-treatment. Urinary and faecal excretion during eight days after treatment accounted for 16% and 15% of the dose, respectively. Urinary excretion of chromium was more prolonged than faecal excretion. This study, which focused on tissue levels of chromium, demonstrated fairly slow clearance of chromium in rats following i.t. instillation of a single dose of welding fume in suspension.

Human data

Elevated levels of chromium in RBCs have been reported in MMA/SS welders (Emmerling *et al.* 1984).

Elevated urinary chromium (U-Cr) levels have been reported in a number of investigations of stainless steel welders (Angerer *et al.* 1987; Bonde and Christensen 1991; Emmerling *et al.* 1984; Gylseth *et al.* 1977; Kilburn et al. 1990; Mutti *et al.* 1979; Rahkonen *et al.* 1983; Tola *et al.* 1977; Verschoor *et al*. 1988; Vyskocil *et al*. 1992; Welinder *et al.* 1983). Patterns of excretion of chromium were examined in some of these studies, and the results showed that U-Cr levels increased during each shift, during each working week, and sometimes over longer periods. Overall, these studies, which were mostly based on groups of MMA/SS welders, provide evidence of chromium absorption in humans following exposure to welding fume. Further, the findings from some of the studies indicate that chromium may accumulate to some extent in the body following repeated exposure to welding fume.

In a study of MMA/SS welders by Welinder *et al.* (1983), the pattern of urinary excretion of chromium following discontinued exposure demonstrated at least two phases of elimination. During a two-day period away from exposure, average U-Cr levels in one group of welders (20 subjects) fell from 34 to 19 µmol/mol creatinine [15.7 and 8.8 µg/g creatinine]. In another group (14 subjects), U-Cr levels decreased during a 4-week period without exposure from 45 to 9 µmol/mol creatinine [20.7 and 4.1 µg/g creatinine]. The existence of a second slow phase of excretion was also indicated by the occurrence of raised U-Cr levels in retired welders, on average 4.5 years after leaving employment. Half-times for the two phases of excretion were estimated to be a few hours (fast compartment), and weeks to years (slow compartment).

Summary of toxicokinetics

Deposition and lung clearance of fume particles from MMA/SS and MIG/SS welding have been investigated in animals following inhalation exposure and i.t. instillation. Slow clearance of particles and/or chromium ions has been demonstrated. However, as high dose levels used in some of the studies may have interfered with normal lung clearance mechanisms, the relevance of these results to human occupational exposure is uncertain.

Information on the toxicokinetics of fume from the welding of stainless steel in humans comes from studies which have measured chromium levels in the blood or urine in mostly MMA/SS welders. The elevated urinary chromium levels reported, and in one study elevated RBC levels, provide evidence of chromium absorption as a result of exposure to welding fume. In some studies, the results indicated that repeated exposure may lead to accumulation of chromium.

3.1.4 Toxicity

Acute toxicity

Animal data

The effect of inhaled MIG/SS welding fume was studied in male rats following a single period of exposure (Hicks *et al.* 1983, 1984). The welding fume was generated using a mild steel workpiece and stainless steel electrode wire (Borstrand 61). Details of the chemical composition of the fume have previously been reported (see *Section 3.1.3).* Twenty-four rats were exposed to fume (mean particle concentration 400 mg/m^3) for 184 minutes; groups of six animals were killed and examined at 3, 24 and 48 hours and 7 days after exposure. In another treatment group, 30 rats were exposed to fume (mean particle concentration 580 mg/m^3) for 173 minutes; groups of six animals were examined at 12, 21, 28, 200 and 300 days after exposure. Unexposed animals served as controls. Results from the two exposure groups were combined. Early effects in the lungs consisted of inflammatory changes (pneumonitis and bronchiolitis) which occurred 2-48 hours after exposure, followed by accumulation of particle-laden macrophages throughout the lung and alveolar epithelial thickening (7-21 days). Particle clearance from the alveoli was incomplete 28 days after exposure; particle-laden cells were visible as peribronchial and subpleural aggregates, and distributed throughout the lung. Foam cells, giant cells and marked epithelial thickening were also evident. These changes persisted 200-300 days after exposure. No collagen formation was observed at any time after exposure. This study showed that exposure by inhalation to MIG/SS welding fume at a particle concentration of 400 or 580 mg/m^3 for approximately three hours induced inflammatory changes in the lungs of rats.

Inhalation toxicity of MMA/SS welding fume was investigated in rats following single exposure (Uemitsu *et al.* 1984). Welding fume was generated under laboratory conditions using SUS 304 stainless steel plate and a Lime-titania electrode. Eight male rats were exposed to welding fume by the nose-only for one hour. In the control group, eight animals were exposed to air only. The particulate content of the fume, which was monitored periodically during the exposure period, was 1088 [13] ± 125 mg/m^3. Particle size distribution data were as follows: median diameter 0.56 µm; mass mean diameter 0.80 µm; aerodynamic diameter 1.51 µm. Chemical composition of the fume included the following oxides: 7.59% Cr (3.46% as soluble); 1.27% Ni (trace amounts as soluble). Animals were examined two, seven and fourteen days after exposure. During the 14-day post-treatment period, no deaths occurred in the

[13] The actual fume concentration was also reported to be 1008 ± 106 mg/ m^3

treatment group and no effects were observed in terms of food intake, body weight and general symptoms. Pathological changes occurred in the lungs of treated animals (macroscopic pigmentation, granular deposits in bronchioles and alveoli, influx of granule-laden alveolar macrophages, epithelial cell hyperplasia). These changes were observed two days after treatment and some lesions persisted until day 14. Other tissues were not examined. The findings of this study show that inhalation of MMA/SS welding fume at a particulate concentration of approximately 1000 mg/m^3 for a period of one hour caused inflammatory changes in the lungs of rats.

Pulmonary toxicity of i.t. instilled MIG/SS welding fume was studied in rats (Hicks *et al.* 1983, 1984). The welding fume was generated using a mild steel workpiece and stainless steel electrode wire (Borstrand 61). Details of the chemical composition of the fume have previously been reported (see *Section 3.1.3).* Groups of male rats were treated with a single dose of fume particulate in suspension (0.4 ml volume) containing either 10 mg particulate (20 animals) or 50 mg particulate (30 animals). Vehicle-only animals served as controls. Groups of treated animals were killed and examined at different times after exposure, ranging from 90 to 450 days. Lungs were examined for particle deposition (reported in *Section 3.1.3*) and signs of toxicity. Pulmonary changes were observed in both treatment groups. At 90 days after exposure, aggregates of particle-laden macrophages were visible, predominantly in the peribronchial region, together with accumulation of giant cells and accompanied by thickening of alveolar epithelium. Nodules of particle-laden cells were still visible at 270-450 days after exposure. There was some evidence of reticulin formation, but little or no sign of collagen formation. The results of this investigation show that a single i.t. instillation containing 10 mg or 50 mg MIG/SS welding fume particulate in suspension caused inflammatory changes to occur in the lungs of rats.

The effect of MMA/SS welding fume particulate on the lung surface was examined in rats following a single i.t. instillation (White *et al.* 1981). The welding fume was generated under laboratory conditions using a stainless steel workpiece (SIS 2333; 18.5% Cr, 9.5% Ni) and a rutile basic-coated electrode (Arosta 316L; 18% Cr, 11% Ni). Fume particles were collected onto Acropore AN 1200 filters. Elemental composition of the particulate fraction, determined by AAS, was as follows: 2.5% Cr (*"nearly all"* of this was reported to be Cr^{VI}); 16% SiO_2, 13% F, 2% Fe, 3% Mn, 2% Cu; 90% of particles were <1.5 µm diameter. Anaesthetised rats ($\geq$4 animals in each treatment group) received a single instillation of particulate in saline suspension (0.5-5.0 mg/animal). Vehicle-only animals served as controls. Animals were killed one week after treatment and lung lavage fluid was examined for several constituents that are early indicators of damage to the lung surface. The lung/body weight ratio was significantly increased in treated animals at all doses. Examination of the lung lavage fluid from treated animals showed statistically significant increases in several parameters (increased lung surfactant; changes in the free cell population; increased levels of hydrolytic enzymes). Some of these changes occurred at the lowest dose level, although a dose-response was not always apparent.

The results of this experiment show that i.t. instillation of MMA/SS welding fume particulate as a single dose as low as 0.5 mg/animal can cause changes in the lung surface in rats indicative of early cellular damage. However, the toxicological significance of such early changes is uncertain. As part of the same experiment, male

rats received a single i.p. injection of MMA/SS welding fume particulate in suspension (1, 5 and 10 mg/animal). Peritoneal lavage fluid, which was collected 22 hours post-treatment, contained increased protein levels in treated animals compared to vehicle-only controls, suggestive of increased blood vessel permeability.

In a follow-up study, the effects of soluble and insoluble fractions of MMA/SS welding fume were separately investigated (White *et al.* 1982). MMA/SS welding fume was generated using SIS 2361 stainless steel plate (23.5% Cr, 21.5% Ni) and a stainless steel rutile basic-coated electrode (Arosta 316L; 18% Cr, 11% Ni). Welding fume particulate was prepared as a suspension in saline and, after centrifugation, was divided into the soluble fraction (supernatant) and the insoluble fraction (pellet). Rats received a single i.t. instillation of either the soluble fraction (containing 3.4 µmol Cr^{VI}) or the insoluble fraction (containing no Cr^{VI}). Other groups of rats were treated with potassium dichromate (0.34, 0.68, 1.7 and 3.4 µmol Cr). Lung lavage fluid was collected and examined 1, 4 and 13 weeks post-treatment. The number of animals in each treatment group was four (1 and 4 weeks post-treatment examination) or two (13 weeks post-treatment examination). In animals treated with the soluble fraction of welding fume, several lung parameters were increased (lung weight, pulmonary surfactant, number of free cells, polymorphonuclear lymphocyte population, acid RNAase activity, lung DNA) compared to controls. These changes occurred mainly one week after treatment. The insoluble fraction of welding fume induced changes in lung parameters that were less marked, suggesting that this fraction had a lower toxicity than the soluble fraction. Potassium dichromate at the highest dose (3.4 µmol Cr^{VI}) induced similar changes in lung parameters to those caused by the soluble fraction of welding fume, containing the same Cr^{VI} concentration. The results of this study indicate that the soluble fraction of MMA/SS welding fume particulate may be more toxic to the lungs than the insoluble fraction, but provide no basis for establishing what airborne concentrations might lead to such toxicity.

Local effects of welding fume particulate administered by i.m. injection were investigated in rats and guinea pigs (Hicks *et al.* 1987). Three different welding fumes were investigated, all generated from welding of stainless steel. Elemental composition of the three welding fumes was as follows:

Welding method/ base metal	**Electrode**	**Elemental composition (%)**		
		Ni	**Cr (total)**	**Cr^{VI} (% of total Cr)**
MMA/SS	Nicrex-1	0.9	4.7	82.2
MMA/SS	LF 308L	1.0	10.4	1.8
MIG/SS	Borstrand 316	6.4	12.5	4.1

Animals received an i.m. injection (0.1 ml) of fume particulate in suspension in saline at a concentration of 1, 10 or 100 mg/ml. It is assumed that animals received a single injection, although this was not stated in the methodology. Local tissue reaction was examined 2 days to 8 weeks after treatment, and the results reported as graded

responses in terms of irritancy, fibrogenicity and cytotoxicity. In both species, MMA/SS (Nicrex-1) fume induced the most severe reaction, causing severe local inflammation, marked fibrosis, and destruction of muscle fibres. The remaining two fumes caused only slight irritation and no cytotoxicity, although MMA/SS (LF 308L) fume induced a fibrogenic response with formation of granulomatous nodules. The findings of this investigation indicate that different welding fumes vary in their capacity to cause tissue damage. This variation appears to be related to different chemical compositions of the fumes, possibly the Cr^{VI} content which was highest in the fume associated with the greatest toxicity. However, as these effects occurred after i.m. treatment, it is uncertain whether this variation might also occur with inhalation exposure. This study therefore contributes little useful information to the hazard and risk assessment of fume from welding of stainless steel.

Studies in humans

No studies are available which have investigated or reported acute toxicity in humans following exposure to fume from the welding of stainless steel.

Summary of acute toxicity

The acute toxicity of fume from the welding of stainless steel has been investigated in animals following exposure by inhalation and by i.t. instillation. Inhalation of high concentrations of fume (400 or 580 mg/m^3 MIG/SS fume for 3 hours; 1000 mg/m^3 MMA/SS fume for 1 hour) induced inflammatory changes in the lungs of rats. A NOAEL was not identified from the available inhalation data. The results of i.t. instillation studies also provide evidence of inflammatory changes in the lungs following exposure of fume particulate in suspension. Instillation of a single dose of 0.5 to 5 mg MMA/SS fume particulate into the trachea in rats was associated with changes in lung surface parameters which are early indicators of cell damage; however the toxicological significance of these changes is uncertain.

There are no studies available which have investigated or reported acute toxicity in humans following exposure to fume from the welding of stainless steel.

Irritation and sensitisation

No animal studies are available which have investigated the potential of fume from the welding of stainless steel to cause either skin or eye irritation, or to cause skin sensitisation. Further, there are no studies available that have investigated or reported such effects in humans. Human data relating to respiratory sensitisation are reported under "*Effects of repeated exposure*".

Effects of repeated exposure

Animal data

Pulmonary toxicity of inhaled MIG/SS welding fume was investigated in rats following repeated exposure (Hicks *et al.* 1983). Information regarding the chemical composition of the fume has previously been reported (see *Section 3.1.3).* Thirty

animals were exposed (head-only) to welding fume for 30 minutes/day for 6 days, followed by 40 days of non-exposure, followed by 30-minutes/day for 8 days (mean chamber concentration during exposure 380 mg particulate/m^3). Animals were killed and examined at different intervals after exposure, ranging from 3 hours to 56 days. Unexposed animals served as controls. Pulmonary effects in treated animals were briefly reported and consisted of aggregates of particle-laden macrophages in the peribronchial and alveolar areas of the lung, and nodules of fume particles with associated collapsed epithelial tissue. No collagen formation was visible. This study therefore shows evidence of lung damage as a result of repeated inhalation exposure to fairly high concentrations of MIG/SS welding fume.

Inhalation toxicity of MMA/SS welding fume was investigated in rats following repeated exposure (Uemitsu *et al.* 1984). Welding fume was generated under laboratory conditions using SUS 304 stainless steel plate and a Lime-titania electrode. Eight male rats were exposed to welding fume by the nose only (30 minutes/day, 6 days/week for 2 weeks). In the control group, eight animals were exposed to air only. The particulate content of the fume, which was monitored periodically during the exposure period, had a mean value over the 14-day period of 412 ± 30 mg/m^3. Particle size distribution was determined (median diameter 0.56 µm; mass mean diameter 0.80 µm; aerodynamic diameter 1.51 µm). Information on the elemental composition of the fume was as follows: 7.59% Cr (3.46% as soluble); 1.27% Ni (trace amounts as soluble).

During the exposure period, no signs of toxicity were reported in treated animals in terms of food intake, body weight, general symptoms, haematology or clinical chemistry. One reported death was attributed to suffocation. Pathological changes in the tissues of treated animals were confined to the lungs (discolouration of lung tissue, increased organ weight, granular deposits in the airways, accumulation of granule-laden macrophages, epithelial cell hyperplasia, and bronchiectasia). No such changes were seen in control animals. This small investigation used only one, fairly high, concentration of welding fume and therefore provides a limited amount of information. The results show that repeated exposure to MMA/SS welding fume at a concentration of approximately 400 mg/m^3 (30 minutes/day for two weeks) resulted in pulmonary toxicity in rats. However, no other conclusions may be drawn from this study.

Pulmonary toxicity, as evidenced by pneumonia, alveolar bronchiolisation and emphysema, was reported in guinea pigs exposed by repeated i.t. instillation to MMA/SS and MIG/SS welding fume particulate in a carcinogenicity study (Reuzel *et al.* 1986). This study is reported fully later in this section under "*Carcinogenicity*".

Summary of the effects of repeated exposure in animals

Only two animal inhalation studies are available which have investigated the effects of repeated exposure to fume from the welding of stainless steel. Neither study was conducted according to internationally agreed procedures for a repeat-dosing study. Both studies used only a single exposure level and this was much higher than exposure levels likely to be encountered in the workplace. Results from the two studies showed that repeated exposure by inhalation to welding fume (MIG/SS or

MMA/SS) at approximately 400 mg/m^3 (30 minutes/day for up to 14 days in total) resulted in histopathological signs of pulmonary toxicity in rats. More marked effects appeared to be associated with MMA/SS fume. The data did not allow identification of a NOAEL for this effect.

Human data

Investigations of repeated exposure to welding fume in humans have focussed either on the effect on kidney function or the effect on respiratory health.

Investigations of renal function

Alsbirk *et al.* (1981) studied renal function in a group of ten stainless steel welders. Details of the steel used and information on possible nickel exposure were not presented, but serum chromium did increase during the course of the working week indicating absorption of chromium from the welding fume. No changes in urinary excretion of albumin or ß$_2$-microglobulin to suggest renal damage were detected, but a number of other, larger, studies of stainless steel welders have followed throwing further light on this subject. Reported effects on liver function, which was also investigated in this study, appear to be associated with alcohol consumption and are therefore not considered relevant.

Littorin *et al.* (1984) investigated renal function in a group of 17 MMA/SS welders from six different industries. Urine was collected from the welders pre- and post-shift on a Monday; blood samples were collected post-shift. Urine and blood samples were also collected from 17 control subjects, matched for age, sex, smoking status and alcohol consumption. The welders had worked as welders for a median of 20 years (range 7-41). Job title was reported and urinary chromium was measured. Median urinary chromium concentrations were 6 µg/g creatinine (pre-shift; range 0.9 - 29) and 11 µg/g creatinine (post-shift; range 1.5 - 71). Urinary chromium was higher in the welders than controls, and increased across the work shift. No measurements of urinary nickel or other estimates of exposure to nickel were made. No differences which might suggest an effect on renal function were identified between the groups in the concentrations of a range of urinary proteins thought to reflect both glomerular and tubular function. No air monitoring data were presented in this study, and details of the stainless steel base metal and electrode were absent. Nevertheless, this study provides no evidence for an effect on kidney function among MMA/SS welders with long-term experience of welding.

Verschoor *et al.* (1988) studied renal function in 29 male chrome plating workers, 21 stainless steel welders, 18 boilermakers working largely with the same materials and in the same workshop as the welders, and a further group of 24 stainless steel welders. A group of 71 subjects from a variety of workplaces who were not exposed to chromium were also studied. Subjects with hypertension, known concurrent renal disease or concurrent use of medication were excluded. Urine and blood samples were collected at the end of the working day on the last day of the working week for all subjects. Samples were analysed for urinary and serum chromium levels, and the urinary concentration of a range of proteins (albumin, ß$_2$-microglobulin, retinol binding protein, immunoglobulin G (IgG), *N*-acetyl-ß-*D*-glucosaminidase (NAG), ß-

galactosidase, and lysozyme). None of the groups were significantly different from each other with respect to age, smoking status or alcohol consumption. No specific details of the stainless steel(s) used by the welders and boilermakers were given, or regarding the welding method used. No air monitoring data were presented. Geometric mean urinary chromium levels were 3 µg/g creatinine (range 1-62) in the welders and 1 µg/g creatinine (range 0.3-1.5) in the boilermakers; the mean level in the controls was 0.4 µg/g creatinine (range 0.1-2).

No significant differences in urinary proteins between the groups were detected, but mean serum creatinine was slightly and significantly higher among the stainless steel welders than the other groups. No significant relationship was demonstrated between urinary or serum chromium and any parameter of renal function. The authors nonetheless claim some evidence for an effect on glomerular function among the chrome platers and welders by categorising this group as exposed to Cr^{VI} and comparing them to the groups exposed to dust (boilermakers) and to unexposed controls for a combination of "glomerular function parameters". They do not explain how this combination was arrived at and interpretation of the difference in "glomerular function parameters" between the combined chrome platers/welders and the boilermakers/controls is difficult.

These findings do not provide strong evidence of an effect on the kidneys in this group, particularly in view of the lack of evidence for a relationship between work with stainless steel and renal function in this study.

Overall, this study provides no evidence of impaired renal function among welders of stainless steel.

One of the more informative investigations of renal function in stainless steel welders is a study by Vyskocil *et al.* (1992). The study involved 52 MMA/SS welders, with an average duration of exposure of 18 years, and 51 unexposed administrative workers. Nickel and chromium exposures were estimated in the two groups by quantifying urinary nickel and chromium excretion at the beginning and end of the working week. Personal air samples were also collected from ten welders at the *"five most representative workplaces"* and analysed for nickel and chromium. Data for total fume concentration were not presented.

Exposure data for the two groups are summarised in the following table:

Exposure measure	Welders[a] (n=52)	Controls[a] (n=51)
Nickel in air (µg/m^3)	28 (3 - 70)	-
Chromium[b] in air (µg/m^3)	64 (7 - 161)	-
Urinary nickel (nmol/mmol creatinine)	8.7 (2.5 - 36.1)	4.4 (0.95 - 30.8)
Urinary nickel (µg/g creatinine)	5.1 (1.5 - 21.2)	-
Urinary chromium (nmol/mmol creatinine)	38.7 (4.3 -1.68[c])	2.4 (0.54 - 15)
Urinary chromium (µg/g creatinine)	17.8	-

a. geometric mean values (range);
b. it is assumed that this represents total chromium;
c. the value 1.68 appears to be an error.

Urinary nickel and chromium levels in the welders were reported to be *"significantly different"* from the control levels, although P-values were not reported. As an indication of the level of exposure to Cr^{VI} in air, the authors noted that 50% of the samples collected from the welders exceeded 50 µg Cr/ m^3. [It is uncertain as to the reliability of this statement as it appears to be based on measurement of total chromium in air for 10 welders and the authors assumption that 70-90% of total chromium in MMA/SS welding fume occurs as Cr^{VI}]. Urinary concentrations of total protein, retinol binding protein, "protein 1", transferrin, ß$_2$-microglobulin, albumin, lysozyme, NAG and lactate dehydrogenase were also determined.

There were no significant differences between the two groups in any of the protein levels. Within the welding group, there were no significant changes in protein levels in urine samples collected at the beginning of the week compared to samples collected at the end of the working week. When the results for the nine welders with the highest urinary chromium was compared with the unexposed group, there was a significant difference in the level of urinary ß$_2$-microglobulin (mean 16.6 µg/mmol creatinine for welders; 9.6 µg/mmol creatinine for controls). This difference was not observed with any other parameter of renal function, and furthermore, no significant correlation was demonstrated between the urinary concentration of nickel and chromium and any of the parameters of renal function. The results of this fairly comprehensive study show no significant effect on renal function among MMA/SS welders with long-term experience of welding. These results were associated with recent airborne levels of total chromium and nickel which, for ten of the welders, averaged 64 µg/m^3 and 28 µg /m^3, respectively.

Air monitoring data were also presented in a study of renal function conducted by Bonde and Vittinghus (1996). This study involved 35 TIG/SS welders[14], 46 mild steel welders, 21 ex-welders, and 33 electricians and other workers who had never welded. Renal function was assessed by the *"Kampmann index"* (a measure of glomerular function based on a subject's serum creatinine and weight) and urinary excretion of albumin, IgG, transferrin, orosomucoid, and ß$_2$-microglobulin (tubular function). Exposure to welding fume was estimated using personal air samples collected from the welders and by measuring post-shift urinary chromium levels in all subjects. Exposure data are summarised in the following table:

Exposure measurement[a]	**TIG/SS welders (35)**	**Mild steel welders (46)**	**Ex– welders (21)**	**Never-welders (33)**
Total fume in air (mg/m^3)	1.3 ± 0.8	3.1 ± 1.0[b] 4.7 ± 2.7[c]		
Urinary chromium (mmol/mol creatinine)	2.2 ± 1.1	1.2 ± 0.6	1.2 ± 0.6	0.7 ± 0.2

a. mean values ± standard deviation; **b.** low level exposure mild steel welders;
c. high level exposure mild steel welders

Urinary chromium levels were significantly higher in stainless steel welders compared to never-welders (P<0.01). No measurement of urinary nickel was made. Urinary albumin, IgG and transferrin concentrations were significantly increased among the stainless steel welders compared with the never-welders. However, urinary albumin, IgG, transferrin and orosomucoid concentrations were also significantly increased among the mild steel workers, and urinary albumin excretion was increased among the ex-welders. There were no significant differences between the groups in urinary concentrations of ß$_2$-microglobulin, nor in the *"Kampmann index"* used to assess glomerular function. Thus, whilst this paper provides some equivocal evidence of an effect on renal tubular function among welders, this effect does not appear to be limited to stainless steel welders. This study provides no clear evidence that TIG welding of stainless steel has an effect on renal function.

Investigations of respiratory health

A brief report was presented of a cross-sectional study involving 158 welders and 159 controls (Schneider *et al.* 1982). Respiratory health was assessed by symptom questionnaire, clinical examination, chest radiography and spirometry. Exposure was assessed by air monitoring and by analysis of hair samples for chromium and aluminium content. Full details of the work performed by the welders was not given although the group comprised both stainless steel and aluminium workers, and as air samples were collected from 91 welding workplaces it is likely that their exposure

[14] TIG = gas tungsten arc welding (GTAW)

was relatively heterogeneous. No details were given of much of the methodology used, including statistical analysis. Few details of the exposure data were given except the authors noted that samples from ten welders in six workplaces "*exceeded MAC values*". The concentration of metals in hair samples was higher in the welders, but this is difficult to relate to exposures from the details given. The health investigations revealed that the welders complained of cough and sputum (indicative of bronchitis) more often than the controls, after allowing for smoking. Also, the welders reported nasal symptoms more frequently, but no significant differences in spirometry were noted. This paper contained insufficient detail to be able to distinguish whether the health effects reported were specific to any particular workplace exposure, or even whether they might be attributable to aluminium welding, stainless steel welding, or both. Whilst seemingly reassuring, it is difficult to assign great importance to these results as they are so incompletely reported.

Kalliomäki *et al.* (1982b) reported a cross-sectional study of respiratory health among a group of 83 stainless steel welders (MMA and TIG technique) and 29 mild steel welders (MMA technique). Symptoms and lung function testing were used as measures of respiratory health. A technique called "magneto pulmography"[15] was used to assess lung dose of metal ("lung dust"). Urinary chromium was also measured in some subjects. MMA/SS welders had increased levels of lung dust and urinary chromium compared with TIG/SS welders, and higher lung dust than mild steel welders (urinary chromium was not measured in the mild steel welders). Welders were compared for health effects in five groups: MMA/SS welders (≥80% MMA); TIG/SS welders (≤10% MMA); two mixed groups of stainless steel welders (11-40% MMA and 50-89% MMA); and MMA mild steel welders. Regression analysis suggested that stainless steel welders reported dyspnoea more frequently as the proportion of time using an MMA technique increased. Similarly, in the stainless steel welders maximum expiratory flow at 25% and 50% of forced vital capacity (MEF_{25} and MEF_{50}, respectively) showed a greater decrease from reference values as the proportion of MMA welding increased. The authors also noted that vital capacity (VC) decreased at a rate faster than expected for all stainless steel welders (48 ml/year vs 28 ml/year predicted), but they did not make clear where the predicted values were derived from. This finding is therefore difficult to interpret. No other significant effect of stainless steel welding on symptoms or lung function was noted. Results of lung function tests for the mild steel welders indicated more marked effects in this group than in the stainless steel welders.

As no unexposed subjects were included in this study, estimates of the effect of exposure to the various types of welding fume and other confounding factors were derived from regression estimates from within the exposed study population. This may decrease the ability to identify adverse effects.

Two cross-sectional studies were conducted among mixed groups of welders including some stainless steel welders (Mur *et al*. 1985; Sjögren and Ulfvarson 1985). Again, respiratory symptoms and measurements of lung function were used to assess respiratory health. The study of Mur *et al.* also included a measurement of non-specific airway responsiveness to acetylcholine. Both investigations reported an

[15] "Magneto pulmography" appears to be similar to the "magnetopneumography" technique employed by Huvinen *et al.* (1997) and reported in *Section 2.3*.

increased prevalence of cough and phlegm or chronic bronchitis among the welders, although in one study this was not statistically significant. Neither study presented plausible evidence of any effect on any of the parameters of lung function used. Mur *et al.* did report a greater change in FEV_1 following inhalation of acetylcholine among the welders than the controls. However, the technique used for measuring airway responsiveness was not one that had been used elsewhere and so the significance of this finding is unclear. Crucially, neither study presented sufficient details of the results of the stainless steel welders separately to allow a separate analysis, although the paper of Mur *et al.* did state that no significant differences were identified between the different groups of welders. Evaluating these papers is made more complex as one failed to detect any effect of smoking on respiratory health, suggesting its power to detect differences may have been limited, and both studies were cross-sectional in nature with the inherent problems of interpretation this brings.

Nielsen *et al.* (1993) reported a cross-sectional study of respiratory health among 25 male welders working with aluminium and stainless steel, and 25 male warehouse workers. Each subject underwent a medical examination, skin tests, measurement of serum immunoglobulin E (IgE), lung function testing, and a measurement of airway responsiveness to methacholine using a non-standard technique. Personal air samples were collected from 19 welders; workshift time-weighted average concentrations were 2.8 mg/m^3 (total dust), 1.4 mg/m^3 (aluminium, during aluminium welding) and 8 $\mu g/m^3$ (water soluble chromium, during stainless steel welding).

Significant differences between welders and controls were found only for a number of symptoms including pharyngitis and airway responsiveness; and for conjunctivitis, which was also evaluated. There was also a suggestion of a dose-response effect on airway responsiveness: when the welders were divided into those with more or less than two and a half years of exposure, one measure of airway responsiveness was increased in the group who had welded for a longer period. However, there were more smokers in this group. No other significant differences in symptoms or lung function were detected. The authors concluded that the results suggest that exposure to welding fume increased the reactivity of small airways. However, this study has several deficiencies that make interpretation of the results difficult. It is cross-sectional and therefore subject to bias; also the number of subjects is small. The data for aluminium and stainless steel welders are not presented separately; this is a major limitation in the study as exposure to workplace contaminants is likely to differ considerably between the two types of welders. Further, the test of airway responsiveness used in the study is a non-standard test and thus of uncertain reliability. At present, the relationship between airway responsiveness to clinical disease remains unclear even when standardised methods of quantifying airway responsiveness are used.

In conclusion, the findings of this study do not allow any conclusions to be drawn regarding the effects of welding of stainless steel on respiratory health.

Wang *et al.* (1994) included 67 current and 16 ex-stainless steel welders in their study of 209 current welders, 64 ex-welders, and 128 vehicle assemblers. All the welders had between six months and ten years experience as a welder. The stainless steel welders worked a minimum of 50% of their time with stainless steel for at least four days per week and more than four hours each day. Measures of respiratory health

used included respiratory symptoms, measurements of lung function, and a measure of airway responsiveness to methacholine. Cough and phlegm were reported more frequently by some groups of welders (cough by ex-mild steel welders, phlegm by current stainless and mild steel welders), but no other consistent differences between groups were identified in symptoms, lung function or airway responsiveness. When smoking status was taken into account, the incidence of symptoms in stainless steel welders was no higher in smokers than in non-smokers. However, in mild steel welders symptoms were more frequent in smokers than non-smokers.

Using a definition based on a combination of the presence of symptoms and airway responsiveness, the authors estimated the incidence of asthma among the welders to be 8 cases per 1000 welding years. The authors compared this figure with an estimate derived from a different study (on a non-welding US population) of 2.1 per 1000 person years, which the authors suggest provides evidence that welding fume exposure does have an effect on the incidence of asthma. Overall, the evidence in this paper provide little, if any, evidence of an effect on respiratory health attributable to welding of stainless steel. The comparisons of the estimates of the incidence of asthma are based on different populations at different times by different researchers using a non-standard definition of asthma, and as such are of limited value. No significant differences were identified between stainless steel and mild steel welders, suggesting that there is little additional adverse effect from welding stainless steel over and above that arising from welding mild steel (and in this study, vehicle assembly also).

A paper by Bogadi-Sare (1990) reported a cross-sectional study of respiratory symptoms and function among 106 stainless steel workers, only some of whom were welders, and 80 unexposed controls. The authors report these groups were matched for age, sex, height, smoking status and social class. However, given the discrepancy in numbers in the groups, individual matching seems unlikely and it may be that in fact the two groups were not significantly different in these respects. There were no significant differences between the groups in the prevalence of any respiratory symptoms, except the steelworkers reported significantly more *"dyspnoea and choking"* than the unexposed group. Also, the steelworkers had a significantly lower FEV_1, peak expiratory flow rate (PEFR), and other measures of airway function. These changes suggested an obstructive effect of exposure to dust/fume from the processing of stainless steel.

However, as in all cross-sectional studies, the populations included would be prone to selection bias. Also, as no exposure data were presented in the study, and the exposed group in fact comprised a heterogeneous group of 47 welders and 59 turners and metal polishers, it is difficult to be confident as to which particular environmental contaminant may have been responsible for any effect detected. The authors suggest there were no major differences within the exposed group in their symptoms and lung function, but insufficient data were presented to assess this further. The case for the workplace environment causing respiratory function abnormalities is further weakened as no correlation could be demonstrated between duration of exposure and respiratory function abnormalities. It is therefore difficult to draw any conclusions from this study regarding the effect of stainless steel welding on respiratory health.

Kilburn *et al.* (1990) reported a cross-sectional and cross-shift study of respiratory symptoms among workers in a plant manufacturing nuclear reactors using a steel containing approximately 10% nickel, 18% chromium, and 7% molybdenum. Results from these workers were compared with data from a stratified random population of 340 men, previously reported by Miller *et al.* (1986). Cross-sectional data were analysed for 90 welders of stainless steel and "black steel" (no details of these two steels were given; it is possible that the "black steel" is carbon steel). This analysis showed an increased incidence of "chronic bronchitis" (18%) among those included in the study. Both mean FEV_1 and FVC were significantly lower than predicted values (94.5% and 95.4% of predicted values, respectively; $p<0.05$). Among the "black steel" welders, and ten fitters and helpers, no significant cross-shift changes in lung function were seen. No air monitoring data were presented in this study. Urinary and serum levels of nickel and chromium were measured in samples collected pre- and post-shift at the beginning of the working week. Mean pre-shift urinary chromium levels were increased in the stainless steel welders (6.9 ± 5.8 µg/g creatinine) and the "black steel" welders and fitters and helpers group combined (4.7 ± 4.1 µg/g creatinine) compared with a group of controls (0.16 ± 0.11 µg/g creatinine). Urinary chromium levels only increased cross-shift in the stainless steel welders. Mean pre-shift urinary concentrations of nickel were also increased in the stainless steel welders (5.2 ± 1.8 µg/g creatinine) and the "black steel" welders and the fitters and helpers group (5.6 ± 4.4 µg/g creatinine) compared with the controls (1.5 ± 1.0 µg/g creatinine). No significant increases in urinary nickel were seen cross-shift in any group. Serum chromium and nickel levels showed a similar pattern.

Thus, while the authors showed evidence of significant exposure to nickel and chromium among the steel workers, the effect on respiratory health was less clear. From the cross-sectional data, the authors report an increase in "chronic bronchitis" among the welders compared with their comparison population. However, the incidence of "chronic bronchitis" in their comparison population appears to be very low compared with many other industrial populations, and the reported changes in lung function represent if anything a "restrictive" respiratory impairment which would not usually accompany chronic bronchitis. From these results, it is difficult to be confident that any difference reported is due to work rather than some other factor. There is no evidence for the non-welders or either of the welding groups suffering any adverse effects on respiratory health due to workplace exposures apparent from the cross-shift data.

In a briefly reported investigation of 210 stainless steel welders, Emmerling *et al.* (1989) recorded an increased incidence of symptoms of chronic bronchitis and abnormal *x*-ray findings (small linear opacities) in the welders compared to referents. The welding group involved MMA welders (61), MIG welders (46) and TIG welders (16). It was noted that the respiratory effects appeared to occur most frequently in the MIG welders. Exposure data were available for the three welding groups. Mean total fume levels were 2.7 mg/m^3 (MMA welders), 5.3 mg/m^3 (MIG welders) and 1.5 mg/m^3 (TIG welders); total chromium levels were 59, 180 and 13 $\mu g/m^3$, respectively; Cr^{VI} levels were 17.5, 8.0 and 1.5 $\mu g/m^3$, respectively. Elevated U-Cr were reported for all three welding groups and, in the MMA welders, elevated Cr levels in RBCs were also reported. The study report provided few details of the methodology used and is therefore difficult to critically evaluate.

Keskinen *et al.* (1980) reported on two subjects with asthma associated with fume from the welding of stainless steel. The subjects had been thoroughly investigated and had had the cause of their asthma confirmed by a positive specific airway challenge when welding stainless steel using a MMA technique. No reaction was seen when the same subjects performed welding on mild steel, nor when they welded stainless steel using a TIG technique. The authors suggested that the most likely cause of this asthma was the chromium content of the welding fume. Evidence of allergy to chromium was provided in one subject with a positive "chamber" test to chromium (the specific chromium compound was not reported). The subject also had a history of contact dermatitis when working with cement. While this paper provides good evidence that welding stainless steel can evoke asthmatic symptoms in some individuals, it is uncertain whether the subjects had previous sensitisivity. Further, the report gives little indication of the strength of this effect, and the evidence that the chromium content of the welding fume was responsible is suggestive rather than conclusive.

A subsequent case-report by Moller *et al.* (1986) of asthma in a single welder again suggested that chromium in welding fume could be associated with respiratory hypersensitivity. In this case, an asthmatic reaction occurred after welding with an unspecified steel containing chromium. Sensitisation to chromium was confirmed by a positive specific airway challenge to aerosolised sodium chromate. This reaction could not be replicated in other asthmatic subjects, suggesting that the changes in lung function were probably not due to an irritant effect. The subject additionally gave a positive response to Cr^{VI} in a skin test. In this case, it is not clear how the subject became sensitised to chromium. As the subject had previously worked for a period of approximately ten years in both welding and plating, sensitisation may have been induced by exposure to chromium in plating operations rather than by exposure to welding fume. This case-report indicates that chromium in welding fume may evoke an asthmatic response in a possibly pre-sensitised subject. However, as it is uncertain whether the welding fume was generated from stainless steel or some other chromium-containing steel, this report contributes little information to this review.

Summary of the effects of repeated exposure in humans

Several studies are available which have investigated renal function in groups of workers which have included welders of stainless steel. A number of the studies suffer from deficiencies which do not allow any potential effect of welding of stainless steel on renal function to be fully explored. The most reliable data on this subject come from two studies of long-term MMA/SS welders, one of which presented air monitoring data; neither study demonstrated a significant effect on renal function. Overall, the available data provide little evidence of any appreciable risk of renal disease from the welding of stainless steel at exposure levels which are likely to occur in modern industry.

The respiratory effects of exposure to welding fume have been extensively studied and many of these studies include a proportion of stainless steel welders. However, there are relatively few studies where the data have been collected exclusively for

stainless steel welders, or where the data for such welders can be distinguished from those of other welders. Overall, the available data suggest that welding of stainless steel may be associated with an increased risk of reporting respiratory symptoms, particularly cough and phlegm, but there is little convincing evidence of any increased risk of developing lung function abnormalities

The data on respiratory effects are similar to those observed in studies of mild steel welders, and, significantly, no study reviewed has yet demonstrated a difference in respiratory health between mild steel welders and stainless steel welders. One explanation for this could be that the effects on respiratory health are associated with a constituent found in all types of steel welding fume, and are not specific to stainless or mild steel.

Available case-reports indicate that fume from welding of stainless steel can elicit asthmatic symptoms in some individuals. However, there is no evidence to suggest that fume from welding of stainless steel can induce respiratory hypersensitivity.

Mutagenicity

In vitro studies in bacterial cells

Samples of fume particulate from welding of stainless steel have been investigated in several bacterial reverse mutation assays which have been conducted according to currently accepted protocols.

Samples of MMA/SS and MIG/SS fume particulate gave positive results in a *Salmonella* reverse mutation assay (Maxild *et al.* 1978). Two types of MMA/SS fume were used in the experiment: one generated using a 18/10 low-carbon metal electrode for welding 18/10 austenitic stainless steel; another using a 18.5/12.5 + 3% Mo low-carbon metal electrode. Fume particulate was collected on filters and prepared as a suspension in dimethylsulphoxide (DMSO). Particulate fractions from both MMA/SS fumes were positive in *S.typh.* TA98 and TA100, with and without metabolic activation. Concentrations up to 0.5 mg particulate per plate caused a dose-dependant increase in the number of revertant colonies. Two different MIG/SS samples were also tested: one generated using low-carbon wire for welding 18/8 austenitic stainless steel; the other generated using low-carbon wire containing 18/8 + 2.5% Mo for welding high corrosion-resistant steel. Suspensions of these samples in DMSO also gave positive results with both bacterial strains without metabolic activation, although the mutagenic activity was less than that of the MMA/SS fume. Concentrations up to 3 mg/plate caused a dose-dependent increase in revertant colonies. The MIG/SS fume particulate showed reduced activity in TA100 when a metabolic activation system was present. No data were provided regarding the chemical composition of the welding fumes tested.

Positive results were reported with the water-soluble fraction of MMA/SS fume particulate in a reverse mutation assay (Hedenstedt *et al.* 1977). Particulate fractions from four different MMA/SS welding fumes were tested. The welding fumes were generated under laboratory conditions and samples were collected on filters. The source of each MMA/SS sample, as described in the study, was as follows:

Sample	Base metal	Electrode
1	Steels with poor welding quality	Austentitic/ferritic electrode
2	Stainless steel containing 18% Cr, 12% Ni, 2-3% Mo	Low hydrogen electrode
3	Low carbon Cr/Ni/Mo stainless steel	Rutile coated electrode
4	Austentitic stainless steel (18/12 + Mo)	Rutile coated electrode

Aqueous solutions of all four MMA/SS samples caused a dose-dependent increase in revertant colonies in *S. typh.* TA100 in the absence of a metabolic activation system. The most marked activity occurred with sample number 4; at the highest concentration tested (0.4 mg/plate), the number of revertant colonies was increased approximately six-fold. With all MMA/SS samples, mutagenic activity was virtually eliminated by the addition of a metabolic activation system. MMA/SS sample number 4 was also positive in *S.typh.* TA98; this activity was also eliminated by addition of a metabolic activation system. Mutagenic activity of the MMA/SS fume appeared to be associated with the water-soluble fraction of the particulate; when ethanol was used as the solvent, mutagenic activity was virtually eliminated. Samples of MIG/SS fume were also tested in study. Aqueous fractions of MIG/SS fume particulate showed weaker mutagenic activity than MMA/SS fume. One sample of MIG/SS fume gave a positive but weak response with *S. typh.* TA100, without metabolic activation. Another MIG/SS sample gave a negative response in this assay. DNA damaging potential was also investigated in this study using the *E. coli* growth inhibition assay and positive results were obtained with particulate fractions from MMA/SS welding fume. Samples of MIG/SS fume particulate were negative in this assay.

The following studies have also reported results of reverse mutation assays, but presented too few details to enable critical evaluation of the data.

A positive Ames test result was reported for MMA/SS welding fume particulate in a briefly reported study by Reuzel *et al.* (1986). MIG/SS fume particulate induced a *"marginal effect"* in this study.

Positive results were also reported with stainless steel welding fume in another reverse mutation assay, with MMA/SS fume showing greater activity than MIG/SS fume (Hooftman *et al.* 1988). This study was reported as an abstract only; no other details were provided.

In vitro studies in mammalian cells

The sample of MMA/SS fume particulate that showed the highest activity in the bacterial reverse mutation assay was tested for mutagenicity in mammalian cells (Hedenstedt *et al.* 1977). The sample caused a significant increase in 6-thioguanine resistant mutants in V79 Chinese hamster cells, although this was accompanied by fairly marked toxicity. A concentration of 10 µg/ml fume particulate, which caused a significant increase in mutants ($p<0.01$), also caused a 42% reduction in cell survival. The toxicity observed in this assay casts some doubt on the validity of this result.

MMA/SS and MIG/SS welding fume particulates both gave negative results in gene mutation assays which used the hypoxanthine guanine phosphoribosyl transferase (HGPRT) mutational system, according to a briefly reported study by Reuzel *et al.* (1986). As no further details were provided, evaluation of this assay is difficult.

Positive results were reported with MMA/SS, and to a lesser extent MIG/SS fume, in a chromosome aberration test, but not in a HGPRT gene mutation assay (Hooftman *et al.* 1988). These results were reported as an abstract only; no other details were provided.

Positive results were reported in a cell transformation assay using Baby Hamster Kidney (BHK) 21 cells (Hansen and Stern 1985). MMA/SS welding fume particulate was collected on filter paper. The elemental composition of the particulate fraction was: 3.8% Cr (3.6% as water-soluble Cr^{VI}), 0.53% Ni. BHK 21 cells were incubated in medium containing a suspension of the particulate for 20 hours. The highest concentration used (50 µg/ml), which caused ~40% reduction in cell survival, resulted in an increase in cell transforming frequency (~17 colonies/$5x10^5$ survivors; 1-2 colonies in controls). MIG/SS fume, which was investigated in the same experiment, showed much weaker cell transforming activity than the MMA/SS fume. The MIG/SS fume was generated using either short arc (low voltage) or spray arc (high voltage) methods, and contained 10.8% Cr (0.5% as water-soluble Cr^{VI}) and 4.1% Ni (short arc); or 14.3% Cr (0.05% as water-soluble Cr^{VI}) and 6.5% Ni (long arc). Concentrations of 800 µg/ml MIG/SS fume were required to induce a transformation frequency in BHK 21 cells similar to that induced by the MMA/SS fume.

In a briefly reported study, a positive result was reported for MMA/SS welding fume particulate in a SCE assay by Reuzel *et al*. (1986). MIG/SS fume gave a *"marginal effect"* in this assay. No further details were presented.

Particulate fractions of six different welding fumes, all from welding of stainless steel, were investigated in a SCE assay in Chinese Hamster Ovary (CHO) cells (de Raat and Bakker 1988). Four different MMA/SS welding fumes and two MIG/SS welding fumes were tested. The fume was generated under laboratory conditions and the particulate was collected on filters. Details of the fumes tested are as follows:

Welding method	Electrode	Base metal	Composition of fume (mg/g)	
			Cr[a]	Ni
MMA/SS	E316	AISI 316	36	4.20
MMA/SS	E310	AISI 356[b]	29	3.80
MMA/SS	E308	AISI 316	36	2.70
MMA/SS	E430	AISI 316	44	0.11
MIG/SS	E316LT-2	AISI 316	143	40.6
MIG/SS	ER316	AISI 316	132	40.3

a. in MMA/SS fume this was mostly soluble Cr (i.e. Cr^{VI}); in MIG/SS fume this was mostly insoluble Cr (i.e. Cr^{III}); **b.** "AISI 356" was reported as the base metal, although this is not a stainless steel grade and may therefore represent an error in the paper.

With all the samples tested, exposure of CHO cells to suspensions of the welding fume particulate in medium for either 3 hours (without serum present) or 21 hours (with serum present) caused a statistically significant, dose-dependent increase in the number of SCE per metaphase. The greatest activity occurred with MMA/SS fume particulate. The amount of MIG/SS fume particulate required to give comparable increases in SCE was approximately 100-fold the amount of MMA/SS particulate.

MMA/SS welding fume particulate, generated using a JIS D 308-16 electrode, caused an increase in SCE frequency in Chinese hamster lung (Don) cells (Koshi 1979). The welding fume was collected on glass fibre filters and prepared as a suspension. The concentration of specific elements in the culture medium was: Cr 38.6 µg/ml; Mn 1.2 µg/ml; Ni 0.3 µg/ml; Fe 0.1 µg/ml; Mg 1.9 µg/ml. Cells were incubated with the suspension (1, 2 or 4 µg particulate/ml) for 28 or 48 hours. The fume caused a significant, dose-dependent increase in SCE (14, 19 and 33 SCE/cell, respectively; controls: 5 SCE/cell); the highest concentration caused some toxicity. In the same experiment, MIG/SS fume particulate, generated using a JIS Y 308 electrode, also caused an increase in SCE frequency, but required much higher concentrations (50, 100 and 200 µg/ml) to elicit this response. With both types of welding fume, the supernatant from the suspension (containing the aqueous fraction) was also reported as causing an increase in SCE frequency, although these results were not presented.

A negative result was reported with MMA/SS welding fume particulate in a unscheduled DNA synthesis (UDS) assay using human cells (Reuzel *et al.* 1986). The study was briefly reported and no further details were given. This study is therefore difficult to evaluate.

MMA/SS welding fume particulate, generated using a JIS D 308-16 electrode, caused an increase in chromosome aberrations in Chinese hamster lung (Don) cells (Koshi 1979). The welding fume, which was collected on glass fibre filters and prepared as a suspension (1, 2 and 4 µg/ml), caused a significant, dose-dependent increase in chromosome aberrations, predominantly gaps and chromatid exchanges. MIG/SS fume particulate, which was investigated as part of the same experiment, also caused an increase in chromosome aberrations, but required much higher concentrations (50 and 100 µg/ml) to elicit this effect. The MIG/SS fume was generated using a JIS Y 308 electrode.

In vivo assays

A positive result was reported in an *in vivo* mammalian spot test using MMA/SS welding fume particulate (Knudsen 1980a, 1980b; Knudsen and Stern 1980). Pregnant C57BL/65/BOM mice (52 animals) were treated with welding fume particulate, administered as an aqueous solution by i.p. injection on day 8, 9 and 10 of pregnancy (100 mg/kg/day; particle diameter <0.5mm). The welding fume was reported to contain 3.6% as Cr^{VI}, although no further details were provided. There was a significant increase in the number brown/grey spots on the coats of resulting offspring compared to control animals, indicating a positive result. These spots represent genetic alteration of pigment precursor cells, that is somatic cell mutations. Other spots, such as mid-ventral or mammae spots, were excluded. The assay was conducted largely according to standard procedures, although only one dose level was used (at least two dose levels are recommended). The results of this assay, although limited by the use a single dose level, provide some indication that the water-soluble components of MMA/SS fume particulate are mutagenic to somatic cells *in vivo*.

Human data

Several studies are available which have investigated genetic damage in peripheral lymphocytes from stainless steel welders. Some of these studies have reported significantly increased frequency of chromosome aberrations in the welders compared to matched controls.

A group of 127 welders were studied by Knudsen *et al.* (1992) and compared with non-welding controls, matched for age, gender and smoking status. The welders were classified according to the predominant welding method used during the preceding six-month period (63 MMA + TIG welders; 52 TIG welders; 12 MIG welders). The mean duration of employment as welders for the three groups ranged from 9-10 years. Personal air monitoring data were available for each subject. Mean air concentrations of chromium (total) were 17 $\mu g/m^3$ (MMA + TIG), 28 $\mu g/m^3$ (TIG) and 15 $\mu g/m^3$ (MIG); 4.9, 2.3 and 1.7 $\mu g/m^3$ respectively as Cr^{VI}. Mean nickel levels were 12 $\mu g/m^3$, 15 $\mu g/m^3$ and 12 $\mu g/m^3$, respectively. Urinary and serum levels of chromium in welders were significantly higher than control levels; urinary nickel was elevated in MMA + TIG welders and TIG welders. Peripheral lymphocytes in pre-shift blood samples, collected from each subject during the middle of the working week, were examined for the following genetic end-points: chromosome aberrations, SCE and UDS.

Frequency of chromosome aberrations (dicentrics, translocations, double minutes and rings) was significantly higher in the welding cohort compared to non-welding controls; when analysed according to welding sub-cohort, the significant increase was only seen in MMA + TIG welders. When subjects were further grouped according to smoking status, increased incidence of chromosome aberrations remained for welders and MMA + TIG welders who were non-smokers, but there were no significant differences between welders who were smokers and controls. Other genetic end-points investigated (SCE and UDS) showed no significant increase over the control incidence; moreover the incidence of these end-points showed a significant decrease in some of the welding sub-cohorts.

A significant increase in chromatid breaks was reported in a study of MMA/SS welders, although other specific chromosome aberrations were not increased (Jelmert *et al.* 1994). Forty-two welders, with a mean duration of welding of 2.5 years, were investigated and compared with non-welding controls, matched for age, gender and smoking status. A second, larger reference group was also used in the study. Air monitoring and biological monitoring data were available. Levels of chromium (total) in personal air samples averaged 75 µg/m^3 (8-hr TWA; range 7.5-422), Cr^{VI} 35 µg/m^3 (0.6-252), and nickel 33 µg/m^3 (2.7-432). Urinary levels of chromium and nickel (post-shift samples) averaged 11.1 and 2.9 µg/g creatinine, respectively. Mean chromium and nickel levels in whole blood (post-shift samples) were 3.2 and 0.9 µg/l, respectively. There was a significant increase in the frequency of chromatid breaks in welders compared to either reference population. The number of cells with chromosome aberrations was significantly increased when the second reference population was used for comparison, but not when matched referents were used. Other specific chromosome aberrations (chromosome breaks, structural rearrangements, chromatid exchanges and dicentric chromosomes) occurred with a similar frequency in welders and referents. Investigation of SCE incidence showed no difference between welders and referents.

In contrast, several other studies of welders have shown no such increase in chromosome aberrations or other genetic end-points. Husgafvel-Pursiainen *et al.* (1982) failed to demonstrate increases in chromosome aberrations or SCE in peripheral lymphocytes from 23 MMA/SS welders, with a mean duration of employment of 21 years. Elias *et al.* (1989) found no increase in chromosome aberrations in a group of 15 predominantly TIG/SS welders with on average 15 years welding experience and 8.3 years experience using that particular technique.

Absence of cytogenetic effect in lymphocytes was also reported in another study involving 24 MMA/SS welders (Littorin *et al.* 1983). Personal sampling data for the welders, monitored on one day only, showed mean air levels of chromium (total) to be 81 µg/m^3 (range 4-415) and levels of Cr^{VI} to be 55 µg/m^3 (range 5-321). The frequency of chromosome aberrations in peripheral lymphocytes showed no significant difference between welders and non-welding matched referents. Likewise, there was no difference in SCE incidence or in micronucleus formation in lymphocytes.

A study by Jelmert *et al.* (1995) provided no evidence of cytogenetic damage in stainless steel welders using either TIG methods (23 welders) or MIG/MAG methods (21 welders). The mean duration of welding for the two groups was 4 or 6.4 years, respectively. Personal air sampling data for 17 TIG welders and 14 MIG/MAG welders, collected during a full-shift on 3-5 consecutive days, showed Cr (total) concentrations to average 4.3 and 127.2 µg/m^3, respectively. Mean Cr^{VI} levels were 0.7 and 2.9 µg/m^3, respectively. Mean Ni levels were 3.1 and 49.7 µg/m^3, respectively. Cytogenetic damage was examined in lymphocytes from post-shift blood samples collected at the end of the week of monitoring. Using two types of culture conditions (conventional cultures and inhibited cultures), none of the chromosome aberration parameters showed an increased incidence in welders compared to their respective reference group. Further, some parameters (chromosome breaks, cells with aberrations) showed a reduced incidence in welders compared to

referents. Two possible explanations for this reduction, suggested by the authors, namely enhanced DNA repair capacity resulting from low Cr^{VI} levels in biological fluids or death of damaged cells involving apoptosis, so far remain unsubstantiated. The other genetic end-point investigated in the study, SCE incidence, also showed no increase in either welding group compared to their respective referents.

Summary of mutagenicity data

The genotoxicity of fume particulate from the welding of stainless steel has been investigated in a number of *in vitro* assays. The particulate fraction of MMA/SS fume, and to a lesser extent that of MIG/SS fume, has generated positive results in assays for the following end-points: reverse mutation in bacterial cells; induction of SCE, cell transformation and chromosome aberrations in mammalian cells. Equivocal results have been obtained in mammalian cell mutagenicity assays. These results give some indication that certain constitutents of the particulate fraction of welding fume from stainless steel, most likely water-soluble constituents, may possess mutagenic activity. A single *in vivo* assay provides some indication that water-soluble components of MMA/SS fume particulate are mutagenic to somatic cells *in vivo*.

Investigations of genetic damage in lymphocytes from stainless steel welders have generated generally inconclusive results.

Carcinogenicity

Animal data

No animal studies are available which have investigated the carcinogenicity of fume from the welding of stainless steel following exposure by inhalation, the most relevant route of exposure for humans. Animal carcinogenicity data are limited to an i.t. instillation study and an intrabronchial instillation study, neither of which conformed to current internationally agreed protocols.

The long-term effects of repeated i.t. instillation of welding fume were investigated in Syrian golden hamsters in a briefly reported study by Reuzel *et al.* (1986). Two different welding fumes were investigated: MMA/SS fume (generated using type E308-150 electrode) and MIG/SS fume (generated using metal wire type ER 308L***).*** The elemental composition of the MMA/SS fume included 0.4% nickel and 5.0% chromium. The MIG/SS welding fume had an elemental composition which included 2.4% nickel and 0.4% chromium. Animals (35 males in each treatment group) received a weekly instillation of the fume particulate as a saline suspension (0.2 ml) for 56 weeks. Two dose levels of MMA/SS fume were used (0.5 or 2.0 mg particulate in each instillation); MIG/SS fume was administered at one dose level (2.0 mg particulate per instillation). Due to poor survival in the high dose MMA/SS treatment group, the frequency of dosing after 26 weeks in that group was reduced to one instillation per month. Saline treated animals served as controls. Tumour incidence was examined approximately two years after the start of treatment. Pulmonary toxicity (pneumonia, alveolar bronchiolisation and emphysema) affected animals in all three treatment groups, but was reported to be most severe in animals

treated with MIG/SS fume. One lung tumour occurred in each of the MMA/SS treatment groups: in the high dose group, an adenocarcinoma was reported; in the low dose group, an anaplastic tumour was reported. No lung tumours appear to have occurred in the MIG/SS treatment group or in the control group. The results of this study, including data relating to survival, toxicity and tumour incidence, were reported very briefly and therefore preclude critical examination. In addition, this study does not conform to recognised procedures and, being further limited by the apparent poor survival rate, cannot be taken as a reliable measure of the carcinogenic potential of the welding fumes tested.

The carcinogenicity of fume particulate from the welding of stainless steel was investigated in Sprague Dawley rats using the intrabronchial pellet implantation technique (Berg *et al.* 1987). Fume from MMA/SS welding using a rutile electrode was collected onto a glass fibre filter. The particulate fraction was removed from the filter with care to avoid contamination by filter material. The elemental composition of the particulate fraction, determined using particle-induced X-ray emission, was as follows: Cr (3.6% by weight, including 0.8% as Cr^{VI}); Ni (0.25%); Fe (3.4%); Mn (2.9%). Stainless steel pellets impregnated with a mixture of welding fume particulate and cholesterol (1:4 w/w) were implanted in the left bronchus of each rat. Each pellet contained, on average, 7.0 ± 1.0 mg of the mixture. Negative control animals received cholesterol-only pellets; positive control animals received benzo(a)pyrene + cholesterol pellets. There were 100 animals (50 females and 50 males) in each treatment and control group. Animals were killed 34 months after implantation.

Body weight gain, organ weights and survival rates were similar in treatment and control groups. The only lung tumour in the welding fume treatment group was a sub-pleural squamous cell carcinoma in the right lung which appeared to be unrelated to the treatment. There were 3/100 lung tumours in the positive control group. No lung tumours occurred in the negative control group. Local fibrosis and squamous metaplasia affected the lungs of some animals in treatment and control groups. Tumour incidence in other tissues showed no significant variation between the three groups. The study deviates from the recommended procedure in several respects. A single dose level was used, amounting to a dose of approximately 1.4 mg particulate per animal. Further, the intrabronchial implantation method does not accurately reflect patterns of exposure that occur in the workplace and therefore does not provide the most appropriate means for assessing carcinogenicity under conditions of occupational exposure. The fairly low incidence of lung tumours in the positive control group also casts some doubt on the reliability of this study. Nevertheless, the findings of this study provide no evidence for carcinogenicity of the particulate fraction of the MMA/SS welding fume tested.

Summary of animal carcinogenicity data

No carcinogenicity bioassays have been conducted with fume from the welding of stainless steel involving exposure by inhalation. The available animal carcinogenicity data are limited to an i.t. instillation study and an intrabronchial implantation study, neither of which conform to internationally agreed guidelines for carcinogenicity

testing. The former study was poorly conducted and contributes no reliable data. The latter study, although deficient in several respects, provides no evidence for the carcinogenicity of the MMA/SS welding fume tested.

Human data

Milatou-Smith et al. 1997

Mortality in two cohorts of welders was investigated by Milatou-Smith *et al.* (1997). This paper includes the follow-up of an earlier study by Sjögren *et al.* (1987). One cohort comprised 233 males with at least five years experience of welding stainless steel during the period 1950-1965. Most of the subjects had welded using coated electrodes (i.e. MMA welding); a small number had used the TIG method. The second cohort comprised 208 railway track welders, with at least five years experience during the same period. Both cohorts were followed through to 1992. The first cohort was reported as having high exposure to Cr^{VI} relative to the second cohort. The only exposure data presented were from a national survey of welders in 1975; median TWA *"chromium"* levels for MMA welding were reported to be 110 µg/m^3, with maximum levels of 750 µg/m^3. It is assumed that these values refer to total chromium, although this is not stated. There were no exposure data which specifically related to subjects in this study. Expected numbers of deaths were based on national mortality rates, adjusted for age, sex and calendar period.

In the *"high exposure"* cohort, overall mortality was less than expected (Observed 60, Expected 76.1, SMR 79, 95% CI 60 to 102). There were six lung cancer deaths in this cohort (Expected 3.65, SMR 164, 95% CI 60 to 358). In the *"low exposure"* cohort, both overall mortality and lung cancer mortality were below the expected incidence. There were 80 deaths (all causes) in this cohort compared to 110 expected (SMR 73, 95% CI 58 to 91), and two lung cancer deaths (Expected 4.88, SMR 41, 95% CI 5 to 148). With both cohorts, exposure to asbestos may have occurred, although the study authors assume that exposure to asbestos was *"very low"*.

This study indicated a non-significant excess of lung cancer among MMA/SS welders, although the cohort size was small. An association between these lung cancers and exposure to welding fume remains uncertain. Further, possible involvement of asbestos cannot be excluded.

Becker et al. 1991

A cohort mortality study was conducted among 1221 arc welders exposed to fumes containing nickel and chromium and an internal reference group of 1694 turners (Becker *et al.* 1991). All workers were employed at one of 25 factories from the German metal processing industry; it is not clear whether all 25 factories were processing stainless steels. All study subjects had worked as either welders or turners for at least six months in the period 1950-70. The period of observation is not clearly stated; it would seem to be 1950-88, although the title of the paper which includes the phrase "results of a second follow up 1983-8" could leave a different impression.

The mortality experiences of the two sub-cohorts were compared directly by the use of an internal standard (with suitable adjustment for differences in age-distributions). In addition, the mortality of each group was compared with expectations based on national mortality rates. There was no significant difference between the lung cancer mortality of welders compared with that of turners (RR 1.2, 95% CI 0.6 to 2.2). Corresponding relative risks for cancers of the stomach, colon and rectum did not approach levels of statistical significance (stomach: RR 0.6, 95% CI 0.2 to 2.3; colon: RR 2.4, 95% CI 2.4 0.1 to 39.3; rectum: RR 4.0, 95% CI 0.4 to 45.8). Among the group of welders, SMRs for these four sites of cancer were unexceptional (stomach: Obs 3, Exp 5.3, SMR 57, 95% CI 18 to 177; colon: Obs 1, Exp 3.0, SMR 33, 95% CI 5 to 237; rectum: Obs 2, Exp 1.9, SMR 105, 95% CI 26 to 422; lung: Obs 14, Exp 12.4, SMR 113, 95% CI 67 to 191).

SMRs were calculated by successive ten-year periods from first employment and a non-significant trend (P=0.08) was shown for lung cancer risks in welders. The corresponding trend-statistic for the group of turners was also not significant (P=0.09). Trend-statistics have been calculated by the current reviewers, from data shown in Table 8 of the published paper.

Among the welders there was a significant excess for mesothelioma (Obs 3, Exp 0.3, SMR 961, 95% CI 310-999), with asbestos exposure indicated. There was also a significant excess for bladder cancer (Obs 4, Exp 1.3, SMR 304, 95% CI 114-810), although urogenital tumours as a group showed no relationship with time since first exposure.

The findings from this study were unexceptional and do not provide any convincing evidence of occupational cancers having occurred in the study cohorts which could be specifically associated with stainless steel welding.

Simonato et al. 1991

A study of the largest (to date) cohort of welders (stainless steel, mild steel and shipyard welders) was published by Simonato *et al.* (1991). The cohort comprises 11,092 male welders from 135 companies located in nine European countries (Denmark, England, Finland, France, Germany, Italy, Norway, Scotland and Sweden). The observation period and the criteria for inclusion into the cohort (e.g. minimum period of employment, entry cohort/census cohort) differed from country to country.

Workers were classified under one of three headings: stainless steel welders, mild steel welders and shipyard welders. Shipyard welders - predominantly mild steel welders - were considered separately because of the potential for exposure to asbestos. The sub-cohort of mild steel welders thus refers to mild steel welders working in factories rather than shipyards. Stainless steel welders were considered separately because these welders were potentially exposed to compounds of chromium and nickel. In addition, the stainless steel sub-cohort (ever stainless steel welders) was further sub-divided into "predominantly stainless steel welders" and others. The "predominantly stainless steel group" referred to study subjects "*who had at least one occupational period welding stainless steel only or were employed in a*

company with at least 70% of stainless steel activity...." A definition of "occupational period" was not supplied.

Overall, mortality from all causes was close to an expectation based on country-, age-, year- and sex-specific mortality rates (Obs 1093, Exp 1189.1, SMR 93, 95% CI 87 to 98). Overall, mortality from lung cancer was in excess (Obs 116, Exp 86.8, SMR 134, 95% CI 110 to 160). The excess was statistically significant. The paper provided tabulations of lung cancer mortality data for the four sub-cohorts by duration of employment (<10 and ≥10y) and by years from first exposed employment (0-19 and ≥20y). Consequently, confident interpretation of the results is difficult because of the problems of multiple testing and the fact that findings for individual "cells" tend to be based on small numbers. Regarding the first twenty years of observation for the "predominantly stainless steel welding group", findings were similar for shorter term and longer term stainless steel welders (<10y employment: Obs 5, Exp 5.9, SMR 85, 95% CI 28 to 198; ≥10y employment: Obs 2, Exp 2.9, SMR 69, 95% CI 8 to 251). Regarding the later periods of observation (≥ 20y), findings were also similar for shorter term and longer term stainless steel welders (<10y employment: Obs 2, Exp 1.2, SMR 161, 95% CI 20 to 583; ≥10y employment: Obs 11, Exp 6.2, SMR 176, 95% CI 88 to 315). Attempts were also made to estimate individual exposures to total fume, total chromium, hexavalent chromium and nickel; no association was found between any of these variables and lung cancer risks (details of analysis not supplied in paper).

The overall excess mortality from lung cancer in this study was not associated with duration of employment or with cumulative exposure to total fume, total chromium, hexavalent chromium or nickel.

Gerin et al. 1993

A further analysis of the IARC multicentre welding study (Simonato *et al.* 1991) was carried out by Gerin *et al.* (1993). The new analysis incorporated a *"welding process exposure matrix"* in an attempt to provide individual exposure estimates for total welding fumes, total chromium, chromium^{VI} and nickel. The exposure matrix was developed from a literature review and some company data. Analyses were based on small numbers but in the group of *"ever stainless steel welders"* no significant trends were obtained for lung cancer risks over four categories of chromium^{VI} exposure (<0.05, 0.05-, 0.5-, ≥1.5 mg.y.m^{-3}). SMRs for these four categories were 0, 130, 193 and 141, based on 0, 7, 9 and 5 deaths respectively. The P-value for trend for these data, calculated by the current authors, is 0.66. Similar analyses for three categories of nickel exposure (<0.1, 0.1-, ≥0.5 mg.y.m^{-3}) also provided no evidence of a trend for lung cancer risks (P = 0.85). Neither trend approaches levels of statistical significance. Both analyses were repeated for a sub-group of *"predominantly stainless steel welders"*. There were only 12 deaths in total available for these analyses, no significant trends were observed. The analyses reported by Gerin *et al.* represent more sophisticated analyses than those reported by Simonato *et al.* (1991). These analyses made use of many untestable assumptions and there was no convincing evidence of occupational cancer risks in stainless steel welders.

Moulin et al. 1993b

Mortality was studied among welders and non-welders from 13 factories in France (Moulin *et al.* 1993b). The study population comprised subjects with at least one year of employment. The welding cohort comprised 2721 males (34,311 person-years; average duration of employment of 19.5 yr). The welding cohort was sub-divided into five sub-cohorts according to a job exposure matrix (ever stainless steel welders; stainless steel welders predominantly exposed to Cr^{VI}; mild steel welders; shipyard welders; boilermakers and part-time welders). The stainless steel welders predominantly exposed to Cr^{VI} included predominantly MMA welders. The non-welding cohort comprised 6683 male manual workers (84,429 person-years; average duration of employment 21.9 yr). Mortality was studied from 1975 to 1988. Mortality rates were compared with national rates, adjusted for age, sex and calendar period.

Overall mortality for welders was similar to that expected (Observed 203, Expected 198.17, SMR 102). Lung cancer mortality in the welding cohort showed a non-significant excess (Observed 19, Expected 15.33, SMR 124), and in the non-welding cohort showed a slight deficit (Observed 44, Expected 46.72, SMR 94). The ratio of the SMRs was 1.32 (non-significant). Information on smoking habits, available for 87% of the total cohort, did not indicate that smoking differences were responsible for the excess lung cancer mortality in welders. For both cohorts, there was no association between lung cancer mortality and either duration of employment or time since first employment. Analysis of lung cancer mortality data according to welding activity showed no increase in the two stainless steel sub-cohorts: ever stainless steel welders (Observed 3, Expected 3.26, SMR 92); stainless steel welders predominantly exposed to Cr^{VI} (Observed 2, Expected 1.95, SMR 103). A non-significant excess of lung cancer mortality was found in the mild steel welders when a five-year lag period was incorporated into the analysis (Observed 9, Expected 5.65, SMR 159). In the shipyard welding sub-cohort, which allowed for possible exposure to asbestos, the SMR for lung cancer mortality was 91, and in the boilermakers and part-time welders sub-cohort was 114. In mild steel welders, the highest risk of lung cancer mortality occurred in those with more than 20 years of exposure (Observed 5, SMR 324) and those with more than 20 years of follow-up since first exposure (Observed 8, SMR 242). In both instances, the excess was statistically significant. Similar findings were not shown for either of the two stainless steel cohorts. The period of observation in the study, 1975-88, was fairly short and the number of lung cancer deaths occurring in the welding sub-cohorts was small.

This study did not show any increased risk of lung cancer in workers involved in welding stainless steel.

Danielsen et al. 1996

An investigation of cancer incidence among Norwegian boiler welders included a sub-cohort of stainless steel welders (Danielsen *et al.* 1996). The cohort comprised 2957 electrical welders registered from 1942 to 1981, followed through to 1992 (68,993 person-years). A sub-cohort of stainless steel welders was identified, comprising 606 welders, although it was noted that these subjects had also been mild steel welders prior to welding stainless steel. The welding methods used were MMA and, increasingly, gas-shielded methods such as TIG, but data regarding the relative

distribution of these methods within the total cohort or within the stainless steel welding sub-cohort were not available. Expected numbers of cancers were based on national rates adjusted for age and calendar year period. For the total cohort, cancer incidence (all sites) was similar to the expected incidence (Observed 269, Expected 264, SIR 102, 95% CI 90 to 115). The number of lung cancer cases in this cohort was slightly increased (Observed 50, Expected 37.5, SIR 133, 95% CI 99 to 176). For the stainless steel welding sub-cohort, overall cancer incidence and lung cancer incidence were close to expectation. The observed number of cancers (all sites) was 41 (Expected 41.2, SIR 100) and the observed number of lung cancer cases was 6 (Expected 5.8, SIR 103). Three cases of pleural mesothelioma occurred in total cohort and one case in the stainless steel welding sub-cohort; the possibility of asbestos exposure was noted.

This study did not demonstrate any increase either in overall cancer incidence or in lung cancer incidence among mixed stainless steel/mild steel welders.

Hansen et al. 1996

Stainless steel welders and stainless steel grinders were included in the study population in an investigation of cancer incidence among Danish metal workers (Hansen *et al.* 1996). The total cohort comprised 10,059 workers, employed for at least one year during 1964-1984, with follow-up to 1986. The cohort comprised welders (stainless steel, mild steel, and mixed stainless steel/mild steel), stainless steel grinders, and other non-welding metal workers. Expected numbers of cancers were based on national incidence rates, adjusted for sex, age and calendar period. Lung cancer incidence was significantly increased in those subjects "ever employed in a welding company" (Observed 105, Expected 69.95, SIR 151, 95% CI 124 to 183). This excess remained, albeit slightly reduced, in the "ever employed as a welder" sub-cohort (Observed 51, Expected 36.84, SIR 138, 95% CI 103 to 181). Lung cancer incidence in different welding groups showed a non-significant increase in the "stainless steel only welders" (Observed 5, Expected 2.10, SIR 238, 95% CI), was close to expectation in the "stainless steel ever welders" (Observed 23, Expected 19.39, SIR 119, 95% CI 75 to 179), and was significantly increased in the "mild steel only welders" (Observed 28, Expected 17.42, SIR 161, 95% CI 107 to 233). Lung cancer incidence was also significantly increased in the "non-welding metal workers" (Observed 50, Expected 30.23, SIR 165, 96% CI 122 to 258). Lung cancer incidence in the welding cohort showed no consistent relationship with either duration of employment or time since first exposure. [Findings from this study relating to stainless steel grinders are shown separately in the appropriate section of this document.]

This study provides evidence of increased risk of lung cancer in welders, although fails to clearly implicate or exclude either stainless steel welding or mild steel welding in the causation of these cancers. A sub-group of this cohort was included in the IARC study, reported previously (Simonato *et al.* 1991).

Moulin 1997

A meta-analysis involving 36 epidemiology studies of lung cancer risk in welders was conducted by Moulin (1997). The analysis involved case-referent studies and cohort studies. Combined relative risks were calculated according to the following welding categories: all or unspecified (19 studies); shipyard welding (14 studies); non-shipyard welding (7 studies); mild steel welding (4 studies); stainless steel welding (5 studies). When the combined relative risk of lung cancer was based on all studies within each category combined, for the "all or unspecified" welding category the relative risk was 138 (95% CI 129-148). The relative lung cancer risk in the stainless steel welding category, which was based on three case-referent studies and two cohort studies, was 150 (95% CI 110-205). This relative risk was the same as for the mild steel welding category (RR 150, 95% CI 118-191). Relative risks in the shipyard welding and non-shipyard welding categories, which were determined to control for asbestos as a confounding factor, were similar for both categories: shipyard welding (RR 130, 95% CI 114-148); non-shipyard welding (RR 135, 95% CI 115-158). Overall, the meta-analysis demonstrated an elevated relative risk of lung cancer in the 2all or unspecified" welding category, but no evidence to suggest that any increased risk is specifically associated with stainless steel welding.

Summary of epidemiological investigations

A number of investigations into cancer risks in workers engaged in the welding of stainless steel have been performed. These are summarised in Table 3.3. The lung cancer findings from many of these studies are based on small numbers and interpretation is also hindered by the absence of reliable exposure histories. Nevertheless, these studies provide no consistent pattern of excess lung cancer risk attributable specifically to stainless steel. In addition, a meta-analysis of lung cancer in welders (Moulin 1997) concluded that the elevated lung cancer rates in welders *"cannot be explained by hexavalent chromium and nickel exposures among stainless steel welders"*.

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Table 3.3. **Epidemiological studies of stainless steel welders**

Reference	Study population	Reference population	Cancers of respiratory tract		Cancers of other sites		Other information
			Site (no.)	SMR	Site (no.)	SMR	
Milatou-Smith *et al.* 1997	Males employed ≥5 years during 1950-1965; follow-up to 1992 (a) "high" exposure group; 233 SS welders (b) "low" exposure group: 208 males	National population	(a) Lungs (6) (b) Lungs (2)	164 ns 41 ns	(a) Rectum (2)	431 ns	Possible exposure to asbestos.
Becker *et al.* 1991	1221 welders from 25 German factories employed for ≥6 months during 1950-1970; follow-up to 1988; 31,122 person-years	National population	Lungs (14) Mesothelioma (3)	113 ns 961 s	Colon (3) Rectum (2) Stomach (3) Bladder (4)	33 ns 105 ns 57 ns 304 s	Asbestos exposure indicated.
Simonato *et al.* 1991	IARC multicentre study, 11,092 welders, incl. SS welders; 164,077 person-years. [Included data from Sjögren *et al.*1987, Becker *et al.* 1985, 1991, Moulin *et al.* 1993a. and Hansen *et al.* 1996]	National populations	Lungs - all welders (116) Mesothelioma (5)	134 s	Bladder (15) Colon (17) Rectum (7)	191 s 118 ns 68 ns	Lung cancer mortality for stainless steel welding sub-cohorts showed association with time since first exposure, but not with duration of exposure. Asbestos exposure indicated.

s: statistically significant; ns: not significant; SS: stainless steel; *a:* Standardised incidence ratio (SIR)

Table 3.3. **Epidemiological studies of stainless steel welders, cont'd**

Reference	Study population	Reference population	Cancers of respiratory tract		Cancers of other sites		Other information
			Site (no.)	SMR	Site (no.)	SMR	
Moulin *et al.* 1993b	2721 welders from 13 French factories employed for ≥1year; observation period 1975-1988; 34,311 person-years; including SS welders	National population	Lungs - all welders (19) Lungs - ever SS welders (3) Lungs - predominantly SS (2)	124 ns 92 ns 103 ns	Colon (1) Rectum (1)	33 ns 66 ns	No association between lung cancer mortality and duration of employment or time since first employment. Highest lung cancer risk in mild steel welders.
Danielsen *et al.* 1996	Norwegian welders employed during 1942-1981; follow-up to 1992 (a) whole cohort - 2957 males; 68,993 person-years (b) SS welding sub-cohort - 606 males	National population	(a) Lungs (50) Mesothelioma (3) (b) Lungs (6) Mesothelioma (1)	(a) 133[a] ns 273[a] ns (b) 103[a] ns 500[a] ns	(a) Colon (20) Rectum (19) (b) Colon (4) Rectum (4)	94[a] ns 131[a] ns 121[a] ns 182[a] ns	Possible asbestos exposure noted
Hansen *et al.* 1996	10,059 Danish metal workers employed for ≥1 year during 1964-1984; follow-up to 1986; included some SS welders (a) ever welders - 3916 males (b) SS only welders - 283 males	Danish males	(a) Lung (51) (b) Lung (5)	138[a] s 238[a] ns			Lung cancer incidence increased among 'mild steel only welders' and in "non-welding metal workers".

s: statistically significant ns: not significant; SS: stainless steel; *a:* Standardised incidence ratio (SIR)

Effects on reproduction

Animal data

No studies are available which have investigated the effect of fume from welding of stainless steel on either fertility or on developmental toxicity in animals.

Human data

Several studies are available, mostly conducted by one group of researchers, which have investigated the potential effects of welding of stainless steel on reproductive health.

Effects on fertility

Mortensen (1988) reported an investigation of semen samples from subjects attending a fertility clinic. A case-control design was used. The subjects were classified as cases if they had less than $20x10^6$ spermatozoa/ml semen, less than 50% of spermatozoa were motile, or if less than 50% had normal morphology. Subjects outside these categories were classified as controls. Subjects were sent a postal questionnaire asking details of work, alcohol intake, smoking, use of medicines and any previous illnesses. Of 3119 eligible subjects, 2517 returned a completed questionnaire. Subjects were classified as welders, other metal workers, other industrial workers, or unexposed according to their job in the 6 months before the semen sample had been collected. There was a significantly elevated odds ratio (OR 2.00, 95% CI 1.16-3.45) for welding to be reported as an occupation among the cases rather than the controls. A separate analysis of the data for stainless steel and non-stainless steel welders showed an increased odds ratio for stainless steel welding in particular (OR 2.34, 95% CI 0.95-5.73), although this was no longer statistically significant.

The lack of objective exposure data inevitably weakens the evidence for any effect suggested by this paper. Additionally, although all subjects came from the same clinic they are likely to have been aware of their diagnostic category as they were attending the clinic specifically for investigation; some recall bias is therefore a possibility. Further, the authors have pre-supposed a reversible effect apparent after six months exposure, and there is little evidence to be confident that this is an accurate model. Nonetheless, this paper provides some evidence that employment as a welder may have an affect on semen quality, although not necessarily employment as a welder of stainless steel.

Jelnes and Knudson (1988) reported a study of semen quality among a group of stainless steel welders and non-welding controls who were mostly from the same large workplace. Of 226 potentially eligible subjects, 145 (64%) participated (33 (15%) had undergone a previous vasectomy). In addition to the semen analysis, urine and blood samples were collected. Urine samples were analysed for chromium and nickel content, and assayed for mutagenic activity. Blood samples were analysed for chromium and nickel concentration, immunoglobulin G and total protein; lymphocytes were examined for some genotoxic end-points (chromosome aberrations, SCE and UDS). No detailed measures comparing indices of exposure were given in the results, although the authors stated that welders, and in particular MMA welders,

"are known, and in this study too are shown, to be heavily exposed to chromium, nickel, and dust". No significant differences in any parameter of semen quality were demonstrated between the stainless steel welders and non-welders, nor between the MMA welders and a reference group selected from outside the workplace and so completely unexposed to the relevant environmental contaminants. Results from the mutagenicity assays for the urine samples and the genotoxicity assays conducted in lymphocytes were not given.

Two papers published by the same author provide conflicting evidence about the effect of employment as a welder on semen quality (Bonde 1990a, 1990b). In the first cross-sectional study, semen samples were collected from 81 of 432 welders (46 mild steel welders and 35 stainless steel welders) and 54 of 240 non-welders from six workplaces (Bonde 1990a). The mild steel welders were noted to have a decreased sperm count, reduced numbers with normal morphology, an increased proportion of sperm with none or poor motility (but puzzlingly not a significant reduction in the proportion of motile sperm), and decreased sperm penetration compared with the non-welders. The stainless steel welders had a decreased sperm count, decreased semen volume, an increase in the number of immature forms, a decreased proportion of motile sperm, and an increased proportion of sperm with none or poor motility. However, no significant association was detected between years welding and any parameter of semen quality. No other measure of dose was used in analyses to try to determine a dose-response relationship.

Although considerable effort was put into collecting data on exposure, little use appears to have been made of these in the analyses, and they do not appear to have been used directly to try to determine a dose-response estimate. Additionally, a group of *"high alloy steel welders"* appear to have been included as stainless steel welders although their exposure may have been considerably different. The rather low participation is also possibly of concern. On balance, this paper provides some evidence to support an effect of welding on semen quality, although it is uncertain whether this effect is restricted to the welding of stainless steel, and also which agent(s) may be responsible. Further, the overall effect on fertility is unclear.

The second paper studied semen quality among a group of workers from three workplaces before and three, five and eight weeks after a three-week holiday period (Bonde 1990b). The subjects comprised 19 mild steel welders, 18 stainless steel welders and 16 referents (presumably from the same workplaces, although this is not stated). The stainless steel welders showed no significant difference in semen samples before and after the holiday. In contrast, the referents showed an increase in sperm concentration and the proportion of normal sperm forms at five and eight weeks after the holiday, suggesting that, during the holiday period, they may have been removed from some toxic exposure affecting normal sperm maturation. The author concluded, in contrast to the previous paper, that exposure to either mild or stainless steel welding fume did not have any significant effect on semen quality or that any effect was not reversible with three weeks of non-exposure. This conflicts with the previous paper where if anything a non-cumulative association between welding fume exposure and semen quality was demonstrated.

The number of subjects in this study was relatively small, therefore its power was somewhat limited. Further, no occupational hygiene results were presented; the only estimate of exposure used was the job title. The apparent effect in the reference group also remains unexplained. Overall, the findings of this study contribute little to our knowledge of the effect on fertility of welding stainless steel.

One further paper addressing semen quality in stainless steel and other welders has also been published (Bonde and Ernst 1992). Semen samples were collected from 30 stainless steel welders, 30 mild steel welders, and 47 non-welders who all worked at the same workplace. Participation represented 37.1% of welders and 36.7% of non-welders. Three semen samples were collected from each subject as well as a post-shift urine sample so that urinary chromium could be estimated. The urinary chromium measurements confirmed the greater average exposure to chromium of the stainless steel welders, with more having urinary chromium concentrations in the highest group, but no significant association was demonstrated between urinary chromium and any parameter of semen quality. As with the former study, the number of subjects in the investigation was relatively small and so its power was limited. Also, estimates of exposure were based on job title and urinary chromium concentration. Nevertheless, this study seems to provide reassurance that there is no major effect of exposure to fume from welding of stainless steel, and specifically although not exclusively its chromium content, on semen quality.

In addition to these studies on semen quality, a number of studies have also tried to study fertility among subjects working with stainless steel. Again these mostly refer to welders, and fertility is inevitably a complex parameter to quantify as a number of factors may contribute to fertility in addition to semen quality. Bonde (1990c) published a paper which attempted to quantify fertility in workers of six companies, two concerned mostly with mild steel welding and fabrication, two concerned with stainless steel welding, and two electrical companies. A postal questionnaire was sent to 432 welders and 240 non-welders, of whom 339 and 198 agreed to participate. From the questionnaire, subjects who had had difficulty with conception (defined as two or more years of unprotected intercourse without pregnancy) were identified. Analysis was then undertaken as a case-control study. Exposure to welding was categorised as: (1) welding within ±1 year of first difficulty with conception among the cases, with referents being assigned as welder or not according to employment at the same time; and (2) welding exposure of the cases was categorised at the same time as the controls had had their first or second child, categorisation to the welder group being assigned if either case or controls had welded within a two-year period before the birth.

The first analysis showed no significant association between welding and difficulty with conception. The second analysis suggested a significantly increased incidence of work as a welder among the cases rather than the controls (OR 2.02, 95% CI 1.02-4.00). Unfortunately no data on female partners were available for this study and may obviously have been relevant. In addition, the results for stainless steel welders were not presented separately, and so no conclusions can be reached about any effects that may be attributable specifically to stainless steel welding.

Bonde *et al.* (1990) investigated fertility among welders and other workers in 74 companies manufacturing stainless steel products and five large companies manufacturing mild steel products in Denmark. A total of 3,057 welders were included contributing 29,060 person-years of mild steel welding and 16,252 person-years of stainless steel welding. Additionally a group of stainless steel grinders were included, although they contributed only 890 person-years. Persons were classified as "at risk" for the years they were actively welding and for one year afterwards. Information on births was obtained from the birth register. Information on job history for subjects was collected using a questionnaire to participants.

There was a suggestion that the number of births was decreased during periods classified as "at risk" from welding, but this appeared to be in the mild steel welders; the stainless steel welders showed no effect of exposure on birth rate. No increased effect was seen with increasing duration of welding (i.e. no dose-response effect), and no effect on birth rate was seen in the grinders. The authors concluded that if there was any risk to fertility from welding this arose from welding mild steel rather than stainless steel. No risk from welding or grinding stainless steel was apparent.

The authors however have made some assumptions in interpreting the data, principally that any effect from welding is reversible and lasts for approximately one year after exposure ceases. If this is incorrect, there may have been some misclassification of the "at risk" periods. Also, while the authors state that the mean ages of the "at risk" and "not at risk" groups were approximately the same, it is not possible to be sure that the age distribution in the two populations was the same. If age distribution was different, this could affect fertility and birth rate in the two populations. In addition, exposure was classified only relatively crudely, based on a questionnaire with details of previous work supplemented by information from managers, supervisors, and long-term workers. It is likely that, as well as being relatively crude, there is possibly some misclassification of exposure resulting from this. No account of prior employment could be taken. The large number of subjects however should provide reasonable statistical power and some reassurance can be taken from these results.

Developmental toxicity

Bonde *et al.* (1992) investigated the incidence of congenital malformations, some adverse pregnancy outcomes and the incidence of childhood cancer in the children of a group of welders and other workers. The study population appears to have been based largely on the same subjects as in the previously reported study (Bonde *et al.* 1990). The study population comprised subjects who had worked for a minimum of one year between 1964 and 1986 at one of 79 companies in Denmark employing stainless steel welders and five large companies employing mild steel welders. The father was assigned to the welding group if he had worked as a welder for the year prior to the birth of a child. Workers were identified from pension fund records and the job title verified by managers, supervisors, and other long-term workers. For 10,059 workers, job title could be verified, and members of this group were sent a postal questionnaire asking for further details of work and other relevant factors. 85% returned a completed questionnaire. For 17,012 workers, job title could not be verified beyond the information in pension fund records. Responders to the

questionnaire had a total of 6,775 children, and the non-responders and unverified group had 16,489. Of these, 3,569 were included in the analysis of congenital malformations and adverse pregnancy outcomes, and 5020 in the analysis of childhood malignancy. Details of the birth weight, if pre-term, and of deaths within one year of birth were obtained from the birth registry, as were details of congenital malformations. Data on cancer incidence was taken from the cancer registry. Information was also taken from the birth registry about whether the parents of each child had had a previous spontaneous abortion, although the accuracy of these data could not be verified and the date of any previous spontaneous abortion was not available within these records.

No significant differences in any of the parameters of pregnancy outcome, the incidence of congenital malformations, or the incidence of childhood cancers were detected between the welders and non-welders, and in fact the mild steel welders recorded a significantly reduced incidence of congenital malformations, mostly cardiovascular malformations. The reason for this was not apparent. A group of stainless steel grinders was included within this study population but their results are not presented separately. This might suggest that no effect of their work on the outcome parameters used was detected, but it is impossible to be confident of this without the proper analyses being presented.

Reporting of a previous spontaneous abortion was more common among the stainless steel welders, but it is difficult to know how to interpret these results as the data used were not collected specifically to document previous spontaneous abortions within the different groups and so were inadequate in some respects. As the date of the spontaneous abortion was not available there is likely to be some misclassification of exposure. Also, the data on spontaneous abortions were based on a simple report by the parents at the time of the birth of their first child and may contain some errors.

Finally, it should be borne in mind that, because of the rarity of some congenital malformations, the power of this study to detect a difference in the incidence of all malformations would have been limited despite the inclusion of a large number of subjects.

In summary, the findings of this study show no evidence that the father’s employment as a welder has an effect on pregnancy outcome or the incidence of congenital malformations or childhood cancer. However, the data on spontaneous abortion contain a number of flaws and no conclusions can be drawn.

Fortunately, another study subsequently addressed the issue of work as a welder, particularly stainless steel welding, and the incidence of spontaneous abortion, overcoming some limitations in the previously published data (Hjollund and Bonde 1995). The authors used a previously identified cohort of mild steel and stainless steel welders who had worked for more than a year at one of a number of companies between 1964 and 1984, probably largely the same cohort as the previous study (Bonde *et al.* 1992). They were able to link the data on individual welders to data on their wives and their children through other national registers, and then to the incidence of spontaneous abortion by linking to the Danish in-patient Hospital Register. Subjects were classified as "at risk" for each pregnancy if they had carried

out stainless steel welding in the 38 weeks preceding each live birth or the nine weeks preceding each spontaneous abortion. A similar categorisation was used for classifying "at risk" from mild steel welding. A total of 2,520 pregnancies was identified comprising 1,810 live births, 440 induced abortions, 210 spontaneous abortions, and 60 "other" outcomes.

There was no significant increase in the incidence of spontaneous abortion in pregnancies categorised as "at risk" from stainless steel welding (OR 0.78, 95% CI 0.55-1.1). Additionally, there was no significant increase in the risk of induced abortion for pregnancies 2at risk" from stainless steel welding; this might have occured if there had been an increased incidence of abnormalities detected *in-utero*. No increased risk was seen for spontaneous or induced abortion for pregnancies classified "at risk" from mild steel welding. Overall, the findings of this study provide no evidence of an effect of stainless steel welding in males on the incidence of spontaneous abortion.

Summary of effects on reproduction

No studies are available which have investigated the effect of fume from welding of stainless steel on either fertility or on developmental toxicity in animals.

Several studies are available, mostly conducted by one group of researchers, which have investigated the effect of stainless steel welding in males on fertility and developmental toxicity. Summarising the information from these investigations is difficult as the studies have different designs and each has some flaws which make interpretation problematic. On balance, however, it appears that there is equivocal evidence of an effect of welding of stainless steel on semen quality, although the evidence for or against any effect is limited. Notably, there is little evidence to suggest that this effect has significant implications in terms of fertility. Investigations of developmental toxicity provide no evidence to suggest that welding of stainless steel as an occupation has an effect on developmental toxicity.

3.1.5 Hazard assessment

This section contains a summary of the health effects of fume from welding stainless steel, which have been reviewed in the preceding sections. Although welding fume itself would not be classified in the EU, the summarised data for each toxicological end-point are evaluated against the classification criteria contained in Annex VI of Directive 92/32/EEC, amending Directive 67/548/EEC, with a view to assessing the hazards against objective criteria so that a risk assessment can be conducted on fume from welding stainless steel.

Toxicokinetics

Deposition and lung clearance of fume particles from MMA/SS and MIG/SS welding have been investigated in animals following inhalation exposure and i.t. instillation. Slow clearance of particles and/or chromium have been demonstrated. However, as

high dose levels used in some of the studies may have interfered with normal lung clearance mechanisms, the relevance of these results to human occupational exposure is uncertain.

Information on the toxicokinetics of fume from the welding of stainless steel in humans come from studies of which have measured urinary chromium levels in mostly MMA/SS welders. The elevated urinary chromium levels reported provide evidence of chromium absorption as a result of exposure to welding fume and, in some studies, a suggestion that repeated exposure may lead to accumulation of chromium.

Acute toxicity

The acute toxicity of fume from the welding of stainless steel has been investigated in animals following exposure by inhalation and by i.t. instillation. Inhalation of high concentrations of fume (400 or 580 mg m^3 MIG/SS fume for 3 hours; 1000 mg/m^3 MMA/SS fume for 1 hour) induced inflammatory changes in the lungs of rats. A NOAEL was not identified from the available inhalation data. The results of i.t. instillation studies also provide evidence of inflammatory changes in the lungs following exposure of fume particulate in suspension. Instillation of a single dose of 0.5 to 5 mg of MMA/SS fume particulate into the trachea in rats was associated with changes in lung surface parameters which are early indicators of cell damage; however, the toxicological significance of these changes is uncertain.

There are no studies available which have investigated or reported acute toxicity in humans following exposure to fume from the welding of stainless steel.

Consideration against classification criteria: Animal data on the acute toxicity of welding fume, when evaluated against the Annex VI criteria, provide no basis for considering fume from stainless steel welding as having acute toxicity.

Irritation and sensitisation

No animal studies are available which have investigated the potential of fume from the welding of stainless steel to cause skin or eye irritation, or to cause skin sensitisation. Further, there are no studies available that have investigated or reported such effects in humans.

Available case-reports (reported in "*Effects of repeated exposure*" section) indicate that fume from welding of stainless steel can elicit asthmatic symptoms in some individuals. However, there is no evidence to suggest that fume from welding of stainless steel can **induce** respiratory hypersensitivity.

Consideration against classification criteria: There are no animal data and no data from studies in humans concerning the irritant or skin sensitising properties of fume from welding of stainless steel. However, there are also no reports of such effects in humans. It is therefore reasonable to consider that fume from welding stainless steel does not cause skin or eye irritation, and that it does not cause sensitisation by skin

contact. The available human data provide no evidence that fume from welding of stainless steel can induce respiratory sensitisation. Therefore, there is no basis for considering fume from stainless steel welding as causing sensitisation by inhalation.

Effects of repeated exposure

Only two animal inhalation studies are available which have investigated the effects of repeated exposure to fume from the welding of stainless steel. Neither study was conducted according to internationally agreed procedures for a repeat-dosing study. Both studies used only a single exposure level and this was much higher than exposure levels likely to be encountered in workplace. Results from the two studies showed that repeated exposure by inhalation to welding fume (MIG/SS or MMA/SS) at approximately 400 mg/m^3 (30 minutes/day for up to 14 days in total) resulted in pulmonary toxicity in rats. More marked effects appeared to be associated with MMA/SS fume. The data did not allow identification of a NOAEL for this effect.

Several studies are available which have investigated renal function in groups of workers which have included welders of stainless steel. A number of the studies suffer from deficiencies which do not allow the effect of welding of stainless steel on renal function to be fully explored. The most reliable data on this subject come from two studies of long-term MMA/SS welders, one of which presented air monitoring data; neither study demonstrated a significant effect on renal function. Overall, the available data provide little evidence of any appreciable risk of renal disease from the welding of stainless steel at exposure levels which are likely to occur in modern industry.

The respiratory effects of exposure to welding fume have been extensively studied and many of these studies include a proportion of stainless steel welders. However, there are relatively few studies where the data have been collected exclusively for stainless steel welders, or where the data for such welders can be distinguished from that of other welders. Overall, the available data suggest that welding of stainless steel may be associated with an increased risk of reporting respiratory symptoms, particularly cough and phlegm, but there is little convincing evidence of any increased risk of developing lung function abnormalities

The data on respiratory effects are similar to those observed in studies of mild steel welders, and significantly no study reviewed has yet demonstrated a difference in respiratory health between mild steel welders and stainless steel welders. One explanation for this could be that the effects on respiratory health are caused by factors associated with all types of steel welding fume, and are not specific to stainless or mild steel.

Consideration against classification criteria: There is no evidence, animal or human, to indicate that prolonged or repeated exposure to fume from welding stainless steel causes serious damage to health according to Annex VI classification criteria.

Mutagenicity

The genotoxicity of fume particulate from the welding of stainless steel has been investigated in a number of *in vitro* assays. The particulate fraction of MMA/SS fume, and to a lesser extent that of MIG/SS fume, has generated positive results in assays for the following end-points: reverse mutation in bacterial cells; induction of SCEs, cell transformation, chromosome aberrations in mammalian cells. Equivocal results have been obtained in mammalian cell mutagenicity assays. These results give an indication that certain constituents of the particulate fraction of welding fume from stainless steel, most likely water-soluble constituents, may possess mutagenic activity. Limited *in vivo* data provide some indication that water-soluble components of MMA/SS fume particulate are mutagenic to somatic cells *in vivo*.

Investigations of genetic damage in lymphocytes from stainless steel welders have generated generally inconclusive results.

Consideration against classification criteria: According to the Annex VI criteria, the available data relating to mutagenicity do not provide a basis for considering fume from welding stainless steel as mutagenic.

Carcinogenicity

No carcinogenicity bioassays have been conducted with fume from the welding of stainless steel involving exposure by inhalation. The available animal carcinogenicity data are limited to an i.t. instillation study and an intrabronchial implantation study, neither of these conforming to currently accepted protocols. The former study was poorly conducted and contributes no reliable data. The latter study, although deficient in several respects, provides no evidence that the MMA/SS welding fume tested is carcinogenic in animals.

A number of investigations into cancer risks in workers engaged in the welding of stainless steel have been performed. The lung cancer findings from many of these studies are based on small numbers and interpretation is also hindered by the absence of reliable exposure histories. Nevertheless, these studies provide no consistent pattern of excess lung cancer risk attributable to the welding of stainless steel. In addition, a meta-analysis of lung cancer in welders (Moulin 1997) concluded that the elevated lung cancer rates in welders *"cannot be explained by hexavalent chromium and nickel exposures among stainless steel welders"*.

Consideration against classification criteria: When data concerning the hazards associated with welding are evaluated against the current EU classification criteria, it is clear that welding, per se, may be associated with an increased risk of lung cancer. This position is reflected in the IARC placing of "welding fumes" in Group 2B: "possibly carcinogenic to humans" (IARC, 1990). However, as the welding of stainless steel gives rise to no further increase in the risk, the increased risk associated with the welding process appears not to be specific to the metals being welded.

Effects on reproduction

No studies are available which have investigated the effects of fume from welding of stainless steel on either fertility or on developmental toxicity in animals.

Several studies are available, mostly conducted by one group of researchers, which have investigated the effect of stainless steel welding in males on fertility and developmental toxicity. Summarising the information from these investigations is difficult as the studies have different designs and each has some flaws which make interpretation problematic. On balance, however, it appears that there is equivocal evidence of an effect of welding of stainless steel on semen quality, although the evidence for or against any effect is limited. Notably, there is little evidence to suggest that this effect has significant implications in terms of fertility. Investigations of developmental toxicity provide no evidence to suggest that welding of stainless steel as an occupation has an effect on developmental toxicity.

Consideration against classification criteria: The available human data do not, according to the Annex VI criteria, provide any basis for considering fume from welding stainless steel as toxic to reproduction.

3.1.6 Risk assessment

The most serious occupational health effect from all types of welding fumes is lung cancer. This and other potential effects on health may be controlled by the use of occupational exposure limits. In the UK, the occupational exposure limit for welding fume as a total particulate mixture is 5 mg/m^3. In addition, there are specific occupational exposure limits for individual components of welding fume that need to be adhered to. For example, hexavalent chromium has an occupational exposure limit in the UK of 0.05 mg/m^3. If exposure limits are maintained or, as in the case of hexavalent chromium, exposures are reduced as far below the exposure limit as is reasonably practicable, then risks are considered to be negligible. Exposure data which have been reported in the published literature (see *Section 3.1.2*) suggest that exposure levels are mostly controlled to these limits. However, some measurements have exceeded the limits. How relevant these published exposure data are to current workplace exposures remains uncertain.

3.1.7 Future research needs

Non-cancer respiratory effects of exposure to welding fume have been extensively studied. However, there are relatively few studies where the data have been collected exclusively for welders of stainless steel, or where the data for welders of stainless steel can be distinguished from that of other welders. Further, the available studies include limited exposure data. Investigation of respiratory health among welders of stainless steel therefore appears to warrant further study. Such an investigation should involve the collection of exposure data.

The issue of the potential carcinogenicity of fume from welding of stainless steel remains uncertain. Although fume from welding of stainless steel has been investigated in several genotoxicity assays, there remains some uncertainty as to whether the *in vitro* activity, which appears to be associated with water-soluble components of the fume particulate, could be expressed *in vivo*. It is suggested that further research concerning the carcinogenic potential of fume from welding of stainless steel focuses on this issue; this could involve conducting additional *in vivo* genotoxicity studies in animals or investigating specific genotoxic effects in groups of welders.

3.2 Grinding of stainless steel

3.2.1 General information

Grinding of stainless steel generates dust, the airborne part of which is made up of spinels. Spinels have a different chemical structure from that of stainless steel. They have a standard formula of $A(B)_2O_4$, where A and B represent different metal ions which occupy specific sites in the crystal structure. Examples of spinels which may arise from stainless steel include nickel-chrome-iron spinels and nickel-iron spinels. Available exposure data, summarised in *Table 3.4*, indicates that a proportion of the airborne grinding dust particles are in the respirable size range.

3.2.2 Information on exposure

As grinding dusts from stainless steel are mostly inhalable, grinding operations present the potential for inhalation exposure in the occupational setting. Grinding operations frequently accompany other stainless steel processes, such as welding, and may also take place during the final stages of stainless steel manufacture. Consequently, workers engaged in grinding operations may also be exposed to fume from welding of stainless steel or other processes.

Exposure data for stainless steel grinding have been reported in four published studies. A summary of the data is presented in *Table 3.4*.

Table 3.4 **Grinding of stainless steel - summary of exposure data in published literature**

Reference	Process	Work piece material and main alloying elements	Abrasive material	Sampling strategy[a]	Analytical method(s)[b]	Dust concentration (mg/m^3)	Particle size	Elemental composition of dust (%)	Additional information
Koponen *et al.* 1981a	Surface grinding of slabs and plates	Austenic SS AISI 304 C (0.2%) Cr (18%) Ni (9%)	Aluminium oxide	P + S (15) 2-hr sampling period	Elemental analysis: OES Cr/Ni: AAS Cr^{VI}:colorimetric	5.2 ± 3.2 (mean)[c]	N/R	Fe 17-51 Cr 1.6-13[d] Ni 1.8-6[e] Mo 0.06-0.08 Mn 0.5-1 Mg 0.02-2.5 Al 5-30 Si 0.5-10 Ca 1-3.5 Na 0.1-0.5	Water soluble and acid soluble Cr and Ni were determined for six samples - see footnotes d and e.
Koponen *et al.* 1981b	Surface grinding of process containers (disc grinding and polishing)	Austenitic SS AISI 304 C (0.2%) Cr (18%) Ni (9%)	Aluminium oxide	P (9) + S	N/R	1-11 (range)	Approx. 45% of dust <7µm diameter	Fe 21-51 Cr 3.5-13 Ni 2.5-6 Mo 0.05-0.08 Mn 0.5-1.3 Al >30 Si 0.5-3	50% particles reported to come from workpiece; remainder from abrasives/ polishing materials

Table 3.4 **Grinding of stainless steel - summary of exposure data in published literature, cont'd**

Reference	Process	Work piece material and main alloying elements	Abrasive material	Sampling strategy[a]	Analytical method(s)[b]	Dust concentration (mg/m^3)	Particle size	Elemental composition of dust (%)	Additional information
Koponen *et al.* 1981b	Surface grinding (disc grinding)	High alloyed steel, AISI 316 C (0.08%) Cr (17%) Ni (3.1%) Mo (3.1%)	Aluminium oxide	N/R	N/R	N/R	Approx. 45% of dust <7µm diameter	Fe 30-50 Cr 7-18[f] Ni 3.5-5.2[f] Mo 1.7-1.9 Mn 0.6-1.0 Al 1.0 Si 0.7	Water soluble and acid soluble Cr and Ni were determined - see footnote f.
Koponen *et al.* 1981b	Heavy disc grinding of slabs	AISI 304 C (0.2%) Cr (18%) Ni (9%)	Aluminium oxide/silicon carbide mix	N/R	N/R	N/R	Approx. 60% of dust <7µm diameter	Fe 17-18 Cr 1.6-4.1[g] Ni 1.5-1.8[g] Mo 0.08 Mn 0.5-1.0 Al 5 Si 10	Water soluble and acid soluble Cr and Ni were determined - see footnote g.
Karlsen *et al.* 1992	Ginding of welded part of object (semi-laboratory conditions)	Unspecified SS	N/R	P + S Filters 0.8µm pore size; PVC (Cr^{VI}); cellulose acetate (Ni, Fe, Cr, Mn)	AAS (Cr, Ni, Fe, Mn); colorimetric (Cr^{VI})	Personal samples: 9.7 (mean)	N/R	Personal: Ni 0.43 Fe 5.4 Cr 0.29 Mn 0.16 Static: Ni 0.69 Fe 5.5 Cr 0.31 Mn 0.36	Conc'n ($\mu g/m^3$) Personal: Ni 47 Fe 600 Cr 31 Sol. Cr^{VI} <LOD Mn 17

Reference	Process	Work piece material and main alloying elements	Abrasive material	Sampling strategy[a]	Analytical method(s)[b]	Dust concentration (mg/m^3)	Particle size	Elemental composition of dust (%)	Additional information
Karlsen *et al.* 1994	Grinding and polishing of sinks	Unspecified SS	N/R	P (34), S (10) Collected over whole shift Filters 0.8µm pore size; PVC (Cr^{VI}); cellulose acetate (Ni, Fe, Cr, Mn)	AAS; colorimetric method for Cr^{VI}	Personal samples: 11 (range 3.1-51) Static samples: 2 (range 0.4-3.0)	N/R	Conc'n ($\mu g/m^3$) Personal samples (34): Ni 250 (79-650) Fe 2300 (780-6400) Cr 1100 (270-4300) Cr^{VI} <LOD (<LOD-0.9) Mn 46 (11-120) Static samples (10): Ni 35 (5.7-75) Fe 320 (73-670) Cr 95 (20-250) Cr^{VI} <LOD (<LOD-0.4) Mn 6.3 (<LOD-11)	

Footnotes to Table 3.4:

a. P - personal samples; S - static samples

b. OES - optical emission spectroscopy; AAS - atomic absorption spectroscopy

N/R - nothing reported

c. It is uncertain whether this value was determined from personal samples, static samples, or both types of samples.

d. Six samples were used for determination of total Cr (3.5% of total dust), acid-soluble Cr (1.6% of total dust) and water-soluble Cr (<0.02% of total dust); it is uncertain whether these samples were personal or static.

e. The same six samples were used for determination of total Ni (1.8% of total dust), acid-soluble Ni (1.6% of total dust) and water-soluble Ni (<0.02% of total dust)

f. Water soluble Cr <0.02% of total dust; acid soluble Cr 6.7%; water soluble Ni 0.04%; acid soluble Ni 5.2%

g. Water soluble Cr <0.02% of total dust; acid soluble Cr 1.6%; water soluble Ni <0.02%; acid soluble Ni 1.6%

3.2.3 Toxicokinetics

Animal data

The only data available relating to the toxicokinetics of stainless steel grinding dust are from an i.t. instillation study.

Nickel clearance was investigated in an i.t.-dosing carcinogencity study in hamsters using 18/10 Cr/Ni steel (Muhle *et al*. 1988). The Cr-Ni steel dust was given to animals as 12 instillations, administered at 14-day intervals. Two dose levels were used (3 or 9 mg dust/instillation; cumulative dose 36 mg or 108 mg, respectively). Nickel content of lung tissue was determined at different intervals during the treatment period (4 animals from each group at each of three different time intervals). The half-time of nickel clearance was estimated to be 481 days for animals treated with 12 x 3 mg instillations and 415 days for animals treated with 12 x 9 mg instillations.

Human data

No data are available regarding the toxicokinetics of stainless steel grinding dust in humans.

3.2.4 Toxicity

Acute toxicity

Information on the acute toxicity of grinding dust from stainless steel comes from a single animal study. No studies are available which have investigated or reported such effects in humans.

The effect of a single dose of 18/10 Cr-Ni stainless steel grinding dust was investigated in hamsters (Muhle *et al.* 1988). The test was conducted largely according to internationally agreed guidelines, although it used a different route of exposure. The grinding dust was generated under workplace conditions and collected using an impact separator to separate the dust into coarse and fine fractions. Only the fine fraction was used in this experiment. 90% of these dust particles had an aerodynamic diameter of less than 6 µm[16]. The elemental composition of the fine dust was 59.2% Fe, 13.9% Cr, 6.8% Ni, 1.0% Mn, 2.1% Al, 3.9% C; other elements were each <1.0%. Crystallographic analysis showed that the composition of the dust was not identical with the alloy from which it was derived: the dust was composed of a phase mixture of austenite and a cubic spinel $(FeCrNi)_3O_4$. Energy dispersive x-ray analysis indicated that pure forms of neither free nickel nor free nickel oxide could be detected. Four dose levels were used (1.25, 2.5, 5 and 10 mg dust/animal), each treatment group containing five females and five males. Animals were observed for 14 days following a single i.t instillation of the test material suspended in saline.

[16] This value was separately reported as 6.04 µm and 6.4 µm.

No deaths occurred in any treatment group. The LD_{50} value was therefore reported as >10 mg/animal (>112 mg/kg). No information was presented regarding any non-lethal effects. This study showed that i.t instillation of a single dose of stainless steel grinding dust at up to 10 mg/animal was non-lethal in hamsters.

Summary of acute toxicity

Data on the acute toxicity of grinding dust from stainless steel come from a single animal study which used i.t. instillation. This study showed that a single i.t. instillation of grinding dust in suspension at up to 10 mg/animal (112 mg/kg) was non-lethal in hamsters. No animal acute toxicity studies have been conducted using inhalation exposure. Further, no data are available regarding the acute toxicity of grinding dust from stainless steel in humans.

Skin and eye irritation

No animal studies are available which have investigated the irritant properties of grinding dust from stainless steel to the skin or eyes. Further, no human studies are available which have investigated or reported such effects.

Sensitisation

There are no studies available which have investigated the potential of stainless steel grinding dust to induce skin sensitisation in animals. Information on sensitisation in humans is limited to the following single case-report.

Estlander *et al.* (1993) reported one subject with asthmatic symptoms and urticaria which appeared to be associated with employment as a grinder. The subject performed daily grinding of metal castings, reported to contain 9% nickel and 17% chromium. Although it was not specifically stated that the castings were made of stainless steel, this is presumed. Asthmatic symptoms (dyspnoea and cough) were accompanied by skin effects (urticaria and contact dermatitis), and both effects subsided during periods away from work. The subject gave a positive, but late, response to nickel sulphate in bronchial challenge tests. Positive reactions also occurred with nickel in skin patch tests, skin-prick tests and nasal provocation tests. An IgE-mediated allergy to nickel was demonstrated in a radioallergoimmunosorbent (RAST) test. When chromium was used as the challenge substance in these tests, the subject gave a negative response in all cases. The subject had previous sensitivity to nickel.

This case-report provides some evidence that asthmatic symptoms and allergic skin reactions were evoked in a nickel-sensitised subject by exposure during the grinding of (presumably) stainless steel. However, the lack of detail presented on workplace exposure precludes reaching more firm conclusions.

Effects of repeated exposure

Animal data

Animal data relating to the effect of repeated or prolonged exposure to stainless steel grinding dust are based on an i.t. instillation study. No repeat-dosing studies have been conducted involving inhalation exposure.

The sub-chronic toxicity of 18/10 Cr-Ni stainless steel grinding dust was investigated in hamsters in an i.t. instillation study (Muhle *et al.* 1988). Information relating to the chemical and physical properties of the grinding dust has been reported earlier in this section. A suspension of the dust in saline was administered to animals by i.t. instillation at 14-day intervals for a total of 12 treatments. Three dose levels were used: 1, 3 or 9 mg dust/instillation (cumulative dose 12, 36 or 108 mg dust/animal, respectively). Each treatment and control group contained 10 females and 10 males. Only survival data and body weight gain were reported. One female died in the 3 mg/dose group and three males died in the 9 mg/dose group; all fatalities occurred during the first few treatments and may have been caused by obstruction of the airways. A reduction in bodyweight gain compared to controls occurred in females at all doses and in males at the highest dose.

This study appears to have been conducted as a range-finding study for a carcinogenicity test (reported later in this section) and was therefore not conducted according to recommended protocols for a repeat-dosing study. A non-standard exposure route and dosing regime were used, and there appears to have been no investigation of effects other than survival or bodyweight. Consequently, apart from the reported reduction in bodyweight, for which a NOAEL was not identified, this study provides limited information on the effects of repeated exposure to grinding dust.

The sub-chronic toxicity of a *"ferrite chromium-steel"* grinding dust was investigated as part of the previous study (Muhle *et al.* 1988). As with the Cr-Ni stainless steel dust, only the fine dust fraction was used in the experiment. 90% of the dust particles had an aerodynamic diameter of less than 4.5 µm. The elemental composition of the fine dust was 68% Fe, 12.9% Cr, 0.5% Ni, 2.0% Al, 3.4% C; other constituent elements were each <1.0%. A suspension of the dust in saline was administered to hamsters (10 females and 10 males) by i.t. instillation at 14-day intervals for a total of 12 treatments (9 mg dust/dose; cumulative dose 108 mg/animal). Only data relating to survival and body weight gain were reported. No deaths occurred in treated animals and the only sign of toxicity reported was slightly reduced weight gain. As with the first part of the experiment, this study appears to have been conducted as a range-finding study and did not conform to standard procedures for a repeat-dosing study. The limited conclusions that may be drawn from this part of the study are that repeated i.t. instillation of a fairly high dose of *"ferrite chromium-steel"* grinding dust (9 mg x 12 doses) was non-lethal to hamsters and had a slightly reducing effect on weight gain.

Human data

No studies are available which have investigated the effect of repeated exposure to grinding dust from stainless steel in humans.

Summary of effects of repeated exposure

Animal data on the effect of repeated exposure to grinding dust from stainless steel are somewhat limited, coming from an i.t. instillation study which appears to have been conducted as a range-finding study for a carcinogenicity bioassay. Apart from reported effects on bodyweight, which occurred with repeated instillation of 1, 3 and 9 mg dust (total of 12 doses administered at 14-day intervals), the study provides no information about other effects. The available animal data do not allow identification of a NOAEL.

There are no data on the effect of repeated exposure to grinding dust in humans.

Mutagenicity

No studies are available which have investigated the mutagenicity of stainless steel grinding dust.

Carcinogenicity

Animal data

The carcinogenicity of stainless steel grinding dust has been investigated in i.t. instillation studies and also in a single i.p. dosing study. No studies have been conducted involving inhalation exposure, the most relevant route of exposure for humans.

The carcinogenicity of stainless steel grinding dusts was investigated in Syrian golden hamsters following repeated i.t. administration (Muhle *et al.* 1988, 1992). Two grades of stainless steel were used in the study, an austenitic stainless steel (18/10 Cr-Ni steel) and a chromium ferritic steel[17]. With both stainless steels, the fine dust was suspended in saline and administered to animals by i.t. instillation. The animals received a total of 12 instillations, administered at 14-day intervals. The 18/10 Cr-Ni steel dust was given at two dose levels (3 or 9 mg dust/instillation; cumulative dose 36 mg or 108 mg, respectively). The chromium ferritic steel dust was given at one dose level only (9 mg dust/instillation; cumulative dose 108 mg). Vehicle-only

[17] Dusts were generated under workplace conditions, collected from the vicinity of the grinding wheel, and separated into fine and coarse fractions by means of an impact separator. The fine dust fractions were used in this experiment. 18/10 Cr-Ni steel: 90% of fine dust particles had an aerodynamic diameter <6 µm (this value was separately reported as 6.04 µm and 6.4 µm); elemental composition: 59.2% Fe, 13.9% Cr, 6.8% Ni, 1.0% Mn, 2.1% Al, 3.9% C; the dust was composed of a phase mixture of austenite and cubic spinel $(FeCrNi)_3O_4$. Energy dispersive x-ray analysis of the dust indicated the absence of both nickel and nickel oxide in pure form. Chromium ferritic steel: 90% of fine dust particles had an aerodynamic diameter <4.5 µm; elemental composition: 68% Fe, 12.9% Cr, 0.5% Ni, 2.0% Al, 3.4% C; the dust consisted of a phase mixture of ferrite and a cubic mineral $(FeCrAl)_3O_4$.

animals served as controls. The duration of the treatment period was 170 days; animals were observed for a total of 26 months (females) or 30 months (males). Treatment and control groups each contained 30 males and 30 females. Animals which died during the early part of the treatment period were replaced (18/10 Cr-Ni steel: 2 males and 2 females in the low dose group, 5 males and 2 females in the high dose group; chromium ferritic steel: 10 males and 2 females). These early fatalities were suggested as being attributed to obstruction of airways by agglomerated test material; increased homogenising of the suspension was subsequently employed in the study. Histopathological examination of lungs from early decedents revealed acute haemorrhage, bronchial pneumonia and oedema. At eighteen months, survival of animals in the 18/10 Cr-Ni steel treatment groups was reported to be in the range 70-85%, and in the chromium ferritic steel group approximately 65% (~85% survival in controls). Bodyweights of treated animals during the course of the study were similar to controls, with the exception of the high dose 18/10 Cr-Ni steel females. In this group, from approximately 20 months onwards bodyweights were depressed compared to controls, although never by more than 10%. At the end of the observation period, lungs were taken for histopathological examination. No lung tumours occurred in treated or control animals. There was evidence of particle deposition in the lungs of most treated animals. This deposition was accompanied by granulomatous changes and bronchio-alveolar hyperplasia, mostly described as very slight or slight. The granulomatous changes occurred less frequently in the low dose 18/10 Cr-Ni group than the other two treatment groups, and was absent from control animals. The incidence of hyperplastic changes in control animals was 5/30 (males) and 1/30 (females). Squamous metaplasia occurred in one animal in each of the 18/10 Cr-Ni steel groups, although the incidence of this lesion showed no increase over the vehicle-only controls. Histopathological examination of non-pulmonary tissues was not conducted.

This study deviated from the standard EC and OECD protocols for carcinogenicity testing in several respects; the study used fewer than the recommended number of animals, too few dose levels, a different route of exposure and a non-standard dosing regime. It is also uncertain whether any animals were treated with the maximum tolerated dose (MTD) of either stainless steel. It is, however, recognised that administration of an MTD might be difficult to achieve with such materials. Further, the occurrence of fatalities early in the study made interpretation of survival data difficult. Given these limitations, the study nevertheless provides some reassurance that fine grinding dust from the two stainless steels investigated, 18/10 Cr-Ni stainless steel and chromium ferritic steel, failed to induce lung tumours in hamsters following repeated i.t. instillation.

Carcinogenicity of grinding dust from an austenitic stainless steel was investigated in another i.t. dosing study in Syrian golden hamsters (Ivankovic *et al.* 1988). The test material was generated from stainless steel by application of a water jet to molten alloy, followed by milling. Therefore, although referred to as *"stainless steel powder"* in the report, the test material constitutes grinding dust; this is supported by particle size data (particle diameter ranged from 0.5 to 2.5 µm). The elemental composition of the alloy included 26.8% as nickel, 16.2% as chromium, 39.2% as iron, and <0.04% as cobalt. The dust was administered to animals in suspension in saline (0.2 ml per dose). Animals received a single instillation containing 10, 20 or 40

mg of dust per animal. In another treatment group, animals received four separate instillations at six-monthly intervals, each containing 20 mg/animal. Each of the four treatment groups contained at least 50 females and 50 males. Two controls groups were used: one group of untreated animals and a second group of saline-treated animals. Animals were observed until spontaneous death occurred or they became moribund and were killed.

Bodyweight and survival of treated animals was similar to that of controls. Tumour incidence was examined and in all four treatment groups showed no increase over the control incidence. This study deviates from EC and OECD guidelines in that a different route of exposure was employed, and a non-standard dosing regime was used. Further, similar to the previously reported study, it is uncertain whether the MTD was used or was even achievable. With these limitations in mind, this study provides no evidence for the carcinogenicity of the grinding dust from this austenitic stainless steel.

The carcinogenicity of grinding dust from stainless steel, administered by i.p. injection, was investigated in female Wistar rats (Pott *et al.* 1992, 1991). The stainless steel used in the experiment was "nickel alloy 29"; this was milled to give a particle diameter of <10µm. The elemental composition of the alloy before milling included: 32% nickel, 21% chromium, 0.8% manganese, 55% iron; after milling the nickel content was 29.2% (photometric analysis) or 28.0% (analysis by atomic absorption spectrometry). The alloy dust was suspended in saline and homogenised for 1-5 min. The suspension was administered to animals either as a single 1 ml injection containing 50 mg nickel, or as two 1 ml injections each containing 50 mg nickel. Based on the information provided, it is uncertain whether the two injections were administered during a one- or two-week period. Vehicle-only animals served as controls. Animals were killed 30 months after the first injection.

Mean body weight of treated animals, one year into the study, and overall survival were similar to that of controls. Tumour incidence among animals surviving at least 16 weeks after the first injection was reported. In the group treated with a single injection (1 x 50 mg Ni), there were 2/33 animals with abdominal tumours (one mesothelioma and one sarcoma). In the group treated with two injections (2 x 50 mg Ni), there was 1/36 abdominal tumour (one sarcoma). In both groups, tumour incidence showed no significant increase over the control incidence. No information was presented regarding other signs of toxicity in this study. With regard to the fate of the administered alloy dust, it was reported that the dust (estimated as *"the whole dose administered"*) was still visible in the peritoneal area of treated animals at the end of the study. Whilst this study showed no increased cancer incidence in treated animals, major departures from standard protocols for carcinogenicity testing prevent much weight being attached to the study.

Summary of animal carcinogenicity data

The carcinogenicity of grinding dust from stainless steel has been investigated in animals in i.t dosing studies. Although none of the studies were conducted according to currently recognised procedures for carcinogenicity testing, the results of these studies provide some reassurance that the stainless steels tested (two austenitic grades

and one ferritic grade) failed to induce lung tumours in animals. An i.p. dosing study which was conducted contributes little further information to this subject. No animal data are available regarding the carcinogenicity of grinding dust following inhalation exposure.

Human data

Svensson et al. 1989; Jakobsson et al. 1997

A mortality study was carried out for 1164 male workers from a single Swedish plant engaged in the manufacture of stainless steel sinks and pans (Svensson *et al.* 1989). All study subjects had either ground, finished, brushed or polished stainless steel; they were first employed in the period 1927-81 and had a minimum period of employment of three months. Mortality was investigated for the period 1951-83 and cancer morbidity was investigated for the period 1958-83. Observed numbers of deaths and incident cancers were compared with expectations based on relevant sex-, age- and calendar year-specific rates for the local county population.

The stainless steel in use at the factory comprised 18% nickel, 8% chromium; the remaining 74% was iron. Exposure measurements carried out in the period 1975-80 showed dust levels associated with grinding to be 0.7-7.3 mg/m^3 (3-10% chromium, 2-5% nickel) whereas those levels associated with brushing and polishing were 1.6-15.7 mg/m^3 (1% chromium, 0.5% nickel). The authors noted that dust levels were probably much higher before 1950.

The authors supplied cause-specific findings for the overall cohort and for employees with five or more years exposed employment. In the latter instance, observed and expected numbers in the twenty years which followed first employment were ignored. For the total cohort, overall mortality was close to expectation (Observed 194, Expected 214.2, SMR 91, 95% CI 78 to 104). A similar SMR was obtained for lung cancer (Observed 9, Expected 9.8, SMR 92, 95% CI 44 to 179). For stomach cancer there were five observed deaths and an expectation of 7.7 deaths. There were non-significant excesses for cancer of the colon (Observed 6, Expected 3.5, SMR 170, 95% CI 67 to 384) and cancer of the rectum (Observed 5, Expected 2.6, SMR 193, 95% CI 69 to 471). For employees with at least five years of exposed employment, overall mortality was somewhat reduced (Observed 63, Expected 79.9, SMR 79, 95% CI 61 to 101), as was mortality from lung cancer (Observed 2, Expected 3.7, SMR 55, 95% CI 9 to 214). This was not the case for either cancer of the colon (Observed 3, Expected 1.4, SMR 216, 95% CI 52 to 673) or cancer of the rectum (Observed 3, Expected 1.0, SMR 300, 95% CI 72 to 933), although these differences did not approach levels of statistical significance.

The above analyses were repeated for cancer incidence data. For the total cohort, overall cancer incidence was close to expectation (Observed 84, Expected 81.9, SIR 103, 95% CI 82 to 127). There was a non-significant deficit for cancers of the respiratory system (Observed 7, Expected 12.5, SMR 56, 95% CI 24 to 120). For stomach cancer there were four observed deaths and an expectation of 7.4 cases. There was a significant excess for cancer of the colon (Observed 11, Expected 5.7, SMR 194, 95% CI 101 to 356) and a non-significant excess for cancer of the rectum

(Observed 8, Expected 4.7, SMR 170, 95% CI 77 to 346). For employees with at least five years of exposed employment, the standardised incidence ratio for cancers of the respiratory system was somewhat reduced (Observed 0, Expected 4.7, SIR 0, 95% CI 0 to 21). This was not the case for either cancer of the colon (Observed 6, Expected 2.1, SMR 285, 95% CI 112 to 644) or cancer of the rectum (Observed 5, Expected 1.8, SMR 281, 95% CI 100 to 686).

The above study was updated by Jakobsson *et al* (1997). The cohort was re-defined and the minimum period of employment for inclusion in the study was increased from three to twelve months. As a consequence the size of the cohort was reduced from 1,164 study subjects to 727 study subjects. The period of observation began 15 years after the start of employment and mortality was investigated to the end of 1993 (ten additional years of follow-up); cancer incidence was investigated to the end of 1992 (nine additional years of follow-up). The mortality experience of the cohort was compared with that of the local county populations, other cohorts of industrial workers and fishermen. Overall, cancer incidence among workers engaged in the manufacture of stainless steel sinks and pans (grinders, brushers/polishers, welders, finishers) was below expectation (county population comparisons) for cancer of the stomach (Observed 8, Expected 9.6, SIR 83, 95% CI 36 to 164) and for cancer of the lung (Observed 7, Expected 12.4, SIR 56, 95% CI 23 to 116). There were non-significant excesses for cancer of the colon (Observed 12, Expected 8.3, SIR 145, 95% CI 75 to 253) and for cancer of the rectum (Observed 9, Expected 6.7, SIR 134, 95% CI 61 to 255). The authors note that the "limited size of the cohort.. precludes a more detailed exposure-response analysis". Consequently, their conclusion that "historical working conditions conveyed an increased risk for cancer in the sigmoid part of the colon" might be better described as a hypothesis suitable for testing in an independent study.

These findings do not indicate that occupational lung cancers have occurred in this cohort.

Hansen et al. 1996

Stainless steel welders and stainless steel grinders were included in the study population in an investigation of cancer incidence among Danish metal workers (Hansen *et al.* 1996). The total cohort comprised 10,059 workers, employed for at least one year during 1964-1984, with follow-up to 1986. The cohort comprised welders (stainless steel, mild steel, and mixed stainless steel/mild steel), stainless steel grinders, and other non-welding metal workers. Expected numbers of cancers were based on national incidence rates, adjusted for sex, age and calendar period. Analysis of data for the sub-cohort of 521 stainless steel grinders showed non-significant increases for overall cancer incidence (Observed 37, Expected 29.72, SIR 124, 95% CI 87 to 171), for cancers of the respiratory system (Observed 11, Expected 7.02, SIR 157, 95% CI 78 to 281), and for cancers of the male genital organs (Observed 7, expected 2.90, SIR 241, 95% CI 97 to 497). Findings were not shown separately for cancers of the colon and rectum, but the incidence of all cancers of the digestive system was close to expectation (Observed 7, Expected 6.91, SIR 101, 95% CI 41 to 208). [Findings from this study relating to stainless steel welders are shown separately in the appropriate section of this document.]

These findings do not indicate that occupational lung cancers have occurred in this cohort.

Summary of epidemiological investigations

Taken together, the two available studies of cancer risks in grinders of stainless steel do not indicate that such work leads to excess risks of lung cancer. These two studies are summarised in Table 3.5. The Danish study reported cancer findings under broad headings rather than for individual cancer sites. Nevertheless, it provided no support for the hypothesis of an effect on cancers of the colon and rectum suggested by the Swedish study.

Effects on reproduction

No animal data were available regarding the effects on reproduction of exposure to grinding dust from stainless steel. Human data are limited to the few grinders included in the study of Bonde *et al.* (1990) reported on page 86, for whom no effect on birth rate was recorded.

Table 3.5 **Epidemiological studies of stainless steel grinding**

Reference	Study population	Reference population	Cancers of respiratory tract		Cancers of other sites		Other information
			Site (no.)	SIR	Site (no.)	SIR	
Jacobsson, 1997	727 males, manufacture of stainless steel sinks and pans, employed for ≥ 12 months during 1927-81, follow-up to 1993	Local county population	Lung (7)	56 *ns*	Colon (12) Rectum (9)	145 *ns* 134 *ns*	Authors found similar non-significant excess for cancer of the rectum found in studies of other industrial workers.
Hansen *et al.* 1996	521 male SS grinders, included in cohort of 10,059 Danish metal workers employed for 1yr during 1964-1984; follow-up to 1986	Danish males	Resp. system (11)	157[a] ns	Dig. system (7) Genitals (7)	101[a] ns 241[a] ns	

ns. not significant; a. Standardised incidence ratio (SIR)

3.2.5 Hazard assessment

This section contains a summary of the health effects of dust from grinding stainless steel, which have been reviewed in the preceding sections. The summarised data for each toxicological end-point are evaluated against the classification criteria contained in Annex VI of Directive 92/32/EEC, amending Directive 67/548/EEC, with a view to assessing the hazards against objective criteria so that a risk assessment can be conducted on dust from grinding stainless steel.

Acute toxicity

Data on the acute toxicity of grinding dust from stainless steel come from a single animal study which used i.t. instillation. This study showed that a single i.t. instillation of grinding dust in suspension at up to 10 mg/animal (112 mg/kg) was non-lethal in hamsters. No animal acute toxicity studies have been conducted using inhalation exposure. Further, no data are available regarding the acute toxicity of grinding dust from stainless steel in humans.

Consideration against classification criteria: The available animal data provide no basis for considering dust from grinding stainless steel as causing acute toxicity.

Skin and eye irritation

There are no animal or human data available regarding the irritant properties of grinding dust from stainless steel to the skin or eyes.

Consideration against classification criteria: In the absence of data, it is not possible to consider grinding dusts against the classification criteria.

Effects of repeated exposure

Animal data on the effects of repeat exposure to grinding dust from stainless steel are somewhat limited, coming from an i.t. instillation study which appears to have been conducted as a range-finding study for a carcinogenicity bioassay. Apart from reported effects on bodyweight gain, which occurred with repeated instillation of 1, 3 or 9 mg dust (total of 12 doses administered at 14-day intervals), the study provides no information about other effects. The available animal data do not allow identification of a NOAEL.

No data are available concerning the effect of repeated exposure to grinding dust in humans.

Consideration against classification criteria: The limited animal data available do not indicate that dust from grinding stainless steel presents any severe risk to health as a consequence of prolonged exposure.

Carcinogenicity

The carcinogenicity of grinding dust from stainless steel has been investigated in animals in i.t dosing studies. Although none of the studies were conducted according to currently recognised procedures for carcinogenicity testing, the results of these studies provide some reassurance that the stainless steels tested (two austenitic grades and one ferritic grade) failed to induce lung tumours in animals. An i.p. dosing study which was conducted contributes little further information to this subject. No animal data are available regarding the carcinogenicity of grinding dust following inhalation exposure.

The two available studies of cancer risks in grinders of stainless steel do not indicate that such work leads to excess risks of lung cancer. One study reported cancer findings under broad headings rather than for individual cancer sites. Nevertheless, it provided no support for the hypothesis of an effect on cancers of the colon and rectum suggested by the second study.

Consideration against classification criteria: Animal and human data do not provide any basis for considering dusts from grinding stainless steel as carcinogenic.

Effects on reproduction

There are no useful data available, animal or human, regarding the effects of grinding dust from stainless steel on reproduction.

Consideration against classification criteria: In the absence of animal or human data, it is not possible to consider grinding dusts against the classification criteria.

3.2.6 Risk assessment

The database concerning the health effects of grinding dust from stainless steel is limited. In the absence of any toxicological data to indicate otherwise, or any data concerning bioavailability, there appears to be no identifiable hazard associated specifically with grinding dust. Information relating to exposure indicates that a proportion of the airborne dust is respirable, and therefore the operation of grinding stainless steel presents the potential for inhalation exposure in the occupational setting. It is therefore deemed appropriate to treat grinding dust as any other kind of dust and to control exposure by the appropriate exposure limit. In the UK, the occupational exposure limit for such dust is 10 mg/m^3 (total inhalable dust) or 4 mg/m^3 (respirable dust). If exposure levels are controlled according to these limits, the risk to health are considered to be negligible. The limited exposure data on grinding dust which have been reported in the published literature (see *Section 3.2.2*) indicate that levels are mostly within these limits, although there are some measurements which have exceeded the limits. How relevant these published data are to current workplace exposures remains uncertain.

3.2.7 Future research needs

Although the database for grinding dust from stainless steel is very limited, there appear to be no major concerns regarding health effects which suggest that further testing is warranted.

3.3 Other processes

3.3.1 Cutting of stainless steel

General information

Cutting of stainless steel may be performed using mechanical or thermal methods.

Mechanical cutting

Mechanical cutting is used for cutting stainless steel sheets up to 10 mm thick and essentially involves a shearing action. No exposure to airborne materials arising from the stainless steel is likely to occur during this process.

Thermal methods

(i) Laser cutting of stainless steel is conducted as an automatic process and thus exposure of individuals during the process is not anticipated.

(ii) Plasma cutting may be performed using one of two methods. One method, which is used for thin gauge stainless steel, is performed under water and thus generates no airborne materials. An alternative method, which is used with thicker gauge stainless steel, is performed in the atmosphere. The latter method could theoretically lead to the generation of airborne substances, although currently the method is used very infrequently. The composition of fume generated by plasma cutting methods is similar to that formed during plasma welding processes.

Information on exposure

Information concerning the cutting of stainless steels outlined above indicates that only plasma cutting, when performed in the atmosphere, may present the potential for inhalation exposure in the occupational setting. No qualitative or quantitative exposure data appear to be available for this process.

Toxicokinetics and toxicity

Information concerning the toxicokinetics of fume from the cutting of stainless steel comes from the single study, reviewed below, which reported elevated urinary levels of nickel and chromium in a small group of workers engaged in the cutting of stainless steel (Tomokuni *et al.* 1993). These findings indicate some absorption of chromium and nickel compounds in these workers.

Studies of the health effects of exposure to fume from the cutting of stainless steel are limited to a single investigation which included a small group of workers involved in the cutting of stainless steel, and a single case-report.

Tomokuni *et al.* (1993) investigated urinary excretion of NAG and ß-aminoisobutyric acid (AIBA) in 58 workers involved in cutting and grinding of metals. Thirteen of the workers were mainly engaged in the cutting of stainless steel; the remaining workers were engaged either in cutting of steel (27 workers) or grinding of steel (18 workers). A group of 31 office workers was used as an unexposed control population. Cutting of stainless steel was performed as an automatic process using a gas burner. No air monitoring data were presented. Exposure was categorised according to the groups above, and also by quantifying urinary excretion of iron, nickel, and chromium.

The groups working with stainless steel or steel had increased urinary levels of all three metals compared with the office workers. The workers engaged in cutting of stainless steel had the highest levels of urinary nickel and chromium; median levels of urinary nickel were 2.5 µg/g creatinine (range n.d. - 13.3); median urinary chromium levels were 2.3 µg/g creatinine (n.d. - 26.5). In the control group, urinary nickel and chromium levels were undetectable. Urinary levels of NAG and AIBA were determined. NAG was considered a marker of renal tubular dysfunction while AIBA, which is a product of thymine degradation, was used as a marker for metabolic abnormalities possibly caused by metal exposure. No differences in urinary excretion of NAG or AIBA were detected between the groups. Also, no significant correlation could be demonstrated between urinary excretion of either nickel or chromium and either NAG or AIBA.

The authors concluded that no evidence of renal damage or metabolic disturbance was demonstrated by this study which could be attributed to nickel or chromium exposure. However, they noted that the power of the study was limited by the low levels of exposure (as demonstrated by the low levels of urinary nickel and chromium, even in the group working with stainless steel) and by the small number of subjects. In agreement with the authors' conclusions, the findings of this rather small study provide some indication that exposure arising from the cutting of stainless steel does not adversely effect kidney function.

Petersen *et al.* (1994) published a single case report of a plasma cutter of stainless steel who developed renal disease. The subject had relatively high levels of chromium in the blood (52.4 nmol/l; reference value <7.1), urinary chromium (28.5 nmol/mmol creatinine [13.1 µg/g creatinine]; reference value <5.0), and urinary nickel (33.4 nmol/mmol creatinine [19.6 µg/g creatinine]; reference value <10). No air monitoring data were provided. The subject had elevated urinary excretion of albumin and was also hypertensive, with a reported blood pressure of $^{150}/_{100}$. Renal

biopsy showed atrophic renal tubules with focal interstitial fibrosis. Although the authors suggested the chromium component of the fume from plasma cutting as the most likely causative agent, a single case report such as this cannot be accepted as proof of cause and effect, even at these apparently high levels of exposure.

Hazard assessment

The toxicological database for fume from the cutting of stainless steel is extremely limited. The only study which has specifically investigated workers engaged in this activity, which focused on effects on kidney function, reported no evidence of renal toxicity in a small group of workers.

Risk assessment

The limited toxicological database for fume from the cutting of stainless steel precludes the identification of any hazards. Consequently, it is not possible to conduct a risk assessment.

3.3.2 Polishing of stainless steel

There are no data on exposure, toxicokinetics or toxicity relating to the polishing of stainless steel. It is therefore not possible to conduct a hazard assessment or risk assessment for this process.

3.3.3 Forming of stainless steel

There are no data available on exposure, toxicokinetics or toxicity in relation to the forming of stainless steel. It is therefore not possible to conduct a hazard assessment or risk assessment for this process.

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I

(Acts whose publication is obligatory)

EUROPEAN PARLIAMENT AND COUNCIL DIRECTIVE 94/27/EC

of 30 June 1994

amending for the 12th time (*) Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article100a thereof,

Having regard to the proposal from the Commission ([1]),

Having regard to the opinion of the Economic and Social Committee ([2]),

Acting in accordance with the procedure referred to in Article 189b of the Treaty ([3]),

Whereas Article 8a of the Treaty establishes an area without internal frontiers in which the free movement of goods, persons, services and capital is ensured;

Whereas work on the internal market should gradually improve the quality of life, health protection and consumer safety; whereas the measures proposed by this Directive are in line with the Council resolution of 9 November 1989 on future priorities for relaunching consumer protection policy;

Whereas the presence of nickel in certain objects coming into direct and prolonged contact with the skin may cause sensitization of humans to nickel and may lead to allergic reactions; whereas for these reasons the use of nickel in such objects should be limited;

Whereas one Member State has already introduced a set of control measures on its territory to counteract nickel sensitization and nickel allergy and a second Member State plans to introduce on its territory a different set of control measures; whereas there is therefore a risk of barriers to trade;

Whereas the test methods to be used in demonstrating conformity with this Directive should be defined and published before the Directive is implemented; whereas these test methods should be the subject of a European standard;

Whereas limitations already adopted or planned by certain Member States on the use of nickel directly affect the completion and functioning of the internal market; whereas it is therefore necessary to approximate the laws of the Member States in this field and consequently to amend Annex I to Directive 76/769/EEC ([4]),

HAVE ADOPTED THIS DIRECTIVE:

Article 1

Annex I to Directive 76/769/EEC is hereby supplemented

Article 2

1. Member States shall adopt the laws, regulations and administrative provisions necessary to comply with this Directive not later than six months after publication by the Commission in the Official Journal of the European Communities, of the standards adopted by the European Committee for Standardization (CEN) on all the test methods used in demonstrating the conformity of the products with this Directive, or six months after the adoption of this Directive if that date is later than the former, so that:

(*) The Commission proposal was presented at the 14th amendment of Directive 76/769/EEC (OJ No C 116, 27. 4. 1993, p. 18.

([1]) OJ No C 116, 27. 4. 1993, p. 18.

([2]) OJ No C 304, 10. 11. 1993, p. 2.

([3]) Opinion of the European Parliament of 2 December 1993 (OJ No C 342, 20. 12. 1993, p. 15), Council common position of 4 March 1994 (OJ No C 137, 19. 5. 1994, p. 60) and Decision of the European Parliament of 5 May 1994 (not yet published).

([4]) OJ No L 262, 27. 9. 1976, p. 201. Directive as last amended by Directive 91/339/EEC (OJ No L 186, 12. 7. 1991, p. 64).

— six months after the expiry of one or other of those periods, whichever is applicable, no manufacturer or importer may place on the market products which fail

Directive or shall be accompanied by such reference on the occasion of their official publication. The methods of making such reference shall be laid down by the Member States

to comply with this Directive,

— 18 months after the expiry of one or other of those periods, whichever is applicable, products which fail to comply with this Directive cannot be sold or made available to the final consumer, unless they have been placed on the market before the expiry of the period in question.

They shall forthwith inform the Commission thereof.

2. When Member States adopt the measures referred to in paragraph 1, they shall contain a reference to this

States.

Article 3

This Directive is addressed to the Member States.

Done at Brussels, 30 June 1994.

For the European Parliament	*For the Council*
E. KLEPSCH	A. BALTAS
The President	*The President*

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ANNEX

'28. Nickel CAS No 7440-0-20 EINECS No 2311114 and its compounds	May not be used: 1. in post assemblies which are inserted into pierced ears and other pierced parts of the human body during epithelization of the wound caused by piercing, whether subsequently removed or not, unless such post assemblies are homogeneous and the concentration of nickel — expressed as mass of nickel to total mass — is less than 0,05 %; 2. in products intended to come into direct and prolonged contact with the skin such as: — earrings, — necklaces, bracelets and chains, anklets, finger rings, — wrist-watch cases, watch straps and tighteners, — rivet buttons, tighteners, rivets, zippers and metal marks, when these are used in garments if the rate of nickel release from the parts of these products coming into direct and prolonged contact with the skin is greater than 0,5 µg/cm²/week; 3. in products such as those listed in point 2 where these have a non-nickel coating unless such coating is sufficient to ensure that the rate of nickel release from those parts of such products coming into direct and prolonged contact with the skin will not exceed 0,5 µg/cm²/week for a period of at least two years of normal use of the product. Furthermore, products which are the subject of points 1, 2 and 3, may not be placed on the market unless they conform to the requirements set out in those points'.

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