SCOEL/SUM/86
December 2004
After Consultation

Recommendation from the Scientific Committee on

Occupational Exposure Limits:

Risk assessment for Hexavalent Chromium

8 hour TWA:	-
STEL (15 mins):	-
Additional classification:	

Excess Cases of Lung Cancer*

Excess lung cancer cases per 1000 male workers	Exposure (Working Lifetime to a range of Cr^{vi} compounds)
5-28	50 µg/m^3
2-14	25 µg/m^3
1-6	10 µg/m^3
0,5-3	5 µg/m^3
0,1-0,6	1 µg/m^3

* see Table 4 on page 30 for details.

EU Classification:

Chromium (VI) compounds (with the exception of barium chromate and of compounds specified elsewhere in Annex1 of the Directive):

Carc Cat 2 : R49 May cause cancer by inhalation.,
R43 May cause sensitization by skin contact; R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Chromium (VI) trioxide:

O; R9 Explosive when mixed with combustible material.
Carc. Cat. 1; R45 May cause cancer.
Muta. Cat. 2; R46 May cause heritable genetic damage.
Repr. Cat. 3; R62 Possible risk of impaired fertility.
T+; R26 Very toxic by inhalation.
T; R24/25-48/23 Toxic in contact with skin and if swallowed. Toxic: danger of serious damage to health by prolonged exposure through inhalation.
C; R35 Causes severe burns.
R42/43 May cause sensitization by inhalation and skin contact.
N; R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Substance identification:

Hexavalent chromium compounds are one of a number of oxidation states in which chromium occurs. Chromates and dichromates exist as a wide variety of compounds with 20 to 30 being of major industrial importance. These include, ammonium chromate and dichromate, barium chromate, calcium chromate and dihydrate, chromic chromate, chromium (IV) chloride, chromium trioxide (chromic acid), chromyl chloride, lead chromates, molybdenum orange ($PbCrO_4PbMoO_4Pb.SO_4Al_2O_3$), potassium chromate and dichromate, sodium chromate and dichromate and zinc chromates. The solubility of chromates varies widely and ranges from virtually insoluble to highly soluble. The various uses of the term solubility have caused much confusion and to harmonise discussions and classification it has been proposed (Cross *et al*, 1997) that the water solubility of hexavalent chromium compounds can be defined as: poorly soluble (<1g/l), sparingly soluble (1-10g/l); highly soluble (>100g/l). Thus, poorly soluble includes lead and barium chromate, sparingly soluble includes strontium, calcium and zinc chromate and highly soluble would include sodium and potassium chromates and dichromate.

Occurrence and Use:

Hexavalent compounds, with the exception of some small amounts in minerals, do not occur naturally in the environment but are formed from trivalent chromium during chromate-production processes. The starting point for all hexavalent compounds is chromite ore, which contains trivalent chromic oxide and this is oxidised to sodium chromate during kiln roasting in the chromate-producing industry. This is the usual starting material for all other hexavalent compounds. Apart from in the chromate-producing industry, occupational exposure may occur in the production of ferrochromium alloys and chromium metal, production and welding of stainless steels, metal finishing processes (chromium plating) and the manufacture and use of chromium chemicals. These latter include corrosion inhibitors (strontium, calcium, zinc and barium chromates); pigments in paints and in metal primers (lead and zinc chromates and molybdenum orange); wood preservatives (sodium and potassium chromates and chromium trioxide); dye mordants, catalyst and leather tanning (ammonium, sodium and potassium chromate). It should be noted that within the European Community, leather tanneries invariably use basic trivalent chromium sulphate, which contains no measurable hexavalent chromium. Some hexavalent chromium is present in cement as a contaminant arising from its manufacture and possibly from the clinker or gypsum constituents, or from the kiln dust during the firing stage which comes from chromium-containing refractories. The hexavalent form is, however, reduced to the trivalent form by the addition of ferrous sulphate to the cement.

Occupational exposure can be to a simultaneous number of different hexavalent compounds, depending on the industry, and in some industries can be further complicated by exposure to both trivalent and hexavalent compounds. The chromate-producing industry is an example of this. Such mixed exposures can make interpretation problematical for both hazard and risk assessment in human studies in relation to individual compounds, especially when exposures are expressed only as total chromium.

Health Significance:

Toxicokinetics (animal):
Absorption of inhaled hexavalent chromium from the respiratory tract varies according to the solubility of the compound with high or sparingly soluble compounds absorbed more rapidly than poorly soluble or insoluble compounds (Adachi *et al*, 1981; Miyai *et al*, 1980). Repeated inhalation results in the accumulation of chromium in lung tissue and this is more marked for poorly soluble compounds. Absorption of orally-administered hexavalent chromium, which has only been studied with soluble compounds, is poor presumably due to its rapid reduction to the trivalent species in the acidic conditions of the stomach (Mackenzie *et al*, 1959; Donaldson & Barreras, 1966; Ogawa *et al*, 1976). Reduction from hexavalent to trivalent chromium will also take place in the lung (De Flora, 2000). Dermal absorption occurs following direct skin contact with soluble hexavalent compounds in aqueous solutions and this can amount to up to 4% of the applied dose (Wahlberg & Skog, 1963).

Hexavalent chromium absorbed into the blood stream is taken up by blood cells, predominantly red blood cells (RBC), reduced to trivalent chromium in the plasma or distributed to the tissues. RBCs uptake is rapid and involves a specific anion transport carrier in the cell membrane. Following uptake, the hexavalent chromium is reduced and irreversibly bound to haemoglobin. Chromium can only be transported into cells when in the hexavalent oxidation state and extracellular reduction serves to prevent its uptake. Non-enzymatic reducing agents include glutathione, ascorbic acid and cysteine; enzymatic agents include microsomal P450 enzymes.

Inhaled intratracheally-instilled hexavalent chromium has been shown to be distributed to the lungs, liver, kidneys, testes, spleen and GI tract. Parenteral administration studies in pregnant animals have shown that hexavalent chromium compounds can cross the placenta and be distributed within the embryo. These findings however, are of questionable relevance to occupational exposure. Inhaled or i.t. instilled hexavalent chromium is excreted in the urine or faeces with the relative contribution varying with compound solubility. Orally administered compounds are mainly excreted in the faeces.

Toxicokinetics (human):

The limited number of volunteer and worker studies would suggest much of the animal toxicokinetic data is relevant to human. Biological monitoring of occupational exposure is routinely carried out using blood or urine, but the analytical techniques employed tend to express the amounts as total chromium.

Health effects (animal):

Single exposures to hexavalent compounds by inhalation cause inflammation and necrotic changes to the upper respiratory tract with effects in rats reported at 7.4mg Cr/m^3 and above (Suzuki *et al*, 1984; Last *et al*, 1979). LC_{50} values of between 33 and 83mg Cr/m^3 have been reported for rats (Gad et al, 1986). An oral LD_{50} With male rats using sodium chromate, sodium dichromate potassium dichromate and ammonium chromate has given values of 87, 59, 74, and 55mg Cr/kg respectively. Equivalent values for female rats were 13, 16, 17 and 20mg Cr/kg (Gad, 1986). Not surprisingly, higher LD_{50} are seen with sparing or poorly soluble chromate.

A number of studies using highly soluble chromates have shown that they are capable of causing skin and eye irritation. Animal studies have shown that soluble hexavalent compounds are skin sensitisers, inducing a type IV cell-mediated response (Cacciuttolo *et al*, 1980; Siegenthaler *et al*, 1983). There is also evidence of cross-reactivity with trivalent chromium compounds (Siegenthaler *et al*, 1983).

The effect of repeat exposure in animals to hexavalent compounds has been studied in animals using inhalation exposure, intratracheal instillation, oral dosing and parenteral administration, In inhalation studies, near continuous exposure to aerosols of sodium dichromate at concentrations up to 0.1mg Cr/m^3 for 18 months, or 0.2mg Cr/m^3 for 90 days, had no effects on body weight gain, haematology or histopathology (Glaser *et al*, 1985). However, with exposure to 0.5mg Cr/m^3 and above for 28 days or more, there was increased organ weights (lung, liver, spleen and kidney). Similar results were seen in another study (Miyai, 1980) in which sodium chromate or barium chromate dusts at concentrates between 0.01 and 0.13mg Cr/m^3 for up to 8 months. Repeat exposure to chromic acid (1.81mg Cr/m^3 and above) caused irritant and corrosive effects in the respiratory tract of mice (Adachi *et al*, 1986). Exposure to sodium chromate aerosol (0.9mg Cr/m^3 for up to 6 weeks) caused no damage to the respiratory tract epithelium in rabbits, but had a stimulating effect on pulmonary macrophages (Johansson *et al*, 1986 a & b). From these repeat inhalation studies, it is not possible to identify with any confidence a NOAEL for hexavalent chromium compounds.

In a number of oral-dosing studies, administration of highly soluble hexavalent compounds at concentrations up to 100ppm caused no sign of toxicity. One study at 70ppm in drinking water caused reduced body weight gain in rats. In a dietary study, high doses of lead chromate caused reduced weight gain, haematological effects and renal toxicity in rats and dogs although it is possible that both chromium and lead might have contributed to these effects. (Kennedy *et al*, 1976; Christofano *et al*, 1976)

There are a number of studies which have investigated the carcinogenicity of hexavalent chromium compounds, but only a few using the inhalation route and these suffer from several deficiencies in design or reporting. Exposure to sodium dichromate by inhalation (up to 0.1mg Cr/m^3 continuously for 18 months) was associated with increased lung cancer incidence in rats at the highest dose (Glaser *et al*, 1986). Exposure to sodium dichromate by intratracheal instillation (a single dose of 0.5mg Cr/kg/week for 30 months) was associated with an increase in lung tumours in rats, although the same total weekly dose, administered as five separate instillations, failed to increase lung tumour incidence (Steinhoff *et a*l, 1986). Calcium, strontium and zinc chromate have been shown to induce bronchial carcinoma in rats using the bronchial implantation technique (Levy *et al*, 1986).

There are no inhalation studies available to evaluate the potential carcinogenicity of poorly soluble chromates. There are also no acceptable studies on the carcinogenicity of orally-administered hexavalent chromium compounds.

The genotoxicity of hexavalent chromium compounds has been extensively investigated in *in vitro* assays using non-human and mammalian cells. All highly soluble compounds tested have consistently generated positive results in bacterial cell assays and mammalian cell assays providing clear evidence that all highly soluble compounds are *in vitro* clastogens and mutagens.
Medium or sparingly soluble chromates such as those of calcium, strontium and zinc have also yielded positive results in bacterial and mammalian cell assays. In most

tests, the genotoxic activity was enhanced by prior solubilisation with sodium hydroxide. With high, medium or sparingly soluble compounds, the presence of an exogenous metabolising activation system in bacterial cell assay typically decreased genotoxic activity by enhancing the reduction of hexavalent to trivalent chromium. [It is generally accepted that trivalent chromium compounds have not been shown to be genotoxic]. Very poorly soluble chromates such as those of lead and barium are only positive in *in vitro* bacterial mutation assays following chemical solubilisation. However, they have been able to show positive results in some mammalian cell assays.

The *in vitro* genotoxicity of hexavalent compounds has been less well studied although highly soluble compounds have generally yielded positive results in sister chromatid exchange, micronucleus and chromosomal aberration assays. Some limited positive results have also been reported for calcium and lead chromate.

A number of studies have investigated the effect of chromates on reproduction in animals. Parenteral administration of maternally toxic doses of chromium trioxide (3.9mg Cr/kg and above) to pregnant hamsters during gestation resulted in resorption and embryotoxicity (increased foetal resorption; subcutaneous oedema, delayed skeletal ossification and cleft palate in surviving embryos) (Gale, 1974; Gale 1978). Doses, which caused no maternal toxicity, caused cleft palate, hydrocephalus and delayed skeletal ossification in hamsters (2.6mg Cr/kg), but failed to induce embryotoxicity in rats (2mg Cr/kg). (Gale & Bunch, 1979; Mason *et al*, 1989). Repeat injection studies of sodium chromate in male rats (1- 4mg Cr/kg for 5 days) caused a reduction in body weight, a reduction in testicular weight, atrophy of seminiferous tubules and reduced sperm count. Caution is needed in the interpretation as the relevance of these studies on reproduction as the route of introduction by parenteral administration would avoid the normal reducing route by oral or inhalation routes.

Health Effects (human):

Data on the effects of single exposures in human is mainly from case-reports involving accidental exposures and only relates to highly soluble compounds. An incompletely and poorly reported volunteer study of 10 subjects exposed to chromic (IV) oxide reported that "brief exposures" to 10-24µg/m^3 (apparently CrO_3, thus 5-12µg Cr/m^3) caused nasal irritation (Kuperman, 1964). The threshold for irritation was reported to be 2.5µg/m^3 (apparently as CrO_3; thus 1.3µg Cr/m^3).

Severe skin damage and renal toxicity have been reported in two fatal cases involving accidental exposure involving direct skin contact with hot (>90ºC) acidified solutions of highly soluble chromates (Fritz *et al*, 1960). Corrosive damage to the GI tract mucosa and renal toxicity have been reported in cases of accidental or intentional ingestion of soluble hexavalent compounds. In many of the case reports, avoidable death (Cross *et al*) was often the outcome with ingestion of approximately 350mg Cr and above.

Information relating to the irritant effects of hexavalent chromium compounds in human is only available for soluble compounds. Evidence, mainly from case reports, clearly shows that highly soluble compounds cause irritant and corrosive effects to the eyes. There are numerous reports of skin ulcers in workers exposed to soluble chromium compounds, in particular chrome plating workers or chromate-production

workers (Cross *et al*, 1997). These “chrome ulcers” are mostly located on the hands and forearms.

Skin sensitisation resulting from exposure to hexavalent compounds has been demonstrated in patch-testing studies of contact dermatitis patients and in various chromate-exposed occupational groups (Sun, 1984; Samoen *et al*, 1984; Fregert *et al*, 1970; Engel & Calnan, 1963). Hexavalent chromium-sensitised subjects may react to trivalent chromium compounds although the latter are less able to penetrate the skin and thus have a lower skin sensitising potential (Fregert & Rorsman, 1964; Samitz & Shrager, 1966).

Available case reports, together with supporting evidence from bronchial challenge tests, show that inhaling hexavalent chromium compounds can induce occupational asthma (Park *et al*, 1994). As with skin sensitisation, hexavalent chromium-sensitised subjects may react following exposure by inhalation to trivalent chromium compounds.

A large number of studies are available, which have investigated the health of workers with repeated long-term exposure to hexavalent chromium compounds. The two most studied groups are chrome plate and chromate-production workers (Cross *et al*, 1997). Many of these studies have reported effects on the upper respiratory tract but few have presented exposure details for chromium exposure. Effects on the upper respiratory tract include inflammation, atrophy of the nasal mucosa and ulceration or perforation of the nasal septum (Colvin *et al*, 1993; Royle, 1975; Lin *et al*, 1994). In the lower respiratory tract, the reported effects include inflammation and various obstructive disorders (Ameille *et al*, 1983; Wieser *et al*, 1982). Transient impairment of lung function has also been reported (Lindberg & Hedenstierna, 1983). In this latter study on chrome platers, effects on the nasal passages were reported with exposures to average concentrations of 0.002mg Cr/m^3 and above although some effects were even reported at lower average concentrations. However, it should be noted that short-term exposure to higher concentrations or, direct contamination of the nasal mucosa with chromic acid might have been involved in the development of these lesions.

Kidney function has been investigated in chrome platers, chromate production workers, ferrochromium workers and stainless steel welders. Some but not all studies have reported renal dysfunction indicated by altered urinary levels of specific enzymes or proteins (Lindberg & Vesterberg, 1983; Nagaya *et al*, 1994; Verschoor *et al*, 1988; Wang *et al*, 1994; Mutti *et al*, 1985; Littorin *et al*, 1984). Irritant and corrosive effects on the GI tract and hepatotoxicity have been reported but these effects cannot be related to exposure data.

Carcinogenicity:

Case reports:

The first case of cancer associated with chromium compounds was reported by Newman (1890) and described an adenocarcinoma in the nasal passages of a chromate pigment production worker. Since then, there have been several case reports of lung cancer among chromate pigment production workers, chromate-production workers and chrome platers and some case reports of cancer of the GI tract in chromate production workers (IARC, 1990).

Epidemiological studies:

A large number of epidemiological studies are available for the evaluation of carcinogenicity and there have been a number of reviews (IARC, 1990; Cross *et al*, 1997; ATSDR, 2000; EPA, 1998). The studies are best examined when grouped into the following industrial sectors: chromate-production workers, pigment production workers, chrome plating workers, ferrochromium workers, stainless steel production workers and stainless steel welders.

Chromate production workers:

The most extensive studies are those in the chromate production industry and can be grouped into those from the US, the UK, Germany, Italy and Japan (Cross *et al*, 1997). These studies provide clear evidence of increased mortality among chromate workers. Values of standardised mortality ratios (SMRs) from 200 to over 2000 have been reported. In many cases, the study populations involved workers employed in the first half of the 20^{th} century. Results from most recent studies indicate that lung cancer mortality in the industry has decreased in more recent years, probably associated with changes in production processes and/or improved hygiene control. Exposure data are available for two cohorts – Mancuso, 1975 updated in Mancuso, 1997 and Hayes *et al*, 1975 updated in Gibbs *et al*, 2000. These exposure data enable the relationship between airborne chromium, in particular hexavalent chromium and increased lung cancer mortality in the chromate production industry to be investigated (see **Recommendations**). Most importantly, no exposure data are provided regarding types of chromium compounds including specific hexavalent compounds.

Pigments-production workers:

A number of studies have reported excess risk of cancer for workers employed in the chromate pigment production industry. Most of the plants studied produced both lead and zinc chromate and in some, exposure to other chromates including strontium, may have occurred. Therefore, the independent effects of lead chromate and zinc chromate with respect to lung cancer are difficult to identify. However, a series based in three UK factories provided strong suggestive evidence that zinc chromate, and not lead chromate is associated with lung cancer risks in this industry (Davies, 1979; Davies, 1984 a and b). No detailed exposure data are available to enable the relationship between chromium exposure and increased lung cancer mortality in the chromate pigment production industry to be investigated.

Chrome plating workers:

Several studies of chrome plating workers are available for evaluation. One study provides clear evidence of increased lung cancer mortality (Sorahan *et al*, 1987). Exposure data provided in this study suggests that exposure to CrO_3 was generally below $0.05mg/m^3$ ($0.026Cr/m^3$) but this figure should be treated with some caution. Other, less well-conducted studies also report an elevated risk of mortality from lung cancer in chrome platers.

Ferrochromium workers:

Two studies are informative in the possible carcinogenicity of hexavalent chromium to ferrochromium workers. One study reported a non-significant excess of lung cancer (Langård *et al*, 1980; Langård et al, 1990) and one study reported a non-significant

deficit in lung cancer (Axelsson *et al*, 1980). Both studies noted possible co-exposure to other known carcinogens.

Stainless steel production workers:

Two studies in separate groups of French stainless steel production workers have been performed (Moulin *et al*, 1990; Moulin *et al*, 1993). A suggestive increase in lung cancer was considered to be more related to PAH exposure rather than chromium.

Stainless steel welders:

There are several studies that have investigated cancer mortality in stainless steel welders, but few have specifically investigated chromium (Cross *et al*, 1997). Of the available studies, some have reported increased risk of lung cancer mortality in stainless steel welders whilst others have not. By far the most comprehensive is a large study (IARC, 1989; Simonato *et al*, 1991) which reported increased lung cancer mortality in stainless steel welders, although a greater excess was reported for mild steel welders. In most of the studies reported, exposure to asbestos and other confounders were noted. Thus, any association between hexavalent chromium exposure and increased risk of lung cancer in stainless steel welders remains to be elucidated.

Effects on reproduction:

Studies, which have reported complications in pregnancy and childbirth in women employed in the chromate manufacturing industry, provide unreliable data (Shmitova 1978; Shmitova, 1980). Several investigations of male fertility have focussed on welding as an occupation. Some of these studies report effects on semen quality (Mortensen, 1988) whilst others do not (Bonde & Ernst, 1992; Jelnes & Knudsen, 1988). The general absence of exposure data in these studies precludes any assessment of the relationship to hexavalent chromium.

Recommendation:

Non-cancer end-points:

In humans occupationally exposed by inhalation to hexavalent chromium compounds, the main health effects are irritant and corrosive effects on the skin and respiratory tract. Effects on the respiratory tract include inflammation of the nasal septum. Lower respiratory effects include inflammation and obstructive disorders; transient impairment on lung function has been reported. It is uncertain to what extent short-term exposure to high hexavalent chromium levels or direct contamination of the nasal mucosa with chromium may be involved in the development of the nasal lesions and this complicates a clear interpretation of the significance of the reported average exposure levels in relation to these health outcomes. Renal dysfunction has been reported in some studies, indicated by altered urinary protein or enzyme levels. In contrast, some studies have reported no effects on kidney function. Irritant and corrosive effects on the GI tract and effects in the liver have been reported following repeated exposure, but these cannot be related to exposure data. Hexavalent chromium compounds are potent skin sensitisers in humans and can cause respiratory sensitisation, Sensitised individuals may also react to trivalent chromium compounds. In general, the animal investigations from both single and repeated exposures are supportive of the effects seen in humans although the data do not cover the wide range

of hexavalent chromium compounds in common use, most focussed on the highly soluble compounds, and do not allow clear NOAELs to be established for the health endpoints investigated.

Carcinogenicity:

A large number of epidemiological studies are available which have investigated cancer risks. Studies of chromate production workers provide clear evidence of increased lung cancer mortality. Excess risk of lung cancer mortality has also been reported for workers in the chromate pigment industry, producing principally lead and zinc chromates. There is suggestive evidence that zinc chromate, rather than lead chromate, is associated with the increased lung cancer mortality in the pigment producing industry. One study of chrome platers provides clear evidence of increased lung cancer risks and this finding is supported by other less informative studies of chrome platers. Epidemiological investigations of ferrochrome workers, stainless steel production workers and stainless steel welders have generated conflicting results and with the added complication of co-exposure to known carcinogens, allow no conclusions to be reached regarding lung cancer risks in relation to hexavalent chromium exposure in these industries. Overall, only a few of the reported epidemiological studies provide exposure data and no single study includes measurements of occupational exposures for all time periods under investigation. Consequently, any quantification of lung cancer risk is based on limited data.

The carcinogenicity of a number of hexavalent chromium compounds has been investigated in animal studies using various route of exposure; the most informative for the purpose of estimating cancer risks to humans in occupational settings are inhalation, intratracheal instillation and intrabronchial studies. In an inhalation study, in which rats were exposed to sodium chromate (0.025, 0.05 or 0.1mg Cr/m^3), increased lung tumours occurred only at the highest dose. In a mouse inhalation study, increased lung tumours were associated with exposure the calcium chromate at the concentration used of (4.3mg Cr/m^3). Two mouse inhalation studies showed a non-significant increase in lung tumours following exposure to chromium (IV) oxide. These inhalation studies all suffered from some deficiencies in design. Other inhalation studies, some of which investigated less soluble hexavalent chromium compounds, had major deficiencies that prevented any conclusions being drawn. In one intratracheal instillation study, increased lung tumour incidence was reported in rats following exposure to calcium chromate. In the same study, sodium dichromate was associated with increased lung tumour incidence in rats with 1.25mg/kg/week (0.5mg Cr/kg/week) administered as one weekly dose, but not when the same weekly dose was administered in five instillations. Other intratracheal instillation studies had major limitations, which prevented any conclusions being drawn. An intrabronchial implantation study in rats demonstrated elevated lung cancer incidence with calcium chromate, strontium chromate and zinc chromate, but failed to demonstrate evidence for carcinogenicity of poorly soluble compounds (lead chromate or barium chromate) or sodium dichromate, although the method may be inappropriate for highly soluble compounds.

On the basis of the animal carcinogenicity data, it is concluded that there is evidence to suggest a potency difference between hexavalent chromium compounds, probably related to solubility and consequently bioavailability. However, the variation in design of the animal studies and, crucially, the scarcity of reliable data for poorly soluble hexavalent chromium compounds precludes definite distinctions being made,

either qualitative or quantitative, between hexavalent chromium compounds on the basis of the available animal studies done alone.

The genotoxicity of hexavalent chromium compounds has been widely investigated in assays for different genetic endpoints and has, with a few possible exceptions, been uniformly positive in *in vitro* assays for mutagenicity and clastogenicity, with evidence of *in vivo* expression of these effects in some compounds. The possible exceptions are lead and barium chromate and these two compounds have required solubilisation to elicit positive results in bacterial cell assays or to enhance their genotoxic activity in mammalian cells. Although there appears to be a difference in genotoxic potential between the various hexavalent chromium compounds tested based on solubility, positive results were obtained with the poorly soluble compounds in some assays. It is therefore not possible to exclude any compounds tested from possessing some mutagenic or clastogenic potential.

Basis for recommending a limit:

The health effects associated with occupational exposure to hexavalent chromium compounds are carcinogenicity, (specifically lung cancer), sensitisation, renal toxicity and irritancy, and corrosivity of the skin, respiratory and gastrointestinal tract. Clearly, the most serious of these outcomes in health terms is lung cancer and, given the magnitude of occupational cancer risks shown in some of the earlier epidemiological studies, and given that hexavalent chromium compounds are comprehensively genotoxic, it follows that lung cancer is the critical effect upon which to base any occupational exposure limit. Ideally, it would be preferable to develop lung cancer risk estimates for individual hexavalent chromium compounds (or a few groups of compounds). Unfortunately, the quantity and quality of the epidemiological data are not sufficient to rank, with any confidence, the carcinogenic potencies of the various hexavalent chromium compounds encountered in industry. The available animal carcinogenicity investigations do not provide this missing information. Notwithstanding the dearth of appropriate human studies, the available human and experimental animal data indicate that poorly soluble hexavalent chromium compounds have a lower carcinogenic potency than soluble compounds. Such an effect might be explained be the relatively lower delivery of bioavailably-active chromium ions to the intracellular target in the respiratory epithelium.

Lung cancer risk assessment:

The study of Mancuso (1975) currently dominates the risk assessments of hexavalent chromium; USEPA, 1984; Gibb *et al*, 1986; PCHRG 1993; Crump, 1995. However, this survey, with a total of 41 lung cancer deaths available for analysis, does not constitute a large epidemiological study. In addition, the job histories and exposure histories of study subjects seem to be poorly described.
A risk assessment for hexavalent chromium based on epidemiological data, has been prepared for the US Occupational Safety and Health Administration (OSHA) (Crump, 1995). This assessment identified six sets of epidemiological data that provided some quantitative information on chromium exposures (Mancuso, 1975; Hayes *et al*, 1979; Langård *et al*, 1980; Axelsson *et al*, 1980; Pokrovskaya & Shabynina, 1973; Sjögren *et al*, 1987). The risk estimates prepared for OSHA are that some 6-9 excess lung cancer deaths will be experienced over a lifetime by a cohort of 1000 workers followed-up from the age of 20 years and occupationally exposed to 1µg/m^3 of hexavalent chromium until retirement at age 65 years (Crump, 1995). At an

occupational exposure level of 50μg/m^3, the predicted number of occupational lung cancers was in the range 246 to 342. These assessments were based on data from the Mancuso (1975). When the assessments were based on the cohort of Hayes *et al*, (1979) the corresponding figures were 2 excess lung cancer deaths at an exposure level of 1μg/m^3 and 88 excess lung cancer deaths at an exposure level of 50μg/m^3. (The 4 other studies were judged to be less suitable for any primary risk assessment.)

The study cohort of chromate production workers described by Hayes *et al* in 1979 was redefined and updated (Gibb *et al*, 2000). The new cohort comprised 2357 workers first employed between 1950 and 1974; follow-up was to the end of 1992. The new cohort included 990 workers who were employed for less than 90 days. These latter workers were included to increase the size of the low exposure group. Short-term workers are often found to have unusual patterns of mortality and it is unclear whether or not the inclusion of this group has been helpful. The authors put considerable effort into characterising chromium exposures in different jobs and different time periods. Unfortunately, the resulting job-exposure matrix is not reported. What is clear, however, is that many estimated exposures must have been very low because 75% of the cohort have estimated cumulative hexavalent chromium exposures in the range 0 - 0.0769mg/m^3/y. A statistically significant non-monotonic positive trend is shown for lung cancer in relation to four levels of cumulative hexavalent chromium exposure and the study provides further evidence of excess lung cancer risks being causes by hexavalent exposure. The incorporation of the study findings into quantitative risk assessment is problematical in that three of the four exposure categories are so low (0 – 0.00149, 0.0015 – 0.0089 and 0.0090 – 0.0769mg CrO_3/m^3/y)

A further follow-up of 332 workers, first employed at a US chromate plant in the period 1931-37, has been reported by Mancuso (1997); follow-up was to the end of 1993. The study suffers from the absence of standard modern methods of analysis such as Poisson regression. The reader is supplied with much of the raw data in terms of deaths, and person-years-at risk shown by eight age-group categories and seven cumulative chromium exposure categories (total, soluble and insoluble chromium exposure are shown in turn). There then follows a descriptive account of patterns in the data rather than a statistical analysis that seeks to identify the independent effects of different chromium exposures. The data reported does not however, supply sufficient information to carry out the necessary analysis. Interestingly, the overwhelming majority of the Gibb *et al*, 2000 study population (perhaps in order of 90% of the cohort) would be placed in the lowest exposure categories in the Mancuso, 1997 study.

Sorahan *et al* (1998) publishes a worked example of a quantitative risk assessment based on data from a single cohort study of chrome platers. These calculations provided risk estimates that were higher than those shown in the Criteria Document of Cross *et al* (1997). The difference arose, in the main, because different assumptions were made about the exposure conditions pertaining to the study cohort. It is clear that under-or over-estimation of the exposure conditions which gave rise to the observed lung cancer excesses will have dramatic effects on any quantitative risk estimation derived from the epidemiological findings. It seems reasonable to use estimates which are based on more than one study, and the estimates shown in *Table 4* in **Appendix 1** (column 1 relating to assumption 1) which are based on summary epidemiological findings from ten published cohort studies are considered to involve more reasonable assumptions about exposure conditions than do those predictions shown in other columns of *Table 4*.

The preferred risk assessment (see **Appendix 1**) is thus based on a summary of ten published studies (Steenland *et al*, 1996) and it has been estimated that about 5-28 excess lung cancers will occur in a cohort of 1000 male workers, followed-up from age 20 to age 85 and occupationally exposed to 50µ/m^3 of hexavalent chromium until retirement at age 65. The corresponding number of excess lung cancers has been estimated to be 2-14 for an exposure level of 25µg/m^3, 1-6 for an exposure level of 10µg/m^3, 0.5-3 for and exposure of 5µg/m^3 and 0.1-0.6 for and exposure level of 1ug/$m^{3.}$

It is important to recognise that there are a number of limitations attached to all the proceeding estimates. They do not include statistical uncertainty and this will be considerable for the OSHA assessments given the small number of deaths available for that analysis. Uncertainty also exists regarding the appropriateness of the dose-response model employed. The model used assumes linear extrapolation of cancer risks through the origin; there is no "threshold" dose, i.e. no dose or dose rate below which there is no carcinogenic effect. This is particularly important in the case of hexavalent chromium, which, because it is comprehensively genotoxic, could be considered an ideal carcinogenic substance to which to apply a "no threshold" linear extrapolation. However, it should also be recognised that the irritant and inflammatory properties of hexavalent compounds may also contribute to the carcinogenic process and that for these effects there will be thresholds. It is not known to what extent irritancy may contribute towards carcinogenicity but it is quite plausible that linear extrapolation to low doses, below those seen in existing studies and where irritancy does not occur may over-estimate the true cancer risk. One should also take into account the lung's ability to reduce hexavalent chromium to the non-genotoxic and non-carcinogenic trivalent species (De Flora, 2000). Unfortunately, epidemiological data can contribute little to this important issue. Whilst epidemiological data may shown no excess lung cancer risk in a low cumulative exposure category, it is most likely that the confidence intervals attached to any such observed estimate of risk will include the (low) projected risk estimate supplied by linear extrapolation of cancer effects observed at higher cumulative exposures. Consequently, this aspect of model definition cannot be tested. In addition, other aspects of the statistical model used in the risk assessment are not based on the source data themselves. For example, any risk modifying effects of sex, age at exposure and period of follow-up have not been estimated. It is also of concern that the risk assessments have a sizable fraction of the total predicted risk occurring at ages beyond the follow-up ages available in the source data.

The proposed risk estimate has, for reasons discussed, not drawn any distinction between highly, sparingly and poorly hexavalent chromium compounds. However the available evidence, albeit incomplete, strongly suggests that poorly soluble hexavalent compounds carry a lesser lung cancer risk although the size of such a reduction cannot be quantified. Thus, in establishing occupational exposure limits a pragmatic approach may be appropriate. As an example, an exposure limit of 50µg/m^3 of hexavalent chromium may well provide adequate protection for workers exposed to poorly soluble hexavalent chromium compounds but, on the basis of the risk assessments described in **Appendix 1**, consideration could be given to setting exposure limits at 25µg/m^3 or 10µg/m^3 for other hexavalent chromium compounds.

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Appendix 1

Risk assessment for lung cancer from hexavalent chromium based on a summary of studies

A recent review of occupational lung cancer was carried out in order to derive broad approximations of the current toll of occupational factors in current US mortality from this disease (Steenland *et al*, 1996). A number of occupational factors were considered including exposure to hexavalent chromium compounds, and ten studies had been selected as the largest and best designed studies of chromate production workers, chromate pigment production workers and chromium platers (see *Table 1*). This Appendix shows how it is possible to use the overall SMR for lung cancer, obtained from these ten studies, to make a number of predictions regarding the effect of lifetime working at different time-weighted averages (TWA) hexavalent chromium exposure levels. Conveniently this enables a risk assessment to be made which is independent of the study by Mancuso (1975); this latter study was not selected by Steenland *et al* (1996), even though it features prominently in other assessments.

A number of assumptions have to be made and it has been assumed that the mean length of employment of all study subjects included in the ten selected studies is 15 years. Three separate series of calculations have been made in which the typical TWA occupational exposure of these study subjects is assumed to be either 500μg/m^3, 1000μg/m^3 or 2000μg/m^3. Consequently, the mean cumulative exposure of study subjects to hexavalent chromium is assumed to be either 7500μg/m^3/y (assumption 1), 15000μg/m^3/y (assumption 2) or 30000μg/m^3/y (assumption 3). For each of these assumptions, three further possibilities were considered. Firstly, all the excess SMR is due to hexavalent chromium exposure (the SMR of 266 represents an excess SMR of 166, or excess relative risk of 1.666). Secondly, confounding by smoking or other occupational exposures means that the baseline SMR should be 130 and not 100 (i.e. in the absence of hexavalent chromium exposure the overall SMR in the selected cohorts would have been 130); the overall relative excess risk is thus 1.36. Thirdly, confounding by smoking or other occupational exposures means that the baseline SMR should be 160 and not 100; the overall excess relative risk is thus 1.06.

For each set of assumptions, an estimate of the risk coefficient – the excess relative risk due to 1μg/m^3/y of exposure – was obtained by dividing the total estimated excess relative risk by the estimated mean individual cumulative exposure. These risk coefficients were then applied to life-table calculations in which a population of 1000 male workers aged 20 years is exposed to different TWA exposures over a working lifetime and followed to age 85. This population suffers a theoretical attenuation according to age-specific mortality data summarised in the 1981 life-table for England and Wales, in addition to any predicted age-specific occupational cancers.

Table 2 shows the calculation of baseline data in which occupational exposure is assumed to have no effect (risk coefficient = 0.0). The footnotes to the table show how the table is completed. The expected number of lung cancers before age 85 years in a population of 1000 UK males followed from age 20 years is 84.74. *Table 3* shows one set of calculations in which hexavalent chromium exposure is assumed to have a specified effect. In this example, a risk coefficient of 0.0002213 is considered; all the excess relative risk (1.66) is assumed to be the result of hexavalent chromium exposure and the typical exposure conditions pertaining to the selected studies was assumed to be 500μg/m^3. [In all calculations, exposures received more than 40 years

ago are assumed to have no effect. In all other respects, the risk coefficient (a measure of relative risk and not of absolute risk) is assumed to be constant at all ages and periods of follow-up.] The calculations shown in *Table 3* predict a total of 113.18 lung cancers before age 85 years. The number of excess cancers is thus predicted to be 28.4 (113.18 – 84.74) and the predicted SMR is 137 (113.18/82.80 expressed as a percentage).

The calculations shown in *Table 3* were then repeated for a number of TWA values (25, 10, 5, and 1μg/m^3) and then each set of TWA values was considered in conjunction with alternative assumptions (already described) about both the magnitude of the overall excess risk which could be attributed to hexavalent exposure and the exposure conditions pertaining to the published studies. A summary of these calculations is shown in *Table 4*.

Numbers of excess lung cancers in a 1000 male workers exposed for a working lifetime to 50μg/m^3 of hexavalent and followed to age 85 years are predicted to be in the range 5-28. These absolute risks are equivalent to SMRs in the range 106 to 137. The corresponding number of excess lung cancers has been estimated to be about 2-14 for an exposure level of 25μg/m^3, 1-6 for an exposure level of 10μg/m^3, 0.5-3 for and exposure level of 5μg/m^3 and 0.1-0.6 for an exposure level of 1μg/m^3.

Clearly, a large number of pragmatic assumptions have been made in performing the above calculations. Nevertheless, the ranges of assumed values cover a fairly wide range of credible values. The question remains: are the predictions likely to be under-estimates or over-estimates? In at least one important respect they may be over-estimates. The calculations assume that the hexavalent chromium effect is expressed via a relative risk without regard to latency or age at exposure effects. However, if the hexavalent chromium effect is expressed as a constant absolute risk, these predictions will almost certainly need to be lowered (Breslow & Day, 1987). There are also other biological and mechanistic reasons why linear extrapolation at low levels of exposure may markedly over-estimate the risk. One of these relates to the fact that cells in the lung tissue have the capacity to reduce quite large amounts of potentially carcinogenic hexavalent chromium to the non-carcinogenic trivalent form and it can be argued that exposure does not pose a threat of carcinogenicity until this reducing and detoxifying defence system is overwhelmed (De Flora, 2000).

Table 1 Selected studies of Cr^{VI}-exposed workers[a]

Study	**SMR**	**(95% CI)**
Enterline (1974)	943	(733 to 1193)
Hayes *et al* (1979)	203	(155 to 263)
Alderson *et al* (1981)	242	(200 to 290)
Satoh *et al* (1981)	923	(627 to 1310)
Korallus *et al* (1982)	210	(156 to 276)
Frentzel-Beyme (1983)	204	(123 to 319)
Davies (1984a&b)	182	(137 to 243)
Sorahan *et al* (1987)	150	(117 to 189)
Hayes *et al* (1989)	143	(93 to 213)
Takahashi *et al* (1990)	187	(81 to 369)
Overall	266[a]	(243 to 292)

From Steenland *et al* (1996)

a. Mean SMR weighted by the inverse of the variance (obtained from confidence interval) of each individual SMR, on the basis of a fixed effects model. Steenland *et al* (1996) assumed a random effects model and calculated an overall SMR of 278.

Table 2 – Quantitative risk assessment for lung cancer in relation to occupational exosure received over working lifetime
Calculation of baseline data: rxposure Cr^{VI} is assumed to have no effect (ß=0, see footnote for column 11)

Exact Age	Population At risk	Level of exposure	Cumulative expsoure	q_x	d_x	Deaths in general population		Expected no. of death		Predicted no. of lung cancer deaths	Predicted cumulative no. of lung cancer deaths
(3)	I_x					lung cancer	all causes	lung cancer	other causes		
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
20	1000.000										
21	999.070										
22	998.201										
23	997.372										
24	996.564										
25	995.757										
26	994.951										
27	994.135										
28	993.310										
29	992.475										
30	991.622										
31	990.749										
32	989.848										
33	988.917										
34	987.938										
35	986.901										
35	985.786										
37	984.573										
38	983.254										
39	981.798										
40	980.178										
41	978.375										
42	976.360										
43	974.104										
44	971.571										

Table 2 **Quantitative risk assessment for lung cancer in relation to occupational exposure received over working lifetime**
Calculation of baseline data: exposure to Cr^{VI} is assumed to have no effect (β=0, see footnote for column 11)

Exact age (x)	Population at risk l_x	Level of exposure	Cumulative exposure	q_x	d_x	Deaths in general population		Expected no. of deaths		Predicted no. of lung cancer deaths	Predicted cumulative no. of lung cancer deaths
						lung cancer	all causes	lung cancer	other causes		
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
20	1000.000	50	0	0.000930	0.93000	1	1576	0.00059	0.92941	0.00059	0.00
21	999.070	50	50	0.000870	0.86919	1	1576	0.00055	0.86864	0.00055	0.00
22	998.201	50	100	0.000830	0.82851	1	1576	0.00053	0.82798	0.00053	0.00
23	997.372	50	150	0.000810	0.80787	1	1576	0.00051	0.80736	0.00051	0.00
24	996.564	50	200	0.000810	0.80722	1	1576	0.00051	0.80670	0.00051	0.00
25	995.757	50	250	0.000810	0.80656	15	1427	0.00848	0.79809	0.00848	0.01
26	994.951	50	300	0.000820	0.81586	15	1427	0.00858	0.80728	0.00858	0.02
27	994.135	50	350	0.000830	0.82513	15	1427	0.00867	0.81646	0.00867	0.03
28	993.310	50	400	0.000840	0.83438	15	1427	0.00877	0.82561	0.00877	0.04
29	992.475	50	450	0.000860	0.85353	15	1427	0.00897	0.84456	0.00897	0.05
30	991.622	50	500	0.000880	0.87263	26	1754	0.01294	0.85969	0.01294	0.06
31	990.749	50	550	0.000910	0.90158	26	1754	0.01336	0.88822	0.01336	0.07
32	989.848	50	600	0.000940	0.93046	26	1754	0.01379	0.91666	0.01379	0.09
33	988.917	50	650	0.000990	0.97903	26	1754	0.01451	0.96452	0.01451	0.10
34	987.938	50	700	0.001050	1.03733	26	1754	0.01538	1.02196	0.01538	0.12
35	986.901	50	750	0.001130	1.11520	60	2143	0.03122	1.08397	0.03122	0.15
36	985.786	50	800	0.001230	1.21252	60	2143	0.03395	1.17857	0.03395	0.18
37	984.573	50	850	0.001340	1.31933	60	2143	0.03694	1.28239	0.03694	0.22
38	983.254	50	900	0.001480	1.45522	60	2143	0.04074	1.41447	0.04074	0.26
39	981.798	50	950	0.001650	1.61997	60	2143	0.04536	1.57461	0.04536	0.30
40	980.178	50	1000	0.001840	1.80353	172	3392	0.09145	1.71208	0.09145	0.40
41	978.375	50	1050	0.002060	2.01545	172	3392	0.10220	1.91325	0.10220	0.50
42	976.360	50	1100	0.002310	2.25539	172	3392	0.11437	2.14103	0.11437	0.61

Exact age (x)	Population at risk l_x	Level of exposure	Cumulative exposure	q_x	d_x	Deaths in general population		Expected no. of deaths		Predicted no. of lung cancer deaths	Predicted cumulative no. of lung cancer deaths
						lung cancer	all causes	lung cancer	other causes		
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
45	968.725	50	1250	0.003320	3.21617	457	5920	0.24827	2.96789	0.24827	1.13
46	965.509	50	1300	0.003760	3.63031	457	5920	0.28025	3.35007	0.28025	1.41
47	961.878	50	1350	0.004250	4.08798	457	5920	0.31558	3.77241	0.31558	1.73
48	957.790	50	1400	0.004810	4.60697	457	5920	0.35564	4.25133	0.35564	2.08
49	953.183	50	1450	0.005450	5.19485	457	5920	0.40102	4.79383	0.40102	2.49
50	947.988	50	1500	0.006150	5.83013	1199	10969	0.63728	5.19285	0.63728	3.12
51	942.158	50	1550	0.006940	6.53858	1199	10969	0.71472	5.82386	0.71472	3.84
52	935.620	50	1600	0.007810	7.30719	1199	10969	0.79873	6.50846	0.79873	4.64
53	928.313	50	1650	0.008770	8.14130	1199	10969	0.88991	7.25139	0.88991	5.53
54	920.171	50	1700	0.009820	9.03608	1199	10969	0.98772	8.04837	0.98772	6.51
55	911.135	50	1750	0.010980	10.00426	2529	19688	1.28509	8.71918	1.28509	7.80
56	901.131	50	1800	0.012240	11.02984	2529	19688	1.41683	9.61302	1.41683	9.22
57	890.101	50	1850	0.013610	12.11428	2529	19688	1.55613	10.55815	1.55613	10.77
58	877.987	50	1900	0.015090	13.24882	2529	19688	1.70186	11.54696	1.70186	12.47
59	864.738	50	1950	0.016700	14.44112	2529	19688	1.85502	12.58611	1.85502	14.33
60	850.297	50	2000	0.018430	15.67097	3739	27170	2.15656	13.51441	2.15656	16.49
61	834.626	50	2000	0.020280	16.92621	3739	27170	2.32930	14.59691	2.32930	18.82
62	817.700	50	2000	0.022290	18.22653	3739	27170	2.50824	15.71828	2.50824	21.32
63	799.473	50	2000	0.024480	19.57110	3739	27170	2.69328	16.87783	2.69328	24.02
64	779.902	50	2000	0.026870	20.95597	3739	27170	2.88386	18.07211	2.88386	26.90
65	758.946	0	2000	0.029490	22.38132	5094	40298	2.82918	19.55214	2.82918	29.73
66	736.565	0	1950	0.032380	23.84997	5094	40298	3.01483	20.83513	3.01483	32.74
67	712.715	0	1900	0.035550	25.33701	5094	40298	3.20281	22.13420	3.20281	35.95
68	687.378	0	1850	0.039030	26.82835	5094	40298	3.39133	23.43703	3.39133	39.34
69	660.549	0	1800	0.042850	28.30454	5094	40298	3.57793	24.72661	3.57793	42.92
70	632.245	0	1750	0.047030	29.73448	5619	51891	3.21979	26.51469	3.21979	46.14
71	602.510	0	1700	0.051600	31.08954	5619	51891	3.36652	27.72302	3.36652	49.50
72	571.421	0	1650	0.056580	32.33099	5619	51891	3.50095	28.83004	3.50095	53.00

Exact age (x) (1)	Population at risk l_x (2)	Level of exposure (3)	Cumulative exposure (4)	q_x (5)	d_x (6)	Deaths in general population: lung cancer (7)	Deaths in general population: all causes (8)	Expected no. of deaths: lung cancer (9)	Expected no. of deaths: other causes (10)	Predicted no. of lung cancer deaths (11)	Predicted cumulative no. of lung cancer deaths (12)
73	539.090	0	1600	0.061980	33.41279	5619	51891	3.61809	29.79470	3.61809	56.62
74	505.677	0	1550	0.067830	34.30008	5619	51891	3.71417	30.58590	3.71417	60.34
75	471.377	0	1500	0.074160	34.95732	4481	50959	3.07392	31.88340	3.07392	63.41
76	436.420	0	1450	0.080960	35.33254	4481	50959	3.10691	32.22563	3.10691	66.52
77	401.087	0	1400	0.088270	35.40396	4481	50959	3.11319	32.29077	3.11319	69.63
78	365.683	0	1350	0.096100	35.14215	4481	50959	3.09017	32.05198	3.09017	72.72
79	330.541	0	1300	0.104450	34.52501	4481	50959	3.03590	31.48911	3.03590	75.76
80	296.016	0	1250	0.113340	33.55046	2125	35815	1.99064	31.55982	1.99064	77.75
81	262.466	0	1200	0.122780	32.22552	2125	35815	1.91203	30.31350	1.91203	79.66
82	230.240	0	1150	0.132780	30.57127	2125	35815	1.81388	28.75740	1.81388	81.47
83	199.669	0	1100	0.143330	28.61853	2125	35815	1.69801	26.92051	1.69801	83.17
84	171.050	0	1050	0.154400	26.41016	2125	35815	1.56699	24.84317	1.56699	84.74
Total								84.74	770.62	84.74	

(1) 20 = 20 years 0 days.

(2) population at risk at exact age, for purpose of calculation l_{20}=1000. Population then suffers theoretical attenuation; $l_{x+1} = l_x - d_x$ - occupational lung cancers at age x

(3) occupational exposure in $\mu g/m^3$ for working year.

(4) cumulative exposure at exact age in $\mu g.m^{-3}.y$; exposures received more than 40 years ago are ignored.

(5) probability of death before next birthday given subject is alive at exact age *x*, figures shown obtained from 1981 life-table for males in England and Wales.

(6) number of deaths occurring at each age, in the absence of any exposure effect, it is given by col.(2) x col.(5).

(7) male deaths in general population from lung cancer, obtained from 1981 mortality statistics, for relevant five-year age-group.

(8) male deaths in general population from all causes, obtained from 1981 mortality statistics, for relevant five-year age-group.

(9) the expected number of deaths from lung cancer, in the absence of any exposure effect, calculated as [col.(7) / col.(8)] x col.(6).

(10) the expected number of deaths from causes excluding lung cancer, calculated as col.(6) - col.(9).

(cont'd)

(11) mortality from lung cancer is assumed to be influenced by cumulative exposure according to the formula

$$RR = 1 + X\beta$$

where RR = risk of dying given an exposure *x* relative to risk of dying if unexposed
X = cumulative exposure in $\mu g.m^{-3}.y$ (given in col.(4))
β = risk coefficient, estimated from epidemiological studies

The predicted number of lung cancer deaths = col.(9) x RR. For this table exposure is assumed to have no effect ($\beta = 0$). Consequently, the predicted number of lung cancers (col.(11)) is the same as the expected number of lung cancers (col.(9)).

(12) summation of predicted numbers up to and including current age.

Table 3 **Quantitative risk assessment for lung cancer in relation to occupational exposure received over working lifetime**
Final calculations: exposure to Cr^{VI} is assumed to have an effect (β=0.0002213, see footnote for column 11)

Exact age (x)	Population at risk l_x	Level of exposure	Cumulative exposure	q_x	d_x	Deaths in general population		Expected no. of deaths		Predicted no. of lung cancer deaths	Predicted cumulative no. of lung cancer deaths
						lung cancer	all causes	lung cancer	other causes		
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
20	1000.000	50	0	0.000930	0.93000	1	1576	0.00059	0.92941	0.00059	0.00
21	999.070	50	50	0.000870	0.86919	1	1576	0.00055	0.86864	0.00056	0.00
22	998.201	50	100	0.000830	0.82851	1	1576	0.00053	0.82798	0.00054	0.00
23	997.372	50	150	0.000810	0.80787	1	1576	0.00051	0.80736	0.00053	0.00
24	996.564	50	200	0.000810	0.80722	1	1576	0.00051	0.80670	0.00053	0.00
25	995.757	50	250	0.000810	0.80656	15	1427	0.00848	0.79809	0.00895	0.01
26	994.950	50	300	0.000820	0.81586	15	1427	0.00858	0.80728	0.00915	0.02
27	994.134	50	350	0.000830	0.82513	15	1427	0.00867	0.81646	0.00935	0.03
28	993.308	50	400	0.000840	0.83438	15	1427	0.00877	0.82561	0.00955	0.04
29	992.473	50	450	0.000860	0.85353	15	1427	0.00897	0.84455	0.00987	0.05
30	991.618	50	500	0.000880	0.87262	26	1754	0.01294	0.85969	0.01437	0.06
31	990.744	50	550	0.000910	0.90158	26	1754	0.01336	0.88821	0.01499	0.08
32	989.841	50	600	0.000940	0.93045	26	1754	0.01379	0.91666	0.01562	0.09
33	988.909	50	650	0.000990	0.97902	26	1754	0.01451	0.96451	0.01660	0.11
34	987.928	50	700	0.001050	1.03732	26	1754	0.01538	1.02195	0.01776	0.13
35	986.888	50	750	0.001130	1.11518	60	2143	0.03122	1.08396	0.03641	0.17
36	985.768	50	800	0.001230	1.21249	60	2143	0.03395	1.17855	0.03996	0.21
37	984.549	50	850	0.001340	1.31930	60	2143	0.03694	1.28236	0.04389	0.25
38	983.223	50	900	0.001480	1.45517	60	2143	0.04074	1.41443	0.04886	0.30
39	981.760	50	950	0.001650	1.61990	60	2143	0.04535	1.57455	0.05489	0.35
40	980.130	50	1000	0.001840	1.80344	172	3392	0.09145	1.71199	0.11169	0.46
41	978.306	50	1050	0.002060	2.01531	172	3392	0.10219	1.91312	0.12594	0.59
42	976.267	50	1100	0.002310	2.25518	172	3392	0.11435	2.14082	0.14219	0.73
43	973.984	50	1150	0.002600	2.53236	172	3392	0.12841	2.40395	0.16109	0.89
44	971.419	50	1200	0.002930	2.84626	172	3392	0.14433	2.70193	0.18265	1.08

Exact age (x)	Population at risk l_x	Level of exposure	Cumulative exposure	q_x	d_x	Deaths in general population		Expected no. of deaths		Predicted no. of lung cancer deaths	Predicted cumulative no. of lung cancer deaths
						lung cancer	all causes	lung cancer	other causes		
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
45	968.535	50	1250	0.003320	3.21554	457	5920	0.24823	2.96731	0.31689	1.39
46	965.251	50	1300	0.003760	3.62934	457	5920	0.28017	3.34917	0.36077	1.75
47	961.541	50	1350	0.004250	4.08655	457	5920	0.31546	3.77108	0.40971	2.16
48	957.360	50	1400	0.004810	4.60490	457	5920	0.35548	4.24942	0.46561	2.63
49	952.645	50	1450	0.005450	5.19191	457	5920	0.40079	4.79112	0.52940	3.16
50	947.324	50	1500	0.006150	5.82604	1199	10969	0.63683	5.18921	0.84823	4.01
51	941.287	50	1550	0.006940	6.53253	1199	10969	0.71406	5.81847	0.95899	4.97
52	934.509	50	1600	0.007810	7.29852	1199	10969	0.79779	6.50073	1.08027	6.05
53	926.928	50	1650	0.008770	8.12916	1199	10969	0.88858	7.24058	1.21304	7.26
54	918.475	50	1700	0.009820	9.01942	1199	10969	0.98590	8.03353	1.35680	8.62
55	909.084	50	1750	0.010980	9.98175	2529	19688	1.28219	8.69955	1.77876	10.39
56	898.606	50	1800	0.012240	10.99894	2529	19688	1.41286	9.58608	1.97565	12.37
57	887.044	50	1850	0.013610	12.07267	2529	19688	1.55078	10.52189	2.18568	14.56
58	874.337	50	1900	0.015090	13.19374	2529	19688	1.69479	11.49895	2.40739	16.96
59	860.430	50	1950	0.016700	14.36919	2529	19688	1.84578	12.52341	2.64230	19.61
60	845.265	50	2000	0.018430	15.57823	3739	27170	2.14380	13.43443	3.09264	22.70
61	828.738	50	2000	0.020280	16.80680	3739	27170	2.31287	14.49393	3.33654	26.04
62	810.907	50	2000	0.022290	18.07512	3739	27170	2.48741	15.58771	3.58833	29.62
63	791.731	50	2000	0.024480	19.38158	3739	27170	2.66720	16.71438	3.84770	33.47
64	771.169	50	2000	0.026870	20.72131	3739	27170	2.85156	17.86975	4.11367	37.58
65	749.186	0	2000	0.029490	22.09348	5094	40298	2.79280	19.30069	4.02889	41.61
66	725.856	0	1950	0.032380	23.50322	5094	40298	2.97100	20.53222	4.25309	45.87
67	701.071	0	1900	0.035550	24.92307	5094	40298	3.15048	21.77258	4.47516	50.34
68	674.823	0	1850	0.039030	26.33834	5094	40298	3.32938	23.00896	4.69245	55.03
69	647.122	0	1800	0.042850	27.72916	5094	40298	3.50519	24.22397	4.90145	59.94
70	617.996	0	1750	0.047030	29.06436	5619	51891	3.14722	25.91714	4.36607	64.30
71	587.713	0	1700	0.051600	30.32599	5619	51891	3.28384	27.04215	4.51925	68.82
72	556.152	0	1650	0.056580	31.46706	5619	51891	3.40740	28.05966	4.65159	73.47

Exact age (x)	Population at risk l_x	Level of exposure	Cumulative exposure	q_x	d_x	Deaths in general population		Expected no. of deaths		Predicted no. of lung cancer deaths	Predicted cumulative no. of lung cancer deaths
						lung cancer	all causes	lung cancer	other causes		
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
73	523.440	0	1600	0.061980	32.44283	5619	51891	3.51306	28.92977	4.75697	78.23
74	489.754	0	1550	0.067830	33.21999	5619	51891	3.59722	29.62277	4.83111	83.06
75	455.300	0	1500	0.074160	33.76503	4481	50959	2.96907	30.79595	3.95466	87.02
76	420.549	0	1450	0.080960	34.04765	4481	50959	2.99393	31.05373	3.95463	90.97
77	385.541	0	1400	0.088270	34.03168	4481	50959	2.99252	31.03916	3.91967	94.89
78	350.582	0	1350	0.096100	33.69092	4481	50959	2.96256	30.72836	3.84764	98.74
79	316.006	0	1300	0.104450	33.00682	4481	50959	2.90240	30.10441	3.73740	102.47
80	282.164	0	1250	0.113340	31.98048	2125	35815	1.89749	30.08299	2.42238	104.90
81	249.659	0	1200	0.122780	30.65310	2125	35815	1.81873	28.83437	2.30171	107.20
82	218.523	0	1150	0.132780	29.01544	2125	35815	1.72156	27.29387	2.15969	109.36
83	189.069	0	1100	0.143330	27.09927	2125	35815	1.60787	25.49140	1.99928	111.36
84	161.578	0	1050	0.154400	24.94771	2125	35815	1.48021	23.46749	1.82416	113.18
Total								82.80	750.53	113.18	

(1) 20 = 20 years 0 days.

(2) population at risk at exact age, for purpose of calculation l_{20}=1000. Population then suffers theoretical attenuation; $l_{x+1} = l_x - d_x$ - occupational lung cancers at age x

(3) occupational exposure in $\mu g/m^3$ for working year.

(4) cumulative exposure at exact age in $\mu g.m^{-3}.y$; exposures received more than 40 years ago are ignored.

(5) probability of death before next birthday given subject is alive at exact age *x*, figures shown obtained from 1981 life-table for males in England and Wales.

(6) number of deaths occurring at each age, in the absence of any exposure effect, it is given by col.(2) x col.(5).

(7) male deaths in general population from lung cancer, obtained from 1981 mortality statistics, for relevant five-year age-group.

(8) male deaths in general population from all causes, obtained from 1981 mortality statistics, for relevant five-year age-group.

(9) the expected number of deaths from lung cancer, in the absence of any exposure effect, calculated as [col.(7) / col.(8)] x col.(6).

(10) the expected number of deaths from causes excluding lung cancer, calculated as col.(6) - col.(9).

(cont'd)

(11) mortality from lung cancer is assumed to be influenced by cumulative exposure according to the formula

$$RR = 1 + X\beta$$

where RR = risk of dying given an exposure *x* relative to risk of dying if unexposed
X = cumulative exposure in $\mu g.m^{-3}.y$ (given in col.(4))
β = risk coefficient, estimated from epidemiological studies ($1.66/(15y \times 500\ \mu g.m^{-3}) = 0.0002213\ \mu g.y.m^{-3}$)

The predicted number of lung cancer deaths = col.(9) x RR.

(12) summation of predicted numbers up to and including current age.

Table 4 **Predictions of numbers of occupational lung cancer deaths (and SMRs) in a cohort of 1,000 male workers exposed for a working lifetime at various levels of Cr^{VI} exposure**

Excess relative risk from ten published studies [a]	TWA exposure for working lifetime ($\mu g/m^3$)	assumption 1[b]: extra lung cancers and (SMRs)		assumption 2[c]: extra lung cancers and (SMRs)		assumption 3[d]: extra lung cancers and (SMRs)	
1.66[e]	50	28.4	(137)	14.4	(118)	7.2	(109)
	25	14.4	(118)	7.2	(109)	3.6	(105)
	10	5.8	(107)	2.9	(104)	1.5	(102)
	5	2.9	(104)	1.5	(102)	0.7	(101)
	1	0.6	(101)	0.3	(100)	0.1	(100)
1.36[f]	50	23.4	(130)	11.8	(115)	5.9	(108)
	25	11.8	(115)	5.9	(108)	3.0	(104)
	10	4.7	(106)	2.4	(103)	1.2	(102)
	5	2.4	(103)	1.2	(102)	0.6	(101)
	1	0.5	(101)	0.2	(100)	0.1	(100)
1.06[g]	50	18.3	(123)	9.2	(112)	4.6	(106)
	25	9.2	(112)	4.6	(106)	2.3	(103)
	10	3.7	(105)	1.9	(102)	0.9	(101)
	5	1.9	(102)	0.9	(101)	0.5	(101)
	1	0.4	(100)	0.2	(100)	0.1	(100)

a. studies selected by Steenland *et al.* (1996) as representing largest and best designed epidemiological studies of Cr^{VI} -exposed workers.

b. assuming mean length of Cr^{VI}-exposed employment in selected published studies is 15 years and mean Cr^{VI}-in-air concentration is 500 $\mu g/m^3$ (i.e. mean final cumulative exposure of study subjects is 7,500 $\mu g.m^{-3}.y$).

c. assuming mean length of Cr^{VI} -exposed employment in selected published studies is 15 years and mean Cr^{VI}-in-air concentration is 1,000 $\mu g/m^3$ (i.e. mean final cumulative exposure of study subjects is 15,000 $\mu g.m^{-3}.y$).

d. assuming mean length of Cr^{VI} -exposed employment in selected published studies is 15 years and mean Cr^{VI}-in-air concentration is 2,000 $\mu g/m^3$ (i.e. mean final cumulative exposure of study subjects is 30,000 $\mu g.m^{-3}.y$).

e. assuming all excess lung cancer risk (2.66 - 1.00) in published studies represents a Cr^{VI} effect.

f. assumes some of the excess lung cancer risk in published studies (30% above baseline) is due to smoking or other occupational exposures.

g. assumes some of the excess lung cancer risk in published studies (60% above baseline) is due to smoking or other occupational exposure.

SCOEL's response to comments received during the consultation period

SCOEL received a number of comments during the consultation period and all these were considered during a subsequent SCOEL meeting. Some comments referred to minor textual changes and these have been addressed. The most substantial comment related to the risk assessment methodology used for lung cancer risk and attention was drawn, in particular, to a recent publication (Crump *et al*, 2003) which gave a lung cancer risk assessment based upon one well-studied US facility producing chromate chemicals. This study used actual rather than estimated data of exposure and thus one commentator felt this might be more reliable than the estimated data used in the current SCOEL position, which was based on that employed in the ICBA Criteria Document. On balance, however, SCOEL felt that this latter position, which had used data pooled from lung cancer risk from ten studies (Steenland *et al*, 1996), took into account exposure from a wide range of hexavalent chromium compounds. As the Criteria Document had stressed that there was a wide variability in the carcinogenic potency of hexavalent chromium compounds, SCOEL felt that it was more robust to use such a pooled analysis to reflect this carcinogenic variability in potency, in spite of the fact that the actual exposures were based on estimates. For this reason, SCOEL was content to remain with its original position.

References

Steenland K, Loomis D, Shy C, Simonsen N. Review of occupational lung carcinogens. *Am J Ind Med* 1996;**29**:474-490.

Crump C, Crump K, Hack E, Luippold R, Mundt K, Liebig E, Panko J, Paustenbach D and Proctor D. Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. *Risk Analysis* 2003; **23**:1147.