EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C2 - Management of scientific committees; scientific co-operation and networks

Scientific Committee on Food

SCF/CS/NUT/UPPLEV/67 Final
23 April 2003

Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Trivalent Chromium

(expressed in 4 April 2003)

B-1049 Bruxelles/ Brussels - Belgium - Office: BE232 - 6/37.
Telephone: direct line (+32-2) 29 581.10/659.48/648.70, exchange 299.11.11. Fax: (+32-2) 299.48.91
Telex: COMEU B 21877. Telegraphic address: COMEUR Brussels
http://europa.eu.int/comm/food/fs/sc/scf/index_en.html

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FOREWORD

This opinion is one in the series of opinions of the Scientific Committee on Food (SCF) on the upper levels of vitamins and minerals. The terms of reference given by the European Commission for this task, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used in this opinion, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF, at the address: http://www.europa.eu.int/comm/food/fs/sc/scf/index_en.html.

1. INTRODUCTION

Chromium is ubiquitous, occurring in water, soil and biological systems. It occurs in each of the oxidation states from Cr^{0} to Cr^{+6}. The three most stable forms in which chromium occurs in the environment are the 0, +3, and +6 valence state; metal and alloys, trivalent chromium, and hexavalent chromium, respectively. Elemental chromium (Cr^{0}) does not occur naturally. Chromium compounds with oxidation states below +3 are reducing, and above +3 are oxidising. The occurrence of hexavalent chromium compounds is rare and nearly always man-made.

The high energy needed to oxidise the trivalent to the hexavalent form of chromium results in the fact that this oxidation never occurs in biological systems. The strong oxidising property of hexavalent chromium causes its spontaneous reduction in living organisms, irrespective of its solubility.

This evaluation is limited to trivalent chromium (Cr III) because it is the form of chromium found in food and supplements. The biological effects of hexavalent chromium on both animals and man are very different from those of trivalent chromium and are not considered.

1.1 Regulations

Under European legislation (Directive 2002/46/EC), chromium (III) chloride and chromium (III) sulphate are included in the list of substances that can be used in the manufacture of foods for particular nutritional uses and in food supplements. In this list, organic complexes of chromium (e.g. chromium picolinate) are not mentioned. The Committee has concluded that an evaluation of the acceptability of chromium picolinate as a nutrient source of chromium in Foods for Particular Nutritional Uses (FPNUs) is not possible unless data on bioavailability in humans are provided (SCF, 1999).

In Germany, all special permissions for the use of chromium picolinate in food supplements were withdrawn in 2001 due to recent investigations which do not exclude adverse effects on human health (BMVEL, 2001; BgVV, 2002).

2. NUTRITIONAL BACKGROUND

2.1 Food levels and dietary intake

In the UK, a total diet study has shown that the highest concentration of chromium has been found in meat products (230 µg/kg), followed by oils and fats (170 µg/kg), bread (150 µg/kg), nuts and miscellaneous cereals (140 µg/kg), fish, sugar, and preserves (130 µg/kg). The lowest concentrations have been found in milk (10 µg/kg), fresh fruits, and green vegetables (20 µg/kg), and in eggs (40 µg/kg). The concentrations of chromium in uncontaminated drinking water mostly are below 1 µg/L (EGVM, 2002a). A number of multivitamin and mineral food supplements contain up to 100 µg chromium in a daily serving unit (EGVM 2002b). In the USA, relatively high concentrations of chromium have been found in seafood (120-470 µg/kg) followed by meat and fish (110-230 µg/kg), grains and cereals (40-220 µg/kg), fresh fruits (90-190 µg/kg), and fresh vegetables (30-140 µg/kg).

According to WHO (1996) high dietary intakes of chromium reported before 1980 are generally questionable, since the chromium analysis on which they were based, were unreliable due to contamination and by analytical problems. A number of reports indicate that many diets in the US supply less than 50 µg of chromium per day (Anderson and Kozlovsky, 1986; Anderson, 1989; Anderson *et al.*, 1988; Offenbacher *et al.*, 1985).

Table 1. Dietary chromium intake in µg/day

Country	Type of survey / Method	Range	Mean
Germany[a]	Duplicate diet samples	- -	61 (M) 84 (F)
UK[b]	Food (total diet study in 1997) Supplements Drinking water	up to 170[α] up to 100[β] up to 2[γ]	100 - -
Sweden[c]	Randomly selected 24-hour diets	50-580	160
Spain	Calculated from midday meal by extrapolation to 100%[δ]	-	120
	Duplicate diets samples from Southern Spain[ε]	9,4-205	100
USA[d]	7 days self selected diets	22-48 (M) 13-36 (F)	33 (M) 25 (F)
	From supplements based on the NHANES III, 1988-1994[κ]	3,2-100[λ] (M) 4,4-127[λ] (F)	29,5 (M) 30,0 (F)

(M): males; (F): females.

[a] D-A-CH, 2000.

[b] EGVM, 2002b

[α] EGVM used the 97,5th percentile as the "maximum estimated daily intake".

[β] Related to the daily serving unit.

[γ] Estimated intake from 2 litres of water containing <1µg/L.

[c] Abdulla *et al.*, 1989.

[δ] Barberá *et al.*, 1989; [ε] Garcia *et al.*, 2001.

[d] FNB, 2001.

[κ] Third National Health and Nutrition Examination Survey, 1988-1994.

[λ] Ranges from the 5th percentile to the 95th percentile.

2.2 Nutritional requirements and intake recommendations

The Committee stated in 1993 that since data on the essentiality and metabolism of chromium are so sparse, the Committee is unable to specify any requirements (SCF, 1993).

The UK Committee on Medical Aspects of Food Policy calculated a theoretical requirement for adults from balance studies of 23 µg/day by using regression equations and concluded that a safe and adequate level of intake lies above 25 µg for adults and between 0,1 µg/kg bw/day and 1,0 µg/kg bw/day for children and adolescents, respectively (COMA, 1991).

The Societies for Nutrition of Germany (DGE), Austria (ÖGE), and Switzerland (SGE), jointly established an adequate daily intake of 30-100 µg/day for adults (D-A-CH, 2000).

Currently, there is no formal Recommended Dietary Allowance (RDA) for chromium. The US Food and Nutrition Board derived Adequate Intakes (AI) for chromium for different age groups, e.g. 35 µg/day and 25 µg/day for 19 to 50 year old men and women, respectively (FNB, 2001).

2.3 Deficiency

Chromium deficiency has not been seen in humans except in patients during long-term parenteral nutrition without substitution of chromium. The deficiency symptoms (impaired glucose tolerance and glucose utilisation, weight loss, neuropathy, elevated plasma fatty acids, depressed respiratory quotient and abnormalities in nitrogen metabolism) disappeared rapidly after oral supplementation (200 µg/day) (Jeejeebhoy *et al.*, 1977; Freund *et al.*, 1979).

Chromium-deficient rats exhibit a glucose intolerance similar to clinical diabetes mellitus. Other deficiency signs in animals include impaired growth, elevated serum cholesterol and triglycerides, increased incidence of aortic plaques, corneal lesions and decreased fertility and sperm count (Anderson, 1988).

3. BIOLOGICAL CONSIDERATIONS

3.1 Function

Trivalent chromium is considered to be an essential element both in animal feeding and human nutrition. It influences carbohydrate, lipid, and protein metabolism via an effect on insulin action. However, the mechanism still is not quite clear neither is the exact structure of the biologically active form of chromium, the "Glucose Tolerance Factor" (GTF) (WHO, 1996). The GTF tentatively is identified as a chromium-nicotinic acid complex and has been suggested to operate through activation of membrane phosphotyrosine phosphatase in mammals (Mertz, 1993; Davis *et al.*, 1996). Beneficial effects have been reported in presumably chromium-deficient diabetics, where supplementing the diet with chromium decreased fasting blood glucose levels, improved glucose tolerance, lower insulin levels, and decreased total cholesterol and triglyceride levels while HDL-cholesterol levels were increased (Mooradian *et al.*, 1994).

3.2 Absorption, metabolism and distribution

The absorption of ingested trivalent chromium depends, among other factors, on the chemical properties of the ingested compound, on the level of dietary intake, and on the presence of other dietary components in the diet (interactions). Chromium affects the binding of iron to transferrin. Trivalent chromium ingested as chromium picolinate is better absorbed than chromium from the chloride compound. Hepatic and renal chromium concentrations in rats were roughly 2- to 6-fold greater when chromium picolinate was fed compared to chromium chloride (Anderson *et al.*, 1997a). Due to the natural presence of chelating agents in the diet the bioavailability of chromium from food can vary significantly. Absorption of chromium from various sources in man is shown in Table 2.

Trivalent chromium is bound to plasma proteins such as transferrin, whereas hexavalent chromium is taken up selectively by erythrocytes, reduced to trivalent chromium by glutathione, and bound predominantly to haemoglobin. Therefore, chromium is found in both erythrocytes, and plasma, after gastrointestinal absorption of hexavalent chromium, but only in the plasma after gastrointestinal absorption of trivalent chromium.

Table 2. Absorption of chromium from various sources in man

Chromium compound	% absorption	References
Chloride	0.4 0.13	Anderson *et al.*, 1983 Kerger *et al.*, 1996
Picolinate	2.8 ± 1.4 (SD)	Gargas *et al.*, 1994
From food	2.4 0.5 - 2.0[1] 0.4 - 2.5[2]	Bunker *et al.*, 1984 ATSDR, 1993 FNB, 2001
Trivalent chromium (reduced from potassium dichromate [VI] dissolved in orange juice)	0.6	Kerger *et al.*, 1996

[1] Several studies with male and female volunteers.
[2] Based on metabolic balance studies or on urinary excretion from physiological intakes.

4. HAZARD IDENTIFICATION

The toxicity of chromium compounds has been reviewed by several institutions (IPCS, 1988; IARC, 1990; WHO, 1996; EPA, 1998a, b, c and d; EGVM, 2002a and 2002b; ATSDR, 2000; FNB, 2001).

4.1 Acute toxicity

In rats the LD_{50} of orally administered trivalent chromium varies with the compound and the sex of the rat. The LD_{50} for chromium acetate is 2365 mg/kg body weight (ATSDR, 2000) and for chromium nitrate nonahydrate 3250 mg/kg body weight (Registry of Toxic Effects, 1980). The oral LD_{50} values for water soluble trivalent chromium compounds given to rats and mice vary from 140 mg/kg to 422 mg/kg (EGVM, 2002).

4.2 Subchronic toxicity

Groups of 8 four week-old Harlan Sprague-Dawley rats were fed a stock diet to which 0, 5, 25, 50, or 100 mg of chromium per kg diet was added as chloride or picolinate for twenty weeks. For the highest dose group, the authors assumed a chromium intake of 15 mg/kg bw/day. Chromium given as picolinate showed a considerably higher bioavailability than trivalent chromium chloride which was indicated by a 2- to 6-fold greater hepatic and renal chromium concentration in animals fed chromium picolinate. Histologically, no changes in the liver and kidney have been observed but other organs were not examined histologically. However, there were no statistically significant differences in body weight, organ weights, or blood variables among all the groups tested at the age of 11, 17, and 24 weeks (Anderson *et al.*, 1997a).

4.3 Chronic toxicity

Ivankovic and Preussmann (1975) performed a chronic toxicity/carcinogenicity study with BD rats (groups of 60 animals of both sexes) fed 0, 1, 2, or 5% chromium (III) oxide (Cr_2O_3) baked in bread 5 days/week for 840 days (600 feeding days in total). The highest dose corresponds to 2144 mg Cr_2O_3/kg bw/day or to about 1500 mg trivalent Cr/kg bw/day. No toxic or carcinogenic effects were noted at any feeding level. The lack of toxicity may be explained by the poor absorption of the administered pigment Cr_2O_3.

In another group of rats fed during the same study in the same way for 90 days, no changes could be detected in serum protein, bilirubin, haematology, urinalysis, and histopathology but some reductions (12-37%) in the absolute weights of the livers and spleens in the 5%-group.

4.4 Carcinogenicity

4.4.1 Oral administration

In addition to the chronic toxicity/carcinogenicity study carried out by Ivankovic and Preussman (1975) two other oral studies were conducted, one in mice and one in rats.

4.4.1.1 Mice

Swiss mice (groups of 54 males and 54 females) received 5 mg/L chromium acetate in drinking water for life. Only 60% of males survived 18 months. No increased incidence of tumours was observed (Schroeder *et al.*, 1964).

4.4.1.2 Rats

Long Evans rats (groups of 46 males and 50 females) received 5 mg/L chromium acetate in drinking water for life. At least 70% of the animals survived for up to two years. No increased incidence of tumours was observed (Schroeder *et al.*, 1965).

4.4.2 Other ways of administration

Several studies were conducted, mainly in rats and mice by inhalation, intratracheal instillation, intrabronchial, -pleural, -muscular, -peritoneal, -femoral and intravenous administration. No significant increased incidence of tumours was observed. All these studies are reported in the IARC Monograph no. 49 (1990); all of them present strong limitations.

According to IARC (1990) “there is limited evidence in experimental animals for the carcinogenicity of chromium trioxide (chromic acid) and sodium dichromate” and “there is inadequate evidence in experimental animals for the carcinogenicity of metallic chromium, barium chromate and chromium (III) compounds”.

4.4.3 Human data

All the exposures considered by the IARC (1990) in the epidemiological studies described for hexavalent chromium include simultaneous exposure to chromium (III) and chromium (VI) compounds. The chromium (VI) species is widely considered the aetiological agent responsible for the excess cancer risk in chromium workers, but this is based on the results of animal carcinogenicity and genotoxicity as well as on biological considerations. There are no adequate data on the carcinogenicity of trivalent chromium compounds and the overall evaluation of IARC was: “metallic chromium and chromium (III) compounds are not classifiable as to their carcinogenicity to humans” (Group 3) (IARC, 1990).

4.5 Genotoxicity

4.5.1 Experimental data

A very large number of chromium compounds have been assayed with *in vitro* and *in vivo* genotoxicity tests. Comprehensive reviews are, among others, those by Levis and Bianchi (1982), IPCS (1988), IARC (1990), De Flora *et al.* (1990) and EPA (1998 a and d).

When evaluating the results of the genotoxicity tests it is necessary to take into consideration several properties of the tested compound (oxidation state, solubility, ability to penetrate cell membranes, intracellular stability, and reactivity with cellular components).

A very comprehensive review on the genotoxicity of chromium compounds by De Flora *et al.* (1990), showed that the large majority of the results with chromium (VI) compounds were positive for different genetic end-points *in vitro* and *in vivo*, as a function of their solubility and bioavailability to target cells.

On the other hand, chromium (III) compounds, although even more reactive than chromium VI with purified nucleic acids, generally did not produce gene mutations, sister chromatid exchanges (SCE) or cell transformation in cultured mammalian cells (IARC, 1990).

Chromium (III) and chromium (VI) compounds have been shown to decrease the fidelity of DNA synthesis (Raffetto, 1977, Snow, 1994). Trivalent chromium was not mutagenic in bacterial assays (Venitt and Levy, 1974; Petrilli and De Flora, 1978a, 1978b). In one study it was weakly mutagenic in *Bacillus subtilis* (Nakamuro *et al.*, 1978). Conflicting results were obtained in *in vitro* chromosomal aberration assays in mammalian cells: positive results were shown with $CrCl_3$ (Raffetto, 1977), $CrCl_3$, $Cr(NO_3)_3$, $KCr(SO_4)_2$, or $Cr(CH_3COO)_3$ (Levis and Majone, 1979) and hydrated $CrCl_3$ in Don Chinese hamster cells (Ohno *et al.*, 1982) and $Cr(CH_3COO)_3$ in human leukocytes (Nakamuro *et al.*, 1978). Other compounds were not clastogenic, as $Cr_2(SO_4)_3$ in mouse FM_3A cells (Umeda and Nishimura, 1979), $CrCl_3$ or $Cr(NO_3)_3$ in human leukocytes (Nakamuro *et al.*, 1978), and $Cr_2(SO_4)_3$ in Don Chinese hamster cells (Ohno *et al.*, 1982). $CrCl_3 \cdot 6H_2O$ was shown to induce chromosome aberrations in human lymphocytes via indirect action (Friedman *et al.*, 1987).

Blasiak and Kowalik (2000) have reported that both tri-(chromium chloride) and hexavalent (potassium dichromate) chromium were positive in the comet assay carried out in isolated human peripheral lymphocytes. The results of this study also suggest that reactive oxygen species and hydrogen peroxide may be involved in the formation of DNA strand breaks by hexavalent chromium but not by trivalent chromium; for the last compound, the authors speculate that binding to cellular ligands may be important.

Chromic chloride has been shown to covalently bind to DNA in liver and kidney of rats treated with chromium (III) chloride *in vivo* (Cupo *et al.*, 1985).

No DNA damage was observed in cells of animals treated *in vivo* with chromium chloride, and no micronuclei were seen in cells of animals given chromium nitrate (IARC, 1990).

Chromium (III) picolinate was clastogenic in a range of soluble doses of 0,05-1 mM; chromosome damage was inferred to be caused by the picolinate ligand because picolinic acid in the absence of chromium was clastogenic in Chinese hamster ovary cells (CHO). Chromium (III) nicotinate and chromium (III) chloride hexahydrate did not produce chromosome damage at equivalent non-toxic concentrations (Stearns *et al.*, 1995b).

Chromium (III) picolinate, and to a lesser extent chromic chloride, were mutagenic at the *hprt* locus of cultured CHO cells at the equivalent doses of 1 mM. An equivalent dose of 3 mM of picolinic acid was highly cytotoxic and at lower doses produced an increase of *hprt* mutants, not statistically significant (Stearns *et al.*, 2002).

In summary, the presently available data indicate that although chromium (III) compounds may bind to DNA and produce DNA-protein cross-links under certain circumstances, differently from chromium (VI) compounds, generally they did not produce gene mutations, sister chromatid exchanges or cell transformation in cultured mammalian cells. Weak clastogenic effects have been observed in some mammalian *in vitro* systems at relatively high and cytotoxic concentrations. No induction of genetic damage or micronuclei has been observed in experimental animals.

4.5.2. Human data

A recent paper by Medeiros *et al.* (2003) suggests that trivalent chromium can lead to an increase of micronucleated perypheral lymphocytes in chronically exposed tannery workers. A group of 33 tanners exposed to trivalent chromium and a small group of 5 manual metal arc stainless steel welders exposed to hexavalent chromium were examined for two end-points: a chemical one, the formation of DNA-protein crosslinks (DPC) and a biological one, the occurrence of micronuclei in perypheral lymphocytes. These determinations were paralleled by quantitative analysis of chromium in plasma and urine. A significant increase in the formation of DPC was observed in tannery workers compared with controls (0.88 ± 0.19 versus $0.57\pm0.21\%$, $P<0.001$ Mann-Whitney test) and even a higher level of DPC was observed in welders ($2.22\pm1.12\%$, $P=0.03$). Tanners showed a significant increase in micronucleated cells compared with controls (6.35 ± 2.94 versus $3.58\pm1.69\%°$, $P<0.01$), whereas in welders this increase was not significant ($5.40\pm1.67°/°°$). Urinary chromium was increased in both groups, with a greater increase observed in tanners compared with controls (2.63 ± 1.62 versus 0.70 ± 0.38 µg/g creatinine, $P<0.001$) than in welders (1.90 ± 0.37 µg/g creatinine, $P<0.005$). Plasma chromium was also increased in both groups.

The results of this study support the causal relationship between chromium exposure (both hexavalent and trivalent) and increased lymphocyte DPC levels.

The interpretation of the increased incidence of micronuclei in tanners is difficult; leather processing involves a considerable number of other substances including formaldehyde and benzidine, whereas in welders trivalent chromium is accompanied by variable amounts of hexavalent chromium and other metals, including nickel, a potential suppressor of chromium-dependend cytogenetic damage (Katsifis *et al.*, 1998). On the other hand, these results are in contrast with the negative findings reported by IARC (1990), according to which no DNA damage was observed in animals treated *in vivo* with chromium chloride, and no micronuclei were seen in animals given chromium nitrate.

4.6 Reproductive toxicity

Chromium (III) chloride dissolved in tap water was given to sexually mature male and female Swiss mice (day 50 of age). Males received water with 1000 or 5000 mg/L chromium chloride and females with 2000 or 5000 mg/L *ad libitum* for 12 weeks. Controls were given tap water, only. Treated animals consumed less water per day than controls did. Chromium chloride reduced fertility and seminal vesicle weights significantly. Body weights were reduced in males but not in females. Testes and ovarian weights were increased whereas uterine weights were significantly reduced. The number of resorptions and dead foetuses was increased in females impregnated by males exposed to the trivalent compound and the number of resorptions in exposed females as well (Elbetieha and Al-Hamood, 1997). Unfortunately, the authors did not report the actual quantitative exposure to chromium chloride but EGVM (2002b) estimated from the given data oral doses for trivalent chromium of approximately 500 or 1250 mg/kg bw/day for females and 250 or 1250 mg/kg bw/day for males.

The fertility of male Sprague Dawley rats exposed to chromium (III) chloride in drinking water at a concentration of 1000 mg/L for 12 weeks, which is equivalent to about 50 mg $CrCl_3$/kg body weight or about 16,5 mg trivalent chromium/kg body weight, was unaffected but significant reductions in the weight of testes and seminal vesicles were observed (Bataineh *et al.*, 1997).

There are no reports of developmental toxicity studies on chromium (III) compounds given orally.

4.7 Human data

In some case reports, the ingestion of chromium picolinate was associated with a number of adverse effects which might be due to the picolinate ligand (Martin and Fuller, 1998; Young *et al.*, 1999; Huszonek, 1993; Wasser and Feldmann, 1997; Cerulli *et al.*, 1998). In controlled clinical supplementation studies, however, no adverse effects have been observed following oral administration of daily doses up to 1 mg chromium, mostly as picolinate, for 6-64 weeks (Table 3). These studies are limited because they were primarily designed as studies on efficacy.

Only one lethal case was reported of a woman, who ingested trivalent chromium as 400 mL of a leather tanning solution containing 48 g of basic chromium sulphate ($CrOHSO_4$), equivalent to about 15 g Cr. She died of cardiogenic shock, complicated by acute renal shock, pancreatitis, haemorrhage, and gut mucosal necrosis (Van Heerden *et al.*, 1994).

Table 3. Randomized Controlled Trials with chromium

Reference	Daily dose (µg Cr)	Compound	Subjects/group	Duration (weeks)
Campbell *et al.*, 1999	924	CrPic	9 men (56-69 yr)	12
Walker *et al.*, 1998	200	CrPic	7 wrestlers	14
Lukaski *et al.*, 1996	182 172	$CrCl_3$ CrPic	12 men	8
Pasman *et al.*, 1997	200	CrPic	11 obese women	64
Kato *et al.*, 1998	400	CrPic	10 obese women	8
Anderson *et al.*, 1997b	200[1] 1000[1]	CrPic CrPic	60 men and women free of disease other than type 2 diabetes (35-65 yr)	16
Thomas and Gropper, 1996	200	CrNic	14 healthy adults and 5 adults with non-insulin-dependent diabetes	8
Hallmark *et al.*, 1996	200	CrPic	8 untrained men (23±4yr)	12
Wilson and Gondy, 1995	220	CrNic	15 (mean age 36 yr)	13
Clancy *et al.*, 1994	200	CrPic	18 football players	9
Hasten *et al.*, 1992	200	CrPic	18 male and 12 female college-age students	12

[1] 100 µg Cr or 500 µg Cr as CrPic two times per day.
CrPic = Chromium (III) picolinate
CrNic = Chromium (III) nicotinate

5. DOSE-RESPONSE ASSESSMENT AND DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

Data on the oral toxicity of trivalent chromium are limited. Doses up to 15 mg chromium/kg bw/day did not show adverse effects in a feeding study with chromium chloride and chromium picolinate in rats for 20 weeks (Anderson *et al.*, 1997). However, in this study only liver and kidney have been examined histologically. A chronic toxicity/carcinogenicity study was only performed with chromium (III) oxide. Adverse effects were not observed at concentrations up to 5% in the diet, equivalent to about 1500 mg chromium/kg bw/day, fed to rats 5 days per week for 840 days (Ivankovic and Preussmann, 1975). The study, however, can not be used to derive a NOAEL for soluble chromium salts, because the tested substance was a pigment insoluble in water, alkali, and mineral acids.

In mice, doses of 250 to 1250 mg/kg body weight chromium chloride decreased fertility significantly and reduced body weights in males. It reduced semical vesicle and uterine weights and increased testes and ovarian weights. A NOAEL was not observed (Elbetieha and Al-Hamood, 1997). In male rats, exposure to 50 mg/ $CrCl_3$ /kg bw, equivalent to 16,5 mg trivalent chromium/kg body weight decreased significantly body weights and absolute testes and seminal vesicles weights but fertility remained unaffected (Bataineh *et al.*, 1997).

Adequate human data on trivalent chromium are also limited. No adverse side effects were reported in a number of supplementation trials, in which subjects received up to 1 mg

chromium/day, mostly as picolinate for several months. These trials, however, were mainly studies of efficacy and not designed to find potential toxic effects.

The limited data from studies on subchronic, chronic, and reproductive toxicity on soluble trivalent chromium salts and the available human data do not give clear information on the dose response relationship. Therefore, a tolerable upper intake level can not be derived.

The UK Expert Group on Vitamins and Minerals also concluded that overall there are insufficient data from human and animals studies to derive a safe upper level for chromium. However, in the opinion of the EGVM a total daily intake of about 0.15 mg trivalent chromium per kg body weight and day (or 10 mg/person) would be expected to be without adverse health effects. This value is based (using a 100-fold margin of safety) on the study of Anderson *et al.* (1997a) which indicated that 15 mg trivalent chromium/kg bw/day is not associated with adverse effects in the rat. This guidance level applies only to trivalent chromium and not to chromium picolinate which is explicitly excluded from the guidance due to the *in vitro* studies, which indicated that it may damage DNA via a mechanism which is at present still unclear (EGVM, 2002b). The US Food and Nutrition Board also concluded that the data from animal and human studies are insufficient to establish an UL for soluble chromium (III) salts (FNB, 2001).

WHO considered that supplementation of chromium should not exceed 250 µg/day (WHO, 1996).

6. RISK CHARACTERIZATION

In a number of limited human studies, there was no evidence of adverse effects associated with supplementary intake of chromium up to a dose of 1 mg chromium/day. The dietary intake of trivalent chromium in European countries, as shown in Table 1, is well below these doses.

This evaluation is not applicable to chromium picolinate.

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