Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding adviezen herevaluatie bestuurlijke MAC-waarden
Uw kenmerk : ARBO/AMIL/97/00648
Ons kenmerk : U 2706/CB/MP/563-O3
Bijlagen : 18
Datum : 14 december 2000

Mijnheer de staatssecretaris,

Op verzoek van uw ambtsvoorganger bied ik u hierbij de eerste adviezen aan van een reeks over de gezondheidskundige basis van uit het buitenland overgenomen grenswaarden voor beroepsmatige blootstelling aan stoffen. Het verzoek om deze adviezen is in algemene zin vervat in brief nr ARBO/AMIL/97/00648 en in latere stadia door uw departement toegespitst op afzonderlijke stoffen. De adviezen zijn opgesteld door een daartoe door mij geformeerde internationale commissie van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

De beoogde reeks van in het Engels gestelde adviezen zal losbladig worden gepubliceerd onder ons publicatienummer 2000/15OSH en, conform de aan de Gezondheidsraad voorgelegde toespitsingen van de adviesaanvraag, betrekking hebben op 168 stoffen. Het u thans aangeboden eerste pakket bestaat uit een Algemene Inleiding (publicatienummer 2000/15OSH/000) en uit de adviezen genummerd 2000/15OSH/001 tot en met 2000/15OSH/017, respectievelijk betrekking hebbend op:
cesiumhydroxide, cyclopentaan, diboraan, dimethoxymethaan, dipropylketon, fenylfosfine, germaniumtetrahydride, hexachloornaftaleen, methaanthiol, methylcyclohexanol, methylisopropylketon, mica, natriumhydroxide, octachloornaftaleen, silaan, tetrachloornaftaleen, en yttrium en yttriumverbindingen.

Bij afronding van de werkzaamheden van de hierboven bedoelde commissie ontvangt u een Nederlandstalige samenvatting van de in de gehele reeks van adviezen neergelegde bevindingen.

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Gezondheidsraad
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Onderwerp : Herevaluatie uit het buitenland overgenomen grenswaarden
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De u thans aangeboden adviezen heb ik vandaag ter informatie doen toekomen aan de Minister van Volksgezondheid, Welzijn en Sport en aan de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

prof. dr JJ Sixma

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Yttrium and yttrium compounds

Health-based Reassessment of Administrative
Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

No. 2000/15OSH/017, The Hague, 14 December 2000

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1 Introduction

The present document contains the assessment of the health hazard of yttrium and yttrium compounds by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by mrs MA Maclaine Pont, M.Sc (Wageningen University, the Netherlands).

Literature was retrieved from the data bases Medline, Toxline and Chemical Abstracts covering the periods 1989 until January 1997, 1981 until April 1997 and 1937 until July 1997 respectively, and using the following key words: yttrium (and its isotopes), 1314-36-9, 5970-44-5, 7446-33-5, 7446-65-5, 10361-92-9, 12005-21-9, 12008-32-1, 12039-19-9, 12071-35-1, 12186-97-9, 12255-48-0, 12294-01-8, 13469-98-2, 13494-98-9, 13709-49-4, yttrium compounds and its isotopic compounds (excluding health effects from radiation); aluminium yttrium oxide or antimony compounds; compound with yttrium (1 : 1) or carbonic acid; compounds, yttrium (3+) salt, trihydrate or nitric acid; compounds, yttrium (3+) salt, hexahydrate or sulphuric acid; compounds, yttrium (3+) salt (3 : 2) octahydrate. Data considered to be critical were evaluated by reviewing the original publications. The final literature search has been carried out in July 1997, followed by an additional search in May 1999.

The literature search focused on those yttrium compounds, of which some information could be found in either the Dictionary of chemical names and synonyms (How92) or in the Handbook of chemistry and physics (Lid96).

In December 1998, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organizations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland), dr P Wardenbach (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

2 Identity

The following data have been found:

name	molecular formula	synonyms	CAS reg nr
aluminum yttrium oxide	$Y_3Al_5O_{12}$	yttrium aluminum oxide	12005-21-9
yttrium	Y		7440-65-5
yttrium antimonide	YSb	antimony, compounds, compound with yttrium (1: 1)	12186-97-9
yttrium arsenide	YAs		12255-48-0
yttrium boride	YB_6		12008-32-1
yttrium bromide	YBr_3		13469-98-2
yttrium carbide	YC_2		12071-35-1
yttrium carbonate, trihydrate	$Y_2(CO_3)_3.3H_2O$	carbonic acid, compounds, yttrium (3+) salt, trihydrate	5970-44-5
yttrium chloride	YCl_3		10361-92-9
yttrium fluoride	YF_3		13709-49-4
yttrium nitrate, hexahydrate	$Y(NO_3)_3.6H_2O$	nitric acid, compounds, yttrium (3+) salt, hexahydrate	13494-98-9
yttrium oxide	Y_2O_3	yttria	1314-36-9
yttrium phosphide	YP		12294-01-8
yttrium sulfate, octahydrate	$Y_2(SO_4)_3.8H_2O$	sulfuric acid, compounds, yttrium (3+) salt (3 : 2), octahydrate	7446-33-5
yttrium sulfide	Y_2S_3		12039-19-9

Yttrium (Y) is one of the rare earth metals. The estimated abundance in the earth's crust is 28 - 31 ppm (Bud96).

Yttrium consists of the isotope 89 only, but radionuclides, such as ^{90}Y and ^{91}Y get into the environment through radioactive fallout and as a product of nuclear fission reactions (Deu91). Isotopes with masses 78 through 102 can be synthesized, but they usually do have a short half-life time (from 0.36 sec to 106.6 days) (Lid96).

3 Physical and chemical properties

name	physical form	mol weight	solubility in water	melting point	boiling point
Y	silvery metal, hexagonal	88.91	reacts	1522°C	3345°C
$Y_3Al_5O_{12}$	green cubic crystals	593.62			
YSb	cubic crystals	210.67		2310°C	
YAs	cubic crystals	163.83			
YB_6	refractory solid	153.77		2600°C	
YBr_3	colourless hygroscopic crystals	328.62	very soluble	904°C	
YC_2	refractory solid	112.93		2400°C approx.	
$Y_2(CO_3)_3.3H_2O$	red-brown powder	411.89	insoluble		
YCl_3	white monoclinic hygroscopic crystals	195.26	very soluble	721°C	
YF_3	white hygroscopic powder	145.9	insoluble	1150°C approx.	
$Y(NO_3)_3.6H_2O$	hygroscopic crystals	383.01	very soluble		
Y_2O_3	white cubic crystals	225.81	soluble	2439°C	
YP	cubic crystals	119.88			
$Y_2(SO_4)_3.8H_2O$	red monoclinic crystals	610.13	soluble		
Y_2S_3	yellow cubic crystals	274.01		1925°C	

Data from Lid96.

Conversion factors for the concentration in air are not applicable; the concentration can only be expressed in mg/m^3.

Further, no data on flash point, explosion limits and log $P_{oct/water}$ values were found.

Yttrium darkens on exposure to light. It oxidizes on heating in air or oxygen; it reacts with water.

Yttrium oxide readily absorbs ammonium from the air; it displaces ammonia from ammonium salts (Bud96).

4 Uses

Yttrium is used in nuclear technology, in iron and other alloys, in television screen phosphors, in lasers, superconductors, catalysts and ceramics (ACG91, Hir96).

5 Biotransformation and kinetics

The data found on biotransformation and kinetics of yttrium and yttrium compounds in humans and laboratory animals are presented in annex A.

In summary, after oral uptake yttrium is poorly absorbed from the gastrointestinal tract, more than 90% is excreted via the faeces in rats. Guinea pigs excreted approximately 0% via the faeces. The uptake after inhalation exposure varied between 25% in mice and 50% in rats. In humans 11 - 55% is retained after inhalation (Bai82, Bai85). After intravenous injection yttrium accumulated in liver, lung and spleen, with a half-life time for clearance from the liver of 144 days in rats. Accumulation of yttrium in bone is possible, but it is less than in other organs and there seems to be a maximum to the uptake by bone. Also the excretion of yttrium from the bone is slow. After inhalation exposure the clearance of yttrium has three phases, two rather quick, with a half-life time of approximately 8 and 20 days in humans, the third one very slow, with a half-life time of 420 days or 1 - 3 years.

When an yttrium compound is chelated its kinetics change drastically. Several studies are available on the effects of chelating agents, also called carriers (Gra59, Kut81, Kut86, Las56, Ros63, Saw62, Sch64a and b).

6 Effects and mechanism of action

Human data

In a Chinese yttrium mine the dust concentration ranged from 1.3 to 25.9 mg/m^3. The dust contained 64.1% yttrium oxide, 12.5% of other heavy rare-earth oxides, 15.2% of light rare-earth oxides and 0.1% of free silicon dioxide. The incidence of the 0^+ stage of pneumoconiosis was 16% in 25 workers with an average working history of 8.8 years. Some parameters of respiratory function and laboratory examinations showed significant difference in the workers exposed to yttrious dust as compared with control workers. Additional cytotoxicological experiments and rat dust exposure experiments showed that more damaged macrophages and fibrosis were found in the yttrious dust group than in the cerium dust group; and both were significantly less than the quartz group. A concentration of 3 mg Y/m^3 is recommended as an occupational exposure standard (Zou91). The committee considered the presentation of the data to be insufficient.

Animal data

The chlorides of rare earths cause eye irritation and transient conjunctivitis (Ger84). Yttrium nitrate is a moderate skin irritant and a severe eye irritant in rabbits (Lam93a). Yttrium oxide is not skin irritating and mildly irritating to the eyes of rabbits (Lam93b).

Symptoms of acute yttrium toxicity in experimental animals are anorexia, asthenia, and a progressive depression of general activity. Death is due to cardiac and respiratory failure. Precise determination of the role of yttrium is difficult because of its protein-precipitating capacity and the unusually great influence of the non-metallic components. Differences in sensibility of animal strains may be another factor. As a result of poor gastrointestinal absorption the most severe toxic effects occur after inhalation or injection of Y-compounds (Deu91).

Single intratracheal instillation in rats of Y or yttrium oxide resulted in effects on the lungs (Deu91, Mog63, Xia92, Zha92). Single intra venous injection of Y or yttrium chloride to rats or mice led to a decrease in blood glucose level, an increase in Ca-content of spleen, lungs and liver, acute liver necrosis and an increased relative spleen weight (Hir93, Nak93b, Mag63, Shi90).

Data on acute toxicity of yttrium and yttrium compounds are presented in the table below.

animal species	Y-compound and quantity	dosing regimen and quantity of Y	results	ref
rats	Y_2O_3, 50 mg/animal	single intratracheal instillation, 39 mg Y/animal	after 8 months: in the lung: granulomatous nodules; in the peribronchial tissue: nodules which compressed and deformed several bronchi; surrounding lung areas were emphysematous; interalveolar walls were thin and sclerotic; alveolar cavities dilated	Deu91 Mog63
rats	Y or Y_2O_3	single intratracheal instillation	up to 18 months after each treatment: lung granulomas; inhibition of several enzymes	Xia92
rats	Y or Y_2O_3	single intratracheal instillation	lung fibrosis, but less than that caused by silica dust; no effect on growth, hepatocytes and blood	Zha92
male Wistar rats	YCl_3	single intratracheal instillation; 10 - 200 µg Y/rat; rats were killed at several time points from 3 h to 162 days after treatment	significant increase in ß-glucuronidase activity and Ca and P-content of the alveolar lavage fluid, even at 10 µg Y/rat	Hir90
rabbit	$Y(NO_3)_3$	single iv injection	LD_{50}: 515 mg/kg bw (167 mg Y/kg)	Lew92
rats	YCl_3	single iv injection; 5 or 10 mg Y/kg bw	dose-related increase in Ca-content in spleen, lung, liver	Nak93b
male mice	Y	single iv injection; 20 mg/kg bw	increase in Ca-content in spleen, lung and liver	Shi90
rat	Y	single iv injection, 9 mg/kg bw	lowering of blood glucose level; acute liver damage as intralobular necrosis; no fatty changes	Mag63
male Wistar rats	YCl_3	single iv injection; 0, 0.1, 0.2, 0.5 or 2 mg Y/rat; rats were killed at several time points from 10 min to 182 days after injection	no effect on relative liver weight; increased relative spleen weight 50 h - 14 days after injection; increase in liver enzyme activity at 20 h; increase in Ca-content of the liver at 3 h - 14 days (peak: 10-fold); increase in Ca-content of the spleen at all time points (peak: 100-fold)	Hir93
rats	$Y(NO_3)_3$, 8 - 32 mg/kg bw	single intragastric dose; 2.6 - 10.3 mg Y/kg bw	at 4 mg/kg: almost no effect on gastric acid secretion; at higher doses: dose-related decrease in gastric acid secretion; decrease in the secretion of Alcian blue binding mucous	Luo91
Sprague Dawley rats (5 males, 5 females)	$Y(NO_3)_3$; 5000 mg/kg bw	single oral dose; 1617 mg Y/kg bw	LD_{100} after 14 days	Lam93a
Sprague Dawley rats (5 males, 5 females)	Y_2O_3, 5000 mg/kg bw	single oral dose; 1969 mg Y/kg bw	LD_0 after 14 days	Lam93b

The data on toxicity of yttrium and yttrium compounds after repeated exposure are presented in the table below.

animal species	Y-compound and quantity	dosing regimen and quantity of Y	results	ref
rats, mice, rabbits, dogs	^{91}Y, at 0.1 of the LD_{50}	fed by stomach tube daily for 3 months; 20 - 30 µg Y/kg bw	intestinal lesions with obstruction	Bru46
male and female Slc:Wistar rats	$YCl_3.6H_2O$; 0, 40, 200 or 1000 mg/kg bw per day	oral gavage for 28 days, followed by 14 days recovery; 0, 12, 59 or 293 mg Y/kg bw	Y accumulated in the kidneys, femur, liver and spleen in a dose-dependent manner; dose-related decrease of Fe-content in liver, kidney and spleen and of Ba- and Sr-content in the femur; at doses higher than 200 mg/kg: decreased serum cholinesterase activity in females; at 1000 mg/kg: hyperkeratosis of the forestomach, eosinophilic leukocyte infiltration in the submucosa of the stomach. In males: erosion and dilatation of the gastric gland; in females: swelling of the glandular stomach epithelium	Oga94
Swiss mice	$Y(NO_3)_3$	via the drinking water; 5 ppm Y; lifetime	no effect on organ content of Cr, Cu, Mn, Zn	Sch76

Carcinogenicity

Groups of male and female Swiss mice were given yttrium nitrate, 5 ppm Y, in the drinking water for lifetime. Males showed a 10 - 20% decrease in body weight during the first 180 days of treatment; female mice schowed a 10 - 20% decrease in body weight during the whole experimental period (540 days). The lifespan of both males and females, however, was increased compared with the control groups. The number of malignant tumours found upon autopsy was higher in the treatment group (33.3%) than in the control group (14.6%), but this was not statistically significant. In the control group (80 animals) two lymphoma-leukaemias and four adenocarcinomas in the lung were found. In the treatment group (72 animals) eight lymphoma-leukaemias and three adenocarcinomas of the lung were found (Sch71).

Solid rods of Al_2O_3 containing yttrium oxide and rods of ZrO_2 containing yttrium oxide were implanted in the thigh muscle of C57BL/6N mice for 24 months. There was no evidence of carcinogenic or toxic effects (Tak94).

Mutagenicity and genotoxicity

YCl_3 was negative in the Ames assay using *S. typhimurium* strains TA98, TA100, TA102, TA1537 and TA2637, in the presence and absence of 9-aminoacridine (Iye87). There is no explanation why 9-aminoacridine was added.

YCl_3 did not induce micronuclei in mouse bone marrow *in vitro* (Lia88).

YCl_3 induced DNA damage and micronuclei in human lymphocytes *in vitro* (Yan98a,b).

Reproduction toxicity

No data on reproduction toxicity of yttrium and yttrium compounds have been found.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) in the Netherlands is 1 mg/m^3, 8 h TWA, for yttrium, and also for yttrium compounds (measured as Y).

Existing occupational exposure limits for yttrium and yttrium compounds in some European countries and in the USA are summarized in annex B.

8 Assessment of health hazard

The toxicity of yttrium is rather aspecific. When workers inhaled yttrium or one of its compounds as a dust, the toxicity was limited to effects on the lungs, including pneumoconiosis, respiratory effects and fibrosis (Zou91). Also after intratracheal instillation in rats only lung effects have been reported (Zha92). After lifetime dosing of mice via the drinking water no carcinogenic or toxic effects were observed. The dosing regimen increased the lifespan of the animals (Sch71, Sch76).

Some of the yttrium compounds are irritating for skin and/or eyes.

The half-life time of yttrium in humans is very long, 1 to 3 years (Bai82, Cop47).

The available data suggest that the target organ for toxicity after exposure to yttrium or yttrium compounds is the lungs. The committee expects

differences in water-solubility of the various yttrium compounds to play an important role in the toxic effects.

The human data that are available on exposure to yttrium are insufficiently documented to be used for a health-based occupational exposure limit. Repeated dose inhalation studies in animals have not been found.

The committee considers the toxicological data base on yttrium and yttrium compounds too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

References

ACG91 American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of the threshold limit values and biological exposure indices. 6th ed. Cincinnati, Ohio, USA: ACGIH, 1991; 1746-7.

ACG00 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values -2000. Cincinnati, Ohio, USA: ACGIH, 2000.

Arb96 Arbejdstilsynet. Exposure limit values for substances and materials. Copenhagen, Denmark: The Working Environment Service; Instruction no. 3.1.0.2. 1996.

Bru46 Brues AM, Lisco H, Finkel MP. Carcinogenic action of some substances which may be a problem in certain future industries. Am Assoc Advance Sci, Sect on Chemistry, Gibson Island Research Conf on Cancer 1946. Chem Abstr 41:4226e.

Bud96 Budavari S, O'Neill MJ, Smith A, *et al*. The Merck index. An encyclopedia of chemicals, drugs, and biologicals. 12 th ed. Whitehouse Station, NJ, USA: Merck & Co, 1996; 1728-9.

Cop47 Copp DH, Axelrod DJ, Hamilton JG. The deposition of radioactive metals in bone as a potential health hazard. Am J Roentgenol Radium Therapy 1947; 58: 10-6. Chem Abstr 42:231f.

Dai63 Daigneault EA. The distribution of intravenously administered yttrium chloride (carrier free) in the rhesus monkey. Toxicol Appl Pharmacol 1963; 5: 331-43.

Deu91 Deuber R, Heim T. Yttrium. In: Merian E, ed. Metals and their compounds in the environment; occurrence, analysis, and biological relevance. Weinheim, Germany: VCH Verlagsgesellschaft mbH, 1991; 1299-308.

DFG99 Deutsche Forschungsgemeinschaft (DFG). List of MAK and BAT values 1999. Commission for the investigation of health hazards of chemical compounds in the work area. Weinheim, Germany: VCH Verlagsgesellschaft mbH, 1999. Report nr. 35.

Ekm61 Ekman L, Åberg B. Excretion of niobium-95, yttrium-91, cerium-144 and promethium-147 in goats. Res Vet Sci 1961; 2: 100-5. Chem Abstr 55:20220i.

Gen63 Gensicke F, Nitschke HW, Spode E. Die Verteilung von Radioyttrium im Organismus der weissen Maus nach Inhalation von ^{91}Y-Flüssigkeitsaerosolen. [Distribution of radioactive yttrium in the organism of the white mouse after inhalation of Y^{91} spray aerosols.] German. Fortschr Gebiete Roentgenstrahlen Nuklearmed 1963; 98: 338-41.

Ger84 Gerhardsson L, Wester PO. Chromium, cobalt and lanthanum in lung, liver and kidney tissue from deceased smelter workers. Sci Total Environ 1984; 37: 233-46.

Gra57 Graul EH, Hundeshagen H. [Absorption and removal of radioactive fission products in the body.] German. Z Aerosol-Forsch u Therap 1957; 6: 95-104. Chem Abstr 52:8367b.

Gra59 Graul EH, Hundeshagen H. Investigations of radio-yttrium (Y^{90}) metabolism. Int J Appl Radiat Isotopes 1959; 5: 243-52.

Hir90 Hirano S, Kodama N, Shibata K, *et al.* Distribution, localization, and pulmonary effects of yttrium chloride following intratracheal instillation into the rat. Toxicol Appl Pharmacol 1990; 104: 301-11.

Hir93 Hirano S, Kodama N, Shibata K, *et al.* Metabolism and toxicity of intravenously injected yttrium chloride in rats. Toxicol Appl Pharmacol 1993; 121: 224-32.

Hir96 Hirano S, Suzuki KT. Exposure, metabolism, and toxicity of rare earths and related compounds. Environ Health Perpect 1996; 104 (suppl.1): 85-95.

Hoo56 Hood SL, Comar CL. Behavior of radioactive yttrium in the blood of ruminants. US Atomic Energy Comm Oak Ridge Inst Nucl Studies 1956; 12: 301-10. Chem Abstr 51:2179f.

How92 Howard PH, Neil M, ed. Dictionary of chemical names and synonyms. Chelsea, USA: Lewis Publishers, 1992.

HSE99 Health and Safety Executive (HSE). Occupational exposure limits 1998. Sudbury, England: HSE Books, 1999; Guidance note EH 40/99.

Hun97 Hunter WJ, Aresini G, Haigh R, *et al.* Occupational exposure limits for chemicals in the European Union. Occup Environ Med 1997; 54: 217-22.

Iye87 Iyehara OH, Tsuruta S, Niyitani Y, *et al.* Mutagenicity of metal salts in combination with 9-aminoacridine in *Salmonella typhimurium*. Jpn J Genet 1987; 62: 159-62. Chem Abstr 107:91632z.

Kid51 Kidman BP, Tutt ML, Vaughan JM. Excretion of yttrium^{91} in rabbits. Nature 1951; 167: 858. Chem Abstr 45:8658f.

Kut81 Kutzner J, Mittas M, Grimm W. [Distribution in rats after intravenous injection of yttrium-88 compounds.] German. Nuklearmedizin (Stuttgart) 1981; 20: 35-9. Chem Abstr 95:57282j.

Kut86 Kutzner J, Alfter G, Grimm W. [Effects of carrier on the organ distribution of radioactive yttrium in the rat.] German. Nucl Med (Stuttgart) 1986; 25: 78-80. Chem Abstr 105:93678b.

Lam93a Lambert CE, Barnum EC, Shapiro R. Acute toxicological evaluation of yttrium nitrate. J Am Coll Toxicol 1993; 12: 629.

Lam93b Lambert CE, Barnum EC, Shapiro R. Acute toxicological evaluation of yttrium oxide. J Am Coll Toxicol 1993; 12: 630.

Las56 Laszlo D. Distribution of lanthanum and yttrium in the mammalian organism. US Atomic Energy Comm Oak Ridge Inst Nucl Studies 1956; 12: 193-217. Chem Abstr 52:131 11i.

Lew92 Lewis sr. RJ, ed. Sax's dangerous properties of industrial materials. 8th ed. New York, USA: Van Nostrand Reinhold, 1992; 3533-4.

Lia88 Liao M, Wang Z, Yu T. [Study of 45 metal compounds using micronucleus test.] Chinese. Weisheng Dulixue Zazhi 1988; 2: 83-6. Chem Abstr 112:134189h.

Lid96 Lide DR, Frederikse HPR, ed. CRC Handbook of chemistry and physics. 77th ed. Boca Raton, USA: CRC Press, 1996; 4-96, 11-58, 11-59.

Luo91 Luo G. [Effects of yttrium nitrate on gastric mucosa and gastric acid secretion in the rat.] Chinese. Zhongguo Yaolixue Yu Dulixue Zazhi 1991; 5: 50-2. Chem Abstr 115:2727j.

Mac52 MacDonald NS, Nusbaum RE, Alexander GV. The skeletal deposition of yttrium. J Biol Chem 1952; 195: 837-41.

Mag63 Magnusson G. The behavior of certain lanthanons in rats. Acta Pharmacol Toxicol 1963; suppl 3: 95 pp. Chem Abstr 60:16403f.

Men82 Menczel J, Rosoff B, Spencer H. Tissue distribution of orally administered yttrium-91 and scandium-46 in mice. Health Phys 1982; 42: 727-30. Chem Abstr 96:213358s.

Mog63 Mogilevskaya OY, Raikhlin NT. [Biological effects of rare, dispersed, and other metals and their compounds used in industry-rare earth elements.] Russian. Toksikol Redkikh Metal 1963; 195-208. Chem Abstr 60:2246b.

Mos64 Moskalev YI, Semenov DI, Buldakov LA. [The distribution of yttrium-91, zirconium-95, and niobium-95 in rats after inhalation.] Russian. Raspredelenie, Biol Deistvie, Uskorenie Vyvedeniya Radioaktivn Izotopov, Sb Rabot 1964; 23-8. Chem Abstr 62:9426c.

Nak91a Nakamura Y, Tsumura-Hasegawa Y, Tonogai Y, *et al.* [Excretion of dysprosium, europium, ytterbium, and yttrium in the rat after oral administration.] Japanese. Eisei Kagaku 1991; 37: 418-25. Chem Abstr 116:53107k.

Nak91b Nakamura Y, Tsumura-Hasegawa Y, Tonogai, Y, *et al.* [Studies on the biological effects of rare earth elements. II. Distribution and the histological effects of dysprosium, europium, ytterbium, and yttrium in the rat after intravenous administration.] Japanese. Eisei Kagaku 1991; 37: 489-96. Chem Abstr 116:167971t.

Nak91c Nakamura Y, Tsumura-Hasegawa Y, Tonogai, Y, *et al.* [Studies on the biological effects of rare earth elements. III. Fate of chlorides of dysprosium, europium, ytterbium, and yttrium in the rat after intravenous administration.] Japanese. Eisei Kagaku 1991; 37: 497-506. Chem Abstr 116:145617e.

Nak93a Nakamura Y, Tsumura Y, Tonogai Y, *et al.* [Studies on the biological effects of rare earth elements. IV. Effects of chlorides of dysprosium, europium, ytterbium, and yttrium on rare earth elements, calcium, magnesium, and phosphorus contents in various organs in the rat after intravenous administration.] Japanese. Jpn J Toxicol Environ Health 1993; 39: 44-55. Chem Abstr 118:162762g.

Nak93b Nakamura Y, Tsumura Y, Tonogai Y, *et al.* [Studies on the biological effects of rare earth elements. V. Relationship between the concentration of rare earth elements and 9 minerals in various organs in the rat after intravenous administration of dysprosium, europium, ytterbium, and yttrium by low or high dose.] Japanese. Jpn J Toxicol Environ Health 1993; 39: 121-31. Chem Abstr 119:2757b.

Nak97 Nakamura Y, Tsumura Y, Tonogai Y, *et al.* Differences in behavior among the chlorides of seven rare earth elements administered intravenously to rats. Fundam Appl Toxicol 1997; 37: 106-16.

NBO96 National Board of Occupational Safety and Health. Occupational exposure limit valus. Solna, Sweden: NBOSH, 1996: Ordinance AFS 1996/2.

Oga94 Ogawa Y, Suzuki S, Naito K, *et al.* [Studies on the biological effects of yttrium. Effects of repeated oral administration tests in rats.] Japanese. Jpn J Toxicol Environ Health 1994; 40: 374-82. Chem Abstr 121:273992p.

Ros63 Rosoff B, Siegel E, Williams GL, *et al.* Distribution and excretion of radioactive rare-earth compounds in mice. Intern J Appl Radiation Isotopes 1963; 14: 129-35. Chem Abstr 59:4249h.

Saw62 Sawitsky A, *et al.* Yttrium-90 in hematological disorders. Proc Intern Congr Hematol, 8th, Tokyo, 1960; 1: 239-42 (Pub 1962). Chem Abstr 58:8210f.

Sch50a Schubert J, Finkel MP, White MR. Plutonium and yttrium content of the blood, liver, and skeleton of the rat at different times after intravenous administration. J Biol Chem 1950; 182: 635-42.

Sch50b Schubert J, White MR. The effect of different dose levels of zirconium on the excretion and distribution of plutonium and yttrium. J Biol Chem 1950; 184: 191-6.

Sch63 Schmidtke I, Schiessle W, Philipp K. [The influence of carrier additives in inhalation studies with $^{91}YCl_3$.] German. Strahlentherapie 1963; 122: 123-36. Chem Abstr 62:1954h.

Sch64a Schmidtke I. [The effect of diethylenetriaminepentaacetic acid (DTPA) upon the excretion of inhaled yttrium-91. Preliminary report.] German. Zentr Biol Aerosol Forsch 1964; 11: 432-9. Chem Abstr 61:6237e.

Sch64b Schmidtke I. Removal of inhaled radioactive yttrium by the use of diethylenetriaminepentaacetic acid (DTPA). Health Phys 1964; 10: 1235-41. Chem Abstr 63:3288h.

Sch71 Schroeder HA, Mitchener. Scandium, chromium (VI), gallium, yttrium, rhodium, palladium, indium in mice: effects on growth and life span. J Nutr 1971; 101: 1431-8.

Sch76 Schroeder HA, Nason AP. Interactions of trace metals in mouse and rat tissues; zinc, chromium, copper and manganese with 13 other elements. J Nutr 1976; 106: 198-203.

Sem66 Semenov DI, Moskalev YI, Buldakov LA. [Fate of cesium, strontium, yttrium, cerium, zirconium, niobium, and ruthenium in rats after administration by inhalation.] Russian. Tr Inst Biol, Akad Nauk SSSR, Ural Filial 1966; 46: 49-87. Chem Abstr 66:62422k.

Shi90 Shinohara A, Chiba M. [Distribution of administered elements and effect on calcium concentrations in organs of the mice injected with lanthanide or yttrium compounds.] Japanese. Biomed Res Trace Elem 1990; 1: 273-4. Chem Abstr 116:189246n.

SZW00 Ministerie van Sociale Zaken en Werkgelegenheid (SZW): Arbeidsinspectie. [De nationale MAC-lijst 2000]. Dutch. The Hague, the Netherlands: Sdu Servicecentrum Uitgeverijen, 2000.

Tak94 Takamura K, Hayashi K, Ishinishi N, *et al.* Evaluation of carcinogenicity and chronic toxicity associated with orthopedic implants in mice. J Biomed Mater Res 1994; 28: 583-9. Chem Abstr 121:91644u.

TRG00 TRGS 900. [Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe]. German. B Arb Bl. 2000; 2.

Wil82 Williams MW, Hoeschele JD, Turner JE, *et al.* Chemical softness and acute metal toxicity in mice and *Drosophila*. Toxicol Appl Pharmacol 1982; 63: 461-9.

Xia92 Xiao B, Li Q. [Lung granuloma induced by the powder of yttria and its mineral in rats - observations on histopathology and enzymes.] Chinese. Gongye Weisheng Yu Zhiyebing 1992; 18: 79-81. Chwem Abstr 118:53787y.

Yan98a Yang H, Ji Q, Zhang X, *et al.* [DNA damage in human lymphocytes induced by yttrium chloride and praseodymium chloride.] Chinese. Yichuan 1998; 20: 16-8. Chem Abstr 129: 256337b.

Yan98b Yang H, Ji Q, Zhang X. [Studies on effects of yttrium chloride and praseodymium chloride on frequency of micronucleus in human blood lymphocytes.] Chinese. Zhonghya Yufang Yixue Zazhi 1998: 32: 156-8. Chem Abstr 130: 11455.

Zha92 Zhao G, Li S. [Experimental pathologic observation of rare earth element dusts.] Chinese. Gongye Weisheng Yu Zhiyebing 1992; 18: 86-9. Chem Abstr 118:53789a.

Zou91 Zou S. [Study of biological effects of yttrium dust and its hygienic standard in the workplace air.] Chinese. Gongye Weisheng Yu Zhiyebing 1991; 17: 272-5. English translation.

Annex A

Data on biotransformation and kinetics of yttrium and yttrium compounds.

humans/ animals	Y-compound and quantity	dosing regimen; quantity of Y given	results	ref
humans (?)	not given	injection for radiotherapy	deposits in uncalcified organic matrix of the bone; half-life time for excretion 1 - 3 years	Cop47
rats	^{91}Y	inhalation	deposition: 60% in the head, 30% in the skin, 47% in the gastrointestinal tract, 12% in the lungs (together exceeding 100%; this is not explained); the exhalation occurred in three parts, with different biological half-life times	Mos64
albino rats	^{91}Y aerosol	inhalation for 5 - 10 min; 2 - 10 µCi inhaled per rat	"10 - 18% in the lungs, 60% in the nose and pharynx; resorption approx. 50%. Sodium EDTA decreased the deposition of ^{91}Y in organs and increased the urinary excretion	Sem66
white mice	$^{91}YCl_3$; 394 µCi/l air; mean diameter 2.75 µm	inhalation for 1 hour to 30 days; total activity inhaled: approx. 0.2 µCi/mouse	After 30 min: 3.6% in the bones, 28% in the lungs, 25% in the gastrointestinal tract, 1.2% in blood, kidneys and spleen. After 30 days: 7.65% in the liver.	Gen63
guinea pigs	$^{91}YCl_3$, with inactive chelating agent	inhalation for 8 weeks	in spite of a 10^6-fold increase of Y the distribution pattern (not given) differs only slightly from the one obtained after inhalation of a carrier-free solution. This does not agree with the results obtained after intra venous injection, but it agrees with the results obtained after intra muscular and intra peritoneal injection of larger amounts of Y	Sch63
male Wistar rats	YCl_3	single intra-tracheal instillation; 100 µg Y/rat; rats were killed at several time points from 3 h to 162 days post treatment	half-life time for clearance from lungs: 168 days; alveolar surface fluid could retain at most 5 µg Y; no accumulation in liver or kidneys	Hir90
weanling rabbits 7-mo old rabbits	^{91}Y idem	injection idem	0.63% was retained in bone; 12% urinary excretion 0.33% was retained in bone; 24% urinary excretion	Kid51
guinea pigs	$^{90}YCl_3$	injection	no difference in distribution after intra peritoneal injection or oral dosing; 50% concentration of Y in the pancreas within 1 - 4 days; not more than 30% of Y in the bone in the first 8 days; after 8 days: 2.5% is excreted	Gra57 Gra59
	idem	oral	51% resorption; 65% concentration of Y in the pituitary gland after 4 days; not more than 15% of Y in the bone after 12 days; after 8 days: 49% is excreted	

Continuation table

humans/ animals	Y-compound and quantity	dosing regimen; quantity of Y given	results	ref
cattle	^{91}Y	single iv injection	approx. 1.5% excretion in milk in 2 weeks; this is approx. 8-20 times less than excretion via urine and faeces	Hoo56
goats	^{91}Y idem	iv injection oral	major elimination via the faeces: approx. 4%; 0.05 - 0.3% was excreted via the urine; excretion via the milk was significant on the 2nd and 3rd day	Ekm61
male and female Rhesus monkeys rats mice	$^{91}YCl_3$ idem idem	single iv injection 80 µCi/kg bw idem idem	half-life time for clearance from the blood: 10 min; after 4 h: high concentrations in liver (highest: 8.9%), femur, urine, skull bone, kidneys (lowest: 2.8%). The results obtained on rats, killed 24 h after treatment, closely parallel those obtained for the monkey. The mice differed by exhibiting a high lung and spleen concentration.	Dai63
female Sprague Dawley rats	$^{91}Y^{3+}$ (together with $^{239}Pu^{4+}$)	single iv injection; 0.3 µCi/animal	after 5 min: 80% had disappeared from the blood; after 6 h the Y-content of bone was at its maximum: 45% of the dose; it remained constant till the end of the experiment (48 h)	Sch50
male Wistar rats	YCl_3	single iv inectionj; 1 mg Y/animal; rats were killed at several time points from 10 min to 182 days post treatment	Y distributed predominantly into the plasma; half-life time for clearance from liver: 144 days	Hir93
rats	^{91}Y	single iv injection	the concentration in the liver rapidly increased to 25-30% of the dose, but thereafter diminished quickly. Urinary excretion was a few percent in the first 3 h	Mag63
fasted rats	YCl_3, 100 and 1000 mg/kg bw	single oral dose, 46 and 455 mg Y/kg bw	at 100 mg/kg: 92-98% was excreted via the faeces within 4 days; at 1000 mg/kg: 94-98% was excreted within 7 days	Nak91a
rats	YCl_3, 10 - 50 mg/kg bw	single iv injection, 4.6 - 22.8 mg Y/kg bw	after 8 days: accumulation in the liver, spleen and bone	Nak91b
rats	YCl_3, 10 mg/kg bw	single iv indection, 4.6 mg Y/kg bw	after 7 days: 5 - 18% excreted via the faeces; no Y detected in the urine; disappearance from the blood within 4 h	Bak91c
rats	YCl_3	single iv injection, 10 mg Y/kg bw	half-life time for blood: 0.43 h; for liver: 19.3 days	Nak93a
male Wistar rats	YCl_3	single iv injection, 5 or 10 mg Y/kg bw	after 1 day: distribution in the liver: 68-72%; the distribution in the following organs was dose-related: spleen: 4.4 and 16% resp. ($p<0.01$); bone: 15 and 9% ($p<0.05$); lungs: 0.73 and 2.3% ($p<0.05$); kidneys: 0.56 and 0.32% ($p<0.01$); blood: 9.2 and 0.61% ($p<0.01$)	Nak97

Continuation table

humans/ animals	Y-compound and quantity	dosing regimen; quantity of Y given	results	ref
rats	YCl_3	single iv injection, 10 mg Y/kg bw	half-life time for blood: 0.43 h; for liver: 19.3 days	Nak93a
male Wistar rats	YCl_3	single iv injection, 5 or 10 mg Y/kg bw	after 1 day: distribution in the liver: 68-72%; the distribution in the following organs was dose-related: spleen: resp. 4.4 and 16% ($p<0.01$); bone: 15 and 9% ($p<0.05$); lungs: 0.73 and 2.3% ($p<0.05$); kidneys: 0.56 and 0.32% ($p<0.01$); blood: 9.2 and 0.61% ($p<0.01$)	Nak97
female mice	^{91}Y	orally	most of the dose was in the gastrointestinal tract; after 4 h: 0.02% in the kidneys, < 0.01% in bone, liver and muscle	Men82
male white rats	YCl_3	ip injection every two days up to 5 months; max 936 mg Y/animal	Y-content of the bone never exceeded 330 ppm; no linear increase with increasing dosage; Y-content of liver, kidneys, spleen and lungs ranged from 1000 to 10,000 ppm	Mac52

Annex B

Occupational exposure standards for yttrium and yttrium compounds in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[b]	lit ref[c]
	ppm	mg/m^3				
the Netherlands						
- Ministry	-	1	8 h	administrative		SZW00
Germany						
- AGS	-	5	8 h	administrative		TRG00
- DFG MAK-Kom.	-	-				DFG99
Great Britain						
- HSE	-	1	8 h	OES		HSE99
		3	15 min	STEL		
Sweden	-	-				NBO96
Denmark	-	1	8 h			Arb96
USA						
- ACGIH	-	1	8 h	TLV		ACG00
- OSHA	-	1[f]	8 h	PEL		
- NIOSH	-	1[f]	10 h	REL		
European Union						Hun97
- SCOEL	-	-				

[b] S = skin notation; which means that skin absorption may contribute considerably to the body burden, sens = substance can cause sensitization

[c] reference to the most recent official publication of occupational exposure limits