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
Health Council of the Netherlands

Onderwerp : Herevaluatie uit het buitenland overgenomen grenswaarden
Ons kenmerk : U
Pagina : 2
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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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Sodium hydroxide

(CAS reg no: 1310-73-2)

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/015, The Hague, 14 December 2000

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1 Introduction

The present document contains the assessment of the health hazard of sodium hydroxide 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 JJC Paulussen, M.Sc., and H Stouten, M.Sc. (TNO Nutrition and Food Research Institute, Zeist, the Netherlands).

The evaluation of the toxicity of sodium hydroxide has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the online data bases Medline, Toxline, and Chemical Abstracts covering the period 1966 to 26 February 1998 (19980226/UP), 1965 to 24 February 1998 (19980224/ED), and 1967 to 3 March 1998 (980303/ED; vol 128, iss 10), respectively. Medline was searched with the CAS Registry Number 1310-73-2 and the names sodium hydroxide, caustic soda, Na OH, and NaOH, Toxline with the CAS Registry Number 1310-73-2 only, and CA with 1310-73-2 (in the Sections “Toxicology” and “Air polution and industrial hygiene” only). HSDB and RTECS, data bases available from CD-ROM, were consulted as well (NIO98, NLM98). The final literature search has been carried out in March 1998.

In March 2000, 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), AG Berends (Solvay S.A., Brussels, Belgium), 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

name	:	sodium hydroxide
synonyms	:	caustic soda lye caustic flake liquid caustic sodium hydrate
molecular formula	:	NaOH
CAS reg nr	:	1310-73-2

Data from ACG91 and Pie93.

3 Physical and chemical properties

molecular weight	:	40.01
boiling point	:	1390^{o}C
melting point	:	318.4^{o}C
flash point	:	-
vapour pressure	:	-
solubility	:	soluble in water (420 g/l at 0^{o}C) insoluble in acetone and ether very soluble in alcohol and glycerine
log $P_{oct/water}$	:	-
conversion factors (20^{o}C, 101.3 kPa)	:	-

Data from ACG91 and Pie93.

Sodium hydroxide is a white, corrosive, alkaline, deliquescent solid, which can be encountered in various forms (pellets, flakes, sticks, cakes). It can also be in solutions, usually 45-75% in water. A 1% solution has a pH of 13. Sodium hydroxide rapidly absorbs water and carbon dioxide from the air. When dissolving it in water, which is an exothermic process, mists can be formed.

According to Cooper *et al*, atmospheric humidity determines whether sodium hydroxide aerosol particles will be solid or liquid. Dry particles will become droplets if humidity exceeds 35%. Anyway, the residence time of these sodium hydroxide particles in the atmosphere is seconds only, and sodium

carbonate particles (probably solid $Na_2CO_3.10H_2O$ particles) are formed rapidly (Coo79).

4 Uses

Sodium hydroxide is used in the manufacture of chemicals, rayon, soap and other detergents, pulp and paper, petroleum products, cellophane and textiles, and explosives. It is also used in metal descaling and processing, and in batteries (ACG91).

5 Biotransformation and kinetics

No data have been found on the metabolism of sodium hydroxide *per se*.

In view of the chemical properties, the humidity of the nasal passages and the upper respiratory tract, and the high CO_2 concentrations in the upper respiratory tract, conversion to the less alkaline sodium carbonate is likely to occur rapidly after inhalation of sodium hydroxide.

Since sodium hydroxide is fully ionized, some data on the metabolism of sodium summarized by US EPA (Mar88) will be presented.

Radiolabeled sodium appeared promptly in the blood after application to the intact skin and after (amongst others) subcutaneous and intramuscular injection. After ingestion, it appeared in the blood of man after 3 minutes.

Following injection of radiolabeled sodium to man, the elimination occurred in three phases with biological half-lifes of 8.5 days (49% of the dose administered), 13.5 days (51%), and 460 days (0.4%). The urine is the main excretion route, but small amounts are excreted in other body discharges (e.g. faeces, sweat, tears) as well.

6 Effects and mechanism of action

Human data

The corrosive properties of alkaline materials in general and of sodium hydroxide in particular to the skin and eyes are well documented by human case reports (Kuc93, Moo83, NIO75).

In a recently reported human 4-hour patch test, sodium hydroxide (0.5%) was a very clear skin irritant in several test facilities. About half of the volunteers reacted so vigorously after just one hour of treatment that exposure

for a greater duration was not undertaken (Gri97). In an *in vitro* skin corrosion test based on the use of reconstructed human skin cultures, a 10% solution of sodium hydroxide reduced cell viability significantly, and was judged to be corrosive (Per96).

There are only a few reports on the effects following exposure to sodium hydroxide aerosols or mists. In the first edition of 'Patty's' published in 1949, it was stated that based on experience with caustic mists with concentrations of 1 to 40 mg/m^3, a concentration of 2 mg/m^3 would be noticeably, but not excessively, irritant (ACG91, NIO75, Smy56). However, this statement was not included in the most recent editions (Pie93, Wan81). Furthermore, it was stated that sodium hydroxide concentrations of 250 mg/m^3 are immediately dangerous to life or health (Pie93), but no reference was given.

In two reports, both effects and concentrations have been described. Irritation of the nose, throat, or eyes was observed in workers engaged in cleaning operations where concentrations up to 0.7 mg/m^3 were found. However, the workers were exposed to other compounds as well among which Stoddard solvent, also an irritant, for which concentrations as high as 780 mg/m^3 were present (ACG91, NIO75). In another unpublished study, eye or throat irritation was reported in a small number of users of an oven spray at concentrations up to approximately 2 mg/m^3 for up to 15 minutes. However, other compounds may have been involved and the sampling and analytical procedures may have been compromised (NIO75). Two cases of obstructive airway injury and one case of pneumothorax ascribed to exposure to aerosols from sodium hydroxide-containing products (caustic soda, boiling lye solution) have been reported (Han91, Nas88, Rub92).

No increase in mortality in relation to duration or intensity of exposure to caustic dust was found in a group of 265 workers for periods ranging from less than 1 year to up to 30 years. Based on measurements and subjective response data, time-weighted average exposure levels were estimated to be approximately 0.5 to 2 mg/m^3, depending on the job. Medical record data showed that medical aid was sought more for skin contact than for eye contact and least for inhalation (Ott77).

No clinically or statistically significant changes in lung function were found in 14 male volunteers with mild asthma following 20-min exposures to alkaline aerosol concentrations of 10-120 mg/m^3. The aerosols were stated to consist of sodium carbonate, sodium bicarbonate with some sodium hydroxide. The mass median aerodynamic diameter of the aerosol was 1 µm, the pH 9.8 to 10.3 (Esc91).

There are many accounts of accidental and suicidal poisonings with sodium hydroxide, describing the corrosive effects following oral exposure. Necrosis of the mouth, oesophagus, and gastric mucosa, and hypersalivation, emesis, cardiovascular collapse, tracheal obstruction and dyspnea, retching, and severe pain may occur. Ingestion might be fatal, as a result of, *e.g.*, shock, infection of the corroded tissues, pulmonary necrosis, or asphyxia (ACG91, NIO75, Tra74). Several cases of oesophageal carcinomas in patients with chronic oesophageal stricture due to the ingestion of lye have been presented. It was suggested that these carcinomas might have been the result of tissue destruction and scar formation due to the caustic effects of sodium hydroxide itself rather than a carcinogenic potential (Mar88).

Animal data

Irritation

In rabbits, mice, and pigs, sodium hydroxide was reported to be irritating as a 1% solution and corrosive at higher concentrations after dermal application (ECB95). Four-hour dermal exposure of rabbits to a 5% solution caused severe necrosis of the skin (Ric94, ACG91). Furthermore, it is reported that a 2% solution was corrosive, while a 1% solution was not (Ver77). When tested for eye irritation in rabbits, no or hardly any irritation (maximum Draize score: 3) was seen following instillation of 0.01, 0.03, or 0.1 ml of a 0.5% solution. Instillation of 0.003 ml of a 10% solution was irritating (Draize score: 22), but the eyes returned to normal by day 7. Instillation of 0.01, 0.03, or 0.1 ml caused permanent damage at the higher doses of such severity that the animals had to be killed (Gri80). In a separate study performed according to OECD test guideline 405, 0.1 ml of a 1% or 10% solution of sodium hydroxide was irritating and severely irritating, respectively. Effects induced by the 1% solution were reversible, but those induced by the 10 % solution were still present at the end of the 21-day observation period (Bag92, ECE92). When 0.1 ml of a 1% solution was instilled into the eyes of a monkey according to the method of Draize, no eye irritation was observed. However, when a device developed to permit an insult to the cornea without a corresponding insult to the conjunctiva was used, a definite opacification and central ulceration was noted which definitely improved by day 7. In rabbits, treatment according to ‘Draize’ produced considerable conjunctivitis, iritis, and a slight to moderate

corneal opacity which returned to normal by day 14, while using the device, permanent corneal damage occurred (Bue64).

Acute toxicity

Young and adult rats were exposed for 2 hours to 65 (nose-only) or 250-3200 (whole-body) mg/m^3 of aerosols generated by melting sodium and passing the vapour into an ageing chamber to reach equilibrium with atmospheric carbon and water and stabilize its particle size before flowing into the 1 m^3 exposure chamber. The mass median aerodynamic diameter of the aerosols was usually between 0.5 and 1.5 µm with a geometric standard deviation of approximately 3. The larynx appeared to be the target organ. No effects were seen on the nasal turbinates, lungs, oesophagus, and stomach. In addition, exposure did not result in skin or eye damage (it is noted that most skin is protected by fur and most animals kept eyelids closed during exposure, thus protecting conjunctiva and cornea). No effects were seen in the young and adult rats (n=12/group) nose-only exposed to 65 mg/m^3. Whole-body exposure to 3200 mg/m^3 killed 6 out of 11 (6/11) rats (only adults exposed), while another 3 died during the 10-day postexposure period. No mortality was observed in the other experiments (highest concentration: 940 mg/m^3). Incidence and severity of the effects were higher for young than for adult rats. As to adult rats, no laryngitis was observed in animals exposed to 280 mg/m^3. After exposure to 340 mg/m^3, 1/6 and 2/5 animals killed after 1 hour and 1 day, respectively, were affected; after exposure to 550 mg/m^3 (the next higher level) incidences were 2/6 and 3/6, respectively. The aerosols mainly consisted of Na_2CO_3. Using dilution air with a 85% relative humidity or from which all CO_2 had been removed, an aerosol consisting of a high percentage of hydroxide or 100% hydroxide, respectively, could be generated. However, when flowing into the exposure chamber, the hydroxide rapidly reacted with CO_2 exhaled by the rats to form an aerosol primarily consisting of Na_2CO_3 (Zwi79).

From experiments performed in the 1930s, it may be concluded that rabbits may survive single oral doses up to 200 mg/kg bw, and that doses higher than 400 mg/kg bw will be lethal (Tra74). Oral intubation of a 4% solution of sodium hydroxide caused mucosal and submucosal necrosis of the oesophagus in 10 seconds in rabbits. A 12% solution eroded into the muscles, and a 28% solution caused perforations (ACG91).

For acute dermal toxicity, an LD_{50} of 1350 mg/kg in rabbits was reported (ECB95). Intraperitoneal injection in mice gave an LD_{50} of 40 mg/kg (Ric94, ECB95).

Repeated dose toxicity

In a study reported in a Czechoslovakian journal, 10 female white rats were exposed to aerosols generated from a 40% sodium hydroxide solution for two daily periods of 30 min for 2.5 months. The sodium hydroxide concentrations were not specified. After 3 weeks, exposure was interrupted for 10 days, because animals badly tolerated exposure. At necropsy one week after ending exposure, the lungs were grayish-brown coloured, resembling those of the control animals (n=5). However, histological examination revealed a number of changes in the lungs of the exposed animals, while no changes were seen in the controls (NIO75).

No toxic effects (not specified), effects on body or organ weights, or microscopic lesions (only one animal examined) were observed in 5 female rats intubated with approximately 1 mg/kg bw sodium hydroxide, 3 times a week, for 93 days (study from 1941, cited in LSR76, NIO75)

In rats (strain unknown; males: 2-3/group; females: 4/group; no controls; study duration not indicated) given drinking water containing 0.5 and 1.0% sodium hydroxide (approx. 500, 1000 mg/kg bw*), stunted growth, nervousness, irritability, sore eyes, and diarrhoea were observed in the high-dose group. No such effects were reported in the low-dose group. None of the females conceived at either dose level (study from 1932, cited in LSR76, NIO75).

Carcinogenicity

In a skin painting study, application of a 10% solution (amount unknown) twice weekly (duration unknown) induced a benign tumour in 1/7 mice, while in the positive control group treated with 1,2,5,6-dibenzanthracene malignant tumours were found in 16/33 mice. There was no untreated or a pH control group in this study (study from 1935 referred, cited in LSR76, NIO75).

The potential carcinogenicity of sodium hydroxide was examined by intubating mice with doses up to 200 mg/kg bw, 5 times a week during the first few months, and three times a week thereafter (duration: 10 months), alone and

* Calculated by assuming a body weight of 200 mg and a drinking water intake of 20 ml/day.

in combination with 1,2,5,6-dibenzanthracene. No cancerous or precancerous lesions were observed in the stomach of any of the mice used in this study. The only lesions seen were petechial haemorrhages over a very small area of the glandular portion of the gastric mucosa in 9% of the treated animals (study from 1946, cited in LSR76, NIO75).

No increase in the incidence of intestinal metaplasia or stomach carcinomas or sarcomas was found in male rats (n=18) following intubation of 0.5 ml of 0.1 N sodium hydroxide, once a week, for 12 weeks (sacrifices of 2 animals each at 1, 4, 18, 26, 34, 43, 58, 69 weeks from the start of the experiment). In the upper one-third of the pyloric glands ulceration was found and in the focal area a generative cell zone was involved in the ulceration. In animals given 100 µg/ml N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) in their drinking water for 12 weeks, superficial and focal ulceration were found at week 1 and 4, respectively. The appearance of intestinal metaplasia and carcinomas was observed sequentially (from week 26 onwards). The cumulative incidence of intestinal metaplasia reached about 56% at week 69. Gastric and intestinal carcinomas or sarcomas were found in 6/12 and 9/12 rats killed after 26 weeks, respectively. In neither groups, treatment had effect on the body weights. In a separate experiment with rats, treatment with 100 µg/ml ENNG for 12 weeks was followed by administration of 0.5 ml of 0.1 N sodium hydroxide, once a week, for 12 weeks. Two other groups treated with ENNG and sodium hydroxide alone were included as well. All animals were killed after 56 weeks. Comparable incidences of intestinal metaplasia were found in the group receiving ENNG alone and the group receiving both ENNG and sodium hydroxide, while the incidence in the sodium hydroxide group was a factor 3 lower. In the latter group, no carcinomas were found in the stomach or small intestine. Incidences of stomach carcinomas (well-differentiated adenocarcinomas + signet-ring cell carcinomas) were 2/6 and 8/14 in the ENNG-treated and the ENNG/sodium hydroxide-treated group, respectively. No statistical analysis was presented (Koj87).

In a study on experimental asbestosis in rats inhaling chrysotile dusts, one group was pre-treated by intratracheal application of 0.05 ml of a 5% aqueous sodium hydroxide solution in order to impair clearance from the lungs of subsequent inhaled chrysotile dusts. Eleven out of 81 rats receiving this intratracheal treatment died but the cause of death was not stated. In the experiment, a control group consisting of 15 animals that were treated intratracheally with sodium hydroxide (no details on amount and number of

applications) was included. No lung cancer was found in the 14 animals that were alive at the end of the experiment at 16 months (Gro67).

Mutagenicity and genotoxicity

An *in vitro* chromosomal aberration test with Chinese hamster ovary K1 cells with metabolic activation was positive. However, the clastogenic activity appears to be related to the non-physiological pH (Mor89). In an Ames test and a DNA repair test with *S. typhimurium* strains TA1535, TA100, TA1538, TA98, and TA1537 and *E. Coli* strains WP2, WP67, and CM871, respectively, no mutagenic effects were observed (DeF84). In other studies, sodium hydroxide was reported to be not mutagenic in several *E. Coli* strains (WP2, WP2 uvr A, WP67, CM611, WP100, W3110 pol A^+, p3478 pol A^-, Sd-4) (McC81, LSRO76).

Sodium hydroxide did not enhance transformation of Syrian hamster embryo cells by a simian adenovirus, SA7 (Cas79).

Reproduction toxicity

Apart from a study in which sodium hydroxide (2 µl of a 1 mM solution) was administered intraamniotically to the foetuses in the right uterine horn of 7 mice (foetuses of the other horn served as controls) on the 13^{th} day of gestation, no studies were found on the reproduction toxicity potential of sodium hydroxide. This treatment did not result in teratogenic effects (parameter: cleft palate), but induced a high incidence of fetal lethality (45% or 11/24 foetuses vs 1/33 in controls) (Mar88).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for sodium hydroxide in the Netherlands is a ceiling limit of 2 mg/m^3.

Existing occupational exposure limits for sodium hydroxide in some European countries and in the USA are summarized in the annex.

8 Assessment of health hazard

No valid human or experimental animal studies were found in which well characterized exposure by inhalation of sodium hydroxide was related to

systemic effects. However, sodium is a normal body electrolyte. The average daily intake was estimated to be 10-12 grams (Tra74). Therefore, no systemic effects are expected from amounts that would be taken up by inhalation at the maximal accepted respirable nuisance dust level of 5 mg/m^3 (which results in a daily dose of 50 mg assuming a worker inhales 10 m^3 of air during an 8-hour working day, and an absorption of 100%).

However, the most outstanding effect of sodium hydroxide is its local irritation and corrosion. These effects on the skin and eyes of solid sodium hydroxide and its solutions are well documented. However, no valid data were available on the relationship between effects on the skin, eyes, or respiratory tract and concentrations of sodium hydroxide in dusts or aerosols from which an no observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL) could be derived.

The committee considers the toxicological data base on sodium hydroxide 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.

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Annex

Occupational exposure standards for sodium hydroxide in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	lit ref[b]
	ppm	mg/m^3				
The Netherlands						
-Ministry	-	2	ceiling	administrative		SZW00
Germany						
-AGS	-	2[c]	ceiling			TRG00
-DFG MAK-Kom.	-	-[d]				DFG99
Great-Britain						
-HSE	-	2	15 min	OES		HSE99
Sweden	-	2	ceiling			NBO96
Denmark	-	2	ceiling			Arb96
USA						
-ACGIH	-	2	15 min, ceiling	TLV		ACG00
-OSHA	-	2	ceiling	PEL		
-NIOSH	-	2	ceiling	REL		
European Union						
-SCOEL						

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Inhalable dust.

[d] Listed among compounds for which the toxicological information available was not sufficient to derive at an occupational exposure limit.