II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational injury and disease arising from exposure to sodium hydroxide. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health of workers from exposure to hazardous chemical and physical agents. It should be pointed out that any criteria for a recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work environments and mere compliance with the recommended standard should not be used as a final goal.

These criteria and recommended standard for sodium hydroxide are in a continuing series of criteria developed by NIOSH. The proposed standard applies to the processing, manufacture, and use of sodium hydroxide as applicable under the Occupational Safety and Health Act of 1970.

These criteria were developed to ensure that the standard would (1) protect against the development of acute and chronic sodium hydroxide

poisoning and damage from local contact, (2) be measurable by techniques that are valid, reproducible, and available to industry and governmental agencies, and (3) be attainable with existing technology.

From the health hazard standpoint, sodium hydroxide must be handled with utmost care because of its highly damaging effect on the eyes, skin, alimentary tract, and respiratory tract. The importance of good work practices is emphasized.

The standard was not designed for the population at large and any extrapolation beyond general occupational exposure may not be warranted.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Sodium hydroxide, or caustic soda, is a strongly alkaline substance, which is soapy to feel, dissolves freely in water with the evolution of heat, is deliquescent, and in the moist state absorbs carbon dioxide from the air to form sodium hydrogen carbonate and sodium carbonate. [1,2] The chemical and physical properties of concentrated solutions of sodium hydroxide and anhydrous sodium hydroxide are shown in Table X-1.

In the United States sodium hydroxide is manufactured either by an electrolytic process or by a combination of lime and soda ash, the latter process becoming uncommon. [3] The electrolytic process consists of passing an electric current through a sodium chloride solution in specially designed cells. [3] The salt, which serves as the basic raw material can be obtained from natural brines, mines, or by the evaporation of sea water. Once in solution, the brine is heated and treated to remove calcium, magnesium, and sulfates. The salt brine is then decomposed by electrolysis to form a 10-12% sodium hydroxide solution while hydrogen is liberated at the cathode and chlorine is liberated at the anode.

Sodium hydroxide is one of the most widely used chemicals in industry. During 1974, 10.9 million tons of sodium hydroxide were produced in the United States. [4] It is used in the manufacture of rayon, mercerized cotton, soap, paper, aluminum, petroleum, chemicals, and dyestuffs. It is also used in chemical industries, in metal cleaning, electrolytic extraction of zinc, tin plating, oxide coating, laundering, and bleaching. [3,5] The commercial uses are listed in Table X-2.

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Sodium hydroxide is sold in various grades: USP, CP, reagent, and commercial. The common solid forms are flakes, granules, grinds, sticks, lumps, and drops (pellets). [3,6] Common assays of sodium hydroxide in marketed solids are in the range of 77-98%. Aqueous solutions are usually either 50% or 70-74% sodium hydroxide. Solids are sold in drums, bags, barrels, cans, bins, and bottles. Liquids are marketed in insulated tank cars, trucks, barges, ocean-going tankers, drums, and barrels. Most of the sodium hydroxide produced in the United States is made by the electrolytic process [3,7,8] and sold as a solution. [3]

The occupations in which workers may have exposure to sodium hydroxide are listed in Table X-3. [9,10]

The number of workers with potential exposure to sodium hydroxide has been estimated by NIOSH to be 150,000.

Historical Reports

In 1713, Ramazzini [11] reported occupational injuries from sodium hydroxide. He found that laundresses and washerwomen developed fissures, sometimes deep and troublesome, in their hands, followed by inflammation and fever. [11] He further noted that the feet and other parts of soap boilers were excoriated when in contact with the "strong and acrid water," presumably an impure sodium hydroxide-potassium hydroxide solution.

In the early part of the 20th Century, an Austrian factory inspector [12] reported to the International Labour Office (ILO) that a workman got caustic soda in his eye which resulted in corneal opacity.

Kober [13] wrote that over 13,000 people were engaged in the manufacture of soap in the United States in 1910. He reported a high

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incidence of morbidity and mortality among female tallow and soap workers.

In 1925, Hinkel [14] cited leaky valves, bursting tanks, fume line leaks, and poor recovery equipment as major culprits in producing injury from sodium hydroxide. Although he presented no data he noted that engineering and accident prevention programs had been effective in markedly reducing the number of cases.

Later Terry [15] reported that on-the-spot eye wash and treatment stations in British alkali plants were beneficial, but presented no data. He also mentioned that the application of bicarbonate of soda to form sodium carbonate, one of the forms of skin treatment for alkali burns prior to 1930, was unsatisfactory. He found that despite early treatment of sodium hydroxide burns of the eye, ie, washing with a boric acid solution for 2-5 minutes, there was a prolonged period of inflammation, the formation of granules over the sclerotic and inner surfaces of the eyelid, and an adhesion between the tarsal and bulbar conjunctivas. Even more serious consequences followed corneal burns. It was recommended [15] that there be immediate irrigation (within 30-40 seconds) of skin or eye injuries with aqueous 5% ammonium chloride solution from gravity-fed containers placed about the plant, educational and medical programs, and the use of personal protective equipment. For eye burns, irrigation with ammonium chloride solution was followed by treatment with a warm boric acid-saline solution in the clinic for 1 hour with subsequent shorter rinses with other agents and water as required. He reported that this program reduced the severity of eye and skin injury markedly during the period 1930-42 and shortened the recovery periods 5- to 7-fold as compared to older methods.

Effects on Humans

Eye injury has probably been the most severe effect from contact with sodium hydroxide. [12,14-19] Damage to the skin, [11,12,14,15,20-25] loss of hair, [23] and injury of mucous membranes have also been severe. However, only in rare instances were the concentrations of airborne sodium hydroxide reported. [2,26, TR Lewis, written communication, November 1974] Ingestion of sodium hydroxide, although infrequently reported in the occupational setting, [27,28] has had severe consequences. [27-33]

(a) Effects on Eye

In the early part of the 20th Century, a workman was reported [12] to have suffered corneal opacity following exposure to sodium hydroxide dust. Other reports [14-19] have also described the extreme hazard of eye contact with sodium hydroxide, with blindness a frequent consequence. Terry [15] observed some of the long term sequelae as a result of contact of the eye with sodium hydroxide. These included formation of granulation tissue over the sclerotic and inner surfaces of the eyelids and sticking of the eyelid to the eyeball. He also reported the development of tough bands of adhesion between the eyelids and the eyeball, thereby limiting eye movement. He also commented on the severity of corneal burns.

Hughes [16,17] compiled a general chronology of events following contact of the eye with sodium hydroxide; it is presented in Table III-1. He concluded that the alkalinity and not the specific cation determined the severity of the eye burn.

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TABLE III-1

CHRONOLOGY OF THE PROMINENT CHARACTERISTICS
OF SEVERE ALKALI BURNS OF THE EYE*

Time	Characteristics
1-10 min	Rapid penetration of alkali through cornea into anterior chamber; diminished tactile sensitivity of cornea; disintegration and sloughing of conjunctival and corneal epithelium; opalescent opacification of cornea; washed-out appearance of substantia propria with beginning of disintegration of stromal cells; fragmentation of corneal endothelium; hyperemia of iris
2 hr	Edema and ischemia of conjunctiva and limbal (corneo-scleral) region of the eyeball; infiltration of poly-morphonuclear cells into conjunctiva; episcleral tissues and periphery of cornea; corneal edema, giving rise to opalescent haziness of cornea, with wrinkling of Descemet's membrane ("striate keratitis"); exudation of serum into anterior chamber; Greef blebs and edema of ciliary processes
18 hr	Beginning regeneration of corneal epithelium; marked edema, loss of metachromatic staining of corneal mucoid, disappearance of stromal cells; increase of purulent infiltration into conjunctiva, cornea, and anterior chamber; opacity of anterior capsular and subcapsular region of lens
24-48 hr	Moderate mucopurulent discharge in cul-de-sac; intensi-fication of opacification, edema, and purulent infiltra-tion of cornea; appearance of spindle-shaped cells at periphery of lesion; regeneration of corneal endothelium
3-6 days	Petechial hemorrhages in ischemic areas of conjunctiva; varying amounts of superficial corneal ulceration, without apparent progression of corneal infiltration or opacification; persistence of iritis

TABLE III-1 (CONTINUED)

CHRONOLOGY OF THE PROMINENT CHARACTERISTICS
OF SEVERE ALKALI BURNS OF THE EYE*

Time	Characteristics
7-13 days	Stage of gradual recovery or progression of corneal opacification and ulceration; varying amounts of muco-purulent discharge from eye; formation of adhesions between severely burned portions of bulbar and palpebral conjunctivas, localized corneal infiltrates of polymorphonuclear and mononuclear cells, with ulceration over such areas; beginning vascularization of cornea from limbal vessels, superficial loops from unthrombosed conjunctival vessels or brush-like projections from deep scleral plexus in ischemic regions; continued proliferation of spindle-shaped cells in cornea; subsidence of corneal edema; improvement of iritis
14 days and over	Abatement or progression of symptoms previously described; great resistance of Descemet's membrane to perforation; healing of corneal ulceration by proliferation of opaque fibrous tissue and blood vessels
	Complications of severe burns: Symblepharon with overgrowth of cornea by a vascularized membrane; progressive or recurrent corneal ulceration, occasionally leading to perforation; permanent corneal opacification; staphyloma of cornea; persistent or exudative iritis, at times ending in phthisis bulbi, secondary glaucoma or cataract

* Derived from reference 16

In 1954, Dennis [19] reported a case of occupational eye burns from alkalis. A 63-year-old textile worker was splashed in the face and eyes with sodium hydroxide. Affected areas were immediately irrigated with water for an unspecified time and the worker was later treated in a

hospital. Examination showed excessive edema of the conjunctivas,
photophobia, and pain. Both corneas were gray. Treatment consisted of
irrigations with saline, neutralization with acetic acid solution, topical
anesthetics and antibiotics, and removal of all devitalized tissue. The
patient's eyes healed well, but he developed a wing-like overgrowth of
conjunctival tissue in the area of the deepest corneal burn.

The value of prompt treatment in order to alter the course of events
in eye burns was demonstrated in a case reported by Horwitz [18] in 1966.
In this case, a 28-year-old member of an oil-well drilling crew sustained
extensive splash burns of the left eye from sodium hydroxide and received
emergency care from a general physician prior to being hospitalized. At
the hospital, initial examination showed vision limited to light
perception, corneal clouding to such an extent that iris markings were not
discernible, necrosis of most of the bulbar conjunctiva, some sloughing in
the nasal area of the cornea, blanched and necrotic cul-de-sac, and some
involvement of the lids and adjacent skin.

The treatment for the patient at the hospital consisted of daily
debridement of necrotic areas, local atropine, antibiotics, and steroids,
systemic ACTH, vitamins, antacids, and proteolytic enzymes.

The treatment produced some improvement with time so that usual,
late sequelae such as vascular invasion and symblepharon did not occur, and
the cornea cleared sufficiently within 7 weeks that vision returned to near
normal.

(b)   Effects on Skin

Cutaneous exposure has resulted in severe damage to skin. [11,
12,14,15,20-25] Davidson, [21] in an effort to determine the latent period

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between the exposure of skin to sodium hydroxide and the sensation of irritation, put aqueous 50% or 25% solutions on the skin of 3 human volunteers and noted that neither concentration of sodium hydroxide caused any sensory stimulation within 3 minutes after application. Acids were used as positive controls; an aqueous 50% solution of either nitric or sulfuric acid promoted responses in all 3 persons in 22.6-50 seconds, and a 37% hydrochloric acid solution elicited a response in 2 people in 15 and 17 seconds, respectively.

Later Terry [15] also described a similar latent period in his observations of sodium hydroxide burns in an alkali plant in England.

Chiego and Silver [22] found that keratin material in the skin underwent rapid decomposition in sodium hydroxide above pH 9.2. In their in vitro experiments, they mixed aliquots of washed human hair and fingernails with various amounts of sodium hydroxide solution and measured the extent of keratin breakdown by estimating the cystine produced. They found that the cystine portion of the keratin complex of human hair or nails was readily cleaved by sodium hydroxide in the S-S bond. After 20 hours of contact with 0.1N or 0.25N sodium hydroxide, 61.4% and 97.6%, respectively, of the nail keratin were decomposed. Thus a high degree of destruction of tissue even by a dilute sodium hydroxide solution can occur from prolonged contact.

An occupational accident involving hair was reported by Morris. [23] A 42-year-old man was working at a bench under a clogged pipe. A sodium hydroxide solution of pH 13.5 had been put into the pipe in an effort to unclog it. This solution had destroyed part of the pipe and dripped on the worker's head. He experienced neither burning nor pain at

that time and merely wiped the material off with his hand. The next morning, when combing his hair, he noticed that some of the hair came loose from the roots and he became aware of a burning sensation on his scalp. The lesion consisted of erythematous skin studded with minute pustules in the areas of baldness. After washing with water, the burn subsided and in time the hair grew back. This incident demonstrates that there is not necessarily an immediate sensation of pain or irritation following cutaneous exposure to sodium hydroxide. In this case, however, abundant flushing with water, even several hours after exposure, seems to have limited the injury.

In an effort to relate injury from sodium hydroxide to rate of water loss from tissue, Malten and Spruit [24] cemented a small cylindrical plastic cup with cover to the forearm of a human volunteer. In a series of experiments, sodium hydroxide or potassium hydroxide solutions of various concentrations were placed in the cup for various time periods. Clinical observations were made and water vapor loss was measured as a function of time in each of the experiments. After every exposure the cup was removed. It was placed on the same spot in serial experiments. The authors observed perceptible erythema of the skin with 0.0675N (0.27%) sodium hydroxide within 1/2 hour, and less marked erythema with 0.03N (0.12%) sodium hydroxide after 1 hour. The rate of water vapor loss from injured skin was greater than from normal skin, but decreased with time. The authors proposed the use of this decrease as an index of damage. Their experiment with an aqueous potassium hydroxide solution indicated that 0.0675N potassium hydroxide produced damage equivalent to that caused by 0.045N sodium hydroxide. They suggested that this difference was significant and

that damage might not be governed solely by the hydroxyl ion concentration and that, based on the rate of water vapor loss, damage from 0.0675 N potassium hydroxide was only half as severe as that produced by 0.0675 N sodium hydroxide. The authors also found that, as skin injured by sodium hydroxide or potassium hydroxide regenerated, the rate of water vapor loss approached that of normal skin. In a later experiment [34] using the same technique, these authors showed that adhesive-tape stripping of the skin produced reactions equivalent to treatment with sodium hydroxide.

In this later study, Spruit and Malten [34] noted that following exposure to sodium hydroxide solutions in a manner similar to that described above, [24] at pH's 11.5-11.7, injury to the horny layer was sufficient to cause approximately 8 times the rate of water vapor loss as was caused by a solution of pH 11.3. Basing their evaluation of skin injury on the increase in water vapor loss rate, the authors found that injury to skin from sodium hydroxide of pH 11.75 was equal to injury to skin which had been pretreated with petrolatum and exposed to sodium hydroxide of pH 11.95.

In order to simulate a normal exposure to alkali, the authors [34] exposed the same patch of skin of each of 2 volunteers to 0.5 ml of 0.03 N sodium hydroxide/sq cm for 1 hour/day for 6 successive days. In general, repeated applications of sodium hydroxide produced increasing damage to the skin. Because of variation of response during various times of the year and the differences in the skin textures in the 2 individuals tested, the authors concluded that various climates and skin textures may influence the seriousness of skin injury.

In 1972 Nagao et al [25] reported a study of human primary irritant dermatitis. Part of the experiment used sodium hydroxide as the irritant. Twenty microliters of 1N sodium hydroxide was applied 1, 2, or 3 times at 30-minute intervals to the flexor surface of the forearms of 7 healthy volunteers, aged 21-31. The subjects included Caucasian, Negro, and Japanese males and one Caucasian female. Under local anesthesia, 4-mm punch biopsies were taken 15, 30, 45, and 60 minutes after application of the sodium hydroxide. Control specimens were prepared from each subject. One-half of each specimen was fixed in a 10% formalin solution, embedded in paraffin, stained with hematoxylin and eosin, and examined under light microscopy. The other half was fixed in cacodylate-buffered osmium tetroxide for 2-3 hours, dehydrated, embedded in resin, sectioned, stained with toluidine blue, and examined by electron microscopy. Some thick sections were also prepared in the above manner and examined with light microscopy. Clinical observations made during and after sodium hydroxide application showed a slight erythema 25-30 minutes after application, then a "waxy" appearance, and swollen hair follicles in several test sites. With light microscopy, it was apparent that 1N sodium hydroxide produced changes more rapidly than 1N HCl. After 15 and 30 minutes, the sodium hydroxide caused the horny layer to be swollen and the prickle-cell layer to display a few pyknotic nuclei. At 45 and 60 minutes, intercellular edema was pronounced and cleft formation was seen in the middle and lower prickle-cell layers. The entire epidermis in the test areas of several subjects was destroyed at 60 minutes. The authors believed that it was possible that partially neutralized sodium hydroxide that failed to cause visible changes in the relatively insoluble lower horny layer cells could

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be of sufficient concentration to affect living cells of the stratum malpighii.

(c)   Effects on Alimentary Tract

In 1965, Moeschlin [27] reported the case of a 37-year-old carpenter who accidentally drank a concentrated solution of sodium hydroxide from a Chianti bottle, which he thought was apple cider. Signs and symptoms included violent pain in the esophagus and stomach, severe corrosion of the lips, mouth, pharynx, and tongue, and the vomiting of large pieces of mucosa. Because he received prompt on-the-spot treatment and follow-up medical treatment there were no sequelae.

Palmer [28] reported about 1,500 serious casualties incurred by the drinking of schnapps that had been adulterated with lye. The boobytrapped schnapps had been left in France and Germany by the retreating German army or given to inebriated Allied soldiers during the later stages of World War II. Most injured soldiers obtained medical help months after consuming the adulterated spirits and the most serious sequela was esophageal stenosis with a few cases severe enough to lead to antropyloric stenosis.

Several reports [29-33,35] have implicated the massive ingestion of sodium hydroxide as causing esophageal cancer. None of these cases were of occupational origin and all were cases involving severe stricture of the esophagus requiring a gastrostomy. Latent periods ranged from 12 years [35] to 42 years. [30] All identified tumors were classified as squamous-cell carcinomas. It should be pointed out that carcinoma at the site of damage is also an even more frequent late sequela to severe thermal burns. [30] While there seems no question that the various cases of cancer were causally related to sodium hydroxide ingestion, it seems clear that these

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cancers were sequelae of tissue destruction and possibly scar formation and not from a direct carcinogenic potential of sodium hydroxide itself.

(d) Effects on Respiratory Tract

Most authors concerned with hazards from sodium hydroxide have emphasized the prevention of contact with eyes and skin, and of its ingestion. Inhalation of sodium hydroxide has received little attention. [2,26, TR Lewis, written communication, November 1974] It may be presumed that the irritating nature of the aerosol on mucous membranes has prompted the maintenance of airborne concentrations of sodium hydroxide at tolerable levels. Patty [2] made reference in his 1949 review of the literature to the concentration of sodium hydroxide in workroom air. After commenting that he was unable to find any published record of measurements of airborne sodium hydroxide in industry, he stated, apparently based upon his own experience, that "from the irritant effects of caustic mists encountered in concentrations of 1 to 40 mg per cubic meter of air, 2 mg sodium hydroxide per cubic meter is believed to represent a concentration that is noticeably, but not excessively, irritant." He further suggested that this figure be used as a "bench mark" until further information is presented.

In May 1974, NIOSH [26] reported an investigation of the possible hazards associated with a chemical degreasing operation. The degreasing vat was 11 x 11 x 3 ft and contained a caustic solution maintained at 200 F by steam bubbling through it. The caustic solution contained primarily sodium hydroxide, but also sodium gluconate, tetrasodium pyrophosphate, and minor amounts of nonsodium compounds otherwise unspecified. The pH of the bath was 12.5-13.5. (This pH is equivalent to a hydroxyl ion concentration of 0.032-0.32 moles/liter or a sodium hydroxide concentration of 0.13-1.3

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g/liter). Operations adjacent to the vat involved the use of other substances (eg Ensis 254 oil, Stoddard solvent, Zyglo, and Magna flux).

In September 1972, 2 employees experienced irritation of the nose and throat and frequent chest pains associated with shortness of breath. One was treated with antibiotics. A week later a third person, a vat operator, experienced nausea, vomiting, and nose and throat irritation. Antibiotic therapy was an effective treatment; the vat operator was transferred and experienced no recurrence of these signs and symptoms. The other 2 employees remained in the vat area and intermittently had irritation of the nose and throat. In December 1972 NIOSH made a preliminary survey of the establishment. In May 1973 NIOSH found the airborne concentration of Stoddard solvent to be 14-780 mg/cu m; other solvent vapors (undescribed) were 276-725 mg/cu m, reported as Stoddard solvent, according to a written, internal NIOSH laboratory report series. Airborne sodium concentration, reported as sodium hydroxide, was <0.1-0.7 mg/cu m; airborne sulfuric acid concentrations were 0.3-2.2 mg/cu m. Another survey was made in September 1973, but no data were reported.

In October 1973, a more comprehensive survey was made by NIOSH. At this time the airborne concentrations of sodium, reported as sodium hydroxide, were 0.005-0.12 mg/cu m. The airborne Stoddard solvent concentrations were <10-62 mg/cu m and the airborne n-butyl acetate concentrations were <0.2-0.4 ppm.

Fifteen workers (aged 21-63) in the vicinity of the degreasing vat which contained sodium hydroxide and 10 workers (aged 24-59) from another unspecified area of the plant filled out questionnaires and were given medical examinations limited to the skin and upper respiratory tract

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structures. Employees in both groups were in good health. All personnel who participated in this study had worked for at least 16 months. The employees supplied information relating to symptomatology, that is, the occurrence of any given symptom at a minimum frequency of 4 times/year while on the job. Of the 15 who worked in the vicinity of the vat, 8 reported burning/redness of the eyes, 9 burning/redness of the nose, 7 burning/dryness of the throat, 2 burning in the chest, 1 headache, 1 rhinorrhea, and 3 skin eruption. There were no reports of sneezing or wheezing. None of the control group reported any of these symptoms at a frequency greater than 4 times/year. Apparently, half the workers in the vicinity of the vat experienced some symptoms of irritation of the upper respiratory tract. The authors concluded that the 3 persons with skin eruptions did not develop them as a result of in-plant factors, but presented no supporting data. They also concluded that caustic mist exposure was responsible for the symptoms reported.

Two possibly significant factors the authors presented, but did not fully evaluate, were that (1) the temporal occurrence of symptoms during the normal work shift did not correlate well with the degree of ventilation in effect at these times and (2) some of the effects may have been caused by Stoddard solvent. There was a greater incidence of sneezing and burning/dryness of the nose when the vat cover was on than when it was off. Burning/redness of the eyes occurred with equal frequencies with the vat cover on or off, and burning/dryness of the throat occurred only slightly more frequently with the vat cover on than off. These observations are not entirely consistent with the conclusion reached by the investigators that the mist from the vat produced the signs and symptoms.

Another factor which may have been important was the presence of rather high airborne concentrations of Stoddard solvent in the workplace.

In 1974, in another study by NIOSH designed for purposes not directly relevant to the determination of sodium hydroxide aerosol dose-response relationships, 9 persons recorded their responses while they used a spray oven-cleaner which contained sodium hydroxide, among other ingredients (TR Lewis, written communication, November 1974). Personal samples of airborne sodium were taken with 0.8 μm pore size filters, both during a spray application and during the manual cleaning process which followed. Samples were analyzed for total sodium by atomic absorption spectrophotometry and reported as sodium hydroxide. Subjects used the spray cleaner on their home ovens, so exposures and breathing-zone samplings were unsupervised.

Some of the persons who cleaned their home ovens with the aerosol reported symptoms of irritation of the respiratory tract. Because the study was not designed for the purpose of evaluating the irritancy of sodium hydroxide, but rather to evaluate the general irritancy of the aerosol, air sampling and chemical analysis for sodium hydroxide and other ingredients was not extensive enough to allow identification of the specific agents responsible for this irritancy.

Animal Toxicity

Two studies [21,36] have evaluated the effects of sodium hydroxide on skin, and the effectiveness of treatments. In 1927 Davidson [21] studied the various treatments for alkali burns of the skin and described the etiology of these burns. In his first experiment, he used 3 groups of

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3 rats each, all anesthetized with ether. The hind legs of all 9 animals were dipped into a solution of 50% sodium hydroxide for 1 minute with no treatment for the next 5 minutes. One group of 3, regarded as a control, then had the excess sodium hydroxide wiped away with cotton. In the second group, the sodium hydroxide was neutralized with 1% acetic acid. Rats in the third group were treated by vigorous washing with water. Control animals over an 18-hour period gradually developed edema and maceration of the skin with the formation of thick, edematous sloughs. The author also performed similar experiments with nitric, sulfuric, hydrochloric, and trichloroacetic acids and noted that damage from sodium hydroxide was unlike that produced by acids. Rats whose lesions were treated by neutralization developed edema and redness of the foot at the end of 24 hours; gradually the skin of the thigh and flank sloughed but the animals recovered. The hair of the rats treated with water remained intact and there was no sloughing of the skin. The only evidence of a burn in these animals was moderate edema of the toes and excoriation of the skin of the foot; healing took place promptly and without deformity. Based on these observations, the author concluded that the preferred treatment for sodium hydroxide burns was vigorous washing with water followed by neutralization of the residual alkali.

Bromberg et al [36] in 1965 published a study in which the clipped backs of anesthetized, A/He, and C57 black adult mice weighing 25-35 g were painted with 50% sodium hydroxide on a 3-sq cm area. The animals were treated in various manners, as shown in Table III-2. All mice except those treated immediately developed a rapidly progressive burn in both extent and depth. The severity of the burn increased with delay in treatment. Two

hours after application, 2 untreated mice were dead, and after 24 hours a hard, dark brown eschar had developed in both the untreated group and in the group treated 2 hours after the burn. The group irrigated 30 minutes after the burn showed a rather limited, spotty, superficial burn compared to the burn in untreated animals. Groups irrigated 1 and 2 hours after the burn developed progressive changes in both depth and extent of burn, with severity increasing with time to treatment. The group irrigated 2 hours after sodium hydroxide application exhibited changes similar to those of the untreated group but with less local edema in the area peripheral to the burned zone. Biopsy sections obtained 24 hours after application exhibited some edema and cellular infiltration in the mice given immediate irrigation. In biopsy of untreated mice severe necrosis was found.

TABLE III-2

MORTALITY IN MICE FROM TOPICAL APPLICATION OF SODIUM HYDROXIDE
(50% SOLUTION OF SODIUM HYDROXIDE APPLIED TO A 3-SQ-CM AREA)

Treatment	Time of Treatment	Number of Animals	Mortality
Continuous irrigation with water for 1 hour	Immediately	5	0/5
"	30 minutes after application	5	1/5
"	1 hour after application	5	2/5
"	2 hours after application	5	4/5
None	--	7	5/7

Derived from reference 36

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Several studies [17,37-49] have evaluated the effects of sodium hydroxide on the eye. Cosgrove and Hubbard [37] placed a drop of 40% sodium hydroxide solution in the eyes of an unspecified number of anesthetized rats. One group of rats received 2% acetic acid to neutralize the base. Another group was treated by washing the eye with water. Eyes of both positive controls (untreated) and of those treated with acetic acid were completely degenerated at the time of death 2-3 days later. Fifty percent of the eyes treated by washing with water had cloudy corneas and the remainder had complete degeneration of the cornea. Results were similar with lesser concentrations of sodium hydroxide and none of the eyes treated by neutralization were saved; only about 50% of the eyes treated by washing were saved. Unlike skin damage, [21] the authors [37] found there was no detectable latent period for eye damage.

In 1937 Hubbard [38] reported instilling 20% sodium hydroxide into the eyes of an unspecified number of rabbits where it remained for 10 seconds. One eye of each animal was irrigated with water for an unspecified time; the other was irrigated with an aqueous 2% solution of acetic acid. The author reported that in 75% of the eyes tested, washing with dilute acetic acid resulted in less damage than washing with only water, but he presented only limited supporting data.

In another experiment, Hubbard [39] introduced an amount of aqueous 20% sodium hydroxide into the eyes of rabbits sufficient to fill the conjunctival sac and allowed it to remain for 10 seconds. Eyes of all rabbits were irrigated with water for an unspecified time. This was followed by no further treatment, or by irrigations with: (1) 5% tannic acid solution, or (2) 5% tannic acid solution followed by 2% silver nitrate

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solution, or (3) 1% methylrosaniline solution followed by 2% silver nitrate solution, or (4) 1% methylrosaniline solution followed by 5% tannic acid solution and additional methylrosaniline solution, immediately and once on the following day. After treatment (1), the eyeball had degenerated 19 days later; after (2), (3), and (4) necrosis of the cornea occurred 27-29 days later. In the case where there was no further treatment, the cornea ruptured in 18 days. Although corneal rupture was delayed by the various treatments, it eventually occurred.

In 1946 Hughes [17] irrigated a rabbit eye for 3 minutes with 0.2% sodium hydroxide made isotonic by the addition of sodium chloride. A moderately severe lesion which healed in about 10 months was produced. He observed and described in detail the progress of the lesion with time; it was similar to that outlined in Table III-1.

In 1955 Grant and Kern [40] dropped test solutions in the eyes of rabbits for 15 minutes at room temperature after scraping off the corneal epithelium. Sodium hydroxide, 0.23M, was adjusted to pH 11 and produced slight and reversible injury; when adjusted to pH 12, it produced severe injury with opacity. The authors did not describe the method of adjusting pH. Other alkaline materials, namely, potassium hydroxide, calcium hydroxide, barium hydroxide, strontium hydroxide, ammonium hydroxide, tetramethylammonium hydroxide, tetraethylammonium hydroxide, trimethylamine, triethylamine, tributylamine, diethanolamine, and piperidine produced similar injuries, indicating that injury was likely caused by the hydroxyl ion at high concentration and not by cations.

In a series of experiments by Brown and co-workers [41-46] in which a solution of 0.5N sodium hydroxide (2.0%) on cotton pads was applied to

the eyes of anesthetized albino rabbits for 30 seconds, severe corneal burns resulted. In each report, ulcerated or perforated corneal tissue developed within 3 weeks of exposure, and the ulcerated tissue was shown to produce collagenase while normal tissue of control animals did not. In their more recent works, [45,46] subsequent application of cysteine proved beneficial in 13-16 eyes so treated. In similar experiments, the presence of collagenase after application of 0.5N (2.0%) sodium hydroxide to eyes of rabbits was also noted by Francois and Feher [50] in 1972.

In 1971 Chiang et al [47] reported applying 0.05 ml of 0.125N (0.5%), 0.5N (2.0%), and 2.0N (8.0%) sodium hydroxide, respectively, into the eyes of 3 anesthetized albino rabbits and finding that the intraocular pressure increased 5, 18, and 37 mm Hg, respectively, within 2.5 minutes.

Geeraets et al [48] reported a study in which 0.5 ml of 0.5N sodium hydroxide was added to both eyes of 62 rabbits after the nictitating membrane had been sutured open. Half of the animals had both eyes irrigated with 1 liter of tap water starting 1 minute after the injury, while the other half was treated similarly 4 minutes after injury. After the water wash, some eyes were treated with 10% neutral ammonium tartrate (NAT) solution and some with water. The results appear in Table III-3. Although neutral ammonium tartrate was not more effective than water in preventing descemetoceles or perforations, the repeated washing at intervals was decidedly more effective than single washes in preventing damage.

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TABLE III-3

OBSERVED DESCEMETOCELES AND PERFORATIONS IN EYES TREATED SINGLY
OR HOURLY FOR 8 HOURS WITH NAT AND CONTROL EYES TREATED IN A
SIMILAR MANNER WITH TAPWATER

Alkali-cornea Interaction	Hourly Application	Total No. of Eyes	Descemetocele or Perforation
1 minute	NAT	19	6
	Water	19	7
4 minutes	NAT	19	6
	Water	19	6
	Single Application		
1 minute	NAT	12	8
	Water	12	10
4 minutes	NAT	12	10
	Water	12	11

It should be noted that even 1 minute of exposure to 0.5 N sodium hydroxide was sufficient to produce descemetoceles or perforations of corneas in 65-91% of the eyes which were inadequately washed.

Shapiro [49] immersed the corneas removed from rabbits in 1N (4.0%) and 0.2N (0.8%) sodium hydroxide solutions and found immediate clouding and an increase in both their size and weight which continued for 200 minutes; at that time the weight had more than tripled. In experiments with living rabbits, 4-mm circles of filter paper were soaked in 1N sodium hydroxide and the excess solution was removed. They were then applied to the center of the cornea of living rabbits for 1- to 60-second periods after which the

eye was irrigated with running tap water for 14 minutes. Animals were killed and their corneas examined microscopically. Shapiro found that significant swelling had occurred in as little as 2 seconds and that the amount of swelling was directly proportional to the contact time.

Dluhos et al [51] in Poland reported a later study dealing with the inhalation of sodium hydroxide aerosol. White, female, 5-months-old rats with an average weight of 150 g were used. Ten rats were exposed to a sodium hydroxide aerosol for 30 minutes, twice daily, for 2.5 months. Another 10 rats exposed to sodium hydroxide in the same manner and also to an aerosol generated from an aqueous 8% ammonium chloride solution for 30 minutes immediately after each exposure to sodium hydroxide. A group of 5 rats served as controls and were not exposed. This routine was interrupted for 10 days 3 weeks into the experiment because the animals tolerated it badly and 2 from the second group died. The airborne concentration of sodium hydroxide was not determined; however, the sodium hydroxide aerosol was generated from a 40% solution of sodium hydroxide and 80% of the particles were less than 1 μm in diameter. The animals were killed 1 week after the last exposure. The lungs of the first group were grayish-brown, but resembled those of the control group; those of the second group were more strongly brownish-discolored. Undescribed, isolated tumors were found in 3 animals exposed to sodium hydroxide aerosols.

Rats in the first group had what was described as inflated pulmonary tissue. In places the chamber barriers (presumably alveolar walls) were thickened, with cell proliferation, and congested. The bronchial epithelium was damaged, flattened, and ulcerated; there was thickened lymphadenoidal tissue, penetrating the muscle under the epithelium in

several places. At other points, the proliferated lymphadenoid tissue adhered to the bronchial lumen. In the bronchial lumen there often were stripped epithelia, dystrophic to a great extent, thoroughly mixed with amorphous protein substances and leukocytes. In several areas on the lung parenchyma very small, often fused together beds of bronchial pneumonia were observed.

The second group of rats suffered greater damage. Bronchi were more dilated and had markedly flattened epithelium with progression to apparent metaplasia of the epithelium. The walls of the bronchi had granulation tissue structurally alternating with the formation of fibroblasts. The bronchial wall was entirely destroyed in places and elsewhere epithelium was completely absent. Animals in this group died exhibiting interstices significantly infiltrated with round cells of the lymphocyte type, plasma cells, and histiocytes. The control group appeared to be normal.

In another experiment, Vyskocil et al [52] found that 27 white rats died within a month, mostly from bronchopneumonia, after twice-weekly exposures to an aerosol of unknown airborne concentration generated from an aqueous 40% sodium hydroxide solution. When exposed to an aerosol generated from aqueous 20% sodium hydroxide solution, the septa were emphymatously (sic) dilated and cracked, the bronchi were dilated and their epithelial cover was thin and frequently desquamated, and a light round-cell infiltration of the submucous membrane tissue occurred. Other rats were exposed to aerosols generated from 10% and 5% solutions of sodium hydroxide. In the group exposed to aerosols from 10% sodium hydroxide, little change occurred. In the group exposed to aerosols from 5% sodium hydroxide, rats had dilatation of the bronchi and a slight degeneration of

the mucous membrane and thickened strata of the lymphadenoid tissue surrounding the bronchi. All rats in these experiments were exposed to quartz dust at a concentration of 10 g/cu m. It is unclear what effect this exposure may have had on the results.

Correlation of Exposure and Effect

There are 4 principal occupational hazards associated with the manufacture and use of sodium hydroxide: (1) contact with the eyes, [2,15-21,53,54] (2) contact with the skin, [2,11,12,14,15,20,21] (3) ingestion, [27,28] and (4) inhalation of sodium hydroxide aerosol. [2] All these hazards reflect the destructive action of sodium hydroxide on tissue. [2,12,14-21,27,28,53,54]

When sodium hydroxide comes into contact with the eye, even for a matter of seconds, some damage results. [15-19,36-40,42-47,49,53,54] One of the shortest contact times recorded [49] as capable of inducing ocular injury from 1N (4%) sodium hydroxide was 2 seconds. Contact with 0.5 N (2%) sodium hydroxide [48] for 1 minute, the shortest period used, caused descemetoceles or perforations in 65-91% of the corneas tested. Immediate availability of treatment for accidental eye contact consisting of sufficient flushing with water, followed by appropriate clinical therapy, is of the greatest importance.

Sodium hydroxide of sufficient concentration produces damage if it remains in contact with the skin for a long enough time. [2,11,12,14,15,20-22,24,25,34] Damage to healthy skin has been reported [24] following contact with sodium hydroxide solutions as weak as 0.03N (0.12%) for 1 hour. Contact with 50% sodium hydroxide, followed by immediate irrigation

with water for 1 hour, [36] produced some edema and cellular infiltration, but no apparent destructive damages. Regardless of the concentration, the severity of the damage and the extent of its irreversibility increase with increasing contact time. [15,21,22,24,25,34,36] There is a latent period [15,21,23] following skin contact with sodium hydroxide during which no sensation of irritation occurs, about 3 minutes with 25-50% solutions [15,21] and several hours with 0.4-4% solutions. [23] Because damage to the skin will occur before the sensation of irritation, good work practices including prompt attention to accidental skin contact are of paramount importance.

Ingestion of sodium hydroxide has rarely occurred as a result of exposure in the occupational setting. [27,28] Accidental ingestion has caused violent pain in the esophagus and stomach, severe corrosion of the lips, mouth, pharynx, and tongue, and vomiting of large pieces of mucosa, [27] and esophageal and antropyloric stenosis. [28] In other isolated case reports, [29-33,35] burns resulting from ingestion of sodium hydroxide have apparently led to squamous-cell carcinomas of gastric tissue. As previously commented on these cancers were undoubtedly caused by the tissue destruction and regeneration and not by a direct carcinogenic action of the compound.

The inhalation of sodium hydroxide can result in irritation and damage [2,51, TR Lewis, written communication, November 1974] of the tissue of the respiratory system. As the concentration of sodium hydroxide in the inhaled aerosol increases, the extent of irritation or damage evidently increases. [51] At present, probably the only reports in the literature which discuss either human or animal response to a known, low concentration

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of sodium hydroxide are (1) a NIOSH Health Hazard Evaluation, [26] (2) a written communication from TR Lewis describing the irritative effects on the upper respiratory tract from oven cleaners, and (3) a statement by Patty [2] which was: "Judging from the irritant effects of caustic mists encountered in concentrations of 1 to 40 mg per cubic meter of air, 2 mg sodium hydroxide per cubic meter is believed to represent a concentration that is noticeably, but not excessively, irritant." No further description of what led Patty to this conclusion was given, but Smyth [55] in his critical review of Threshold Limit Values avouched that it was based upon observations of exposed workmen.

The authors of a NIOSH Health Hazard Evaluation [26] reported that some of the employees tending a cleaning vat had upper respiratory irritation such as burning/redness of the nose and throat, and also burning/redness of the eyes from sodium hydroxide exposure. Airborne concentrations of sodium were found to be 0.005-0.7 mg/cu m (as sodium hydroxide). The Stoddard and other unspecified solvents in the workplace were assumed not to have been responsible for the upper respiratory and eye irritation, but based on the information presented by the authors, this assumption is not necessarily valid. They found airborne concentrations of Stoddard and other unspecified solvents as high as 780 mg/cu m. These solvents may have played an important role in the production of upper respiratory irritation. The Threshold Limits Committee of the American Conference of Governmental Industrial Hygienists [56] recommended a Threshold Limit Value (TLV) for the Stoddard solvent of "approximately 800 or 1100" mg/cu m on the basis of its similarity in composition to unleaded gasolines. The TLV documentation [56] cited the work of Davis et al [57]

in which men were exposed to unleaded gasoline at airborne concentrations of 150-220 ppm (800-1210 mg/cu m) for 30 minutes and reported itching or burning of the throat and of eyes and headaches. Because of these effects of gasoline and the probable similarities between gasoline and Stoddard solvent, it is unlikely that sodium hydroxide was conclusively and solely responsible for the effects the authors found.

In the study by TR Lewis, reviewed in the section on Effects on Humans, 1 person felt throat irritation when the airborne sodium concentrations, as sodium hydroxide, were 0.24 and 1.86 mg/cu m. Another person developed watering eyes when exposed at 0.80 mg sodium/cu m, reported as sodium hydroxide. Another person did not experience irritation when the airborne sodium concentration was 0.28 mg/cu m as sodium hydroxide. It is apparent that since these were all short-term exposures, of 2-15 minutes duration, irritation may result in a rather short period of time. Two factors limit the extent of correlation that can be made between the amount of exposure and effect. One of these is the uncertainty that the irritation from the use of the oven cleaner was due to sodium hydroxide. One subject, for example, noted that other sprays (eg spray deodorant) also caused a choking feeling. The other factor is the possibility that the sampling process, being unsupervised, was not accurate enough to allow a meaningful conclusion to be drawn.