NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for BOOT AND SHOE MANUFACTURE AND REPAIR

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Summary Statement

The International Agency for Research on Cancer found *sufficient* evidence that employment in the boot and shoe manufacture and repair industry is carcinogenic to humans (IARC, 1981). The IARC assessment was based on increased risk for nasal adenocarcinoma and other types of nasal cancer in European workers; the risk appeared to be associated primarily with exposure to leather dust. Increased risks were also found for other sites including urinary bladder cancer and leukemia. Although there is little documentation of actual exposures, these risks were ascribed to exposure to benzene and other solvents, dyes, and metallic compounds.

Studies conducted in Europe and published since IARC (1981), including a series of studies based on the Swedish Cancer Environment Registry, have found increased cancer risks at several tissue sites with little confirmation for any individual site. The studies based on the Swedish Cancer Environment Registry all involved employment in 1960 or earlier, although employment may have continued beyond that date. Studies of boot and shoe manufacture and repair in the United States have, with one exception, employed designs which cannot either confirm or rule out the possibility of increased risk. Walker *et al.* (1993), in a retrospective cohort mortality study of workers employed between 1940 and 1979 in two U.S. shoe factories, found an increased risk for cancer of the trachea, bronchus, and lung (SMR = 1.47; 95% CI = 1.20-1.80). The risk of lung cancer was reduced, but not eliminated, by indirect adjustment for smoking.

Employment in shoe manufacture and repair has involved exposure to many agents known or reasonably anticipated to be human carcinogens. Some of these agents are no longer used in the U.S. industry. Industrial hygiene data describing actual exposures to these agents are minimal. Assessment of hazards associated with employment in the U.S. industry is complicated by the fact that changes in both manufacturing processes and industrial hygiene standards may have altered exposure conditions. This could entail either increases or decreases in exposures to specific agents.

It is recommended that Boot and Shoe Manufacture and Repair be included in the Report on Carcinogens as having been reviewed, but not formally listed, because available data are insufficient to characterize either the exposures or the risks entailed by employment in the U.S. industry.

1.0 IDENTIFICATION

Workers in the nonrubber boot and shoe industry are exposed to dust and other atmospheric contaminants, adhesives, solvents, cleaners, and finishes that are a part of manufacturing and repair processes (IARC, 1981). Known or suspected carcinogens comprise a subgroup of these substances (Table 1-1). In the past, boot and shoe manufacture and repair has been associated with significantly increased incidences of cancer and other toxicities in numerous countries (IARC, 1981). Comprehensive U. S. health and safety standards have eliminated many of the agents that continue to be a part of boot and shoe manufacturing processes in some other countries. While this review focuses on current occupational cancer risks in the United States, relevant historical data and reports from other countries are included.

1.1 Dust

Leather dust, composed of both fibers and grains, is produced in several of the operations common to boot and shoe manufacturing. The fibers can vary from 30-1200 μm in length and from 10-30 μm in diameter. Grains are usually below 10 μm in size. Dust may also contain particles of plastic, rubber, textiles (cotton, nylon, wool, polyester, etc.), zinc stearate, and leather finishing products (IARC, 1981).

1.2 Other Atmospheric Contaminants

Workplace air in footwear manufacturing facilities may contain solvents and other respirable substances from the polyurethane unit and molded-on processes, from the use of spray silicones and waxes, from the welding of two PVC compounds, and from the heating of plastics and rubber (IARC, 1981).

1.3 Industrial Chemicals

Occupational exposure to the array of industrial chemicals used in boot and shoe manufacture and repair varies by country and by mode of production. IARC (1981) notes the following chemicals have been found in adhesives, cleaners, and finishes used in the manufacture of boots and shoes: carbon disulfide, carbon tetrachloride, trichloroethylene, dichloromethane, 1,1,1,-trichloroethane, tetrachloroethylene, benzene, toluene, xylene, 2-methylpentane, 3-methylpentane, hexane, methylcyclopentane, cyclohexane, ethyl acetate, butyl acetate, amyl acetate, acetone, methyl ethyl ketone, tetrahydrofuran, methyl isobutyl ketone, ethanol, isopropyl alcohol, dimethylformamide, surfactants, ammonia, waxes (natural), shellac, acrylic resins (various), nitrocellulose, cellulose acetate butyrate, polyurethanes (linear, "one-part"), isocyanates (various), halogenation agents based on organic chlorine donors, natural rubber, poly(vinyl acetate), polychloroprene rubbers, tackifying resins (unspecified), polyamides, polyesters, ethyl vinyl acetate, urea-formaldehyde resins, and various plasticizers (e.g., tri-*o*-cresyl phosphate). IARC (1981) also lists 86 dyes used in leather finishing.

1.3.1 <u>Adhesives</u>

The three main types of adhesives used in footwear manufacture are latex [natural or synthetic rubber or poly(vinyl acetate)], hot-melt (solvent-free), and solvent solution adhesives (polymers, hydrocarbons, ketones, esters, and isocyanates) (IARC, 1981).

1.3.2 Cleaners

Cleaning solvents are applied by hand or machine. The degree of exposure to evaporating solvents depends on the volume used, drying conditions, and ventilation (IARC, 1981).

1.3.3 Finishes

Dyes and transparent coatings are applied by dipping, sponging, or spraying. The degree of exposure depends on the volume applied and the technique used (IARC, 1981).

TABLE 1-1. Known and Suspected Carcinogens Associated with Boot and Shoe Production [Adapted from IARC (1981) and Garabrant and Wegman (1984)]

Table 1-1 includes some agents no longer found in U. S. production processes.

Exposure	Eighth Report on Carcinogens Classification (1997)	IARC Carcinogenicity Evaluation	Process
Cadmium sulfide	Reasonably Anticipated To Be a Human Carcinogen. Probable/planned listing in Ninth RoC as Known To Be a Human Carcinogen.	Carcinogenic in humans	leather finishing
Lead chromate	Known To Be a Human Carcinogen.	Chromium(VI) compounds are carcinogenic in humans	leather finishing
Potassium dichromate, sodium dichromate	Known To Be a Human Carcinogen.	Chromium(VI) salts are carcinogenic in humans	leather preparation
Sodium arsenate, arsenious anhydride, arsenious oxide, arsenic sulfide	Known To Be a Human Carcinogen	Arsenic compounds are carcinogenic in humans	leather preparation
Benzene	Known To Be a Human Carcinogen.	Carcinogenic in humans	adhesive solvent
1,4-Dioxane	Reasonably Anticipated To Be a Human Carcinogen.	Carcinogenic in animals	leather finishing
Ethylene oxide	Reasonably Anticipated To Be a Human Carcinogen. Probable listing in Ninth RoC as Known To Be a Human Carcinogen.	Probably carcinogenic in humans	leather preparation
Mineral oil	Known To Be a Human Carcinogen.	Carcinogenic in humans	leather preparation
Carbon tetrachloride	Reasonably Anticipated To Be a Human Carcinogen.	Possibly carcinogenic in humans	rubber solvent and cleaner
Dichloromethane (Methylene chloride)	Reasonably Anticipated To Be a Human Carcinogen.	Possibly carcinogenic in humans	rubber solvent and cleaning
4,4′-Methylenebis(2-chloroaniline) (MOCA)	Reasonably Anticipated To Be a Human Carcinogen.	Probably carcinogenic in humans	molding
Tetrachloroethylene	Not Listed. To be listed as Reasonably Anticipated To Be a Human Carcinogen in Ninth RoC.	Probably carcinogenic in humans	cleaning
Trichloroethylene	Reasonably Anticipated To Be a Human Carcinogen.	Probably carcinogenic in humans	rubber and adhesive solvent, cleaning
N-Nitrosodimethylamine (NDMA)	Reasonably Anticipated To Be a Human Carcinogen.	Carcinogenic in animals	leather preparation
Dyes: Direct Black 38 Solvent Yellow 34*	Reasonably Anticipated To Be a Human Carcinogen. *Not Listed.	Carcinogenic in humans	leather finishing
Dyes: Acid Violet 49 Direct Blue 14 Food Red 5	Not Listed.	Carcinogenic in animals	leather finishing

2.0 HUMAN EXPOSURE

The footwear industry has experienced a serious decline in the United States over the past three decades. In 1966, over 214,000 workers were employed in footwear production in the United States. By 1986 that number was reduced to 75,000, and by 1996 only 37,000 production workers remained in the industry (Footwear Industries of America, 1996). In 1997, the total for U.S. shipments of nonrubber footwear was approximately 129 million pairs, down from approximately 165 million pairs in 1994 (Current Industrial Reports, 1998).

Table 2-1. U.S. Footwear Manufacturing in 1992[a]

	Number of Companies	Number of plants with >20 employees	Number of production workers
Stock cutting	94	38	3,100
House slippers	28	21	3,000
Men's footwear (except athletic)	108	88	20,000
Women's footwear (except athletic)	99	77	13,200
Footwear (except rubber)	84	41	5,200
Rubber and plastic footwear	53	39	11,200
Total	466	304	55,700

[a] 1992 is the last year for which figures are available.
Source: U.S. Bureau of the Census (1996)

2.1 NIOSH Health Hazard Surveys

In 1991, NIOSH (National Institute for Occupational Safety and Health) industrial hygienists evaluated occupational exposures to methyl ethyl ketone (MEK), acetone, and naphtha at U.S. Shoe Corporation in Ohio following a request from employees concerned about the incidence of cancer among workers in the repair and reconditioning area of the facility (Miller et al., 1993). Eight cases of cancer occurred among 39 (34 women, 5 men) workers employed in this area over a 10-year period (1981-1991): three cases of breast cancer, one case of renal cell carcinoma, one case of lung cancer, one case of prostate cancer, and two cases of unknown primary etiology.

MEK, acetone, and naphtha were detected in the personal breathing zones of eight employees of this facility and in general area air samples. While MEK and acetone are not associated with cancer development in humans or animals, there is limited evidence that petroleum naphtha is carcinogenic to animals. Naphtha may contain benzene, a known human carcinogen, as a manufacturing process impurity. Airborne concentrations of naphtha (9.5 to 147 mg/m^3), MEK (1.4 to 24.0 ppm), and acetone (1.6 to 41 ppm) were measured below their NIOSH Recommended Exposure Limits (RELs) for time-weighted average (TWA) exposures and short-term exposure limits (STEL). [TWA refers to the average airborne concentration of a chemical substance during an 8- to 10-hour work day. TWAs are supplemented by STELs for some substances which have recognized toxic effects from high short-term exposures]. Benzene at a concentration of 0.01 ppm (due to solvent contamination) was found in one personal air sample. The authors concluded that current chemical exposure levels in the facility did not appear to have appreciable cancer-causing potential and that the distribution of cancer cases observed among employees was not suggestive of any single occupational cause (Miller et al., 1993).

NIOSH health hazard surveys outlined below provide data on shoeworker exposure to potentially hazardous chemicals in the workplace, but do not address cancer incidence in relation to exposure to these chemicals.

In 1975 at the Lange Company, a ski boot factory in Colorado, NIOSH investigators found higher than recommended levels of 4,4′-methylenebis(2-chloroaniline) (MOCA; MBOCA) and toluene diisocyanate (TDI) in molding department breathing zone samples (Gunter et al., 1975). The highest concentration found of MOCA (zero exposure recommended by NIOSH) was 0.042 mg/m^3. TDI concentrations up to 0.54 mg/m^3 were found in the same area; the NIOSH recommended exposure limit was 0.005 mg/m^3. Other potentially hazardous chemicals present in the facility, including carbon monoxide, methylene chloride, and Stoddard solvent, were within NIOSH recommended exposure limits.

MEK concentrations (up to 306 ppm) measured in applicators' breathing zones were above the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 200 ppm in a 1976 NIOSH survey at B-W Footwear Company in Massachusetts (Rivera, 1976). Although individual concentrations of other solvents, including toluene, hexane, acetone, ethyl acetate, isopropyl alcohol, ethanol, methyl isobutyl ketone (MIBK), and butyl acetate were not above recommended maximum levels, the author contended that employees were exposed to toxic or potentially toxic levels of organic vapors due to elevated concentrations of solvent mixtures.

Roundbehler (1978) tested air, water used for soaking leather, and rubber sole stock samples taken in the manufacturing facility of Bostonian Shoes in Maine for the presence of *N*-nitroso compounds. *N*-Nitrosodimethylamine (NDMA) was not detected in air samples taken from seven departments in the facility. Results were positive in two samples of water where NDMA was found at a concentration of less than 10 μ/L. The author concluded that these levels of NDMA were comparable to those found in bacon and not a deemed a health concern.

A 1979 NIOSH survey found that air sample concentrations of toluene (up to 20 ppm) were well below the TLV of 100 ppm at U.S. Shoe Corporation in Ohio (Salazar and Zerwas, 1979). Other 1979 surveys found toluene air sample concentrations below TLVs at the International Shoe Company in Missouri (Patterson et al., 1979a) and at the Johnston and Murphy Shoe Company in Tennessee (Patterson et al., 1979b).

When NIOSH investigators measured exposure to acetone, MEK, toluene, hexane, and MIBK in personal air samples at Beaver Shoe Company in Pennsylvania, levels of individual solvents did not exceed their respective individual NIOSH criteria of 590, 590, 375 (skin), 360, and 200 mg/m^3, but calculated exposure to mixtures of acetone, MEK, and toluene exceeded acceptable limits recommended by NIOSH (Chrostek, 1980).

A NIOSH health hazard survey in 1981 at the Texas Boot Company in Tennessee reported that in one personal air sample each, benzene (15 mg/m^3) and petroleum naphtha (354 mg/m^3) exceeded their respective OSHA standards of 3.2 and 350 mg/m^3 (White et al., 1981) on the first visit. On a follow-up visit, the values were found to be 3.3 mg/m^3 and 367 mg/m^3, respectively.

A 1982 NIOSH survey found that naphtha (range 19-522 mg/m^3) and methylene chloride (range 96-172 ppm) exceeded their respective recommended exposure limits of 350 mg/m^3 and 75 ppm at the Red Wing Shoe Company in Minnesota. Investigators also found higher than recommended levels of combinations of heptane, acetone, toluene, ethyl acetate, MEK, isopropyl alcohol, and tetrahydrofuran. Workers reported symptoms of solvent overexposure including headaches and irritations of the eye, skin, and upper respiratory tract. The investigators concluded that a solvent exposure hazard existed at this company (Tharr et al., 1982).

Another NIOSH survey conducted in 1982 reported that natural rubber, zinc stearate, latex adhesives, urethane cement (containing MEK, toluene, acetone, and isopropyl alcohol), hexane, and naphtha were used at the Converse Shoe Plant in Lumberton, North Carolina in the manufacture of canvas and leather upper shoes. No measurements of worker exposures to chemicals were reported (Mortimer, 1982). A similar 1983 survey at Drew Shoe Plant in Lancaster, Ohio, reported that a [poly]chloroprene-containing adhesive dissolved in a mixture of aliphatic and aromatic hydrocarbon solvents was in use there, along with a solvent-based rubber cement, a urethane-based adhesive, and latex adhesives. No worker exposure measurements were reported. The author reported that the ventilation appeared adequate for the adhesives used at this plant, noting that the solvent odor was "barely noticeable" (Mortimer, 1983).

Table 2-2. NIOSH Health Hazard Surveys

Survey Location and Date	Type of Production	Number of Workers	Environmental Safety Measures	Chemical Exposure	Comments	Reference
U.S. Shoe Corporation OH, 1991	shoe repair, reconditioning packaging	138	NIOSH recommended use of gloves, adding local exhaust ventilation	Naphtha (9.5-147 mg/m^3) MEK (1.4-24.0 ppm) Acetone (1.6-41 ppm) Benzene (0.01 ppm) Airborne concentrations below evaluation criteria.	8 cases of cancer (3 breast, 1 renal cell, 1 lung, 1 prostate, 2 unknown) reported among workers over 10-year period. Authors concluded current conditions did not appear to have cancer-causing potential and that reported cancers not suggestive of any single occupational cause.	Miller et al. (1993)
Lange Co. CO, 1975	ski boot manufacture	not reported	local exhaust ventilation, enclosure of parts of production process	MOCA (0.042 mg/m^3) TDI (0.54 mg/m^3) Breathing zone samples above recommended exposure levels. NIOSH recommends no exposure to MOCA (carcinogen) and limit of 0.005 mg/m^3) for TDI. Other chemicals present including carbon monoxide, methylene chloride, and Stoddard solvent were within recommended limits.	NIOSH recommended respirators for MOCA and TDI exposed employees until installation of closed ventilation system. Also, recommended replacing MOCA with non-carcinogenic compound.	Gunter (1975)
B-W Footwear MA, 1976	shoe manufacture (mostly synthetic materials)	311	some local exhaust hoods, respirators available	MEK concentrations (up to 306 ppm) in personal air samples were above ACGIH TLV (200 ppm) Other solvent concentrations (toluene, hexane, acetone, ethyl acetate, 2-propanol, ethanol, MIBK, butyl acetate) not above individual recommended maximum levels.	Author concluded that employees were exposed to toxic or potentially toxic levels of organic vapors due to elevated concentrations of solvent mixtures. NIOSH recommended upgrades/additions to ventilation systems and use of gloves.	Rivera (1976)

Table 2-2. NIOSH Health Hazard Surveys (Continued)

Survey Location and Date	Type of Production	Number of Workers	Environmental Safety Measures	Chemical Exposure	Comments	Reference
Bostonian Shoes ME, 1978	hand-sewn men's leather shoes	125	not reported	Evaluation was for N-nitroso compound concentrations only in air, process water, rubber stock. NDMA found in two samples of leather soak water at concentration of >10 ppb. Author noted that few chemicals are used in this type of manufacturing.	NDMA exposure not deemed to be health concern at this facility.	Round-behler (1978)
U.S. Shoe Corp. OH, 1979	women's leather shoe manufacture	300	extensive ventilation systems added 1-2 years before survey	Toluene air concentrations up to 20 ppm (TLV = 100 ppm). Low air concentrations of hexane (2.6-4.5 ppm) and ethyl acetate (0.09-45 ppm).	New, extensive ventilation system credited for low air concentrations of solvents; past exposures probably higher.	Salazar and Zerwas (1979)
International Shoe Co. MO, 1979	women's leather shoe manufacture	428	Dust collectors; enclosed spray areas; respirators used for spraying dye, adhesives.	Toluene air concentrations (20-25 ppm) and total hydrocarbons, measured as hexane (100-200 ppm), were below TLV throughout facility.	Toluene air concentrations in personal samples taken on adhesive users expected to be higher than those measured in this survey.	Patterson (1979a)
Johnston and Murphy Shoe Co., TN, 1979	men's leather shoe manufacture	460	local exhaust ventilation; spraying hoods; respirators not required; gloves used in some operations	Toluene air concentrations (7-60 ppm) and total hydrocarbons, measured as hexane (38-580 ppm), were below TLV.		Patterson (1979b)
Beaver Shoe Co., PA, 1980	women's leather or plastic shoe manufacture	350	some local exhaust	Exposures to acetone, MEK, toluene, hexane, MIBK did not exceed respective criteria of 590, 590, 375, 360, and 200 mg/m^3 although exposure to solvent mixtures did exceed NIOSH criteria in 5 of 22 samples	Benzene was found at a concentration of 0.10 of total bulk in 3 of 5 solvent samples and no benzene was found in 2 samples, therefore no environmental air sampling was done for this contaminant.	Chrostek (1980)

Table 2-2. NIOSH Health Hazard Surveys (Continued)

Survey Location and Date	Type of Production	Number of Workers	Environmental Safety Measures	Chemical Exposure	Comments	Reference
Texas Boot Co. TN, 1981	leather boot manufacture	487-501	local exhaust ventilation	Exposures to benzene, Cellosolve, *n*-butyl acetate, methyl ethyl ketone, isopropyl alcohol, and naphtha distillates/refined petroleum solvent were evaluated in approx. 40 personal and general air samples. Two benzene personal samples with concentrations of 3.3 and 15 mg/m^3 exceeded evaluation criteria of 3.2 mg/m^3. Petroleum naphtha at 354 and 407 mg/m^3 exceeded criteria of 350 mg/m^3. Toluene at 407 and 476 mg/m^3 exceeded criteria of 375 mg/m^3 in 2 samples.	NIOSH recommended augmenting ventilation system and providing employees with gloves.	White (1981)
Red Wing Shoe Co., MN 1981 and 1982	leather shoe manufacture	not reported	inadequate ventilation	Exposures to naphtha of up to 522 mg/m^3 exceeded the NIOSH criteria of 350 mg/m^3. Exposures to methylene chloride of up to 172 ppm exceeded NIOSH criteria of 75 ppm. Workers were also overexposed to combinations of heptane, acetone, toluene, ethyl acetate, methyl ethyl ketone, naphtha, isopropyl alcohol, and tetrahydrofuran.	NIOSH report concluded that a solvent exposure hazard existed at this company. Numerous recommendations included eliminating solvent-based adhesives, improving engineering controls and workplace hygiene.	Tharr (1982)
Converse Shoe Facility, NC 1982	leather and canvas shoe manufacture	2000	extensive ventilation; enclosed spray areas	Natural rubber, zinc stearate, latex adhesives, urethane cement (containing MEK, toluene, acetone, and isopropyl alcohol), hexane, and naphtha present at this plant. Exposures were not measured.		Mortimer (1982)

Table 2-2. NIOSH Health Hazard Surveys (Continued)

Survey Location and Date	Type of Production	Number of Workers	Environmental Safety Measures	Chemical Exposure	Comments	Reference
Drew Shoe Facility, OH 1983	women's leather shoes and sandals	300	ventilation adequate for adhesives use	A [poly]chloroprene-containing adhesive dissolved in a mixture of aliphatic and aromatic hydrocarbon solvents, a solvent-based rubber cement, a urethane-based adhesive, and latex adhesives were in use at this plant. Exposures were not measured.		Mortimer (1983)

2.2 NIOSH Occupational Exposure Data

NIOSH collected data on potential occupational exposure to specific substances in the National Occupational Hazard Survey (NOHS) from 1972 to 1974 (NIOSH, 1976) and in the National Occupational Exposure Survey (NOES) from 1981 to 1983 (NIOSH, 1990). NIOSH provided NTP two listings of chemicals to which persons working in the boot and shoe manufacturing industry were potentially exposed.

The first listing was for persons employed in plants producing primarily leather footwear (Standard Industrial Classification [SIC] codes 3131, 3142, 3143, and 3144). In the NOHS survey, the carcinogens listed in order of numbers exposed and the total numbers of employees potentially exposed to each were benzene, 62, and dichloromethane (methylene chloride), 16. In the NOES survey, benzene exposures were not reported. The carcinogens and total numbers of potentially exposed employees from the NOES survey were carbon tetrachloride, 3,340; cadmium compounds (benzoate, octanoate), 3,325; formaldehyde, 2,745; dichloromethane, 442; lead chromate, 411; bis(2-ethylhexyl phthalate) (DEHP), 369; ethyl acrylate, 120; ethylene oxide, 70; and nickel (unspecified species), 48.

The second listing was for persons employed in plants producing rubber and plastics footwear (SIC code 3021) and children's footwear including vulcanized rubber (SIC 3149). In the NOHS survey, potential exposures were to formaldehyde, 512, formalin, 8, and chloroform, 32. In the NOES survey, by far the largest number of employees, 22,623, were exposed to DEHP. Other carcinogens with high frequencies of potential exposures in the NOES survey were formaldehyde, 6,025, and formalin, 4,298, total 10,323; cadmium compounds (cadmium mercury sulfide, cadmium oxide, and cadmium sulfide), 8,518; Direct Black 38, 5,747; lead chromate, 4,357; carbon tetrachloride, 1,974; and epichlorohydrin, 1,337. Carcinogens with lower frequencies of potential exposures were dichloromethane, 632; trichloroethylene, 368; and ethyl acrylate, 315.

Thus, both leather footwear workers and rubber and plastics footwear workers were potentially exposed, as reported in the NOHS and/or NOES surveys, to the carcinogens cadmium compounds, carbon tetrachloride, DEHP, dichloromethane, ethyl acrylate, ethylene oxide, formaldehyde or formalin, and lead chromate. Except for benzene and carbon tetrachloride, the total numbers of employees potentially exposed to these carcinogens were higher in the more recent survey.

2.3 Exposure Data from U.S. Epidemiology Studies

One of the six U.S. epidemiology studies included in Section 3 of this background document contains data concerning exposure of workers in the boot and shoe industry to specific industrial chemicals at individual manufacturing facilities. Exposure data from this study, and those other studies that contain descriptions of potential worker exposures, are summarized below.

OSHA measured personal solvent exposures at two Ohio shoe factories in 1977-1979 (Walker et al., 1993) (Table 2-3). With the exception of MEK, solvent concentrations were well below their respective TLVs. Material safety data sheets from these plants listed solvents other than those reported in Table 2-1 including aliphatic petroleum naphtha, isopropyl alcohol, methyl alcohol, ethylene glycol monoethyl ether, mineral spirits, xylene, formaldehyde, 1-methyl-2-pyrrolidone, trichloroisocyanuric acid, and ammonia. No data on worker exposure to these chemicals were given. No data were available concerning airborne concentrations of benzene, leather dust, or dust from other materials. Managers at these plants reported that no benzene-based adhesives had ever been used in these plants since operations began in the 1930s. The authors noted that "there was no clear evidence that benzene had ever been used in the plants, although there was historical evidence that benzene was an impurity in industrial-grade toluene in the United States before the mid-1950s."

Table 2-3. Personal Solvent Exposures in Two U.S. Shoe Plants

Substance	TLV (ppm)	Number of samples	TWA Mean (ppm)	TWA Range (ppm)
Plant 1				
Toluene	100	4	50	38-72
MEK	200	4	133	63-250
Acetone	750	4	223	200-270
Hexane	500	2	55	30-80
Plant 2				
Toluene	100	6	22	10-43
MEK	200	6	153	48-330
Acetone	750	6	46	25-146
Hexane	500	6	22	13-45

Source: Walker et al., 1993 (TLV = threshold limit value; TWA = time-weighted average)

Decouflé and Walrath (1987) asserted that environmental conditions associated with sino-nasal cancer in the British boot and shoe industry "may or may not be comparable" to the U.S. industry. The authors suggested that U.S manufacturing processes may be different and that working practices may differ in the following areas: use of protective clothing, dust control mechanisms, housekeeping practices, and personal hygiene habits. It was also noted that in England, sino-nasal cancers were seen in those who worked with vegetable-tanned leather, but not among those who worked with chrome-tanned leather.

Decouflé and Walrath (1983) cited personal communications relating to asbestos use in the manufacture of boots and shoes: in the United Kingdom asbestos was a constituent of sole fillers, and heating molds for shoe manufacture in England were insulated with asbestos. The authors stated that they did not know whether these practices ever occurred in the United States. Decouflé and Walrath (1983) cited two reports from the first half of the century relating to benzene use in the U.S. boot and shoe manufacturing industry. In a shoe manufacturing plant that employed 600 people, three workers came into contact with benzene on a regular basis (Smith, 1928; cited by Decouflé and Walrath) and seven of 35 shoe plants used benzene in a 1940 survey of the U.S. leather industry (McConnell et al., 1942; cited by Decouflé and Walrath, 1983).

2.4 Air Emissions from U.S. Footwear Manufacturing Plants

The 1996 U.S. EPA Toxic Chemicals Release Inventory (TRI) reported air emissions of 24 chemicals from 41 footwear manufacturing facilities in 19 U.S. states and Puerto Rico including the following carcinogens: 1, 3-butadiene, chloroprene, chromium, dichloromethane (methylene chloride), di(2-ethylhexyl) phthalate, formaldehyde, polychlorinated biphenyls, and trichloroethylene.

Table 2-4. Chemicals Emitted in Air from U.S. Footwear Manufacturing Plants in 1996

Compound Name	SIC code(s)[a]	CASRN[b]	Number of Plants Reporting	Total Air Emissions (lb/yr)	Carcinogen[c]?
ALUMINUM (FUME OR DUST)	3021	7429-90-5	1	500	N
AMMONIA	3021	7664-41-7	1	10	N
BUTADIENE, 1,3-	3021	106-99-0	1	1,500	Known (9th RoC)
CHLOROPRENE	3021	126-99-8	1	10	RAHC (9th RoC)
CHROMIUM	3021	7440-47-3	1	500	Known [Cr(VI)]
DI(2-ETHYLHEXYL) PHTHALATE	3021	117-81-7	3	500	RAHC
DICHLOROMETHANE	3143	75-09-2	2	21,507	RAHC
DIISOCYANATES	3021, 3131, 3143, 3144, 3149	NA	10	378	Toluene diisocyanate is RAHC
ETHYLENE GLYCOL	3021	107-21-1	1	0	N
FORMALDEHYDE	3021, 3131	50-00-0	2	260	RAHC
HEXANE, n-	3021, 3149	110-54-3	3	705,019	N
ISOPROPYL ALCOHOL	3021	67-63-0	1	500	N
METHYL ETHYL KETONE	3021, 3131, 3143, 3144, 3149	78-93-3	12	273,783	N
METHYL ISOBUTYL KETONE	3021	108-10-1	1	500	N
PHTHALIC ANHYDRIDE	3021	85-44-9	1	500	N
POLYCHLORINATED BIPHENYLS	3021	1336-36-3	1	255	RAHC
QUINOLINE	3021	91-22-5	1	10	N
STYRENE	3021	100-42-5	1	500	N
THIRAM	3021	137-26-8	1	500	N
TOLUENE	3021, 3131, 3143, 3144, 3149	108-88-3	15	434,377	N
TRICHLOROETHANE, 1,1,1-	3021	71-55-6	1	74,000	N
TRICHLOROETHYLENE	2295, 3021, 3131	79-01-6	2	67117	RAHC (9th RoC)
TRICHLOROFLUOROMETHANE	3021	75-69-4	1	57,298	N
ZINC COMPOUNDS	3021	NA	4	720	N

[a]SIC (Standard Industry Classification) code(s): (2295) Coated fabrics, not rubberized; (3021) Rubber and plastic footwear; (3131) Footwear cut stock; (3143) Men's footwear, except athletic; (3144) Women's footwear, except athletic; (3149) Children's footwear, except rubber; [b]Chemical Abstracts Service Registry Number; [c]NTP (1997) evaluation; RAHC = Reasonably Anticipated to be a Human Carcinogen

Source: U.S. EPA Toxic Chemical Release Inventory 1996 (TRI) (1998)

3.0 HUMAN STUDIES

3.1 Studies Reviewed in IARC (1981; 1987)

IARC (1981; 1987) concluded that employment in the boot and shoe industry was causally associated with the development of nasal adenocarcinomas and possibly associated with other types of nasal cancers. Increased rates of nasal adenocarcinomas were associated with employment in areas with the greatest exposure to leather dust in studies conducted in England and Italy. Cancer incidence was highest among workers with the highest level of exposure to dust. Increased rates of leukemia in footwear industry workers in several countries have been linked to benzene exposure. Employment in the leather industry was found to be associated with an increased risk of bladder cancer. Boot and shoe makers were included in studies providing this evidence, but risk for this subgroup was not calculated separately. The design of published studies, suggesting associations between boot and shoe manufacture/repair and cancers of the lung, oral cavity, pharynx, and stomach, prevented the evaluation of their findings.

3.2 Studies Published Post-IARC (1981)

Walker et al. (1993) studied the mortality of workers in two similar shoe factories in Ohio. The study population included 7,814 (2,529 male, 5,285 female) white employees who worked in these factories for at least one month between the beginning of 1940 and the end of 1979; a follow-up study continued through the end of 1982. No significant changes in manufacturing processes over time were reported at either plant; major vapor control mechanisms were added at both plants in the late 1970s. The authors noted that workers were potentially exposed to solvents (including toluene) and solvent-based adhesives and that benzene may have been present as an impurity of toluene.

Death certificates of workers employed at the plants were reviewed to determine the underlying cause of death. The total person-years at risk were calculated and expected deaths and Standardized Mortality Ratios (SMRs) were computed for specific causes of death using the NIOSH life table analysis system. Statistically significant ($p < 0.01$) excess mortality (SMR = 1.47, 95% Confidence Interval [CI] = 1.20-1.80) due to cancer of the trachea, bronchus, and lung was observed in the total cohort. There was also a statistically significant trend ($p < 0.001$) in standardized relative risk (SRR) with increasing potential latency, but not with increasing duration of employment. Adjustment for the potential effects of smoking reduced, but did not eliminate, the increased risk of lung cancer (Walker et al., 1993). The strengths of this study include a reasonably long follow-up period and a low lost-to-follow-up rate (2%). The relatively small number of workers in the study, resulting in imprecise SMR estimates for some causes of death, and the limited industrial hygiene data are weaknesses.

Another mortality study found significant excess deaths from digestive cancers and multiple myeloma among both men and women who had worked in a New York shoe factory and died between 1960 and 1979 (Walrath et al., 1987). Investigators began by using local newspaper obituary notices to identify 4,734 (3,512 men, 1,222 women) former factory employees. Using their death certificates and the general U.S. population for comparison, Proportionate Mortality Ratios (PMRs), as well as Proportionate Cancer Mortality Ratios (PCMRs), were calculated for cancer sites of particular interest. Confidence intervals, however, were not reported.

Among men, significantly elevated PMRs and PCMRs were seen for cancers of the stomach (PCMR = 1.70) and colon (PCMR = 1.40), but only the PMR (not PCMR) for rectal cancer mortality (PMR = 1.42) was significantly elevated. Deaths from nasal cancer (0 observed, 1.9 expected) and lung and pleural cancer (163 observed, 175.7 expected) were less than expected. Bladder cancer deaths were close to the number expected (PMR = 0.91) (Walrath et al., 1987).

Among women, significantly elevated PCMRs were seen for cancers of the colon (PCMR = 1.32) and rectum (PCMR = 1.87). The significant stomach cancer excess seen among men was not observed in women. Mortality from bladder cancer was lower than expected (1 observed, 4.5 expected), and no observed deaths were from nasal or nasopharyngeal cancer (Walrath et al. 1987).

Significantly elevated PMRs for bone cancer (6 observed, 2.7 expected) were observed in men, but no deaths due to bone cancer were observed in women (1.1 expected). Significantly elevated PMRs for multiple myeloma were observed both in men (PMR = 1.93) and women (PMR = 3.46).

A strength of this study is the high rate of death certificate retrieval (97.1%). The PMR method, the use of obituaries, the small number of deaths for some specific cancers, and the lack of exposure and confounder data are limitations.

The results of a linked proportional mortality case-referent study of shoe and leather workers found a statistically significant excess of bladder cancer among female shoe workers and demonstrated an association of lung cancer with work in leather-tanning jobs (Garabrant and Wegman, 1984). Death certificates of 2,798 (1,l953 male, 845 female) former shoe and leather workers who died in areas near Boston, Massachusetts, between 1954 and 1974 were reviewed for cause of death. While shoe and leather workers have often been grouped together for study purposes, the investigators in this study chose to classify them separately. PMRs were calculated using the general U.S. population for comparison.

Among leather workers, deaths due to cancer at all sites were slightly fewer than expected (Garabrant and Wegman, 1984). A statistically significant (PMR = 1.69, 95% CI = 1.04-2.73; p = 0.03) excess of stomach cancer was seen among male leather workers, and a nonsignificant numerical excess of stomach cancer was seen among females (PMR = 2.80). No deaths due to nasal cancer were reported among leather workers

Among shoe workers, deaths due to cancer were slightly fewer than expected (Garabrant and Wegman, 1984). A statistically significant (PMR = 1.39, 95% CI = 1.13-1.70) excess of digestive tract cancer was seen among male shoe workers. Analysis by anatomical site revealed nonsignificant numerical excesses of cancer of the esophagus, stomach, pancreas, and large intestine. The rates of cancers of the rectum and liver were slightly less than expected. No deaths due to nasal cancer were reported among shoe workers. The authors consider the statistically significant (PMR = 2.51, 95% CI = 1.23-5.13; p = 0.01) excess of bladder cancer seen among female shoe workers to be additional evidence of excess risk for this type of cancer in the shoe manufacturing industry. Noting that elevated stomach cancer mortality has been reported for the areas of Massachusetts in which this study was conducted, the authors state that factors other than work in the shoe and leather industry may be responsible for the excess risk of digestive tract cancer seen in the study (Garabrant and Wegman, 1984).

The case-referent component of this study found an excess risk of lung cancer among male leather workers involved in tanning. The authors note numerous suspected or established carcinogens associated with the leather industry, and suggest that hexavalent chromium compounds and arsenicals may have contributed to the excess rate of lung cancer seen among leather workers. For cases of lung cancer, the odds ratio for employment in tanning was 4.2 (95% CI = 1.09-16.2; $p = 0.04$). As this finding is not supported by the PMR study and is based on a small number of cases, the authors urged caution in interpreting these results (Garabrant and Wegman, 1984).

This study has several notable weaknesses. The identification of occupation from death certificates may have led to incomplete ascertainment (including missed short-term workers). The number of shoe workers was relatively small for the precise estimation of risk of some of the specific cancers. There was no direct information on confounders or exposures and the use of the proportional mortality approach limits interpretation.

Decouflé and Walrath (1983) looked for unusual patterns of fatal disease among white members of two national shoeworkers unions in seven eastern and midwestern U.S. states. Investigators used death notices published in union newsletters to identify 3,754 (2,144 male, 1,610 female) former members who died between 1966 and 1977. Their death certificates were reviewed and PMRs were calculated using the general U.S. white population as a reference.

Significantly ($p < 0.05$) elevated rates of death from cancer were observed in both men and women (PMRs = 1.10, 1.12, respectively). Regarding specific cancer sites, a significantly ($p < 0.05$) greater number of deaths was observed for both men and women for death from cancer of the rectum, liver and gallbladder.

Among women, cervical cancer deaths were almost twice as frequent as expected (32 observed, 16.6 expected) which the authors speculate may be related to the relatively low socioeconomic status of the study group. Although 2.2 deaths from nasal cancer were expected for both sexes combined, none were observed, nor were there any deaths due to nasopharyngeal cancer. The authors concluded that results from this study contradict previous results of excess nasal cancer in shoeworkers. Deaths from bladder cancer were close to the expected rate (Decouflé and Walrath, 1983).

The authors reported three deaths attributable to mesothelioma and cite sources that link asbestos use to shoe manufacturing in the United Kingdom. The authors noted a lack of evidence linking these deaths to occupational asbestos exposure, as well as a lack of evidence that asbestos was ever used in U.S. shoe manufacturing (Decouflé and Walrath, 1983).

This study has several notable limitations including the use of a proportionate mortality approach, a restricted cohort (only eligible union members who claimed death benefits), and a lack of information regarding duration of employment and specific job title. In addition, death certificates for 14% of the cohort could not be located.

Studies conducted in England document a striking association between employment in the shoemaking industry and nasal cancer (Acheson et al., 1970, 1982; Pippard and Acheson, 1985). Using these data as a point of comparison, one study explored the apparent absence of nasal cancer risk demonstrated by three large-scale proportionate mortality studies of U.S. shoeworkers (Decouflé and Walrath, 1987).

None of the three U.S. studies designed to determine if particular causes of death occurred significantly more frequently among shoeworkers reported any deaths due to nasal cancer. Based on national mortality data, 5.6 deaths due to nasal cancer would have been expected among the 10,450 deaths reported in these studies (Decouflé and Walrath, 1987).

The authors maintain that the statistical power of the U.S. studies was similar to British studies for the determination of cancer risk. The authors note significant differences in design between the British and U.S. studies: the British studies began with identification of nasal cancer and then proceeded with occupational histories of the subjects, the U.S. studies began with identification of deceased shoeworkers and then determined their cause of death. Another point presented for consideration in an analysis of epidemiological methodology is that obituary notices supporting the U.S. studies might not be reliable and may not provide comprehensive information about all shoeworkers in the United States. The authors do not rule out the possibility of increased risk of sinonasal cancer for U.S. shoeworkers, but conclude that the risk is probably not as great as that seen in the British industry. Vegetable-tanned leather dust is the agent most closely linked to nasal cancer in the British studies (Decouflé and Walrath, 1987).

One descriptive study investigated the possibility that an excessive rate of brain-tumor mortality in a Kansas town was related to employment in the shoe industry (Morantz et al., 1985). Representing an age-adjusted mortality 4.1 times greater than the expected incidence, six deaths due to primary brain neoplasms occurred among the town's 3000 residents between 1973 and 1982.

Background data on brain-tumor cases was collected from either the patient or the next-of-kin by telephone interviews and written questionnaires. Death certificates were reviewed; six of the seven tumors identified in the study were histologically confirmed as glioblastoma multiforme. No excess incidences of other malignancies were found. Three of the residents who died from brain cancer were male, three were female. A fourth female diagnosed with brain cancer was alive at the end of the study. Four of the six subjects who died had been shoe factory employees; one had been the spouse of a shoe factory employee. The authors do not assert that association with the shoe factory is a more likely source of brain cancer risk than other noted environmental exposures, but noted the need for case-control analytical studies to determine the relevance of identified environmental factors (Morantz et al., 1985).

Data from the United Kingdom suggest that leather workers in that country are at greater risk for the development of nasal cancer than their U.S. counterparts. Mineral oils, present in leather dust in the United Kingdom, but not in the United States where animal oils are used, might account for striking differences in risk observed between the two countries (Randell, 1990; cited by Battista et al., 1995).

A case-control study of Italian shoemakers that investigated nasal cavity tumors that occurred between 1968 and 1982 concluded that cancer risk was highest for workers exposed to the highest levels of leather dust, and that even those in jobs with relatively low exposure had a significantly higher risk (Merler et al., 1986).

In a historical cohort study, a comparison of English and Italian shoeworkers showed that nasal cancer was the only cancer excess significantly increased in both cohorts (Fu et al., 1996). The authors noted apparent associations between cancer risk and the level of exposure to leather dust and solvents. Bone cancer was the only other cancer in excess in the English cohort, but stomach, colon, and kidney cancer, as well as multiple myeloma and leukemia, were in excess in the Italian cohort. Of the solvents used, exposure to benzene, which has been linked to leukemia, is identified by the authors as the greatest cancer concern. The factory that employed the Italian workers in this study is known to have used a shoe glue that contained a high percentage of benzene for approximately 10 years beginning in the early 1950s (Fu et al., 1996).

Table 3-1. Studies of Cancer Incidence in Boot and Shoe Manufacture and Repair Workers (Post-IARC, 1981)

Study Design	Study Population	Exposure	Effects	Comments	Reference
retrospective cohort mortality; reviewed death notices; obtained death certificates used national mortality data specific for sex, race, age at death, year of death to calculate SMRs	7,814 workers employed for at least one month in either of two similar shoe factories in Ohio 1940-1979. race: white sex: 2,529 males 5,285 females	No significant process changes at either plant over period studied; both upgraded vapor control in late 1970s. No specific exposure data given; workers may have been exposed to toluene, benzene, solvent-based adhesives.	Statistically significant excess total cohort mortality (SMR 1.47, 95% CI 1.20-1.80) due to cancer of the trachea, bronchus, and lung.	Lung cancer SMR's adjusted for smoking. Some SMRs imprecise due to small cohort. 2% of workers lost to follow-up.	Walker et al. (1993)
retrospective cohort mortality reviewed obituary notices in local newspapers; obtained death certificates (97%) used national mortality data specific for sex, race, age at death, year of death to calculate PMRs and PCMRs	4,734 workers employed at a New York shoe factory between 1960 and 1979. race: white (unknown for one individual) sex: 3,512 males 1,222 females	No data specific to study group available. No data given on length of employment.	Statistically significant excess cancer mortality for men at specific sites: stomach (PCMR = 1.7), colon (PCMR = 1.4), rectum (PMR = 1.42), bone (PMR = 2.2). Statistically significant excess cancer mortality for women at specific sites: colon (PCMR = 1.32), rectum (PCMR = 1.87). Statistically significant excess mortality due to multiple myeloma was observed for both men (PMR = 1.93) and women (PMR = 3.46).	No deaths from nasal cancer. Lung cancer deaths were fewer than expected. Bladder cancer deaths were close to the number expected. Use of PMR method and obituaries are potential study weaknesses, as is the small number of observations of certain cancers.	Walrath et al. (1987)

Table 3-1. Studies of Cancer Incidence in Boot and Shoe Manufacture and Repair Workers (Post-IARC, 1981) (Continued)

Study Design	Study Population	Exposure	Effects	Comments	Reference
Retrospective cohort mortality linked to case-referent study; reviewed death certificates Used national mortality data specific for sex, race, age at death, year of death to calculate PMRs	2,798 employees of shoe and leather plants in Massachusetts who died between 1954 and 1974. race: not given sex: Leather / Shoe male: 758 / 1195 female: 767 / 78 Shoe workers and leather workers classified separately in this study.	No data specific to study group given. The authors note numerous suspected or established carcinogens associated with the leather industry, and suggest that hexavalent chromium compounds and arsenicals may have contributed to the excess rate of lung cancer seen among leather workers. No direct data regarding potential confounders given.	Leather workers: Significant excess of stomach cancer (PMR = 1.69, 95% CI = 1.04-2.73, p = 0.03) among males; nonsignificant numerical excess of stomach cancer (PMR = 2.80) among females. Case-referent component of study found excess risk of lung cancer among male leather workers. This finding not supported by PMR study. Shoe workers: Statistically significant excess of digestive tract cancer (PMR = 1.39, 95% CI = 1.13-1.70) for men. Statistically significant excess of bladder cancer (PMR = 2.51, 95% CI = 1.23-5.13, p = 0.01) among females. The authors noted elevated stomach cancer mortality in the general population in the study area.	No deaths due to nasal cancer reported among leather or shoe workers; overall, cancer deaths were fewer than expected for both groups. The identification of occupation from death certificates may have led to incomplete ascertainment (including missed short-term workers). The relatively small cohort and the use of proportional mortality approach limits interpretation of study data.	Garabrant and Wegman (1984)

Table 3-1. Studies of Cancer Incidence in Boot and Shoe Manufacture and Repair Workers (Post-IARC, 1981) (Continued)

Study Design	Study Population	Exposure	Effects	Comments	Reference
Retrospective cohort mortality; reviewed death listings in union newsletter; obtained death certificates Used national mortality data specific for sex, race, age at death, year of death to calculate PMR's	3,754 national shoeworker union members who died from 1960 to 1977. race: white sex: 2,144 males 1,610 females	No specific exposure data given; benzene (as impurity of toluene), asbestos, carbon tetrachloride, carbon disulfide listed as potential exposure hazards. No data given on length of employment or specific job titles.	Statistically significant excess total cohort mortality (PMRs = 1.10, 1.12 for men and women, respectively) for cancer. significant (p< .05) excess mortality at specific sites (no. obs./no. exp.) rectum / liver and gallbladder men (22/14.0) (14/7.7) women (19/10.5) (17/8.4) Authors note that this study contradicts previous findings of excess nasal cancer; no nasal cancer deaths were observed, although 2.2 were expected.	The incidence of deaths from bladder cancer was close to the expected rate. Authors attribute high rate of cervical cancer (32 observed, 16.6 expected) to low socioeconomic status of study group. Limitations of this study include use of a proportionate mortality approach and a restricted cohort (only union member death benefit claimants). In addition, 14% of death certificates were not retrieved.	Decouflé and Walrath (1983)

Table 3-1. Studies of Cancer Incidence in Boot and Shoe Manufacture and Repair Workers (Post-IARC, 1981) (Continued)

Study Design	Study Population	Exposure	Effects	Comments	Reference
Comparison of 3 large scale U.S. proportionate mortality studies of shoeworkers (Decoufle and Walrath, 1983; Garabrant and Wegman, 1984; Walrath et al., 1987) to 3 British studies (Acheson et al., 1970, 1982; Pippard and Acheson, 1985)	Data from 10,450 (combined total) deaths from all causes reported in 3 U.S. studies compared to data specific to nasal cancer from British studies.	Vegetable-tanned leather dust linked to nasal cancer in British studies.	British studies document a striking association between employment in the shoemaking industry and nasal cancer. This association is entirely absent in U.S. studies.	The authors maintained that the statistical power of the U.S. studies was similar to that of the British studies for determination of cancer risk. Study design differences may account for the contrasting findings. The authors do not rule out the chance of increased risk of sinonasal cancer for U.S. shoeworkers, but concluded that the risk is probably not as great as in the United Kingdom.	Decouflé and Walrath (1987)
Descriptive; collected data from the patient or next-of-kin by telephone or written questionnaire; reviewed death certificates calculated SMRs based on Missouri statistics	6 residents of small (3,000 residents) Kansas town who died from brain cancer, 1 surviving resident diagnosed with brain cancer. race: white sex: 3 males, 4 females	5 of the 6 subjects who died had been a shoe factory employee or the spouse of one. No data given regarding specific chemicals.	Age-adjusted mortality due to brain cancer 4.1 times greater than expected for the studied town. No excessive incidences of other malignancies found. 6 of 7 study tumors were glioblastoma multiforme.	The authors do not assert that association with the shoe factory is a more likely source of brain cancer risk than other noted environmental exposures.	Morantz et al. (1985)

4.0 EXPERIMENTAL CARCINOGENESIS

No adequate animal studies of possible carcinogenic effects of occupational exposure in the boot and shoe industry are available. A study of the carcinogenic effect of leather factory dust extracts on mice (Lahiri et al, 1988) did not describe experimental methodology and is not presented here for evaluation.

5.0 GENOTOXICITY

No studies on the genotoxic effects of occupational exposures in the boot and shoe industry were reviewed by IARC (1981). Lynge et al. (1997) reviewed genotoxicity data for many of the organic solvents noted by IARC (1981) to be associated with boot and shoe production and concluded that none were "overtly genotoxic".

6.0 OTHER RELEVANT DATA

Saber et al. (1998) did not find conclusive evidence of a link between leather-dust associated-sinonasal adenocarcinomas and specific K-*ras* protooncogene mutations in a study of archival tumor tissue in Sweden. Mutations were found in the K-*ras* gene in adenocarcinoma from a sinonasal cancer patient that had been occupationally exposed for an estimated 10 years to leather dust 40 years before diagnosis. The authors detected a GGC → GAC mutation in this individual, who had a papillary adenocarcinoma. A similar mutation was seen in two patients exposed to wood dust. All three of these mutations were G:C → A:T transitions: two were at position 2 of codon 12, one was at position 2 of codon 13. The two other patients in the study exposed to leather dust had intestinal-type adenocarcinomas (no further specifics provided on these patients).

7.0 MECHANISMS OF CARCINOGENESIS

A number of substances previously or currently present in the boot and shoe industry are known or suspected human carcinogens (IARC, 1981; 1998 IARC Overall Evaluations). Though conclusive studies are not available regarding the carcinogenic effects of these agents on boot and shoe industry workers, separate bodies of literature describe industry-specific occupational exposures (see Section 2) and epidemiological cancer studies (see Section 3).

Trichloroethylene, tetrachloroethylene (perchloroethylene), carbon tetrachloride, dichloromethane (methylene chloride), and benzene are organic industrial solvents associated with boot and shoe manufacturing (IARC, 1981). Most of these solvents have been eliminated from U.S. manufacturing processes, but may still be used in other countries. Most of these solvents display organ toxicity which may be related to induction of cell proliferation; occupational exposure levels (not specific to the boot and shoe industry) have often been high enough to induce organ toxicity.

Lynge et al. (1997) reviewed epidemiological evidence of the relationship between cancer and the solvents listed above. In animal cancer studies, the liver has been a target site for trichloroethylene, tetrachloroethylene, carbon tetrachloride, dichloromethane, and chloroform. Trichloroethylene, dichloromethane, and benzene were also related to cancer development in some other tissues.

Benzene is a carcinogen associated with the risk of leukemia. A large Chinese cohort study also suggested a link to increased risk of lung and nasopharyngeal cancer (Yin et al., 1996;

cited by Lynge et al., 1997). Apart from the evidence for an association between benzene and increased leukemia risk, the available data on the relationship between cancer risk and exposure to organic solvents is not conclusive. There is some evidence of increased risk of cancer of the liver and the biliary tract and for non-Hodgkin's lymphoma after exposure to trichloroethylene. There is also some evidence for increased risk of cancers of the esophagus and cervix, and for non-Hodgkin's lymphoma following exposure to tetrachloroethylene, but these data are obscured by several confounders. Some excess risk of lymphohematopoietic malignancies following exposure to carbon tetrachloride has been suggested. In a study of dichloromethane, an excess risk of liver and biliary tract cancers was indicated in the cohort with the highest exposure, but was not found in other cohorts where a risk of pancreatic cancer was suggested. A few studies have linked 1,1,1-trichloroethane to a risk of multiple myeloma (Lynge et al., 1997).

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APPENDIX A

DESCRIPTION OF ONLINE LITERATURE SEARCHES FOR BOOT AND SHOE INDUSTRY

DESCRIPTION OF ONLINE LITERATURE SEARCHES FOR BOOT AND SHOE INDUSTRY

Initially, NIOSHTIC (NIOSH's database of Occupational Safety and Health) searches were done for the Boot and Shoe Industry and titles were examined. The strategy involved closely linking terms for footwear with terms for manufacturing and, in a later search, with terms for repair. The industry terms were linked with terms for exposure, including monitoring, sampling, and analysis, to give 236 titles from which records were selected for retrieving abstracts. An additional 38 records were retrieved for the repair industry. In NLM files MEDLINE, CANCERLIT, and TOXLINE, the 641 records containing footwear manufacturing terms were combined with the MESH heading neoplasms+all to give 245 records after duplicate removal. Searches for records on epidemiology and exposure were also done in EMBASE and BIOSIS. Computerized removal of duplicates from all 6 databases gave 251 records that were not in the NIOSHTIC results. These were examined and further selections were printed and combined in the search results package.

APPENDIX B

STUDIES OF CANCER INCIDENCE IN EUROPEAN AND CANADIAN BOOT AND SHOE INDUSTRY WORKERS (POST-IARC, 1981)

Studies of Cancer Incidence in European and Canadian Boot and Shoe Industry Workers (Post-IARC, 1981)

A series of Swedish studies examined the relationship between occupation and the risk of biliary tract cancer (Malker et al., 1986), bladder cancer (Malker et al., 1987), liver cancer (McLaughlin et al., 1987), leukemia (Linet et al., 1988), non-Hodgkin's lymphoma (Linet et al., 1993), colon cancer (Chow et al., 1994), and melanoma (Linet et al., 1995). The studies found a weak or moderate association between most of these cancers and employment in the shoe fabrication industry as shoe and leather workers, or as shoemaker or shoe repairers, depending upon the specific classification code. The studies were based on a similar design and thus share the same strengths and weaknesses.

In terms of strengths, the studies were truly population-based including incident cases identified from the national registry system of Sweden. In addition, for most of the cases studied, the total number of cases was relatively large. However, there were important study limitations including the use of only the 1960 census data to assign job title, and the lack of specific employment duration data. Further, there were no direct data on potential confounding factors. The analysis of liver cancer did indirectly address one condition for confounding, the association between alcohol consumption and job title. The potential confounding bias for other cancers is uncertain. If one uses statistical significance testing as an important criterion for the evaluation of epidemiologic associations, then the multiple comparisons or multiple testing problem may be invoked to raise concern about the large number of tests performed and the possibility that some positive results are due simply to chance. The analyses were generally well conducted including the use of three-digit occupation codes to evaluate the associations with more specificity.

Compared to other epidemiological studies, the study of occupation and bladder cancer from England and Wales (Dolin and Cook-Mozaffari, 1992) included a large number of cases, but was based on deaths (not incident cases). Occupation was derived from death certificates, and census data was used to estimate the number of expected cases. The study attempted to control for smoking by adjusting for a potentially poor surrogate, "degree of urbanization". The Italian case-control study of bladder cancer (Bonassi et al., 1989) was population-based and directly adjusted for smoking, but was very small (121 cases); thus the effect estimate for shoe-repair workers was very imprecise (OR = 2.2; CI = 0.2-25.2). The German bladder cancer study (Claude et al., 1988) was relatively large (531 cases) but was hospital-based, including 26 controls that were not from the urological wards of the study hospitals but from homes for the elderly in the same area. Despite the large overall study size, the odds ratio for shoemaker/saddler was imprecise with a wide confidence interval (0.4-2.0). The Montreal case-control study (Fritschi and Siemiatycki, 1996) of occupation and lymphoma and multiple myeloma was well designed including a detailed assessment of occupational history, control of potential confounders, and analysis of duration of employment. There was an apparent association between working in the leather industry and lymphoma. No dose-response was found, although the number of subjects was small. Data specific to shoe workers within this group were not presented.

These studies are summarized in Table Appendix B.

Table Appendix B. Studies of Cancer in European and Canadian Boot and Shoe Industry Workers (Post-IARC, 1981)

Study Design	Study Population	Exposure	Effects	Comments	Reference
Registry-based analysis	Swedish citizens from 1960 census (employment categories) and 1,304 cases of gall bladder cancer 1961-1979	Occupational and industrial classification from 1960 census; no exposure assessment	Biliary tract cancer incidence (1961-1979) linked to census data on industry and occupation (over 500 groups); calculated standardized incidence ratios (cumulative 19 yr); significant ($p < 0.05$) increase in gall bladder cancer risk (SIR = 2.1) for workers in shoe making and repairing	SIR adjusted for age and region; no correction for other risk factors	Malker et al. (1986)
Registry-based analysis	Swedish citizens from 1960 census (employment categories) and 11,702 cases of bladder cancer 1961-1979	Occupational and industrial classification from 1960 census; no exposure assessment	Bladder cancer incidence (1961-1979) linked to census data on industry and occupation (over 450 groups); calculated standardized incidence ratios (cumulative 19 yr); no increase in risk of bladder cancer among shoe and leather workers	No data on other risk factors	Malker et al. (1987)
Registry-based analysis	Swedish citizens from 1960 census (employment categories) and 2,629 cases of liver cancer 1961-1979	Occupational and industrial classification from 1960 census; no exposure assessment	Liver cancer incidence (1961-1979) linked to census data on industry and occupation (300 groups); calculated standardized incidence ratios (cumulative 19 yr); significant ($p < 0.05$) increase in liver cancer risk (SIR = 1.9) among workers in shoe fabrication	Parallel mortality analysis showed no excess of liver cirrhosis and alcoholism among	McLaughlin et al. (1987)
Registry-based analysis	Swedish citizens from 1960 census (employment categories) and 5,351 cases of leukemia 1961-1979	Occupational and industrial classification from 1960 census; no exposure assessment	Leukemia incidence (1961-1979) linked to census data on industry and occupation; calculated standardized incidence ratios (cumulative 19 yr); significant ($p < 0.05$) increase in cancer risk (SIR = 1.9) among workers in shoe fabrication	Parallel mortality analysis showed no excess of liver cirrhosis and alcoholism among	Linet et al. (1988)

Table Appendix B. Studies of Cancer in European and Canadian Boot and Shoe Industry Workers (Post-IARC, 1981) (Continued)

Study Design	Study Population	Exposure	Effects	Comments	Reference
Registry-based analysis	Swedish citizens from 1960 census (employment categories) and 4,496 non-Hodgkin's lymphoma cancer cases 1961-1979	Occupational and industrial classification from 1960 census; no exposure assessment	non-Hodgkin's lymphoma incidence (1961-1979) linked to census data on industry and occupation; calculated standardized incidence ratios (cumulative 19 yr); significant ($p < 0.05$) increase in non-Hodgkin's lymphoma risk SIR = 1.8 (23 observed, 12.6 expected) among workers in shoe repair SIR = 1.7 (23 observed, 13.4 expected) among shoemakers SIR = 1.8 (22 observed, 12.3 expected) for shoemaker in shoe repairs	SIR adjusted for age and region	Linet et al. (1993)
Registry-based analysis	Swedish citizens from 1960 census (employment categories) and 18,832 colon cancer cases 1961-1979	Occupational and industrial classification from 1960 census; no exposure assessment	Colon cancer incidence (1961-1979) linked to census data on industry and occupation; calculated standardized incidence ratios (cumulative 19 yr); significant ($p < 0.01$) increase in colon cancer risk (SIR = 1.5; 135 observed) among men in shoe and leather work (SIR = 1.6; 80 observed) among male shoemakers	SIR adjusted for age and region	Chow et al. (1994)
Registry-based analysis	Swedish citizens from 1960 census (employment categories) and 3,850 cutaneous melanoma cases 1961-1979	Occupational and industrial classification from 1960 census; no exposure assessment	Malignant melanoma incidence (1961-1979) linked to census data on industry and occupation ; calculated standardized incidence ratios (cumulative 19 yr); significant ($p < 0.05$) increase in malignant melanoma risk (SIR = 1.8; 17 observed) among men in shoe fabrication from leather and skins	SIR adjusted for age and region	Linet et al. (1995)

Table Appendix B. Studies of Cancer in European and Canadian Boot and Shoe Industry Workers (Post-IARC, 1981) (Continued)

Study Design	Study Population	Exposure	Effects	Comments	Reference
Cohort	2,457 men in England and Wales, aged 25-64 who died from bladder cancer between 1965-1980	Information on occupation or employment from death certificates; prepared job exposure matrix	Calculated standardized mortality ratios (SMRs) for bladder cancer using population and occupation based rates corrected for the degree of urbanization as the reference SMR (95% CI; no. observed, no. expected) 4.47 (1.93-8.81; 8, 1.8) for leather workers classified as shoemaker, shoe repairer 6.40 (2.57-13.19; 7, 1.1) for workers in the boot, shoe repair industry	No information on smoking so "urbanization" used as proxy measure	Dolin and Cook-Mozaffari (1992)
Population-based case-control	121 cases of histologically-confirmed bladder cancer in males; 342 male controls from same area of Italy and matched by age	Personal interviews to determine work history; classification into 11 occupational categories identified *a priori*; prepared job exposure matrix	Calculated OR using unconditional maximum likelihood logistic regression OR (95% CI; no. cases, no. controls) = 2.21 (0.19-25.2; 1, 2)		Bonassi et al. (1989)
Hospital-based case-control in Germany	531 pairs of men; cases with histologically-confirmed bladder cancer; controls had other urinary tract diseases and matched by sex and age	Personal interviews to obtain lifetime occupational history; occupational categories defined by coding and analyses; no exposure measurements	Calculated odds ratio (OR) of bladder cancer using logistic regression models OR (95% CI) = 0.92 (0.42-2.02) for shoemaker, saddler	Estimates corrected for smoking	Claude et al. (1988)

Table Appendix B. Studies of Cancer in European and Canadian Boot and Shoe Industry Workers (Post-IARC, 1981) (Continued)

Study Design	Study Population	Exposure	Effects	Comments	Reference
Case-control	215 cases with non-Hodgkin's lymphoma, 54 cases with Hodgkin's lymphoma, 23 cases with myeloma Three control groups (cancer - 533, population - 533, pooled - 533)	Participants gave detailed description of all jobs in working lifetime; level and frequency of exposure to 294 substances evaluated by chemists and industrial hygienists; each job categorized by Canadian classification and industry	Calculated cancer risk using unconditional logistic regression and the Mantel-Haenszel method. Hodgkin's lymphoma ORs significant for leather workers OR (95% CI; no. observed) 7.8 (2.2-28.0; 4) for 1-9 yr occupation as leather worker No classification of workers in shoe manufacture or repair	Adjusted for age, proxy status, income, ethnicity	Fritschi and Seimiatycki (1996)

APPENDIX C

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Volume 25 (Wood, Leather and Some Associated Industries) Boot and Shoe Manufacture and Repair pp. 249-277, 1981

1. HISTORICAL OVERVIEW OF THE INDUSTRY

1.1 Boot and shoe manufacture

Climatic conditions and the nature of terrain have influenced the development of footwear, first used by man as protection against the heat of the ground and sharp stones, or to disguise his tracks. Wood, palm leaves and, particularly, skins were used. Sandals made of a single layer of leather with the 'flower', the outer surface, turned to the inside are the earliest known type of footwear, found in Egyptian tombs of the predynastic era (5000 BC) (Waterer, 1956). Later, more elaborate models were made, with soles comprising several layers.

Sandals, half-boots and buckskins were worn in ancient Greece and in countries of the Near East. The ancient Romans produced shoes - especially those for soldiers - on a large scale, in well organized 'factories'. The soles were made of two or three layers of leather, which were sewn and tacked, while the uppers were composed of strips. This design remained practically unchanged until the sixteenth century, although in northern countries the uppers were slightly modified to adapt them for wear in cold climates.

At the end of the sixteenth century, when footwear was strengthened to meet the needs of military campaigns, the main characteristics of the modern shoe were introduced; and heels and seaming largely as we known them today were developed at that time.

1.2 Boot and shoe repair

In the past, when shoes were made mainly of leather, it was usual for soles and heels to be repaired regularly. This was done by repairers or by the shoe manufacturers. As the durability of solings and the cost of repairs increased, the need for repairing declined and, with it, the numbers of shoe repairers. There are still many repairers, who specialize in the replacement of heels and soles and of uppers when necessary.

2. DESCRIPTION OF THE INDUSTRY

2.1 Processes used previously and changes over time

The parts for the upper were cut by hand with a shoemaker's knife to his own models. They were then sewn together, the edgings were made and any eyelets pierced. The inner linings, made of finer skins or thinner slices, were sewn and glued together with natural glues.

A piece of leather was then wetted and struck with a hammer, and a sole cut from it with a shoemaker's knife, either following a shape drawn on the leather, or by cutting around a template. The sole was applied to the upper with tacks, glued with natural fish, bone or flour glue, and subsequently sewn by hand.

Sewing was done with a needle and hemp thread that was reinforced at one end with pig hair embedded by hand. The thread was lubricated with natural wax and pitch. Small holes were made in the sole to facilitate sewing.

Afterwards, the edges were trimmed with a shoemaker's knife, polished with a file and glass paper and burnished with a warm metal plate. The surface of the sole was polished first with a file and then with the warm metal plate.

These traditional hand processes are still used in many countries.

In the twentieth century, what was once a handicraft industry has been industrialized by the introduction of machines and the splitting up of the production process into several separate operations. Different groups of workers have become responsible for designing and preparing the models, cutting the uppers and the soles, preparing the uppers, assembling the parts and packing.

From the beginning of the century machines were used for stitching the uppers, and the various stages of making up the shoes were organized on the principles of the assembly line, so that the finished product had passed through several hands.

Industrialization of shoemaking at first led to a concentration of the work force, although in some countries it was subsequently dispersed. In Italy, for example, more than 80% of the production units employ fewer than 20 people: the splitting up of the manufacturing process has made it possible to decentralize production. In other countries, however, shoemaking factories are fairly large (average: USA, 195.0 workers; UK, 116.5 workers; Federal Republic of Germany, 162.0 workers; France, 132.9 workers).

Prior to 1950, footwear was made mainly from leather uppers and soles usually stitched together. All cutting and preparation of leather was done in a shoe factory. The outer parts of uppers were made mainly of chrome-tanned leather and the linings of vegetable-tanned leather. Insoles and outsoles were made almost entirely of vegetable-tanned leather. Other materials used included cotton fabric linings; nitrocellulose toe puff and stiffener materials; some satin (silk) for evening wear; natural rubber; inorganic solvents and natural rubber latexes as adhesives. The current trend in many countries is the substitution of natural soles by synthetic materials.

The dustiest operations were the preparation of leather soles and insoles and the scouring and finishing of those components on the manufactured shoes. The latter operations produce the finest dusts. Cyclone extraction systems are available, but even so the workers were certainly subjected to dusty working conditions. The volume of adhesives used was small by comparison with that used in modern manufacturing methods, because most of the shoe bottoms were attached by stitching. Some exposure to solvents, such as petroleum hydrocarbons (naphthas), benzene, carbon disulphide, carbon tetrachloride, acetone and amyl acetate, occurred. Hydrocarbon mixtures, benzene and carbon tetrachloride were used in rubber solutions for laminating linings to uppers and in attaching crepe and rubber soles. Acetone and amyl acetate were used for softening nitrocellulose products such as toe puffs. The adhesives used were natural rubber latex or solutions; water-based paste adhesives made of starch, dextrin or natural gums were used widely for laminating and for sock insertion.

In 1950, footwear was made largely from natural products such as leather and textile uppers, leather and crepe soles, and a proportion of vulcanized natural rubber soles. In the mid 1950s, in some countries, leather soles were slowly replaced by resin rubbers, which were sewn or stuck on, and by directly moulded-on rubber soles. These tough, durable rubbers were used particularly for work boots and childrens' shoes. During the mid 1960s, plasticized polyvinyl chloride (PVC) began to be used in place of moulded-on rubber, and stuck-on PVC units appeared on the market several years later. PVC-coated fabric upper materials were also being developed as a cheaper substitute for leather.

Later in the 1960s, polyurethane soling and better quality PVC-coated fabrics were developed. Research progressed on water-vapour-permeable upper materials (poromerics), which were designed to be as comfortable as upper leather. With improved polyurethane technology in the mid 1970s, the use of coated textiles as upper materials increased. Cellular polyurethane soles became popular at that time and continue to do so.

These developments in soling materials and constructions led to increased usage of solvent-based adhesives for attaching the soles to the uppers. Use of polychloroprene adhesives coincided with use of resin rubber and polyurethane adhesives with that of PVC; there were also considerable developments in use of hot-melt adhesives. The composition of many components, e.g., linings, toe puffs, stiffeners and insoles, was adapted to the newer processes or to use of cheaper alternatives.

2.2 Processes used currently

(a) Boot and shoe manufacture

The operations that may be used in the manufacture of the most usual types of shoes are shown in Figure 1, grouped in the order in which they are carried out. Some of the operations mentioned are optional. A short description of each step follows.

(i) *Typical operations:*

Clicking - cutting upper shoe components, by hand or machine. The most common machine in use is a swing-arm press; modern machines are hydraulically operated.

Splitting - producing a uniform thickness of leather with a band-knife splitting machine

Flow moulding - forming a surface pattern on PVC-coated upper fabric by high-frequency heating

Stitch marking - marking the position of subsequent stitching lines on the upper

Skiving - a machine process which reduces the thickness of the edges of materials to facilitate joining and folding

Cutting out - removing parts of the upper to produce an open-work effect on the shoe

Edge binding - binding the edges of the upper

Fitting - attaching linings to the upper

Attachment of toe puffs - attaching the stiffener which shapes the toe to the upper, usually by heat to activate the adhesive

Stitching - sewing together components and stitching decorative effects

Machine cutting - cutting sole materials, with machines such as a clicking press, a travelling head press or a revolution press

Bevelling - reducing thickness of the edge of the sole material

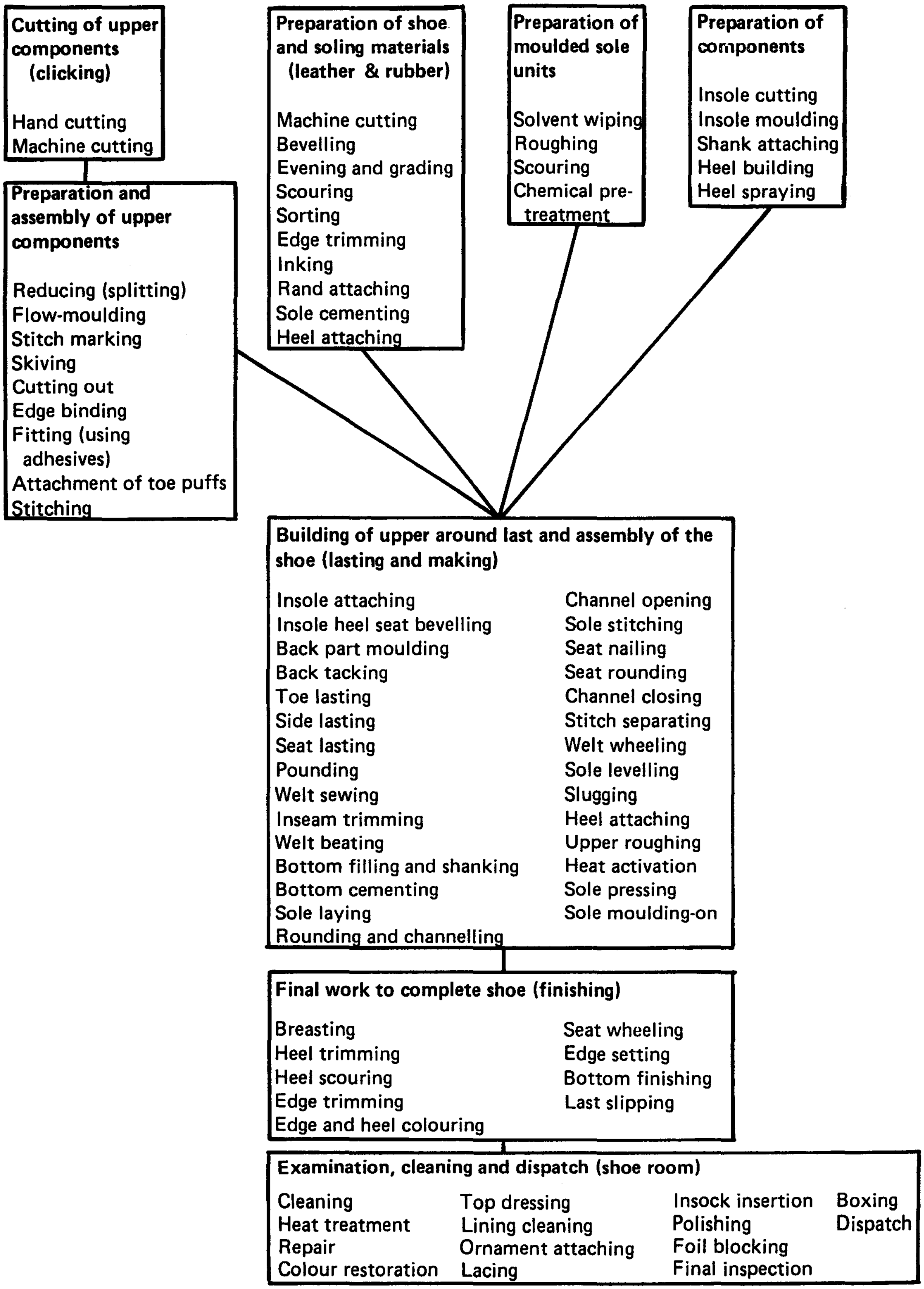
Evening and grading - sorting into consistent groups

Scouring - removing surface layer on heels and soles in preparation for staining and colouring

Rand attaching - attaching decorative edging materials to soles

Sole cementing - applying adhesive to soles

Fig. 1. Typical operations in shoe manufacture



Heel attaching - attaching the heel, usually with nails or staples

Solvent wiping - cleaning the surface of the sole

Roughing - abrading surfaces to provide a rough surface for adhesive application

Chemical pretreatment - surface modification by chemicals to improve subsequent bonding

Insole moulding - shaping the insole to conform to the bottom shape of the last

Shank attaching - attaching a strip of wood or steel to the insole for reinforcement

Heel building - joining together layers of material comprising the heel

Heel spraying - surface coating of heel

Back part moulding - shaping the back part of the upper

Back tacking - tacking the upper to the insole at the back

Lasting (toe side seat) - pulling the upper over the last and fixing it to the insole

Pounding - beating the lasted margin of the upper

Bottom filling - filling the space between the edges of the lasted margin and the insole

Shanking - fixing the shank in the shoe

Bottom cementing - applying adhesive to the bottom of the upper

Sole laying - temporarily attaching the sole to the upper in the welted process

Rounding - cutting off surplus material from edge of sole

Channelling - making a groove to receive the welt seam

Seat nailing - tack-lasting the heel part of the shoe

Welt wheeling - pressing a pattern onto the top of the welt

Sole levelling - compressing the sole by levelling

Slugging - attaching the wearing surface of the heel

Heat activation - heating the adhesive-coated surface to facilitate bonding

Sole moulding-on - the moulding of a synthetic sole directly onto the lasted upper

Breasting - trimming the heel breast to shape

Edge setting - sealing the edge of the sole by applying heat and wax

Bottom finishing - finishing the sole after scouring

Last slipping - removing the completed shoe from the last

Heat treatment - application of heat to remove thread ends and wrinkles from the shoe upper

Top dressing - applying finishes to improve the appearance of the upper

Foil blocking - printing of gold or silver motifs on sole or sock

In modern factories, shoe components are transported on conveyors systems to machinery and work positions; in the past, shoe parts were moved to the various work stations on small trolleys pushed manually. Recently, conveyors have been fitted with a central extractor linked to the positions where cementing operations are carried out. The whole conveyor, or at least the parts nearest to the cementing positions, may be covered with transparent plastic sheets. Several completely automatic shoemaking systems, beginning with lasting and ending with sole attaching, have been designed, and these have worked successfully on long production runs of simple styles. Modular automatic systems are being developed for short runs of more intricate shoe designs.

(ii) *Significant processes used currently:*

Welting: A process by which the sole is attached to the upper by stitching to a presewn welt. Many operations are required in this process, and it is very labour intensive. The use of welted soles has declined over the years, and it will probably become a minor process. It is essentially used for men's footwear, especially for high-priced shoes.

Machine-sewing: Another process involving the stitching of soles onto uppers. It is widely used for the production of moccasins.

Veldts: A method of producing footwear by sewing the out-turned upper to a runner (an extended insole) and then sticking the outsole to the runner. It is widely used for childrens' sandals and for leisure footwear.

Moulded-on rubber: The uppers for outdoor footwear are made almost exclusively of full chrome leather, since it has sufficient heat resistance to withstand the pressure and temperatures involved. Basically, the upper is lasted, cemented (with a solvent-based adhesive) and placed in a heated mould containing an unvulcanized rubber blank. A cure time of about 10 minutes at 180°C is usually sufficient to cure the rubber adequately and to bond it to the shoe bottom.

At present, the process is used mainly for safety footwear. A similar process is still widely used for the production of slippers with sponge-moulded bottoms. Tennis and canvas uppered plimsolls are also made by the moulded-on process, although the techniques, e.g., autoclaving and preparation of the soles, are somewhat different.

Moulded-on plastics: The first plastic shoe bottoms of commercial value were made from injection moulded-on plasticized PVC. The main advantage of this process over rubber moulding is that the hot PVC melt is injected onto the cemented shoe bottom but the sole mould is not heated. Many other plastics, including thermoplastic rubber, solid polyurethane, nylon and polyesters, have been used successfully in this process; and thermoplastic rubber is likely to replace PVC, at least to some extent. Other plastics are used for special applications such as football boots.

The latest development, made in the early 1970s, is a moulded cellular polyurethane sole. The process involves a chemical reaction brought about by mixing and metering two reactive chemicals and pouring or injecting them into a mould to form the shoe sole. The final product is a tough, durable, cellular material. The process does not involve the use of adhesives.

Stuck-on process: This method of attaching a sole to a shoe upper is the most versatile of all sole attaching processes: it comprises applying adhesive to the shoe bottom and to the sole, allowing each adhesive to dry, reactivating the adhesive (usually by radiant heat) and then pressing the two coated surfaces together.

The stuck-on process makes particular use of prefabricated and premoulded units, which may be made or moulded in a shoe factory or be purchased. The units may be moulded from rubber, PVC, thermoplastic rubber, polyurethane, polyesters or nylon.

Since its development in the 1950s, the stuck-on process has been used widely and is likely to continue to be in the foreseeable future. Its versatility and simplicity are vital to the ability of the footwear industry to adapt to current fashions.

Finishing processes: Finishing processes involve many parts of the shoe. Some components (e.g., heels and units) may be prefinished before reaching the shoe factory. Depending on their properties, finishes may be applied by dip, sponge, brush or spray. When spray processes are used in shoe factories, extractor fans are normally available for removing the excess spray and hence the bulk of the chemicals.

(iii) *Materials used in footwear:*

Uppers: Currently, the uppers of footwear are made from leather (mainly full-chrome), textiles (natural and synthetic fibres), coated fabrics of various kinds (PVC- or polyurethane-coated) and poromerics (porous polymeric material).

Linings: These may be of leather, nylon, textiles or coated fabrics.

Stiffeners: Premoulded stiffeners based on cellulose fibres and resin (polystyrene)-impregnated cloths, which are moulded by heating, are the most common types.

Toe-puffs: Nitrocellulose-impregnated cloths, softened with solvent before use, are used mainly for welted work. Impregnated fabrics and polymer films (extruded sheet or hot metal) that can be softened with heat are now more common. Some rubber-impregnated puffs are used when soft toes are required.

Insoles: Some vegetable-tanned leathers are used in men's high-grade footwear. More commonly, insoles are made of scrap leather (vegetable and/or chrome-tanned) bonded with natural rubber, or of cellulose fibres (fibreboard from chemical wood pulp) bonded with polychloroprene. Newer types of stitch-bonded textiles are becoming popular.

Insock: A cover for the insole of a shoe, made of coated fabrics or cork.

Heels: Low heels are usually moulded from polyethylene, while high heels are more often moulded from high-impact polystyrene, PVC or poly-acrylonitrile-butadiene-styrene (ABS). Leather and a special grade of polyethylene-impregnated fibreboard are also used in the manufacture of heels.

Soling materials: Leather for soling is usually vegetable-tanned but may be partially or fully chrome-tanned. Rubber is used widely, in the following forms: crepe (unvulcanized), vulcanized natural and synthetic, vulcanized butadiene-acrylonitrile copolymer and polychloroprene. Thermoplastic rubber (styrene-butadiene-styrene block copolymer) is the latest development in rubber injection moulding.

PVC is used widely in its plasticized form. Ethylene vinyl acetate (EVA) is used in two forms, depending on its end use: linear EVA for units and cellular cross-lined EVA for sheet soling.

Polystyrene, acrylonitrile-butadiene-styrene polycarbonate and rope have also been used. Polyurethane soling is made by mixing and metering two reactive chemicals (a polyol and an isocyanate) and pouring or injecting them into a mould to form the shoe sole. The process may be carried out in a shoe factory, or units may be purchased.

Cork: Cork is used in surgical footwear and unit soles. Shoe manufacturers can buy cork in precut, prefinished form, but they may shape the cork mechanically. Shaping of cork may also be done by specialized unit sole manufacturers. Cork for use in shoes comes in two forms: plank cork is the natural product and comes in sheet form; granulated cork is made up of cork particles bonded together into blocks ready for machining.

Wood: Wood, usually hardwood, is used for the manufacture of lasts, clogs, heels and shanks. Some rigid fibreboards used as footwear components are made from compressed wood pulp.

Lasts are made by last makers and purchased by shoe manufacturers.

Clogs may be made wholly of wood, or uppers may be attached. Clogs for industrial use may have grinding on the wearing surface; those for everyday use have rubber or plastic soles. The wood (solid or laminated) is usually shaped by unit manufacturers, but some shoe factories manufacture their own products. The wood is seamed and finally polished or coloured.

Wooden heels are usually produced in specialized factories and purchased by shoe manufacturers.

Shanks are slim pieces of roughly shaped wood placed between the sole and insole in the heel area.

Adhesives: Adhesives used in footwear manufacture fall into three main categories: latex, hot-melt and solvent solution adhesives.

Latex adhesives are made up of a dispersion of polymer (natural rubber, synthetic rubber or polyvinyl acetate) in water. They are widely used.

Hot-melt adhesives are solvent-free thermoplastic adhesives in rod, block or granule form. They are used essentially for lasting, folding and shank insertion (polyamide, EVA and polyester types); they are applied directly as a liquid hot melt and a bond is formed immediately. Hot-melt adhesives may be applied to components (such as toe puffs) and be reactivated by heat to form the bond.

Solvent solutions of rubber and polymers (natural, polychloroprene and polyurethane) are used widely. Natural rubber solutions are used for laminating, but the polychloroprenes and polyurethanes are used mainly for the bonding of soles to uppers. The adhesives may contain plasticizers, tackifiers and stabilizers. The solvents in rubber solutions are petroleum hydrocarbons or chlorinated hydrocarbons, and those in the synthetic rubber adhesives are mixtures of ketones, esters and hydrocarbons. Isocyanates may be incorporated into adhesives, but the use of two-component adhesives is not common in all countries.

(b) Boot and shoe repair

Many different types of repairs are carried out; the main ones are described below.

Welted leather soles: The worn out sole is removed and replaced with a half-sole using the same techniques as in shoe manufacture.

Cemented-on soles: The original sole is usually removed by ripping it off; the adhesive bond may be softened with heat or solvent to facilitate removal. The repair sole is stuck to the upper by the usual manufacturing procedure.

Stuck-on soles: These are premoulded or PVC soles which are stuck to the worn out, original sole without removing it from the shoe. The worn out sole may be levelled by scouring before the stuck-on sole is attached.

Heeling: This term applies to the replacement of the wearing surface of the heel of a shoe. The common materials for heeling are leather, rubber or plastics, and they are attached by adhesives after grinding. If the heel base requires levelling before being repaired, this is done by scouring.

Heel attaching: Heels, the base and the wearing surface, may need to be replaced completely. Sometimes they are removed from the plastic with heated pincers. New heel bases are attached after grinding.

Upper stitching: This repair is fairly uncommon. It may also be termed 'patching'. The patch is stitched.

Recolouring: This is occasionally done by repairers but is more often done by the owners of shoes who can buy recolour commercially.

Minor repairs: Loose buckles and trims are sewn on.

2.3 Qualitative and quantitative data on exposures

(a) Exposure to dust

Scouring and roughing operations produce the greatest volume of dust.

(i) *Scouring:* Scouring occurs most commonly during hand finishing (edges and bottoms), and the dust is fine. When plastic heel blocks and rubber top-pieces are used, the dust also contain particles of these materials. Dust extraction is widespread, and dust extractors are usually fitted to machinery used for scouring rubber soles.

(ii) *Roughing:* Upper materials are usually roughed by high-speed wire brushes using machines with dust extractors. Leather uppers are commonly prepared in this way, and the dust comprises leather and finish. Automatic roughing machines with built-in dust collectors are fairly common. Other materials may be roughed using similar techniques.

(iii) *Edge trimming and rounding:* These are cutting operations which produce small pieces of the soling material.

(iv) *Cutting:* When shoe components are cut to shape, various dusts can arise, consisting of leather (all tannages), rubber, textiles (cotton, nylon, wool, polyester, etc.). The handling both of the materials and the cut components can generate dust.

(v) *Moulded-on rubber sole process:* Unvulcanized rubber sheet used in this process is usually dusted with zinc stearate to prevent the sheets from sticking together. Over-dusting may contaminate the work place with zinc stearate dusts.

(vi) *Quantitative measurements:* The results of one survey carried out in the UK in the summer of 1976 are given in Table 1. The factory produced welted footwear with leather uppers and soles.

(b) Exposure to chemicals

The application of cleaners, adhesives and finishes is the main source of exposure to chemicals. These are listed in Table 2, although not all of them are used in all countries. (See also Appendix 5.).

(i) *Cleaner and adhesive application:* Cleaners and adhesives may be applied by hand or machine. The degree of exposure to evaporating solvents depends on the volume of cleaner or adhesive used, the conditions of drying and the use of extraction systems.

Table 1. Survey of dust levels in a footwear factory in the UK (summer, 1976)

OPERATION	STATIC SAMPLES OF GENERAL WORKROOM AIR					PERSONAL SAMPLES	
	Concentration	Particle size distribution (%)				Concentration (mg/m^3)	
	(mg/m^3)	< 1.53 μm	1.53-4.15 μm	4.15-13.65 μm	> 13.65 μm	Day 1	Day 2
Insole scouring	0.32	7	12	43	38	0.56	0.89
Upper cutting (hand)	0.17	14	17	41	28	0.48 0.34	0.41 0.26
Upper cutting (press)	0.30	31	12	32	25	0.30	0.27
Sole cutting (press)	0.12	73	13	14	0	0.49	1.10
Upper skiving (i)	0.37	34	9	38	19	0.46	0.28
Upper skiving (ii)	0.20	29	18	32	21	-	-
Sole stitching (i)	0.18	36	10	35	19	0.47	0.44
Sole stitching (ii)	0.23	31	23	26	20	-	-
Edge trimming	0.23	52	20	22	6	0.71	0.69
Heel scouring (i)	0.56	13	15	38	34	7.5	3.9
Heel scouring (ii)	0.27	42	11	28	19	0.88 0.20	0.91 0.05
Sole scouring	-	-	-	-	-	2.4 0.05	2.8 0.07
Upper roughing	-	-	-	-	-	0.50 0.68	0.58 0.49
Heel polishing	-	-	-	-	-	0.65	0.96
Edge polishing	0.15	26	17	33	24	0.29	0.30
Mean	0.26	32	15	32	21		

Table 2. Chemicals that are or have been found in adhesives and finishes used in boot and shoe manufacture

Chemical	Use
Carbon disulphide	Rubber solvent and cleaner
Carbon tetrachloride	Rubber solvent and cleaner
Trichloroethylene	Rubber solvent and cleaner; adhesive solvent
Dichloromethane	Rubber solvent and cleaner
1,1,1-Trichloroethane	Rubber solvent and cleaner
Tetrachloroethylene	Cleaner
Benzene	Adhesive solvent
Toluene	Adhesive solvent
Xylene	Adhesive solvent
2-Methylpentane	Cleaner, diluent, adhesive solvent
3-Methylpentane	Cleaner, diluent, adhesive solvent
Hexane	Cleaner, diluent, adhesive solvent
Methylcyclopentane	Cleaner, diluent, adhesive solvent
Cyclohexane	Cleaner, diluent, adhesive solvent
Ethyl acetate	Adhesive solvent, lacquer solvent, cleaner
Butyl acetate	Adhesive solvent, lacquer solvent, cleaner
Amyl acetate	Adhesive solvent, lacquer solvent, cleaner
Acetone	Adhesive solvent, lacquer solvent, cleaner
Methyl ethyl ketone	Adhesive solvent, lacquer solvent, cleaner
Tetrahydrofuran	Cleaner
Methyl isobutyl ketone	Adhesive solvent, lacquer solvent, cleaner
Ethanol	Cleaner
Isopropanol	Cleaner

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e 2 (contd)

Chemical	Use
Dimethylformamide	Lacquer solvent
Surfactants	Cleaners
Ammonia	Cleaner
Waxes (natural)	Finishes
Shellac	Finish
Acrylic resins (various)	Upper and units finishes, emulsion or solvent-based
Nitrocellulose	Upper and units finishes, usually solvent-based
Cellulose acetate butyrate	Upper and units finishes, usually solvent-based
Polyurethanes (linear, one-part)	Upper and units finishes, usually solvent-based
Isocyanates (various)	Active primers and in two-part adhesives
Halogenation agents based on organic chlorine donors	Primers
Natural rubber	Adhesives
Polyvinyl acetate	Adhesives
Polychloroprene rubbers	Adhesives
Polyurethanes	Adhesives
Tackifying resins (unspecified)	Adhesive modifiers
Polyamides	Hot-melt adhesives
Polyesters	Hot-melt adhesives
Ethyl vinyl acetate	Hot-melt adhesive
Urea-formaldehyde resins	Toe puffs
Various plasticizers (e.g., tri-*ortho*-cresyl phosphate)	

(ii) *Finish application:* Both soles and uppers are cleaned before finishing. Finishes include coloured and transparent surface coatings for soles and uppers. Soles may be coloured by dipping, sponging or spraying. Uppers are sponged or sprayed. The degree of exposure depends on the volume of finish applied and the technique used. Extractors are commonly used to remove overspray, and, hence, chemicals in shoe upper finishing departments. A partial list of dyes known to be used in boot and shoe manufacture and repair is given in Appendix 6.

(iii) *Miscellaneous atmospheric contamination:* A number of shoe or component manufacturing processes involve special procedures, and atmospheric contamination may arise from:

- *release agents* (silicones and waxes) used to spray moulds

- *vinyl chloride monomer* (VCM): When two PVC compounds are welded together, hydrogen chloride and possibly VCM may be evolved; however, the operation is usually carried out by machines that are fitted with an efficient extractor system.

- *isocyanates* from the polyurethane unit and moulded-on processes. The processes may or may not be totally enclosed during the chemical reaction needed to produce the soling.

- *the heating of plastics* in general, especially when high temperatures are involved; e.g., the removal of grindery from acrylonitrile-butadiene-styrene components (heels and units) may lead to localized acrylonitrile pollution.

- *the fumes from hot vulcanized rubber* may result in exposure to petroleum distillates, curing agents, retarders, amines, sulphur and *N*-nitroso compounds. Although release of the latter has been suggested (Fajen *et al*., 1979), no air measurements of these compounds in shoe factories have been reported in the published literature.

(iv) *Exposure to solvents:* It is unusual for an adhesive or finishing material to contain a single solvent; the solvent mixtures used in manufacture vary widely, not only between products but between different batches of the same product. A recognized technique for calculating the TLV of a mixture is given by the Health & Safety Executive (1978).

A survey of six shoe factories in the UK was carried out to determine the exposure of workers to solvent inhalation (Table 3). The atmospheric levels of solvent found, using personal samplers, are quoted as a fraction of the TLV calculated for the particular solvent mixture in the bulk product which was being used.

Table 3. Solvent vapour levels found in a survey of 6 UK shoe factories

Operation	Efficiency of extraction	Level of solvent vapour
Sole cementing	satisfactory	½ x TLV
	poor	4 x TLV
Solvent cleaning	moderate	¾ x TLV
	poor	3 x TLV
Bottom cementing	none	¾ x TLV
Bottom filling	none	½ x TLV
Closing	none	¾ to 1¼ x TLV
Heel covering	none	3 x TLV

In a second survey of 28 factories, 17 were found to have areas in which the solvent vapour concentration was greater than the TLV. The areas with the highest concentrations were sole cleaning and cementing and bottom cementing, where racks were used to store the work during drying. When conveyor systems were used, the level of solvent vapour after cementing shoe bottoms was substantially lower.

Vigliani (1976) and Vigliani & Forni (1976) reported that benzene concentrations in the air in the working environments of shoe manufacturing industries in Pavia, Italy, ranged from 25 - 600 ppm, although in most analyses it was 200-500 ppm.

Levels of benzene in plants engaged in shoe, slipper and handbag manufacture in Istanbul, Turkey, reached a maximum of 210-650 ppm (Aksoy *et al.*, 1974).

Carapella (1977), in a study in 19 shoe factories in the Marches (Italy), found concentrations of more than 500 ppm hexane in the air. De Rosa *et al.* (1977), in a study of solvent concentrations in the air in adhesive application areas in 20 shoe factories in Italy, found that in 45 of 71 working places examined the total concentration of solvents identified was higher than the mixture TLV, and that in 25 of 71 places hexane and its isomers occurred at levels of more than 500 ppm, the TLV of the American Conference of Governmental Industrial Hygienists (1979).

(c) Boot and shoe repair

Shoe repairers may be exposed to all the chemicals contained in adhesives, paints and dust because one operator carries out all the operations. However, exposure to chemicals is usually limited to adhesives and paints for edges. Repairers are exposed to the dusts generated during scouring, which may be any of the materials used in shoe manufacture, but modern machines are usually fitted with extractors.

2.4 Biological factors

No data were available to the Working Group.

2.5 Current regulations and recommendations on exposures

See 'General Remarks on Wood, Leather and Some Associated Industries', p. 23 .

2.6 Number of workers involved

See 'General Remarks on Wood, Leather and Some Associated Industries', p. 19 .

3. TOXIC, INFLAMMATORY AND ALLERGIC EFFECTS IN HUMANS

The chronic toxic effects observed most frequently among shoemakers involve the haematopoietic system and the nervous system. Various peripheral blood abnormalities have been related to the use of benzene in the gluing process. Among these disorders, thrombocytopenia and depression of red blood cell, platelet and white cell counts have been described; pancytopenia, caused by chronic or acute bone-marrow atrophy, is the major such disorder (Robbins & Cotran, 1979). Although benzene appears to be the agent mainly responsible for this effect, some minor abnormalities of peripheral blood have also been attributed to the use in the gluing process of solvents other than benzene (Bartolucci *et al.*, 1978; Ceccarelli & Mastrangelo, 1978).

Peripheral neuropathy was found to be frequent among workers in leather goods and shoemaking factories in several countries. The preliminary symptoms of this disease usually occur bilaterally and include weakness and pain in the lower limbs, paraesthesia, sensitivity reduction and muscle spasms in the upper limbs and hands. At the same time, abnormally low maximal motor conduction velocity of the median nerve is observed; later, abnormally low nerve conduction velocity can occur, especially in the limbs (Buiatti *et al.*, 1978). This disease, which was first related to exposure to tri-*ortho*-tolylphosphate (Crepet *et al.*, 1968; Chauderon & Lévêque, 1969) is now mostly related on the basis of clinical and experimental data to exposure to low boiling-point solvents such as hexane (Inoue *et al.*, 1970; Foa *et al.*, 1976).

Electroencephalographic changes, possibly due to solvent exposure, have also been described in shoemakers (Guiliano *et al.*, 1974). Vestibular disorders were found to be more frequent in shoemakers exposed to solvents (D'Andrea *et al.*, 1979). Liver damage, as evidenced by increased γ-glutamyltranspeptidase (Bartolucci *et al.*, 1978), dermopathies (Fernandez, 1972) and behavioural changes (Murphy & Colligan, 1979) have also been reported in connection with exposure to solvents.

4. CARCINOGENICITY DATA[1]

(a) Nasal cancer

During 1958-1968, 30 male patients with cancer of the nasal cavities were treated in a hospital in Belgium. Among 20 patients with adenocarcinoma, 2 were shoemakers (Debois, 1969). Among 16 patients with adenocarcinoma observed in The Netherlands during 1944-1967, one was reported to be a shoemaker (Delemarre & Themans, 1971). One further case of adenocarcinoma in a shoemaker was reported from the German Democratic Republic (Löbe & Erhardt, 1978).

One nasal cancer (histological type not given) in a shoe repairer was found in a general survey of relationships between occupation and cancer at the Roswell Park Memorial Institute in New York State (Decouflé, 1979).

Incident cases of nasal cancer diagnosed in Northamptonshire, UK, between 1953-1967 were identified by Acheson *et al.* (1970a). Of 46 cases collected, 29 were in males (10 adenocarcinomas, 15 squamous-cell carcinomas, 4 transitional-cell carcinomas) and 17 in females (3 adenocarcinomas, 7 squamous-cell carcinomas, 4 transitional-cell carcinomas and 3 unclassified tumours). Crude annual incidence rates per million were 5.1 in males and 2.3 in females for squamous-cell carcinomas and 3.4 and 1.0 for adenocarcinomas. For all but 9 cases the patient himself or a relative was questioned about occupational history. The proportion of men who had ever worked in the boot or shoe trade was 7/10 with adenocarcinomas, 7/15 with squamous-cell carcinomas and 3/4 with transitional-cell carcinomas. Based on incidence rates for southern England, 0.2 cases of adenocarcinoma would have been expected in the population of shoe and boot workers in the area, compared with 7 observed [an observed/expected (O/E) ratio of 35]. The expected number for squamous-cell cancers was 1.6 (O/E ratio, 4) and that for transitional-cell cancers 0.4 (O/E ratio, 7.5). Two of the men with nasal adenocarcinoma had worked in the shoe and boot industry at a time prior to diagnosis. Of the women, 2 of the 17 had worked as boot and shoe operatives

[1] This section should be read in conjunction with Appendices 1 and 3, pp. 295 and 305.

and two others were the wives of a boot and shoe factory foreman and of a handbag manufacturer. Fifteen other cases of nasal cancer in Northamptonshire diagnosed before 1953 and after 1967 were collected: 5 of them were in workers in the shoe and boot industry. This brings to 61 the total number of cases observed in the population and to 26 those occurring among workers in the boot and shoe industry. Details on work in the boot and shoe industry have been obtained for 20 of the latter. Of these, 13 had been employed in the finishing room and 4 in areas where leather was sorted and cut for soles and heels.

In a subsequent report (Acheson *et al.*, 1970b), crude annual incidence rates for male workers in different departments of shoe industries in Northamptonshire are given. The rates for workers in the press and finishing rooms were 7/100,000 for both adenocarcinomas and other nasal carcinomas. The incidence rate of all nasal cancers in other departments of the industry was 1/100,000. Less than 5% of women employed in the boot and shoe industry work in the press and finishing rooms, compared with 32% of men.

Acheson (1976) described 11 further cases of nasal cancer that occurred during 1970-1974 among boot and shoe workers in Northamptonshire. Two of the patients had worked in the shoe industry for only 6 months and 3 years. In a systematic search of the death register of the town of Northampton, no deaths from nasal cancer in workers in the boot and shoe industry were found before 1950.

Acheson *et al.* (1972) identified all cases of adenocarcinoma of the nasal cavity and sinuses recorded in cancer registries in England (except for the Oxford Regional Register) for the period 1961-1966. Each case was matched by age (within 5 years), sex and registry with a control patient with a nasal cancer other than adenocarcinoma. In response to a questionnaire requesting full occupational history, posted to both cases and controls, usable occupational data was obtained for 107 of the 149 cases (72%) and for 110 of 133 controls (83%). Among the men, 7/80 with adenocarcinomas (9%) reported employment as leather workers at some time; the corresponding proportion among controls was 1/85 (1%) ($P < 0.001$, according to the authors), and 0.5 cases of adenocarcinoma would have been expected in male leather workers on the basis of census data (O/E ratio, 14). In this series, a total of 12 cases and controls had at some time been leather workers, including 7 men and 1 woman with adenocarcinoma and 3 men and 1 woman with squamous-cell carcinoma. All had entered the leather industry before 1930; 4 had left it before 1945, 2 had left during the 1960s, and 4 were still working in the leather industry at the time of diagnosis. The occupations of the 8 patients with adenocarcinomas were reported as shoe repairer (3 cases), leather cutter in boot repair shop (1 case), supervisor in footwear retail and repair shop (1 case), worker in shoe factory (2 cases) and worker in glove trade and upholstery (1 case). The 4 patients with squamous-cell carcinomas reported employment as finisher and cleaner in a shoe factory, boot and shoe operative, shoemaker in a boot and shoe factory, handbag maker at home. It is stressed that the risk is limited to workers exposed to dusty work in the preparation and finishing departments; there is a suggestion of a risk among boot and shoe repairers.

Cecchi *et al.* (1980) collected 69 cases of nasal cancer diagnosed in the province of Florence during 1963-1977, i.e., 13 adenocarcinomas (12 in men), 38 epidermoid and anaplastic carcinomas (23 in men, 15 in women), 15 other primary cancers (11 in men, 4 in women) and 3 not histologically proven. Twenty-two hospital controls were matched to the 13 patients with adenocarcinoma (aged 44-73 years) by age (within 5 years), sex, place of residence, smoking habits and date of hospital admission (within 5 years). Occupational histories were collected from all patients or relatives and controls. Four patients (including 2 with adenocarcinoma) could not be located and were not included in the analysis. Seven of the 11 men with adenocarcinomas were shoemakers *versus* 0/22 controls. In an analysis of male patients aged 45-75, 6/9 adenocarcinomas, 2/19 epidermoid and anaplastic carcinomas and 0/5 other primary cancers occurred in shoemakers. Of the 7 shoemakers with adenocarcinomas, 5 were engaged in trimming, 1 was a shoemaker and repairer and 1 was a shoemaker also exposed to wood dust. In addition, one patient who had reported woodwork as his main occupation had repaired shoes at home for 10 years.

(b) Lung cancer

Menck & Henderson (1976) identified 2161 death certificates on which lung cancer was mentioned in white males between the ages of 20 and 64 for the years 1968-1970, as well as 1777 incident cases of lung cancer in white males of the same age group who had been reported to the Los Angeles County Cancer Surveillance Program for 1972 and 1973. They then classified subjects according to the last known industry of employment. Using 1970 census data, expected deaths and expected incident cases were calculated for each specific occupation, assuming that the age-specific rates of cancer in each occupation were the same as those for all occupations. The ratio of observed deaths plus incident cases to expected deaths plus incident cases was calculated as the risk ratio. Among 1350 shoe repairers, they found 3 deaths between 1968-1970 and 4 incident cases between 1972-1973, a risk ratio of 2.33 ($P < 0.05$). [No information was given on smoking habits.]

(c) Bladder cancer

Versluys (1949) compared the proportional mortality from cancer of different organs among shoemakers and shoehands to that of the general population in The Netherlands during 1931-1935. The comparison was restricted to persons over 30 years of age. A total of 317 male shoe workers died during 1931-1935. Occupations were identified from the death cards of each deceased person as either 'occupation' or 'former occupation'. Fourteen deaths from bladder cancer were observed *versus* 8.1 expected, a ratio of 1.7. No differences were observed among shoemakers' wives. [The expected numbers do not appear to have been age-standardized.]

Wynder *et al.* (1963) reported the results of a case-control study of bladder cancer (excluding papillomas) carried out in various hospitals in New York City during 1957-1961 inclusive. The study included 300 men and 70 women with transitional-cell or squamous-cell carcinoma and 15 men and 4 women with bladder adenocarcinoma. An equal number of age- and sex-matched controls were obtained from the same hospitals during the same period. Twelve cases and 3 controls reported long-term jobs involving shoe or leather repair or production. The 12 cases included 6 lifelong shoe repairers and one who had worked as a shoe repairer for 20 years. The remaining 5 cases reported pocket-book making (5 years), shoemaking (lifelong), shoe store owning (22 years), leather cutting (lifelong) and leather working (lifelong). Of the 3 controls without bladder cancer who had worked in the leather industry, 2 reported shoemaking for more than 5 years and one had been a shoe repairer for more than 5 years. Two of the 12 cases were nonsmokers, 2 smoked less than 20 cigarettes/day and 8 smoked more than 20 cigarettes/day. The smoking habits of the 3 controls were not given. None of the women with transitional-cell or squamous-cell carcinoma of the bladder nor their controls reported having worked in the leather/shoe industry; the same was true for all patients with adenocarcinoma and for their controls.

Veys (1974) analysed 144 death certificates in the period 1965-1970 on which a bladder tumour was mentioned in relation to a possible occupational exposure to carcinogens. Two shoe repairers were reported out of 36 male cases with suspected exposure. None of the female cases had an occupational history related to the leather industry.

(d) Haematopoietic and lymphoreticular cancer

Vigliani (1976) and Vigliani & Forni (1976) reported on benzene haemopathies seen at the Institutes of Occupational Health of Milan and Pavia (Italy). A total of 66 cases (37 men and 29 women) had been hospitalized in Milan since 1942, 11 of which were diagnosed as leukaemias; 18 patients (2 with leukaemia) had been engaged in shoe manufacture. During 1959-1974, 135 cases of benzene haemopathy associated with shoe manufacturing industries were seen in or reported to the Institute of Occupational Health in Pavia. Twelve of the patients died of acute myeloblastic leukaemia and one died of erythroleukaemia; the ages of 9 cases were reported: 3 were 40-49 and 6 were over 50 years old. The duration of exposure to glues and adhesives containing benzene was reported for 8 cases: less than 2 years in 2 cases, 8 years in 1 case and 30+ years in the remaining 5 cases. [See also section 2.3(*b*) (iv), p. 265 .]

Mazzella di Bosco (1964) described 3 cases of acute or subacute leukaemia diagnosed during 1961-1963 in 3 workers engaged in shoe production in the province of Florence (Italy), who were reported to have been exposed to benzene.

During 1967-1973, 26 workers engaged in the manufacture of shoes, slippers and handbags in Istanbul, Turkey, were admitted to one of the 4 major hospitals of that city and diagnosed with leukaemia. Fourteen were diagnosed as having acute myeloblastic leukaemia, 3 acute erythroleukaemia, 3 acute lymphoblastic leukaemia, 1 acute monocytic and 1 acute promyelocytic leukaemia. The remaining 4 cases were diagnosed as pre-leukaemia. Average age at diagnosis was 34.2 years (range, 16-58). All patients had been exposed to benzene, with an average exposure of 9.7 years (range, 1-15). [See also section 2.3 (*b*) (iv), p. 265 .] There were reported to be 28,500 workers in the shoe, slipper and handbag industries in the catchment area of the 4 hospitals, and a crude annual incidence rate of leukaemia of 13/100,000 was reported (19.7 during 1971-1973). This is compared with a crude rate of 6/100,000 in the general population (Aksoy *et al.*, 1974).

A further 8 cases (3 acute erythroleukaemias, 3 other leukaemias and 2 preleukaemias), all of which involved exposure to benzene, were diagnosed in 1974. Five of the patients had worked in the shoe/leather industry and had been exposed to benzene for 1-20 years. On the basis of the 26 cases reported previously and the 5 cases reported in this study, a crude annual incidence rate of 13.5/100,000 was calculated for leukaemia in shoemakers (Aksoy *et al.*, 1976).

It has been reported that since 1969, benzene has gradually been replaced by petrol in shoe manufacturing plants. The absolute number of newly diagnosed leukaemias among shoe workers in Istanbul decreased in 1974 and 1975, and none occurred in 1976 (Aksoy, 1978).

A total of 44 pancytopenic patients were observed in Istanbul in 1961-1977 who had previously been exposed to benzene. The adhesives for shoemaking that were prepared in benzene were both introduced and abandoned during this period. Thirty-four of the patients were shoeworkers. Average exposure to benzene was 6.7 years (range, 0.3-15). In 6 of the 21 patients who died, leukaemia developed after periods of 0.5-6 years (Aksoy & Erdem, 1978).

Cancer incidences in shoemakers were estimated in a historical cohort study in which rates were compared with those in the general population. A total of 579 diagnoses of cancer were identified, and a significant excess of leukaemia (ICD 204) was found (21 observed *versus* 13.5 expected; SMR = 156) (Englund, 1980).

(e) Other cancers not previously specified

Versluys (1949) [see above, section (*d*)] also found 5 deaths from cancer of the mouth and pharynx in shoemakers/shoehands, compared with 1.9 expected, i.e., a ratio of 2.6.

In a general survey of the occupations of cancer patients undertaken between 1956-1965 at the Roswell Park Memorial Institute in New York State as a hypothesis-generating study, case-control analyses were performed for patients diagnosed with oral and pharyngeal cancer and for controls diagnosed with non-neoplastic diseases. Eight male patients had been employed as shoemakers or shoe repairers, resulting in a risk relative to that of clerical workers of 3.6 ($P < 0.05$). The relative risk was 3.0 among those employed 5 or more years (8 cases). The relative risk did not change substantially when smoking habits were taken into consideration (Decouflé *et al.*, 1977; Decouflé, 1979).

5. SUMMARY OF DATA AND EVALUATION

5.1 Summary of data

The incidence rates of nasal cancers in workers engaged in boot and shoe manufacture in Northamptonshire, UK, in the 1960s were more than ten times greater than those of the general population. The relative risks were in the order of 35-fold for adenocarcinomas and 4 for squamous-cell carcinomas. A study in Florence has confirmed the association between shoemaking and nasal adenocarcinoma. This is also supported by a number of case reports from other countries.

A UK case-control study (in which the occupational histories of patients with nasal adenocarcinomas were compared with those of patients with other nasal cancers) indicated a relative risk of about 8 associated with work in the leather industry. A substantial proportion of the cases had been engaged in shoe production or repair. In the Northamptonshire study, the elevated risk was confined almost entirely to workers in the preparation and finishing departments: work in these areas entailed cutting, trimming and sanding, which were the dustiest operations.

A substantial proportion of the nasal cancer patients described in the study in Florence were engaged in trimming.

No observations on laryngeal cancer specifically related to boot and shoe manufacturers were available. In a large, multi-tumour-site case-control survey in New York State, the relative risk for development of laryngeal cancer associated with employment for more than five years in the 'leather industry' was 5.5 (based on six cases).

In England and Wales in 1951, SMRs for lung cancer in factory and non-factory-employed boot and shoemakers were 73 and 158, respectively ($P < 0.05$ for both); in 1961, the SMR for all shoemakers was 154 ($P < 0.05$). SMRs for lung cancer in footwear workers in the US and for shoemakers or repairers and leatherworkers in Washington State were slightly but not significantly elevated. In a cross-sectional study in Los Angeles in 1972-1973, the risk ratio for shoe repairers was 2.33 ($P < 0.05$, based on 7 cases).

None of these studies took smoking habits into consideration.

Increased risks of bladder cancer were found in death certificate surveys in The Netherlands in the 1930s (PMR = 170 for shoemakers) and in the US in 1950 (SMR = 288, based on 9 cases, for shoemakers and repairers). No increases were seen in the UK or in Washington State more recently.

An association between work in the leather industry and bladder cancer is supported by three (all in the US) of four case-control studies, with relative risks in the order of 2-6. In two of the studies, no distinction was made between shoemakers and other leather workers. In one of these, 8 of 16 cases among leather workers had worked in the same shoe-manufacturing company, which also included a leather tannery. In a third study, with equal numbers of cases and controls, there were seven shoe repairers and one shoemaker among the cases, and one shoe repairer and two shoemakers among the controls.

SMRs for leukaemia in England and Wales in 1951 and in 1961 and the PMR in Washington State ranged between 131 and 186, all based on 7 to 8 deaths.

Series of cases of benzene haemopathies[1] among shoemakers have been described in Italy and in Turkey. Erythroleukaemia was particularly frequent in these groups. Benzene was a constituent of the adhesives, and benzene levels were measured in some of the shoe factories in which leukaemia patients had worked. A study in Sweden showed 21 observed cases of leukaemia *versus* 13.5 expected. The association with benzene is further supported by a report suggesting that the occurrence of leukaemia in shoemakers has decreased following the replacement of benzene with petrol.

The PMR for lymphomas among shoemakers and repairers in Washington State was 40 (based on 2 deaths). In a large multi-tumour-site case control study in New York State, the relative risk for workers in the leather industry was 3.4 in men (based on 7 cases, $P < 0.05$) and 2.6 in women (based on 8 cases, $P < 0.05$).

The PMR for cancer of the oral cavity and pharynx among shoemakers/'shoehands' in The Netherlands in the 1930s was 260 (based on 5 deaths). In a large, multi-tumour-site case-control study in New York State, the relative risk for shoemakers/shoe repairers was 3.6 ($P < 0.05$, based on 8 cases).

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[1] Benzene-associated haemopathies include pancytopenia, erythroleukaemia and leukaemia.

In England and Wales in 1951, SMRs for stomach cancer in factory- and non-factory-employed boot and shoemakers were 122 and 120, respectively; in 1961, the SMR for shoemakers was 106 and that for cutters in the footwear industry 135.

Handling of leather in boot and shoe manufacture may entail exposure to some of the chemicals used in the tanning and finishing processes and to other chemicals for which there is evidence of carcinogenicity in humans and/or experimental animals (see Appendix 5).

5.2 Evaluation

Employment in the boot and shoe industry is causally associated with the development of nasal adenocarcinomas; and relative risks well in excess of 10-fold have been reported in England and in Italy. It is most likely that exposure to leather dust plays a role in the association. There is also evidence that an increased risk may exist for other types of nasal cancers for employment in boot and shoe repairing shops.

There is evidence of an increased risk of bladder cancer associated with employment in the leather industry. Although boot and shoemakers were included in these studies, it is not possible to determine whether the risk relates to them in particular or to other occupational subgroups.

The occurrence of leukaemia and aplastic anaemia among shoemakers exposed to benzene is well documented (see also IARC, 1974).

Hypothesis-generating surveys have suggested associations between boot and shoe manufacture/repair and cancer of the lung, oral cavity and pharynx and stomach. The same surveys have suggested associations between work in the leather industry (occupation not further specified) and cancer of the larynx and lymphoma. Most of these associations were positive. In view of the design of the pertinent studies these findings cannot be evaluated.

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APPENDIX D

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Supplement 7 (Overall Evaluations of Carcinogenicity to Humans: An Updating of IARC Monographs Volumes 1-24) Leather Industries: Boot and Shoe Manufacture and Repair pp. 232-235, 1987

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LEATHER INDUSTRIES: BOOT AND SHOE MANUFACTURE AND REPAIR (Group 1)

Evidence for carcinogenicity to humans (*sufficient*)

Nasal adenocarcinoma has been caused by employment in boot and shoe manufacture and repair. Relative risks well in excess of ten fold have been reported from studies in the boot and shoe manufacturing industry in England and in Italy. There is also evidence that an increased risk exists for other types of nasal cancer[1-3]. A far higher risk of nasal cancer was found for people who worked in the dustiest operations, and for those classified into the category of 'heavy' exposure to leather dust, strongly suggesting a role for exposure to leather dust[2,3]. Thus, in comparison with the 'nonexposed' category, the sex-adjusted standardized odds ratio for the 'uncertain or light exposure' category was 7.5, and for the 'heavy exposure' category, 121.0. A similar, highly significant pattern was noted when only adenocarcinomas were considered. Exposure to solvents or to tobacco smoking could not account for the noted increased risk[3]. A mortality study of over 5000 men known to have been employed in the boot and shoe manufacturing industry in three towns in the UK in 1939 showed a large, significant excess of deaths from nasal cancer (10 observed, 1.9 expected). An observed:expected ratio of 14 was found among workers in the finishing room[4]. The elevated nasal cancer risk was almost totally confined to employees in the preparation and finishing rooms, where most of the dusty operations occurred. It was estimated that the risk to those men was 4.5 relative to that in other operations, and 9.8 relative to that of men resident in the area who had never been employed in the footwear industry[2].

Case reports have also suggested an association between exposure to leather, including during shoe manufacture, and mucinous adenocarcinoma of the nose and ethmoidal cancer in Switzerland and France, respectively[5,6].

One mortality study conducted in London, UK, showed no association between nasal cancer deaths occurring between 1968 and 1978 and occupation in the boot and shoe industry, as recorded on death certificates[7]. A proportionate mortality analysis of 3754 deaths among US shoeworkers revealed no death from nasal cancer, whereas 2.2 were expected on the basis of data for the general population[8]. Similar results were obtained from a study of 2798 deaths between 1954 and 1974 in a shoe and leather industry area in Massachusetts, USA; detailed occupational information was available, however, for only 289 of the deceased[9].

Early death certificate surveys showed an increased risk of bladder cancer among shoemakers and repairers. Later studies provided evidence of an increased risk associated with employment in the leather industry. Although boot and shoemakers were included in these studies, it was not possible to determine whether the risk was related to them in particular[1]. A nonsignificant increased risk for bladder cancer was reported in association with work in the boot and shoe industry in a case-control study based on deaths of male residents in certain London boroughs from 1968-1978. When data for these workers were combined with those for leather workers, the estimated risk became significant[7]. A significant association of leather work (leather or tanning industry, manufacture of leather goods, or shoemaking) with cancer of the lower urinary tract was found in a collaborative case-control study in the USA and the UK, but not in Japan[10]. A statistically significant increase was found among female shoe workers (7 deaths observed and 2.8 expected) in another, independent study in the USA. Male shoeworkers and leather workers showed no excess of bladder cancer in this study[9]. In Sweden, an increase in the incidence of bladder cancer (22 cases observed, 14.5 expected) was reported among shoe factory workers[11]. An elevated risk that was not statistically significant was also found among boot and shoe repairers in a British county. Smoking did not appear to account for the increase[12]. In another study in the UK, in a cohort of 5108 boot and shoe workers, 32 deaths from bladder cancer were observed, with 39.2 expected[13].

A possible increase in risk for kidney cancer among shoe workers was suggested by a study in Sweden[11]. However, a large cohort study among boot and shoe workers in the UK did not support this hypothesis[13]. Three cases of mesothelioma were reported among 3806 deaths in shoe workers[14]; it has further been reported that a female shoemaker (whose husband was also a shoemaker) died of mesothelioma[15].

The occurrence of leukaemia among shoemakers exposed to benzene (see p. 120) has been well documented[1,16], and this association has been supported further by a recent mortality study in one town in the UK[4].

Surveys conducted in the The Netherlands, the UK and the USA have suggested positive associations between boot and shoe manufacture/repair and cancers of the lung, oral cavity and pharynx and stomach[1]. These suggestions were later confirmed by a mortality survey in the USA, which also showed a significant increase in the proportion of deaths due to cancers of the rectum and of the liver and gall-bladder, in people of each sex[8]. Excess mortality from rectal cancer was also found among boot and shoemakers in two towns in the UK; the excess was significant for workers in the lasting and making room, who were probably exposed to solvents, glues and leather dust[4]. Exposure to solvents, dyes or metallic compounds in the footwear industry, among nonfactory shoemakers and repairers and among operatives making leather and leather products, was deemed to be associated with the increased risk of bowel cancer noted in a US study[17]. An increased proportion of cancer of the digestive tract among male shoeworkers was found in another US study; however, it was suggested that factors other than their occupation could have been responsible for the excess noted[9]. In a study of gall-bladder cancer occurring in Sweden between 1961 and 1969, in which information on occupation was drawn from 1960 census data, the incidences of cancers of the gall-bladder and of the biliary tract were found to be significantly elevated among men employed in shoemaking and repair[18]. In view of the exploratory nature and design of these studies, the findings were considered to be inadequate for a definite evaluation.

No indication of a link between Hodgkin's disease and work in 'textile, shoes, leather' industries emerged from investigations in Italy[19].

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LEATHER GOODS MANUFACTURE (Group 3)

Evidence for carcinogenicity to humans (*inadequate*)

A few cases of leukaemia have been reported following exposure to benzene (a known human carcinogen[1]; see p. 120) during the manufacture of leather goods other than boots and shoes. The number of cases of nasal cancer reported is insufficient to make an association with employment in the manufacture of leather goods (other than boots and shoes)[2]. A positive association between bladder cancer and employment in the leather products industry is suggested by a number of studies. A case-control study in West Yorkshire, UK, showed a statistically nonsignificant risk of bladder cancer associated with employment in leather goods production (as well as tanning, and boot and shoe repairing)[3]. Indications of an association with dusty leather occupations (not only shoemaking) came from a similar study in London[4]. In two of three areas in which a collaborative study of environmental risk factors for bladder cancer was conducted, a significant association with employment in 'leather' was found; the term 'leather' comprised the manufacture of leather goods, the leather and tanning industries and shoemaking[5]. Leather goods manufacture was most probably included in the leather exposure found to be statistically significantly associated with bladder cancer in another study in the USA[6]. None of the studies provides sufficient grounds to evaluate the specific role of the production of leather goods in the established association of leather work and cancer risk to humans.

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