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Gen Corp Automotive
Marion, Indiana

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PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer and authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

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Health Hazard Evaluation Report 94–0072–2648
Gen Corp Automotive
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SUMMARY

The National Institute for Occupational Safety and Health (NIOSH) received a request to conduct a health hazard evaluation (HHE) at Gen Corp Automotive in Marion, Indiana, from the United Rubber Workers Union (now part of the United Steel Workers Union), Local 466. The union was concerned about employee exposures in all three departments of the plant, and specifically to nitrosamines, inks, glues, styrene, divinyl benzene, and organic peroxides. An initial site visit was conducted on February 16, 1994, during which several general area (GA) samples were collected, and then a follow–up visit was conducted on May 3–5, 1994, to perform more extensive air sampling and to evaluate the ventilation systems. Both of these site visits included medical interviews, informal conversations with employees, and review of records, Material Safety Data Sheets (MSDSs), and health and safety programs. During these two site visits, high nitrosamine concentrations were measured in the Vehicle Sealing (VS) Department of this plant. Since the total biologically effective dose of nitrosamines received by workers cannot be ascertained solely by air monitoring, on January 25 – February 2, 1995, biological monitoring of DNA adducts in peripheral white blood cells and excised DNA adducts in the urine were used, in combination with air monitoring and a questionnaire that addressed confounding factors and non–occupational nitrosamine exposures, to better estimate exposures and body burdens of nitrosamines.

Eighty-one personal breathing zone (PBZ) nitrosamine samples were collected in the VS area (28 on the second site visit and 53 on the third), and concentrations were as high as 16.34 micrograms per cubic meter ($\mu g/m^3$), 11.44 $\mu g/m^3$ of which was nitrosodimethylamine (NDMA). A salt bath curing process was generating the nitrosamines, and a combination of insufficient local exhaust ventilation (LEV) and exhaust re–entering the work area was contributing to a build–up of nitrosamines. Although there is no numerical occupational exposure limit for nitrosamines in the United States, both NIOSH and the Occupational Safety and Health Administration (OSHA) consider NDMA to be an occupational carcinogen. Also, 64% of the PBZ samples were higher than the German occupational exposure standard for total nitrosamines of 2.5 $\mu g/m^3$. The other air sampling data for volatile organic compounds and aromatic hydrocarbons indicated no overexposures. Many of the biological monitoring results did not show a statistically significant association with the assessed occupational nitrosamine exposures; however, there was a significant positive trend between working in an area with higher airborne nitrosamine concentrations (exposure category) and having detectable O^6–methyldeoxyguanosine (O^6mdG) adducts in peripheral white blood cells. Therefore, a worker in the VS area had a higher probability of having detectable levels of O^6mdG adducts, which have mutagenic potential and have been associated with carcinogenesis. There was also a statistically significant negative correlation between occupational nitrosamine exposure and concentrations of O^6–alkylguanine–DNA alkyltransferase (AGT), an enzyme that repairs the O^6mdG adducts.

Based on the air sampling data, the significant positive trend between exposure category and having detectable concentrations of O^6mdG adducts in peripheral white blood cells, and the negative correlation between nitrosamine exposure and AGT activity, the NIOSH investigator concluded that there is a health hazard from exposures to nitrosamines in this workplace. Recommendations were made to reduce nitrosamine exposures either through elimination of the source by reformulation of the rubber stock or redesign of the curing process, or through properly designed and well–maintained local exhaust ventilation systems. Based on the medical evaluation, the NIOSH Medical Officer concluded that there were no clusters of heart disease, lung disease, or cancers in this workplace, but that there was a significant ergonomics problem. Recommendations were made to improve the proposed Gen Corp Automotive Ergonomics Program.

Keywords: SIC Code 3061 (Molded, Extruded, and Lathe–cut Mechanical Rubber Goods), rubber, rubber vehicle sealing, sheet molding compound, nitrosamines, nitrosodimethylamine (NDMA), nitrosopiperidine (NPIP), nitrosomorpholine (NMOR), nitrosodiethylamine (NDEA), nitrosodibutylamine (NDBA), nitrosodipropylamine (NDPA), nitrosopyrrolidine (NPYR), DNA adducts, N^7–methyldeoxyguanosine, O^6–methyldeoxyguanosine, O^6–alkylguanine–DNA alkyltransferase (AGT), volatile organic compounds (VOCs), isocyanates, methylene diisocyanate (MDI)

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INTRODUCTION

The National Institute for Occupational Safety and Health (NIOSH) received a request to conduct a health hazard evaluation (HHE) at Gen Corp Automotive in Marion, Indiana, from the United Rubber Workers Union (now part of the United Steel Workers Union), Local 466. The union was concerned about employee exposures in all three departments of the Marion plant — the rubber vehicle sealing (VS) area, the mix house, and the liquid composite molding (LCM) area — specifically, exposures to nitrosamines, inks, glues, styrene, divinyl benzene, and organic peroxides. Also, the request reported employee concerns about cancer, heart attacks, breathing difficulties, and chemical sensitivities. An initial site visit was conducted on February 16, 1994, during which several general area (GA) samples were collected and several employees were interviewed. A follow–up visit was conducted on May 3–5, 1994, to perform more extensive air sampling and to evaluate the ventilation systems. Both of these site visits included medical interviews, informal conversations with employees, and review of records, Material Safety Data Sheets (MSDSs), and health and safety programs. Also, an ergonomic evaluation was performed by the NIOSH medical officer, and these results were presented in a letter to management and union representatives on June 28, 1994.

During the first two site visits, high nitrosamine concentrations were measured in the VS area of this plant. These exposures raised a concern because most nitrosamines are considered probable or possible human carcinogens. However, since nitrosamines currently do not have numerical occupational exposure limits in the United States, air sampling results cannot be compared to any enforceable standards and therefore may not provide enough incentive for changing a work process to reduce exposures. Also, the total biologically effective dose of nitrosamines received by workers cannot be ascertained solely by air monitoring. Hence, on January 25 – February 2, 1995, biological monitoring of DNA adducts in peripheral white blood cells and of excised DNA adducts in the urine were used, in combination with air monitoring and a questionnaire that addressed confounding factors for nitrosamine exposure, to better estimate exposures and body burdens of nitrosamines.

Thus, this HHE consisted of two major evaluations. The first was the plant–wide exposure survey and medical evaluation that was conducted during the first two site visits. The second was the DNA adduct study that was prompted by the documentation of high nitrosamine exposures in the VS area. Both of these evaluations are described in this report, which has been divided into four sections. Part I provides information about the HHE request, the plant processes, and the evaluation criteria used when evaluating exposures at this plant. Part II provides the details and results of the first two site visits. Part III provides the background information necessary to understand the DNA–adduct study, and the methods and results of the study. Part IV provides the overall conclusions and recommendations of this HHE. Appendix A contains all the tables and figures for this report, and Appendix B contains all the raw data for the DNA–adduct study. Appendices C–F are copies of the various interim reports and letters that are associated with this HHE.

GENERAL BACKGROUND

At the time of the NIOSH site visits, the Gen Corp Automotive plant in Marion, Indiana, had three departments. The VS process (Department 137) began operation in 1979–1980 producing strips of rubber vehicle sealing. It employed approximately 400 workers over three shifts, and the major exposure concerns in this area were nitrosamines and volatile organic compounds (VOCs). The mix house (Department 335) began operation in 1974–1975 producing sheet molding compound for use in forming automotive parts and siding. It was

a relatively small department, employing only 20–30 employees over three shifts, and the major exposure concerns were VOCs and fiberglass. The Liquid Composite Molding (LCM) area (Department 324) was a prototype process started in 1992 that produced bumper beams. It only employed 7–10 workers over one 8–hour shift, and the major exposure concern here was isocyanates. All three areas were remote from one another, and the plant had several open areas where a discontinued process had operated.

In 1990, the Indiana Occupational Safety and Health Administration (IOSHA) cited Gen Corp Automotive for nitrosamine exposures. This citation was based on the general duty clause and referenced the German occupational exposure limits for nitrosamines, but Gen Corp contested the citation and IOSHA rescinded it.

Process Descriptions

Rubber Vehicle Sealing

Department 137, the largest area of the plant, produced rubber vehicle sealing (VS). Approximately 400 workers were employed over three shifts, five days a week, working along the extruder lines and at various finishing machines. The eight production lines made continuous strands of rubber vehicle sealing, which were then molded and cut to specific profiles to fit the order. The process began with wire and polyester mesh (wire warfs) being formed into a channel while dense rubber was extruded around it and sponge rubber was extruded on top of it to form the bulb portion of the vehicle sealing. The 4–inch wide rubber stock was received from the Gen Corp facility in Wabash, Indiana, and was stored in temperature controlled rooms.

Following extrusion, the rubber sealing was cured by mechanically pulling it through an enclosed salt bath tunnel. Molten salt (sodium nitrate, sodium nitrite, and potassium nitrate in lines one through seven, and lithium nitrate, potassium nitrate and sodium nitrate in line eight) flowed through a slitted trough along the top inside of the tunnel and showered the rubber as it was pulled through the enclosure. The entire salt bath was lined with access doors which were all opened during start–up for 10 to 20 minutes. Throughout most of the work day these doors remained closed, except when each door was repeatedly opened and slammed shut to knock off the accumulated salt. This procedure occurred about two times a day, depending on the individual operator.

Each salt bath had four ducted exhausts — zone A at the beginning and zone D at the end. All the exhausts exited the building through roof–top stacks that were all approximately 6 feet high on the first NIOSH site visit. All the D zone stacks had been raised to 16 feet by the time of the second visit to try to alleviate some of the problem of exhaust re–entering the work space through the air–handling units and the open doors of the building.

As the rubber exited the salt baths, it was cleaned with steam and high pressure air to remove the salt and then cooled in a water drum. Next, small holes were drilled into the bulb portion (sponge rubber) at specified intervals. Also, the date, time, and specification number were printed on the rubber with ink by a video jet marking process. On some lines the rubber sealing then passed through a preheating oven, a ventilated silicone spray booth, and an infrared curing oven. Toluene was the carrier solvent for the silicone. This mixture was combined and stored in the sponge rubber storage room. Other lines had mastic injection, a process in which a starch and clay mixture was injected into the groove of some parts for ensuring a tight liquid seal.

At the end of the line, the rubber was cut into the specified lengths and either plugged and boxed for shipping to the customer or processed further at this facility. To plug the ends, a cylindrical rubber plug was manually dipped into plug cement and inserted into the end of the rubber sealing. Approximately 60% of the rubber sealing was shipped to customers as it came off the lines, and 40% was further processed before shipping. The rubber lines operated 24 hours a day, but the finishing procedures were usually performed only during the first shift.

The finishing processes included three types of joining procedures as well as adding tape and

double–sided adhesive strips, cutting notches in the rubber, and spraying the new joints and notches with silicone. The three joining procedures were: (1) transfer molding, where small rubber pellets and a press were used to form a joint or molded details; (2) cold splicing, where glue and an accelerator were used to join two ends in a press; and (3) hot splicing, where glue and heat were used to join two ends in a press. The new notches and joints were then sprayed with silicone in a ventilated spray booth. Any open wire ends that stuck out of the rubber sealing were then covered with a black adhesive and Freon™ accelerator to prevent rusting.

Some of the finishing processes had local exhaust ventilation (LEV), such as the hot presses. The A–, B–, and C–pillar processes did not have LEV, nor did the tape machine or the processes at the end of the salt bath lines, in the middle of the VS area. The VS area had 11 make–up air units, three of which were added after 1989 when a test and balance ventilation survey revealed only 90,000 cubic feet per minute (cfm) of make–up air and over 300,000 cfm of exhausted air. A fourth make–up air unit was added in 1992.

Mix House

Department 335 had one process line that produced sheet molding compound (SMC), a fiberglass product used to make automotive siding. Resins, solvents, and other additives were mixed and spread onto a nylon sheet. Chopped fiberglass was then spread on top and covered by another layer of resin mixture and a top nylon sheet. Finally, the SMC was compressed by a series of rollers, the nylon edges were folded over the sides

of the SMC, and it was folded into boxes to cure for four to five days before shipping.

Liquid Composite Molding

Fibrous glass–reinforced plastic bumper beams for the Chevrolet Corvette were produced in Department 324. Bumper beams were manufactured in two areas within this department, depending on the type of injection molding press used in the process. The Cannon press area made bumper beams for recent model Corvettes; the Klockner press made an older bumper beam style. The process was the same regardless of the press or bumper beam type.

Woven fibrous glass roving was cut into rectangular sheets with approximate dimensions of 5 feet by 2 feet. Several of these sheets were stacked into a mat and heated in an enclosed infrared system. The mat was conveyed to the preform area and inserted into a heated press, which formed the mat into the shape of the bumper beam. After a cold press, the formed bumper beam was placed on a bench, and the excess fibrous glass mat was manually removed with scissors.

The mold on the Cannon press and Klockner press was sprayed with a mold–release agent composed primarily of VM & P naphtha. A formed bumper beam was placed on the mold, and the press was engaged for approximately 5 minutes. During this time period, a two–component polyurethane coating system was injected into the mold. The material safety data sheets for this system listed the ingredients of component A as being 40–50% 4,4'–diphenylmethane diisocyanate, and 50–60% polymethylene polyphenyl isocyanate, and component B as being 29% polyether polyol, 19% diethylene glycol, and the balance a proprietary polyol/glycol blend. When the press released, the polyurethane coating had set and hardened. The worker removed the bumper beam from the press, trimmed the plastic flash, and placed the bumper beam on a cooling rack. After cooling, the bumper beam was placed in a water jet drill to remove excess plastic and drill large holes. The final step was the drill station, where small holes were drilled with handheld power drills, and the beam's black finish was inspected and touched–up with a spray can of black paint.

EVALUATION CRITERIA

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH field staff employ environmental evaluation criteria for the assessment of a number of chemical and physical agents. These criteria are intended to suggest levels of exposure to which most workers may be exposed up to 10 hours per day, 40 hours per week for a working lifetime without experiencing adverse health effects. It is, however, important to note that not all workers will be protected from adverse health effects even though their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a pre-existing medical condition, and/or a hypersensitivity (allergy). In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the worker to produce health effects even if the occupational exposures are controlled at the level set by the criterion. These combined effects are often not considered in the evaluation criteria. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus potentially increase the overall exposure. Finally, evaluation criteria may change over the years as new information on the toxic effects of an agent become available.

The primary sources of environmental evaluation criteria for the workplace are: (1) NIOSH Recommended Exposure Limits (RELs),[1] (2) the American Conference of Governmental Industrial Hygienists' (ACGIH) Threshold Limit Values (TLVs®),[2] and (3) the U.S. Department of Labor, OSHA Permissible Exposure Limits (PELs).[3] In July 1992, the 11th Circuit Court of Appeals vacated the 1989 OSHA PEL Air Contaminants Standard. OSHA is currently enforcing the 1971 standards which are listed as transitional values in the current Code of Federal Regulations; however, some states operating their own OSHA approved job safety and health programs continue to enforce the 1989 limits. NIOSH encourages employers to follow the 1989 OSHA limits, the NIOSH RELs, the ACGIH TLVs, or whichever are the more protective criterion. The OSHA PELs reflect the feasibility of controlling exposures in various industries where the agents are used, whereas NIOSH RELs are based primarily on concerns relating to the prevention of occupational disease. It should be noted when reviewing this report that employers are legally required to meet those levels specified by an OSHA standard and that the OSHA PELs included in this report reflect the 1971 values.

A time-weighted average (TWA) exposure refers to the average airborne concentration of a substance during a normal 8-to–10-hour workday. Some substances have recommended short-term exposure limits (STEL) or ceiling limits (CL) which are intended to supplement the TWA where there are recognized toxic effects from higher exposures over the short-term.

Nitrosamines

Nitrosamines are compounds characterized by the –N–N=O functional group. They result from the combination of primary, secondary, or tertiary amines with nitrite. These reactions can occur in the laboratory; in various food, household, or industrial products; in industrial processes; and *in vivo* (in the body). Because of the variety of amines and reaction conditions possible, there are hundreds of nitrosamines; and because of the large number of exposure sources, including formation in the body, there is a complicated matrix of total nitrosamine exposure. Occupational exposures have been observed in rubber industries, leather tanning industries, metal–working industries, chemical industries, mining, pesticide production, detergent production, and fish processing factories.

Most nitrosamines are suspected to be human carcinogens, but direct causal associations have not yet been proven. Cancer is believed to be a multistage process, beginning with (1) *exposure* to a carcinogen or procarcinogen and followed by (2) *initiation* of a cell to a genetically altered cell by damage to the deoxyribonucleic acid (DNA); (3) *promotion* of the altered cell to a pre–neoplastic lesion; (4) *conversion* of the pre–neoplastic lesion to a malignant tumor through a genetic change; and finally (5) *progression* of the tumor to clinical cancer. Exposure to a carcinogen must result in a

genetic change in order to initiate a cell; likewise, there must also be a genetic change for a pre–neoplastic lesion to convert into a malignant tumor.[4] These genetic changes can occur from spontaneous mutations, and they can also occur with DNA adduct formation from exposure to carcinogens that are initiators, promoters, or both. (A DNA adduct is a compound that attaches to the DNA and, if not removed before replication, can cause a mutation in the DNA.) These genetic changes also must occur in certain chromosomal locations in order to cause the next step in carcinogenicity. Mutations in some of these chromosomal locations have been identified, such as activation of proto–oncogenes or inactivation of tumor suppressor genes, but these and other processes are still being researched.[4]

There are many factors that prevent every exposure to a carcinogen from resulting in clinical cancer. Genetic predisposition—inheritance of certain genetic mutations, variations in activity of metabolizing enzymes and DNA repair enzymes, variations in immunity and immune cell enzymes—plays an important role in the development or lack of development of cancers. Variations in lifestyle and overall health can also play a part as these may affect immune function and intracellular repair processes.

The suspected mechanism of carcinogenesis of nitrosamines is that nitrosamines, from exogenous or endogenous sources, are metabolized into reactive intermediates which can then covalently bind to macromolecules, including DNA. If the DNA adducts are not repaired before replication, a mutation or error in the DNA can result; and, if that mutation is in certain areas of the genome, the cell could undergo the second and third stages of carcinogenesis—initiation and promotion. If there was a second genetic change in the right place, conversion to a malignant tumor could result.

Although a causal association between nitrosamine exposure and human cancer has not yet been firmly established, there is circumstantial evidence that nitrosamines cause cancer in humans. In 1956, Magee and Barnes demonstrated the carcinogenic potential of nitrosodimethylamine (NDMA) in rats.[5] Since then, nitrosamines have been studied extensively in laboratory animals. Approximately 90% of the 300 tested nitrosamines have shown carcinogenic effects in bioassays and laboratory animals. The animals that have been studied include mammals, birds, fish, and amphibia. Of the approximately 40 animal species tested, none has been resistant. The tumor sites depend on the specific nitrosamine, the species tested, and the route of administration. Nitrosamine effects have been demonstrated in the bladder, bronchi, central nervous system, earduct, esophagus, eyelid, duodenum, forestomach, glandular stomach, hematopoietic system, intestine, jaw, kidney, larynx, nasal cavity, oral cavity, ovary, liver, mammary glands, pancreas, pelvis, peripheral nervous system, pharynx, respiratory tract, skin, testes, trachea, uterus, and vagina.[6] Dose–response studies with rats have shown "no effect levels" corresponding to dietary concentrations of 1 part per million (ppm) NDMA, 1 ppm nitrosodiethylamine (NDEA), and 1 ppm nitrosopyrrolidine (NPYR).[6] These nitrosamines and others appear to be very potent carcinogens.

All of the biochemical, pathological, and experimental data provide little evidence that humans might be resistant to the carcinogenic potential of nitrosamines.[7] Human tissues from the trachea, bronchus (lung), esophagus, colon, pancreatic duct, bladder, and buccal mucosa have been shown to metabolize nitrosamines into DNA–binding compounds.[7] Human liver tissue appears to metabolize nitrosamines with an activity similar to that of rodent liver tissue, and rodents have the acute affects of liver necrosis and cirrhosis that have been observed in humans with high exposures.[7] A few human DNA adduct studies have revealed higher levels of nitrosamine–related DNA adducts in cancer cases than in controls.[8,9] Studies in experimental animals have shown DNA adduct formation similar to that detected in the human studies.[10,11,12]

Only one nitrosamine, NDMA, is regulated in the United States. Both OSHA and NIOSH regulate NDMA as an occupational carcinogen, but neither have an established *numerical* exposure limit.

Der Ausschuβ für Gefahrstoffe (AGS) in Germany has strict regulations for occupational exposures to nitrosamines. In general industry, the total exposure to all nitrosamines may not exceed 1 $\mu g/m^3$. In special cases, such as rubber vulcanization, exposures to all nitrosamines may not exceed 2.5 $\mu g/m^3$. In addition to these regulations, eight nitrosamines are regulated individually—nitrosodimethylamine, nitrosomorpholine, nitrosopiperidine, phenyl-ethylnitrosamine, phenyl–methylnitrosamine, di–N–butylnitrosamine, di-iso-propylnitrosamine, and diethylnitrosamine.

Volatile Organic Compounds

Exposure to organic solvents can occur through inhalation of the vapors and absorption through the skin. Acute effects from exposure to high concentrations of solvents often include anesthesia, central nervous system (CNS) depression, impaired motor function, respiratory arrest, unconsciousness, and death.[13] At lower concentrations, symptoms of dizziness, headaches, fatigue, lightheadedness, weakness, poor concentration, and mucous membrane irritation may occur.[13,14] Chronic effects that have been reported among some workers exposed to organic solvents include peripheral neuropathies, organic affective syndrome, and mild chronic toxic encephalopathy. Organic affective syndrome is characterized by fatigue, memory impairment, irritability, difficulty in concentration, and mild mood disturbance. Mild chronic toxic encephalopathy is manifested by sustained personality or mood changes such as emotional instability, and diminished impulse control, motivation, and learning capacity. The extent to which chronic neurotoxicity is reversible remains to be established.[13] The relevant evaluation criteria for the organic solvents that were detected and characterized at the facility are listed in Table 1 (see Appendix A).

Methylene Diisocyanate (MDI)

The unique feature common to all diisocyanates is that they consist of two -N=C=O (isocyanate) functional groups attached to an aromatic or aliphatic parent compound. Because of the highly unsaturated nature of the isocyanate functional group, the diisocyanates readily react with compounds containing active hydrogen atoms (nucleophiles). Thus, the diisocyanates readily react with water (humidity), alcohols, amines, etc.; the diisocyanates also react with themselves to form either dimers or trimers. When a diisocyanate species reacts with a primary, secondary, or tertiary alcohol, a carbamate (–NHCOO–) group is formed which is commonly referred to as a urethane. Reactions involving a diisocyanate species and a polyol result in the formation of cross–linked polymers; *i.e.* polyurethanes. Hence, they are widely used in surface coatings, polyurethane foams, adhesives, resins, elastomers, binders, sealants, etc. Diisocyanates are usually referred to by their specific abbreviation; *e.g.*, TDI for 2,4– and 2,6–toluene diisocyanate, HDI for 1,6–hexamethylene diisocyanate, MDI for 4,4'–diphenylmethane diisocyanate, NDI for 1,5–naphthalene diisocyanate, etc. Commercial–grade TDI is an 80:20 mixture of the 2,4– and 2,6– isomers of TDI, respectively.

In general, the type of exposures encountered during the use of diisocyanates in the workplace are related to the vapor pressures of the individual compounds. The lower molecular weight diisocyanates tend to volatilize at room temperature, creating a vapor inhalation hazard. Conversely, the higher molecular weight diisocyanates do not readily volatilize at ambient temperatures, but are still an inhalation hazard if aerosolized or heated in the work environment. The latter is very important since most reactions involving diisocyanates are exothermic in nature, thus providing the heat for volatilization. In an attempt to reduce the vapor hazards associated with the lower molecular weight diisocyanates, prepolymer and oligomer forms of these monomers were developed, and have replaced the monomers in many product formulations. Many product formulations that contain MDI actually

contain a combination of MDI monomer and MDI oligomer (polymethylene polyphenyl isocyanate). Experience with both the monomeric and oligomeric forms of diisocyanates has shown that the occurrence of health effects is dependent on exposure, not molecular weight.

Exposure to the diisocyanates produces irritation to the skin, mucous membranes, eyes, and respiratory tract. High concentrations may result in chemical bronchitis, chest tightness, nocturnal dyspnea, pulmonary edema, and death.[14,15] The most common adverse health outcome associated with diisocyanate exposure is increased airway obstruction (asthma), and to a lesser extent dermal sensitization and hypersensitivity pneumonitis.[14,16,17]

Whenever there is a potential for a hazardous exposure to diisocyanates, traditional industrial hygiene practice dictates that the following hierarchy of controls, in decreasing order of desirability and effectiveness, be implemented to protect worker health:

1. Elimination of the toxic substance from the workplace.
2. Substitution of the toxic substance with a less toxic substance.

3. Installation of engineering controls designed to reduce exposure.
4. Use of administrative controls to reduce exposure.
5. Use of personal protective equipment to reduce exposure.

In many instances, it is not possible to eliminate or substitute a diisocyanate from a production process without altering the integrity of the desired product. Thus, most strategies for reducing diisocyanate exposure center on the use of engineering controls and personal protective equipment. Local exhaust ventilation and/or process isolation are commonly used controls for diisocyanate exposure reduction. Personal protective equipment should only be used when engineering controls are not feasible, in the interim when engineering controls are being installed or repaired, or when engineering controls have not sufficiently reduced exposures. NIOSH recommends that whenever there is a potential for exposure to diisocyanates, including concentrations below the NIOSH recommended exposure level (0.005 ppm TWA and 0.020 ppm CL for MDI), that the employer provide the worker with supplied–air respiratory protection.[15] Air–purifying respirators are not appropriate; diisocyanates have poor odor warning properties. Personal protective equipment should also be used to prevent skin and eye contact with diisocyanates.

NIOSH recommends both preplacement and periodic medical surveillance programs for all workers potentially exposed to diisocyanates.[15] The preplacement examinations should consist of detailed medical and work histories with emphasis on pre–existing respiratory and/or allergic conditions, a physical examination that centers on the respiratory tract, a baseline pulmonary function test that measures FEV_1 and FVC, and a judgement on the worker's ability to wear a supplied–air respirator. Workers should be provided with annual examinations which update the medical and work histories, and measure the worker's FEV_1 and FVC. NIOSH also recommends that employers conduct exposure monitoring campaigns every 6 months.[15] Workers' exposure should be determined for each operation in each work area, and should also be measured whenever there are changes in the process or engineering controls. The only effective control for workers with diisocyanate–induced asthma or HP is cessation of all diisocyanate exposure. This can be accomplished by removing the worker from the work environment where diisocyanate exposure occurs, or by providing the worker with supplied–air respiratory protection.

INDUSTRIAL HYGIENE METHODS

Rubber Vehicle Sealing Department

Nitrosamines and hydrocarbons were evaluated in the VS area. During the first site visit, three sets of duplicate samples were collected along lines five and six and analyzed for nitrosamines. These general area (GA) air samples were collected over a four–hour period using Gillian® high–flow air pumps at a flowrate of 2 liters per minute (l/min). Since the analytical method for nitrosamine analysis can vary, one of each duplicate set was analyzed in the NIOSH laboratory and one was sent to a contract laboratory. The outside laboratory, like most laboratories, used gas chromatography (GC) and thermal energy analysis (TEA) for nitrosamine analysis. Identification of specific nitrosamines by TEA depends on two events. First, the chemical bond between two nitrogen atoms (N–NO) of the N-nitroso compound is thermally broken in the TEA pyrolyzer, resulting in the formation of a nitrosyl radical (NO) and subsequent detection by TEA. Second, the GC retention time of the analyte occurs at the same retention time as the standard. Unfortunately, other N–nitroso compounds can elute at retention times very close to those of the nitrosamine compounds being measured and the chromatographic peaks may not be separated. For the same reason, a nitrosamine compound that elutes at a similar retention time as a nitrosamine standard may be mistakenly identified as that nitrosamine if the retention times are too close. The NIOSH method used a capillary column instead of a packed column for the analysis — a process that better separates the elution peaks. Also, a high–resolution mass spectrometer (MS) operated in the selected–ion–monitoring (SIM) mode was used to confirm the identity of any compound that eluted at the same retention time as the nitrosamine standards by monitoring its molecular ion. In this way, the chromatographic peak is confirmed as the nitrosamine compound of interest.

The NIOSH method was chosen to do the future analyses because the NIOSH analysis identified and confirmed the presence of nitrosodiethylamine (NDEA) on two samples that the outside laboratory did not. Also, the NIOSH laboratory did not detect nitrosodipropylamine (NDPA) on three samples that the outside laboratory did. The NIOSH laboratory showed that the retention time for NDPA is 6:31 and that the sample peak eluted at 6:39. Peaks eluting this close could not be separated using a packed column, which was used by the outside laboratory, but could be separated by a capillary column, which was used by NIOSH. Finally, the NIOSH analysis detected two chromatographic peaks near the retention time specific for nitrosomorpholine (NMOR), only one of which was NMOR. The outside laboratory recorded higher amounts of NMOR and could have been summing the two peaks because they were not separated using the packed column.

During the second visit, the nitrosamine samples were collected in the same manner as during the first. Over three days, 28 personal breathing zone (PBZ) air samples and 8 GA air samples were collected throughout the entire VS area. In addition, two bulk water samples were collected for nitrosamine analysis—one from the steam bath and one from the cooling drum. All of these samples were analyzed by the NIOSH laboratory.

Thermal desorption tubes were used to collect GA samples in VS during the first site visit. These samples were collected at a flowrate of 50 milliliters per minute (ml/min) using Gillian® low–flow pumps, and then qualitatively analyzed for volatile organic compounds in the NIOSH laboratory. During the second visit, charcoal sorbent tubes were used to collect PBZ samples for toluene, pyridine, limonene, and total hydrocarbon analysis. These analytes were chosen based on the results from the thermal desorption tubes and from a few area samples taken on the second visit. Also, Orbo–90 sorbent tubes were used to collect PBZ methyl ethyl ketone (MEK) samples. The charcoal tube and Orbo tube samples were collected using Gillian® low–flow pumps at a flowrate of 50 ml/min.

Mix House

Hydrocarbon concentrations were measured in the Mix House as in the VS area. During the first visit, thermal desorption tubes were used to collect GA samples; during the second visit, charcoal sorbent tubes were used to collect PBZ samples that were analyzed for styrene, toluene, acetone, and methyl styrene.

Liquid Composite Molding

Hydrocarbon concentrations were measured in the LCM area as in the other two areas—using thermal desorption tubes on the first visit and charcoal tubes for PBZ samples on the second visit. Again, the samples were collected using Gillian® low–flow pumps at a flowrate of 50 ml/min. A bulk sample of the mold release spray was also obtained. The PBZ samples were analyzed for toluene and total hydrocarbons.

Methylene diisocyanate was sampled during the second visit using NIOSH Analytical Method 5522. GA samples were collected with midget impingers and Gillian® high–flow air pumps at a flowrate of 2 l/min.

INDUSTRIAL HYGIENE RESULTS AND DISCUSSION

Rubber Vehicle Sealing

Nitrosamines

During the first site visit, three GA samples were collected and analyzed for nitrosamines in the VS area. Sample 1 was collected by the drill press on line 5; sample 2 was collected just past the infrared oven on line 6; and sample 3 was collected midway along the salt bath on line 6. All had detectable amounts of nitrosodimethylamine (NDMA), nitrosopiperidine (NPIP), and nitrosomorpholine (NMOR). Samples 1 and 2 had detectable amounts of nitrosodiethylamine (NDEA); and none of the samples had detectable amounts of nitrosodibutylamine (NDBA), nitrosodipropylamine (NDPA), or nitrosopyrrolidine (NPYR). The sampling media for sample 3 had a defective case on the pump side and therefore the numerical concentration is questionable; therefore, the analytical result can only be considered qualitative. The concentrations of NDMA detected on samples 1, 2, and 3 were 37.7 $\mu g/m^3$, 6.3 $\mu g/m^3$, and 0.78 $\mu g/m^3$, respectively. The concentrations of NPIP detected on samples 1, 2, and 3 were 7.6 $\mu g/m^3$, 3.9 $\mu g/m^3$, and 0.28 $\mu g/m^3$, respectively. The concentrations of NMOR detected on samples 1, 2, and 3 were 0.2 $\mu g/m^3$, 0.37 $\mu g/m^3$, and 0.13 $\mu g/m^3$, respectively. The concentrations of NDEA detected on samples 1 and 2 were 0.16 $\mu g/m^3$ and 0.38 $\mu g/m^3$, respectively. All of these sample results are time–weighted averages and each sample was collected over approximately four hours.

The GA samples suggested that volatile nitrosamines were present in this department. Thus, on the second site visit, PBZ and GA samples were collected for nitrosamines on all three days of the site visit. The sampling results are displayed in Tables 2, 3, and 4, located at the end of this report (see Appendix A). All of the 28 PBZ samples had detectable concentrations of NDMA, NDEA, NPIP, and NMOR; 27 of the 28 samples had detectable concentrations of NPYR. None of the PBZ or GA samples had detectable concentrations of NDPA or NDBA. Five of the eight GA samples had detectable concentrations of NDMA, NDEA, NPIP, NPYR, and NMOR. The other three had detectable concentrations of NDMA, NPIP, NPYR, and NMOR, but no NDEA. Those three samples were taken at the drill press area of lines 5, 6, and 8 on May 5, 1994.

Many of the PBZ measurements were higher than the German occupational standard of 2.5 $\mu g/m^3$. The highest PBZ exposures were collected on salt bath line operators, assistant operators, and coil packers. The PBZ exposures were highest for NDMA, ranging from 0.47 $\mu g/m^3$ to 11.44 $\mu g/m^3$. Next highest was NPIP, ranging from 0.20 $\mu g/m^3$ to 4.39 $\mu g/m^3$. Nitrosamine concentrations from the GA samples collected at the drill presses on different lines were very high, ranging from 2.29 $\mu g/m^3$ NDMA at line 6 on May 5, 1994, to 88.47 $\mu g/m^3$ NDMA at line 3 on May 5, 1994.

A GA sample was collected inside the smoking break room on May 4, 1994, and in the non–smoking break room on May 5, 1994. These samples both had detectable concentrations of NDMA, NDEA, NPIP, NPYR, and NMOR. A concentration of 4.17 $\mu g/m^3$ of NDMA was detected in the smoking break room; and a concentration of 10.37 $\mu g/m^3$ of NDMA was detected in the non–smoking break room. Since cigarette smoke contains nitrosamines, their presence was expected in the smoking room. A probable cause of the high amount in the non–smoking room was that on May 5, 1994, the wind was out of the west/southwest. This wind direction blew the exhaust from the salt bath lines in the direction of the rooftop air handling units (AHUs) that served the offices and break rooms in the VS area. Specifically, the exhaust from line 8, zone D was observed flowing directly into the AHUs.

Two bulk water samples were collected and analyzed for nitrosamines — one from the bottom of the steam bath that cleans the rubber as it exits the salt bath, and the other from the cooling drum. Neither bulk sample contained detectable amounts of nitrosamines — less than 0.02 μg per gram of water.

Volatile Organic Compounds

Samples were collected and analyzed for the following volatile organic compounds in the VS area: 6 samples were analyzed for pyridine; 18 for methyl ethyl ketone (MEK); 2 were qualitatively analyzed for aromatic hydrocarbons; and then 54 were quantitatively analyzed for toluene, limonene, and total hydrocarbons (n–decane standard) based on the 2 qualitative analyses. No samples had detectable amounts of MEK, pyridine, or limonene. Four of 54 samples analyzed for total hydrocarbons (as n–decane) had detectable amounts of hydrocarbons, but they were not quantifiable. The other 50 samples did not have detectable amounts of total hydrocarbons. Toluene was detected on 20 of the 54 samples. However, only seven were quantifiable and had concentrations less than 2 ppm, well below any applicable occupational exposure limits.

Ventilation

Exhaust re–entering the building appeared to be a problem in the VS offices and break areas, and also in the entire VS area. When the winds were from the west/southwest, exhaust flowed into the AHUs that supplied the VS offices and break areas (as was observed on May 5, 1994). When the winds were from the north, the exhaust was blown into the courtyard between the VS building and the empty warehouse. There were two AHUs in this courtyard that supplied make–up air to the VS area. Also, there was a large garage door on the side of the VS building that opened up to this courtyard. Exhaust was observed flowing into the AHUs and into the garage door opening on May 4, 1994. Similarly, when the wind was from the south, exhaust was blown to the other side of the VS building where there was a large water tank approximately 20 feet away from the building. Exhaust became trapped in eddies between the water tank and the building and was observed flowing into the make–up air AHU in this area on February 16, 1994.

Inside the VS building, some of the local exhaust ventilation (LEV) was not working properly. In some cases the exhaust was overpowered by floor fans or make–up air currents, such as along line 8 at the UV ink spray jet. The LEV along the salt bath lines worked well in some areas, but not others. Some local exhaust fans that were not working included: line 7, zone D on May 3, 1994; and line 3, zone A, line 7, zone D, and line 8, zone D on May 4, 1994. In zones where the LEV fans were not working, emissions could be seen flowing out of the salt baths.

Among the various finishing operations, only some had LEV. The hot presses at the end of the salt bath lines and MM–12 area did not have LEV, nor did the A–pillar, B–pillar, and C–pillar presses. The silicone spray booths and the hot presses in the southeast corner of the VS area did have LEV.

Mix House

PBZ and GA samples were only collected in the mix house on May 3 and May 4, 1994. Based on two GA samples collected and analyzed qualitatively for aromatic hydrocarbons, the other air samples collected were analyzed quantitatively for acetone, toluene, styrene, and methylstyrene isomers. Acetone was detected on all 16 PBZ samples and the one GA sample, ranging from 3.1 ppm to 43.2 ppm, well below the applicable exposure limits. Styrene was also detected on all of the samples, at concentrations ranging from less than 4.0 ppm to 19.3 ppm, also well below the applicable standards. Methyl styrene isomers were detected on only nine of the samples, but in amounts too small to quantify (between 0.05 ppm and 4.0 ppm). Toluene was not detected on any of the quantitated samples (minimal detectable concentrations ranged from 0.04 ppm to 0.06 ppm).

When silicate glass beads were used for the low–density formulations, there was no LEV or containment system to reduce the amount of airborne particulates. The process did not appear excessively dusty when observed during the site visit, but there was a worker whose job it was to agitate the beads as they were sucked up into the A–mix bin. This worker wore a respirator by personal choice, but was wearing organic vapor cartridges and not dust/mist or high efficiency particulate air (HEPA) filter cartridges. Any employee issued a respirator, for voluntary use or not, must be part of the respiratory protection program, which involves a medical determination that the employee is physically able to wear a respirator, a fit test, and proper training on the use and maintenance of respirators. The worker that wore the respirator on May 4, 1994, clearly did not have the proper training.

Liquid Composite Molding

GA air samples were collected and analyzed for MDI monomer and oligomer, and concentrations were all below detectable amounts. One GA air sample was qualitatively analyzed for aromatic hydrocarbons and based on the results, 11 PBZ air samples were analyzed for toluene and total hydrocarbons. The total hydrocarbon analysis was performed using a bulk sample of the mold release used in the process as the standard. Nine of the 11 samples had detectable amounts of toluene, but the amounts were very low. Six of those nine were below the minimal quantifiable concentration, and the other three had concentrations below 0.2 ppm, well below any applicable standards. The total hydrocarbon amounts were also quite low, most being below the minimal quantifiable concentrations.

MEDICAL EVALUATION METHODS

At the initial site visit, the NIOSH medical officer conducted interviews with employees in the VS Department and the Mix House to determine the types of concerns employees had about exposures and their health. The medical officer initially chose the interviewees randomly, but, for practical reasons, was influenced by convenience and the desire of some non–selected employees to be interviewed. VS employees selected for interviews included 2 of the 8 scheduled extruder operators, 6 of the 21 scheduled assistant extruder operators, and 3 of the 29 scheduled molding press operators. Four of the six scheduled Mix House employees were also interviewed.

The union requesters for this NIOSH health hazard evaluation expressed concern about the number of employees who had developed heart disease, lung disease, or cancer. They provided NIOSH with a list of 65 current and former employees reported to have developed these chronic illnesses. Gen Corp provided NIOSH with insurance records for 55 of the 65 listed employees, but the insurance records did not include information about department and job titles. The NIOSH medical officer examined the information to verify the reported diagnoses.

The NIOSH medical officer examined the OSHA Logs and Summaries of Occupational Injuries and Illnesses (Form 200) from January 1989 through April 1994 to look for repetitive trauma and carpal tunnel cases because during the NIOSH interviews, employees had reported surgical treatment for many of these conditions. The Medical Department confirmed that many had undergone surgical treatment. Because many of these affected employees were not available for interview at the time of the site visit, a questionnaire survey was distributed by mail to 26 finishing area employees with repetitive trauma or carpal tunnel illnesses recorded on the OSHA 200 logs from January 1992 through April 1994. Questions included type of treatment, effectiveness of treatment, workplace changes, effectiveness of workplace changes, and ergonomic training.

MEDICAL RESULTS, DISCUSSION, AND CONCLUSIONS

Evaluation of Cancer, Lung Disease, and Heart Problems

Although most of the 11 interviewed VS employees attributed health effects to workplace exposures, the exposures and effects varied from person to person. Symptoms included nasal congestion, sore throat, and chest tightness, which the workers attributed to foaming agents; bronchitis and pneumonitis attributed to silicone; skin lesions attributed to lime–away or salt; headache, shortness of breath, and nausea attributed to ultraviolet ink or fumes from the production lines; enlarged liver attributed to hexane; and itching skin attributed to fibrous glass.

In the Mix House, current concerns included styrene and special solvent exposures, which employees associated with headaches, upper respiratory symptoms, and nausea. Some employees also stated that stress and the potential for violence were concerns. However, the biggest concerns raised by interviewed employees were about cancers and heart disease related to past exposures to asbestos and methylene chloride.

Only 31 of the 65 names provided by the union listed information such as date of birth, date of hire, date of termination, reported diagnoses, and Gen Corp departments and job titles. All but 1 of these 31 employees worked in more than one department and in more than one job title over their career at Gen Corp. None of the insurance records included information on departments and job titles. Neither the union list nor the insurance records included employees' smoking history. Except for one employee who worked at GenCorp only briefly, all of the 55 employees with insurance records had worked at GenCorp Automotive for nine or more years. At the time when a diagnosis was first noted on the insurance records, eight or more years had elapsed since the date of hire. Of the 55 employees whose insurance records were reviewed, 39 had diagnoses of cardiovascular diseases (mostly coronary heart disease), 35 had diagnoses of respiratory diseases (mostly chronic obstructive lung disease), and 32 had diagnoses of tumors (21 cancers and 11 benign tumors). The most frequent organ system affected by cancer was kidney or other urinary organ (3). Other cancer sites included lung, prostate, skin, breast, skin, and lymph nodes.

Unfortunately, heart disease, lung disease, and cancers are common in the United States. About one–third of all deaths in the United States are related to coronary heart disease.[18] Risk factors for arteriosclerosis that can lead to ischemic heart disease include elevated serum fats (including cholesterol), high blood pressure, smoking, stress, personality, and lack of exercise.[18] Other contributing factors include diabetes mellitus, family history, and obesity.[18] Chronic obstructive

lung disease is also common. It is the fifth leading cause of death in the United States.[19] Most cases can be attributed to cigarette smoking.

About one in three people will eventually develop cancer and about one of every five deaths is from cancer.[20] Because cancers are so common, they often appear to occur in clusters. Cancers, however, are of different cell types, involve different types of tissues or organs, have different causes, and have different expected outcomes. When these factors are not taken into consideration, the number of cancer cases may seem high, particularly among a small group of people who have something in common, such as working in the same building or department. Sometimes, cancers that occur close together in time and in place (geographically) have a common cause. On the other hand, they might have occurred coincidentally from unrelated causes. Confirming that a cancer "cluster" is work–related depends on confirming the specific cancer cell type (for example, squamous cell carcinoma or adenocarcinoma) and site of origin (for example, lung), then either identifying a potential causative factor (for example, asbestos) or showing a consistent epidemiologic association with a specific job title, occupation, process, or industry. The rate for the specific cancer in "exposed" workers must be higher than the rate for that cancer in comparison populations, such as "unexposed" workers or the population–at–large. To be biologically reasonable, the exposure must have taken place before the diagnosis was made. In addition, sufficient time (latency period) must have passed between the time of exposure and date of diagnosis to allow development and detection of the cancer. Most cancers require a period of 10 to 20 years from time of first exposure to a cancer–causing agent until clinical detection.[21] Because cancer is the second leading cause of death in the United States, determining whether exposures at a workplace could have caused a cancer "cluster" can be difficult, especially when: (1) the cluster includes many types of cancer, (2) the types of cancer are common in the U.S. population, (3) the number of each type of cancer is small, or (4) the association is not biologically reasonable.

Methylene chloride is metabolized to carbon monoxide, which can severely interfere with the delivery of oxygen to body tissues.[22] This was one of the bases for the NIOSH recommendation to limit workplace exposures to methylene chloride.[22] Subsequent studies showed methylene chloride to be carcinogenic in animals.[23] Therefore, NIOSH recommended that methylene chloride be considered a “potential occupational carcinogen,” and recommended that worker exposure be controlled to the lowest feasible limit.[23]

Numerous studies of workers exposed to asbestos have demonstrated an excess of asbestos-related disease, including lung and other cancers. In testimony to OSHA, NIOSH has testified that there is no safe airborne concentration of fibers for any asbestos mineral.[24,25,26] In testimony, NIOSH supported the OSHA proposal to reduce the permissible exposure limit (PEL) for asbestos to 0.1 fibers per cubic centimeter of air (f/cc) for all workers. The current NIOSH recommended exposure limit (REL) for asbestos is 0.1 f/cc.[26] However, even at this concentration, OSHA has estimated that the mortality risk would be 3.4 deaths per 1000 workers for a lifetime of exposure to asbestos.[27] Therefore, NIOSH has urged that the goal be to eliminate exposures to asbestos fibers or, where they cannot be eliminated, to limit them to the lowest feasible concentration.[24,26] NIOSH investigators therefore believe that any detectable concentration of asbestos in the workplace warrants further evaluation and, if necessary, the implementation of measures to reduce exposures. The OSHA PEL for asbestos limits exposure to 0.2 fibers per cubic centimeter (cc) as an 8-hour TWA.[28] OSHA has also established an asbestos excursion limit for the construction industry that restricts worker exposures to 1.0 fiber/cc averaged over a 30-minute exposure period.[29]

Because heart disease, lung disease, and cancers are so common in the U.S. population, it is

difficult to determine the role of workplace exposures in the illnesses of employees at this Gen Corp Automotive plant. It is possible that, if exposed, an individual's health might have been adversely affected by workplace exposures such as asbestos or methylene chloride. In addition, the time period between the date of hire and the date of diagnosis was long enough to explain some cancers. However, such relationships between workplace exposures and health outcomes cannot be established by this investigation. Too many of the other criteria for establishing causal relationships have not been clearly fulfilled. Individual employees worked in different departments or in different job titles. Thus, potentials for workplace exposure changed over time. The departments, the materials used, and the products manufactured also changed over time. For groups of employees, the types of diagnoses were either too common (such as heart disease and lung disease) in the overall United States population or were too varied (such as various cancers) to establish a cluster.

Ergonomic Evaluation

Nine of the eleven interviewed VS employees reported musculoskeletal conditions, which included muscle or joint pain, ganglion cysts, carpal tunnel syndrome, and trigger finger. Two of these employees had been treated surgically. One of these two employees had surgeries for two different repetitive trauma conditions. The nine employees with musculoskeletal conditions attributed their problems to a variety of factors, such as repeating the same motion more than 300 times daily, the amount of force required on buttons to activate presses, pulling rubber, lifting 50–pound salt bags, short stature relative to the work station, and high production goals.

Work–related musculoskeletal conditions in the Liquid Composite Molding area on the OSHA logs included three cases recorded in 1989, three in 1990, three in 1992, and one in 1993. In VS, one case was recorded in 1989, two cases in 1990, and seven in 1991. The numbers of recorded cases increased to 13 in 1992 and 11 in 1993. Two cases were recorded during the first four months of 1994. The affected employees were mostly mold press operators, finishers, and assistant extrusion operators. Approximately two–thirds of the recorded cases involved the wrist. However, elbows, fingers, or shoulders were involved in the other one–third of the recorded cases. The Medical Department reported surgical treatment for approximately 20 recorded cases. Some employees had undergone more than one surgical procedure.

Only 9 (35%) of the 26 employees with recorded repetitive trauma injuries returned completed questionnaires. The nine respondents cannot be said to be representative of all of those who received questionnaires. Seven of them had undergone surgical treatment. Less than half of the nine respondents reported that they had been trained in ergonomics.

At the time of the NIOSH initial site visit, the plant Safety Manager and head of the Medical Department agreed with the NIOSH Medical Officer that the plant had serious, documentable ergonomics problems. Gen Corp had begun to address the problem by making equipment changes. For example, a number of presses had newly installed light–activated switches, replacing buttons that had to be firmly pushed to activate the press. The Safety Manager was also in the process of developing a training program for supervisors. The NIOSH medical officer reviewed the training materials and offered comments and recommendations in a letter dated June 28,1994 (Appendix F). The NIOSH medical officer confirmed that the plant had retained an ergonomics consultant to address problems that required customized solutions.

BACKGROUND FOR THE DNA–ADDUCT STUDY

Nitrosamine Exposure

Nitrosamines result from the combination of primary, secondary, or tertiary amines with nitrite. These reactions can occur in the laboratory; in various food, household, or industrial products; in industrial processes; and *in vivo* (in the body). Because of the variety of amines and reaction conditions possible, there are hundreds of nitrosamines; and because of the large number of exposure sources, including formation *in vivo*, there is a complicated matrix of total nitrosamine exposure.

Nitrosamine exposure to humans, as stated above, can occur from both exogenous (external) and endogenous (internal) sources. Non–occupational exogenous exposures to nitrosamines include tobacco products and tobacco smoke; food; alcohol; cosmetics; prescription and nonprescription drugs; chemotherapy agents; and various household commodities such as dishwashing liquid, surface cleaners, and rubber products.[30] Occupational exposures have been observed in rubber industries, leather tanning industries, metal working industries, chemical industries, mining, pesticide production, detergent production, and fish factories.[30] Endogenous exposure to nitrosamines can occur following the uptake of nitrate and nitrite, and nitrosable amino compounds. Sources of these substances include food, drinking water, fertilizers, pesticides, and medications. Nitrosamine formation has been demonstrated *in vitro* (in the laboratory) and *in vivo* combining nitrate or nitrite with amino compounds under physiologic conditions in the laboratory or administering the reactants to experimental animals.[7,31,32,33] Oshima and Bartsch (1981) developed a non–invasive method to quantitatively estimate endogenous nitrosamine formation in humans using nitrate and proline, which will form nitrosoproline, a noncarcinogenic nitrosamine, 90% of which is excreted in the urine unmetabolized.[34]

Because of all the various sources of nitrosamine exposure, one could only estimate a total exposure by estimating the endogenous exposure and combining that with an estimate of exogenous exposures. In 1985, Choi developed a mathematical model to create indices of nitrate, nitrite, and nitrosamine exposure from both exogenous and endogenous sources.[35] This model can be used to analyze data obtained from questionnaires regarding the diet, tobacco product use, alcoholic beverage consumption, and other exposures. The estimate of endogenous exposure is based on the fact that approximately 5% of the dietary nitrate intake is converted to nitrite in the saliva. (The formation of nitrite in the stomach and intestines in adults is somewhat controversial, and no percentage of nitrite formation has been quantified.) The model also takes into account the formation of a nitrosamine with a nitrite source (NO_2^-) and an amine intake of approximately 4,000 milligrams (mg). Nitrosodimethylamine (NDMA) is used as a representative of all nitrosamines because it is the most extensively studied nitrosamine. In a 900–milliliter (ml) human stomach, the formation of nitrosoproline (NPRO) has been quantified to be:[36]

$$[\mu g\ NPRO] = 0.04865\ [mg\ NO_2^-]^2$$

Since the nitrosation rate of NDMA is 22 times slower than that of NPRO, the conversion constant for NDMA is 0.0022,[35] so that:

$$[\mu g\ NDMA] = 0.0022\ [mg\ NO_2^-]^2$$

In this study, Choi used this model on a group of 210 human control subjects from a case–control study and found the mean per capita daily intake for NDMA from food, tobacco products, and beverages to be (mean ± standard error):

Exogenous nitrate	=	44.31 ± 4.04 mg/day
Exogenous nitrite	=	0.50 ± 0.05 mg/day
Exogenous NDMA	=	1.14 ± 0.25 μg/day
Total nitrite	=	2.71 ± 0.34 mg/day
Total NDMA	=	1.21 ± 0.25 μg/day

Occupational exposures to nitrosamines have been considered to be the highest exposures; but with the elimination of nitrosodiphenylamine (NDPhA), the reduction of nitrogen dioxide levels, and the use of lesser amounts of amine accelerators, occupational exposures have been reduced considerably in the rubber industry.[30] This NIOSH investigation has found, however, that the nitrosamine exposures are still potentially high during certain processes in the rubber industry.

DNA Adducts and DNA Repair Enzyme Related to Nitrosamine Exposure

Nitrosamines are broken down or metabolized by cytochrome P450IIE1 (CYP2E1) into metabolites that can bind to DNA, which results in a DNA adduct, the alkylation at the N or O atoms of the various DNA bases. The gene that codes for CYP2E1 is polymorphic, meaning that it can differ in a population, which is why different people will metabolize nitrosamines at different rates.

Two specific DNA adducts related to nitrosamine exposure that have been studied are N^7–methyldeoxyguanosine (N^7–mdG) and O^6–methyldeoxyguanosine (O^6–mdG). The majority of adducts (70% to 90%) from nitrosamine exposure are N^7–mdG, and these adducts have half–lifes of about 150 hours.[37] The O^6–mdG adducts are more actively removed from DNA and are therefore not as stable. These adducts, however, may have more of a mutagenic potential than the N^7–mdG adducts and may play more of a role in carcinogenesis.[38,39] Both of these adducts can be quantified in peripheral blood cell DNA. Another possible method for assessing formation of these adducts is to quantify them in exfoliated urothelial cells in the urine, or to quantify the amount of excised adducts (adducts that had been attached to DNA but were removed by a repair process and then eliminated) in the urine. If either of these measurements correspond well with the air sampling data or with the results from the analyses of peripheral blood cell DNA, then future analyses may only require collection of urine samples.

An important factor to consider when measuring the concentration of DNA adducts is the activity of the repair enzymes that remove the DNA adducts. O^6–mdG adducts are repaired by O^6–alkylguanine–DNA alkyltransferase (AGT) in a 1:1 stoichiometric irreversible reaction.[40,41,42] There is suspected to be a large interindividual variation of enzyme activity due to genetic differences, and a decreased activity of this repair enzyme could increase the risk of cancer from exposure to nitrosamines. Since the reaction is irreversible, it is also possible for high exposures to nitrosamines to reduce the repair activity by exhausting the supply of the repair enzyme. This was demonstrated in a study of patients treated with methylating chemotherapeutic agents such as procarbazine,[43] and in a study that looked at both health care workers who handle chemotherapeutic agents and tire storage workers.[44] The activity of this repair enzyme can also be quantified in peripheral blood cells.

Objectives of the DNA–Adduct Study

The overall objectives of this study were to assess whether employees in the VS area were experiencing an increased formation of DNA adducts due to occupational exposures and to increase the understanding of the biological effects in humans from nitrosamine exposure.

The primary aims of this part of the study were to answer the following questions:

- Is there a correlation between the occupational exposure to volatile nitrosamine concentrations and the concentration of DNA adducts formed, as measured by either DNA adducts in peripheral blood cells, exfoliated urothelial cells, or excised DNA adducts in the urine?
- Is there a difference between the concentration of nitrosamine–related DNA adducts in an occupationally exposed group and an unexposed

group?

- Is there a correlation between the occupational exposure to volatile nitrosamine concentrations and the level of AGT activity measured in peripheral blood cells?
- Is there a difference between the AGT activity in an occupationally exposed group and an unexposed group?

METHODS FOR THE DNA–ADDUCT STUDY

Study Population

This study was approved by the NIOSH Human Subjects Review Board. Participants were recruited from the Gen Corp Automotive plant in Marion, Indiana, and also from the Toyo Department of the Gen Corp plant in Logansport, Indiana. The exposed group was from the vehicle sealing (VS) department of the Marion plant. Unexposed and low–exposed groups were from the other departments of the Marion plant, and another unexposed group was chosen from the Logansport plant to ensure adequate numbers of unexposed workers. The Logansport plant was chosen for an unexposed control group because no volatile nitrosamines were detected there in the Toyo department, it had a work force similar to the Marion plant, and it was in a similar geographic area.

Eligibility Criteria

Current first–shift workers in the VS department of Gen Corp Automotive in Marion, Indiana, were eligible to participate in this study if they had worked in the VS area for at least six months and were not pregnant. First–shift workers from the other two departments and the office staff at this facility were also eligible to participate in this study as part of an unexposed control group if they had not worked in the VS department, did not routinely spend time in the VS department, had worked at this facility for at least 6 months, and were not pregnant. Workers from the Gen Corp Automotive plant in Logansport, Indiana, were eligible to participate in this study as part of an unexposed control group if they worked first shift, had worked first shift at Logansport for at least six months, had never worked in the VS department in Marion, and were not pregnant.

Sample Size

Studies of DNA adducts and repair enzymes have not been conducted in the rubber processing industry. Therefore, calculations to determine necessary sample size were performed using related studies. For the DNA adduct analyses, the study by Mustonen and Hemminki[45] that compares 7–methylguanine concentrations in DNA of smokers' and non–smokers' total white blood cells, granulocytes, and lymphocytes was used. For a level of significance (alpha) of 0.05 and a power greater than 80%, a sample size of at least 17 exposed and 17 unexposed workers would be necessary to detect a geometric mean DNA adduct level that is twice as high in one group as the other. The biggest assumption for this calculation is that the data from Mustonen and Hemminki is remotely comparable to the exposed/unexposed groups being sampled, and that the variances in DNA adduct levels for smokers and non–smokers are the same as those for the exposed and unexposed populations in this study. Other assumptions are lognormality of the data and independent samples.

For the repair enzyme analyses, the study by Oesch and Klein[44] that compares the repair capacity for O^6–methylguanine in peripheral blood lymphocytes of automobile workers exposed to rubber and tires and clinical workers that handle chemotherapeutic agents to control groups was used. By using the variance from the tire industry, we calculated that for a level of significance (alpha) of 0.05 and a power greater than 80%, a sample size of at least 30 exposed and 30 unexposed workers is necessary. By using the variance from the clinical workers, we calculated that for a level of significance (alpha) of 0.05 and a power greater than 80%, a sample size of at least

25 exposed and 25 unexposed workers is necessary. Again, we must assume that the data from Oesch and Klein is remotely comparable to the exposed/unexposed groups being sampled, and that the variances in DNA adduct levels are the same as those for the exposed and unexposed populations in this study.

The exposed population that worked the first shift at Marion was approximately 120 employees. The unexposed population at Marion was much smaller — at least 10 employees were unexposed, and approximately 50 others were potentially unexposed. Therefore, it was necessary to recruit other unexposed workers from the Logansport plant, which had approximately 500 employees, 96 of whom worked in the Toyo department over three shifts.

Recruitment

After the workers were educated about the purpose and procedures of the study by means of communication through the union and a personal letter from the NIOSH investigator, the current workers were telephoned to answer any questions regarding the study and to ascertain eligibility and willingness to participate in the study. If an individual initially refused to participate in the study, he or she was asked to reconsider and asked whether a NIOSH researcher may call again in a few days. If the individual did not want to be contacted again, he or she was eliminated from the list of potential participants.

The individuals who were eligible and willing to participate received a thank–you letter which provided further information about the study, and reinforced the fact that this study was research–based and that individual sample results would not be interpretable.

Consent

A consent form was presented to and signed by the participants at the beginning of the study. This form provided a description and the conditions of the study. It also explained the role of the participant and the use of the information collected.

Data Collection

The NIOSH investigator established a schedule with the Gen Corp Automotive plant managers for administering the questionnaire and drawing the blood samples during work hours. The urine samples had to be first void samples and therefore had to be collected by the workers at home.

Non–occupational Exposure to Nitrosamines (Questionnaire)

A questionnaire was used to try to identify the participants' non–occupational exposure to nitrosamines (see Appendix D). Designated groups of workers were scheduled to come to a conference room in the plant during the workshift to complete the questionnaire with instruction and guidance provided by a NIOSH investigator. The questionnaire required about 30 minutes and was reviewed upon completion by the NIOSH investigator for completeness.

Occupational Exposure to Nitrosamines, Nitrate, and Nitrite

Occupational exposure to the volatile nitrosamines, nitrosodimethylamine (NDMA), nitrosodiethylamine (NDEA), nitrosodipropylamine (NDPA), nitrosodibutylamine (NDBA), nitrosopiperidine (NPIP), nitrosopyrrolidine (NPYR), and nitrosomorpholine (NMOR) was measured. PBZ air samples were collected for all of the participants in the VS area, and GA air samples were collected in the other departments. Samples were collected on Thermosorb–N® tubes using Gillian® high–flow air pumps at a flowrate of 1 l/min.

Since ingested nitrate and nitrite can be converted to nitrosamines in the body, occupational exposure to nitrate and nitrite were also assessed during this survey. GA samples were collected on washed silica gel sorbent tubes using Gillian® low–flow air pumps at a flowrate of 0.5 l/min.

Blood Samples

Forty–milliliter (ml) blood samples were collected at the end of the workshift by trained phlebotomists. Concentrations of N^7–mdG and O^6–mdG were measured in peripheral white blood cells. Also, small amounts of the DNA isolated from the blood samples were used to search for restriction fragment length polymorphisms (RFLPs) of the gene that codes for CYP2E1. This RFLP analysis allowed for comparison between DNA adducts and genetic ability to metabolize nitrosamines. From the same peripheral blood cells, total cell–extract protein was used to quantify the AGT activity.

Urine Samples

First void urine samples were provided by the workers on the morning following the day of their exposure sampling and blood collection, and excised DNA adducts were quantified from the urine. It had been planned that DNA from exfoliated cells in the urine would be analyzed for N^7–mdG and O^6–mdG adducts, but sufficient amounts of DNA could not be recovered from the cells and these analyses could not be performed.

Data Analysis

The occupational exposures to nitrosamines were evaluated for associations with the biological sample results, as were occupational exposures to nitrate and nitrite. Questionnaire data (occupational history, residential water supply history, consumption of alcoholic beverages, diet history, tobacco use, fertilizer use, pesticide use, and medical history) were also evaluated for associations with the biological sample results. The comparisons included simple calculations of means of variables, according to exposure status, and correlations between biological samples and PBZ sample results, accounting for the various potential confounding factors (for example, linear regressions, multiple regressions, analyses of variance and covariance, and type III sum of squares tests).

Measures of Nitrosamine, Nitrate, and Nitrite Exposure

The PBZ and GA air samples were analyzed for NDMA, NDEA, NDPA, NDBA, NPIP, NPYR, and NMOR in a NIOSH laboratory using gas chromatography (GC) and a mass spectrometer (MS) in the selected–ion–monitoring (SIM) mode. The NIOSH laboratory used a capillary column instead of a packed column for the analysis — a process that separates the elution peaks better. Also, a mass spectrometer in the selected–ion–monitoring (SIM) mode was used to confirm the identity of any compound that eluted at the same retention time as the nitrosamine standards. In this way, the chromatographic peak was confirmed as the nitrosamine compound that it was suspected to be.

The analysis of samples for nitrate and nitrite was performed by treating each PVC filter with a solution of 10% methanol and 90% eluent (1.8 mM sodium carbonate and 1.7 mM sodium bicarbonate in water). Then the samples were analyzed by ion chromatography using a 25 cm by 4 mm packed column of AS9–SC anion exchange resin at a flowrate of 2 mL/min.

Analysis of DNA Adduct Concentrations in Peripheral White Blood Cell DNA

Lymphocytes were isolated from whole blood using Histopaque^R, and then DNA was isolated from peripheral blood lymphocytes using a MicroProbe DNA isolation kit. After enzymatic hydrolysis to the 3' phosphate nucleotides, the N^7–methyldeoxyguanosine and O^6–methyldeoxyguanosine adducts were separated from non–adducted nucleotides by HPLC/UV detection (254 nm) with an ion–pair column. Each of the adducts and deoxyguanosine were collected in three one–milliliter aliquots using a fraction

collector. The aliquots were then pooled and lyophilized. The fraction containing N^7–methyldeoxyguanosine was further purified by HPLC/Diode Array UV detection at 254 nm equipped with a C18 reverse phase column. Three one–milliliter aliquots were again collected and lypholized. The lyophilized N^7–methyldeoxyguanosine fractions were dissolved in water and one microliter of the corresponding deoxyguanosine fraction diluted 1:100 was added. N^7–mehtyldeoxyguanosine fractions were enzymatically labeled with ^{32}P–ATP at the 5' position. N^7–methyldeoxyguanosine was separated from deoxyguanosine on 20 x 20 cm polyethyleneimine cellulose plates by two–dimensional thin–layer chromatography. Deoxyguanosine and N^7–methyldeoxyguanosine were localized using a radioisotope image analyzer and the radioactivity measured. Lypholized fractions of O^6–methyldeoxyguanosine and deoxyguanosine from each sample were dissolved in HCl and hydrolized for one hour to O^6–methylguanine and guanine, and then the hydrolized fractions were concentrated. O^6–methylguanine and guanine were quantified using HPLC electrochemical detection equipped with a C18 reverse phase column and a direct ratio of O^6–methylguanine to guanine was determined.

Analysis of DNA Adduct Concentrations from Exfoliated Cells in the Urine

Exfoliated urothelial cells in urine would be isolated using a 5 μm pore, 47 mm diameter filter. The cells were to be rinsed off the filter and DNA isolated using a MicroProbe DNA isolation kit. Unfortunately, there was not enough urothelial cells present in the overnight urine samples to isolate sufficient DNA to perform the postlabeling assay for the analysis of N^7 –methyldeoxyguanosine and O^6–methyldeoxyguanosine adducts.

Analysis of Excised DNA Adducts in the Urine

Excised methyladenine and methylguanine DNA adducts (2–, 6–, and 7–-methylguanine, and 2–, 3–, 6–, and 7–methyladenine) in the urine were quantified. The urine samples were initially filtered to remove debris and exfoliated cells, and then were processed by solid phase extraction using a Zymark BenchMate II®. The methylated DNA adducts were derivatized using N–(tert–butyldimethylsilyl)–N–methyltrifluoroacet amide and the derivatives were then analyzed by gas chromatography and mass spectrometry (GC/MS) using a Hewlett–Packard Model 5890A gas chromatograph and 5970 Mass Selective Detector.

Analysis of AGT Activity from Peripheral White Blood Cells

AGT activity was determined by the transfer of radioactivity from [^{3}H]–labeled O^6–methylguanine (prepared as described in Swenson and Lawley, 1978[46]) from DNA substrate to cell–extract protein isolated from peripheral lymphocytes using a slight modification of the method described by Preuss *et al.*, 1995.[47] Lymphocytes were isolated from whole blood using Histopague.® Cell extracts were prepared by sonication of the cell suspensions. Cellular protein was concentrated by Centricon 10 or Microcon 10 Concentrators then incubated with ^{3}H–labelled DNA. The protein was precipitated and washed. Radioactivity associated with the precipitated protein was determined using a liquid scintillation counter, and the AGT activity was expressed as femtomoles (fmol) of ^{3}H–methyl transferred to precipitated protein per milligram (mg) of total cell extract protein.

Genetic Analysis of Polymorphisms in the CYP2E1 Gene

Restriction fragment length polymorphism (RFLP) analysis was performed on DNA isolated from lymphocytes for use in the analysis of DNA adduct concentrations in peripheral blood cells as described above. DNA (0.5 –1.0 μg) was amplified by the polymerase chain reaction (PCR) using primers appropriate to the regions of interest

within the CYP2E1 gene. The region of the gene encompassing intron 6 contains a *Dra I* polymorphism. For analysis of RFLPs, aliquots of the amplified DNA were digested with the restriction enzyme *Dra I* and analyzed by agarose gel electrophoresis. DNA was visualized by ethidium bromide fluorescence and the size of the DNA ascertained by comparison with authentic size standards. The presence of a *Dra I* restriction site yields a 572 base pair fragment; in the absence of the site an 874 base pair fragment will result. DNA from individuals that are heterozygous for the restriction site will display a mixture of each of the bands.

RESULTS AND DISCUSSION

Questionnaire Data

Eighty–five workers participated in this study, 59% male and 41% female. The average age of the participants was 50 years, with a range from 28 years to 65 years (3 workers did not report their age). The participants were assigned exposure categories based on where they worked:

Category I — Vehicle Sealing (VS) department employees who worked along the salt bath lines (17 workers);
Category II — VS department employees who did not work along the salt bath lines (12 workers);
Category III — non–VS department employees who worked frequently in and near the VS area (14 workers);
Category IV — non–VS department employees who worked remotely from the VS area (19 workers);
Category V — employees from the Logansport plant (23 workers).

The ratio of male to female participants was not the same in each exposure group. Category I had 69% male and 31% female; category II had 64% male and 36% female; category III had 39% male and 62% female; category IV had 81% male and 19% female; and category V had 46% male and 55% female.

Several questions were asked to ascertain tobacco use among the participants. Thirty–one percent (26 of 84, 1 did not answer) were current cigarette smokers, and 66% (55 of 83) reported having ever smoked cigarettes. Only 2% (2 of 85) were currently pipe smokers, and 18% (15 of 85) reported having ever smoked pipes routinely. Seven percent (6 of 85) were current users of chewing tobacco or snuff, and 10% (8 of 84) reported having ever been users of chewing tobacco or snuff. The percent of cigarette smokers in each exposure category were similar to each other and to the overall percentages. Category I had 29% current smokers and 59% ever–smokers; category II had 33% current smokers and 67% ever–smokers; category III had 31% current smokers and 58% ever–smokers; category IV had 16% current smokers and 74% ever–smokers; and category V had 44% current smokers and 70% ever–smokers.

Nitrosamine Air Sampling

The air sampling results are presented in Appendix A; Table 5 presents the GA results, Tables 6 through 9 present the PBZ results for the participants in the biological monitoring study, and Table 10 presents the PBZ results for workers who, regardless of participation, were cleaning the salt baths. Every worker sampled in the Marion plant had detectable nitrosamine exposure, even those in areas remote from the VS area. If workers are grouped according to job title and proximity to the salt bath lines (as done in Tables 6–9), there does appear to be a reduction of exposure for those further away from the lines, which would be expected. In the VS area (Tables 6–8), the PBZ sample concentrations ranged from 0.4–9.3 $\mu g/m^3$, and 57% of the samples were higher than the German occupational standard of 2.5 $\mu g/m^3$ for rubber vulcanizing and processing industries. Figure 1 (see Appendix A) displays the average

exposures compared to the German standard.

The GA sample concentrations ranged up to 187 $\mu g/m^3$ for NDMA, which is considered an occupational carcinogen by both NIOSH and the OSHA. Of interest is that the GA samples collected on the lines which were running a developmental stock that was intended to not produce nitrosamines also had high nitrosamine concentrations.

Nitrosamines were not detected on any of the GA samples collected in the Toyo Department of the Logansport plant.

Nitrate/Nitrite Air Sampling

Employees who participated in the study and worked on the salt baths lines were sampled for exposure to nitrate and nitrite particulate. Seventeen employees were sampled and the results are presented in Table 11. Nitrite was not detected on 16 of the samples, and only in trace amounts (between 3.2–7.5 $\mu g/m^3$) on the seventeenth sample. This could suggest that quantities of nitrite on the field samples are below the analytical limit of detection, or that the analytical method has poor recovery at low nitrite concentrations. (The analytical recovery curve for nitrite suggests that recovery of nitrite from 37–mm PVC filters is poor at low concentrations of nitrite.) The concentrations of nitrate ranged from trace (<4.7 $\mu g/m^3$) to 26.1 $\mu g/m^3$.

The significance of these exposures is not known. The concentrations are very low, but it is known that ingested nitrate and nitrite can be converted to nitrosamines in the body. There is no way to calculate the amount of this airborne particulate exposure that was ingested, and it is not known if inhalation of these compounds can also contribute to endogenous nitrosamine formation. The utility of this data is merely to provide information about another potential confounder in this study, and it was used in the same way that the questionnaire data was used when performing the overall analyses.

Biological Monitoring

All the raw data from the biological monitoring analyses are presented in Appendix B. There are four categories of biological monitoring data: genotype of the CYP2E1 gene, DNA adducts in peripheral white blood cells, AGT activity in peripheral white blood cells, and excised DNA adducts in the urine. As stated previously, the DNA–adduct analysis from exfoliated cells in the urine could not be performed.

Polymorphisms in the CYP2E1 Gene

The purpose of the genotype analyses was to provide information about a possible confounder. The CYP2E1 gene is responsible for encoding an enzyme that metabolizes nitrosamines. A polymorphism can occur in this gene at the *Dra1* cleavage site within intron 6; the absence of this site in one or both alleles has been associated with an increased risk of lung cancer and an increased amount of the type of DNA adducts expected to occur following exposure to nitrosamines.[48] A genotype of DD means that there are two normal copies of the gene; a genotype of CD means that one copy of the gene is normal and one is a variant; and a genotype of CC means that both copies of the gene are variant. In this study, 15 participants had the CD genotype and 70 had the DD genotype. The frequency of the CD genotype was approximately 9% [15/(2x85)], which is consistent with other studies of non–Asian populations. None had the CC genotype, which is also consistent with other studies of non–Asian populations. The 15 participants with the CD genotype might be expected to have higher DNA–adduct concentrations from the same exposures than the DD genotype participants,[48] and therefore, genotype was controlled when analyzing air exposures and biological monitoring data.

AGT Activity in Peripheral White Blood Cells

The AGT activity results ranged from zero activity to 809.43 femtomoles per milligram of protein

(fmol/ mg protein), and there was not a significant difference in average AGT concentrations between each exposure category ($p>0.25$). However, there was large variability within each exposure group, as illustrated by the averages and standard deviations: category I — 203.82 $\pm$ 138.03, category II — 178.08 $\pm$ 178.05, category III — 144.13 $\pm$ 119.17, category IV — 168.70 $\pm$ 165.21, and category V — 212.37 $\pm$ 152.40 fmol/mg protein. There was a statistically significant negative correlation between total nitrosamine exposure and AGT concentrations ($p=0.0513$). Biologically, this correlation is plausible because nitrosamines can cause the specific adducts (O^6mdG) that AGT repairs by an irreversible reaction. No other significant correlations existed between AGT concentrations and biological results (O^6mdG or 6mG concentrations) or questionnaire data. Nor did the AGT results have any significant effect on the association of O^6mdG or 6mG results with occupational exposures.

DNA Adducts in Peripheral White Blood Cells

The DNA–adduct concentrations were quantified for two different adducts, N^7–methyldeoxyguanosine (N^7mG) and O^6–methyldeoxyguanosine (O^6mG) from peripheral white blood cell DNA. The majority of adducts (70% to 90%) from nitrosamine exposure are N^7mdG, which have half–lifes of about 150 hours.[37] The O^6mdG adducts are more actively removed from DNA and are therefore not as stable. These adducts, however, may have more of a mutagenic potential than the N^7–mdG adducts and may play more of a role in carcinogenesis.[12,38,39]

The N^7mdG adduct concentrations ranged from 0.1–133.2 adducts per 10^7 deoxyguanosine nucleosides. Every participant had detectable concentrations of these adducts, and no significant association between adduct formation and occupational nitrosamine exposure was found, even when considering several potential confounders, such as tobacco use, genotype, eating processed meats, and eating charred or well–done meats.

One published study documents significantly increased concentrations of these adducts in peripheral white blood cells of smokers (6.9 adducts per 10^7 deoxyguanosine nucleosides) compared to non–smokers (3.4 adducts per 10^7 deoxyguanosine nucleosides).[45] Both of these concentrations are low relative to the average concentrations documented in this NIOSH study. The average concentrations from this study were as follows: category I — 18.4, category II — 29.2, category III — 11.1, category IV — 17.1, and category V — 13.5 adducts per 10^7 deoxyguanosine nucleosides. However, the individual results varied markedly within each exposure group. For example, the range of adduct concentrations for those who worked in and near the VS area (categories I–III) was 0.1–133.2 adducts per 10^7 deoxyguanosine nucleosides, and the range for those who did not work anywhere near the VS area (categories IV–V) was similarly 0.1–128.2 adducts per 10^7 deoxyguanosine nucleosides. The fact that no significant association was found between these adduct concentrations and personal occupational nitrosamine exposure could be due to the fact that there are so many other exogenous and endogenous nitrosamine exposures, and also that the half–life of these adducts is 150 hours. The occupational exposures may not be significant for the formation of N^7mdG relative to all the other exposures, or this study may not have been able to assess the other exposures well enough to document any significance.

The concentration of N^7mdG adducts did appear to have a significant association with eating smoked sausage at least one time a week over the year previous to the data collection ($p<0.03$). This routine eating of smoked sausage was also statistically associated with higher concentrations of O^6mdG adducts ($p<0.009$). None of the other potential confounders when assessed individually had a statistically significant association with either of the adducts ($p>0.05$).

The O^6mdG adduct concentrations were much lower than the N^7mdG results; many of the participants (40/85) did not have detectable concentrations of O^6mdG adducts in their blood cells. These non–detectable (ND) results cannot be recorded as zero because the analytical procedure only is able to measure as low as 0.03 O^6mdG adducts per 10^7 deoxyguanosine nucleosides. Therefore, these ND results could represent anywhere from 0 to 0.03 adducts per 10^7 deoxyguanosine nucleosides. Because there was a high percentage of results that were ND, the data was first evaluated using nonparametric statistics. In this case, the presence of any O^6mdG adducts was tested for association with exposure category, tobacco use, and CYP2E1 genotype. A chi–square test of independence demonstrated a statistically significant positive trend between exposure category and having detectable levels of O^6mdG adducts ($p<0.05$). That is, those employees who worked where there were higher nitrosamine exposures were more likely to have detectable O^6mdG adducts; or, those employees who worked where there were lower or no nitrosamine exposures were less likely to have detectable O^6mdG adducts (see Appendix A, Figure 2). The percent of ND results are as follows: category I – 38% ND; category II – 33% ND; category III – 39% ND; category IV – 64% ND; and category V – 76% ND. It appears that categories I–III had similar percentages of ND results, and these three categories all represent employees who work routinely in the VS area of the plant. If employees are categorized by VS area (categories I–III, 37% ND) and non–VS area (categories IV–V, 72% ND), there is an even stronger statistically significant association between work location (which is related to exposure categories) and having detectable levels of O^6mdG adducts ($p<0.005$).

Since the use of tobacco products also produces DNA adducts, the O^6mdG results were also tested for an association with current cigarette smoking, past cigarette smoking, and any current or past exposures to tobacco products (which included current or past cigarette smoking, living with a smoker, frequenting the smoking break room at work, current or past pipe or cigar smoking, and current or past use of chewing tobacco or snuff). A chi–square test of independence demonstrated no statistically significant association between tobacco use and having detectable levels of O^6mdG adducts.

Since polymorphisms in the CYP2E1 gene can affect the metabolism of nitrosamines into compounds that will actively bind to DNA, the O^6mdG results were also tested for an association with CYP2E1 genotype. As with tobacco use, a chi–square test of independence demonstrated no statistically significant association between genotype and having detectable levels of O^6mdG adducts.

There are methods for assigning a numerical value to the ND values so that a parametric statistical analysis could be performed. However, the normality of this data set was not certain and about half of the results were ND, so that assigning a numerical value to the ND results was not considered the best choice. Nevertheless, a few parametric analyses were performed with all ND results assigned the value of the analytical limit of detection divided by two (LOD/2). These tests were done so that the O^6mdG could be compared as a continuous variable with the other continuous variables of total nitrosamine exposure, AGT activity, and 6mG concentrations; however, no significant associations were found. Using O^6mdG as a continuous variable, the results were similar to those of the chi–square tests for associations with exposure category, tobacco use, and genotype. Of most interest is that the genotype and the AGT activity did not affect the results; the significant association between detectable O^6mdG concentrations and exposure category was present whether these potential confounders were included in the models or not.

Excised DNA Adducts in the Urine

Every participant had detectable concentrations of all seven excised adducts that were evaluated, which would be expected since there are so many sources of nitrosamine exposure. However, as with the N^7mdG adduct concentrations in peripheral blood cells, no significant associations were detected between occupational nitrosamine exposures and any of the excised DNA adducts,

even when several potential confounders were considered.

Two of the excised adducts correspond with the DNA adducts that were measured in peripheral blood cells — 7–methylguanine (7mG) with N^7mdG, and 6–methylguanine (6mG) with O^6mdG. A significant negative correlation was found between the 7mG in the urine and the N^7mdG in the peripheral white blood cells (Pearson correlation coefficient = –0.23274, p=0.0163). Likewise, a significant negative correlation was found between the 6 mG in the urine and the O^6mdG in the peripheral white blood cells (Spearman Rank correlation coefficient = –0.44581, p=0.00251). These data suggest that as the DNA adduct concentrations in peripheral blood cells decrease, the excised adduct concentrations in the urine increase, which has biologic plausibility because the excised adducts result when adducted DNA is repaired.

The above negative correlations, combined with the fact that no significant association was found between occupational exposures and excised adducts, suggest that concentration of excised adducts in the urine might be a useful marker of adducted DNA repair, but is probably not a useful marker of occupational nitrosamine exposure. However, two significant confounders that could not be completely assessed during this study were interindividual variations in nitrosamine metabolism and in DNA excision repair mechanisms. (CYP4502E1 was evaluated, but other enzymes also metabolize nitrosamines. Also, AGT is only one enzyme that repairs DNA.) If all these variables could have been evaluated, it is plausible that excised DNA adducts in the urine might be a useful marker for occupational exposure to nitrosamines.

DISCUSSION AND CONCLUSIONS

The air sampling data documents worker exposures to nitrosamines in this plant. The salt bath curing process was generating the nitrosamines, and a combination of insufficient LEV and exhaust re–entering the work area was resulting in a build–up of the nitrosamines. Although there is no numerical occupational exposure limit for nitrosamines in the United States, both NIOSH and OSHA consider NDMA to be an occupational carcinogen. Also, many of the measured exposures are higher than the German occupational exposure standard. The other air sampling data suggested that exposures in the VS area (other than nitrosamines), the mix house, and the LCM area were below recommended exposure limits.

When conducting the DNA–adduct study, there were many variables to consider, such as multiple external nitrosamine exposures, as well as endogenous formation of nitrosamines, metabolism of nitrosamines into compounds that will bind to DNA, and DNA repair mechanisms — all of which will vary by individual. External occupational nitrosamine exposures were measured, and other external exposures were qualitatively assessed using a questionnaire. However, the internal variability, which certainly does affect biological monitoring results, could not be assessed. Also, the study population was limited in that only one plant and one department of another was available for this study, and none of the variables could be controlled, only assessed. Considering these limitations, the fact that many of the biological monitoring results did not show a significant association with occupational nitrosamine exposures is not remarkable. There may be no true association, or there may be an association that could not be detected due to the limitations of this study.

Even with these limitations, there was a significant positive trend between exposure category or work location and having detectable O^6mdG adducts in peripheral blood cells. It is important to understand that many factors other than an occupational exposure can affect an individual's biologic response, including genetic predisposition, diet, medications, hobbies, and life style. A significant association does not prove a cause–effect relationship, nor does it mean that every person with an occupational exposure will have detectable levels of O^6mdG adducts. By examining the raw data in Appendix B, one can see that not every employee from the VS area had detectable concentrations of O^6mG adducts, and not every employee in exposure category V (no occupational exposure) had ND results. What can be concluded is that there is a significant association between exposure group or work location and having detectable levels of O^6mdG adducts; a worker in the VS area or in a higher exposure group has a higher probability of having detectable levels of O^6mdG adducts. Since these adducts have mutagenic potential and may play a role in carcinogenesis,[38,39] this finding is important.

Another important finding was the negative correlation between occupational nitrosamine exposure and AGT concentrations, which suggests that workers with higher nitrosamine exposures have decreased AGT activity because it is being used to repair DNA adducts. This finding is consistent with the association between exposure category and O^6mdG adducts.

Based on the air sampling data, the significant positive trend between exposure category and having detectable concentrations of O^6mdG adducts in peripheral white blood cells, and the negative correlation between nitrosamine exposure and AGT activity, the NIOSH investigator concluded that there is a health hazard from exposures to nitrosamines in this workplace.

RECOMMENDATIONS

1. NIOSH considers NDMA to be an occupational carcinogen.[1] Since most nitrosamines have similar properties to NDMA and are

suspected to be human carcinogens, the exposures to all nitrosamines in the VS area should be reduced. The best solution is elimination of the source. A few of the rubber stocks contain dinitrosopentamethylene tetramine. Also, the rubber stock and various curatives and additives contain amines that can combine with the nitrite salts from the salt baths to form nitrosamines. Using a curing process other than salt baths and developing different rubber stocks which do not contain nitrosamines or will not result in nitrosamine formation are two ways of eliminating the source. Until the source of nitrosamines can be eliminated, better engineering controls are necessary. Properly designed LEV along the entire salt bath lines will help to reduce the volatile nitrosamine concentrations. An example would be to have the salt bath and drill areas totally enclosed while the rest of the line was ventilated with either down–draft tables or side–slot LEV. Also, routine maintenance is necessary to ensure that the LEV systems are always functioning properly.

2. The ventilation system should be redesigned to ensure that no exhaust is re–entering the work place. Bringing in outside air that is contaminated with exhaust negates the function of the exhaust systems. Outside air intakes, such as the ones on the AHUs on the roof or on the outside of the VS building, should be located in areas where exhaust does not flow directly into them or where it is not likely that exhaust will accumulate.

3. Proper protective gloves, not cotton gloves, should be worn when working with solvents. Solvents are readily absorbed through the skin, which can significantly contribute to overall exposure, and cotton gloves can actually increase the dermal exposure because cotton will absorb the solvents and hold them against the skin. Nitrile rubber and Viton® gloves are two types that offer good protection from a variety of solvents.

4. Any employee issued a respirator, for voluntary use or not, must be part of the respirator protection program, which involves a medical determination that the employee is physically able to wear a respirator, a fit test, and proper training on the use and maintenance of respirators. This involves implementing an effective respiratory protection program, in accordance with the requirements described in 29 CFR 1910.134.[49] Publications developed by NIOSH which should also be referenced when developing an effective respirator program include NIOSH Respirator Decision Logic and the NIOSH Guide to Industrial Respiratory Protection.[50,51] It is recommended that the written program designate one individual with the responsibility for administering the respiratory protection program. The written respirator program should also contain information on the following topics: (a) the departments/operations which require respiratory protection; (b) the correct respirators required for each job/operation; (c) specifications that only NIOSH/MSHA approved respiratory devices shall be used; and (d) the criteria used for the proper selection, use, storage and maintenance of respirators, including limitations. A respiratory protection program should include the following elements:

a. written operating procedures
b. appropriate respirator selection
c. employee training
d. effective cleaning of respirators
e. proper storage
f. routine inspection and repair
g. exposure surveillance
h. program review
i. medical approval
j. use of approved respirators

5. The Hearing Conservation Program (HCP) should be updated. Noise level measurements should be performed in the plant, especially the VS area. Once noise levels have been measured, mark clearly any areas that exceed an 8–hour TWA of 85 decibels–A weighted (dBA) as high noise areas if the levels cannot be lowered by engineering controls. Employees working in these high noise

areas should be provided with a variety of hearing protection devices and training in their use until such time as engineering or administrative controls can reduce the personal noise level exposures to below 85 dBA. Also, annual audiograms on these employees should be performed to detect any temporary or permanent threshold shifts. Records of all noise level monitoring, training, and audiograms should be kept. The NIOSH Guide to Effective Hearing Conservation Programs in the Workplace[52] is helpful in developing an HCP.

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Table 1. Relevant Evaluation Criteria for Aromatic Hydrocarbons Sampled at Gen Corp Automotive in Marion, Indiana. May 3 to May 5, 1994. HETA 94–0072

Solvent	NIOSH REL (ppm)	OSHA PEL (ppm)	ACGIH TLV (ppm)	Target Organs[1,2]	Symptoms[1,2]
TOLUENE	100 ST 150	200 CL 300	50 skin	CNS, liver, kidneys, skin	fatigue, weakness, confusion, dizziness, headaches, muscle fatigue, insomnia, dermatitis, narcosis
ACETONE	250	1000	750	respiratory system, skin	eye, nose, throat irritation; headaches, dizziness; dermatitis
STYRENE	50 ST 100	100 CL 200	50 skin	CNS, eyes, skin, respiratory	eye, nose, throat irritation; drowsiness; weakness; narcosis; unsteady gait; defattening dermatitis
MEK	200 ST 300	200	200	CNS, lungs, skin	eye, nose, throat irritation; headache; dizziness; vomiting; dermatitis
PYRIDINE	5	5	5	CNS, liver, kidneys, skin, GI tract	headache, nervousness, dizziness, insomnia, nausea, anorexia, frequent urination, eye irritation, dermatitis, liver and kidney damage, vertigo, vomiting
LIMONENE	—	—	—	—	—

NIOSH REL = National Institute for Occupational Safety and Health recommended exposure limit (10–hour time–weighted average)
OSHA PEL = Occupational Safety and Health Administration permissible exposure limit (8–hour time–weighted average)
ACGIH TLV = American Conference of Government Industrial Hygienists threshold limit value (8–hour time–weighted average)
ST = short–term exposure limit (15–minute time–weighted average)
CL = ceiling limit
MEK = methyl ethyl ketone (synonym, 2–butanone)
skin = dermal and mucous membrane absorption can significantly contribute to exposure
CNS = central nervous system
GI tract = gastrointestinal tract

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Table 2. Nitrosamine Air Sampling Results on May 3, 1994
Gen Corp Automotive, Marion, Indiana
HETA 94–0072

		Nitrosamine Concentration ($\mu g/m^3$)							
Sample Number	**Job/Location (type of sample)**	**Volume (L)**	**NDMA**	**NDEA**	**NDPA**	**NDBA**	**NPIP**	**NPYR**	**NMOR**
E59518	line 6 operator (PBZ)	676	5.17	0.64	ND	ND	2.57	0.06	0.10
E59515	injection molding press operator (PBZ)	808	0.53	0.01	ND	ND	0.20	0.01	0.01
E59516	press operator (PBZ)	670	1.07	0.03	ND	ND	1.02	0.03	0.09
E59517	line 5 coil packer (PBZ)	694	11.44	0.16	ND	ND	4.39	0.09	0.26
E59513	line 2 coil packer (PBZ)	728	5.40	0.04	ND	ND	2.22	0.01	0.16
E59511	feeder (PBZ)	872	1.40	0.14	ND	ND	0.64	0.01	0.07
E59519	line 5 operator (PBZ)	870	5.69	0.25	ND	ND	2.44	0.08	0.09
E59520	line 8 operator (PBZ)	672	1.68	0.19	ND	ND	1.10	0.04	0.04
E59501	line 8 coil packer (PBZ)	822	1.82	0.13	ND	ND	1.40	0.06	0.06
E59512	line 2 operator (PBZ)	566	6.48	0.28	ND	ND	2.54	0.05	0.09

ND = none detected
$\mu g/m^3$ = micrograms per cubic meter
PBZ = personal breathing zone air sample
GA = general area air sample

NDMA = nitrosodimethylamine
NDEA = nitrosdiethylamine
NDPA = nitrosodipropylamine
NDBA = nitrosodibutylamine

NPIP = nitrosopiperidine
NPYR = nitrosopyrrolidine
NMOR = nitrosomorpholine

minimal detectable concentration is 0.01 $\mu g/m^3$

Table 3. Nitrosamine Air Sampling Results on May 4, 1994
Gen Corp Automotive, Marion, Indiana
HETA 94–0072

		Nitrosamine Concentration (µg/m^3)							
Sample Number	**Job/Location (type of sample)**	**Volume (L)**	**NDMA**	**NDEA**	**NDPA**	**NDBA**	**NPIP**	**NPYR**	**NMOR**
E59502	silicone spray booth operator (PBZ)	830	2.84	0.07	ND	ND	1.79	0.06	0.13
E59510	line 8 assistant operator (PBZ)	814	2.96	0.07	ND	ND	1.72	0.12	0.18
E59508	press operator (PBZ)	810	1.35	0.03	ND	ND	1.62	0.04	0.06
E59507	line 2 coil packer (PBZ)	846	5.67	0.11	ND	ND	2.35	0.08	0.15
E59503	molding press operator (PBZ)	776	1.47	0.12	ND	ND	0.98	0.06	0.17
E59764	line 3 operator (PBZ)	844	4.35	0.10	ND	ND	1.88	0.06	0.18
E59509	feeder (PBZ)	908	0.47	0.03	ND	ND	0.27	0.01	0.03
E59506	line 2 operator (PBZ)	854	3.90	0.07	ND	ND	1.59	0.04	0.16
E59505	line 3 assistant operator (PBZ)	706	4.67	0.13	ND	ND	1.91	0.06	0.20
E59768	smoking break room (GA)	738	4.17	0.71	ND	ND	1.35	0.05	0.14
E59504	line 5 drill (GA)	766	9.99	0.03	ND	ND	2.92	0.15	0.25

ND = none detected
µg/m^3 = micrograms per cubic meter
PBZ = personal breathing zone air sample
GA = general area air sample

NDMA = nitrosodimethylamine
NDEA = nitrosdiethylamine
NDPA = nitrosodipropylamine
NDBA = nitrosodibutylamine

NPIP = nitrosopiperidine
NPYR = nitrosopyrrolidine
NMOR = nitrosomorpholine

minimal detectable concentration is 0.01 µg/m^3

Table 4. Nitrosamine Air Sampling Results on May 5, 1994
Gen Corp Automotive, Marion, Indiana
HETA 94–0072

		Nitrosamine Concentration ($\mu g/m^3$)							
Sample Number	**Job/Location (type of sample)**	**Volume (L)**	**NDMA**	**NDEA**	**NDPA**	**NDBA**	**NPIP**	**NPYR**	**NMOR**
F62821	line 7 operator and coil packer (PBZ)	768	1.10	0.04	ND	ND	0.64	0.03	0.06
F62812	silicone spray booth operator (PBZ)	818	3.80	0.21	ND	ND	2.61	0.06	0.15
F62818	C–pillar press operator (PBZ)	768	1.94	0.08	ND	ND	1.71	0.03	2.42
F62819	line 5 operator (PBZ)	846	5.58	0.20	ND	ND	3.25	0.08	0.16
F62811	line 8 operator (PBZ)	822	1.40	0.81	ND	ND	1.03	0.04	0.08
F62809	press operator (PBZ)	724	1.18	0.40	ND	ND	1.31	0.05	0.10
F62817	punch press operator (PBZ)	780	1.12	0.05	ND	ND	1.35	0.03	0.07
F62822	feeder (PBZ)	898	2.89	0.32	ND	ND	1.18	ND	0.12
F62810	A–pillar press operator (PBZ)	766	1.19	0.05	ND	ND	1.12	0.03	0.10
F62824	line 3 drill (GA)	718	88.47	0.19	ND	ND	10.17	0.14	0.55
F62820	line 5 drill (GA)	814	13.08	ND	ND	ND	4.03	0.16	0.06
F62826	line 6 drill (GA)	368	2.29	ND	ND	ND	1.98	0.15	0.08
F62816	line 7 drill (GA)	804	20.50	0.04	ND	ND	4.13	0.12	0.33
F62814	line 8 drill (GA)	428	4.84	ND	ND	ND	2.20	0.05	0.13
F62813	non–smoking break room (GA)	708	10.37	1.03	ND	ND	4.32	0.06	0.55

ND = none detected
$\mu g/m^3$ = micrograms per cubic meter
PBZ = personal breathing zone air sample
GA = general area air sample

NDMA = nitrosodimethylamine
NDEA = nitrosdiethylamine
NDPA = nitrosodipropylamine
NDBA = nitrosodibutylamine

NPIP = nitrosopiperidine
NPYR = nitrosopyrrolidine
NMOR = nitrosomorpholine

minimal detectable concentration is 0.01 $\mu g/m^3$

Table 5. General Area Air Sampling Results for Nitrosamines. January 25 – February 2, 1995. HETA 94–0072.

			Nitrosamine Concentration (µg/m^3)			Stock Numbers
Location	Date	Sample Volume (L)	NDMA	NPIP	NMOR	(sponge/dense)
line 1 drill	1/25/95	428	6.5	1.2	0.3	10105/46966
line 3 drill	1/25/95	417	127	60	0.4	10104/46966
line 4 drill	1/25/95	422	69	10	0.3	10107/20106
line 8 drill	1/25/95	428	107	5.1	0.7	10104/46997
non–smoking break room	1/25/95	432	0.7	0.3	0.1	NA
smoking break room	1/25/95	467	1.2	0.7	0.2	NA
line 2 drill	1/26/95	415	157	34	2	23488/46685
line 3 drill	1/26/95	420	133	131	0.8	10104/46966
line 4 drill	1/26/95	415	120	29	1.4	DEV 2.0
line 5 drill	1/26/95	414	31	2.4	0.4	DEV
line 6 drill	1/26/95	401	187	30	1.6	DEV
line 7 drill	1/26/95	462	121	19	1.3	23672/46966
line 8 drill	1/26/95	402	35	3	0.6	20106/10104
line 8, 4 inches from drill	1/26/95	398	78	3.3	0.5	20106/10104
non–smoking break room	1/26/95	468	0.7	0.4	0.1	NA
smoking break room	1/26/95	471	1.2	0.8	0.2	NA
line 1 cutter	2/1/95	411	3.2	2.0	0.04	10106/20137
line 2 drill	2/1/95	430	158	16	1.0	10104/20107
line 3 drill	2/1/95	433	150	35	0.3	10104/46966
line 4 drill	2/1/95	435	9.0	3.4	0.4	10107/20106
line 5 drill, during running and cleaning	2/1/95	439	22	3.6	0.5	DEV
ine 5 drill, development product	2/1/95	78	14	9.0	0.5	DEV
line 5, during cleaning only	2/1/95	129	2.2	1.6	0.2	DEV
line 6 drill	2/1/95	444	19	3.8	0.5	10104/20107
line 8 drill	2/1/95	313	83	6.1	0.3	20106/10104
non–smoking break room	2/1/95	451	4.4	1.2	1.1	NA
smoking break room	2/1/95	468	1.0	1.0	0.1	NA
line 1 cutter	2/2/95	118	2.6	1.7	0.2	10105/46966
line 1, during cleaning	2/2/95	149	2.3	2.5	0.07	10105/46966

			Nitrosamine Concentration (µg/m^3)			Stock Numbers
Location	**Date**	**Sample Volume (L)**	**NDMA**	**NPIP**	**NMOR**	**(sponge/dense)**
line 2 drill	2/2/95	419	138	43	0.7	10104/20107
line 3 drill	2/2/95	418	134	53	0.7	10104/46966
line 4, after salt bath	2/2/95	409	34	13	0.7	46927/20106
line 5 drill	2/2/95	417	103	10	0.9	10104/20106
line 6 drill	2/2/95	420	11	3.3	0.2	10104/20106
line 8 drill	2/2/95	420	16	1.7	0.02	20106/10104
non–smoking break room	2/2/95	428	0.9	0.6	0.1	NA
smoking break room	2/2/95	440	1.0	0.8	0.3	NA

µg/m^3 = micrograms per cubic meter
L = liters
NDMA = nitrosodimethylamine
NPIP = nitrosopiperidine
NMOR = nitrosomorpholine
DEV = a developmental stock
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 µg/m^3.

Table 6. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures of Salt Bath Line Workers. January 25 – February 2, 1995. HETA 94–0072.

				Nitrosamine Concentration ($\mu g/m^3$)			
#	Job Title	Date	Sample Volume (L)	NDMA	NPIP	NMOR	Total
001	front end feeder	1/25/95	430	1.4	1.3	0.2	2.9
013	line 3 assistant operator	1/25/95	435	1.2	0.7	0.2	2.1
009	line 8 assistant operator	1/25/95	458	1.2	1.1	0.3	2.6
014	line 2 operator	1/26/95	199	2.2	1.2	0.3	3.7
016	front end feeder	1/26/95	428	1.1	0.8	0.1	2.0
007	line 7 operator	1/26/95	452	2.0	0.9	0.3	3.2
015	line 5 assistant operator	2/1/95	463	3.0	2.0	0.4	5.4
010	line 2 assistant operator	2/1/95	453	4.6	2.4	0.6	7.6
006	line 2 assistant operator	2/1/95	363	3.3	1.9	0.6	5.8
017	line 5 operator	2/1/95	438	2.7	1.8	0.4	4.9
012	line 3 operator	2/1/95	451	4.4	3.1	0.1	7.6
011	line 6 assistant operator	2/1/95	361	1.3	0.9	0.1	2.3
005	line 3 assistant operator	2/2/95	438	5.9	3.0	0.4	9.3
028	line 4 operator	2/2/95	462	1.7	1.1	0.2	3.0
002	silicone booth operator	2/2/95	438	1.8	1.3	0.3	3.4
018	line 4 assistant operator	2/2/95	459	2.8	2.0	0.3	5.2
004	line 2 assistant operator	2/2/95	465	2.6	1.5	0.3	4.4
Average Exposure				2.5±1.4	1.6±0.7	0.3±0.2	4.4±2.2

# = sample number
L = liters
$\mu g/m^3$ = micrograms per cubic meter
NDMA = nitrosodimethylamine
NPIP = nitrosopiperidine
NMOR = nitrosomorpholine
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 $\mu g/m^3$.

Table 7. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures of Vehicle Sealing Department Workers Who do not Work on the Salt Bath Lines. January 25 – February 2, 1995. HETA 94–0072.

				Nitrosamine Concentration (µg/m³)			
#	Job Title	Date	Sample Volume (L)	NDMA	NPIP	NMOR	Total
024	skive press operator	1/25/95	426	1.2	1.5	0.1	2.8
020	a–pillar assembly	1/25/95	462	1.4	1.4	2.4	5.2
027	press operator	1/25/95	464	1.3	1.3	1.3	3.9
043	a–pillar press operator	1/25/95	457	1.0	1.1	1.6	3.7
039	punch press operator	1/25/95	446	1.4	1.4	0.2	3.0
055	box making	1/25/95	458	0.5	0.8	0.07	1.4
032	cold splice operator	1/26/95	456	0.9	1.3	0.3	2.5
030	press operator	1/26/95	463	1.4	0.9	0.9	3.2
034	a–pillar press operator	1/26/95	461	2.4	1.2	1.4	5.0
116	a–pillar press operator	1/26/95	440	0.6	0.6	0.8	2.0
021	end–dip operator	2/1/95	451	0.9	0.9	0.1	1.9
019	end–dip operator	2/1/95	433	0.9	0.7	0.09	1.7
042	skive press operator	2/1/95	447	2.7	1.0	0.07	3.8
037	b–pillar press operator	2/2/95	454	1.2	1.3	0.6	3.1
036	sand blaster repair	2/2/95	447	1.0	0.9	0.2	2.1
031	b–pillar press operator	2/2/95	453	0.9	0.9	0.5	2.3
Average Exposure				1.2±0.6	1.1±0.3	0.7±0.7	3.0±1.1

# = sample number
L = liters
µg/m³ = micrograms per cubic meter
NDMA = nitrosodimethylamine
NPIP = nitrosopiperidine
NMOR = nitrosomorpholine
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 µg/m³.

Table 8. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures of Workers Who do not Work in the Vehicle Sealing Department but are often in the Vehicle Sealing Area. January 25 – February 2, 1995. HETA 94–0072.

				Nitrosamine Concentration ($\mu g/m^3$)			
#	Job Title	Date	Sample Volume (L)	NDMA	NPIP	NMOR	Total
044	trainer, end of extruder line	1/25/95	431	0.9	0.7	0.07	1.7
062	maintenance	1/25/95	452	0.8	1.2	0.3	2.3
058	process engineer	1/25/95	441	0.7	0.5	0.1	1.3
068	engineer	1/25/95	378	0.2	0.2	0.03	0.4
047	engineer	1/26/95	465	3.7	1.7	0.3	5.7
115	electrician	1/26/95	452	1.6	1.0	0.3	2.9
063	quality engineer	1/26/95	435	0.6	0.5	0.07	1.2
061	maintenance	1/26/95	449	1.8	1.0	0.5	3.3
077	sales manager	1/26/95	418	1.0	0.5	0.1	1.6
073	inventory analyst	1/26/95	445	2.5	2.2	0.1	4.8
051	maintenance	2/1/95	450	2.0	1.1	0.4	3.5
050	personnel office	2/1/95	448	0.2	0.1	0.04	0.4
057	purchasing agent	2/1/95	408	2.3	1.7	0.07	4.1
054	maintenance	2/2/95	453	1.0	0.7	0.1	1.8
064	maintenance	2/2/95	470	1.2	0.7	0.2	2.1
049	maintenance	2/2/95	449	1.2	0.9	0.2	2.3
052	janitor	2/2/95	405	0.7	0.6	0.1	1.4
048	maintenance	2/2/95	428	1.0	0.7	0.2	1.9
072	maintenance office	2/2/95	452	1.1	0.8	0.2	2.1
070	shipping and receiving office	2/2/95	407	0.8	0.7	0.05	1.6
Average Exposure				1.3±0.8	0.9±0.5	0.2±0.1	2.3±1.4

# = sample number
L = liters
$\mu g/m^3$ = micrograms per cubic meter
NDMA = nitrosodimethylamine
NPIP = nitrosopiperidine
NMOR = nitrosomorpholine
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 $\mu g/m^3$.

Table 9. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures of Workers that are not in the Vehicle Sealing Area. January 25 – February 2, 1995. HETA 94–0072.

				Nitrosamine Concentration ($\mu g/m^3$)			
#	Job Location	Date	Sample Volume (L)	NDMA	NPIP	NMOR	Total
086	mix house	1/25/95	451	0.1	0.1	0.04	0.2
085	mix house	1/25/95	444	0.2	0.1	0.2	0.5
025	union hall	1/25/95	400	0.2	0.2	0.05	0.5
084	mix house	1/25/95	432	1.6	0.4	ND	2.0
082	mix house	1/25/95	454	0.07	0.02	ND	0.09
076	mix house	1/25/95	433	0.5	0.8	0.07	1.4
067	mix house	1/26/95	455	0.1	0.09	ND	0.2
080	mix house	1/26/95	440	0.2	0.1	0.02	0.3
078	mix house	1/26/95	424	1.4	0.5	ND	1.9
066	mix house	1/26/95	441	0.2	0.1	0.05	0.4
083	mix house	1/26/95	441	0.4	0.07	0.02	0.5
081	union hall	2/1/95	411	0.1	ND	ND	0.1
Average Exposure				0.4±0.5	0.2±0.2	0.04± 0.06	0.7±0.7

# = sample number
L = liters
$\mu g/m^3$ = micrograms per cubic meter
NDMA = nitrosodimethylamine
NPIP = nitrosopiperidine
NMOR = nitrosomorpholine
ND = none detected, minimum detectable concentration was 0.02 $\mu g/m^3$
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 $\mu g/m^3$.

Table 10. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures During Salt Bath Cleaning Operations. January 25 – February 2, 1995. HETA 94–0072.

			Nitrosamine Concentration ($\mu g/m^3$)			
Location	**Date**	**Sample Volume (L)**	**NDMA**	**NPIP**	**NMOR**	**Total**
line 8	2/1/95	25	4.0	1.2	4.4	9.6
line 1	2/2/95	65	3.8	4.9	0.3	9.0
line 1	2/2/95	118	1.8	1.1	0.3	3.2
Average Exposure			3.2±1.2	2.4±2.2	1.7±2.4	7.3±3.5

$\mu g/m^3$ = micrograms per cubic meter
L = liters
NDMA = nitrosodimethylamine
NPIP = nitrosopiperidine
NMOR = nitrosomorpholine
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 $\mu g/m^3$.

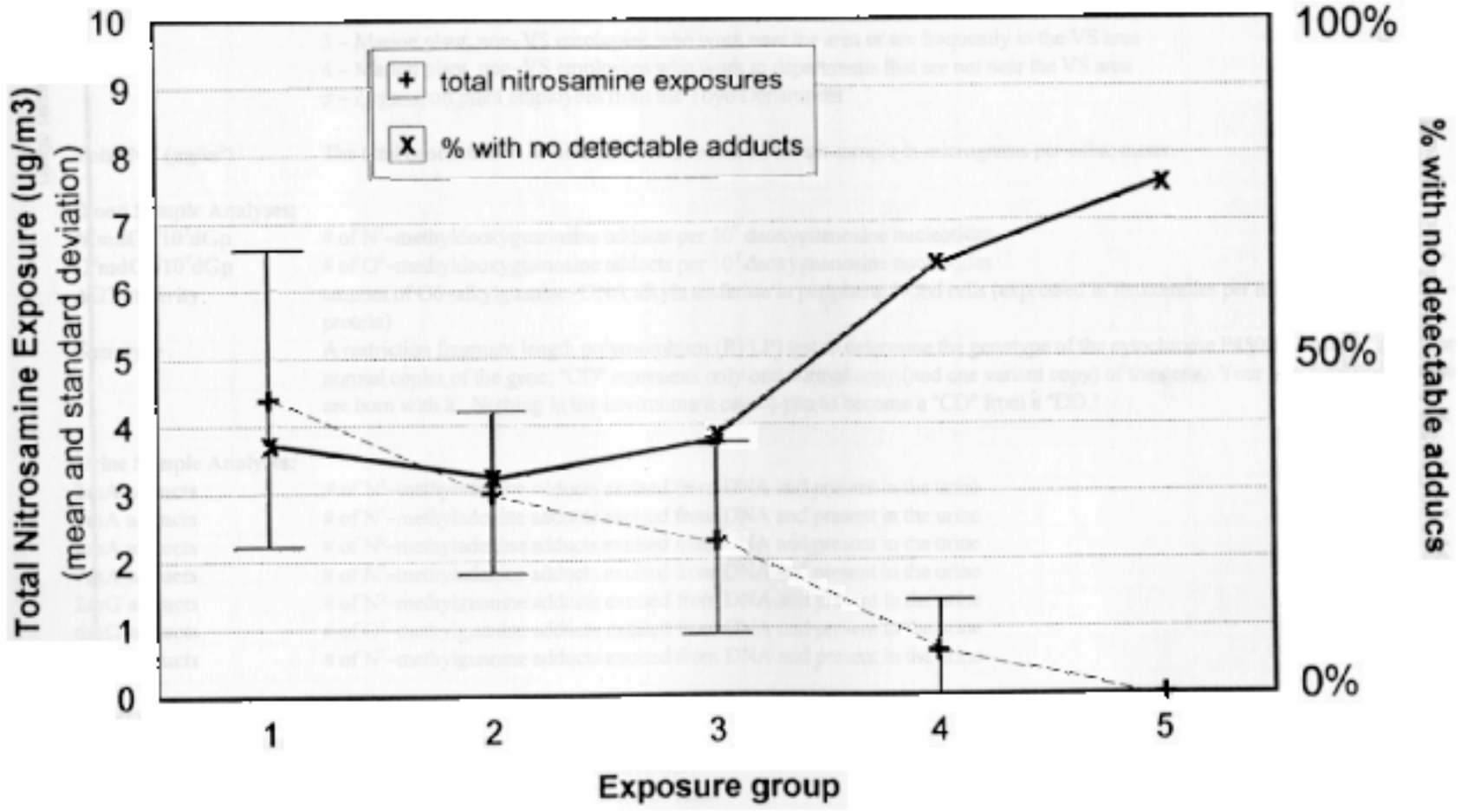
Table 11. Personal Breathing Zone Air Sampling Results for Nitrate and Nitrite Particulate Exposures During Salt Bath Operations. January 25 – February 2, 1995. HETA 94–0072.

Sample #	Job	Date	Sample Volume (L)	Nitrate ($\mu g/m^3$)	Nitrite ($\mu g/m^3$)
1	Front end feeder	1/25/95	858	8.8	ND
9	Line 8 assistant operator	1/25/95	882	17.5	ND
13	Line 3 assistant operator	1/25/95	870	6.1	ND
7	Line 7 operator	1/26/95	902	20.1	ND
14	Line 2 operator	1/26/95	916	19.1	ND
16	Front end feeder	1/26/95	854	trace	ND
10	Line 2 assistant operator	2/1/95	906	21.5	ND
12	Line 3 operator	2/1/95	902	18.1	ND
15	Line 5 assistant operator	2/1/95	926	26.1	trace
17	Line 5 operator	2/1/95	876	14.0	ND
6	Line 2 assistant operator	2/1/95	726	15.8	ND
11	Line 6 assistant operator	2/1/95	718	24.9	ND
2	Spray booth maintenance	2/2/95	874	8.0	ND
4	Line 2 assistant operator	2/2/95	930	trace	ND
5	Line 3 assistant operator	2/2/95	874	12.1	ND
18	Line 4 assistant operator	2/2/95	916	trace	ND
28	Line 4 operator	2/2/95	878	trace	ND
Minimum detectable concentrations (based on lowest and highest air volumes, 854 and 930 liters)				1.6–1.8	3.2–3.5
Minimum quantifiable concentrations (based on lowest and highest air volumes, 854 and 930 liters)				5.4–5.9	7.5–8.2

$\mu g/m^3$ = micrograms per cubic meter
L = liters
trace = above the minimum detectable concentration but below the minimum quantifiable concentration
ND = none detected, below the minimum detectable concentration

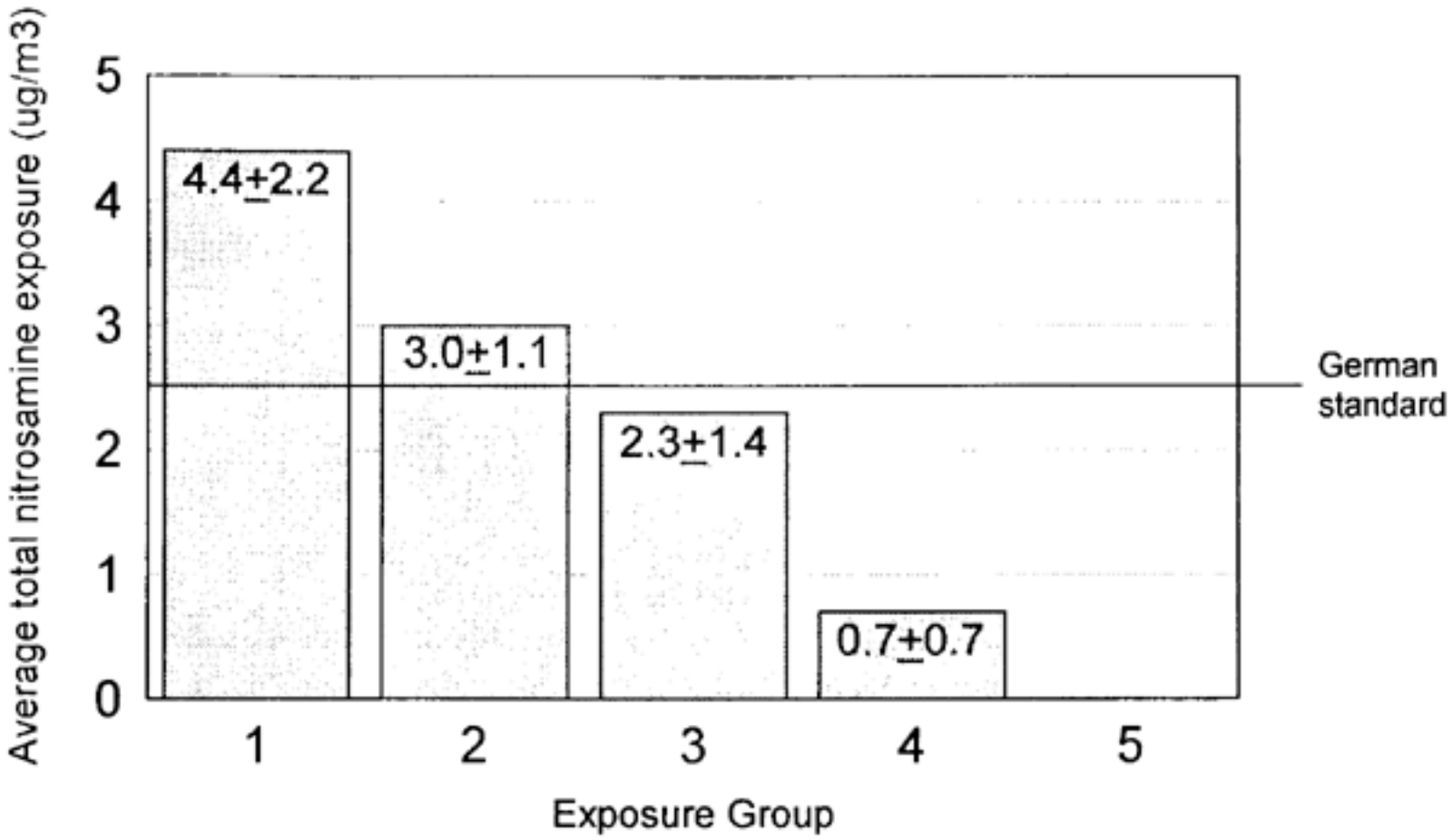
Figure 2

Total Occupational Nitrosamine Exposure and Percent of Employees With No Detectable O^6-methylguanine Adducts by Exposure Group. Gen Corp Automotive, Marion, Indiana. HETA 94-0072.



There is a significant positive trend between exposure group and having detectable levels of O^6-methylguanine adducts (p=0.05).
There was no significant association between tobacco use and having detectable levels of O^6-methylguanine adducts.
There was no significant association between genotype and having detectable levels of O^6-methylguanine adducts.

Figure 1
Average Exposure to Total Nitrosamines by Job Location.
Gen Corp Automotive, Marion, Indiana. HETA 94-0072.



Exposure Group:
1 - vehicle sealing department, salt bath line workers
2 - other vehicle sealing department employees
3 - non-vehicle sealing department employees, but often in or near area
4 - non-vehicle sealing employees, not near area
5 - Logansport plant employees

Appendix B

Biological Monitoring Results

(Note: individual results do not have significance, only population results can be evaluated)

Biological Sampling Results, Gen Corp Automotive, HETA 94–0072, January 25 – February 2, 1995

Key for Reading the Table

Sample #	A personal identification number known only to NIOSH researchers and the individual
Exp. Cat. (exposure category)	1 – Marion plant employees who work directly on the salt bath lines in the Vehicle Sealing (VS) Department 2 – Marion plant employees who do not work on the salt bath lines but do work in the VS Department 3 – Marion plant, non–VS employees who work near the area or are frequently in the VS area 4 – Marion plant, non–VS employees who work in departments that are not near the VS area 5 – Logansport plant employees from the Toyo Department
Total NA ($\mu g/m^3$)	The total concentration of nitrosamines detected on the air sample in micrograms per cubic meter.
Blood Sample Analyses:	
N^7mdGp/10^7dGp	# of N^7–methyldeoxyguanosine adducts per 10^7 deoxyguanosine nucleotides
O^6mdGp/10^7dGp	# of O^6–methyldeoxyguanosine adducts per 10^7 deoxyguanosine nucleotides
AGT Activity	amount of O6–alkylguanine–DNA alkyltransferase in peripheral blood cells (expressed in femtomoles per milligram of total cell–extract protein)
Genotype	A restriction fragment length polymorphism (RFLP) test to determine the genotype of the cytochrome P450IIE1 gene. "DD" represents two normal copies of the gene; "CD" represents only one normal copy (and one variant copy) of the gene. Your genotype does not change; you are born with it. Nothing in the environment causes you to become a "CD" from a "DD."
Urine Sample Analyses:	
2mA adducts	# of N^2–methyladenine adducts excised from DNA and present in the urine
3mA adducts	# of N^3–methyladenine adducts excised from DNA and present in the urine
6mA adducts	# of N^6–methyladenine adducts excised from DNA and present in the urine
7mA adducts	# of N^7–methyladenine adducts excised from DNA and present in the urine
2mG adducts	# of N^2–methylguanine adducts excised from DNA and present in the urine
6mG adducts	# of O^6–methylguanine adducts excised from DNA and present in the urine
7mG adducts	# of N^7–methylguanine adducts excised from DNA and present in the urine

Abbreviations:

LOD	– analytical limit of detection
ND	– none detected, below the limit of detection (LOD)
int.peak	– interfering peak, the measurement could not be read
instr.fail	– instrument failure, the sample was lost and no measurement recorded
—	– no result for this sample (either not enough sample for the test or instrument failure)

Biological Sampling Results, Gen Corp Automotive, HETA 94–0072, January 25 – February 2, 1995

#	Exp. Cat.	Total NA (ug/m^3)	DNA Adducts in Blood Cells		AGT Activity (fmol/mg protein)	Geno–type	Methylated Adenine Excision Products in the Urine				Methylated Guanine Excision Products in the Urine		
			N^7mdGp/ 10^7dGp	O^6mdGp/ 10^7dGp			2mA	3mA	6mA	7mA	2mG	6mG	7mG
1	1	2.9	21.4	3.2	—	DD	81.6	78.3	906.9	18424.7	14129.5	33.2	403.6
2	1	3.4	2.2	0.5	80.07	DD	68	33.3	530.3	37686.1	4893.5	6443.1	2724
4	1	4.4	3.2	0.5	77.39	CD	7295.1	2404.3	56830.3	2652630	423.1	763.3	6538.4
5	1	9.3	30.2	0.3	42.91	DD	145.1	41.5	848.9	15811.4	8967.3	112.4	3208.3
6	1	5.8	1.5	ND	422.18	CD	62.3	52.4	8134.1	15101.5	8696.9	249.3	2814.9
7	1	3.2	0.1	ND	232.08	DD	—	—	—	—	1075.3	776.2	2716.3
9	1	2.6	40.9	9.8	—	DD	—	—	—	—	9706.1	36.5	3250.7
10	1	7.6	0.1	ND	376.03	DD	301.4	150.8	791.2	114510.6	437.4	518.7	2250.5
11	1	2.3	0.9	ND	158.67	DD	466.1	3101.4	4050.4	85084	595.9	252.3	2818.7
12	1	7.6	3.9	0.4	276.13	DD	57167.9	9382.8	15824.5	1466646	49075.9	21969.8	21921.4
13	1	2.1	45.9	3.7	—	DD	128	28.3	725.8	22623.7	7764.2	22	3490.9
14	1	3.7	0.1	ND	98.75	DD	74.6	62.1	2689.7	27933.7	1370.6	28.8	3673.8
15	1	5.4	17.7	0.5	366.74	DD	3523.8	830.8	13622.7	447752	6889.3	810.3	2432.9
16	1	2	67.1	interf. pea	—	DD	3935.8	5189.7	10110.4	1678629	21540	2324	18053.2
17	1	4.9	72.4	12.7	278.47	DD	58.7	71.6	1183.2	22177.2	82989.8	2876.8	12451.2
18	1	5.2	0.2	ND	0.00	DD	79.6	28.5	750.8	25107.6	12771.7	143.8	2050
19	2	1.7	1.3	ND	269.93	DD	38	42.6	786.1	8249.6	9108.7	34.9	3074
20	2	5.2	40.9	9.2	—	DD	35.3	38.8	660.8	8979	597.9	777.1	4575.6
21	2	1.9	0.3	ND	507.87	DD	60	26.4	566.8	27394.7	6851.5	28.1	3948.8
24	2	2.8	23.1	interf. pea	—	DD	215	65.3	1427.2	78775.4	13399.5	1249	4946.9

#	Exp. Cat.	Total NA (ug/m^3)	DNA Adducts in Blood Cells		AGT Activity (fmol/mg protein)	Geno–type	Methylated Adenine Excision Products in the Urine				Methylated Guanine Excision Products in the Urine		
			N^7mdGp/ 10^7dGp	O^6mdGp/ 10^7dGp			2mA	3mA	6mA	7mA	2mG	6mG	7mG
25	4	0.5	49.5	1.8	—	DD	47.1	28.6	1078.6	8746.9	403.3	22.2	1097.1
27	2	3.9	22.2	1.6	—	DD	258	63.6	705.1	8845.8	2623.3	188.3	3228
28	1	3	4.3	0.5	240.21	DD	61.1	53.3	2719.3	58771.5	11589.6	407.4	4042.1
30	2	3.2	2.0	0.4	0.00	DD	3832.6	728.2	3866.4	1058531	415	594.6	3125.3
31	2	2.3	1.2	0.4	33.85	DD	3236.3	5411.3	8774.6	881942.3	9058.9	204.3	3717.9
32	2	2.5	1.0	ND	51.61	DD	43.2	83.4	4177.1	35630.1	6007.6	300.1	3028.4
34	2	5	1.1	0.4	137.69	DD	871.3	1442.9	3838	243567.1	3026.2	2625.5	3517.4
36	2	2.1	1.4	ND	253.92	DD	1950.1	1514.1	56149.4	1007935	673.2	574.6	5322.3
37	2	3.1	2.5	interf. pea	0.00	CD	72.7	56.9	1784.9	15758.5	901.4	22	4920.9
42	2	3.8	59.9	0.9	347.81	DD	69.1	60.4	1610.4	47243.6	9977.5	228.5	3862.1
43	2	3.7	133.2	2.5	—	DD	261.1	54.1	4459.6	29501.8	534.3	85608.8	5181
44	3	1.7	1.8	ND	—	DD	3.3	2.2	66.7	868.6	909.9	709.3	1927.5
47	3	5.7	0.3	ND	—	DD	25906.4	18032.5	25390.4	1753454	446.1	3946	4117
48	3	1.9	40.9	0.7	67.66	DD	15897	1476.1	94719.7	3609345	12129.7	11151.2	4802.6
49	3	2.3	9.6	2.4	219.93	CD	195.2	58.5	1038.4	80162.4	311.4	15376.4	4869.1
50	3	0.4	2.4	0.2	222.45	DD	4416.9	426.5	26247.4	999895.5	216868.1	2615.8	11251.7
51	3	3.5	0.6	ND	53.08	DD	3299.6	1247.6	30043.9	869116.8	10540.5	370.4	5318.6
52	3	1.4	1.9	0.5	108.08	DD	6161.9	1632.4	16019.2	3620015	512.7	8043.5	14024.2
54	3	1.8	0.1	ND	121.27	DD	216.2	82.6	608.7	39628.6	18437.8	45945.2	5293.5

#	Exp. Cat.	Total NA (ug/m^3)	DNA Adducts in Blood Cells		AGT Activity (fmol/mg protein)	Geno–type	Methylated Adenine Excision Products in the Urine				Methylated Guanine Excision Products in the Urine		
			N^7mdGp/ 10^7dGp	O^6mdGp/ 10^7dGp			2mA	3mA	6mA	7mA	2mG	6mG	7mG
55	2	1.4	118.4	7.8	—	DD	251.1	78.6	221.6	1931	2551.6	1503.9	1282.5
57	3	4.1	79.7	ND	456.63	DD	79.6	62.4	1936.4	45936.1	8873.4	503	4068.6
58	3	1.3	1.1	ND	152.66	DD	451.8	110.2	10485.6	290477	12736.4	487.8	4918.7
61	3	3.3	8.9	0.4	109.51	DD	222.7	43.4	1086	41827	6332.7	227.5	3329.2
62	3	2.3	11.6	2.6	—	CD	59.9	98.4	1603.9	77867.3	1099	717	4573.4
63	3	1.2	0.5	0.03	—	DD	15876.6	4886.5	60390.3	8253263	1824.2	274631.3	26666.9
64	3	2.1	7.1	1.4	178.35	CD	96.6	20.4	779.8	17351.7	9194.6	28.6	1418.2
66	4	0.4	0.1	ND	20.04	DD	294.9	72.4	716.7	4974.4	922943.7	3948502	60680.2
67	4	0.2	0.6	ND	485.03	DD	57.4	18.3	2152.8	22523	8399.9	21.9	3154.1
68	3	0.4	5.6	0.9	—	DD	233	60.7	1597.6	82876.1	288.7	12021.2	6742.6
70	3	1.6	8.9	0.4	76.38	CD	344.7	107.5	1682.7	19165.1	3407.1	3480.1	4783.2
72	3	2.1	1.9	ND	2.08	CD	85.8	42.6	615.9	40235.7	13330.8	21162	2587.8
73	3	4.8	26.9	interf. pea	0.00	DD	116.3	50.3	1327.3	7994.7	12127.2	55.7	4263.1
76	4	1.4	69.7	instr. fail.	—	DD	289.5	420.4	411.4	7848.3	569.4	110	1796.4
77	3	1.6	0.9	0.2	249.71	DD	110.4	169.2	893.6	9932.6	1247.2	9613.4	4300
78	4	1.9	0.2	ND	148.28	DD	166.6	26.8	624.2	37649.9	279.1	39789.6	5035.8
80	4	0.3	0.2	ND	173.95	DD	442.8	120.6	436.9	26292	864.1	35.9	2175.4
81	4	0.1	0.9	0.3	125.90	DD	191.2	315.2	996.4	68107	21212.5	31029.6	7791.4
82	4	0.09	40.9	8.6	—	DD	38.1	15.7	567.4	21349	2587.2	25.3	2774.1
83	4	0.5	0.1	ND	59.01	CD	135.3	158.4	654	12716.4	1167.3	11341.7	3629.7
84	4	2	0.6	ND	—	DD	134	41.5	780.4	20516.2	2340.4	50.5	2126.5

#	Exp. Cat.	Total NA (ug/m^3)	DNA Adducts in Blood Cells		AGT Activity (fmol/mg protein)	Geno–type	Methylated Adenine Excision Products in the Urine				Methylated Guanine Excision Products in the Urine		
			N^7mdGp/ 10^7dGp	O^6mdGp/ 10^7dGp			2mA	3mA	6mA	7mA	2mG	6mG	7mG
85	4	0.5	5.6	ND	—	DD	37.8	60.5	604.1	37004.8	11407.2	36.7	3758.2
86	4	0.2	36.5	9.6	—	DD	90.4	51.8	2275.9	51008.4	18251.1	109.7	3689.3
87	5	0	1.4	ND	50.08	DD	3912.3	1418.7	93706.1	2229594	183.8	388.3	5115.5
88	5	0	23.1	0.4	240.51	DD	126.7	97	693.2	16866.5	1113.7	1863.1	6668.9
89	5	0	128.2	1.6	188.65	DD	96	40.4	4590.1	45494.6	1367.2	3801.5	5010.4
91	5	0	28.0	2.4	60.54	DD	155.1	52.6	1214.1	56348.3	5849.8	393	4648
93	5	0	17.1	ND	130.00	DD	910.5	489.6	822.9	18401.5	22315.5	4597.6	5525.4
94	5	0	0.2	ND	24.59	DD	123.8	185.4	851.3	24392.8	7153.3	33.3	4147.8
95	5	0	0.4	ND	373.36	DD	14964.2	0	19787.7	142090.6	16215.5	10.1	2282.3
96	5	0	0.1	ND	230.25	DD	134.7	70.5	644.6	24734.4	1762.9	1500	4353.7
98	5	0	0.2	0.1	179.05	DD	102.4	1139.6	1338.8	9430.6	2354713	7797432	66468.8
101	5	0	36.5	1.4	182.21	DD	156.7	41	571.8	29010.4	1338.9	44.9	2515.4
102	5	0	1.1	ND	809.43	CD	3278.1	93.9	1899.2	490055.5	955.1	3656.9	6861.5
103	5	0	0.1	instr. fail.	175.79	DD	14577.3	6410.9	64927.4	518053.2	3199.6	68933.5	16252.3
104	5	0	0.1	ND	129.02	DD	—	—	—	—	—	—	—
105	5	0	0.6	ND	152.90	CD	337.4	399.7	2027.8	69144.5	2416.5	68056.9	14571.6
108	5	0	0.6	ND	244.17	CD	133.2	62	525.5	9713.8	1137.2	671.8	4106.1
109	5	0	1.3	ND	191.54	CD	3522.1	499.4	29560.6	761166.6	2204561	38713.6	40530
110	5	0	69.7	interf. pea	159.71	DD	29.2	89.7	631.4	37210.1	24552.6	261.4	3068.3

#	Exp. Cat.	Total NA (ug/m^3)	DNA Adducts in Blood Cells		AGT Activity (fmol/mg protein)	Geno–type	Methylated Adenine Excision Products in the Urine				Methylated Guanine Excision Products in the Urine		
			N^7mdGp/ 10^7dGp	O^6mdGp/ 10^7dGp			2mA	3mA	6mA	7mA	2mG	6mG	7mG
112	5	0	0.2	ND	217.41	CD	59.6	24.4	59.1	17091.8	8339.1	181.6	1401
113	5	0	0.2	ND	203.89	DD	63.1	55	560.7	39010.6	486.3	8607.5	5386.6
114	5	0	0.1	ND	297.00	CD	43.6	12.5	22.1	17389.2	911.6	1154.1	2740.2
115	5	0	0.2	ND	293.39	DD	2742.2	1026.7	61779.8	762416.5	14404.9	464.2	5436.7
116	5	0	0.4	ND	196.10	DD	3740.7	3336.9	74382	4111230	401.4	5390.3	6631.8
117	5	0	0.3	ND	154.93	DD	146.6	51.8	527	39294.4	16731.9	6977.5	6751.7

Appendix C

Interim Report
October 12, 1994

INTERIM REPORT
HETA 94-0072
GEN CORP AUTOMOTIVE
MARION, INDIANA

Project Officer: Beth Donovan, M.H.S.

I. INTRODUCTION

On February 16, 1994, National Institute for Occupational Safety and Health (NIOSH) investigators conducted a walk-through survey of the Gen Corp Automotive in Marion, Indiana, and collected general area samples in the following departments: the rubber vehicle sealing (VS) department, the sheet molding compound department (Mix House), and the liquid composite molding (LCM) department. In the VS area, n-nitrosamine, hydrocarbon, and polynuclear aromatic hydrocarbon (PNA) samples were collected. In the Mix House and LCM area, hydrocarbon samples were collected. N-nitrosamines and several organic solvents were detected on the area samples, but PNAs were not.

A follow-up site visit was conducted on May 3 to 5, 1994, to collect personal breathing zone air samples and additional general area air samples for n-nitrosamines and organic solvents. During this visit, methylene diisocyanate (MDI) samples were collected in the LCM area because MDI is used in the process. Also, the ventilation systems were evaluated.

Both site visits included medical interviews; informal conversations with employees; and review of records, Material Safety Data Sheets (MSDSs), and health and safety programs.

II. EVALUATION METHODS

Rubber Vehicle Sealing

Both nitrosamines and hydrocarbons were evaluated in the VS area. During the first site visit, three sets of duplicate samples were collected along lines five and six and analyzed for nitrosamines. These general area (GA) air samples were collected over a four hour period using Gillian® high-flow air pumps at a flow rate of 2 liters per minute (l/min). One of each duplicate set was analyzed in the NIOSH laboratory and one was sent to an outside laboratory. The outside laboratory, like most laboratories, uses gas chromatography (GC) and thermal energy analysis (TEA) for nitrosamine analysis. Identification of specific nitrosamines by TEA depends on two events. First, the chemical bond between two nitrogen atoms (N-NO) of the n-nitroso compound is thermally broken in the TEA pyrolyzer, resulting in the formation of a nitrosyl radical (NO) and subsequent detection by TEA. Second, the GC retention time of the analyte occurs at the same retention time as the standard. Unfortunately, other n-nitroso compounds can elute at retention times very close to those of the n-nitrosamine compounds being measured and the chromatographic

peaks may not be separated. For the same reason, an n-nitrosamine compound that elutes at a *similar* retention time as a nitrosamine standard may be mistakenly identified as that nitrosamine if the retention times are too close. The NIOSH method uses a capillary column instead of a packed column for the analysis – a process that separates the elution peaks better. Also, a high-resolution mass spectrometer (MS) operated in the selected-ion-monitoring (SIM) mode is used to confirm the identity of any compound that elutes at the same retention time as the nitrosamine standards by monitoring its molecular ion. In this way, the chromatographic peak is confirmed as the nitrosamine compound of interest.

The NIOSH method was chosen to do the future analyses because the NIOSH analysis identified nitrosodiethylamine (NDEA) on two samples that the outside laboratory did not; and confirmed the identification. The NIOSH laboratory did not detect nitrosodiphenylamine (NDPA) on three samples that the outside laboratory did. The NIOSH laboratory showed that the retention time for NDPA is 6:31 and that the sample peak eluted at 6:39. Peaks this close could not be separated using a packed column, which was used by the outside laboratory, but could be separated by a capillary column, which was used by NIOSH. Finally, the NIOSH analysis detected two chromatographic peaks near the nitrosomorpholine (NMOR) peak, only one of which was NMOR. The outside laboratory recorded higher amounts of NMOR and could have been summing the two peaks because they were not separated using the packed column.

During the second site visit, the nitrosamine samples were collected in the same manner as during the first. Over three days, 28 personal breathing zone (PBZ) air samples and 8 GA air samples were collected throughout the entire VS area. These samples were analyzed by the NIOSH laboratory. In addition, two bulk water samples were collected for nitrosamine analysis--one from the steam bath and one from the cooling drum.

Thermal desorption tubes were used to collect GA samples in VS during the first site visit. These samples were collected at a flowrate of 50 milliliters per minute (ml/min) using Gillian® low-flow pumps, and then qualitative analysis was performed in the NIOSH laboratory. During the second visit, charcoal tubes were used to collect PBZ samples for toluene, pyridine, limonene, and total hydrocarbon analysis. These analytes were chosen based on the results from the thermal desorption tubes and from a few area samples taken on the second visit. Also, Orbo-90 tubes were used to collect PBZ methyl ethyl ketone (MEK) samples. The charcoal tube and orbo tube samples were collected using Gillian® low-flow pumps at a flow rate of 50 ml/min.

Mix House

Hydrocarbon concentrations were measured in the Mix House as in the VS area. During the first visit, thermal desorption tubes were used to collect GA samples, which were collected at a flow rate of 50 ml/min using Gillian® low-flow pumps and

qualitatively analyzed in the NIOSH laboratory. During the second visit, Gillian® low-flow pumps at a flow rate of 50 ml/min were used to collect PBZ samples on charcoal tubes. These samples were analyzed for styrene, toluene, acetone, and methyl styrene.

Liquid Composite Molding

Hydrocarbon concentrations were measured in the LCM area as in the other two areas--using thermal desorption tubes on the first visit and charcoal tubes for PBZ samples on the second visit. Again, the samples were collected using Gillian® low-flow pumps at a flow rate of 50 ml/min. A bulk sample of the mold release spray was also obtained. The PBZ samples were analyzed for toluene and total hydrocarbons.

Methylene diisocyanate was sampled for during the second visit using NIOSH Analytical Method 5522. GA samples were collected with midget impingers and Gillian® high-flow air pumps at a flow rate of 2 l/min.

III. EVALUATION CRITERIA

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH field staff employ evaluation criteria for the assessment of a number of chemical and physical agents. The primary sources of environmental evaluation criteria for the workplace are the following: (1) NIOSH Criteria Documents and Recommended Exposure Limits (RELs), (2) the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs), and (3) the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs).[1,2,3] The objective of these criteria is to establish levels of exposure to which the vast majority of workers may be exposed without experiencing adverse health effects.

Full-shift and shorter duration criteria are available depending on the specific physiologic properties of the agent. Full-shift limits for chemical agents are based on the time-weighted average (TWA) airborne concentration of a substance that workers may be repeatedly exposed to during an 8 or 10 hour work day, up to 40 hours a week for a working lifetime, without adverse health effects. Some substances have short-term exposure limits (STELs) or ceiling limits (CLs) which are intended to supplement the full-shift criteria where there are recognized irritative or toxic effects from brief exposures to high airborne concentrations. STELs are based on 15 minute TWA concentrations, whereas CL concentrations should not be exceeded even momentarily.

Occupational health criteria are established based on the available scientific information provided by industrial experience, animal or human experimental data, or epidemiologic studies. It should be noted that RELs and TLVs are guidelines,

whereas PELs are standards which are legally enforceable. OSHA PELs are required to take into account the technical and economical feasibility of controlling exposures in various industries where the agents are present. The NIOSH RELs are primarily based upon the prevention of occupational disease without assessing the economic feasibility of the affected industries and as such may be lower. The ACGIH is not a government agency, it is a professional organization whose members are industrial hygienists or other professionals in related disciplines and are employed in the public or academic sector. TLVs are developed by consensus agreement of the ACGIH TLV committee and are published annually. The documentation supporting the TLVs (and proposed changes) is periodically reviewed and updated if believed necessary by the committee.

Not all workers will be protected from adverse health effects if their exposures are maintained below these occupational health exposure criteria. A small percentage may experience adverse effects due to individual susceptibility, a pre-existing medical condition, previous exposures, or a hypersensitivity (allergy). In addition, some hazardous substances may act in combination with other workplace exposures, or with medications or personal habits of the worker (such as smoking) to produce health effects even if the occupational exposures are controlled to the limit set by the evaluation criterion. These combined effects are often not considered by the chemical specific evaluation criteria. Furthermore, many substances are appreciably absorbed by direct contact with the skin and thus potentially increase the overall exposure and biologic response beyond that expected from inhalation alone. Finally, evaluation criteria may change over time as new information on the toxic effects of an agent become available. Because of these reasons, it is prudent for an employer to maintain worker exposures well below established occupational health criteria.

The evaluation criteria for the compounds analyzed during this health hazard evaluation are discussed below.

N-nitrosamines

Nitrosamines are compounds characterized by the -N--N=O functional group. They result from the combination of primary, secondary, or tertiary amines with nitrite. These reactions can occur in the laboratory; in various food, household, or industrial products; in industrial processes; and in vivo. Because of the variety of amines and reaction conditions possible, there are hundreds of nitrosamines; and because of the large number of exposure sources, including formation in vivo, there is a complicated matrix of total nitrosamine exposure. Occupational exogenous exposures have been observed in rubber industries, leather tanning industries, metal working industries, chemical industries, mining, pesticide production, detergent production, and fish factories.

Most nitrosamines are suspected to be human carcinogens, but direct causal associations have not yet been proven. Cancer is believed to be a multistage

process, beginning with (1) *exposure* to a carcinogen or procarcinogen and followed by (2) *initiation* of a cell to a genetically altered cell by damage to the DNA; (3) *promotion* of the altered cell to a preneoplastic lesion; (4) *conversion* of the preneoplastic lesion to a malignant tumor through a genetic change; and finally (5) *progression* of the tumor to clinical cancer. Exposure to a carcinogen must result in a genetic change in order to initiate a cell; likewise, there must also be a genetic change for a preneoplastic lesion to convert into a malignant tumor.[4] These genetic changes can occur from spontaneous mutations, and they can also occur with DNA adduct formation from exposure to carcinogens that are initiators or promoters, or both. These genetic changes also must occur in certain chromosomal locations in order to cause the next step in carcinogenicity. Mutations in some of these chromosomal locations have been identified, such as activation of proto-oncogenes or inactivation of tumor suppressor genes, but these and other processes are still being researched.[4]

There are many confounding factors that prevent every exposure to a carcinogen from resulting in clinical cancer. Genetic predisposition--inheritance of certain genetic mutations, variations in activity of metabolizing enzymes and DNA repair enzymes, variations in immunity and immune cell enzymes--plays an important role in the development or lack of development of cancers. Variations in lifestyle and overall health can also play a part as these may affect immune function and intracellular repair processes.

The suspected mechanism of carcinogenesis of nitrosamines is that nitrosamines, from exogenous or endogenous sources, are metabolized into reactive intermediates which can then covalently bind to macromolecules, including DNA. If the adducts to the DNA result in a genetic mutation during the replication process, and if that mutation is in certain areas of the genome, the cell could undergo the second and third stages of carcinogenesis--initiation and promotion. If there was a second genetic change in the right place, conversion to a malignant tumor could result.

Although a causal association between nitrosamine exposure and human cancer has not yet been firmly established, there is circumstantial evidence that nitrosamines could cause cancer in humans. In 1956, Magee and Barnes demonstrated the carcinogenic potential of nitrosodimethylamine (NDMA) in rats.[5] Since then, nitrosamines have been studied extensively in laboratory animals. Approximately 90% of the 300 tested nitrosamines have shown carcinogenic effects in bioassays and laboratory animals. The animals that have been studied include mammals, birds, fish, and amphibia. Of the approximately 40 animal species tested, none has been resistant. The tumor sites depend on the specific nitrosamine, the species tested, and the route of administration. Nitrosamine affects have been demonstrated in the bladder, bronchi, central nervous system (CNS), earduct, esophagus, eyelid, duodenum, forestomach, glandular stomach, hematopoietic system, intestine, jaw, kidney, larynx, nasal cavity, oral cavity, ovary, liver, mammary glands, pancreas, pelvis, peripheral nervous system, pharynx, respiratory tract, skin, testes, trachea, uterus, and vagina.[6] Dose-response studies with rats

have shown "no effect levels" corresponding to dietary concentrations of 1 part per million (ppm) NDMA, 1 ppm NDEA, and 1 ppm NPYR.[6] These n-nitrosamines and others appear to be very potent carcinogens.

All of the biochemical, pathological, and experimental data provides little evidence that humans might be resistant to the carcinogenic potential of nitrosamines.[7] Human tissues from the trachea, bronchus (lung), esophagus, colon, pancreatic duct, bladder, and buccal mucosa have been shown to metabolize nitrosamines into DNA-binding compounds.[7] Human liver tissue appears to metabolize nitrosamines with a similar activity to rodent liver tissue, and rodents have similar acute symptoms of liver necrosis and cirrhosis that have been observed in humans.[7] A few human DNA adduct studies have revealed higher levels of nitrosamine-related DNA adducts in cancer cases than in controls.[8,9] Studies in experimental animals have shown similar DNA adduct formation to those detected in the human studies.[10-12]

Only one nitrosamine, NDMA, is regulated in the United States. Both the OSHA and NIOSH regulate NDMA as an occupational carcinogen, recommending that its exposure be reduced to the lowest feasible concentration. There are no established numerical exposure limits in this country.

Germany has strict regulations for occupational exposures to nitrosamines. In general industry, the total exposure to all nitrosamines present may not exceed 1 microgram per cubic meter ($\mu g/m^3$). In special cases, such as the tire storage warehouses, exposures to all nitrosamines present may not exceed 2.5 $\mu g/m^3$. In addition to these regulations, eight nitrosamines are regulated individually--nitrosodimethylamine, nitrosomorpholine, nitrosopiperidine, phenyl-ethylnitrosamine, phenyl-methylnitrosamine, di-N-butylnitrosamine, di-iso-propylnitrosamine, dimethylnitrosamine.

Methylene Diisocyanate (MDI)

Diisocyanates are usually referred to by their specific acronym; e.g., TDI for 2,4- and 2,6-toluene diisocyanate, HDI for 1,6-hexamethylene diisocyanate, MDI for 4,4'-diphenylmethane diisocyanate, NDI for 1,5-naphthalene diisocyanate, etc. The unique feature common to all diisocyanates is they consist of two -N=C=O (isocyanate) functional groups attached to an aromatic or aliphatic parent compound. Because of the highly unsaturated nature of the isocyanate functional group, the diisocyanates readily react with compounds containing active hydrogen atoms to form urethanes. The chemical reactivity of diisocyanates, and their unique ability to cross-link, makes them ideal for polymer (polyurethane) formation. Hence, they are widely used in surface coatings, polyurethane foams, adhesives, resins, elastomers, binders, and sealants.

In general, the type of exposures encountered during the use of diisocyanates in the workplace are related to the vapor pressures of the individual compounds.

The lower molecular weight diisocyanates tend to volatilize at room temperature, creating a potential vapor inhalation hazard. Conversely, the higher molecular weight diisocyanates do not readily volatilize at ambient temperatures, but are still a potential inhalation hazard if aerosolized or heated in the work environment. The latter is very important since most reactions involving diisocyanates are exothermic in nature, thus providing the heat for volatilization. In an attempt to reduce the vapor hazards associated with the lower molecular weight diisocyanates, prepolymer and oligomer forms of these monomers were developed, and have replaced the monomers in many product formulations. Many product formulations that contain MDI actually contain a combination of MDI monomer and MDI oligomer (polymethylene polyphenyl isocyanate). Experience with both the monomeric and oligomeric forms of diisocyanates has shown that the occurrence of health effects is dependent on exposure, not molecular weight.

Exposure to the diisocyanates can produce irritation to the skin, mucous membranes, eyes, and respiratory tract. High concentrations may result in chemical bronchitis, chest tightness, nocturnal dyspnea, pulmonary edema, and death.[13,14] The most common adverse health outcome associated with diisocyanate exposure is increased airway obstruction (asthma), and to a lesser extent dermal sensitization and hypersensitivity pneumonitis (HP).[14-16]

Whenever there is a potential for a hazardous exposure to diisocyanates, traditional industrial hygiene practice dictates that the following hierarchy of controls, in decreasing order of desirability and effectiveness, be implemented to protect worker health:

1. Elimination of the toxic substance from the workplace.

2. Substitution of the toxic substance with a less toxic substance.

3. Installation of engineering controls designed to reduce exposure.

4. Use of administrative controls to reduce exposure.

5. Use of personal protective equipment to reduce exposure.

In many instances, it is not possible to eliminate or substitute a diisocyanate from a production process without altering the integrity of the desired product. Thus, most strategies for reducing diisocyanate exposure center on the use of engineering controls and personal protective equipment. Local exhaust ventilation and/or process isolation are commonly used controls for diisocyanate exposure reduction. Personal protective equipment should only be used when engineering controls are not feasible, in the interim when engineering controls are being installed or repaired, or when engineering controls have not sufficiently reduced diisocyanate exposures. NIOSH recommends that whenever there is a potential for exposure to diisocyanates, including concentrations below the NIOSH recommended exposure

level of 0.005 ppm TWA and 0.020 ppm CL, that the employer provide the worker with supplied-air respiratory protection.[13] Air-purifying respirators are not appropriate; diisocyanates have poor odor warning properties. Personal protective equipment should also be used to prevent skin and eye contact with diisocyanates.

NIOSH recommends both preplacement and periodic medical surveillance programs for all workers potentially exposed to diisocyanates.[13] The preplacement examinations should consist of detailed medical and work histories with emphasis on pre-existing respiratory and/or allergic conditions, a physical examination that centers on the respiratory tract, a baseline pulmonary function test that measures forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), and a judgement on the worker's ability to wear a supplied-air respirator. Workers should be provided with annual examinations which update the medical and work histories, and measure the worker's FEV_1 and FVC. NIOSH also recommends that employers conduct exposure monitoring campaigns every 6 months.[13] Workers' exposure should be determined for each operation in each work area, and should also be measured whenever there are changes in the process or engineering controls. The only effective control for workers with diisocyanate-induced asthma or HP is cessation of exposure. This can be accomplished by removing the worker from the work environment where diisocyanate exposure occurs, or by providing the worker with supplied-air respiratory protection.

Organic Solvents

Exposure to organic solvents can occur through inhalation of the vapors and absorption through the skin. Acute effects from exposure to high concentrations of solvents often include anesthesia, central nervous system (CNS) depression, impaired motor function, respiratory arrest, unconsciousness, and death.[17] At lower concentrations, symptoms of dizziness, headaches, fatigue, lightheadedness, weakness, poor concentration, and mucous membrane irritation may occur.[17,18] Chronic effects that have been reported among some workers exposed to organic solvents include peripheral neuropathies, organic affective syndrome, and mild chronic toxic encephalopathy. Organic affective syndrome is characterized by fatigue, memory impairment, irritability, difficulty in concentration, and mild mood disturbance. Mild chronic toxic encephalopathy is manifested by sustained personality or mood changes such as emotional instability, diminished impulse control and motivation, and learning capacity. The extent to which chronic neurotoxicity is reversible remains to be established.[17]

The relevant evaluation criteria for the organic solvents that were detected and characterized at the facility are listed below.

Table 1. Relevant Evaluation Criteria for Aromatic Hydrocarbons Sampled at Gen Corp Automotive in Marion, Indiana. May 3 to May 5, 1994. HETA 94-0072

Solvent	NIOSH REL (ppm)	OSHA PEL (ppm)	ACGIH TLV (ppm)	Target Organs[18,19]	Symptoms[18,19]
TOLUENE	100 ST 150	200 CL 300	50 skin	CNS, liver, kidneys, skin	fatigue, weakness, confusion, dizziness, headaches, muscle fatigue, insomnia, dermatitis, narcosis
ACETONE	250	1000	750	respiratory system, skin	eye, nose, throat irritation; headaches, dizziness; dermatitis
STYRENE	50 ST 100	100 CL 200	50 skin	CNS, eyes, skin, respiratory	eye, nose, throat irritation; drowsiness; weakness; narcosis; unsteady gait; defattening dermatitis
MEK	200 ST 300	200	200	CNS, lungs, skin	eye, nose, throat irritation; headache; dizziness; vomiting; dermatitis
PYRIDINE	5	5	5	CNS, liver, kidneys, skin, GI tract	headache, nervousness, dizziness, insomnia, nausea, anorexia, frequent urination, eye irritation, dermatitis, liver and kidney damage, vertigo, vomiting
LIMONENE	--	--	--	--	--

NIOSH REL - National Institute for Occupational Safety and Health recommended exposure limit (10-hour time-weighted average)
OSHA PEL - Occupational Safety and Health Administration permissible exposure limit (8-hour time-weighted average)
ACGIH TLV - American Conference of Government Industrial Hygienists threshold limit value (8-hour time-weighted average)
ST - short-term exposure limit (15-minute time-weighted average)
MEK - methyl ethyl ketone (synonym, 2-butanone)
skin - dermal and mucous membrane absorption can significantly contribute to exposure
CNS - central nervous system
GI tract - gastrointestinal tract

IV. RESULTS AND DISCUSSION

Rubber Vehicle Sealing Results

Nitrosamines

During the first site visit, three GA samples were collected and analyzed for n-nitrosamines in the VS area. Sample 1 was collected by the drill press on line 5; sample 2 was collected just past the infrared oven on line 6; and sample 3 was collected midway along the salt bath on line 6. All three samples had detectable amounts of nitrosodimethylamine (NDMA), nitrosopiperidine (NPIP), and nitrosomorpholine (NMOR). Samples 1 and 2 had detectable amounts of nitrosodiethylamine (NDEA); and none of the samples had detectable amounts of nitrosodibutylamine (NDBA), nitrosodipropylamine (NDPA), and nitrosopyrrolidine (NPYR). The sampling media for sample 3 had a defective case on the pump side and therefore the numerical concentration is questionable; therefore, any numerical value reported can only be considered qualitative. The concentrations of NDMA detected on samples 1, 2, and 3 were 37.7 $\mu g/m^3$, 6.3 $\mu g/m^3$, and 0.78 $\mu g/m^3$, respectively. The concentrations of NPIP detected on samples 1, 2, and 3 were 7.6 $\mu g/m^3$, 3.9 $\mu g/m^3$, and 0.28 $\mu g/m^3$, respectively. The concentrations of NMOR detected on samples 1, 2, and 3 were 0.2 $\mu g/m^3$, 0.37 $\mu g/m^3$, and 0.13 $\mu g/m^3$, respectively. The concentrations of NDEA detected on samples 1 and 2 were 0.16 $\mu g/m^3$ and 0.38 $\mu g/m^3$, respectively. All of these sample results are time-weighted averages and each sample was collected over approximately four hours.

The GA samples suggested that volatile n-nitrosamines were present in this department. Thus, on the second site visit, PBZ and GA samples were collected for nitrosamines on all three days of the site visit. The sampling results are displayed in Tables 2, 3, and 4, located at the end of this report. All of the 28 PBZ samples had detectable concentrations of NDMA, NDEA, NPIP, and NMOR; 27 of the 28 samples had detectable concentrations of NPYR. None of the PBZ or GA samples had detectable concentrations of NDPA or NDBA. Five of the eight GA samples had detectable concentrations of NDMA, NDEA, NPIP, NPYR, and NMOR. The other three had detectable concentrations of NDMA, NPIP, NPYR, and NMOR, but no NDEA. Those three samples were taken at the drill press area of lines 5, 6, and 8 on May 5, 1994.

The highest PBZ exposures were collected on salt bath line operators, assistant operators, and coil packers. The PBZ exposures were highest for NDMA, ranging from 0.47 $\mu g/m^3$ to 11.44 $\mu g/m^3$. Next highest was NPIP, ranging from 0.20 $\mu g/m^3$ to 4.39 $\mu g/m^3$. Nitrosamine concentrations from the GA samples collected at the drill presses on different lines were very high, ranging from 2.29 $\mu g/m^3$ NDMA at line 6 on May 5, 1994, to 88.47 $\mu g/m^3$ NDMA at line 3 on May 5, 1994.

A GA sample was collected inside the smoking break room on May 4, 1994, and in the non-smoking break room on May 5, 1994. These samples both had detectable

concentrations of NDMA, NDEA, NPIP, NPYR, and NMOR. A concentration of 4.17 $\mu g/m^3$ of NDMA was detected in the smoking break room; and a concentration of 10.37 $\mu g/m^3$ of NDMA was detected in the non-smoking break room. Since cigarette smoke contains n-nitrosamines, their presence was expected in the smoking room. The probable cause of the high amount in the non-smoking room was that on May 5, 1994, the wind was out of the west/southwest. This wind direction blew the exhaust from the salt bath lines in the direction of the rooftop air handling units (AHUs) that served the offices and break rooms in the VS area. Specifically, the exhaust from line 8, zone D was visually observed flowing directly into the AHUs.

Two bulk samples were collected and analyzed for n-nitrosamines. One was a sample of the water in the bottom of the steam bath that cleans the rubber as it exits the salt bath. The other was a sample of water from the cooling drum. Neither bulk sample contained detectable amounts of n-nitrosamines--less than 0.02 μg per gram of water.

Volatile Organic Compounds

Samples were collected and analyzed for volatile organic compounds in the VS area. Six samples were analyzed for pyridine; eighteen were analyzed for methyl ethyl ketone (MEK); two were qualitatively analyzed for aromatic hydrocarbons; and fifty-four were quantitatively analyzed for toluene, limonene, and total hydrocarbons (n-decane standard) based on the qualitative analyses. The samples did not have detectable amounts of MEK, pyridine, or limonene. Four of 54 samples analyzed for total hydrocarbons (as n-decane) had detectable amounts of hydrocarbons, but they were not quantifiable. The other 50 samples did not have detectable amounts of total hydrocarbons. Toluene was detected on 20 of the 54 samples. However, only seven were quantifiable and had concentrations less than 2 ppm, well below any applicable standards.

Ventilation

Exhaust re-entering the building appears to be a problem in the VS offices and break areas, and also in the entire VS area. As mentioned above, when the winds are from the west/southwest, exhaust flows into the AHUs that supply the VS offices and break areas, which was observed on May 5, 1994. When the winds are from the north, the exhaust is blown into the courtyard between the VS building and the empty warehouse. There are two AHUs in this courtyard that supply make-up air to the VS area. Also, there is a large garage door on the side of the VS building that opens up to this courtyard. Exhaust was visually observed flowing into the AHUs and into the garage door opening on May 4, 1994. Similarly, when the wind is from the south, exhaust is blown to the other side of the VS building. Approximately 20 feet from this side of the building, there is a large water tank. Exhaust becomes trapped in eddies between the water tank and the building. There is another make-up air AHU in this area, and exhaust was seen flowing into it on February 16, 1994.

Inside the VS building, some of the local exhaust ventilation (LEV) was not working properly. In some cases the exhaust is overpowered by floor fans or make-up air currents, such as along line 8 at the UV ink spray jet. The LEV along the salt bath lines worked well in some areas, but not others. Some local exhaust fans that were not working included: line 7, zone D on May 3, 1994; and line 3, zone A, line 7, zone D, and line 8, zone D on May 4, 1994. In zones where the LEV fans were not working, fumes could be seen flowing out of the salt baths.

Among the various finishing operations, only some had LEV. The hot presses at the end of the salt bath lines and MM-12 area do not have any LEV, nor do the A-pillar, B-pillar, and C-pillar presses. The silicone spray booths and the hot presses in the southeast corner of the VS area do have LEV.

Mix House Results

Samples were only collected in the mix house on May 3 and May 4, 1994. Two GA samples were collected in the Mix House and analyzed qualitatively for aromatic hydrocarbons. Based on these analyses, the other samples collected in the mix house were analyzed quantitatively for acetone, toluene, styrene, and methylstyrene isomers. Acetone was detected on all 16 PBZ samples and the one GA sample, ranging from 3.1 ppm to 43.2 ppm, well below the applicable standards. Styrene was also detected on all of the samples, at concentrations ranging from less than 4.0 ppm to 19.3 ppm, also well below the applicable standards. Methyl styrene isomers were detected on only nine of the samples, but in amounts too small to quantify (between 0.05 ppm and 4.0 ppm). Toluene was not detected on any of the quantitated samples (minimal detectable concentrations ranging from 0.04 ppm to 0.06 ppm).

When silicate glass beads are used for the low-density formulations, there is no LEV system or containment system to reduce the amount of airborne particulates. The process did not appear excessively dusty when observed during the site visit, but there was a worker whose job it was to agitate the beads as they were sucked up into the A-mix bin. This worker wore a respirator by personal choice, but was wearing organic vapor cartridges and not dust/mist or high efficiency particulate air (HEPA) filter cartridges. Any employee issued a respirator, for voluntary use or not, must be part of the respiratory protection program, which involves a medical determination that the employee is physically able to wear a respirator, a fit test, and proper training on the use and maintenance of respirators. The worker that wore the respirator on May 4, 1994, clearly did not have the proper training.

Liquid Composite Molding Results

GA air samples were collected and analyzed for MDI monomer and oligomer, and concentrations were all below detectable amounts. One GA air sample was qualitatively analyzed for aromatic hydrocarbons and based on the results, 11 PBZ air samples were analyzed for toluene and total hydrocarbons. The total

hydrocarbon analysis was performed using a bulk sample of the mold release used in the process as the standard. Nine of the 11 samples had detectable amounts of toluene, but the amounts were very low. Six of those nine were below the minimal quantifiable concentration, and the other three had concentrations below 0.2 ppm, well below any applicable standards. The total hydrocarbon amounts were also quite low, most being below the minimal quantifiable concentrations.

V. PRELIMINARY CONCLUSIONS

Occupational exposure to n-nitrosamines appears to be occurring in the VS area of Gen Corp Automotive in Marion, Indiana. A combination of insufficient LEV and exhaust re-entering the work area results in a build-up of volatile n-nitrosamines in this work place.

Exposure through inhalation to volatile organic solvents and aromatic hydrocarbons in the VS area, the mix house, and the LCM area does not appear to be a problem. However, cotton gloves are not appropriate when handling these compounds.

VI. RECOMMENDATIONS

1. NIOSH considers NDMA to be an occupational carcinogen and recommends that its exposure be reduced to the lowest feasible concentration.[1] Since most nitrosamines have similar properties to NDMA and are suspected to be human carcinogens, the exposures to all nitrosamines in the VS area should be reduced as low as feasibly possible. The best solution is elimination of the source. A few of the rubber stocks contain dinitrosopentamethylene tetramine. Also, the rubber stock and various curatives and additives contain amines that can combine with the nitrite salts from the salt baths to form nitrosamines. Using a curing process other than salt baths and developing different rubber stocks which do not contain nitrosamines or will not result in nitrosamine formation are two ways of eliminating the source. Gen Corp Automotive has been in the process of developing new curative chemicals. Until the source of nitrosamines can be eliminated, better engineering controls are necessary. Better LEV along the salt baths and adding a LEV system at each drill press along the lines will help to reduce the volatile n-nitrosamine concentrations. Routine maintenance is necessary to ensure that the LEV systems are always functioning properly.

2. The ventilation system should be redesigned to ensure that no exhaust is re-entering the work place. Bringing in outside air that is contaminated with exhaust negates the function of the exhaust systems. Outside air intakes, such as the ones on the AHUs on the roof or on the outside of the VS building, should be located in areas where exhaust does not flow directly into them or where it is not likely that exhaust will accumulate.

3. Proper protective gloves, not cotton gloves, should not be worn when working with solvents. Solvents are readily absorbed through the skin, which can significantly contribute to the overall exposure, and cotton gloves can actually increase the dermal exposure because cotton will absorb the solvents and hold them against the skin. Nitrile rubber and Viton® gloves are two that offer good protection from a variety of solvents.

4. Any employee issued a respirator, for voluntary use or not, must be part of the respirator protection program, which involves a medical determination that the employee is physically able to wear a respirator, a fit test, and proper training on the use and maintenance of respirators. This involves implementing an effective respiratory protection program, in accordance with the requirements described in 29 CFR 1910.134.[20] Publications developed by NIOSH which should also be referenced when developing an effective respirator program include NIOSH Respirator Decision Logic and the NIOSH Guide to Industrial Respiratory Protection.[21,22] It is recommended that the written program designate one individual with the responsibility for administering the respiratory protection program. The written respirator program should also contain information on the following topics: (a) the departments/operations which require respiratory protection; (b) the correct respirators required for each job/operation; (c) specifications that only NIOSH/MSHA approved respiratory devices shall be used; and (d) the criteria used for the proper selection, use, storage and maintenance of respirators, including limitations. A respiratory protection program should include the following elements:

   a. written operating procedures
   b. appropriate respirator selection
   c. employee training
   d. effective cleaning of respirators
   e. proper storage
   f. routine inspection and repair
   g. exposure surveillance
   h. program review
   i. medical approval
   j. use of approved respirators

5. Update the Hearing Conservation Program (HCP). Noise level measurements should be performed in the plant, especially the VS area. Once noise levels have been measured, mark clearly any areas that exceed an 8-hour TWA of 85 decibels-A weighted (dBA) as high noise areas if the levels cannot be lowered by engineering controls. Employees working in these high noise areas should be provided with a variety of hearing protection devices and training in their use until such time as engineering or administrative controls can reduce the personal noise level exposures to below 85 dBA. Also, annual audiograms on these employees should be performed to detect any temporary or permanent threshold shifts. Records of all noise level monitoring, training, and audiograms

should be kept. The NIOSH Guide to Effective Hearing Conservation Programs in the Workplace[23] is helpful in developing an HCP.

VII. FUTURE PLANS

NIOSH plans to investigate the nitrosamine exposure in the VS area in more depth. The total exposure and body burden of nitrosamines cannot be ascertained solely by air monitoring. Hence, biological monitoring techniques will be used in addition to air monitoring. Blood and urine samples will be collected to measure n-nitrosamine-specific DNA adducts in peripheral blood cells and urothelial cells, the activity of the DNA repair enzyme that repairs these adducts, and the excised DNA adducts in the urine. Also, the genetic variability of the enzyme that activates n-nitrosamines in the body will be assessed by a restriction fragment length polymorphism (RFLP) technique. Specifically, this study will assess whether the amount of occupational nitrosamine exposure is related to an increase in DNA adducts and a decrease in the bodily enzyme that repairs these adducts in exposed employees.

DNA is a molecule that is present in every cell, except red blood cells, and it carries all the genetic information for an organism. DNA adducts are formed when a chemical attaches to a DNA molecule. Some DNA adducts are removed from the DNA molecule by a repair enzyme; others are not removed and can result in a mutation in the DNA sequence. Mutations in DNA occur naturally and also as a result of exposure to certain chemicals, such as n-nitrosamines. Some mutations can affect the functioning of your DNA and others do not affect it at all. Just measuring the concentration of nitrosamines in the air does not reveal how much is actually affecting a worker. Thus, this study will assess the amount of DNA adducts as a measure of the biologically effective dose of n-nitrosamine exposure.

This study will allow the NIOSH investigator to estimate the biologically effective dose of n-nitrosamines in the exposed workers. Also, since the question of the human carcinogenicity of nitrosamines is still unresolved, the association of exposure with genotoxic events such as formation of DNA adducts and interference with DNA repair activity will provide useful information on the subject.

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Table 2. n-Nitrosamine Air Sampling Results on May 3, 1994
Gen Corp Automotive, Marion, Indiana
HETA 94-0072

		n-Nitrosamine Concentration ($\mu g/m^3$)							
Sample Number	Job/Location (type of sample)	Volume (L)	NDMA	NDEA	NDPA	NDBA	NPIP	NPYR	NMOR
E59518	line 6 operator (PBZ)	676	5.17	0.64	ND	ND	2.57	0.06	0.10
E59515	injection molding press operator (PBZ)	808	0.53	0.01	ND	ND	0.20	0.01	0.01
E59516	press operator (PBZ)	670	1.07	0.03	ND	ND	1.02	0.03	0.09
E59517	line 5 coil packer (PBZ)	694	11.44	0.16	ND	ND	4.39	0.09	0.26
E59513	line 2 coil packer (PBZ)	728	5.40	0.04	ND	ND	2.22	0.01	0.16
E59511	feeder (PBZ)	872	1.40	0.14	ND	ND	0.64	0.01	0.07
E59519	line 5 operator (PBZ)	870	5.69	0.25	ND	ND	2.44	0.08	0.09
E59520	line 8 operator (PBZ)	672	1.68	0.19	ND	ND	1.10	0.04	0.04
E59501	line 8 coil packer (PBZ)	822	1.82	0.13	ND	ND	1.40	0.06	0.06
E59512	line 2 operator (PBZ)	566	6.48	0.28	ND	ND	2.54	0.05	0.09

ND = none detected
$\mu g/m^3$ = micrograms per cubic meter
PBZ = personal breathing zone air sample
GA = general area air sample

NDMA = nitrosodimethylamine
NDEA = nitrosdiethylamine
NDPA = nitrosodipropylamine
NDBA = nitrosodibutylamine

NPIP = nitrosopiperidine
NPYR = nitrosopyrrolidine
NMOR = nitrosomorpholine

minimal detectable concentration is 0.01 $\mu g/m^3$

Table 3. n-Nitrosamine Air Sampling Results on May 4, 1994
Gen Corp Automotive, Marion, Indiana
HETA 94-0072

		n-Nitrosamine Concentration ($\mu g/m^3$)							
Sample Number	Job/Location (type of sample)	Volume (L)	NDMA	NDEA	NDPA	NDBA	NPIP	NPYR	NMOR
E59502	silicone spray booth operator (PBZ)	830	2.84	0.07	ND	ND	1.79	0.06	0.13
E59510	line 8 assistant operator (PBZ)	814	2.96	0.07	ND	ND	1.72	0.12	0.18
E59508	press operator (PBZ)	810	1.35	0.03	ND	ND	1.62	0.04	0.06
E59507	line 2 coil packer (PBZ)	846	5.67	0.11	ND	ND	2.35	0.08	0.15
E59503	molding press operator (PBZ)	776	1.47	0.12	ND	ND	0.98	0.06	0.17
E59764	line 3 operator (PBZ)	844	4.35	0.10	ND	ND	1.88	0.06	0.18
E59509	feeder (PBZ)	908	0.47	0.03	ND	ND	0.27	0.01	0.03
E59506	line 2 operator (PBZ)	854	3.90	0.07	ND	ND	1.59	0.04	0.16
E59505	line 3 assistant operator (PBZ)	706	4.67	0.13	ND	ND	1.91	0.06	0.20
E59768	smoking break room (GA)	738	4.17	0.71	ND	ND	1.35	0.05	0.14
E59504	line 5 drill (GA)	766	9.99	0.03	ND	ND	2.92	0.15	0.25

ND = none detected
$\mu g/m^3$ = micrograms per cubic meter
PBZ = personal breathing zone air sample
GA = general area air sample

NDMA = nitrosodimethylamine
NDEA = nitrosdiethylamine
NDPA = nitrosodipropylamine
NDBA = nitrosodibutylamine

NPIP = nitrosopiperidine
NPYR = nitrosopyrrolidine
NMOR = nitrosomorpholine

minimal detectable concentration is 0.01 $\mu g/m^3$

Table 4. n-Nitrosamine Air Sampling Results on May 5, 1994
Gen Corp Automotive, Marion, Indiana
HETA 94-0072

		n-Nitrosamine Concentration ($\mu g/m^3$)							
Sample Number	Job/Location (type of sample)	Volume (L)	NDMA	NDEA	NDPA	NDBA	NPIP	NPYR	NMOR
F62821	line 7 operator and coil packer (PBZ)	768	1.10	0.04	ND	ND	0.64	0.03	0.06
F62812	silicone spray booth operator (PBZ)	818	3.80	0.21	ND	ND	2.61	0.06	0.15
F62818	C-pillar press operator (PBZ)	768	1.94	0.08	ND	ND	1.71	0.03	2.42
F62819	line 5 operator (PBZ)	846	5.58	0.20	ND	ND	3.25	0.08	0.16
F62811	line 8 operator (PBZ)	822	1.40	0.81	ND	ND	1.03	0.04	0.08
F62809	press operator (PBZ)	724	1.18	0.40	ND	ND	1.31	0.05	0.10
F62817	punch press operator (PBZ)	780	1.12	0.05	ND	ND	1.35	0.03	0.07
F62822	feeder (PBZ)	898	2.89	0.32	ND	ND	1.18	ND	0.12
F62810	A-pillar press operator (PBZ)	766	1.19	0.05	ND	ND	1.12	0.03	0.10
F62824	line 3 drill (GA)	718	88.47	0.19	ND	ND	10.17	0.14	0.55
F62820	line 5 drill (GA)	814	13.08	ND	ND	ND	4.03	0.16	0.06
F62826	line 6 drill (GA)	368	2.29	ND	ND	ND	1.98	0.15	0.08
F62816	line 7 drill (GA)	804	20.50	0.04	ND	ND	4.13	0.12	0.33
F62814	line 8 drill (GA)	428	4.84	ND	ND	ND	2.20	0.05	0.13
F62813	non-smoking break room (GA)	708	10.37	1.03	ND	ND	4.32	0.06	0.55

ND = none detected
$\mu g/m^3$ = micrograms per cubic meter
PBZ = personal breathing zone air sample
GA = general area air sample

NDMA = nitrosodimethylamine
NDEA = nitrosdiethylamine
NDPA = nitrosodipropylamine
NDBA = nitrosodibutylamine

NPIP = nitrosopiperidine
NPYR = nitrosopyrrolidine
NMOR = nitrosomorpholine

minimal detectable concentration is 0.01 $\mu g/m^3$

Appendix D

DNA–Adduct Study Protocol

PROJECT TITLE: An Assessment of the Concentration of DNA Adducts N^7-methylguanine and O^6-methylguanine and the Activity of DNA Repair Enzyme O^6-alkylguanine-DNA alkyltransferase in Workers at a Rubber Vehicle Sealing Plant:
Gen Corp Automotive
Rubber Vehicle Sealing Department
Marion, Indiana
HETA 94-0072

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INTRODUCTION

In November of 1993, the National Institute for Occupational Safety and Health (NIOSH) received a request for a health hazard evaluation (HHE) at Gen Corp Automotive in Marion, Indiana. The United Rubber, Cork, Linoleum, and Plastic Workers of America, Local 466 requested the HHE because employees were concerned about exposures to nitrosamines, inks, glues, styrene, divinyl benzene, and organic peroxides.

In February of 1994, NIOSH investigators conducted an initial site visit at the facility. This visit included an opening conference with company management and union representatives and a walk through evaluation of the three departments listed on the request, the rubber vehicle sealing department (VS), the liquid composite molding department (LCM), and the sheet molding compound department (mix house). Several general area (GA) air samples were collected during this site visit. In the VS area, nitrosamine, hydrocarbon, and polynuclear aromatic hydrocarbon (PNA) samples were collected. In the Mix House and LCM area, hydrocarbon samples were collected. Nitrosamines and several organic solvents were detected on these area samples, but PNAs were not.

A follow-up site visit was conducted on May 3 to 5, 1994, to collect personal breathing zone (PBZ) samples for nitrosamines and organic solvents. During this visit, methylene diisocyanate (MDI) samples were also collected in the LCM area because MDI is used in the process. The organic solvents and MDI were not detected at concentrations near their respective exposure limits. The nitrosamine samples, however, revealed significant concentrations of volatile nitrosamine exposures in the VS department. Every PBZ sample (n = 28) had detectable concentrations of nitrosodimethylamine (NDMA), nitrosodiethylamine (NDEA), nitrosopiperidine (NPIP), and nitrosomorpholine (NMOR). Twenty-seven of the twenty-eight PBZ samples had detectable concentrations of nitrosopyrrolidine (NPYR). The concentrations of nitrosamines detected for both the PBZ and GA samples collected during the May site visit are displayed in Table 1. The individual sample data is displayed in Appendix A.

Table 1. Nitrosamine concentrations measured in the Vehicle Sealing Department of Gen Corp Automotive in Marion, Indiana, on May 3 to May 5, 1994. HETA 94-0072 (minimal detectable concentration is 0.01 $\mu g/m^3$)

N-nitrosamine	PBZ (n=28) ($\mu g/m^3$)	GA (n=8) ($\mu g/m^3$)
NDMA	0.47-11.44	2.29-88.47
NDEA	0.01-0.81	ND-1.03
NDPA	ND	ND
NDBA	ND	ND
NPIP	0.20-4.39	1.35-10.17
NPYR	ND-0.12	0.05-0.16
NMOR	0.01-2.42	0.06-0.55

$\mu g/m^3$ - micrograms per cubic meter
PBZ - personal breathing zone air sample
GA - general area air sample
ND - none detected; below the minimal detectable concentration of 0.01 $\mu g/m^3$
NDMA - nitrosodimethylamine
NDEA - nitrosdiethylamine
NDPA - nitrosodipropylamine
NPIP - nitrosopiperidine
NPYR - nitrosopyrrolidine
NMOR - nitrosomorpholine
NDBA - nitrosodibutylamine

The total biologically effective dose of nitrosamines received by workers cannot be ascertained solely by air monitoring. Hence, biological monitoring of DNA adducts and DNA repair enzymes in peripheral lymphocytes and exfoliated urothelial cells in the urine will be used, in combination with air monitoring and a questionnaire that addresses confounding factors for nitrosamine exposure, to better estimate exposures and body burdens of nitrosamines. Moreover, since the question of the human carcinogenicity of nitrosamines is still unresolved, the association of exposure with genotoxic events such as formation of DNA adducts or decrease in DNA repair activity will provide useful information on the subject.

The nitrosamine exposures in this workplace, the stability of this workforce, and the interest of the union provide a suitable group of workers to study. By measuring the external

nitrosamine exposures and comparing DNA adduct and repair enzyme concentrations in the occupationally exposed group to the concentrations in an occupationally unexposed group, we expect to increase the understanding of nitrosamine toxicity in humans.

BACKGROUND

Nitrosamine Exposure

N-nitrosamines (N-nitroso compounds or NOCs) result from the combination of primary, secondary, or tertiary amines with nitrite. These reactions can occur in the laboratory; in various food, household, or industrial products; in industrial processes; and in vivo. Because of the variety of amines and reaction conditions possible, there are hundreds of nitrosamines; and because of the large number of exposure sources, including formation in vivo, there is a complicated matrix of total nitrosamine exposure.

Nitrosamine exposure to humans, as stated above, can occur from both exogenous and endogenous sources. Non-occupational exogenous exposures to nitrosamines include tobacco products and tobacco smoke; food; alcohol; cosmetics; prescription and nonprescription drugs; chemotherapy agents; and various household commodities such as dishwashing liquid, surface cleaners, and rubber products.[1] Occupational exposures have been observed in rubber industries, leather tanning industries, metal working industries, chemical industries, mining, pesticide production, detergent production, and fish factories.[1] Endogenous exposure to nitrosamines can occur following the uptake of nitrate and nitrite, and nitrosable amino compounds. Sources of these substances include food, drinking water, fertilizers, pesticides, and medications. Nitrosamine formation has been demonstrated in vitro and in vivo combining nitrate or nitrite with amino compounds under physiologic conditions in the laboratory or administering the reactants to experimental animals.[2-5] Oshima and Bartsch (1981) developed a non-invasive method to quantitatively estimate endogenous nitrosamine formation in humans using nitrate and proline, which will form nitrosoproline, a noncarcinogenic nitrosamine of which 90% is not metabolized and is excreted in the urine.[6]

Because of all the various sources of nitrosamine exposure, one could only estimate a total exposure by estimating the endogenous exposure and combining that with an estimate of exogenous exposures. In 1985, Choi developed a mathematical model to create indices of nitrate, nitrite, and N-nitrosamine exposure from both exogenous and endogenous sources.[7]

This model can be used to analyze data regarding the diet, tobacco product use, alcoholic beverage consumption, and other exposures obtained from questionnaires. The estimate of endogenous exposure is based on the fact that approximately 5% of the dietary nitrate intake is converted to nitrite in the saliva. (The formation of nitrite in the stomach and intestines in adults is somewhat controversial, and no percentage of nitrite formation has been quantified.) The model also takes into account the formation of a nitrosamine with a nitrite source (NO_2^-) and an amine intake of approximately 4,000 milligrams (mg). Nitrosodimethylamine (NDMA) is used as a representative of all nitrosamines because it is the most extensively studied nitrosamine. In a 900-milliliter (ml) human stomach, the formation of nitrosoproline (NPRO) has been quantified to be:[8]

$$[\mu g \text{ NPRO}] = 0.04865 [\text{mg } NO_2^-]^2$$

Since the nitrosation rate of NDMA is 22 times slower than that of NPRO, the conversion constant for NDMA is 0.0022,[7] so that:

$$[\mu g \text{ NDMA}] = 0.0022 [\text{mg } NO_2^-]^2$$

In this study, Choi used this model on a group of 210 human control subjects from a case-control study and found the mean per capita daily intake for NDMA from food, tobacco products, and beverages to be (mean ± standard error):

Exogenous nitrate	=	44.31 ± 4.04 mg/day
Exogenous nitrite	=	0.50 ± 0.05 mg/day
Exogenous NDMA	=	1.14 ± 0.25 μg/day
Total nitrite	=	2.71 ± 0.34 mg/day
Total NDMA	=	1.21 ± 0.25 μg/day

Occupational exposures to nitrosamines have been considered to be the highest exposures; but with the elimination of nitrosodiphenylamine (NDPhA), the reduction of nitrogen dioxide levels, and the use of lesser amounts of amine accelerators, occupational exposures have been reduced considerably in the rubber industry.[1] This NIOSH investigation has found, however, that the nitrosamine exposures are still potentially high during certain processes in the rubber industry.

Carcinogenicity of Nitrosamines

Cancer is believed to be a multistage process, beginning with (1) *exposure* to a carcinogen or procarcinogen and followed by (2) *initiation* of a cell to a genetically altered cell by damage to the DNA; (3) *promotion* of the altered cell to a preneoplastic lesion; (4) *conversion* of the preneoplastic lesion to a malignant tumor through a genetic change; and finally (5) *progression* of the tumor to clinical cancer. Exposure to a carcinogen must result in a genetic change in order to initiate a cell; likewise, there must also be a genetic change for a preneoplastic lesion to convert into a malignant tumor.[8] These genetic changes can occur from spontaneous mutations, and they can also occur with DNA adduct formation from exposure to carcinogens that are initiators or promoters or both. These genetic changes also must occur in certain chromosomal locations in order to cause the next step in carcinogenicity. Mutations in some of these certain locations have been identified, such as activation of proto-oncogenes or inactivation of tumor suppressor genes, but these and other processes are still being researched.[9]

There are many confounding factors that prevent every exposure to a carcinogen from resulting in clinical cancer. Genetic predisposition--inheritance of certain mutations, variations in activity of metabolizing enzymes and DNA repair enzymes, variations in immunity and immune cell enzymes--plays an important role in the development or lack of development of cancers. Variations in lifestyle and overall health can also play a part as these may affect immune function and intracellular repair processes.

Most nitrosamines are suspected to be human carcinogens, but direct causal associations have not yet been proven. The suspected mechanism of carcinogenesis is that nitrosamines, from exogenous or endogenous sources, are metabolized into reactive intermediates, which can then covalently bind to macromolecules, including DNA. If the adducts to the DNA result in a genetic mutation during the replication process, and if that mutation is in certain areas of the genome, the cell could undergo the second and third stages of carcinogenesis--initiation and promotion. If there was a second genetic change in the right place, conversion could result.

Although a causal association between nitrosamine exposure and human cancer has not yet been firmly established, there is a vast amount of circumstantial evidence that nitrosamines could cause cancer in humans. In 1956, Magee and Barnes demonstrated the carcinogenic potential of NDMA in rats.[10] Since then, nitrosamines have been studied extensively in laboratory animals. Approximately 90% of the 300 tested nitrosamines have shown carcinogenic effects in bioassays and laboratory animals. The animals that have been studied include mammals, birds, fish, and amphibia. Of the approximately 40 animal species tested, none have been resistant. The tumor sites depend on the specific nitrosamine, the species tested, and the route of administration. Tumors have been demonstrated in the bladder, bronchi, central nervous system, earduct, esophagus, eyelid, duodenum, forestomach, glandular stomach, hematopoietic system, intestine, jaw, kidney, larynx, nasal cavity, oral cavity, ovary, liver, mammary glands, pancreas, pelvis, peripheral nervous system, pharynx, respiratory tract, skin, testes, trachea, uterus, and vagina.[11] Dose-response studies with rats have shown "no effect levels" corresponding to dietary concentrations of 1 ppm NDMA, 1 ppm NDEA, and 1 ppm NPYR.[12] These nitrosamines and others appear to be very potent carcinogens.

All of the biochemical, pathological, and experimental data provides little evidence that humans might be resistant to the carcinogenic potential of nitrosamines.[5] Human tissues from the trachea, bronchus (lung), esophagus, colon, pancreatic duct, bladder, and buccal mucosa have been shown to metabolize nitrosamines into DNA-binding compounds.[5] Human liver tissue appears to metabolize nitrosamines in a similar manner as rodent liver tissue, and rodents have similar acute symptoms of liver necrosis and cirrhosis that have been observed in humans.[5] A few human DNA adduct studies have revealed higher levels of nitrosamine-related DNA adducts in cancer cases than in controls.[13,14] Studies in experimental animals have shown similar DNA adduct formation to those detected in the human studies.[15-17]

Nitrosamine Occupational Exposure Limits

Only one nitrosamine, N-nitrosodimethylamine (NDMA), is regulated in the United States. Both the Occupational Safety and Health Administration (OSHA) and NIOSH regulate NDMA as an occupational carcinogen. NIOSH recommends that exposure be reduced to the lowest feasible concentration. There are no established numerical exposure limits in this country.

Germany has strict regulations for occupational exposures to N-nitrosamines. In general industry, the total exposure to all nitrosamines present may not exceed 1 $\mu g/m^3$. In special cases, such as tire storage warehouses, exposures to all N-nitrosamines present may not exceed 2.5 $\mu g/m^3$. In addition to these regulations, the following eight nitrosamines are regulated individually--nitrosodimethylamine, nitrosodiethylamine, nitrosomorpholine, nitrosopiperidine, phenyl-ethylnitrosamine, phenyl-methylnitrosamine, di-N-butylnitrosamine, and di-iso-propylnitrosamine.

DNA Adducts and DNA Repair Enzyme Related to Nitrosamine Exposure

N-nitrosamines are metabolized by cytochrome P450IIE1 into metabolites that can bind to DNA, which results in the alkylation at the N or O atoms of the various DNA bases. The gene that codes for P450IIE1 is polymorphic, meaning that it can differ in a population, which is why different people will metabolize nitrosamines at different rates.

Two specific DNA adducts that have been studied that are related to nitrosamine exposure are N^7-methyldeoxyguanosine (N^7-mdGua) and O^6-methyldeoxyguanosine (O^6-mdGua). The majority of adducts (70% to 90%) from nitrosamine exposure are N^7-mdGua and these adducts have half-lifes of about 150 hours.[18] The O^6-mdGua adducts are more actively removed from DNA and are therefore not as stable. These adducts, however, may have more of a mutagenic potential than the N^7-mdGua adducts, and may play more of a role in carcinogenesis.[19,20] Both of these adducts can be quantified in peripheral blood cell DNA.

An important factor to consider when measuring the concentration of DNA adducts is the

activity of the repair enzymes that remove the DNA adducts. O^6-mdGua adducts are repaired by O^6-alkylguanine-DNA alkyltransferase (AGT) in a 1:1 stoichiometric irreversible reaction.[21-23] There is suspected to be a large interindividual variation of enzyme activity due to genetic differences, and a decreased activity of this repair enzyme could increase the risk of cancer from exposure to nitrosamines. Since the reaction is irreversible, it is also possible for high exposures to nitrosamines to reduce the repair activity by exhausting the supply of the repair enzyme. This was demonstrated in a study of patients treated with methylating chemotherapeutic agents such as procarbazine,[24] and in a study that looked at both tire storage workers and health care workers that handle chemotherapeutic agents.[25] The activity of this repair enzyme can also be quantified in peripheral blood cells.

OBJECTIVES

The overall objective of this study is to increase the understanding of the biological effects in humans of N-nitrosamine exposure.

The primary aims of this study are to answer the following questions:

- Is there a correlation between the occupational exposure to volatile N-nitrosamine concentrations and the concentration of DNA adducts formed?
- Is there a significant difference between the concentration of N-nitrosamine-related DNA adducts in an occupationally exposed group and an unexposed group?
- Is there a correlation between the occupational exposure to volatile N-nitrosamine concentrations and the level of O^6-alkylguanine-DNA alkyltransferase activity?
- Is there a significant difference between the O^6-alkylguanine-DNA alkyltransferase activity in an occupationally exposed group and an unexposed group?

METHODS

Study Population

The study population will be recruited from the Gen Corp Automotive plant in Marion, Indiana, and the one in Logansport, Indiana. The exposed group will be from the vehicle sealing (VS) department of the Marion plant. One unexposed group will be from the other departments of the Marion plant, and another unexposed group will be from the Logansport plant. The Logansport plant was chosen for an unexposed control group because no volatile nitrosamines were detected there in the Toyo department, it has a similar work force to the Marion plant, and it is geographically in a similar area. Unexposed controls will be recruited first in the Toyo department and then in the other departments if more volunteers are necessary.

Eligibility Criteria

Current first-shift workers in the VS department of Gen Corp Automotive in Marion, Indiana, will be eligible to participate in this study if they have worked in the VS area for at least six months and are not pregnant. Workers from the other two departments and the office staff at this facility will be eligible to participate in this study as part of an unexposed control group if they have not worked in the VS department, do not routinely spend time in the VS department, have worked at this facility for at least 6 months, and are not pregnant. Workers from the Gen Corp Automotive plant in Logansport, Indiana, will be eligible to participate in this study as part of an unexposed control group if they work first shift, have worked first shift at Logansport for at least six months, have never worked in the VS department in Marion, and are not pregnant.

Sample Size

Studies of DNA adducts and repair enzymes have not been conducted in the rubber industry. Therefore, calculations to determine necessary sample size were performed using related studies. For the DNA adduct analyses, we used the study by Mustonen and

Hemminki[26] that compares 7-methylguanine concentrations in DNA of smokers' and non-smokers' total white blood cells, granulocytes, and lymphocytes. To have a level of significance (alpha) of 0.05 and a power greater than 80%, a sample size of at least 17 exposed and 17 unexposed workers is necessary to detect a geometric mean DNA adduct level that is twice as high in one group as the other. The biggest assumption for this calculation is that the data from Mustonen and Hemminki is remotely comparable to the exposed/unexposed groups being sampled, and that the variances in DNA adduct levels for smokers and non-smokers is the same as those for the exposed and unexposed populations in this study. Other assumptions are lognormality of the data and independent samples.

For the repair enzyme analyses, we used the study by Oesch and Klein[25] that compares the repair capacity for O^6-methylguanine in peripheral blood lymphocytes of automobile workers exposed to rubber and tires and clinical workers that handle chemotherapeutic agents to control groups. By using the variance from the tire industry, we calculated that to have a level of significance (alpha) of 0.05 and a power greater than 80%, a sample size of at least 30 exposed and 30 unexposed workers is necessary. By using the variance from the clinical workers, we calculated that to have a level of significance (alpha) of 0.05 and a power greater than 80%, a sample size of at least 25 exposed and 25 unexposed workers is necessary. Again, we must assume that the data from Oesch and Klein is remotely comparable to the exposed/unexposed groups being sampled, and that the variances in DNA adduct levels are the same as those for the exposed and unexposed populations in this study.

The exposed population that works first shift at Marion is approximately 120 employees. The unexposed population at Marion is much smaller. At least 10 employees are unexposed, and approximately 50 others might be unexposed. The Logansport plant has approximately 500 employees, 96 of whom work in the Toyo department over 3 shifts.

Recruitment

After the workers are educated about the purpose and procedures of the study by means of communication through the union (Appendix B) and a personal letter (Appendix C), the list

of current workers from the company will be telephoned to answer any questions regarding the study and to ascertain eligibility and willingness to participate in the study. If an individual initially refuses to participate in the study, he or she will be asked to reconsider and asked whether a NIOSH researcher may call again in a few days. If the individual does not want to be contacted again, he or she will be eliminated from the list of potential participants.

The individuals who are eligible and willing to participate will receive a thank you letter (Appendix D) which will provide further education about the study, reinforcing the fact that this study is research-based and that individual sample results are not interpretable.

Consent

A consent form will be presented to and signed by the participants at the beginning of the study (Appendix E). This form provides a description and the conditions of the study. It also explains the role of the participant and the use of the information collected.

Data Collection

The NIOSH investigator will establish a schedule with the Gen Corp Automotive plant managers for administering the questionnaire and drawing the blood samples during work hours. The urine samples must be first void samples and therefore must be collected by the workers at home.

Non-occupational Exposure to Nitrosamines (Questionnaire)

A questionnaire will be used to try to identify the participants non-occupational exposure to nitrosamines (Appendix F). Designated groups of workers will be scheduled to come to a conference room in the plant during the work shift to complete the questionnaire with instruction and guidance provided by a NIOSH investigator. The questionnaire requires about 30 minutes and will be reviewed upon completion by the NIOSH investigator for

completeness.

Occupational Exposure to N-Nitrosamines, Nitrate, and Nitrite

The occupational exposure to the volatile N-nitrosamines, nitrosodimethylamine (NDMA), nitrosdiethylamine (NDEA), nitrosodipropylamine (NDPA), nitrosodibutylamine (NDBA), nitrosopiperidine (NPIP), nitrosopyrrolidine (NPYR), and nitrosomorpholine (NMOR) will be measured. Personal breathing zone (PBZ) air samples will be collected for all of the participants in the VS area, and general area (GA) air samples will be collected in the other departments. Samples will be collected on Thermosorb-N® tubes using Gillian® high-flow air pumps at a flow rate of 1 liter per minute (l/min).

Occupational exposure to nitrate and nitrite will also be assessed during this survey. Samples will be collected on washed silica gel sorbent tubes using Gillian® low-flow air pumps at a flow rate of 0.5 l/min.

Biological Samples

Blood Samples

Forty milliliter (ml) blood samples will be collected at the end of the workshift by trained phlebotamists. Concentrations of N^7-methyldeoxyguanosine (N^7-mdGua) and O^6-methyldeoxyguanosine (O^6-mdGua) will be measured in peripheral blood cells, and the same blood samples will be used to quantitate the O^6-alkylguanine-DNA alkyltransferase (AGT) activity. Also, small amounts of the DNA collected will be used to search for restriction fragment length polymorphisms (RFLPs) of the gene that codes for cytochrome P450 P450IIE1. This RFLP analysis will allow for comparison between DNA adducts and genetic ability to metabolize nitrosamines.

Urine Samples

First void urine samples will be provided by the workers on the morning following the day of their exposure sampling and blood collection. DNA from exfoliated cells in the urine will be analyzed for N^7-mdGua and O^6-mdGua adducts. Also, excised DNA adducts N^7-

methyladenine and N^3-methyladenine will be quantified from the urine. These urine analyses will be compared to the blood analyses. If the DNA adduct concentrations correlate between the blood and the urine samples, it may be a future possibility to use only the less invasive urine samples for DNA adduct studies.

Data Analysis

Description of Study Population

The occupational exposures to nitrosamines will be compared with the biological sample results, as will occupational exposures to nitrate and nitrite. Occupational history, residential water supply history, consumption of alcoholic beverages, diet history, tobacco use, fertilizer use, pesticide use, and medical history will all be analyzed from the questionnaire for comparison with the biological sample results. Also, information about tobacco use, diet, and consumption of alcoholic beverages will be used to estimate a quantitative exposure to NDMA from non-occupational sources as was done by Choi in 1985.[7] This quantitative exposure will be compared with the biological sample results as well. The comparisons will include simple calculations of means of variables, according to exposure status, correlations between biological sample and personal breathing zone sample results, and multiple linear regression to account for the various confounding factors.

Measures of N-nitrosamine, Nitrate, and Nitrite Exposure

The PBZ and GA air samples will be analyzed for NDMA, NDEA, NDPA, NDBA, NPIP, NPYR, and NMOR in a NIOSH laboratory using gas chromatography (GC) and a mass spectrometer (MS) in the selected-ion-monitoring (SIM) mode. The NIOSH laboratory uses a capillary column instead of a packed column for the analysis--a process that separates the elution peaks better. Also, a mass spectrometer in the selected-ion-monitoring (SIM) mode is used to confirm the identity of any compound that elutes at the same retention time as the nitrosamine standards. In this way, the chromatographic peak is confirmed as the nitrosamine compound that it is suspected to be.

The analysis of samples for nitrate and nitrite will be done following NIOSH Method No. 7903.

Analysis of DNA Adduct Concentrations in Peripheral Blood Cell DNA

Lymphocytes will be isolated from whole blood using Histopaque®. DNA will be isolated from peripheral blood lymphocytes using a MicroProbe DNA isolation kit. After enzymatic hydrolysis to the 3' phosphate nucleotides, the N^7-methyldeoxyguanosine and O^6-methyldeoxyguanosine adducts will be separated from non-adducted DNA nucleotides by HPLC/Diode Array UV detection at 254 nm equipped with an ion-pair column. The individual adducts will be collected using a fraction collector. The fractions will be pooled, deoxyguanosine added as an internal standard, then lyophilized. The lyophilized fractions will be dissolved in water and enzymatically labeled with ^{32}P at the 5' position. For the N^7-methyldeoxyguanosine, the labeled mixture will be spotted on 20 x 20 cm polyethyleneimine cellulose plates and developed in two dimensions. For the O^6-methyldeoxyguanosine, the labeled mixture will be spotted on 20 x 20 cm cellulose plates and developed in two dimensions. Normal and adducted nucleotides will be localized using a radioisotope image analyzer and radioactivity measured. A direct ratio of adduct to deoxyguanosine will be determined.

Analysis of DNA Adduct Concentrations from Exfoliated Cells in the Urine

Exfoliated urothelial cells in urine will be isolated using a 5 μm pore, 47 mm diameter filter. The cells will be rinsed off the filter and DNA isolated using a MicroProbe DNA isolation kit. After enzymatic hydrolysis to the 3' phosphate nucleotides, the N^7-methyldeoxyguanosine and O^6-methyldeoxyguanosine adducts will be separated from non-adducted DNA nucleotides by HPLC/Diode Array UV detection at 254 nm equipped with an ion-pair column. The individual adducts will be collected using a fraction collector. The fractions will be pooled, deoxyguanosine added as an internal standard, then lyophilized. The lyophilized fractions will be dissolved in water and enzymatically labeled with ^{32}P at the 5' position. For the N^7-methyldeoxyguanosine, the labeled mixture will be spotted on 20 x 20 cm polyethyleneimine cellulose plates and developed in two dimensions. For the O^6-

methyldeoxyguanosine, the labeled mixture will be spotted on 20 x 20 cm cellulose plates and developed in two dimensions. Normal and adducted nucleotides will be localized using a radioisotope image analyzer and radioactivity measured. A direct ratio of adduct to deoxyguanosine will be determined.

Analysis of Excised DNA Adducts in the Urine

A fluorometric assay will be utilized for quantification of carcinogenic methylating agents. Those reactive compounds are known to give rise to N^3- and N^7-methyladenine (3- MA and 7-MA) as the major DNA adduct repair product after exposure to such compounds. Methylated adenine residues are nonvolatile and, after excision repair, typically are excreted in the urine. After suitable concentration and/or cleanup of urine, previously filtered to remove the exfoliated urothelial cells, samples will be derivatized by reaction with a malondialdehyde reagent. Subsequently, samples will be processed by a solid phase extraction cleanup and the highly fluorescent 3-MA and 7-MA derivative will be analyzed by reversed phase HPLC utilizing a fluorescence detector (derivative excitation nm = 294; emission nm = 504), a procedure which is both highly sensitive and specific. The amounts of 3- MA and 7-MA in urine will be correlated with that found in tissue DNA by analysis of ^{32}P postlabelled DNA adducts, and may ultimately allow determination of the cumulative internal dose and activation of a wide range of methylating agents which are found as part of industrial complex mixtures, ranging from cutting fluids to cleanup sites, without the difficult and invasive blood collection requirement.

Analysis of O^6-alkylguanine-DNA alkyltransferase Activity from Peripheral Blood Cells

O^6-alkylguanine-DNA alkyltransferase (AGT) activity will be determined in preparations from lymphocytes isolated from whole blood, following the procedure described by Klein and Oesch, 1992. Blood samples from exposed and control subjects will be transported in heparinized tubes on ice for lymphocyte isolation using Ficoll-metrizoate (Histopaque^R) centrifugation. The lymphocytes will be suspended in buffer at a density of 10^7/ml and homogenized by sonication at 4°C. The homogenate will be centrifuged, and the supernatant stored at -100°C until AGT analysis. Lambda phage DNA containing one ^{32}P-labeled O^6-

methylguanine in each BamH1 site will be used as substrate for determining the activity of AGT in the lymphocyte homogenates. The O^6-methylguanine DNA substrate will be synthesized following procedures described in Klein and Oesch, 1990. The O^6-methylguanine DNA substrate will be incubated with homogenate from 0.5-1.5 X 10^6 cells for 1.5 hr at 37°C, purified by phenol extraction, and hydrolyzed with spleen phosphodiesterase/micrococcal endonuclease to 3'nucleoside monophosphates (3'-dGMP^{32} 3'-dO^6-meGMP^{32}, 3'-dCMP, 3'-dAMP, 3'-dTMP, 3'-dGMP). The 3'nucleoside monophosphates in the hydrolysates will be separated by HPLC using a Knauer Nucleosil SAX column and isocratic solvent conditions. Fractions of 1 ml will be collected and quantitated for ^{32}P radioactivity by scintillation counting. Comparison of the radioactivity in the 3'-dGMP^{32} fraction (repaired 3-dO^6-meGMP) to the radioactivity in the 3'-dO^6-medGMP^{32} (not repaired) fraction, represents the repair capacity of the lymphocyte preparations. AGT activity will be measured by calculating the decrease of radioactivity in the 3'-dO^6-meGMP^{32} fraction following incubation with the lymphocyte preparation, compared to the radioactivity in the 3'-dO^6-meGMP^{32} fraction in the DNA substrate before incubation with the lymphocyte preparation. Triplicate determinations will be conducted on each specimen.

Genetic Analysis of Polymorphisms in the Cytochrome P450IIE1 Gene

Restriction fragment length polymorphism (RFLP) analysis will be performed on DNA isolated from lymphocytes for use in the analysis of DNA adduct concentrations in peripheral blood cells as described above. DNA (0.5 -1.0 µg) will be amplified by the polymerase chain reaction (PCR) using primers appropriate to the regions of interest within the P450IIE1 gene. The 5'-flanking region of the gene contains sites of *Rsa I* and *Pst I* polymorphisms. The region of the gene encompassing intron 6 contains a *Dra I* polymorphism. For analysis of RFLPs, aliquots of the amplified DNA will be digested with each restriction enzyme (*Dra I, RsaI,* or *Pst I*) individually and analyzed by agarose gel electrophoresis. DNA will be visualized by ethidium bromide fluorescence and the size of the DNA ascertained by comparison with authentic size standards. The presence of a *Pst I* restriction site yields a fragment 290 base pairs long while the presence of a *Rsa I* restriction site yields a fragment of 360 base pairs. For the *Dra I* polymorphism, the presence of this site yields a 133 base pair fragment; in the absence of the site a 373 base pair fragment will result. DNA from

individuals that are heterozygous for any restriction site will display a mixture of each of the bands.

Notification

At the completion of the data analysis, participants will be notified in writing (Appendix G) of the results of their personal breathing zone air monitoring, their DNA adduct concentrations, and their O^6-alkylguanine-DNA alkyltransferase activity. The notification will also include a summary of the results for the exposed and two unexposed control groups. Emphasis will be placed on communicating the idea that personal DNA adduct concentrations and repair enzyme activities cannot be interpreted or causally linked to any future effect. A copy of the final report will be sent to the union and the company and to any participant who requests one.

Emergency Plan

It is extremely unlikely that any medical emergencies will result from participation in the study. Nevertheless, a health care professional trained in CPR and emergency response will be available with appropriate medical emergency supplies. An emergency field plan for the field team (Appendix H) will be provided to each team member.

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APPENDIX A

Nitrosamine Air Sampling Results
in the Vehicle Sealing Department of Gen Corp Automotive
in Marion, Indiana, on May 3 to May 5, 1994
HETA 94-0072

Table 2. Nitrosamine Air Sampling Results on May 3, 1994
Gen Corp Automotive, Marion, Indiana
HETA 94-0072

		Nitrosamine Concentration ($\mu g/m^3$)							
Sample Number	Job/Location (type of sample)	Volume (L)	NDMA	NDEA	NDPA	NDBA	NPIP	NPYR	NMOR
E59518	line 6 operator (PBZ)	676	5.17	0.64	ND	ND	2.57	0.06	0.10
E59515	injection molding press operator (PBZ)	808	0.53	0.01	ND	ND	0.20	0.01	0.01
E59516	press operator (PBZ)	670	1.07	0.03	ND	ND	1.02	0.03	0.09
E59517	line 5 coil packer (PBZ)	694	11.44	0.16	ND	ND	4.39	0.09	0.26
E59513	line 2 coil packer (PBZ)	728	5.40	0.04	ND	ND	2.22	0.01	0.16
E59511	feeder (PBZ)	872	1.40	0.14	ND	ND	0.64	0.01	0.07
E59519	line 5 operator (PBZ)	870	5.69	0.25	ND	ND	2.44	0.08	0.09
E59520	line 8 operator (PBZ)	672	1.68	0.19	ND	ND	1.10	0.04	0.04
E59501	line 8 coil packer (PBZ)	822	1.82	0.13	ND	ND	1.40	0.06	0.06
E59512	line 2 operator (PBZ)	566	6.48	0.28	ND	ND	2.54	0.05	0.09

$\mu g/m^3$ - micrograms per cubic meter
PBZ - personal breathing zone air sample
GA - general area air sample

NDMA - nitrosodimethylamine
NDEA - nitrosodiethylamine
NDPA - nitrosodipropylamine
NDBA - nitrosodibutylamine
NPIP - nitrosopiperidine
NPYR - nitrosopyrrolidine
NMOR - nitrosomorpholine

minimal detectable concentration is 0.01 $\mu g/m^3$

Table 3. Nitrosamine Air Sampling Results on May 4, 1994
Gen Corp Automotive, Marion, Indiana
HETA 94-0072

		Nitrosamine Concentration ($\mu g/m^3$)							
Sample Number	Job/Location (type of sample)	Volume (L)	NDMA	NDEA	NDPA	NDBA	NPIP	NPYR	NMOR
E59502	silicone spray booth operator (PBZ)	830	2.84	0.07	ND	ND	1.79	0.06	0.13
E59510	line 8 assistant operator (PBZ)	814	2.96	0.07	ND	ND	1.72	0.12	0.18
E59508	press operator (PBZ)	810	1.35	0.03	ND	ND	1.62	0.04	0.06
E59507	line 2 coil packer (PBZ)	846	5.67	0.11	ND	ND	2.35	0.08	0.15
E59503	molding press operator (PBZ)	776	1.47	0.12	ND	ND	0.98	0.06	0.17
E59764	line 3 operator (PBZ)	844	4.35	0.10	ND	ND	1.88	0.06	0.18
E59509	feeder (PBZ)	908	0.47	0.03	ND	ND	0.27	0.01	0.03
E59506	line 2 operator (PBZ)	854	3.90	0.07	ND	ND	1.59	0.04	0.16
E59505	line 3 assistant operator (PBZ)	706	4.67	0.13	ND	ND	1.91	0.06	0.20
E59768	smoking break room (GA)	738	4.17	0.71	ND	ND	1.35	0.05	0.14
E59504	line 5 drill (GA)	766	9.99	0.03	ND	ND	2.92	0.15	0.25

$\mu g/m^3$ - micrograms per cubic meter
PBZ - personal breathing zone air sample
GA - general area air sample

NDMA - nitrosodimethylamine
NDEA - nitrosodiethylamine
NDPA - nitrosodipropylamine
NDBA - nitrosodibutylamine
NPIP - nitrosopiperidine
NPYR - nitrosopyrrolidine
NMOR - nitrosomorpholine

minimal detectable concentration is 0.01 $\mu g/m^3$

Table 4. Nitrosamine Air Sampling Results on May 5, 1994
Gen Corp Automotive, Marion, Indiana
HETA 94-0072

		Nitrosamine Concentration ($\mu g/m^3$)							
Sample Number	Job/Location (type of sample)	Volume (L)	NDMA	NDEA	NDPA	NDBA	NPIP	NPYR	NMOR
F62821	line 7 operator and coil packer (PBZ)	768	1.10	0.04	ND	ND	0.64	0.03	0.06
F62812	silicone spray booth operator (PBZ)	818	3.80	0.21	ND	ND	2.61	0.06	0.15
F62818	C-pillar press operator (PBZ)	768	1.94	0.08	ND	ND	1.71	0.03	2.42
F62819	line 5 operator (PBZ)	846	5.58	0.20	ND	ND	3.25	0.08	0.16
F62811	line 8 operator (PBZ)	822	1.40	0.81	ND	ND	1.03	0.04	0.08
F62809	press operator (PBZ)	724	1.18	0.40	ND	ND	1.31	0.05	0.10
F62817	punch press operator (PBZ)	780	1.12	0.05	ND	ND	1.35	0.03	0.07
F62822	feeder (PBZ)	898	2.89	0.32	ND	ND	1.18	ND	0.12
F62810	A-pillar press operator (PBZ)	766	1.19	0.05	ND	ND	1.12	0.03	0.10
F62824	line 3 drill (GA)	718	88.47	0.19	ND	ND	10.17	0.14	0.55
F62820	line 5 drill (GA)	814	13.08	ND	ND	ND	4.03	0.16	0.06
F62826	line 6 drill (GA)	368	2.29	ND	ND	ND	1.98	0.15	0.08
F62816	line 7 drill (GA)	804	20.50	0.04	ND	ND	4.13	0.12	0.33
F62814	line 8 drill (GA)	428	4.84	ND	ND	ND	2.20	0.05	0.13
F62813	non-smoking break room (GA)	708	10.37	1.03	ND	ND	4.32	0.06	0.55

$\mu g/m^3$ - micrograms per cubic meter
PBZ - personal breathing zone air sample
GA - general area air sample

NDMA - nitrosodimethylamine
NDEA - nitrosdiethylamine
NDPA - nitrosodipropylamine
NDBA - nitrosodibutylamine
NPIP - nitrosopiperidine
NPYR - nitrosopyrrolidine
NMOR - nitrosomorpholine

minimal detectable concentration is 0.01 $\mu g/m^3$

APPENDIX B

Union Newsletter Article

The National Institute for Occupational Safety and Health (NIOSH) is currently conducting a health hazard evaluation (HHE) at the Gen Corp Automotive Plant in Marion, Indiana. The HHE was requested by the United Rubber, Cork, Linoleum, and Plastics Workers of America (URW), Local 466. NIOSH conducted a walk through investigation of the plant on February 16, 1994, and then returned to perform extensive air sampling in all three of the departments on May 3 to May 5, 1994. The continuation of the HHE will focus on a study of nitrosamine exposure in the rubber vehicle sealing (VS) department. The purpose of the study in this department is to determine whether there are biological effects related to nitrosamine exposure among workers in the plant. Specifically, this study will assess whether the amount of occupational nitrosamine exposure is related to a higher concentration of DNA adducts and a lower concentration of the enzyme that repairs these adducts.

DNA is a complex molecule that is present in every cell (except red blood cells) in your body. It carries all of your genetic information. DNA adducts are formed when a chemical attaches to a DNA molecule. Some DNA adducts are removed from the DNA molecule by a repair enzyme; others are not removed and can result in a mutation or change in the DNA. Mutations in your DNA can occur naturally and also as a result of exposure to certain chemicals. Some mutations can affect the functioning of your DNA and others do not affect it at all. Just measuring the concentration of nitrosamines in the air does not reveal how much your body is being affected. Thus, this study will assess the amount of DNA adducts as a measure of the biologic effect of nitrosamine exposure.

NIOSH is asking for participants for this study. If you currently work for Gen Corp Automotive in the Marion, Indiana plant, in any department, have been working there for at least six months, and are not pregnant, you may be contacted by NIOSH and asked to take part in this study. Also, if you currently work for Gen Corp Automotive in the Logansport,

Indiana plant, in any department, have been there at least six months, and are not pregnant, you may be contacted. Volunteers are needed from departments other than the VS department in Marion because a population similar to the one in the VS department, but that is not occupationally exposed to nitrosamines, is necessary for comparison of results.

As a participant, you will be part of a study that will contribute to the understanding of some of the biologic effects of nitrosamine exposure. As you know from working at the plant, nitrosamines are known animal carcinogens, but it is not proven what effects they have in humans. This study is important because it will increase our understanding of nitrosamine exposure in humans. However, it will in no way prove or disprove that nitrosamines cause cancer in humans. It will only be a first step in that research.

Your participation in this study is completely voluntary. NIOSH investigators hope that all eligible persons will take part because this is an important study and a high rate of participation is necessary for a scientifically strong study.

The study can be conducted during your usual work hours, but Gen Corp has the option to not pay your wages during this time. You also have the option of doing the questionnaire and providing the blood sample after work hours. The study involves filling out a questionnaire about your work and health, wearing an air sampling pump during one work shift to collect an external nitrosamine exposure, having a blood sample collected at the end of the work shift during which you wore the personal air sampler, and collecting a urine sample first thing in the morning following the day your blood sample was taken.

You will receive a written summary of your personal results and of the group results. The personal results are protected by the federal privacy laws and will not be shared with the company or the union. The company and the union will only receive reports that summarize the group results and that do not identify the individual participants.

Within the next few weeks, a letter will be sent to your home to explain the study further. Then a NIOSH representative will call you to answer any questions and ask you to participate in the study. If you have any questions before then, contact Beth Donovan, the project officer, at (513) 841-4374. The mailing address is:

Beth Donovan, M.H.S.
NIOSH/HETAB, R-11
4676 Columbia Parkway
Cincinnati, Ohio 45226

APPENDIX C

Introductory Letter to Potential Study Subjects

Dear _____:

The National Institute for Occupational Safety and Health (NIOSH), which is part of the Centers for Disease Control and Prevention (CDC), is the principal federal agency engaged in occupational health research. NIOSH was created by the Occupational Safety and Health Act of 1970 and was given responsibility to conduct research and investigations of health and safety hazards in the work place. One way that NIOSH meets these responsibilities is by conducting investigations called health hazard evaluations (HHEs) at the request of employers, employees, or unions.

NIOSH is currently conducting an HHE at the Gen Corp Automotive Plant in Marion, Indiana. The HHE was requested by the United Rubber, Cork, Linoleum, and Plastics Workers of America (URW), Local 466. NIOSH conducted a walk through investigation of the plant on February 16, 1994, and then returned to perform extensive air sampling in all three of the departments on May 3 to May 5, 1994. The continuation of the HHE will focus on nitrosamine exposure in the rubber vehicle sealing (VS) department. **The purpose of the study in this department is to determine whether there are biological effects related to nitrosamine exposure among workers in the plant. Specifically, this study will assess whether the amount of occupational nitrosamine exposure is related to a higher concentration of DNA adducts and a lower concentration of the enzyme that repairs these adducts.**

DNA is complex molecule that is present in every cell (except red blood cells) in your body. It carries all of your genetic information. DNA adducts are formed when a chemical attaches to a DNA molecule. Some DNA adducts are removed from the DNA molecule by a repair enzyme; others are not removed and can result in a mutation or change in the DNA. Mutations in your DNA can occur naturally and also as a result of exposure to certain

chemicals. Some mutations can affect the functioning of your DNA and others do not affect it at all. Just measuring the concentration of nitrosamines in the air does not reveal how much your body is being affected. Thus, this study will assess the amount of DNA adducts as a measure of the biologic effect of nitrosamine exposure.

If you are a current employee at the Marion or Logansport plants, have worked there at least six months, and are not pregnant, you are eligible to participate. Your participation in this study is completely voluntary. You are under no obligation to participate. Although we cannot compensate you for your involvement, we hope that all eligible persons will take part because this is an important study. It will help us understand some of the changes, or biologic effects, in a persons body resulting from nitrosamine exposure. As you know from working at the plant, nitrosamines are known animal carcinogens, but it is not proven what effects they have in humans. This study will increase our understanding of nitrosamine exposure in humans. However, it will in no way prove or disprove that nitrosamines cause cancer in humans. It will only be a first step in that research.

If you agree to take part in this study, you will be asked to do the following:

1. Complete a questionnaire during or after work hours (approximately 30 minutes).
2. Wear a personal breathing zone air sampler during one work shift to collect an external nitrosamine exposure. These samplers are small and portable, and will not interfere with your work.
3. Have a blood sample collected at the end of the work shift during which you wore the personal air sampler. This blood sample is a routine medical procedure and will only cause slight, if any, discomfort. It will be collected by a qualified medical professional.
4. Collect a urine sample first thing in the morning following the day your blood sample is taken and return the sample to the NIOSH investigator that morning at work.

The questionnaire may be filled out during work hours, but Gen Corp has the option to not pay your wages during this time. If you choose to do this, the time for the questionnaire will be scheduled ahead of time with your supervisor to occur at a convenient time during the work day. The blood sample must be collected at the end of the work shift. If you

wish to do this during work hours, it will be collected during the last half-hour of your shift. Again, Gen Corp may elect not to pay you for this time. You may also have the blood sample taken after your work shift has ended. All study procedures will be performed at the your work place or in the union hall at your work place by NIOSH employees or by contractors working for NIOSH. **Gen Corp Automotive personnel will not be involved. Company personnel will not have access to any of your personal information unless you give them written permission.**

NIOSH's legal authority to conduct occupational health studies is included in the Occupational Safety and Health Act of 1970. All information collected about you will be protected from unwarranted disclosures by the Privacy Act of 1974. At the end of the study, a final report will be issued to the union and the company. The results will be presented in summary form in this report so that none of the individual participants can be identified. We will send you a copy of your own results as well as a summary of the group results. If you request, we will also send you a copy of the final report.

The NIOSH researchers are asking current workers who meet certain criteria to participate in this health hazard evaluation. You will be contacted by telephone to confirm that you received this letter, to answer any questions about this study, to confirm that you are eligible for this study, and to request your participation in this study. If you have any questions, at any time, about this study, please feel free to contact me at 1-800-356-4674 or (513) 841-4374. The mailing address is:

Beth Donovan, M.H.S.
NIOSH/HETAB, R-11
4676 Columbia Parkway
Cincinnati, Ohio 45226

Sincerely yours,

Beth Donovan, M.H.S.

APPENDIX D

Thank You Letter to Willing Participant

Dear _____:

Thank you for agreeing to take part in the NIOSH study of the biological effects of nitrosamine exposure. You are a very important part of this project and we greatly appreciate your help. Your participation will help us understand some of the biologic effects from nitrosamine exposure. This and other studies of human nitrosamine exposure will provide information needed to better protect you and other workers potentially exposed to nitrosamines.

The NIOSH researchers will develop a schedule with the plant managers and supervisors so that the study will occur during work hours, and you will be notified of your appointed time prior to the survey date. Before you fill out the questionnaire, you will be given a consent form to read and sign that will summarize again your role as a participant. If you change your mind at any time, before or after signing the consent form, you may discontinue your participation.

The basic survey plan is as follows:

1. Completion of a questionnaire (approximately 30 minutes) during or after work hours. It is your choice, but Gen Corp is not obligated to pay your wages if done during your work shift. A NIOSH investigator will be present to explain the questionnaire and answer any questions.
2. Wearing a personal breathing zone air sampler during one work shift to collect an external nitrosamine exposure. This will preferably be done on a day later in a work week, such as a Wednesday or a Thursday. Your work will not be interrupted when you wear the air sampler and therefore you will receive your usual wages during this time.
3. Having a blood sample collected at the end of the work shift during which you wore

the personal air sampler. This will be done either a half-hour before the end of your shift or after you have clocked out for the day--it is your choice, but Gen Corp does not have to pay your wages if done during your work shift.

4. Collecting a urine sample first thing in the morning following the day your blood sample is taken and returning the sample to the NIOSH investigator that morning at work.

The individual information collected will not be available to the company or the union. The blood samples and urine samples will be analyzed to determine your DNA adduct concentration and DNA repair enzyme activity during the day of sampling. **Your individual results will not have any medical significance.** This study is research in nature and will assess the results of the study population as a whole. NIOSH is investigating some biologic changes that could occur from nitrosamine exposure--these changes are suspected to be an increase in DNA adducts and a decrease in DNA repair enzyme activity. These biologic changes are not now known to be related to any disease, which is why they do not have any medical significance. It is important for you to understand this point. I will be glad to answer any questions you have to make sure that you understand the study and what the results will represent.

I can be contacted at any time during the study to answer questions at 1-800-356-4674 or (513) 841-4374.

APPENDIX E

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH)
CENTERS FOR DISEASE CONTROL AND PREVENTION
U.S. PUBLIC HEALTH SERVICE
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

You have been asked to participate in a NIOSH research study. We explain here the nature of your participation, describe your rights, and specify how NIOSH will treat your records.

I. DESCRIPTION

1. Title: Health Hazard Evaluation Study of the Concentration of DNA Adducts N^7-methylguanine and O^6-methylguanine and the Activity of DNA Repair Enzyme O^6-alkylguanine-DNA Alkyltransferase in Workers at a Rubber Vehicle Sealing Plant, Gen Corp Automotive in Marion, Indiana (HETA 94-0072)

2. Project Officer: Beth Donovan, M.H.S.

3. Purpose and Benefits: The purpose of this evaluation is to identify any associations between the concentration of DNA adducts and occupational nitrosamine exposure, and between the activity of DNA repair enzymes and occupational nitrosamine

exposure. DNA is complex molecule that is present in every cell (except red blood cells) in your body. It carries all of your genetic information. DNA adducts are formed when a chemical attaches to a DNA molecule. Some DNA adducts are removed from the DNA molecule by a repair enzyme; others are not removed and can result in a mutation or change in the DNA. Mutations in your DNA can occur naturally and also as a result of exposure to certain chemicals. Some mutations can affect the functioning of your DNA and others do not affect it at all. Just measuring the concentration of nitrosamines in the air does not reveal how much your body is being affected. Thus, this study will assess the amount of DNA adducts as a measure of the biologic effect of nitrosamine exposure. Since this study involves research in a developing field, individual results can not be interpreted. Normal ranges have not yet been established and measurements have not been linked to any specific diseases. Therefore the study will provide no practical information about your health. Nevertheless, you, as a part of the study group, will contribute to the knowledge that might ultimately be of benefit to the health of you and your co-workers as a whole, and of other men and women who are exposed to nitrosamines at work.

II. CONDITIONS OF THE STUDY

1. The study will include the following procedures:
   a. A questionnaire about your work history, medical history, and health-related topics, including tobacco use, alcohol consumption, drinking water sources, and diet history. You will complete the questionnaire (approximately 30 minutes) during or after work hours. It is your choice, but Gen Corp is not obligated to pay your wages if done during your work shift. A member of the NIOSH team will be present when you do the questionnaire to explain the instructions and to answer any questions.
   b. Your external exposure to nitrosamines will be measured during one work shift. You will be required to wear a small sampling pump (approximately 4" x 4" x 2") on your belt that is connected with tubing to a sampling tube that will be clipped to your collar. This sample device will be worn for your entire

work shift. This is a common procedure and will not interfere with your work.

c. A 40 milliliter blood sample (approximately 3 tablespoons) will be collected from a vein in your arm at the end of the workshift during which you wore a sampling pump. This will be done either a half-hour before the end of your shift or after you have clocked out for the day--it is your choice, but Gen Corp does not have to pay your wages if done during your work shift. The needle stick may produce momentary discomfort and possibly some residual soreness and discoloration of the skin due to blood leaking from the vein; this discoloration may last a few days but is harmless. Infrequently, the procedure causes someone to faint. This procedure should only take a few minutes. The blood will be used only for the tests specified.

d. A urine sample will be collected on the morning following the day that you wore the sampling pump and had blood drawn. This must be a sample from your first urination of the day. A container will be provided to you when blood is drawn, and the sample should be returned to a NIOSH team member when you arrive at work.

e. The blood and urine samples will be analyzed for DNA adducts. The blood will be used to measure the concentration of two types of DNA adducts, to measure the activity of a DNA repair enzyme that repairs those adducts, and to search for individual differences in how your body breaks down nitrosamines. The urine samples will be used to measure the concentration of the same two DNA adducts, and to measure the amount of DNA adducts that are eliminated in your urine.

2. All of the procedures described above are standard industrial hygiene and medical tests. The only disadvantage is the slight discomfort from the needle when collecting the blood sample.

3. There are no alternative procedures for these analyses.

4. Injury from this project is unlikely. But if it results, only emergency treatment will be

provided; medical care is not provided. If you are injured through negligence of a NIOSH employee ~~or an agent of NIOSH~~, you may be able to obtain compensation under federal law. If you want to file a claim against the Federal government, your contact point is: Public Health Service Claims Office at (301) 443-1904. If an injury should occur to you as the result of your participation, you should contact Beth Donovan, M.H.S. (Project Officer) at (513) 841-4374 or Dr. Michael Colligan, the Chair of the NIOSH Human Subjects Review Board, at (513) 533-8225.

5. If you have any questions about this research or your rights as a participant of this study, contact Beth Donovan, M.H.S., Project Officer, at (513) 841-4374.

6. Your participation is voluntary and you may withdraw your consent to participate in this study at any time without penalty or loss of benefits to which you are otherwise entitled. You will not be compensated for your participation.

7. NIOSH will provide you with a summary of the study results. Your individual results will also be provided to you, but they have no clinical or interpretive value at this point in time. A summary of the overall study results will be included in the final health hazard evaluation report that will be sent to the company and the union. The company is required to post a copy of the final report in a place accessible to employees for a period of 30 days. If you request it, NIOSH will send you a copy of the final report.

III. USE OF INFORMATION

The National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC), an agency of the Department of Health and Human Services, is authorized to collect this information, including your social security number (if applicable), under provisions of the Public Service Act, Section 301 (42 U.S.C. 241); Occupational Safety and Health Act, Section 20 (29 U.S.C. 669); and Federal Mine Safety and Health Act of 1977, Section 501 (30 U.S.C. 95). The information you supply is voluntary and there is no penalty for not providing it.

The data will be used to evaluate the biologic effects of nitrosamine exposure, specifically DNA adduct concentrations. These biologic effects may be related to the development of cancer, but this relationship has not been proven. This research will contribute to the understanding of nitrosamine carcinogenicity or lack thereof. Data will become part of the CDC Privacy Act system 09-20-0147, "Occupational Health Epidemiological Studies", and may be disclosed to private contractors assisting NIOSH; to collaborating researchers under certain limited circumstances to conduct further investigations; to the Department of Justice in the event of litigation; and to a congressional office assisting individuals in obtaining their records. An accounting of the disclosures that have been made by NIOSH will be made available to you upon request. Except for these and other permissible disclosures expressly authorized by the Privacy Act, no other disclosure may be made without your written consent.

IV. SIGNATURES

I have read this consent form and I agree to participate in this study.

PARTICIPANT _____ Age _____

(signature)

Date _____

I, the NIOSH representative, have accurately described this study to the participant.

REPRESENTATIVE _____ Date _____

(signature)

APPENDIX F

Instructions for Completing the Questionnaire

Thank you for participating in this survey. You are a very important part of this project.

- A NIOSH investigator will be present to explain each section of the questionnaire and to answer any questions about it. Please ask any and all questions that you have while filling out the questionnaire.

- Please use pencil to answer the questions.

- Please mark every answer, even if your answer is "no" or "I don't know."

- Please print clearly when the answer must be written.

- This questionnaire asks you to provide information about your work history, medical history, diet history, drinking water, alcohol consumption, tobacco product use, fertilizer use, and pesticide use. All of these topics are important because they can add to your total nitrosamine exposure or interfere with your body's metabolism of nitrosamines. It is very important that you fill out every section.

STUDY # _____

QUESTIONNAIRE
NIOSH HHE 94-0072
GEN CORP AUTOMOTIVE
MARION, INDIANA

A. GENERAL INFORMATION

DATE: _____/_____/_____

Year of birth 19_____ Gender M ☐ F ☐ Height _____ft. _____in.
Marital Status Single ☐ Married ☐ Divorced ☐ Usual weight _____lbs.

Ethnic Origin

White, not of Hispanic descent	☐	American Indian or Alaskan native	☐
Black, not of Hispanic descent	☐	Asian or Pacific Islander	☐
Hispanic	☐	Other (specify) _____	☐

Level of Education (check the highest level achieved)

Did not complete high school	☐
Obtained a high school diploma or GED	☐
Obtained a college degree	☐
Obtained a graduate degree	☐

STUDY # _____

B. OCCUPATIONAL HISTORY

B1. Have you ever worked for Gen Corp Automotive in Marion, Indiana?

- ☐ Yes What years? 19__ to 19__
- ☐ No (go to B5)

Do you presently work for this Gen Corp Automotive?

- ☐ Yes
- ☐ No

B2. Have you ever worked in the Vehicle Sealing (VS) department of Gen Corp Automotive in Marion, Indiana?

- ☐ Yes What years? 19__ to 19__
- ☐ No (go to B3)

Do you presently work in the VS department?

- ☐ Yes
- ☐ No

B3. List the departments for which you work and have previously worked at Gen Corp Automotive. Start with your presant job and go backward.

Department	Job Title	Years in Position
		19____ to 19____
		19____ to 19____
		19____ to 19____
		19____ to 19____
		19____ to 19____

B4. Choose the answer that best describes where you work at Gen Corp Automotive.

- ☐ In VS area, along salt bath lines
- ☐ In VS area, but not on salt bath lines
- ☐ In and out of VS area throughout the day
- ☐ Near VS area
- ☐ Enclosed office near VS area
- ☐ Not in VS area at all (Mix house or remote offices)
- ☐ Other (please specify) _____

STUDY # _____

B. OCCUPATIONAL HISTORY (cont.)

B5. Please list each job you have held for at least 6 months if the job was in either the rubber industry, leather tanning industry, metal working industry, chemical industry, pesticide production, detergent production, chemotherapeutic drug production, or fish factories. Begin with your present job and work back to your first job. If you held different jobs at the same company, please list the different jobs separately, one on each page.

JOB #1 (present or most recent job)

Name of company:
Type of company: (What does it make or do?)
Your complete job title at the company:
Years in this job title: 19_____ to 19_____
Main activities and duties in this job title:
Kinds of materials and chemicals handled in this job title:
Kinds of equipment used in this job title:
Was this: ☐ full-time? ☐ part-time?

STUDY # _____

B. OCCUPATIONAL HISTORY (cont.)

B5. (continued)

JOB #2

Name of company:
Type of company: (What does it make or do?)
Your complete job title at the company:
Years in this job title: 19_____ to 19_____
Main activities and duties in this job title:
Kinds of materials and chemicals handled in this job title:
Kinds of equipment used in this job title:
Was this: ☐ full-time? ☐ part-time?

STUDY # _____

B. OCCUPATIONAL HISTORY (cont.)

B5. (continued)

JOB #3

Name of company:
Type of company: (What does it make or do?)
Your complete job title at the company:
Years in this job title: 19_____ to 19_____
Main activities and duties in this job title:
Kinds of materials and chemicals handled in this job title:
Kinds of equipment used in this job title:
Was this: ☐ full-time? ☐ part-time?

STUDY # _____

B. OCCUPATIONAL HISTORY (cont.)

B5. (continued)

JOB #4

Name of company:
Type of company: (What does it make or do?)
Your complete job title at the company:
Years in this job title: 19_____ to 19_____
Main activities and duties in this job title:
Kinds of materials and chemicals handled in this job title:
Kinds of equipment used in this job title:
Was this: ☐ full-time? ☐ part-time?

STUDY # _____

B. OCCUPATIONAL HISTORY (cont.)

B5. (continued)

JOB #5

Name of company:
Type of company: (What does it make or do?)
Your complete job title at the company:
Years in this job title: 19_____ to 19_____
Main activities and duties in this job title:
Kinds of materials and chemicals handled in this job title:
Kinds of equipment used in this job title:
Was this: ☐ full-time? ☐ part-time?

STUDY # _____

C. RESIDENTIAL AND WATER SUPPLY HISTORY

C1. Please fill in the information about your current address.

Exact Address	Years lived there	Primary source of drinking water
street: _____ city: _____ state: _____ zip: _____	19____ to 19____	☐ community/town ☐ bottled , ☐ home well ☐ don't know ☐ other _____

D. Drinking of NON-ALCOHOLIC, water-based beverages

D1. Answer according to your average drinking habits as an adult (since age 18).

How often do you drink . . . . (NOTE: < means less than, and > means greater than)

(check appropriate box)	never	1-6/ year	<1/ month	1/ month	2-3/ month	1/ week	2/ week	3-4/ week	5-6/ week	1/ day	>2/ day
a glass of water?											
a cup of coffee?											
a cup of hot tea?											
a glass of iced tea?											
a glass of iced tea? (in summer only)											
a glass of fruit juice from concentrate?											
a glass of a mixed powder drink?											
other drinks made with water? Please specify below.											
other_____											
other _____											

STUDY # _____

E. Drinking of ALCOHOLIC Beverages

E1. Did you ever drink alcoholic beverages at least 12 or more times in a single year?

☐ Yes

☐ No (go to Section F)

E2. How old were you when you first drank at least 12 alcoholic beverages in a single year? age_____

E3. How old were you when you last drank at least 12 alcoholic beverages in a single year? age_____

☐ still drink

E4. How many years altogether did you drink at least 12 or more alcoholic beverages in a single year? (including if you still drink) _____# years

E5. Answer the following according to your average drinking habits over the entire time you drank. (* For the questions about hard liquor, write G for gin, V for vodka, B for bourbon, S for scotch, W for whiskey, R for rum, O for other, in the appropriate box.)

How often do you or did you drink . . . (NOTE: < means less than, and > means greater than)

(check appropriate box)	never	1-5/ year	<1/ month	1/ month	2-3/ month	1/ week	2/ week	3-4/ week	5-6/ week	1/ day	> 2/ day
a beer?											
a glass of wine?											
a wine cooler?											
*a mixed drink?											
*a shot of liquor?											
*a glass of straight liquor or on ice?											
a glass of home-brewed liquor? Please specify type below.											
type _____											
type _____											
other alcoholic beverages? Please specify below.											
other_____											
other _____											

STUDY # _____

F. DIET HISTORY

F1. Answer according to your average eating habits in the past year.

How often do you eat or drink . . . . (NOTE: < means less than, and > means greater than)

(check appropriate box)	never	1-5	<1	1	2-3	1	2	3-4	5-6	1	>2	quantity you normally eat based on the medium serving size listed here			
	per year		per month			per week				per day		medium serving size	sm	md	lg
milk and milk products?												8 oz.			
cheese and cheese products?												2 slices			
breads and bread products?												2 slices			
raw vegetables, including salad?												1/2 cup			
cooked vegetables, not including potatoes?												1/2 cup			
fresh non-citrus fruits?												1 piece			
fresh citrus fruits (oranges, grapefruits, etc.)?												1 piece			
orange juice or grapefruit juice?												6 oz.			
fortified fruit drinks (Hi-C, Tang)?												6 oz.			
tomatoes or tomato juice?												1 or 6oz.			
artichokes?												1/2 cup			
asperagus?												1/2 cup			
green beans?												1/2 cup			
lima beans?												1/2 cup			
dry beans?												1/2 cup			
beets?												1/2 cup			
broccoli?												1/2 cup			
brussel sprouts?												1/2 cup			
cabbage?												1/2 cup			
carrots?												1/2 cup			

STUDY # _____

F. DIET HISTORY (cont.)

F1. (continued)

How often do you eat or drink . . . .

(check appropriate box)	never	1-5	<1	1	2-3	1	2	3-4	5-6	1	>2	quantity you normally eat based on the medium serving size listed here			
	per year		per month			per week				per day		medium serving size	sm	md	lg
cauliflower?												1/2 cup			
celery?												1/2 cup			
corn?												1/2 cup			
cucumber?												1/2 cup			
eggplant?												1/2 cup			
endive?												1/2 cup			
kale/collard?												1/2 cup			
leek?												1/2 cup			
lettuce?												1/2 cup			
melon?												1/2 cup			
mushroom?												1/2 cup			
okra?												1/2 cup			
onion?												1/2 cup			
parsley?												1/2 cup			
peas?												1/2 cup			
peppers (sweet)?												1/2 cup			
potatoes (including french fries)?												1/2 cup			
sweet potatoes?												1/2 cup			
pumpkin and squash?												1/2 cup			
radishes?												1/2 cup			

STUDY # _____

F. DIET HISTORY (cont.)

F1. (continued)

How often do you eat or drink . . . .

(mark appropriate box)	never	1-5	<1	1	2-3	1	2	3-4	5-6	1	>2	quantity you normally eat based on the medium serving size listed here			
	per year		per month			per week				per day		medium serving size	sm	md	lg
rhubarb?												1/2 cup			
spinach?												1/2 cup			
turnips?												1/2 cup			
turnip greens?												1/2 cup			
bacon, smoked?												2 pieces			
bacon, unsmoked?												2 pieces			
sausage, smoked?												2 pieces			
sausage, unsmoked?												2 pieces			
beef (steak and roasts)?												4 oz.			
fresh ham?												4 oz.			
processed , smoked, or baked ham?												4 oz.			
corned beef?												4 oz.			
pepperoni?												4 oz.			
bologna sandwich meat?												2 slices			
ham sandwich meat?												2 slices			
salami sandwich meat?												2 slices			
fresh fish?												2 sm or 1 lg piece			
frozen, smoked, or canned fish?												2 sm or 1 lg piece			

STUDY # _____

F. DIET HISTORY (cont.)

F2. How well cooked do you usually eat beef?

- ☐ charred
- ☐ well-done
- ☐ medium well
- ☐ medium
- ☐ medium rare
- ☐ rare

F3. Answer the following according to your average vitamin intake over the past year.

How often do you take . . . . (NOTE: < means less than, and > means greater than)

(check appropriate box)	never	every now and then, not regularly	1/week	> 1/week	1/day	> 1/day	At what age did you start taking these vitamins at this frequency?
a multivitamin?							age _____
vitamin A?							age _____
vitamin C?							age _____
vitamin E?							age _____
cod liver oil?							age _____
other (please specify)? _____							age _____

STUDY # _____

G. TOBACCO USE

G1. Do you currently smoke cigarettes? ☐ Yes ☐ No

G2. Have you ever smoked cigarettes? ☐ Yes ☐ No (go to G8)

G3. Have you ever smoked 100 or more cigarettes during your lifetime? ☐ Yes ☐ No

G4. In what year did you start smoking cigarettes? Year 19____ Age_____

G5. In what year did you stop smoking cigarettes? Year 19____ ☐ Still smoke

G6. Did you smoke cigarettes regularly during this period (at least 1/2 pack per week)? ☐ Yes ☐ No

If no, for how long did you stop smoking? _____#months _____#years

G7. Over the entire time you smoked, on average, how many cigarettes did you smoke per day? _____ #cig./ day _____ #packs/day

---

G8. How many smokers do you currently live with? _____ #smokers

(If none, enter zero and go to G9)

For how long did you live with this smoker(s)? 19___ to 19___

Over the entire time you lived with a smoker(s), on average, how many cigarettes did they smoke per day? _____ #cig./ day _____ #packs/day

G9. Do you frequent the smoking break room at work? ☐ Yes ☐ No

---

STUDY # _____

G10. Do you currently smoke cigars or pipes? ☐ Yes ☐ No

G11. Have you ever smoked cigars or pipes? ☐ Yes ☐ No (go to G17)

G12. Have you ever smoked 100 or more cigars or pipes during your lifetime? ☐ Yes ☐ No

G13. In what year did you start smoking cigars or pipes? Year_____ Age_____

G14. In what year did you stop smoking cigars or pipes? Year____ ☐ Still smoke

G15. Did you smoke cigars or pipes regularly during this period (at least 2 per week)? ☐ Yes ☐ No

If no, for how long did you stop smoking? ___#months ___#years

G16. Over the entire time you smoked, on average, how many cigars or pipes did you smoke per day? _____ #cig./ day _____ #cig./week

---

G17. Do you currently use chewing tobacco or snuff? ☐ Yes ☐ No

G18. Did you ever use chewing tobacco or snuff? ☐ Yes ☐ No (go to Section H)

G19. In what year did you start using chewing tobacco or snuff? Year_____ Age_____

G20. In what year did you stop using chewing tobacco or snuff? Year____ ☐ Still use

G21. Did you use it regularly during this period (at least 1 tin or can per week)? ☐ Yes ☐ No

If no, for how long did you stop using it? ___#months ___#years

G22. Over the entire time you used it, on average, how many tins or cans did you use per day? ____ tins/ day ____ tins/wk

STUDY # _____

H. FERTILIZER USE

H1. Do you apply ferilizers to your yard or family gardan?

- ☐ Yes
- ☐ No (go to H6)

H2. Have you ever applied nitrogen ferilizers at home?

- ☐ Yes
- ☐ No
- ☐ Don't Know

If yes, what type of nitrogen fertilizers? (check all that you use routinely)

- ☐ dry
- ☐ liquid
- ☐ anhydrous nitrogen
- ☐ ammonium nitrate
- ☐ urea
- ☐ manure
- ☐ other (pease specify) _____
- ☐ don't know

H3. During what seasons do you apply fertilizers? (check all that apply)

- ☐ spring
- ☐ summer
- ☐ fall
- ☐ winter

H4. How often and for how many years did you apply the fertilizers? (Write in "don't know" if don't know the type.)

Type of Fertilizer	# days used/year	Start year to Stop year
	#days/year	19_____ to 19_____
	#days/year	19_____ to 19_____
	#days/year	19_____ to 19_____
	#days/year	19_____ to 19_____
	#days/year	19_____ to 19_____
	#days/year	19_____ to 19_____

H5. Have you been applying these fertilizers during the past week?

- ☐ Yes
- ☐ No

STUDY # _____

H. FERTILIZER USE (cont.)

H6. Do you presently own or work on a farm?
- ☐ Yes
- ☐ No (go to Section J)

H7. Have you ever applied fertilizers to the crops?
- ☐ Yes
- ☐ No

H8. Have you ever applied nitrogen fertilizers to the crops?
- ☐ Yes
- ☐ No
- ☐ Don't Know

If yes, what type of nitrogen fertilizers? (check all that you use routinely)
- ☐ dry
- ☐ liquid
- ☐ anhydrous nitrogen
- ☐ ammonium nitrate
- ☐ urea
- ☐ manure
- ☐ other (pease specify) _____
- ☐ don't know

H9. During what seasons do you apply fertilizers? (check all that apply)
- ☐ spring
- ☐ summer
- ☐ fall
- ☐ winter

H10. How often and for how many years did you apply the fertilizers? (Write in "don't know" if don't know the type.)

Type of Fertilizer	# acres to which applied	# days used/year	Start year to Stop year
	#acres	#days/year	19_____ to 19_____
	#acres	#days/year	19_____ to 19_____
	#acres	#days/year	19_____ to 19_____
	#acres	#days/year	19_____ to 19_____
	#acres	#days/year	19_____ to 19_____

H11. Have you been applying these fertilizers during the past week?
- ☐ Yes
- ☐ No

STUDY # _____

J. PESTICIDE USE

J1. Have you ever applied pesticides (insecticides, herbicides, fungicides) to your home yard or family garden?

☐ Yes
☐ No (go to J3)

If yes, please specify the types used.

Pesticide Type (insecticide, herbicide, or fungicide)	Brand or Chemical Name	Start Year to Stop year	Frequency of Use
		19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year
		19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year
		19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year
		19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year
		19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year

J2. Have you been applying these pesticides during the past week?

☐ Yes
☐ No

STUDY # _____

J. PESTICIDE USE (cont.)

J3. **Have you ever applied pesticides (insecticides, herbicides, fungicides) on a farm?**

☐ Yes

☐ No (go to Section K)

If yes, please specify the types used.

Pesticide Type (insecticide, herbicide, or fungicide)	Brand or Chemical Name	# acres to which applied	Start year to Stop year	Frequency of Use
			19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year
			19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year
			19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year
			19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year
			19_____ to 19_____	_____ times per day _____ times per week _____ times per month _____ times per year

J4. **Have you been applying these pesticides during the past week?**

☐ Yes

☐ No

STUDY # ________

K. MEDICAL HISTORY

K1. **Are you currently taking any prescription medications?** ☐ Yes ☐ No

Are you currently taking any nonprescription medications? ☐ Yes ☐ No

K2. **Please list any and all prescription and nonprescription medications that you take presently.**

Medication	Reason for taking	When did you start taking it? (month/year)	How frequently do you take it?
		____/19____	____ mg ____ x per day ____ mg ____ x per week ____ mg ____ x per month ____ mg ____ x per year
		____/19____	____ mg ____ x per day ____ mg ____ x per week ____ mg ____ x per month ____ mg ____ x per year
		____/19____	____ mg ____ x per day ____ mg ____ x per week ____ mg ____ x per month ____ mg ____ x per year
		____/19____	____ mg ____ x per day ____ mg ____ x per week ____ mg ____ x per month ____ mg ____ x per year
		____/19____	____ mg ____ x per day ____ mg ____ x per week ____ mg ____ x per month ____ mg ____ x per year
		____/19____	____ mg ____ x per day ____ mg ____ x per week ____ mg ____ x per month ____ mg ____ x per year

STUDY # _____

K. MEDICAL HISTORY (cont.)

K3. Have you ever been diagnosed with cancer or a tumor by a medical doctor? ☐ Yes ☐ No

If yes, please specify type of cancer or tumor and in what year it was diagnosed.

year _____ type _____

K4. Has a blood relative of yours ever been diagnosed with cancer or a tumor by a medical doctor? ☐ Yes ☐ No

If yes, please fill in below.

Type of Cancer	Don't Know	Relation to You	In what part of the body did it start?	Don't Know	At what age was it diagnosed?	Don't Know

K5. Do you currently have a urinary tract infection? ☐ Yes ☐ No

K6. Have you had a urinary tract infection in the past year? ☐ Yes ☐ No

K7. Have you had two or more urinary tract infections in the past year? ☐ Yes ☐ No

K8. Have you ever been diagnosed with cirrhosis of the liver? ☐ Yes ☐ No

STUDY # _____

What is your name? (Please print.)

_____

(last name) (first name) (middle initial)

Please make sure that you have filled out the entire questionnaire. Again, thank you for your time.

As stated in the consent form, all information will become part of the CDC Privacy Act system 09-20-0147, "Occupational Health Epidemiological Studies", and may be disclosed to private contractors assisting NIOSH; to collaborating researchers under certain limited circumstances to conduct further investigations; to the Department of Justice in the event of litigation; and to a congressional office assisting individuals in obtaining their records. An accounting of the disclosures that have been made by NIOSH will be made available to you upon request. Except for these and other permissible disclosures expressly authorized by the Privacy Act, no other disclosure may be made without your written consent.

APPENDIX G

Notification Letter to Study Participants

Dear _____:

Thank you for your participation in the research study conducted by the National Institute for Occupational Safety and Health (NIOSH) at the Marion, Indiana facility of Gen Corp Automotive. As you know, the purpose of this evaluation was to determine the biologic effects of nitrosamine exposures, specifically its effect on DNA adduct concentrations and DNA repair enzyme activity.

The following pages include your individual test results as well as a summary of the group results. The summary will explain any significant findings from the study. Your individual results are important because they contribute to the study, but they currently do not have any individual health significance because they are not known to be related to any specific disease and do not call for any medical action.

Your participation in this study is greatly appreciated. This study will help us understand some of the biologic effects that might occur from occupational nitrosamine exposure. If you have any questions about your results or the findings of the overall study, please call me at 1-800-356-4674 or (513) 841-4374.

Individual Results

NOTE: The individual blood and urine sample results do not have any individual medical significance. These assays have not yet been linked to any specific disease, and there are no established "normal" ranges for DNA adducts or DNA repair enzyme activity. Please do not try to interpret any meaning from your individual results.

Your personal breathing zone sample collected on ___/___/___ was:

_____ micrograms _____ per cubic meter of air ($\mu g/m^3$)

_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____

The range of personal breathing zone exposures for workers from the vehicle sealing department of Gen Corp Automotive in Marion, Indiana were:

_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	

The range of personal breathing zone exposures for workers from other departments of Gen Corp Automotive in Marion, Indiana were:

_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	

The range of personal breathing zone exposures for workers from Gen Corp Automotive in Logansport, Indiana were:

_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	_____ $\mu g/m^3$ _____
_____ $\mu g/m^3$ _____	

Your blood sample collected on ___/___/___ revealed the following DNA adduct concentrations from your peripheral blood cells:

_____* femtomoles of N^7-methylguanine DNA adduct per _____ nucleotides

_____* femtomoles of O^6-methylguanine DNA adduct per _____ nucleotides

The range of DNA adduct concentrations for workers from the vehicle sealing department of Gen Corp Automotive in Marion, Indiana, were:

_____* femtomoles of N^7-methylguanine DNA adduct per _____ nucleotides

_____* femtomoles of O^6-methylguanine DNA adduct per _____ nucleotides

The range of DNA adduct concentrations for workers from other departments of Gen Corp Automotive in Marion, Indiana, were:

_____* femtomoles of N^7-methylguanine DNA adduct per _____ nucleotides

_____* femtomoles of O^6-methylguanine DNA adduct per _____ nucleotides

The range of DNA adduct concentrations for workers from Gen Corp Automotive in Logansport, Indiana, were:

_____* femtomoles of N^7-methylguanine DNA adduct per _____ nucleotides

_____* femtomoles of O^6-methylguanine DNA adduct per _____ nucleotides

[* the results will be displayed with the appropriate units used by the laboratory]

Your blood sample collected on ___/___/___ revealed the following activity of the DNA repair enzyme O^6-alkylguanine-DNA transferase from your peripheral blood cells:

_____*

The range of DNA repair enzyme activity for workers from the vehicle sealing department of Gen Corp Automotive in Marion, Indiana, were:

_____*

The range of DNA repair enzyme activity for workers from other departments of Gen Corp Automotive in Marion, Indiana, were:

_____*

The range of DNA repair enzyme activity for workers from Gen Corp Automotive in Logansport, Indiana, were:

_____*

[* the results will be displayed with the appropriate units used by the laboratory]

Your blood sample collected on ___/___/___ revealed the following genetic polymorphism of your cytochrome P450IIE1 gene:

_____*

The range of P450IIE1 polymorphisms for workers from the vehicle sealing department of Gen Corp Automotive in Marion, Indiana, were:

_____*

The range of P450IIE1 polymorphisms for workers from other departments of Gen Corp Automotive in Marion, Indiana, were:

_____*

The range of P450IIE1 polymorphisms for workers from Gen Corp Automotive in Logansport, Indiana, were:

_____*

[* the results will be displayed with the appropriate units used by the laboratory]

Your urine sample collected on ___/___/___ revealed the following DNA adduct concentrations from exfoliated cells:

_____* femtomoles of N^7-methylguanine DNA adduct per _____ nucleotides

_____* femtomoles of O^6-methylguanine DNA adduct per _____ nucleotides

The range of DNA adduct concentrations for workers from the vehicle sealing department of Gen Corp Automotive in Marion, Indiana, were:

_____* femtomoles of N^7-methylguanine DNA adduct per _____ nucleotides

_____* femtomoles of O^6-methylguanine DNA adduct per _____ nucleotides

The range of DNA adduct concentrations for workers from other departments of Gen Corp Automotive in Marion, Indiana, were:

_____* femtomoles of N^7-methylguanine DNA adduct per _____ nucleotides

_____* femtomoles of O^6-methylguanine DNA adduct per _____ nucleotides

The range of DNA adduct concentrations for workers from Gen Corp Automotive in Logansport, Indiana, were:

_____* femtomoles of N^7-methylguanine DNA adduct per _____ nucleotides

_____* femtomoles of O^6-methylguanine DNA adduct per _____ nucleotides

[* the results will be displayed with the appropriate units used by the laboratory]

Your urine sample collected on ___/___/___ revealed the following concentrations of excised DNA adducts:

_____* femtomoles of N^7-methyladenine DNA adduct per _____ nucleotides

_____* femtomoles of N^3-methyladenine DNA adduct per _____ nucleotides

The range of DNA adduct concentrations for workers from the vehicle sealing department of Gen Corp Automotive in Marion, Indiana, were:

_____* femtomoles of N^7-methyladenine DNA adduct per _____ nucleotides

_____* femtomoles of N^3-methyladenine DNA adduct per _____ nucleotides

The range of DNA adduct concentrations for workers from other departments of Gen Corp Automotive in Marion, Indiana, were:

_____* femtomoles of N^7-methyladenine DNA adduct per _____ nucleotides

_____* femtomoles of N^3-methyladenine DNA adduct per _____ nucleotides

The range of DNA adduct concentrations for workers from Gen Corp Automotive in Logansport, Indiana, were:

_____* femtomoles of N^7-methyladenine DNA adduct per _____ nucleotides

_____* femtomoles of N^3-methyladenine DNA adduct per _____ nucleotides

[* the results will be displayed with the appropriate units used by the laboratory]

Group Results

[A summary of the group sampling results, possibly specific for various demographic and other risk factors, will be presented. Both the exposed group and unexposed group results will be provided with explanations. The reason for doing this is because the individual results do not have any value to the study participants. The design of this presentation, such as tables, graphs, and text, will not be decided and formatted until the actual results are seen.]

APPENDIX H

Emergency Plan

The member of the field survey team who discovers the emergency, or who is the first to arrive on the scene, is responsible for carrying out the following steps until that responsibility is taken over by another member of the team or the project officer, Beth Donovan.

1. Call for help from another member of the survey team.
2. Follow basic CPR and first aid guidelines. If you are not trained in these, remain calm and keep the situation under control until a trained team member arrives.
3. If appropriate, call 911 and request an ambulance to transport the subject to the emergency department of the nearest hospital. The nearest hospital is:

   Marion General Hospital
   441 North Wabash Street
   Marion, Indiana 46952

4. After the emergency has been handled, notify the project officer, Beth Donovan, who will be at the sampling site, and the Chair of the NIOSH Human Subject's Review Board, Michael J. Colligan, at (513) 533-8225.

To: Dr. Michael J. Colligan, HSRB Chairperson
DTMD, mail stop C-11

From: Beth Donovan, M.H.S.
DSHEFS/HETAB/IHS, mail stop R-11

Re: expedited HSRB proposal for HETA 94-0072

Date:

The following is a proposal submitted for expedited review by the Human Subject's Review Board. The study is part of a health hazard evaluation (HETA 94-0072) and would be defined as a research HHE/TA investigation. The NIOSH HSRB procedures for fiscal year 1994 states that, "Research HHE/TA investigations are subject to NIOSH HSRB review and approval. Their submission to the HSRB should follow the procedures for expedited review, except that peer and statistical reviews. . . are not routinely required; the necessity for peer and statistical reviews will be determined, for each research HHE/TA, by the sponsoring Division/Office." The CDC Manual Guide No. 11 references several research activities that have been published in the Federal Register as eligible for expedited review, including the collection of excreta and the collection of blood samples which do not exceed 450 milliliters in an 8-week period, from subjects 18 years of age or older and who are in good health and not pregnant.

Since this proposal meets the outlined criteria, I am requesting an expedited review. Further reasons for expedited review are that the ventilation at the facility is going to be changed in the near future. This change will be a positive one for the health of the workers and NIOSH investigators support it. However, doing this study before the ventilation change will provide the NIOSH investigators with information to better assess the health hazard to nitrosamines at this facility.

Appendix E

Interim Letter
Air Sampling Results from DNA–adduct Portion of the HHE
June 20, 1995

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institute for Occupational Safety and Health
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati OH 45226-1998

COPY

June 20, 1995
HETA 94-0072

Mr. Roy Clem
United Rubber Workers, Local 466
819 North Butler Avenue
Marion, Indiana 46952

Dear Mr. Clem:

As part of the National Institute for Occupational Safety and Health (NIOSH) health hazard evaluation (HHE) at Gen Corp Automotive in Marion, Indiana, NIOSH investigators conducted a third site visit on January 23 – February 3, 1995. During this visit, worker exposure to nitrosamines was evaluated by collecting personal breathing zone (PBZ) and general area (GA) air samples, blood samples, and urine samples. This report contains air sampling results and discusses the recommendations that were made in the first interim report. The biological sample analyses have not yet been completed, and the original estimate of a final report approximately one year from this latest survey is still expected.

The air sampling results are presented in the enclosed tables. Table 1 presents the GA results, Tables 2 through 5 present the PBZ results for the participants in the biological monitoring study, and Table 6 presents the PBZ results for workers who were cleaning the salt baths. The GA sample concentrations ranged up to 187 micrograms per cubic meter ($\mu g/m^3$) for nitrosodimethylamine (NDMA), a compound which is considered an occupational carcinogen by both NIOSH and the Occupational Safety and Health Administration (OSHA). Of interest are the GA samples collected on the production lines running a developmental rubber stock (intended to not produce nitrosamines) which had high nitrosamine concentrations.

The PBZ sample concentrations ranged up to 9.3 $\mu g/m^3$, quite high when compared to the German occupational standard of 2.5 $\mu g/m^3$ for rubber vulcanizing and processing industries.[a] In fact, every worker sampled at this plant had at least some nitrosamine exposure, even those in areas remote from the vehicle sealing area. If workers are grouped according to job title and proximity to the salt bath lines (as done in Tables 2-5), there does appear to be a reduction of exposure for those further away from the lines, which would be expected. Figure 1 displays the average exposures compared to the German standard.

Although biological monitoring analyses to assess nitrosamine exposure are not completed, air sampling indicate excessive exposures within this plant. As stated in the previous interim report

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[a] Neither OSHA nor NIOSH have established numerical exposure criteria for nitrosamines. NIOSH recommends that exposure to NDMA be maintained as low as is feasible.

dated October 12, 1994, most nitrosamines are suspected human carcinogens. NIOSH considers NDMA to be an occupational carcinogen and recommends reducing exposure to the lowest feasible concentration. Toward this end, Gen Corp should develop rubber stocks or curing processes that do not form nitrosamines. Until this can be achieved, better local exhaust ventilation (LEV) systems are necessary. For example, the drilling stations located along the production lines (used to drill holes in certain types of freshly extruded rubber vehicle sealing) should each have a LEV system. However, these LEV systems should not just be added to the existing salt bath exhaust since the salt bath exhaust system was not designed for it. Additionally, the existing salt bath exhaust should be tested to ensure proper performance and should be maintained routinely. NIOSH investigators also recommend adding LEV along the end of each line where one or two employees were observed to often work for the duration of the shift. Finally, all ventilation systems must be designed so that re-entrainment of exhaust back into the work place does not occur. If engineering or administrative controls cannot be implemented to effectively reduce exposures, NIOSH would recommend the use of respiratory protection for all exposed workers as is outlined below for cleaning operations.

During cleaning operations the salt bath access doors must remain open, a situation which interferes with the effectiveness of the designed LEV. Since exposures during these procedures appear to be even higher than during normal operations (Table 6), NIOSH investigators recommend that employees wear respiratory protection when cleaning the salt baths. Since NDMA is considered an occupational carcinogen, NIOSH recommends that only the most effective respirators be used. Two types of respirators are recommended: either a self-contained breathing apparatus (SCBA) with a full face-piece operated in pressure demand or other positive pressure mode, or a supplied-air respirator (SAR) with a full face-piece operated in pressure demand or other positive pressure mode in combination with an auxiliary SCBA operated in pressure demand or other positive pressure mode.[1,2] Whenever respirators are used in a work place, an effective respiratory protection program, in accordance with the requirements described in 29 CFR 1910.134,[3] must exist. Publications developed by NIOSH which should also be referenced when developing an effective respirator program include the NIOSH Respirator Decision Logic and the NIOSH Guide to Industrial Respiratory Protection.[1,4] The written respirator program should contain information on the following topics: (a) the departments/operations which require respiratory protection; (b) the correct respirators required for each job/operation; (c) specifications that only NIOSH/MSHA approved respiratory devices shall be used; and (d) the criteria used for the proper selection, use, storage and maintenance of respirators, including limitations. The respirator program should also reference the requirements contained in the confined space program to assure that employees are adequately protected when working in these areas. A respiratory protection program should include the following elements:

a. written operating procedures
b. appropriate respirator selection
c. employee training and fit testing
d. effective cleaning of respirators
e. proper storage
f. routine inspection and repair
g. exposure surveillance

h. program review
i. medical approval
j. use of approved respirators

If you have any questions concerning this report or any part of the NIOSH HHE, please call me at (513) 841-4374.

Sincerely yours,

Beth Donovan Reh, M.H.S.
Industrial Hygienist
Industrial Hygiene Section
Hazard Evaluations and Technical Assistance Branch
Division of Surveillance, Hazard Evaluations and Field Studies

Enclosures

cc:
Mr. A.W. Beers, Safety/Security Manager
Mr. William Gorenc, Jr.
Mr. James Frederick

bcc:
Greg Burr
John Fajen
B. Reh
HETA 94-0072

References

1. NIOSH [1987]. NIOSH respirator decision logic. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 87-108.

2. NIOSH [1994]. NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 94-116.

3. Code of Federal Regulations [1993]. 29 CFR 1910.134. Respiratory protection. Washington, DC: Occupational Safety and Health Administration, U.S. Department of Labor, U.S. Government Printing Office.

4. NIOSH [1987]. NIOSH guide to industrial respiratory protection. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 87-116.

Table 1. General Area Air Sampling Results for Nitrosamines. HETA 94-0072.

			Nitrosamine Concentration (µg/m³)			Stock Numbers
Location	Date	Sample Volume (L)	NDMA	NPIP	NMOR	(sponge/dense)
line 1 drill	1/25/95	428	6.5	1.2	0.3	10105/46966
line 3 drill	1/25/95	417	127	60	0.4	10104/46966
line 4 drill	1/25/95	422	69	10	0.3	10107/20106
line 8 drill	1/25/95	428	107	5.1	0.7	10104/46997
non-smoking break room	1/25/95	432	0.7	0.3	0.1	NA
smoking break room	1/25/95	467	1.2	0.7	0.2	NA
line 2 drill	1/26/95	415	157	34	2	23488/46685
line 3 drill	1/26/95	420	133	131	0.8	10104/46966
line 4 drill	1/26/95	415	120	29	1.4	DEV 2.0
line 5 drill	1/26/95	414	31	2.4	0.4	DEV
line 6 drill	1/26/95	401	187	30	1.6	DEV
line 7 drill	1/26/95	462	121	19	1.3	23672/46966
line 8 drill	1/26/95	402	35	3	0.6	20106/10104
line 8, 4 inches from drill	1/26/95	398	78	3.3	0.5	20106/10104
non-smoking break room	1/26/95	468	0.7	0.4	0.1	NA
smoking break room	1/26/95	471	1.2	0.8	0.2	NA
line 1 cutter	2/1/95	411	3.2	2.0	0.04	10106/20137
line 2 drill	2/1/95	430	158	16	1.0	10104/20107
line 3 drill	2/1/95	433	150	35	0.3	10104/46966
line 4 drill	2/1/95	435	9.0	3.4	0.4	10107/20106
line 5 drill, during running and cleaning	2/1/95	439	22	3.6	0.5	DEV
line 5 drill, development product	2/1/95	78	14	9.0	0.5	DEV
line 5, during cleaning only	2/1/95	129	2.2	1.6	0.2	DEV
line 6 drill	2/1/95	444	19	3.8	0.5	10104/20107
line 8 drill	2/1/95	313	83	6.1	0.3	20106/10104
non-smoking break room	2/1/95	451	4.4	1.2	1.1	NA

Table 1. General Area Air Sampling Results for Nitrosamines. HETA 94-0072. (Continued)

			Nitrosamine Concentration ($\mu g/m^3$)			Stock Numbers
Location	Date	Sample Volume (L)	NDMA	NPIP	NMOR	(sponge/dense)
smoking break room	2/1/95	468	1.0	1.0	0.1	NA
line 1 cutter	2/2/95	118	2.6	1.7	0.2	10105/46966
line 1, during cleaning	2/2/95	149	2.3	2.5	0.07	10105/46966
line 2 drill	2/2/95	419	138	43	0.7	10104/20107
line 3 drill	2/2/95	418	134	53	0.7	10104/46966
line 4, after salt bath	2/2/95	409	34	13	0.7	46927/20106
line 5 drill	2/2/95	417	103	10	0.9	10104/20106
line 6 drill	2/2/95	420	11	3.3	0.2	10104/20106
line 8 drill	2/2/95	420	16	1.7	0.02	20106/10104
non-smoking break room	2/2/95	428	0.9	0.6	0.1	NA
smoking break room	2/2/95	440	1.0	0.8	0.3	NA

$\mu g/m^3$ - micrograms per cubic meter
NDMA - nitrosodimethylamine
NPIP - nitrosopiperidine
NMOR - nitrosomorpholine
DEV - a developmental stock
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 $\mu g/m^3$.

Table 2. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures of Salt Bath Line Workers. HETA 94-0072.

				Nitrosamine Concentration (µg/m³)			
#	Job Title	Date	Sample Volume (L)	NDMA	NPIP	NMOR	Total
001	front end feeder	1/25/95	430	1.4	1.3	0.2	2.9
013	line 3 assistant operator	1/25/95	435	1.2	0.7	0.2	2.1
009	line 8 assistant operator	1/25/95	458	1.2	1.1	0.3	2.6
014	line 2 operator	1/26/95	199	2.2	1.2	0.3	3.7
016	front end feeder	1/26/95	428	1.1	0.8	0.1	2.0
007	line 7 operator	1/26/95	452	2.0	0.9	0.3	3.2
015	line 5 assistant operator	2/1/95	463	3.0	2.0	0.4	5.4
010	line 2 assistant operator	2/1/95	453	4.6	2.4	0.6	7.6
006	line 2 assistant operator	2/1/95	363	3.3	1.9	0.6	5.8
017	line 5 operator	2/1/95	438	2.7	1.8	0.4	4.9
012	line 3 operator	2/1/95	451	4.4	3.1	0.1	7.6
011	line 6 assistant operator	2/1/95	361	1.3	0.9	0.1	2.3
005	line 3 assistant operator	2/2/95	438	5.9	3.0	0.4	9.3
028	line 4 operator	2/2/95	462	1.7	1.1	0.2	3.0
002	silicone booth operator	2/2/95	438	1.8	1.3	0.3	3.4
018	line 4 assistant operator	2/2/95	459	2.8	2.0	0.3	5.2
004	line 2 assistant operator	2/2/95	465	2.6	1.5	0.3	4.4
Average Exposure				2.5±1.4	1.6±0.7	0.3±0.2	4.4±2.2

µg/m³ - micrograms per cubic meter
NDMA - nitrosodimethylamine
NPIP - nitrosopiperidine
NMOR - nitrosomorpholine
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 µg/m³.

Table 3. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures of Vehicle Sealing Department Workers Who do not Work on the Salt Bath Lines. HETA 94-0072.

				Nitrosamine Concentration (µg/m³)			
#	Job Title	Date	Sample Volume (L)	NDMA	NPIP	NMOR	Total
024	skive press operator	1/25/95	426	1.2	1.5	0.1	2.8
020	a-pillar assembly	1/25/95	462	1.4	1.4	2.4	5.2
027	press operator	1/25/95	464	1.3	1.3	1.3	3.9
043	a-pillar press operator	1/25/95	457	1.0	1.1	1.6	3.7
039	punch press operator	1/25/95	446	1.4	1.4	0.2	3.0
055	box making	1/25/95	458	0.5	0.8	0.07	1.4
032	cold splice operator	1/26/95	456	0.9	1.3	0.3	2.5
030	press operator	1/26/95	463	1.4	0.9	0.9	3.2
034	a-pillar press operator	1/26/95	461	2.4	1.2	1.4	5.0
116	a-pillar press operator	1/26/95	440	0.6	0.6	0.8	2.0
021	end-dip operator	2/1/95	451	0.9	0.9	0.1	1.9
019	end-dip operator	2/1/95	433	0.9	0.7	0.09	1.7
042	skive press operator	2/1/95	447	2.7	1.0	0.07	3.8
037	b-pillar press operator	2/2/95	454	1.2	1.3	0.6	3.1
036	sand blaster repair	2/2/95	447	1.0	0.9	0.2	2.1
031	b-pillar press operator	2/2/95	453	0.9	0.9	0.5	2.3
Average Exposure				1.2±0.6	1.1±0.3	0.7±0.7	3.0±1.1

µg/m³ - micrograms per cubic meter
NDMA - nitrosodimethylamine
NPIP - nitrosopiperidine
NMOR - nitrosomorpholine
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 µg/m³.

Table 4. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures of Workers Who do not Work in the Vehicle Sealing Department but are often in the Vehicle Sealing Area. HETA 94-0072.

				Nitrosamine Concentration (µg/m³)			
#	Job Title	Date	Sample Volume (L)	NDMA	NPIP	NMOR	Total
044	trainer, end of extruder line	1/25/95	431	0.9	0.7	0.07	1.7
062	maintenance	1/25/95	452	0.8	1.2	0.3	2.3
058	process engineer	1/25/95	441	0.7	0.5	0.1	1.3
068	engineer	1/25/95	378	0.2	0.2	0.03	0.4
047	engineer	1/26/95	465	3.7	1.7	0.3	5.7
115	electrician	1/26/95	452	1.6	1.0	0.3	2.9
063	quality engineer	1/26/95	435	0.6	0.5	0.07	1.2
061	maintenance	1/26/95	449	1.8	1.0	0.5	3.3
077	sales manager	1/26/95	418	1.0	0.5	0.1	1.6
073	inventory analyst	1/26/95	445	2.5	2.2	0.1	4.8
051	maintenance	2/1/95	450	2.0	1.1	0.4	3.5
050	personnel office	2/1/95	448	0.2	0.1	0.04	0.4
057	purchasing agent	2/1/95	408	2.3	1.7	0.07	4.1
054	maintenance	2/2/95	453	1.0	0.7	0.1	1.8
064	maintenance	2/2/95	470	1.2	0.7	0.2	2.1
049	maintenance	2/2/95	449	1.2	0.9	0.2	2.3
052	janitor	2/2/95	405	0.7	0.6	0.1	1.4
048	maintenance	2/2/95	428	1.0	0.7	0.2	1.9
072	maintenance office	2/2/95	452	1.1	0.8	0.2	2.1
070	shipping and receiving office	2/2/95	407	0.8	0.7	0.05	1.6
Average Exposure				1.3±0.8	0.9±0.5	0.2±0.1	2.3±1.4

µg/m³ - micrograms per cubic meter
NDMA - nitrosodimethylamine
NPIP - nitrosopiperidine
NMOR - nitrosomorpholine
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 µg/m³.

Table 5. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures of Workers that are not in the Vehicle Sealing Area. HETA 94-0072.

				Nitrosamine Concentration (µg/m³)			
#	Job Location	Date	Sample Volume (L)	NDMA	NPIP	NMOR	Total
086	mix house	1/25/95	451	0.1	0.1	0.04	0.2
085	mix house	1/25/95	444	0.2	0.1	0.2	0.5
025	union hall	1/25/95	400	0.2	0.2	0.05	0.5
084	mix house	1/25/95	432	1.6	0.4	ND	2.0
082	mix house	1/25/95	454	0.07	0.02	ND	0.09
076	mix house	1/25/95	433	0.5	0.8	0.07	1.4
067	mix house	1/26/95	455	0.1	0.09	ND	0.2
080	mix house	1/26/95	440	0.2	0.1	0.02	0.3
078	mix house	1/26/95	424	1.4	0.5	ND	1.9
066	mix house	1/26/95	441	0.2	0.1	0.05	0.4
083	mix house	1/26/95	441	0.4	0.07	0.02	0.5
081	union hall	2/1/95	411	0.1	ND	ND	0.1
Average Exposure				0.4±0.5	0.2±0.2	0.04± 0.06	0.7±0.7

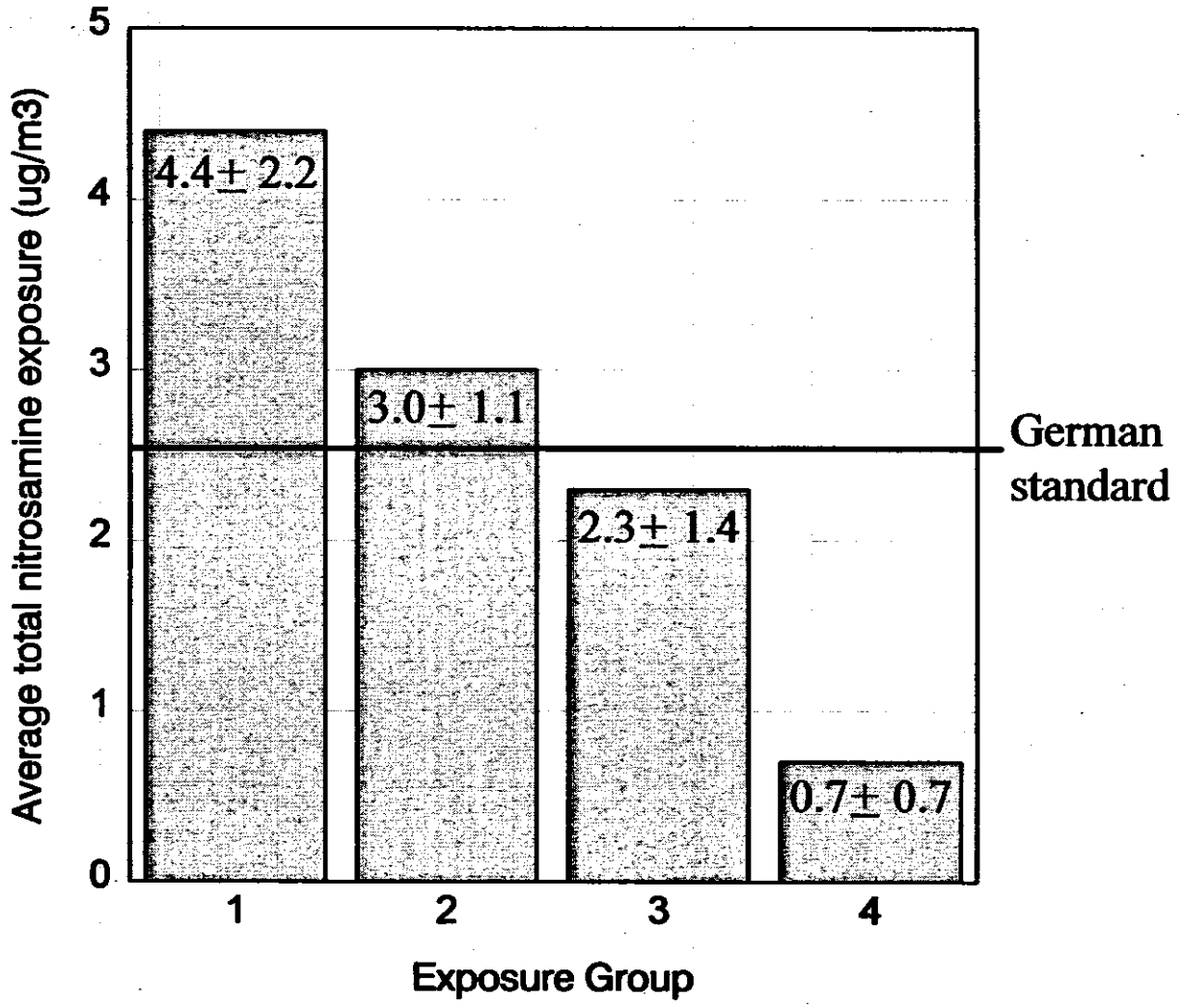
µg/m³ - micrograms per cubic meter
NDMA - nitrosodimethylamine
NPIP - nitrosopiperidine
NMOR - nitrosomorpholine
ND - none detected, minimum detectable concentration was 0.02 µg/m³
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 µg/m³.

Table 6. Personal Breathing Zone Air Sampling Results for Nitrosamine Exposures During Salt Bath Cleaning Operations. HETA 94-0072.

			Nitrosamine Concentration ($\mu g/m^3$)			
Location	Date	Sample Volume (L)	NDMA	NPIP	NMOR	Total
line 8	2/1/95	25	4.0	1.2	4.4	9.6
line 1	2/2/95	65	3.8	4.9	0.3	9.0
line 1	2/2/95	118	1.8	1.1	0.3	3.2
Average Exposure			3.2±1.2	2.4±2.2	1.7±2.4	7.3±3.5

$\mu g/m^3$ - micrograms per cubic meter
NDMA - nitrosodimethylamine
NPIP - nitrosopiperidine
NMOR - nitrosomorpholine
NOTE: Nitrosodibutylamine, nitrosodiethylamine, nitrosodipropylamine, and nitrosopyrrolidine were not detected on any samples. Minimum detectable concentration was 0.02 $\mu g/m^3$.

Figure 1. Average Exposure to Total Nitrosamines by Job Location. HETA 94-0072



Exposure Group:
1 - vehicle sealing department, salt bath line workers
2 - other vehicle sealing department employees
3 - non-vehicle sealing department employees, but often in or near area
4 - non-vehicle sealing employees, not near area

Appendix F

Interim Letter
Review of Ergonomics Program
June 28, 1994

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention
National Institute for
Occupational Safety & Health
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati OH 45226-1998

HETA

June 28, 1994
HETA 94-0072

Mr. A. W. "Bill" Beers
Safety/Security Manager
GenCorp Automotive
1700 Factory Avenue
Marion, Indiana 46952

Dear Mr. Beers:

Thank you for letting me borrow your copy of the GenCorp ergonomics training manual for supervisors. I finally had a chance to look it over and return it to you. I wrote a few minor comments on post-it notes in the manual. I had only one major concern–the treatments included in several sections of the manual. Supervisors may feel that they can recommend the treatments in the manual to employees. Such recommendations may be inappropriate and may result in worsening of an employee's condition. In addition, medical attention may be delayed. It would be more appropriate for the manual to include discussions on supervisors' roles in recognizing and referring previously unrecognized medical problems and in preventing the worsening of already diagnosed conditions. For example, supervisors should be given guidelines on when to refer employees to the medical department and on their role during treatment periods. The discussion should include examples of restricted activities, typical and special-case time periods for restrictions, reasons for the restricted activities and time periods, and examples of activities that could worsen the medical condition.

I spoke with Mr. Brian Pearson, your ergonomics consultant, on May 16, 1994. We discussed the following issues:

- Placement of the light-touch buttons on the finishing machines may be too low for tall employees and too far apart horizontally for short employees. In the future, tall employees who must stoop to reach the buttons may experience back problems and short employees who must abduct at the shoulder may experience shoulder problems.

Maintenance personnel who implement changes (such as installation of the light-touch buttons) should be trained to anticipate potential ergonomics problems that could result from the changes.

New work station designs should be evaluated for potential future ergonomics problems before implementation (such as the placement of the light-touch buttons).

Self-paced faster rates that result from the "expectancies" may cause ergonomic problems in some people.

If you have any questions, please call me at (513) 841-4386.

Sincerely yours,

Melody M. Kawamoto, M.D., M.S.
Medical Officer
Medical Section
Hazard Evaluations and Technical Assistance Branch
Division of Surveillance, Hazard Evaluations, and Field Studies

Enclosure

cc: URW Local 466
Mr. B. Pearson

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