EXPLORING EPOXY USE AT THE OAK RIDGE K-25 FACILITY

and

NEW CONCERNS ABOUT NEUROTOXIC RISKS

Final Report

Prepared by Richard Bird, MD, MPH with significant project contributions by
Ken Silver, DSc, MS and Mohamed B. Abou-Donia, Ph.D.

June 2007

Supported by A Grant from The Citizens' Monitoring and Technical Assessment Fund (The MTA Fund)

The Investigators wish to express a special thanks to the administrators of the MTA Fund for their support of this project and to the Institute for Agriculture and Trade Policy for their sponsorship. We would also like to thank all of the worker’s from the Oak Ridge K-25 Facility, Including Members of the United Steel Worker’s Union (formerly Paper, Allied-Industrial Chemical and Energy Workers’ Union), who provided important information about epoxy usage at the K-25 facility. Many have suffered from serious illnesses impacted by workplace hazards over the years and it is our hope that this project will help to lead to a more systematic means by which comprehensive medical evaluations and health care can take place for Department of Energy workers who are potentially suffering from work related diseases. It is also our goal to further characterize the neurotoxic potential of epoxy usage for the protection of all workers and to systematically begin a worldwide screening process so that neurotoxic industrial materials are more readily identified in the future.
EXPLORING EPOXY USE AT THE OAK RIDGE K-25 FACILITY
AND NEW CONCERNS ABOUT NEUROTOXIC RISKS

Table of Contents

Introduction.................................................................................................................. 2
    Initial Concerns at the Oak Ridge, Tennessee
    K-25 Department of Energy (DOE) Facility...................................................... 2
Objectives and Methods
    Exploring the Neurotoxic Potential of Epoxy Usage and
    Developing a Public Health Strategy ................................................................. 4

Epoxy Industry Review
    Definition of Epoxies for Addressing Neurotoxic Concerns .......... 5
    Comment on the Potential for Inhalation Exposures .............. 5
    Epoxy Constituents and Master List for Literature Review. 6
    Description of the Epoxy Industry................................................................. 7
    Commercial applications today................................................................. 7
    The Workforce at Risk: During Production, Formulation & Usage. 8
    Airborne Exposure Measurements.............................................................. 10
    Existing Recommendations for Protecting Workers......................... 13

Epoxy Usage at The Oak Ridge K-25 Facility - Historically Representing
Circumstances that Involve Higher Exposures ........................................... 14
    The Index Case Details............................................................................. 14
    Epoxy use by Masons, Painters and Centrifuge Workers @ K-25..... 18
    Epoxy use by Masons and Helpers @ K-25........................................... 19
    Epoxy use by Painters @ K-25............................................................... 23
    Epoxy use by Centrifuge and Winding Workers @ K-25....... 25
    Discussion of the Pattern of Symptoms...................................................... 31

The Scientific Basis for Concern that Epoxy constituents are Neurotoxic 33
    Comment on The Lack of Studies Targeting Neurotoxic Impact... 35
    Reports of Neurological Abnormalities in Studies of Epoxy
    Workers That Did Not Consider the Potential Role of Epoxies.... 36
    Epidemiological Study of Centrifuge Workers @ K-25........... 36
    Symptoms Reported in Epoxy Workers in Washington State 37

Conclusions and Recommendations................................................................. 39

Appendix A-List Of Epoxy Compounds For Neurotoxicology Review .......... 44
Appendix B-Worker Interview Questionnaire................................................. 50
Appendix C-Study Description and Consent Form........................................... 57
Appendix D-Description of Rotor and Flywheel Epoxy Winding at K-25....... 58
Appendix E-Some Epoxy Compounds Used At Oak Ridge Winding ~ 1980’s 59
Appendix F-Unclassified Inventory of Y-12 Epoxy Composite Bldg 5/2000 61
Appendix G - Neurotoxicity Of Epoxy Compounds, Dr. Abou-Donia, 6-2007 .... 63
References............................................................................................................. 77
EXPLORING EPOXY USE AT THE OAK RIDGE K-25 FACILITY
AND NEW CONCERNS ABOUT NEUROTOXIC RISKS

Final Report

Prepared by Richard Bird, MD, MPH with significant project
contributions by
Ken Silver, DSc, MS and Mohamed B. Abou-Donia, Ph.D.

June 2007

Introduction

Epoxies are used widely in industrial and domestic applications, and
apart from carcinogenic concerns, they are best known as both sensitizers
and irritants in terms of dermatological and respiratory impacts.
Neurological impacts from epoxy use, however, have not been reported thus
far in the occupational or environmental health literature.

Initial Concerns at the Oak Ridge, Tennessee K-25 DOE Facility

In the later 1990's a group of over 50 sick workers from the K-25
Department of Energy (DOE) Facility in Oak Ridge, Tennessee asked that
outside investigators determine whether their illnesses were related to
workplace exposures. In the course of this investigation, several workers
were found to have neurotoxic abnormalities in addition to illnesses
impacting other systems. The neurological findings included cognitive brain
abnormalities and peripheral neuropathies; the latter included, in some
cases, impacts on the autonomic nervous system. For most of the individuals
who had confirmed neurological illnesses, workplace exposures were
determined likely to have played a significant role. The majority of these
workers were involved in industrial activities in a wide variety of settings
which placed them at risk for exposure to many potentially neurotoxic
materials including solvents, heavy metals, pesticidal products and other
semivolatiles such as PCB’s. In many cases it was not possible to isolate one
exposure situation which led to these illnesses, however, several had
cognitive abnormalities characteristic of specific classes of neurotoxins and
some developed symptoms chronologically after working in specific jobs. (1)

One worker who was not involved in industrial activities developed a
peripheral neuropathy condition within several weeks to a few months
following exposure to epoxy vapors. This occurred when epoxy was applied
over a two week period of time in thick layers to level the floor outside of this
worker’s office. Other epoxy filler materials had been used to patch walls
over a longer period of time near this office as well, and the air conditioner in
this worker’s office was set up to pull in air from the hallway where the epoxy work took place. Because of the unique chronology and single exposure event in this patient’s case, further inquiries were made regarding the nature of epoxy use at K-25 and questions were raised about risks to other workers. Based on direct discussions with sick workers being evaluated, and with their co-workers, it was learned that epoxies were used for a variety of applications at K-25. In addition to epoxy paints, these included covering and coating concrete areas posing a risk of chemical spills, leveling and patching floors, and using winding processes to build centrifuges and motor machinery. Some of the sick workers who had been found with confirmed neurological abnormalities during the detailed clinical evaluations had worked some of the time on these epoxy jobs and several co-workers on these job assignments also described having neurological symptoms.

With a lack of information in the literature about epoxies and neurotoxic concerns, the chemical structures of various epoxy components were considered, and their makeup was discussed with epoxy and industrial chemists. It was determined that, based on their chemical structure, this class of compounds, which includes epoxy reactive diluents (2), contain reactive areas that classically have the potential to damage nerves. (3) Discussions with neurotoxicologists corroborated this potential (4) and it was discovered that unpublished animal studies of epoxy constituents and similar compounds had been pursued, yielding positive neurotoxic findings. (5)

The provocative structure of epoxy compounds in the face of the unpublished animal study findings and the clinical cases at K-25, has posed both a challenge and obligation to further understand epoxy neurotoxic risks. Several applications at the K-25 facility in the past utilized epoxies in a manner that provokes concern: applying them in layers that are several inches thick for leveling and covering concrete, and, in the case of the winding processes, applying them repeatedly in open rooms with questionable ventilatory protection. Epoxy formation usually involves varying degrees of exothermic or heat producing reactions (6) which provides an opportunity for inhalation of vaporized and un-reacted components, a risk which is even greater in the case of inappropriately thick applications. (7) Exposure to un-reacted components is minimized in settings involving more precise epoxy reactions such as very thin epoxy layers and in settings that provide proper ventilatory protection. Ventilation and respiratory protection were often inadequately applied at the K-25 facility over the years for many hazardous operations, as learned during the sick worker evaluations. Thus protection from epoxy vapors was likely to have been frequently inadequate. While the circumstances at K-25, may be unusual, in some respects, they may also be typical of many workplace settings given the widespread use of epoxies.
Objectives and Methods: Exploring the Neurotoxic Potential of Epoxy Usage and Developing a Public Health Strategy

This project was designed to further the understanding of epoxy materials and their applications in terms of the potential for harmful exposures, to understand what is presented in the industry, agency, and other scientific literature relative to exposure opportunities and the potential for neurotoxic impacts, and to document past usage of epoxies at the K-25 facility as a representation of circumstances involving higher exposures. With this information a public health strategy specific to the K-25 population and the epoxy industry as a whole was to be formulated to address potential neurotoxic concerns including the need for further medical care, industrial hygiene measurements, protective measures, toxicology, and epidemiology.

To accomplish these tasks, comprehensive and current industry textbooks and literature were reviewed on epoxy formulation and usage. Key epoxy constituents were identified to complete the search for any existing literature on neurotoxic findings. Regulatory or agency investigations were explored to identify what is known thus far about exposures to these constituents and effects on workers.

Relative to K-25 activities, a formal survey instrument was developed for information gathering purposes only, to ask workers about typical epoxy use practices, and to gain an understanding of the potential level of epoxy exposures in these settings. An epidemiological study was not considered since it was not clear that an isolated group of workers existed, who were exposed to epoxies only, to enable an adequate study design. This was based on impressions, during the sick worker evaluations, that most job classifications at K-25 involved work in multiple settings with multiple exposures. However, the worker interviews were intended to explore this possibility further. Case reports or summaries of neurological symptoms were also not presented here, since confirming whether symptoms were likely to be work related would require detailed clinical evaluations, not appropriate for this project. Workers were chosen for interview by word of mouth. We spoke initially with workers from the sick worker investigations who had worked with epoxies and who provided names of other workers from epoxy use areas. Other epoxy usage information at K-25, including some Material Safety Data Sheets (MSDS), were obtained by speaking with representatives from the United Steel Workers’ Union (formerly Paper, Allied-Industrial Chemical and Energy Workers’ Union). Prior to this, repeated attempts were made to obtain MSDS from Department of Energy industry representatives for the K-25 site. Despite the fact that they verbally agreed to provide these, they did not. Finally, investigators for the bladder cancer study of K-25 centrifuge workers were helpful in discussing epoxy exposures in this group. (17,18)
Epoxy Industry Review

Definition of Epoxies for Addressing Neurotoxic Concerns

The principal purpose for defining epoxies for this project was to enable review of the group as a whole and its individual components to determine if epoxies alone may be intrinsically neurotoxic. In many workplace settings, however, there are many other factors to consider that might obscure the recognition of epoxies as contributors alone to neurotoxic impacts. Solvents, for instance, are known neurotoxins (10) that are sometimes utilized in epoxy applications both to adjust viscosity and for clean up. However, these substances are not a part of the epoxy reaction or the final epoxy network.(6) Epoxies are used in countless industry applications and as a result there are many potential circumstances where workers are exposed to other known neurotoxins during activities that are unrelated to epoxy use. Combination injury to the nervous system whether from other neurotoxins or from other disease states can potentiate the chance for more clinically significant neurotoxic insults. (3,4) Combination exposures can also impact metabolic pathways that more readily lead to neurotoxic byproducts. In some applications, epoxies are combined with non-epoxy materials which themselves may have a potential for neurotoxicity may be released, vaporized or created when heated during the epoxy reaction.

It was a principal concern of this project to determine if the typical components that make up epoxies themselves are potentially neurotoxic. For this purpose, the definition of epoxies and their components specifically refers to any of the materials containing and reacted with an epoxy group or epoxide which is capable of being converted to a useful thermoset form or cured state. (11) Epoxies are classically formed by the reaction of epichlorhydrin and diglycidyl ether (historically and most commonly of the bisphenol A type) and they repeatedly bond to form a cured material, most often exothermically. (2,6)

Comment on the Potential for Epoxy Exposures through Inhalation

It is commonly repeated in the literature that “residual epichlorhydrin, an animal carcinogen, is usually present at less than 1 ppm by weight in the epoxies”. (12) This is misleading in implying that there is adequate information about the exposure potential to this and other epoxy constituents. There is wide variation in conditions of epoxy system formulations, reaction states, and usage and the potential for more concerning exposures under some conditions versus others. (6,7,20) During the curing process there is a variable degree of effective reaction taking place
between epoxy components depending on the quality of the formulation, the rates of reactivity, and varying temperatures resulting in varying degrees of vaporization of un-reacted epoxy constituents and in some cases a real potential for combustion. Products of combustion, in addition to releasing the same ingredients as the original formulation, can themselves vary from the original components, and generate unique concerns. While epoxy constituents are generally not considered volatile this point is relative as well. Epoxy reactive diluents, for instance, are more than one half as volatile as the most abundant volatile aromatics in urban atmospheres which means in practice that they are substantially volatile under hotter conditions. Data on airborne measurements of epoxy constituents that are released during usage, while difficult to locate, is presented in the paragraphs below. Aerosols formed during spraying of epoxy paints and other epoxy coatings facilitate inhalation of all epoxy constituents. Because of the real potential for exposures via inhalation, under many conditions of use, all of the commonly used epoxy constituents were included in our review.

**The Key Categories of Epoxy Constituents and a Master List**

Under the definition above, the key categories of epoxy constituents include the following:

**Epoxy Resin Base or Binder** (not always the largest component) made up of epichlorohydrin combined with glycidyl ethers and similar compounds;

**Hardeners Or Curing Agents** of which amines of the polyamides or polyamidoamine class are the most commonly used (typically co-monomers in the polymerization reaction and make up a significant portion of the epoxy, of up to over 50%), and

**Reactive Diluents**, (typically glycidyl ethers) become part of the final adhesive and are used to adjust properties including viscosity. Reactive diluents are of a higher molecular weight than solvents but lower than the epoxy resin and are more volatile (proportionally made up in the 5-10% range).

**Other categories** of materials that are utilized in epoxy formulations and which are not usually a part of the final epoxy polymer network include: catalytic and latent hardeners, accelerators, inhibitors and retarders, non-reactive diluents, fillers, carriers and reinforcements, solvents, plasticizers and flexibilizers, tackifiers, thickeners and thixotropic agents, film formers, anti-oxidants, anti-fungal agents and other stabilizers, soaps and surfactants, and wetting agents. (6)
Even within the definition above, for the purpose of the neurotoxicology literature review, selection of representative epoxy compounds was a difficult task. A popular industry guide describes over 2,800 currently available epoxy resins, curing agents, compounds and modifiers based on information supplied by 71 manufacturers or distributors of epoxy products. (16) A master list (Appendix A) was selected of epoxy constituents based on whether they were described as more commonly in use in either comprehensive textbooks or listings of epoxy formulations in the industry literature, if they were listed in previous toxicology reviews, or if they were identified as products used at the Oak Ridge K-25 Facility (and only if the constituents from these identified products were revealed by industry suppliers and their material safety data sheets). (2,6,14,15,16)

Description of the Epoxy Industry

Epoxies were first developed in the late 1920’s and into the 1930’s (11). Since being commercially patented in 1940’s and 50’s (13,17) their use has steadily increased with the following representing commercial applications as listed in 1992: (6,18)

Aircraft and aerospace
   Structural parts of aircraft, spacecraft, and satellites
   Adhesives
   Aircraft paints and coatings

Automobile:
   Automotive primers and primer surfaces
   Sealers
   Adhesives
   Structural Components
   Racing Car Bodies
   Tooling Compounds
   Ignition coil impregnators
   Encapsulants for control modules

Construction
   Industrial flooring
   Grouts for roads and bridges
   Antiskid road surfaces
   Tooling Compounds
   Repair compounds
   Adhesives
   Sealants
   Pipes
   Do-it-yourself compounds
   Maintenance paints
   Coil coated steel (such as roofing)

Chemical
   Linings for storage tanks
Chemical plant including coatings
Pipes and pipe linings
Filters

Electrical
Switchgear construction and insulation
Transformer construction and insulation
Turbine alternator insulation
Electric motor insulation
Cable jointing
Coating for domestic electrical appliances

Electronic
Printed Circuit Boards
Packaging of active and passive components
Encapsulation of electronic modules
Adhesives

Food and Beverage
Can and drum coatings
Coatings for flexible tubes

Marine
Primers and protective coatings for ships and marine structures (such as oil rigs)

Leisure
Fishing rods
Tennis rackets
Gold club shafts
Bicycle frames
Skis
Musical Instruments

Textile
Equipment parts
Glass and carbon fiber sizing agents

Light Engineering
Adhesives
Protective and decorative coatings
Composite structures for artificial limbs

Global consumption of epoxy products reached 970,000 metric tons in the year 2002 (2.14 billion pounds), (35% of this in Asia) (6) compared to 110 million pounds in 1965 (11). US figures alone estimated demand at 690 million pounds in the year 2004, representing a 1.4 billion dollar industry. (6)

Workers at Risk: During Production, Formulation, and Usage

Workers are most frequently at risk for exposure during the handling of any of the un-reacted epoxy components. This is particularly true during
spraying and during heat-producing curing applications when vaporization can occur more readily, and when, more rarely, this leads to combustion. In terms of already cured epoxy products, opportunities for exposure exist during machining and repair but are of much greater concern under the unusual circumstances when cured epoxies are burned, such as during centrifuge overheating and aircraft crashes (22) (epoxy composites makeup 60% of some military aircraft today (21)).

Populations at risk for exposure to epoxy components include workers involved in production, formulation and end use applications the later of which includes domestic end users. Of the total liquid epoxy resin demand in the year 2002, 41% was used for coating applications, 31% was used for adhesives applications and 28% was used for other applications. Epoxy resins are seldom used in their unmodified forms. Custom formulators (or compounders) typically buy epoxy resins, modify them using mixing equipment with other materials such as fillers, additives and modifiers, and package them for end use systems. (6) An industry encyclopedia listed 94 epoxy vendors in the United Stated in 1999 of which 26 were “primary material producers”, 48 were “proprietary compounders”, and 18 were “distributors, jobbers, sales agents, etc.” including one “broker”. (11) The three leading producers of epoxy products account for 75% of the world’s capacity and include Resolution Performance Products (formerly Shell), Dow Chemical, and Huntsman (formerly Ciba). Proprietary compounders refers to producers who compound and sell their own special formulations. (6)

The workforce at risk of exposures today is difficult to quantify without current surveys but is quite widespread, especially when considering the scope of end use applications. The National Institute for Occupational Safety and Health (NIOSH) estimated 85,000 workers at risk for exposure to epichlorhydrin based on surveys in 1972-74 (23). While most epichlorhydrin is used in epoxy resin production, it is also used in the production of agricultural chemicals and for other applications. From this same survey, NIOSH estimated 71,000 workers were exposed to Glycidyl ethers, which are used predominantly in epoxy applications and that 36,000 workers were at risk of exposure to diglycidyl ether of bisphenol A (DGEBA), the most commonly used epoxy resin historically. (24) Using figures that estimate US epoxy sales in 1980 at 260 million pounds (13), and comparing these to reports of US epoxy demand at 690 million pounds in the year 2004, it can be extrapolated that the total work force exposed to glycidyl ethers in 2004 was 190,000 compared to 71,000 from the NIOSH surveys in 1972-1974. Epoxy demand was higher in1980 than in the early 1970s so this is very likely to be an underestimate.
Airborne Exposure Measurements

Despite the size of the industry, measurements of airborne epoxy compounds during their use are difficult to locate in part because of the proprietary concerns of large producers and formulators; this was apparent to NIOSH in their criteria document for glycidyl ethers in 1978. (26) NIOSH reported that because information on the composition of certain epoxy resins is proprietary, it is often difficult to obtain information about the glycidyl ether or ethers that are present in a particular epoxy resin. They further state that exposure to the epoxide moiety in both the glycidyl ethers and epoxy resins can occur until the resin is completely cured. Thus, workers must be considered to be at risk of exposure to glycidyl ethers from the time the ethers are synthesized until the curing process of the epoxy resin is completed. Also reported at that time were a lack of validated methods for the sampling and analysis of any of the diglycidyl ethers. The methods that do exist for some of the glycidyl ethers have not been validated at the limits recommended in the 1978 NIOSH standard (e.g. 0.2 ppm [parts per million] or 1 mg/m3 for di(2,3-epoxypropyl)ether (the ether in diglycidyl ether of biphenyl A (DGEBA). Current standards exist for measurement of n-butyl glycidyl ether but at much higher levels ranging from 15 to 60 ppm. They also exist for glycidol at higher levels ranging from 5 to 150 ppm, and for epichlorohydrin at 0.5 to 16 ppm (the lower value being the recommended occupational exposure limit for this compound). (28, 23)

The 1978 criteria document presents measurement data from a manufacturer of both butyl glycidyl ether (BGE) and phenyl glycidyl ether (PGE) of airborne concentrations below 1 ppm for each during two production runs but that during drumming operations concentrations ranged from 2-4 ppm. Finally, the NIOSH report stated that no other data on concentrations of airborne glycidyl ethers had been found at that time. (26)

A NIOSH Health Hazard Evaluation of a Fan manufacturing facility, measured DGEBA in powdered spray paint in 1979, which ranged from 0.005 to 0.200 mg/m3 in personal samples and from 0.002 to 0.008 mg/m3 in area samples. That year, a similar evaluation measured time-weighted averages of DGEBA at 0.002-0.004 mg/m3 in a truck manufacturing plant. (27) Manufacturing facilities typically use high volume airflow spray booths to exhaust and minimize airborne concentrations of paint overspray in addition to other protective measures such as vapor protective respirators and enclosed gun cleaners. These measurements above do not reflect exposures in other settings where such protective measures are not utilized during spraying of epoxy paints or coatings. Solvent levels, for instance, increase over 1,000 times while spray painting in poorly controlled environments. (44)
A 1989 aerospace industry conference, on the occupational health aspects of composite technology, presented a widely varying picture of exposure concerns for workers handling epoxies and very little actual exposure data. (29) Some presenters detailed the real opportunities for exposures and the need for adequate protection of any workers handling partially or uncured epoxy materials, while others presented more cursory reviews that seemed to minimize such concerns. Some of these differences may reflect the widely varying circumstances of use. However, even in workplaces where epoxies are utilized under very controlled conditions, allowing very narrow tolerances on the part of the manufacturer for technical reasons, there remain opportunities for exposure during handling of uncured materials, and many complexities in protecting workers from such exposures. (20, 30, 31)

For instance, particularly problematic is designing adequate ventilation systems for large winding processes where epoxy is applied to fibers wound on large open structures. (31) Another example is reflected in the NIOSH investigation which found relatively high airborne measurements of glycidyl ethers of 2 to 4 ppm in the drumming room of a manufacturing facility, pointing to the risks that occur during transfer and storage of materials (26). Smaller facilities often do not have the resources of large manufacturers for designing and installing protective ventilation equipment. Even in the larger facilities there appears to be variation in the use of protective equipment and respiratory protection. Photographs were presented of workers handling wet epoxy materials without wearing respiratory protection and without nearby exhaust ventilation in large open rooms. (32, 31)

In a large and well-ventilated spray booth operation, air samples for the epoxy hardener 4,4’-methylenedianiline (MDA) were measured at 5 parts per billion (ppb) in worker breathing zones which is equal to the Occupational Safety and Health Administration’s action level. MDA is classified as a probable human carcinogen by the International Agency for Research on Cancer (IARC 1987) and the industrial hygienist presenting this data suggested that workers use air supplied hood type respirators for reasonable protection. (31) A standard method does exist for the measurement of MDA at low levels ranging from 0.025 ppb (parts per billion) to 1.2 ppm (0.0002 to 10 mg/m3). (33) In a filament winding operation utilizing a state of the art ventilation system MDA was found at concentrations of 0.6 ppb or below.

In other locations, MDA was reported to be measurable in the breathing zones of workers during the dispensing and weighing of small amounts of curing agents, and also during activities where ventilation was
not utilized for cutting, trimming and hand layup of uncured and tacky composites. The data was not presented from these measurements, however, and was not presented for the following circumstances: Higher levels were more of a concern when epoxy impregnated materials were stripped or peeled by hand. Ventilation equipment was less likely to prevent higher levels under circumstances where material temperatures reached over 150 °F. There were also descriptions of vapors released near the center of braiding machines despite ventilation equipment on the periphery. Concerns were raised about inhalation of brittle yet still not fully cured dust containing MDA (other constituents not discussed) and exposure potential was described as greatest for clean up of dust in ventilation equipment. Finally, recommendations were made to cover areas of dripping resin on floor surfaces. (31)

3M laboratories studied released materials from epoxy composite products in both uncured and cured forms under various conditions but did not present the actual measurement data probably for proprietary reasons. (34) Glass/epoxy composite was heat cured at temperatures reaching 220-260 °F and released materials that included monuron vapor (a likely byproduct compound which reflects various moieties from epoxy constituents; also a known herbicidal product and is a carcinogen in animal studies) (IARC monographs). The other constituents released were not listed. Another study involved heating epoxy to 300 degrees to initiate exotherm (essentially combustion) which released measurable carbon dioxide, methyl ethyl ketone and methyl chloride; however, there was no mention other compounds released. Finally dust from machine cured glass/epoxy composite was found to contain dioctyl phthalate, but, again, other findings were not reported. An attempt was made to determine the origins of this data by speaking directly with 3M staff, without success. They did provide a document from 1992 introduced by stating: “we are frequently asked for outgassing information on our range of structural adhesives and tapes”, but the only data presented was the percentage loss of the starting mass following precisely controlled reaction conditions. It did not include any information on constituents measured. When asked about this, they stated that such release of information is not possible since it would require clearance by their legal department. (35)

Material safety data sheets (MSDS) were reviewed at the aerospace industry conference and, because composite use involves heating to a temperature commonly ~ 120 °F, it was recommended that the MSDS include information on the concentrations of common off-gassing products at a distance of one foot, so that suppliers and users can determine the worker’s potential for exposure for specific substances ahead of time. (36)
Smaller companies (typically the suppliers and users) do not have the resources to prepare the necessary safety information and depend on the larger manufacturing companies to do so. Under the OSHA Hazard Communication Standard the MSDS is required to include information on the make up and the associated hazards of constituents. However, trade secrecy and liability influence the adequacy of what is actually provided. The only toxicity information that is required is based on a literature search of already published information. This is grossly inadequate when considering that a fraction of the chemicals in the marketplace have been evaluated for toxicity. A sample MSDS provided by 3M of “Scotch-Weld Epoxy Adhesive 2216 B/A” provided only generic constituent information on decomposition byproducts during combustion listing aldehydes, hydrocarbons, amine compounds, carbon monoxide, carbon dioxide and oxides of nitrogen.

Existing Recommendations for Protecting Workers

The National Institute for Occupational Safety and Health (NIOSH) generally recommends making every attempt to keep exposure as low as technically feasible for probable human carcinogens and/or known animal carcinogens (which are potential human carcinogens, as is the case for the epoxy constituents epichlorhydrin, diglycidyl ether (some of the other glycidyl ethers), and methylenedianiline (MDA). (23,24,25,26,38)

In the case of diglycidyl ether, specific measures to keep exposure as low as technically feasible, include the following: control of airborne exposures to below 0.2 ppm (1 mg/m3) over a 15-minute sampling period; medical surveillance (including intermittent work histories); labeling and posting; personal protective clothing and equipment (including gloves and clothing impervious to glycidyl ethers as well as proper shower and handling procedures); splashproof goggles or face shields; either engineering controls (enclosed or local exhaust ventilation systems) or respirator usage for conditions that do not achieve concentrations as low as 1 mg/m3 (0.2ppm). Recommended respiratory protection consists of self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode, or, supplied-air respirator with full facepiece in pressure demand or other positive pressure mode. (26)

Recommendations for protecting workers are also provided, more generally, in some MSDS provided by manufacturers and, in some cases may recommend restrictions the conditions of use for the purpose of minimizing airborne releases. For instance, the MSDS for 3M Scotch-Weld Epoxy Adhesive 2216 B/A states, under Materials and Conditions to Avoid: ”Heat is generated during cure. Do not cure a mass larger than 50 grams” (which is
less than 2 ounces) “in a confined space to prevent a premature reaction (exotherm) with production of intense heat and smoke”. General recommendations include providing eye protection, avoiding skin contact, and avoiding breathing of dust, vapors mists or spray and using either half or full facepiece air-purifying NIOSH approved respirators based on airborne concentrations of contaminants.

**Epoxy Usage at The Oak Ridge K-25 Facility
Historically Representing Circumstances That Involve Higher Exposures**

**The Index Case Details:**

As discussed in the introduction above, one of the workers who presented in the late 1990s to determine if their illnesses were related to workplace exposures, had not been involved in industrial activities but had developed a peripheral neuropathy condition within several weeks to a few months following exposure to epoxy vapors. The chronology raised concerns that the neuropathy condition may have resulted from these or other exposures.

The worker began at the K-25 facility in 1988 and worked in several buildings, including in order, the AMSE Building, K-1225, K-3037, K-1652, K-1330, and finally, K-1001. The worker was concerned that the onset of respiratory and neurological symptoms was related to exposures in the K-3037 building at the time they worked there from October 1989 to April 1991. K-3037 (also known as K-25) is the original U shaped building that was built in the 1940s for uranium gaseous diffusion purification for the atomic bomb used during WWII. This building became a warehousing facility and an office space was apparently partitioned off on the top floor. Details were not available regarding all of the materials stored here. However, the lower level vault areas have generally been utilized to store hazardous wastes. The worker reported that the wall separating the warehouse from the office areas would leak and that they would walk through the warehousing areas on an intermittent basis on route to the offices. Sealants were used to patch the office walls on a regular basis while the worker was there.

In the early spring of 1991 work was done for about one to two weeks to level the floors outside of the office area during which time the worker experienced burning to the eyes, nose, and throat, a choking feeling, a dry cough, nausea and headaches. The worker reported that co-workers in the office experienced similar symptoms at the time. There was a separate air conditioning unit for the office which pulled air in from the contiguous
hallway where the floor work was being done. The worker would turn the air conditioner off because the odor was so strong and described it as oven cleaner-like, however, the odors remained and the symptoms persisted. The worker did filing work several times each day which required walking in the hallway where the floor work was being done. The week after the work ended the odors became mild and dissipated but the cough spells continued. The headache improved within five days of the job ending. The worker then moved to the Security and Fire Truck Building in K-1652 for about one year where the cough became less severe but persisted. The worker returned to the 3037 building almost daily during this time.

Within a few weeks to months of the epoxy work in building 3037, the worker began to notice increasing symptoms of tingling, numbness, and burning pain in the arms and hands that started in the tips and moved more proximally over about a two year period. The worker was evaluated by a neurology center soon thereafter, confirming the diagnosis of both a sensory and motor peripheral neuropathy condition without a known etiology at the time. The symptoms continued to worsen until about 1992 moving proximally to about six inches above both the knees and the elbows after which they remained the same. The worker described the numbness and burning pain as feeling like being a tub of hot water requiring the use of constant pain medication and the use of year round air conditioning. The worker was not able to tolerate any sustained activity walking or standing and experienced great fatigue with activity. By the time the patient was no longer able to work, they had difficulty walking even fifty feet requiring rest.

The worker described that one of two coworkers in the office at the time had many similar symptoms including numbness in their legs but that they were afraid to seek help because of fear of losing their job. The other co-worker reportedly was quite sick, but the worker lost contact and did not know details about their health.

At the time of the sick worker evaluations, inquiries were made with K-25 industrial hygiene and plant representatives who were asked for details about the work that went on in building 3037 at the time the worker first developed the symptoms described above. Information was not provided on the details of the work but ventilation drawings were provided, confirming that a central ventilation system was not connected to the worker’s office area. Instead an air conditioning unit was installed which did not connect to an outside wall or window; rather, it pulled replacement air in from the outside hallway. The worker was therefore forced to shut down the air conditioning unit during the epoxy job.
Independent inquiries were made at the time with former masons. Two were located who had worked frequently in the K-3037 U building during the time the worker was there and had worked on the epoxy floor-leveling job. They described repeatedly using sealants to patch up holes and leaks throughout the area that included large surfaces over a long period of time. They mostly used a product they called vinyl steel which involves mixing a silica aggregate with a liquid. The MSDS indicates that the liquid portion contained 50% acrylic emulsion and 50% H2O without other specifics provided and the company is no longer in existence at the address listed. Based on discussions with industrial chemists, it was determined that acrylamide would not have been a component of this product. A light colored dust was present in the offices prior to the epoxy leveling job, raising questions about the make-up of this dust. The masons reported that Rust Company, an outside contractor, had applied a concrete slab to an area farther away from these offices and that this work involved roughing up the surface of the concrete dispersed dust probably accounting for that seen in the office area at the time.

On the epoxy job next to the offices the masons described applying a layer from one half to three or more inches thick, over a ninety by sixty foot total area approximately, and during several days to level and strengthen the floor. They described a product made by Sika supplied in yellow five gallon buckets on palettes. Respirators had to be used during mixing because symptoms of choking and coughing were severe. They used trowels to apply the mixed epoxy on the floor areas during which the choking and coughing symptoms persisted, but not as severely as when mixing and which they tried to ignore. They reported not wearing respirators generally because of the excessive heat during the work and they were not required to do so during those years. They each described feeling exhausted, fatigued and limp during epoxy work; these symptoms lasted several days after the job was over. Both reported developing burning and numbness in their extremities at some point in their careers that had continued along with other illnesses.

The Sika company was contacted and representatives provided material safety data sheets for Sika42 grout pack, which was a product they thought may have been used for this type job at that time. They described the product as a strong epoxy designed for thicker and stronger applications. However, they stated that with very thick applications the exothermic or heat producing reaction would creat smoke. One mason described that on the floor leveling jobs, the epoxy would frequently smoke up. If they mixed too much material at once, the bucket would also melt at times and could catch fire.
The Sika42 MSDS listed the following constituents: (Part A): epoxy resin (CAS 25068-38-6 = biphenol A), formula RMF-1333, (Part B): amines (formula RMF-1333), nonyl phenol (2,6-Dimethyl-4-heptylphenol), proprietary mix of cyclic and aromatic amines, aromatic hydrocarbon blend, and benzyl alcohol; (Part C): silica, titanium dioxide, silica-alumina alloy, and PVC.

The epoxy for the floor leveling job at the K-3037 was applied in thick layers that produced heat, smoke, and off-gassing according to the masons who used it. This created ample opportunity for volatilization and exposure to many of the components in the product used during mixing and application before the material cured. The masons and office worker described the conditions as quite warm during the leveling job, reflecting the heat involved.

The respiratory symptoms and impacts experienced by the office worker classically reflect inhalation exposure to strong irritants known to be present in epoxy products including, epichlorhydrin, several of the amine hardeners, (particularly aliphatic and cycloaliphatic), and glycidyl ethers (23, 2). Nausea is classically described with acute epichlorhydrin exposure events; headaches are consistent with central nervous system narcosis impacts associated with a variety of toxicant exposures.

The office worker in this case was evaluated extensively by specialists in the fields of internal, occupational, and neurological medicine with experience specifically in the field of clinical neurotoxicology. The details of the medical evaluation are not presented here for reasons of confidentiality. Conditions that might have accounted for or might have contributed to the peripheral neuropathy condition were ruled out. It was concluded that the temporal relationship between exposures while working in the K-25 U building and the onset of this worker’s sensory and motor neuropathy condition was compatible with a causal exposure-effect relationship. The sequence of events with the onset of peripheral neuropathy symptoms occurring following the floor leveling exposures, and the eventual lack of progression after an initial period of injury to the nerves, and after the exposures had stopped, is consistent with what would be expected in the case of nerve injury following exposures to neurotoxicants.

The final portions of this report will present a more complete picture of epoxy usage and exposures at the K-25 facility in the past, the scientific basis for concern about epoxy constituents and neurotoxic impacts, and recommendations for addressing these concerns.
Epoxy use by Masons, Painters and Centrifuge Workers at K-25

The worry about more widespread neurotoxic impacts to other workers from epoxy exposures and what to do about this possibility was raised initially by the case of the office worker. Similar symptoms reported as having occurred in the two office co-workers and by the masons themselves who had worked in that location reinforced these concerns. Similar concerns were raised by the cases of some of the other sick workers who had worked near or with composites in the winding or centrifuge area and who reported having had neurological symptoms at the time. Our access to the K-25 workers provided an opportunity to obtain an understanding of exposure to epoxies under more widely varying conditions of usage in comparison to the more controlled conditions in specialized settings such as printed circuit board and aerospace manufacturing (12).

K-25, which is known today as East Tennessee Technology Park, occupies 4,689 acres or 7.6 square miles and remains a Department of Energy facility. As of the year 2000, it was composed of almost 400 buildings totaling approximately 14.4 million square feet (39) and is increasingly diversified in terms of the numbers of different companies utilizing the campus for a variety of industrial activities. This poses a variety of complex security obstacles. Some epoxy activities of the past have stopped and in the case of the winding technology, the early conditions of the past are reported to have improved since relocating to newer facilities with more sophisticated ventilation systems and protective policies. For these reasons, present day activities were not the focus of the worker interviews for this project. Instead the effort focused on understanding epoxy usage in the past when most of the sick workers who were evaluated during the late 1990’s and into the early 2000’s were working.

Epoxy use was widespread during various points in time at K-25 amongst masons, painters and centrifuge workers at K-25. However, because most job classifications at K-25 involved work in multiple settings with multiple exposures, many other workers assigned officially under other department headings also had opportunities for epoxy exposures either through direct use or because of proximity to epoxy use by other workers (as reflected in the office worker case).

To provide an idea of the scope of epoxy materials used in the past at K-25, an internal memo during the 1990’s stated that 288 drums (151,200 lbs) of surplus epoxy resin from the K-25 Vault 20A had been shipped to an off-site commercial vendor. The total surplus epoxy resins shipped the year of that memo was stated to be 2,158,700 pounds (or over 4,000 drums). (41)
Questionnaire

A formal questionnaire was developed, for information gathering purposes only, to ask workers who had worked at K-25 in the past about typical epoxy use practices there, and to gain a better understanding of the extent of the problem in relation to opportunities for significant exposures. The questionnaire (Appendix B) was designed to determine the type, circumstances, and duration of epoxy work, whether personal protective equipment was available and utilized, whether ventilation systems were installed, provided and perceived to be adequate, and whether there were co-worker's involved. The formal interview allowed for and led to more informal discussions with these workers and others, including those from the former sick worker evaluations and members of the United Steel Workers' Union (formerly Paper, Allied Chemical and Energy Worker's Union [PACE]; prior to that, the Oil Chemical and Atomic Workers Union [OCAWU]). The informal discussions provided further details on epoxy activities at K-25 including non-classified aspects of various processes and MSDS, some of which were still available. Because this was not a formal epidemiological study, questions about health symptoms were limited. The questions were designed to pick up symptoms that might more classically reflect higher levels of solvent exposures (in asking about a drunk-like feeling while working), versus acute and chronic impacts from neurotoxins in general (asking about headaches, cognitive difficulties and fatigue). Symptoms of neuropathy were not asked about since several detailed questions would be required to provide meaningful responses for a given case or an epidemiological study would have been required to compare responses between exposed and unexposed groups to measure symptoms prevalence.

The interviews were conducted by telephone and participating workers were provided a permission slip explaining the project and the commitment to not present any information that would identify them as individuals based on their responses. (Appendix C, Study Description and Consent Form).

Epoxy Use by Masons and Helpers @ K-25

As learned during the office worker evaluation, masons used epoxies for a variety of purposes: patching walls and other areas, leveling floors and sealing areas particularly where at risk for chemical spills or leakage. The huge scale of this work, however, was not previously appreciated. 97% of the K-25 facility buildings were built over 30 to 40 years ago (39) and the floor leveling work alone, for instance, included the whole top floor of the K-3037 (41) or U shaped building, each side of which is one half mile long and the width of the U is 1,000 feet wide (40). This building consisted of steel beams supporting prefab slabs of concrete which were leveled using epoxies to allow
installation of offices there. The concrete would be roughed up initially and then layers of epoxy were applied ranging one half to three or more inches thick which would initially cure over a one to two day period of time but sometimes longer depending on the thickness or cure. Different crew sizes and areas were worked on at a given time in groups of three workers for instance to allow one to mix and supply the other two workers spreading the material out to level and smooth the floors. (41)

Similar large scale epoxy applications took place in the vaults or basement areas of the U building in the late 1980’s and early 1990’s to construct spill barriers or dikes in the event that any of the hazardous and/or radioactive material, leaked or spilled so that it would not run into storm drains present in each vault section. Channels were cut into the concrete sometimes the entire length of the vault and other times less, averaging 100 feet for instance, and epoxy was layered into the bottom of the channel and surrounding floor so that any spilled material would not leak through the concrete. Berms were built up along the edge to prevent spilling over using one foot diameter PVC pipe cut in half and filled entirely with epoxy through the holes. As it hardened, the PVC pipe was removed. Epoxy was layered as small as one quarter and averaging one or three inches on flat areas for leveling and up to six inches in the dike areas. (41)

Masons, laborers, and sometimes painters all worked together in crews of approximately ten for instance having similar tasks described for floor leveling. Epoxy was mixed in five gallon buckets using a heavy duty drill with a paddle, in quantities enough to keep the applicators supplied; the mixed material would heat up but only infrequently to the point of producing smoke from the buckets. The doors were required to remain shut for some of the vaults for security reasons and opened for others and the epoxy work. The entire curing process would sometimes take as long as one to two weeks to fully harden, but would usually cure in one to two days. An attempt was made to put one layer down on an entire surface to eliminate the chance for cracks and then further layering could be done on top of a cured surface. (41)

Symptoms were most bothersome when mixing, and a typical day described by one worker would begin with the odor begin to singe the nose, and soon thereafter initiate a light cough. The cough would become more frequent with burning in the eyes, light headedness, some difficulty orienting or focusing and then nausea which would infrequently develop to the point of causing vomiting. At times when mixing only this worker described a drunken feeling but not always. Headache, fatigue and lack of energy was
always present at varying degrees and the headache were sometimes unbearable. All of these symptoms were present when applying the epoxy but to a lesser degree depending on the location and degree of fresh air. The cough would be infrequent but was usually present, for instance. Epoxy was applied using both hand trowels while down on the knees or squatting as well as a bull float or trowel on a handle which allowed pushing the thicker quantities around for final leveling by hand. The movement and change of position seemed to ease the symptoms some compared to when mixing. (41)

Workers would try to open some nearby doors to allow more fresh air in which they were more often able to do, but not always. A fan was at times set up by the workers themselves because of the degree of discomfort working in the environment but this would sometimes lead to hardening too fast and interfere with proper leveling. Sometimes workers would “sneak in” half face respirators because of the degree of discomfort, particularly when mixing, despite that this was not required by the rules of the job. Sometimes the worker mixing would be overcome with the symptoms above and have to leave; more often a mason applying the epoxy would have to take over mixing for a period of time while the previous mixer had a break in the fresh air or a replacement was required for that day. Respirators were not favored as a requirement on jobs because of the difficulty moving around, the additional heat and discomfort wearing them. There was some conflict between those mixing and those applying since once required all would have to be fit tested for respirator use under all conditions which was never the case. Because of these symptoms the work was less popular than other jobs but the pay was higher apparently. Safety glasses were typically worn, but not goggles since these would fog up. Workers would often use a wet bandana wrapped across their mouth to help ease the cough. Fatigue would diminish usually over a period of several hours to days after working on these jobs. The symptoms were described as being very different than when working in hot conditions which was a common practice in East Tennessee and to which these workers were quite acclimated. In the formal survey, persisting symptoms which continued after the epoxy work ended included light headed or dizziness, headache, difficulty thinking clearly or concentrating and feeling fatigue, tired or lack of energy. (41)

Epoxy patching took place all over the plant but other layering work was also quite extensive. Some work was particularly problematic. For instance, the TSCA incinerator, designed to burn low level radioactive waste and hazardous waste combined was frequently worked on with epoxy patching and layering to protect from leakage through areas where the
concrete would corrode for instance. One episode described at this facility involved work in a pit the size of a residential swimming pool. The epoxy used in this setting was so bothersome, from burning, coughing, nausea, dizziness, headaches, and fatigue, and the workers refused to remain. They requested using a respirator for the job but were refused and another crew was brought in to complete the job instead. During a similar incident, a three part epoxy mix was used with which the worker had severe symptoms. A respirator was refused since the co-worker on the job could not be fit properly would have to be taken off the job, and not able to get the mason’s pay. The entire water plant was layered with epoxies and was quite malodorous apparently and bothersome during this work. (41)

Patching took place in walls all over the plant. Masons would patch concrete holes prior to having painters apply epoxy based paints in containment areas for instance. Former spill areas under acid tanks would be corroded in the concrete, and if large enough, one mason described filling the whole with rubber and mesh before applying the epoxy. (41)

The number of workers involved in mason epoxy work would vary depending on if the plant was on a period of downsizing. During one such period in the 1980's a log sheets of workers in different departments at K-25, listed 31 total general laborers and 11 plant-wide masons. (41)

As stated under objectives and methods, despite repeated attempts, it was difficult to obtain material safety data sheet for epoxies used at the K-25 facility except those provided by workers and union representatives. For masonry epoxy work, the Sikadur product listed above was obtained and contents were reviewed above for the office worker case. An MSDS was obtained for a self leveling clear coat epoxy, Tnemec 201, used on the floors in the vault areas. The constituents included: Resin portion: Reactive Diluent 6-10%; Bisphenol A 71-80%; Nonylphenol 1-5%, and Benzyl Alcohol 6-10% (2.7% volatile organic compounds (VOC) by weight); Hardener portion: Alphatic Amine (11-20%); Modified Cycloaliphatic polyamine (42-50%), Nonylphenol (6-10%); Benzyl Alcohol (41-50%) (4% volatile organic compounds (VOC) by weight).
Similar to masonry work, painters also utilized epoxies extensively at the Oak Ridge K-25 facility. During the 1960s and into the 1970’s green epoxy paint was used throughout the K-25 facility (the exact date when this ended was reported as 1974 by one worker and the late 1970s by another). Respiratory protection was not provided until approximately late 1973 or 1974 for painters generally. Use of respirators however varied. Fans or local ventilation were never provided according to painters interviewed.

After the 1970’s epoxy paints continued to been used regularly and extensively in more specific areas at risk for contamination including where contaminants had already leaked or spilled (hazardous and radioactive) or in areas at risk of corrosion, including for example: acid pits and the ceilings above; various pipes, lines and equipment containing uranium process material; other lines containing various gases; the vaults in the K-3037 (or K-25 U), K-27 and the K-1065 buildings; the ceiling in the maintenance or 1401 building; the entire 1420 decontamination building; the 1131 uranium feed building, the TSCA incinerator facility, floors and walls included; and the inside of the centrifuges. Rollers were more often used for most of these applications with the exception of the ceilings in the various buildings mentioned and the inside of the centrifuges, both of which were sprayed.

For spraying, epoxy paints were mixed in two to five gallon conventional spray pots, to which the hardener was added and mixed. Five gallons would be sprayed over a two hour period of time and a total of 25 to 30 gallons were used in a day. For rolling, one coat of epoxy paint was applied over one eight hours approximately and during this period of time would cure up for some applications, to allow the application of a second coat to begin on the next shift. Two painters were stationed at the 1420 building all day and ever day for instance painting from one end to the other to cover areas of radioactive contamination. Other applications would take one to two days to harden, particularly in the vaults which were moist.

One worker who painted during earlier years described the symptoms as tolerable when using epoxy paints outdoors without a respirator but that when painting indoors, they had trouble getting respirators and often felt quite sick. This worker described having a headache and sinus symptoms most of the time. They would be covered with epoxy paint and would put vasoline on areas of exposed skin such as the face to keep it from sticking.

When respirators were not used for painting with epoxies, the interviewed workers generally described smelling a strong odor and having symptoms of headache, sore throat and nausea. During the later 1970’s
when respirators were available for painting, one worker who would mix the epoxy paint without wearing a respirator described burning in the nose and throat without cough or nausea and that light headedness would develop if they did too much of this. When spray painting inside the centrifuge cylinders, if the respirators were removed even for a short time, they felt dizzy, nauseated, and drunk-like, as well as a headache with a lack of balance. The epoxy paint would stick to all of their clothing.

In terms of acute and more lasting symptoms, the worker who painted during earlier years without a respirator experienced feeling lightheaded with headaches, drunk-like feeling, difficulty thinking and fatigue while painting, but only headache and fatigue continued after stopping work with epoxies. Another worker who had used epoxy paints at times while not wearing a respirator, felt all of these symptoms in an ongoing fashion after stopping work with epoxies (with the exception feeling drunk-like); This worker had also been exposed to several different substances in many different job settings. Finally, a long term painter who had used a respirator for most painting work, described having difficulty thinking clearly or concentrating as well as fatigue, or a lack of energy that continued after stopping work with epoxies. This worker had headaches as well when painting with epoxies but also did not describe a drunk-like feeling. (41)

The number of workers involved in painting work would also vary depending on if the plant was downsized. During one such period in the 1980’s, a log sheets of workers in different departments, listed 37 painters plantwide at the K-25 facility, including material expediters. (41)

MSDS were difficult to locate for epoxy paint work at K-25, but two brand names were consistently mentioned which included Amercoat Epoxy paint to coat the highly contaminated areas including the vaults, ceilings, and decontamination building, and Devoe Epoxy Paint (235, 236, 167), to seal floors and sumps in TSCA. (41)

The Amercoat epoxy paints listed by the company today are used in marine settings typically. Amercoat 240 Tank Pale Blue was chosen as an example of constituents that may have been used at K-25 and included: sodium potassium aluminum silicate (40-70%), epoxy resin (Phenol, 4-(1,1-dimethylethyl)-, polymer with (chloromethyl)oxirane and 4,4’-(1-methylethylidene)bis(phenol) (10-30%), epoxy resin (Epidian) (5-10%), mica (3-7%), titanium dioxide (3-7%), methyl (N-amyl) ketone (3-7%), n-butyl alcohol (1-5%), butandiol diglycidyl ether (1-5%), xylenes (.1-1%).
Devoe products listed by the company today included these numbers but under different names. The constituents for a product with the number 235 was named Bar Rust and included which may be different than that used at K-25 included the following: (%s are listed as a range depending on which product used such as the resin or hardener portions) ethylbenzene (ranging .1-1%), ethanediamine (1-5%), 1,3,5-trimethylbenzene (.1-1%), methyl amyl ketone (1-5%), mica (5-20%), antigorite (1-5%, xylene (.1-5%), titanium dioxide (5-20%), temolite (1-5%), talc (1-5%), anthophyllite (.1-1%), epoxy resin (oxirane, 2,2’-((1-methylethylidene)bis(4,1-phenyleneoxymethylene)bis, homopolymer) or (Diglycidyl ether of bisphenol A) (20-30%), light aromatic solvent naptha (1-20%), alkylated phenolic polyamine (70-80%), n-butanol (1-20%), barium sulfate (1-20%), pseudocumene (1-5%), polyamide (1-5%), castor oil derivative (1-5%), alkyl phenol blocked polyisocyanate (1-10%).

Another Devoe product called, “Pre-prime 167”, contains the following: (% are listed as % in resin / % in hardener); benzyl alcohol (5-10% / 1-5%), ethylenediamine (0% / 1-5%), methyl isobutyl ketone (0% / 5-10%), epoxy resin (Diglycidyl ether of bisphenol A) (40-50% / 0%), ethylenediamine/methyl isobutyl ketone ketimine (0% / 80-90%), glycidyl neodecanoate (30-40% / 0%), c12-c14 alkyl glycidyl ether (10-20% / 0%), 2,4,6-tris(dimethylaminomethyl) phenol (0% / 5-10%).

**Epoxy Use by Centrifuge and Winding Workers @ K-25**

Centrifuge work at the K-25 facility consisted of manufacturing, maintenance, repair, and testing of centrifuge machinery. Much of this work took place in the vicinity of epoxy application as well as destruction of already cured epoxy materials. The centrifuge development program began in November 1960 and ended in 1985. It involved over 30 buildings at K-25 but the principal work took place in the several of the K-1004 laboratories (J,Q,R,S,T and U) as well as the K-1052 and K-1200 series buildings, all of which were connected under the same roof. Centrifuge motors were wound and coated with epoxy materials in the basement of the 1401 building and the centrifuges themselves were destroyed deliberately for testing in buildings K-1052 and K-1600. (39, 41) From 1985 through 1995, fly wheel and motor manufacturing work continued in these facilities under an operation referred to as power electronics and involved similar epoxy winding processes as those used for centrifuge manufacturing. Many of the workers previously involved in centrifuge work continued at K-25 in power electronics and are considered part of this same cohort in terms of epoxy risk. These operations were re-located to more modern facilities at the Y-12 facility in more recent years and other facilities more recently. (41)
...(Epoxy Use by Centrifuge and Winding Workers @ K-25, continued)

Several hundred centrifuges were manufactured and installed in varying sizes ranging from up to 30 inches in diameter and to about 45 feet in length. (39) The primary cylinder consisted of an outer steel shell casing with an inner centrifuge shell consisting of epoxy wound fiber material and coated with epoxy paint. (41) The epoxy inner cylinder was manufactured in a winding or “spin room”. Epoxy was mixed in buckets or dipping tanks and applied onto fiber using various techniques including spraying at times and was wound onto a large mandrel in repeated layers. Each would cure over the course of one shift typically. The spin room was apparently covered with epoxy resin on the floors and walls. (41) The rotors similarly consisted of fiber-reinforced epoxy resins. (39)

The motors, rotors, housings and instrumentation were installed in the centrifuge cylinders and were operated at high speeds and temperatures for various purposes related to the development of uranium purification capability. (39) Deliberate centrifuge destruction in buildings K-1052 and K-1600 took place fairly often, averaging perhaps two to three times each month, but sometimes as often as twice daily. After deliberate destruction, workers were actually lowered inside the cylinders to investigate the findings and to clean up the debris. Destruction or “wrecking” as it was called would create a strong odor that would last for two to three days typically. (41)

The steps involved in rotor and flywheel manufacturing from 1985 to 1995, after the centrifuge program ended at K-25, are described in Appendix D. This was prepared by Dr. Kenneth Silver and was based on interviews with centrifuge workers who were later involved in these processes.

A morbidity study was published in 1992 which identified 500 centrifuge workers who had worked at K-25 on any job defined as having “responsibilities that would very likely provide routine exposure to industrial types and quantities of toxic materials”. (8) This study was conducted in response to concerns that centrifuge workers who worked specifically with epoxy and other materials including solvents, had higher than normal rates of cancer. Incidence of illnesses was calculated as those which occurred prior to the end of the centrifuge operations in 1985, however, as stated above, many workers continued to work on fly wheel, rotor and motor winding operations in these same locations from 1985 to 1995 and had very similar exposure opportunities. The study report provided very little information regarding the operations and opportunities for exposure for the K-25 centrifuge workers and for this reason, the investigators were contacted directly to inquire about what they had learned. As described by the workers
interviewed for this project, and observed during a personal walk through of the centrifuge facilities after the work there had ended, centrifuge operations took place in large open rooms without separating walls which easily allowed airborne material to travel from one area to another. Attempts were made by the study investigators to obtain information on airborne measurements including during wrecking operations but no such data was apparently available. Similarly, the study investigators were not able to or did not obtain information on ventilation efforts for worker protection. It was also their impression that opportunities for exposures were widespread, and that there were little or no barriers between one work area to another, and that respirators were generally not used.

During informal interviews, workers described that odors and symptoms were particularly bad in both the cylinder winding (the entire J lab) and rotor areas, as well as when wrecking took place of centrifuge cylinders. The burnt odor in the wrecking areas lasted about three days apparently. Acute symptoms included burning of the eyes, nose, throat and lungs (involving red eyes, sinus symptoms and infections, sore throat and cough), as well as persistent headache, dizziness at times, and excessive fatigue. Symptoms were improved partially by the following Monday and would worsen later in the week. One worker, who was required to work in all of these areas at different times, including wrecking areas and winding for instance, inquired with the medical department about the safety of being in these areas without respiratory protection. This worker was told that it was not harmful and that a respirator was not necessary. (41)

With the exception of workers involved in spray coating while inside the cylinders all those interviewed stated that respirators were not used for centrifuge operations. There are conflicting reports of ventilation efforts and it seems that more was attempted during later years. Hoods may have been used for some epoxy mixing activities and fiber coating, however, others stated that they were not, that coating of fibers took place out in the open in general and that there was no local ventilation system above the winding mandrel. Exhausts were apparently present on the tall ceiling above the winding area. Other workers described that the buildings were under negative pressure and that intakes allowed for material to re-enter the building in nearby locations causing odors to be present in rooms close to the winding area at times. Ventilation canopies were attempted in later years apparently. (41) An independent investigation of safety and health at the K-25 facility in the past was published in October 2000. In this document it
...(Epoxy Use by Centrifuge and Winding Workers @ K-25, continued)

was reported that in 1991 an industrial hygiene department evaluation of composite material fabrication operations in the T laboratory identified an inadequate design and face velocity for a canopy exhaust system designed for control of methylene chloride vapors. This system was then tagged “out of service”. (39) Similar inadequacies were found in a spray booth there and it was also stated that industrial hygiene sampling data for the J lab in the 1970’s and 1980’s was not available for the independent investigation. (39) Workers reported that methylene chloride and trichloroethylene had been for wiping up epoxy on some surfaces at times. (41)

Questionnaire Results for Centrifuge and Winding Workers

Formal questionnaire results from five of the centrifuge workers were summarized by Dr. Kenneth Silver in the following: (centrifuge cylinder painters and other centrifuge workers who were interviewed informally were not included in this tabulation):

Introduction: Five workers with a cumulative 48 years of exposure to fiber winding on the centrifuge project were administered the questionnaire (Appendix B) by telephone. Although the small sample size does not allow for rigorous statistical analysis, a few evident trends do suggest avenues for further research.

Personal Protective Equipment. Safety glasses were the only items of personal protective equipment routinely worn by all respondents. Respirators were not available to most of the workers. A respirator was worn “sometimes” by a single worker.

Ventilation. Air flow in the work area was rated “fair” or “poor” in a majority of cases. All respondents worked with or near epoxies indoors in a room which was characterized by most as having windows. One respondent was exposed in the enclosed space underneath winding machines that s/he was repairing.

Relative Intensity of Exposure. Respondents reported an average of 7.9 co-workers in their team or group. In aggregate, respondents felt that about one-quarter of their co-workers were more heavily exposed than they were.

Symptoms. The questionnaire elicited the frequency with which respondents had experienced certain symptoms* in terms of: never, rarely, sometimes or

* light headed, headache, drunk feeling, difficulty concentrating, fatigue
often. For the purposes of our analysis, these responses were assigned values of 0, 1, 2, and 3, respectively. Weighted responses were calculated by multiplying these values by the number of positive responses.

Fatigue and headache yielded the highest weighted scores. A “drunk” feeling was least commonly reported.

**Dose-response.** Each individual’s cumulative exposure to epoxies was expressed as a total number of work days, ranging from 450 to 4800. When interviewees reported an approximate interval of years of exposure, along with number of days per week, the cumulative days of exposure was calculated from the mid-point of the interval.

Using the values of 0 through 3 for the symptom frequency (as described above), a symptom score was calculated for each individual.

Figure 1 is a scatter plot of individuals’ symptom scores on cumulative days of exposure to epoxies. A crude dose-response relationship is evident, except for the rightmost data point. Review of the questionnaire for this respondent provides no obvious explanation for the lack of reported symptoms, despite the long duration of exposure.

The overall appearance of the plot raises the possibility that a larger study could reveal a more robust dose-response relationship between symptoms and the number of days exposed to epoxies.
Symptom Score in Relation to Cumulative Days of Exposure

Symptom Score

Cumulative Days of Exposure
Material Safety Data Sheets were obtained from workers in the winding technology areas and some of the epoxy or composite constituents for these areas are listed in Appendix E. However, many epoxy compositions were labeled as trade secret, proprietary, or CAS (Chemical Abstract System) number withheld. An unclassified inventory of chemical products utilized or stored in an epoxy winding building at Y-12 facility are listed for the year 2000 in Appendix F (these are product names and not the total constituents on each individual MSDS). This inventory reflects the vast number of different products and therefore chemicals that are often used in complex industrial operations. However, the relatively small number of materials that totaled over 8 pounds indicates that there are far fewer which are used more readily and a much smaller grouping which accounts for the majority of chemical exposure opportunities in an inadequately protected workplace setting.

Discussion of the Pattern of Symptoms In Epoxy Workers At K-25

The symptoms reported by the centrifuge and other workers who used epoxies at the Oak Ridge K-25 facility consistently reflect impacts from exposure to irritant compounds as would be expected with airborne releases of un-reacted epoxy constituents (in particular epichlorhydrin, several of the amine hardeners, (particularly aliphatic and cycloaliphatic), and glycidyl ethers. These symptoms were also reported by centrifuge workers exposed to releases during wrecking of epoxy cylinders which would be expected due to release these same constituents and potentially others materials formed during combustion of already cured epoxy materials.

The neurological symptoms (light headed or dizziness, headaches, drunk-like feeling, difficulty thinking clearly or concentrating, and tired or lacking energy) all reflect CNS (central nervous system) impacts. Most workers who used epoxies in higher exposure settings at K-25 reported all of these symptoms with the exception of feeling drunk-like. Many notably reported marked fatigue as well as nausea and in some cases pounding headache. Acute drunk-like feeling was reported by painters exclusively who painted inside the centrifuge if they removed the respirator for even a short time and was also reported by those who painted in other areas consistently without a respirator. It is possible that the drunk-like symptom reflects solvent exposure in the case of the painters which is classically reported by workers acutely exposed to higher concentrations of solvents. (42, 10) Solvents are more often used as a carrier in epoxy paint formulations as well and at higher concentrations in comparison to epoxy composite or adhesive formulations. (42, 10, 15, 6) Because solvent neurotoxic impacts are well described, (10) it is our concern that impacts of epoxy constituents may be
masked by the presence of solvents in many workplace settings despite that solvent exposures may be relatively low in most circumstances of epoxy use; further it is our concern that epoxy constituents may be the predominant agents reflected in the symptoms reported by workers at K-25 and other settings. Other confounders in addition to solvents include the very hot conditions that are generated by work in the setting of epoxy reactions. Some of these symptoms can be consistent with those of acute heat stress. However, workers at the K-25 facility in Oak Ridge, TN are highly acclimated to work in very hot conditions and when two workers were specifically asked about this they each stated that the symptoms during epoxy use were clearly distinct from that which they experienced working under very hot conditions.

Most workers had ongoing neurological symptoms after stopping work with or near epoxies in these settings, including headaches, fatigue and difficulty thinking clearly or concentrating, and some had ongoing dizziness or verbally described imbalance. Many reported a burning tingling in the extremities as well which was not formally asked about. While it is not possible to fully interpret these symptoms or to even define the conditions they represent, since this is neither a clinical nor an epidemiological investigation, the pattern warrants further consideration that they may reflect long term neurotoxic impacts from epoxy exposures. Ongoing neurological symptoms are likely to reflect in some of these workers, at least in part, exposures to other known neurotoxic substances (solely, additively or synergistically). This is particular likely for heavy metals and solvents which were present in many settings throughout the K-25 facility over the years.

Finally, the possibility of exposure to other materials used in conjunction with epoxies also posed a potential serious risk to workers specifically in the centrifuge and winding areas. In addition to the symptoms of having difficulty concentrating and thinking clearly, which were reported as ongoing in many of the epoxy workers interviewed, mental status change including psychological effects frequently occur early on and can persist in cases of neurotoxic encephalopathy. In addition to the symptoms above, more than one centrifuge worker described acute and transient mental status changes that occurred concurrently when working in the vicinity of these epoxy materials repeatedly. Some epoxy workers described them as ongoing which would be expected in cases of more sustained brain impacts. One worker described a process of layering epoxy material with virgin rubber during fly wheel manufacturing in a process which may release carbon disulfide, a neurotoxic substance that has been associated with cases of acute psychoses and longer term neuropathic impacts both to the central and peripheral nervous system. The virgin rubber was apparently liquefied using methylene chloride and apparently vacuumed off after which the epoxy layers would be brushed on creating heat as the materials combined.
The Scientific Basis For Concern that Epoxy Constituents are Neurotoxic

Dr. Mohamed B. Abou-Donia, neurotoxicologist at Duke University Medical Center, Department of Pharmacology, was asked to review the literature for any evidence of neurotoxicity for the epoxy compounds provided to him which are listed in Appendix A. His results are presented in Appendix G. The principal purpose for this review was to determine whether the materials intrinsic to the epoxy formulations are likely to be neurotoxic. Dr. Abou-Donia was also asked to elaborate on the structural basis for this concern relative to other known neurotoxins; He was asked to present any animal studies which he is aware of either in the literature or unpublished which confirm this concern in regards to any of the categories of epoxy constituents and to present any actual neurotoxic findings for animal studies involving epoxy constituents. Finally, solvents, which are present in many epoxy formulations, but do not react with the epoxy constituents, are used in widely varying proportions, and in some cases are known to be neurotoxic to humans. However, as discussed previously, it is our concern that this awareness on the part of the scientific, public health and medical communities may have masked the neurotoxic impacts of epoxies themselves in a variety of circumstances. Dr. Abou-Donia commented briefly on solvent constituents as well in terms of neurotoxicity and specifically included considering any impacts that may be likely in combination exposure circumstances involving materials that make up the epoxy formulations.

Dr. Abou-Donia began with a detailed review of the neurotoxic findings in the literature associated with glycidamide. This epoxy compound is not used in commercial epoxy formulations but is formed during the metabolic epoxidation of acrylamide, a well known neurotoxic substance. Glycidamide has been studied in detail using animal assays and found to cause both central or brain and spinal cord as well as peripheral axonal neuropathic injury (see appendix G for details). Glycidamide is neurotoxic when injected into the peritoneum or lining of the abdominal cavity where it rapidly enters the circulation and is easily available to bind with brain and other nervous system proteins. When injected subcutaneously, or in the skin, neurotoxic impacts have not developed. It is likely that this is due to the binding of glycidamide to proteins and its storage in tissues so that it does not become effectively bioavailable to the circulation or nervous system. It is similarly expected that glycidamide ingestion will not lead to significant bioavailability to the nervous system. Glycidamide inhalation, however, would be expected to be absorbed directly into the circulation and become readily available to the nervous system causing neuropathic injury as has been found with the peritoneal injection animal assays.
Dr. Abou-Donia presented unpublished animal study findings involving intraperitoneal injection to rats of acrylamide, glycidamide, glycidol, methacrylamide and propionamide, as well as a control group which received no chemical injections. Glycidol represents an epoxy compound which is specifically used as a reactive diluent in epoxy formulations. Daily intraperitoneal injection of 50 mg/kg of glycidol administered to three Sprague-Dawley rats over 35 days, led to paralysis in two and severe ataxia in the third rat or severe neurotoxic impacts in all three rats injected. Propionamide had negative findings. This compound was also used as a control to demonstrate that neurotoxic impacts were not found unless a very reactive carbon double bond, as in the case of methacrylamide and acrylamide (which is metabolized to an epoxy), or an epoxide group, as in the case of glycidamide and glycidol were present.

Dr. Abou-Donia reviewed all of the medical and toxicological literature for the epoxy compounds listed in Appendix A and was not able to identify neurotoxic findings. He concluded that, “despite the paucity of reports on the neurotoxicity of epoxy compounds, these compounds are highly likely to be neurotoxic because of the presence of the very reactive “oxirane” ring that is capable of reacting with reactive hydrogen atoms present in hydroxyl, sulfhydryl or amino groups in neuronal tissue proteins”. The oxirane rings or epoxide groups are present in the epoxy resin and reactive diluent compounds that make up the epoxy formulations.

In terms of solvent exposures, while many epoxy formulations contain varying concentrations of organic solvents, some of these compounds themselves have been found to lead to neurotoxic impacts both in animal studies and in human exposure circumstances. In reviewing the list of solvents in Appendix A that have been used in epoxy formulations, Dr. Abou-Donia commented on the neurotoxic potential of some chlorinated solvents, some of which were used in the clean up of epoxies at the Oak Ridge K-25 facility, but are in recent times not typically found in epoxy formulations. Dr. Abou-Donia also commented on the aromatic solvents, toluene and xylene, for instance. These have been found to impact on specific neurobehavioral capabilities in chronically exposed workers and there is evidence demonstrating impacts on the peripheral nervous system. They are also associated with reversible symptoms during short-term exposures. (3) Finally, also considered were combined exposure concerns, in the case of the ketone solvents. These are capable of inducing cytochrome P-450 activity and if combined with epoxy compounds are capable of leading to the activation of more potent neurotoxic compounds through oxidation.
Comment on The Lack of Studies Targeting Neurotoxic Impacts

Given the high likelihood, based on their structure alone, that many epoxy compounds have the potential to adversely impact neurological tissues, and as confirmed in the animal studies performed by Dr. Abou-Donia, the questions raised are why these impacts have not been previously investigated and why they have not been found during other animal studies involving these compounds when looking for other outcomes. To address the first question, as described in the epoxy industry review, these compounds are in widespread use throughout the world, including close to 700 million pounds of product in the United States alone in the year 2004 and potentially involving 200,000 workers. This project was developed out of concern that, based on structure alone, these compounds need to be investigated for their potential for neurotoxic impacts. The lack of studies designed to detect neurotoxic impacts of epoxy compounds confirms that industry and regulatory agencies, directing toxicological studies of compounds in widespread use, have not systematically targeted neurotoxic impacts. Animal studies to detect carcinogenic outcomes have been targeted however, and in the case of epoxy compounds for amine hardeners, glycidyl ethers, and epichlorhydrin. Some involving inhalation were found to demonstrate irritant impacts, as expected (25) which was reported by the workers exposed to epoxies at K-25, however many of these cancer outcome studies did not report on irritant impacts either. Neurological abnormalities have not been found generally for epoxy compounds during assays for cancer outcomes because these assays are not adequately designed to address or evaluate the potential for neurotoxic outcomes. This point was confirmed in discussions with Dr. Abou-Donia and is evidenced by the lack of any of neurotoxic findings in his extensive review of the literature.

In addition, the presence of solvents and other combined exposures in many workplace settings, confounds the ability to recognize adverse impacts by classes of compounds that have not been adequately studied and reported on in the literature as is the case with epoxy compounds.
Reports of Neurological Abnormalities in Studies of Epoxy Workers That Did Not Consider the Potential Role of Epoxies

Epidemiological Study of Centrifuge Workers @ K-25

The morbidity study published in 1992 and referred to previously compared and matched the centrifuge workers with other workers at the K-25 facility. (8) This study was conducted in response to concerns that the centrifuge workers who had worked specifically with epoxy and other materials, including solvents, had higher than normal rates of cancer. The exposures to centrifuge workers that were listed in this study included only the following: the curing agents or hardeners: 4,4-methylenedianiline (MDA), and m-[phenylenediamine (MPDA); the resins: bis (2,3-epoxycyclopentyl) ether (BECPE) and diglycidyl ether of bisphenol A (DGEBA); and also the “possibility for exposure to trichloroethylene and methylene chloride used in the “process”. The incidence of new bladder Cancer was statistically elevated in the centrifuge workers (5 vs. 0 cases). The investigators reported that none of the workers with bladder cancer had worked “closely with the epoxy resin material”. However, as reviewed on page 25-31 above, protective measures in the centrifuge area were not likely to limit exposures to only those workers who handled epoxy materials directly. Statistically significant increased death rates from bladder cancer, colon cancer, and lymphosarcoma as well as reticulosarcomas were reported in a study of workers manufacturing helicopter parts utilizing epoxy resins and curing agents. (38)

Other findings in the centrifuge worker study included a statistically significant increased incidence of the following (centrifuge cases/comparison cases): rashes (33 vs. 9), and several neurological symptoms: dizziness (48 vs. 26), numbness or tingling in the limbs (63 vs. 40) and insomnia (32 vs. 15). The investigators focused only on the possibility that solvent exposures accounted for these neurological findings despite that exposure to all substances was poorly defined in the study due to a lack of availability of process, material and exposure information to these investigators. Another factor to consider here is that the centrifuge worker rates were compared to those of other workers at K-25 which meant that many workers were exposed to a variety of other substances as well as epoxies used in other settings. The potential epidemiological consequence of multiple exposures to neurotoxic substances in both groups is to dilute or diminish the difference in the reported rates between the centrifuge and comparison groups. If the centrifuge epoxy workers were compared to unexposed workers the difference in rates of neurological symptoms would likely be greater than those reported above. Another consideration is that the medical effect of exposure to multiple neurotoxic substances in a given worker will potentially worsen the impact experienced by exposure to any given class of neurotoxic agents.
Insomnia was not considered by these investigators to be related to the centrifuge work in the centrifuge worker group since 11 out of the 32 cases of insomnia were reported in or after 1986 or the year after the centrifuge work had ended and 3 of the 15 comparison group cases occurred during that period of time. However, starting in 1986, many of the centrifuge workers continued to work in these same facilities on winding technologies involving very similar materials and exposures. Insomnia, may reflect psychological and brain function impacts which are frequently an early finding and, in more severe cases, an ongoing finding in patients with neurotoxic encephalopathy. Also, as reported above, some workers in the fly wheel winding operation also raised significant concerns regarding symptoms of acute psychological and mental status changes.

Had there been earlier studies and an awareness that epoxy exposures potentially contributed to neurological abnormalities, this knowledge may have led to interventions to treat symptomatic workers and protect others. Medically this would include confirming the diagnoses and then eliminating the chance for ongoing significant exposures to neurotoxic agents by removal of impacted workers from the more dangerous work environments.

Symptoms Reported by Epoxy Workers in Washington State

Industrial hygienists from the State of Washington, Department of Environmental Health, investigated a large manufacturing plant after one worker presented asking for help. (43) Her work involved preparing pre-impregnated panels for vacuum layup which entails applying epoxy resin materials. She had apparently involved working long hours and in very hot conditions. She became concerned about symptoms when a new resin was introduced which contained formaldehyde amongst other substances but not epoxies specifically. Details of the workplace operations, protective measures, materials used and range of potential exposures in the past and at the time of the investigation were not presented. Measurements were performed only of the materials in the new resin. Formaldehyde was measured at .004 ppm (8 hour Time Weighted Average) and .073 ppm (short term exposure limit) in the workplace (these values are over 25 to 200 times below the permissible exposure limits for The State of Washington). Other substances in the resin were either undetectable or measured at very low concentrations as well.

Over 100 workers had been seen by one physician in relation to concerns regarding exposures from this facility and the neurological or psychological symptoms reported by forty-one of the workers included the
following: Headache (32/78%), personality change (27/66%), Fatigue (34/83%), Irritability (32/78%), Depression (28/68%), memory lapse (30/73%) and loss of sex drive (17/41%). Skin rash was reported in 44% and irritant impacts were reported in the eyes (76%), upper respiratory tract (85%) and lower respiratory tract (56% reported cough or wheeze).

The industrial hygienist investigating this facility focused on formaldehyde as a possible explanation for these symptoms, despite very low measurements, however, information was not available to determine the onset of these symptoms in relation to exposure histories. When asked, during a recent telephone discussion, the author confirmed that there was a lack of knowledge as to the onset of these symptoms in relation to exposures or the extent of exposure possibilities at this facility. He also felt that the epoxy materials which had been used predominantly there could have played a significant role. Further efforts are underway to locate details about the reporting of these symptoms. The report of memory lapse is more typical of long term impacts however they can also occur with early psychological changes independent of or related to exposures to neurotoxic substances.
Conclusions and Recommendations

The neurotoxic risks addressed in this project, in relation to epoxy substances, are representative of the problems we face universally in the use of industrial chemicals and the lack of a systematic approach to addressing toxic concerns generally. Close to 700 million pounds of epoxy products were used in the United States alone in the year 2004 and this potentially involves exposures to 200,000 workers. This project developed out of a concern that, based on their structure alone, epoxy compounds needed to be investigated for their potential to lead to neurotoxic impacts. One worker was found to have developed a disabling sensory and motor neuropathy condition after a single period of exposure to epoxy applications and, despite their widespread use, there was no information readily available regarding the potential for epoxies to cause neurological abnormalities. Our review has confirmed that there are no studies published to date which were designed to consider neurotoxic abnormalities for epoxy compounds. The published and unpublished animal studies as reviewed by Dr. Abou-Donia consistently demonstrate that those epoxy constituents which contain epoxide groups are highly likely to be neurotoxic because of their structure. Specific epoxies were found to be positive in the unpublished neurotoxic animal assay summarized on page 34. Because their use is so widespread, the case of epoxies raises serious questions about the lack of attention paid to industrial chemicals and their neurotoxic potential.

Also raised are questions about the ability to adequately evaluate workplaces to allow identifying potentially causative agents. Because of the multiple obstacles preventing us from obtaining available information we tend to consider only that which is more familiar to us. This was the case in considering solvents as an explanation for the neurological symptoms found at higher rates in the epoxy centrifuge worker cancer study (page 36-37). There are several examples, for this project, where information was not obtainable such as: industry measurement data of the constituents found in epoxy vapors (pages 10-13) or measurement data in the centrifuge areas not available to either DOE independent investigators or for the cancer study (39,8); process information was also not available for at K-25 for security reasons and trade secrets were not listed on material safety data sheets. A lack of process information prevents understanding which materials amongst a long list are more likely to play an important role in exposures and illnesses (page 31). Industry liability, trade secrecy and economic considerations also impact on that which is revealed in terms of the potential for materials to be dangerous. Industry reports also tend to focus on more precise and controlled conditions of use rather than less controlled work environments. This was revealed in the review of the aerospace industry conference (pages 10-13) as compared to the conditions of usage found at the K-25 facility (pages 18-31).
...(Conclusions and Recommendations, continued)

The epoxy industry impacts virtually all commercial sectors (page 7), with approximately 40% of the over 2 billion pounds that are used world wide each year, being applied to coatings or paints, 30% in adhesives and 30% for other uses. While the universe of epoxy constituents is potentially very large, (a popular industry guide describes over 2,800 currently available epoxy resins, curing agents, compounds and modifiers (16)), a reasonable list was created after extensive review listing most of the principal constituents used in epoxy formulations (Appendix A-Epoxy Compounds for Neurotoxicology Review).

In terms of neurotoxic impacts to users, the greatest concern occurs with airborne releases and inhalation exposures. Animal studies demonstrate that skin injections, which are very likely to be similar to oral ingestion, do not become effectively available to the neurological tissue because of protein sequestering in deeper tissues. On the other hand intraperitoneal injections of epoxies were rapidly available to impact neurological tissues in animal assays. This would be expected as well during inhalation exposures because of direct absorption to the blood (page 33-35, Appendix G).

The potential for airborne exposures to epoxy constituents is greatest when epoxy materials are produced, transferred, mixed, and applied in open environments without adequate ventilation or respiratory protection and when the conditions of usage maximize the chance for release of uncured materials (page 5). Epoxies were used at the Oak Ridge K-25 facility in huge quantities (for example, over 2 million pounds and 4,000 drums of surplus epoxy were shipped off-site from one building during one year in 1990); They were used for several different purposes which often created high exposure opportunities (pages 17-30, reviews of epoxy use by masons, painters, and centrifuge workers). Spray painting applications create unique opportunities for exposures to vapors and aerosols which can carry epoxy constituents, often combined with solvents, and pigments deep into the respiratory tract.

In addition, there is a potential for airborne exposures to already cured epoxy materials during combustion as in aircraft explosions and other circumstances such as when the centrifuges were wrecked deliberately on a frequent basis at the K-25 facility in Oak Ridge (page 28). Similar exposures occur when mixed epoxy materials create an uncontrollable exothermic reaction which can lead to the production of unique compounds in addition to the original materials which make up the epoxy formulations (page 14).
... (Conclusions and Recommendations, continued)

In more controlled settings, with precise applications, or with limited use circumstances, these exposures can be minimized, particularly when utilizing local ventilation and thin layering (pages 8-13). Measurements of airborne epoxy materials are generally lacking (at least those obtainable) which will be addressed in the recommendations which follow. Even in controlled settings there are opportunities for exposures. (pages 8-13) Anecdotal reports suggest that some individuals could not continue to work in more controlled environments because of adverse neurological symptoms, suggesting the possibility of a variable susceptibility amongst workers. (7)

The protective measures that are recommended for epoxy use are fairly stringent because of carcinogenic concerns for some of the constituents including epichlorhydrin, diglycidyl ether (other glycidyl ethers), and methylenedianiline (page 14-16). However, established methods for monitoring workplaces at these levels are lacking and it is certain that exposures are far greater than these standards in many workplace settings of epoxy usage in the United States and throughout the world. Exposures during epoxy usage at the Oak Ridge K-25 facility during previous decades were quite worrisome in many settings as reviewed in detail (pages 18-30). Fortunately, according to workers interviewed, efforts have been made in recent years, to improve protective measures in current epoxy operations.

The pattern of symptoms reported by interviewed workers were consistent amongst those who worked in conditions that created opportunities for high level exposures to airborne epoxy constituents at K-25 (masons, laborers, painters, and centrifuge or winding workers). These symptoms are consistent with that which would be expected from exposure to airborne irritants and compounds adversely impacting neurological function (page 30). While the major epoxy constituents are known irritants (epichlorhydrin, amine hardeners (particularly aliphatic and cycloaliphatic), and glycidyl ethers), other irritants were also likely to have been present at several settings at the K-25 facility (particularly chlorinated and caustic cleaning agents). Similarly, many concerning neurotoxic materials were used at K-25 and are likely to have impacted many workers including some of those who worked with epoxies over the years. (1)

The pattern of symptoms amongst epoxy workers was specific, however, and was consistently described as worse when exposures were likely to be highest. It appears that drunk-like or a feeling of intoxication, which often reflect high level solvent exposures (10), was not as common in these settings as compared to light headed or dizziness, headaches, difficulty thinking clearly, or fatigue. These later symptoms continued as well for
many of the interviewed workers after stopping work with or near epoxies. Based on interviews, respirators were not generally used for painters during the earlier years, and were never generally used for high exposure masonry epoxy work (except sometimes for those who were mixing because of the severity of the acute symptoms). Centrifuge workers in epoxy areas also did not wear respirators including during the wrecking of centrifuges (except for the spray painters inside the centrifuges). In each group there were workers who reported having sought respirator protection and who many times struggled to obtain them or were refused.

The questions asked during formal and informal interviews were not comprehensive but were designed to enhance the understanding of conditions of epoxy use for workers at K-25 and to help in formulating recommendations for more formal studies in relation to investigating epoxy constituents and neurotoxic impacts. Because the index case worker did not have an exposure history to multiple agents, as is the usual case for more industrial workers at K-25, the similar pattern of symptoms in this worker, during a substantial two week period of exposure to airborne epoxy materials, and the subsequent development of peripheral neuropathy is worrisome relative to implicating epoxy constituents. (page 14-18). Also worrisome are the epidemiological findings reported in the centrifuge worker bladder cancer study which included statistically significant increases in the incidence of dizziness, numbness or tingling in the limbs, and insomnia in epoxy exposed workers. (page 35) While the investigators focused on solvents in this study as a possible explanation, they had little exposure information available to them with which to interpret these findings. The comparison group utilized for this study was also likely to be exposed to widespread materials used at K-25 (including solvents). This makes the differences in the rates found in the centrifuge epoxy workers even more compelling to begin with and further points to epoxy components as unique contributors to the neurological symptoms they reported.

Despite these preliminary findings, several important questions need to be addressed to further characterize the role of epoxy compounds in terms of their potential to lead to neurological abnormalities and to design appropriate responses for the risks they pose. As for animal study information, this project strongly speaks to the need for neurotoxicologist to formally gather to summarize the appropriate animal assays that are available for screening neurotoxic substances and to initiate a system for selecting and studying those industrial agents that are most likely to pose neurotoxic concerns. Epoxy compounds which contain epoxide groups
specifically (epichlorhydrin, resins, and reactive diluents (or glycidyl ethers) will need to be studied using various animal assays and the results summarized to further define absorption, metabolism, and neurotoxic impacts at varying doses and routes of exposure in animals assays.

In terms of understanding epoxy use and the potential for airborne releases, existing measurement data will need to be pursued and more independent industrial hygiene investigations will need to carried out to determine the conditions of epoxy usage that pose the greatest risk for airborne releases and the concentrations of materials found. Standards need to be further established to allow measurement of epoxy compounds at the concentrations that meet the existing recommendations for protecting workers from carcinogenic impacts (pages 13-14).

Further epidemiological investigations are indicated that are designed specifically to look for epoxy neurotoxic impacts, both acute and long term for workers exposed under different conditions. These include, depending on what is possible, workplaces and worker populations involved in the use of epoxy compounds for varying purposes (such as spray painting, composite or adhesives applications, and electronic applications), and at both higher and lower levels of exposure. Important to consider is the possibility of a study to compare predominantly epoxy exposed workers with those exposed in combination with other potentially neurotoxic materials, including solvents, for instance.

A formal public health conference is needed to address the many neurotoxic concerns facing the former Oak Ridge K25 worker populations. The will and the ability to screen and to comprehensively evaluate, diagnose, and treat workers who are at risk for neurotoxic and other illnesses in this population and in other high exposure groups, is of question, in part, because of the numbers of workers involved. Specific medical concerns were raised during the research and interviews carried out for this project which will be addressed to the best of our ability.

Finally, the case of epoxy compounds and their potential to lead to neurotoxic impacts, that was investigated for this project, has exposed the true difficulties faced by medical and public health evaluators in determining the cause of illnesses when workers are exposed to multiple hazards, particularly in complex workplace settings. The case of epoxies has also exposed the fact that we can not rely on industry alone to adequately investigate even widely used compounds for their potential to lead to toxic impacts.
Appendix A- LIST OF EPOXY COMPOUNDS FOR NEUROTOXICOLOGY
REVIEW OF THE LITERATURE
Prepared by Richard Bird, MD, MPH,

(Selected if more commonly used based on documents reviewing Epoxy formulations (6,11,13,14,15,16) & if identified at the Oak Ridge K-25 Facility)

EPOXY RESINS

*Diglycidyl ether of bisphenol A (DEGBA) CAS 1675-54-3, 25068-38-6, 25085-99-8
  Including Epichlorhydrin

Brominated DGEBA CAS # 71033-08-4
  (made from tetrabromobisphenol A epichlorhydrin + brominated biphenol A)

Epoxy Novolac (~ Phenolic, Cresolic, and Trisphenolic)
  Glycidilated-o-cresol novolak resins CAS 37382-79-9
  Epoxy phenol-Novolak Resins CAS 9003-36-5
  Epoxy Novolak (Triphenolic) CAS 6602-38-6

Tetraglycidyl ether of tetraphenolethane CAS 7328-97-4
  (prepared from: Polyphenol 1:1, 2:2-(p-hydroxyphenol)ethane)

Biphenol F-based resins (DGEFB) CAS 87139-40-0
  (2,2’-methylene bisphenol, CAS 2467-02-9) (from formaldehyde + phenol)

Diglycidyl ether of resorcinol CAS 101-90-6

Bis (2,3-epoxycyclopentyl)ether (BECPE) 2386-90-5

AROMATIC AND HETEROCYCLIC GLYCIDYL AMINE RESINS:
THOSE COMMERCIAL SIGNIFICANT:
  Cycloaliphatic and heterocyclic epoxy FILAMENT WINDING FLEXIBLE:
    Glycidyl amine epoxy AEROSPACE COMPOSITS
  Glycidyl ethers of aliphatic polyols
    Tetraglycidylmethylenedianiline-Derived resins
      (N,N,N’N’-Tetraglycidyl-4,4’-diaminodiphenylmethane CAS 28768-32-3)
  Triglycidyl p-aminophenol-Derived Resins EXPLOSIVES, PROPELLANTS,
    (Triglycidyl p-aminophenol CAS 5026-74-7) MILITARY PLARES, PYROTECHNICS

Triazine-Based Resins WEATHERABLE COATINGS, ELECTRONICS
  (Triglycidyl isoycyanurate CAS 2451-62-9) OPTICAL TRANSPARENCY

WATERBORNE EPOXY RESINS: FOR NEW CONCRETE & METAL
  Biphenol A or Novolac Resin emulsified w/
    Titanium Dioxide – surfactant (50% by volume)
    Polyamide or polyamidoamine – Hardener (16% by volume)
EPOXY ACRYLATE RESINS: Vinyl ester resin–esterify epoxy resin via terminal group
with an unsaturated acid such as methacrylate acid derived from epoxy resin
Aromatic difunctional epoxy acrylates
Acrylated oil epoxy acrylates
Epoxy novolac acrylates
Aliphatic epoxy acrylates
Miscellaneous epoxy acrylates – used in pigmented coatings
oligomers with fatty acid modification

EPOXY CURING AGENTS AND CATALYSTS (~5–20% or more; 10% typical)

COMMON POLYAMINES FOR CURING EPOXY RESINS:
- Triethylenetetramine, (TETA)
- Diethylenetriamine (DETA) (CAS 111-40-0)
- Poly(oxypropylene triamine)
- Poly(glycol amine)
- Isophorone Diamine (IPD) – sluggish cure rate, light color, chem. resist
- 1,2-diaminocyclohexane (DAC)
- N-aminoethylpiperazine (AEP)
- 4,4’-diaminodiphenyl methane (MDA)
- 4,4’-diaminodiphenyl sulfone (DDS)
- m-phenylenediamine (CAS 108-45-2)

LESS COMMON
- Triethylamine
- Diethylenetetramine
- Triethylenepentamine
- Tetraethylenepentamine
- Trimethylhexamethyldiamine
- Triethylenetetramine phenol adduct
- Cycloaliphatic polyamines

COMMONLY USED TERTIARY AMINE ACCELERATORS
- Aliphatic amines blush so these help avoid absorbing moisture, etc.
- Phenol
- DMP 30 = o-(dimethylaminomethyl) phenol
- Tris-(dimethylaminomethyl) phenol
- DMP-10 = tris-(dimethylaminomethyl) phenol

Diethyleniminopropylamine: (DEAPA) for curing epoxy adhesives where low heat are required

Aminoethylpiperazone (AEP) used when toughness required
EPOXY CURING AGENTS AND CATALYSTS continued……

MODIFIED ALIPHATIC AMINES
glycidyl adducts of aliphatic amines
N-Hydroxyethylhexylenetriamine
N,N’-Bis(hydroxyethyl)diethylenetriamine
N-(2-Hydroxypropyl)ethylenediamine
N,N,N,N’-tetrahydroxypropylethylenediamine

POLYAMIDES – WIDELY USED in COATINGS & ADHESIVES
Amidodiamines, adheres to POROUS CONCRETE, WOOD & Humidity

AROMATIC AMINES AND MODIFIED
Metaphenylene diamine (MPDA) most common aromatic curing agents
Methylene Di­aniline
Aromatic amine eutectics
Solvent solutions
Diaminodiphenyl­sulfone – best strength for elevated temperature exposure

ANHYDRIDES - casting compounds, encapsulates, molding compounds
MOST COMMON:
hexahydrophthalic anhydride (HHPA)
Phthalic Anhydride (PA)
Nadic Methyl Anhydride (NMA)
Pyromellitic Dianhydride (PMDA)

Dodecyl succinic anhydrides

Catalytic and latent hardeners – do not participate in the reaction
Catalyze homopolymerization of the resin

MOST POPULAR:
Tertiary amines- a type of LEWIS ACID catalyst most widely used:
DMP-10 = tris-(dimethylaminomethyl) phenol
DMP-30= o -(dimethylaminomethyl) phenol
Benzylidimethylamine (BDMA)- mostly used as either sole catalyst
or accelerator w/ anhydride and dicyandiamide cured epoxy resins
Tertiary amine salts – good adhesion to metal
Boron trifluoride complexes – broad commercial use
Imidazoles – for metal, chem., temp resistance and lower exotherm than:
dicyandiamide, (dicy)
Polysulfides and mercaptans – low exotherm… e.g. Capcure
DILUENTS – higher molecular wt. than solvents but lower than other constituents and therefore more volatile, used to lower viscosity primarily and to modify processing conditions (~ 5-10% typical proportion)

MONOFUNCTIONAL EPOXY REACTIVE DILUENTS
Butyl glycidyl ether CAS 2426-08-6
Phenyl Glycidyl ether CAS 12260-1
Diglycidyl ether CAS 30583-72-3
2-Ethylhexyl glycidyl ether
C8-10- Aliphatic monoglycidyl ether
C12-14- Aliphatic monoglycidyl ether
Cresyl glycidyl ether
Neopentyl glycol diglycidyl ether
Butanediol diglycidyl ether
(1,4-Butanediol diglycidyl ether CAS 2425-79-8)

DIFUNCTIONAL EPOXY DILUENTS
Butadiene Dioxide
Vinyl cyclohexene dioxide
Diglycidyl ether of resorcinol CAS 101-90-6

NON-EPOXY reactive diluents:
Triphenyl phosphate (react with hydroxyl group in the resin)
Gamma-butyrolactone
Dibutyl Pthalate CAS 84-74-2
Polymethyl acetal

OTHER REACTIVE DILUENTS
Diglycidyl ether of diphenylol propane
Glycidaledehyde
Glycidol
Isooctyl glycidyl ether
1,2-epoxydodecane
Monoglycidyl ester of a synthetic fatty acid
Monoglycidyl ether of isomeric alcohols
Diglycidyl ether of butanediol
Diglycidyl ether of neopentylglycol
SOLVENTS – used less often than in the past; higher concentrations in formulations for paint spraying but %s widely varying: purpose to lower viscosity of epoxy system to aid mixing, dispersing, wetting in formulation, to lower viscosity for easier mixing at application stage, or to liquefy solid resins and hardeners to apply as a film. They must be completely evaporated from the bond line prior to cure. (true solvents or those for which there is a chance of resin precipitation include: MEK, diacetone alcohol, methylcyclohexanone, glycol ethers and acetates)

KETONES
Acetone
MEK
Methyl Isobutyl Ketone
Diacetone alcohol
Isophorone

ESTERS
Ethyl acetate
n-butyl acetate
cellosolve acetate

ETHER ALCOHOLS
Methyl cellosolve
Ethyl “
Butyl “
Ethyl carbitol
Butyl “

CHLORINATED SOLVENTS:
Trichloropropane
Chloroform

MIXED SOLVENTS
TOLUENE W/
acetone
MEK
MIK
Diacetone alcohol
Isophorone
Isopropyl Alcohol
Cellosolve Acetate

TYPICAL w/DGEBA: Xylene, MIK, Cellosolve, Cyclohexanol
SOLVENTS continued....

SUBSTITUTES: Citra-Safe, EP 921
Teksol EP, X-Caliber
Iso Prep
Safety Prep

Trend to water borne epoxies... rather than replace the solvents

MISCELLANEOUS

Photoinitiator:
{(4-Octylphenyl) phevlodonium hexafluoroantimonate (OPPI) [or other aryl substituents] identified in e-beam curing at OR-LMES}
Who is your current employer?

At the time when you worked with or near epoxies on a regular basis, who was your employer then?

Are you (or were you) a member of any organizations concerned with Oak Ridge labor or health issues, such as:

___ the Masons Union
___ PACE Union
___ Other labor organizations. Which one?: _____________________________
___ A citizens’ organization. Which one?: _____________________________

Which of the following jobs have you worked in where epoxies were being used?

___ leveling and coating of floors, or other masonry work such as grouting or water proofing.
___ fiber winding on the centrifuge project
___ spraying or coating walls with epoxy based paints
___ administrative, clerical, or other type work not directly handling the epoxies but close enough to smell the chemical vapors
What is the name or number of the building where you worked with or near epoxies?

If you worked in more than one building, please help me make a list of where you worked and briefly state what you were doing in that job:

<table>
<thead>
<tr>
<th>Location</th>
<th>Masonry Work</th>
<th>Fiber Winding</th>
<th>Administrative Clerical, or other Work</th>
<th>Spraying epoxy based paints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(list additional locations here)

Tell us how often and for how long you worked with or near epoxies, for instance, how many days a week or month and for how many years?

Total number of days: ____________

Conversion factors: ~5 d/wk; ~22 d/mo; ~250 d/yr

In any of the jobs we’ve discussed, did you directly handle epoxy products?

____ Yes
____ No
I am going to read a list of various kinds of personal protective equipment which are available on some job sites. When I name each kind of personal protective equipment, please tell me whether it was available to you on the job(s) where you were exposed to epoxy vapors.

<table>
<thead>
<tr>
<th>Available?</th>
<th>Used Them?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Always</td>
</tr>
<tr>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>Never</td>
</tr>
</tbody>
</table>

**Respirators**

- If Yes, was the respirator a:
  - * Paper mask
  - * White Face Mask
    w/Charcoal and a yellow or black dot
  - * Cartridge Respirator
  - * PAPR
  - * Supplied Air Respirator

**Did you use:**

- Gloves

- Protective Clothing

- Safety glasses or eye goggles

INTERVIEWER: Use this space to clarify any confusion over whether the person was a bystander or directly handled epoxy products.
On the days while you are working with or near epoxies or after work on those days:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you feel lightheaded or dizzy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you have a headache?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you have a drunk-like feeling?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you have difficulty thinking clearly or concentrating?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you feel fatigue, tired or like you had no energy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tell us now if these symptoms began before you started working with or near epoxies and if they continued after you stopped working with or near epoxies.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Began Before</th>
<th>Continued after stopped working with or near epoxies</th>
</tr>
</thead>
<tbody>
<tr>
<td>lightheaded or Dizziness?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drunk-like feeling?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty thinking clearly or concentrating?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling fatigue, tired or like you had no energy?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

53
FOR RESPONDENTS WHO WORKED DIRECTLY WITH EPOXIES

Overall, how would describe the air circulation and ventilation on the jobs where you handled epoxies?

___ Excellent
___ Good
___ Fair
___ Poor

The safest place to work with unhealthy chemicals is outdoors. The worst place is in a confined space, like a closet or a man-hole. In between these two extremes are enclosed spaces like basements. Also, you can work indoors, in a regular room with windows, which is better than an enclosed space but not as good as being outdoors.

<table>
<thead>
<tr>
<th></th>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often did you work outdoors with epoxies…</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. How often did you work with epoxies indoors in a room with windows …</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. How often did you work with epoxies in enclosed spaces …</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. How often did you work with epoxies in confined spaces …</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often were fans used to blow clean air into the work environment?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often was local exhaust ventilation used to draw the chemical vapors out of the work environment?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FOR RESPONDENTS WHO WORKED *AS CLERICAL OR ADMINISTRATIVE or Other EMPLOYEES, NOT DIRECTLY WITH EPOXIES*

On a normal day when epoxies were NOT being used, how would describe the air circulation and ventilation in the building?

_____ Excellent

_____ Good

_____ Fair

_____ Poor

On days when you were exposed to chemical vapors from epoxies, was the work being done

_____ on the same floor as your office

_____ on the floor below

_____ on the floor above

_____ somewhere in or near the building, but not sure of location

Were there any factors that you feel increased your exposure to epoxies?
**BOTH GROUPS OF WORKERS**

We are trying to get an estimate of the total number of employee who may have had serious exposure to epoxies.

About how many other people were in your work area or on your work crew?

Of this number, how many were more heavily exposed than you…

…and how many had exposure about the same as yours?

Please provide us a detailed description of your job:
Appendix C  STUDY DESCRIPTION AND CONSENT FORM  
Exploring Epoxy Use at the Oak Ridge K-25 Facility and New Concerns About Neurotoxic Risks, 2006-7

Investigators: Richard Bird, MD, MPH  phone/fax: 1-781-646-5770  
Ken Silver, DSc,MS  
Mohamed Abou-Donia, PhD

In the later 1990’s a group of over fifty sick workers from the K-25 DOE Facility in Oak Ridge, Tennessee asked that outside investigators determine whether their illnesses were related to workplace exposures. Several workers were found have neurotoxic abnormalities in addition to other types of illnesses. Because most workers had opportunities for exposures to a variety of substances, including solvents, heavy metals, pesticidal products and PCB’s, it is not possible to know exactly what may have caused the neurotoxic effects. Concern about epoxy products was raised, however, amongst other concerns, because of the timing of exposures.

Epoxies are not readily known to pose a risk of neurotoxic effects, and therefore, we have undertaken a grant from RESOLVE to investigate further whether there is evidence in the literature, including animal studies, and whether there is something unique about the way in which epoxies were used at the K-25 facility to help understand the possibility that epoxy use caused neurotoxic effects. We are also considering whether a formal epidemiological study might be possible to help us to better understand these possible effects.

At this time, we are simply asking questions, over the phone to volunteers, about the conditions of use of epoxies at the K-25 facility including a few questions about symptoms you might have had at the time you worked directly with or were situated near epoxies. The answers are not being used as a formal survey but instead to gather information. The individual identities (including names) of each respondent will remain entirely confidential. It is critical that you answer each question as honestly as possible. If you are not sure about a question it is OK to guess. If you choose to participate, we greatly appreciate your help in our effort to understand more about the possible dangers of working with epoxies.

I, _________________________________, give my permission (printed name of participant) to Dr. Bird or Dr. Silver to ask me questions about epoxy use with the understanding that my identity (including my name as a participant) is confidential and will not be revealed to anyone except the Epoxy Project investigators, whose names are listed at the top of this page.

Signed _________________________________, Date__________________  
(signature of participant)
Appendix D- Description Of Rotor and Flywheel Epoxy Winding At K-25
Prepared by Kenneth Silver, DSc.MS
Based on interviews w/centrifuge workers

Epoxies were used in the fabrication of rotors and flywheels. Complete details of this process are not available, probably because of national security classification concerns. However, it is clear that epoxies were mixed with fiberglass, carbon or graphite fibers, then wound and molded to form rotors and flywheels. The close involvement of engineering and scientific personnel suggests that these components were made to a high degree of precision (small tolerances). It is likely that the rotors and flywheels were being made for use in cutting-edge technology related to national security. Some of these products were also used in the civilian electric power generating industry.

Epoxies and other components were mixed in chemical hoods. After this initial mixing step, however, subsequent steps in the process such as winding and curing were apparently conducted outside of hoods, in the open air of rooms in J-Lab and T-Lab at K-25. In one process, the mixture of epoxy resin and fiberglass, held in vats, was dispensed by an automated machine to a form. Over the course of several days, the material would build up as it solidified and hardened. For the inputted epoxy-fiber material to remain liquefied, heat was applied to bulk quantities (two to three gallons) for hours at a time. Some workers were responsible for maintaining the heaters, a task which entailed both inhalation and skin contact. Coatings, adhesives, iron filings and hardeners were added. Some of these materials were suspended or dissolved in carrier solvents, to which operators and bystanders were exposed. Balancing of rotors, requiring collection and analysis of data, was conducted in close proximity to these operations.

Curing of finished rotors and flywheels was carried out in ovens and autoclaves, as well as with electron beams. Curing probably yielded off-gassing of solvents, uncured material and pyrolysis products. Nothing from our discussions with workers indicates that local exhaust ventilation was provided to reduce exposure to off-gassed materials.

Rotors and flywheels were then subjected to testing, which entailed the collection of electronics data. (Alternator and control electronics are used to convert a flywheel’s mechanical energy into electrical energy). Personnel in some of these testing procedures could have been exposed because of their proximity to the winding and curing operations described above. On occasion, some of these testing personnel might have also had close, hands-on contact with the fiber winding process.
Appendix E- Epoxy Compounds Used At Oak Ridge Winding Operations - As Listed On MSDS provided by Workers;
Prepared by Kenneth Silver, DSc.MS

(Many epoxy components are not included because they were listed on the MSDS as trade secret, Proprietary or CAS number withheld)

Resins:
Epoxy Resin CAS 25068-38-6
Jeffamine T-403 (CAS 38423-51-3)

Curing agents
4,4' sulfonyl dianiline (CAS 80-08-0)
methylene dianiline (on master list (CAS )
diethylenetriamine (on master list - CAS 111-40-0)
m-phenylenediamine (on master list CAS 108-45-2)
n,n-dimethyl-1,2,-propanediamine (CAS 104-78-9)
triethanolamine (102-71-6)

Non-epoxy Diluents
Dibutyltin dilaurate CAS 77-58-7

Solvents:
carbon disulfide
methylene chloride
TCE
Acetone (CAS 67-64-1)
Aromatic hydrocarbon blend (CAS 68477-31-6)
Benzyl alcohol (CAS 100-51-6)
DMF (< 1%) (CAS 68-12-2)
Formamide (CAS 75-12-7)
Fufuryl alcohol (CAS 98-00-0)
Hexane (CAS 10-54-3)
Isopropyl alcohol (CAS 67-63-0)
MEK (CAS 78-93-3)
Methanol (CAS 67-56-1)
Methylene iodide (CAS 75-11-6)
Toluene (< 1%) (CAS 108-88-3)

Fibers:
Polyacrylonitrile-based graphite fiber (synthetic) (CAS 7782-42-5)
Woven graphite fiber (CAS 744-44-0)
... (Appendix E- Epoxy Compounds Used At Oak Ridge Winding Operations)

Metals:
Antimony oxide (CAS 1309-64-4)
Mercury metal (CAS 7439-97-6)

Uncategorized:
“Free Monomeric MDI” (assume Methyl di-isocyanate) (MDI CAS 101-68-8)
MDI (26447-40-5)
Polytetramethylene ether glycol/MDI

Methylene bis(4-cyclohexylisocyanate) (CAS 5124-30-1)
n-methylpyrrolidone (CAS 872-50-4)
nonyl phenol (CAS 25154-52-3)

Diuron (CAS 330-54-1)
Potassium perchlorate (CAS 7778-74-7)

Trade secret, Proprietary or CAS Withheld
“a polymerization catalyst “ (Hercules)
“aromatic isocyanate”
“trace of black dye”
“catalyst”
“amines (Formula RMF-1333)”
(4-octyloxyphenyl) phenyliodonium
Hexafluoroantimonate (OPPI)
Bisphenol F diglycidyl ether
“proprietary catalyzed epoxy mixture” (FiberCote Inds.)
“An aromatic diamino curing agent” (Hercules 1985)
“Fiberglass”
“Mixed polypropylene polyglycols”
“amine/formaldehyde polymer”
“Uncured epoxy resin”
“amine hardener”
“carbon/graphite fibers”
“Amine cured epoxy resin and carbon fiber”
“epoxy resin-sized carbon fiber”
Appendix F-Unclassified Inventory @ Y-12 Building 9204-1 Epoxy Composite Winding Operation 8-17-2000; by Richard Bird, MD, MPH

3M products w/Garnet Mineral (25 POUNDS) (Weights are listed if over 8 #s)
3M scotch-Weld AF-163-2 Structural Adhesive (2,578 POUNDS)
Acetone (48 POUNDS)
Akzo Mobel Fortafil Carbon Fiber (40 POUNDS)
Alconox, Detergent (8 POUNDS)
Aluminum Metal
Apiezon Q compound
Argon (42 POUNDS)
Armstrong World Industries 520 Adhesive
Ashland Chemical Pliogrip 3221 Curative (11 POUNDS)
Babcock & Wilcox Kaoowool Safil Products
BF Goodrich Adhesive Exp 582 E (116 POUNDS)
Bisphenol A Diglycidyl Ether (97 + 50 POUNDS)
Bisphenol F Diglycidyl / Epichlorhydrin Epoxy Resin (50 POUNDS)
Buehler Micropolish Alumina Alpha 1C
Calcium Carbide and Calcium Hydroxide
Cape Unidirectional and Woven Prepreg (1,100 POUNDS)
Copper Metal
CRC 2-26 (aerosol); 3-36 Multipurpose Lubricant; Co Contact Cleaner
Crouse-Hinds Chico AA Sealing Compound
Devcon 5-min Epoxy Hardener, liquid (F-2) resin and (F) putty; Wear Resistant Liquid (WR) Resin
Dexter Hysol EA 9330 & XEA 9361 QT Systems Part A&B (17 + 17 POUNDS)
Dibutyltin Dilaurate
Dow Corning: 3145 RTV Adhesive Sealant (13 POUNDS); Silastic Adhesives 732, JRTV Silicone R, T-2 Curing Agent, T-2 Translucent base (10 #s), 3140 RTV coating; 321 Dry film lubricant; 732 Multipurpose Sealant; G-N Metal Assembly Paste; HS II RTV 20:1 Clear Catalyst; HSII RTV Hi STR MLDMK
Drierite (40 POUNDS)
Electro SPC Water Primer
Enerpac HF/HOF Hydraulic Oil
Ethyl Alcohol (118 POUNDS)
Exxon Superflo ATM D/M
FelPro C5 High Temperature Antiseize
Fibercoat Industries: E-761 Epoxy Aluminized Glass (6,000 #s); Epoxy Graphite prepreg (5,900 #s)
Fiberite E719LT/1583 38” (100 POUNDS)
Formamide
Framatome Connectors Penetrox-A oxide IN
Future Abrasives Glue Bond or Resin Bond (8 POUNDS)
GC Electronics: Rubber to Metal Cement; Thorsen Silicone Rubber; Adhesive/Seal; RTV Silicone SEALant; RTV 60; Silicones Aryl Fuoroantimonate (19 POUNDS); Rubber Sealant RTV159
Germann Instruments: GD-2005 (Refer to RE); RCT-1000 & 1000-1; RCT 1023 (9 POUNDS); 1030 Calibrations; RCT-500
Glycerin
Gulf Gulfcut 45A
Hartrun TTI 353-ND
Helium (56 POUNDS)
Hercules Magnamite Carbon Fiber – G-Size (20 POUNDS)
Hysol TE 0043 ; XEA 9396 Part A (91504) and B (91505)
Indicating Drierite
Isopropyl Alcohol (38 POUNDS)
ITW Devcon Plastic Steel Putty A Resin and Hardener 0200
Jeffamine T-403 (50 + 50 POUNDS)
K&W Products Knock ER Loose
Kester 44 and 285 Flux Cored Solder: 1571 Rosin Flux
Laser Technology Holobath Developer
Loctite Quick set 404 Industrial Adhesive; Waterproofing Solutions
M&T Harshaw M&T AP-20
Measurements Group: CSM -1 Degreaser; and M-Bond: 200 catalyst, 610
adhesive, 610 adhesive kit (94163, 90207), AE RESin, Curing Agent (600/610)
Curing Agent Type 10: M-Coat: A & Flux AR; M-Line: 361A-20R solder Kit;
Rosin Solvent: RTV Primer No 1; M-Prep: Conditioner A, Neutralizer 5;
Metal Cleaner: Neutra Sol: PL-1: Releasing Agent
Mercury Metal (1 pound)
Merit Grind-o-flex) Mini Grind-o-flex (Flap Whee) (25 POUNDS)
Methanol
Methyl Ethyl Keton
Mineral Oil, severely refined and white
Mobil DTE: 24 & 25 (7,311 POUNDS); Mobil SHC: 624 (36 POUNDS)
Moly-Dee Tapping Fluid (# 945)
N-N-Diethyl-1,3-Propanediamine
National Starch Perma-Lok MM 115
NEV-Sz NI LAB NGBT8 8 oz BT/C
NEver Seez nickel Grace
Nitrogen (13,632,331 POUNDS)
Norton Alundum Mortar MA – 176
Permabond 170, 903, 910, 910FS
Phillybond TA-30 Resin (28 POUNDS)
Plastiment Liquid
Potassium Perchlorate
Propane
Ransom and Randolph Grip Cement Liquid
Remgrit TFL 50 Wet lubricant aerosol & dry lubricant
Shell Epi-Cure: Curing Agent 9470 (25 POUNDS) & W (17 POUNDS)
Shell Epon Resin 9405 (47 POUNDS)
Struers Diamond Cut-Off wheel, Metalbonded
Ted Pella Graphite Aerosol
Texwipe Okne Step (canister)
Thornel ACS/ERL 1930-3 Pan Prepreg (25 POUNDS)
Toray Torayca Carbon Fiber Sizing Type 5 (264 POUNDS)
Voltaix Flammable Germane Mixtures: .34-12.3% I
WD-40 Bulk Liquid (40 POUNDS)
YLA RS-14 Resin (469 POUNDS)
Appendix G - NEUROTOXICITY OF EPOXY COMPOUNDS
Prepared by Mohamed Abou-Donia, Ph.D., June 2007

I. Literature search for neurotoxicity of epoxy compounds - Findings:

A. Structural basis in comparison with other known neurotoxins

Glycidamide

Glycidamide (2,3-epoxy-1-propaneamide) produced neurotoxicity in male, Sprague-Dawley rats following intraperitoneal (i.p.) injection of a daily dose of 50 mg (0.7 mmole)/kg/day (Abou-Donia, et.al, 1993). The animals became hyperactive, showed circling and hind-leg weakness and ataxia by day 5. These animals lost control of hindlegs and became jittery by day 7. The clinical condition of glycidamide-treated rats progressed to severe ataxia and paralysis by day 11. The animals were terminated after receiving 13 daily doses, when they became severely paralyzed and weighed 86% of their initial weight compared to 145% for controls. Neurotoxicity induced by peritoneal administration of glycidamide is characterized by symmetrical axonal swelling in distal axons of the peripheral and central nervous systems. The report also indicated that subcutaneous injection (s.c.) of an equimolar daily subcutaneous dose of glycidamide did not cause clinical signs or neuropathological alterations characteristic of neurotoxicity. These results may be attributed to increased bioavailability following i.p. injection, compared to s.c. route of administration. Glycidamide contains a very reactive epoxy group that interacts with proteins, leading to its storage in tissues and decreasing its concentration in circulation and its delivery to the nervous tissues. On the other hand, i.p injected glycidamide is rapidly absorbed and delivered to nervous tissues, resulting in the development of neurological deficits. By inference, it is expected that exposure to glycidamide via inhalation to be very effective in causing neurotoxicity compared to dermal or oral exposure.

Severe lesions were seen in the central nervous system (CNS) compared to the peripheral nervous system (PNS). Glycidamide-induced peripheral nervous alterations in the sciatic, peroneal, and tibial nerves and their branches were mild, even in animals with severe neurological deficits. In these nerves, occasional fragmented axon and myelin formation were seen.

Glycidamide-induced ataxic tremor and circular head movement indicate central nervous system involvement in its neurotoxicity. Also, glycidamide-induced unusual tail posture and early hind limb splay suggest sensory axonal lesion. By analogy, sensory damage in humans is characterized by posturing of the arms and broad-based gait known as “splay” of the legs (Colonnier and Guillery, 1964; Hedley-Whyte et al., 1968). Neuropathological lesions were present in brainstem, cerebellum, and spinal cord. Glycidamide produced swollen degenerated axons in the cervical, thoracic, and lumbar spinal cord. These lesions were characterized by the presence of spongiform changes with vacuoles in the white matter. Such alterations were seen in the spinocerebellar tracts in the cervical spinal cord.

In the cerebellum, Purkinje cells were severely affected and exhibited “fusiform” swellings characterized by reduced length of the cell axon that ended in the granular cell layer with a terminal swelling known as a “torpedoes”. Brainstem exhibited disrupted myelin sheath, swollen giant axons, and ischemic neurons. Damage of the
cerebellum Purkinje cells explains ataxia induced by glycidamide. The cerebellum coordinates muscle action and functions to maintain body balance (Barr and Kiernan, 1988). Thus, lesion of the cerebellar Purkinje cells causes disruption of motor function leading to development of ataxia.

Another study reported that while daily injection of 50 mg/kg glycidamide at accumulative dose of 400 mg/kg did not impair the performance of male Sprague-Dawley rats on the rotarod, a cumulative dose of 800 mg/kg caused significant effect (Costa et al., 1992). The results suggest that neurological deficits reported in this study have resulted from an effect on the central nervous system, since treated animals did not exhibit peripheral nerve lesions. It also suggest that dose level, route of exposure, frequency and duration of exposure, pharmacokinetics and metabolism of glycidamide play a major role in its neurotoxicity. A recent study reported a sensitive and selective analytical method using electrospay tandem mass spectrometry (LC-ES/MS/MS) for the quantification of glycidamide in serum for use in toxicokinetic studies (Twaddle et al, 2004). Intraperitoneal administration of glycidamide caused neurobehavioral deficits in rats (Deng et al., 1997). In vitro, glycidamide caused degeneration of established neuritis of a neuroblastoma cell line (Brat and Brimijoin, 1993).

Few studies have been carried out on the mechanisms of glycidamide-induced neurotoxicity. On the other hand, the pathognomonic feature of glycidamide neurotoxicity is similar to that induced by its parent compound, acrylamide. Acrylamide neuropathological lesions are characterized by the accumulation of 10-nm neurifilaments above the nodes of Ranvier (Spenser and Schaumburg, 1974). Glycidamide has a very reactive epoxide moiety that has been shown to form hemoglobin adducts (Calleman et al., 1990) and DNA adduct (da Costa et al., 2003; Doerge et al., 2005). Thus, the reactive epoxy group in glycidamide undergoes reaction with reactive hydrogen atom present in hydroxyl, sulfhydryl, or amino groups. Such reaction leads to covalent binding of glycidamide with lysine amino groups in neurofilaments, resulting in their cross-linking and accumulation in the distal axon (Abou-Donia et al., 1993). Consistent with this mechanism, is the demonstration in vitro (Lapadula et al., 1989) and in vivo (Carrington et al., 1991) of acrylamide binding to neurofilaments. On the other hand glycidamide may interfere with posttranslational modification processes such as kinase protein-mediated phosphorylation and proteolysis. Rats that developed glycidamide-induced neurotoxicity exhibited increased calcium/calmodulin-mediated kinase–dependent phosphorylation of rat brain neurofilaments (Reagan et al., 1995). Hyperphosphorylation of neurofilaments protects them form proteolysis (Goldstein et al, 1987), inhibits their assembly (Hisanga et al., 1988) and decreases their axonal transport rate (Lews and Nixon, 1988). Previous studies have shown that acrylamid causes decreased axonal transport of neurofilament proteins (Pleasure et al., 1969; Sickles, 1992). These reports suggest that acrylamide- and glycidamide-induced hyperphosphorylation of brain neurofilament proteins leads to the disassembly of the cytoskeleton, decrease of their axonal transport and accumulation of aggregated neurofilaments at distal axons.
STRUCTURAL NEUROTOXICITY RELATIONSHIP FOR VINYL AND THEIR EPOXY COMPOUNDS

Purpose of the study:

This study was carried out to investigate the structure-neurotoxicity relationship for vinyl compound (e.g., acrylamide) and some of their epoxy analogs (e.g., glycidamide). It was hypothesized that such chemicals are able to bind to neurotoxicity target proteins through their reactive double bond of epoxy group, respectively. Propionamide, a compound that does not have either double bond or epoxy group, was used as negative control. All test compounds were dissolved in water and administered via intraperitoneal (i.p) injection to young (approximately two month old), male adult Sprague-Dawley rats. Vehicle control animals were injected with water. Animals were treated daily till they developed ataxia and/or paralysis, but no longer than 90 days.

1. **Acrylamide**

   ![Chemical structure](H2C=CH-C-NH2)

   Chemical formula: H2C=CH-C-NH2

   Chemical name: 2-propenamide

   Treatment

   A daily intraperitoneal injection of 50 mg/kg acrylamide in water (1ml/kg) was administered to four male Sprague-Dawley rats for 12 days.

   Results:

   At the end of dosing, all treated animals became paralyzed. The animals exhibited 5% weight gain compared to 51% weight gain for control.

2. **Glycidamide**

   ![Chemical structure](H2C-C-C-NH2)

   Chemical formula: H2C-C-C-NH2

   Chemical name: 2,3-epoxy-1-propanamide

   Treatment

   A daily intraperitoneal injection of 50 mg/kg glycidamide in water (1ml/kg) was administered to five male Sprague-Dawley rats for 12 days.

   Results:

   At the end of dosing, four treated animals became paralyzed, and one was ataxic. The animals exhibited 20% weight loss compared to 51% weight gain for control.
3. Glycidol

Chemical structure: \( \text{H}_2\text{C}-\text{C}^{-}\text{CH}_2\text{OH} \)

Chemical nomenclature: 2,3-epoxy-1-propanol

Treatment
A daily intraperitoneal injection of 50 mg/kg glycidol in water (1ml/kg) was administered to three male Sprague-Dawley rats for 35 days.

Results:
At the end of dosing, two treated animals became paralyzed, and one was severely ataxic. The animals exhibited 40% weight gain compared to 51% weight gain for control.

4. Methacrylamide

Chemical Structure: \( \text{H}_2\text{C}=\text{CH}^{-}\text{C}^{-}\text{NHCH}_3 \)

Treatment
A daily intraperitoneal injection of 100 mg/kg methacrylamide in water (1ml/kg) was administered to three male Sprague-Dawley rats for 90 days.

Results:
At the end of dosing, one treated animal became paralyzed, another severely ataxic, and the third was ataxic. The animals exhibited 30% weight gain compared to 51% weight gain for control.

5. Propionamide

Chemical Structure: \( \text{H}_3\text{C}-\text{CH}^{-}\text{C}^{-}\text{NH}_2 \)

Chemical nomenclature: Propionamide

Treatment
A daily intraperitoneal injection of 100 mg/kg propionamide was administered to four male Sprague-Dawley rats for 90 days.

Results:
At the end of dosing, all treated animals were normal. The animals exhibited 165% weight gain compared to 51% weight gain for control.
6. Control

Treatment
Three rats were given a daily ip dose of waste for 90 days.

Results
All animals remained normal. The animals exhibited 51% weight gain at 90 days.

Conclusions

The results indicate that vinyl compound and their related epoxy chemicals are capable of causing neurotoxicity to rats following daily i.p injections. The result that propionamide did not produce neurotoxicity following daily ip injections to rats, indicates that either the double bond or its oxidation moiety, the epoxy group is essential for these chemicals to cause neurotoxicity.
B. Literature Search for Neurotoxicity of Epoxy Compounds - Findings:
(Findings and Lack of Findings are listed in italics below)

**EPOXY RESINS**

Diglycidyl ether of bisphenol A (DEGBA) CAS 1675-54-3, 25068-38-6, 25085-99-8
(Literature search found no data on its neurotoxicity)

Brominated DGEBA CAS # 71033-08-4
(made from tetrabromobisphenol A epichlorohydrin + brominated biphenol A)
(Literature search found no data on its neurotoxicity)

Epoxy Novolac (~ Phenolic, Cresolic, and Trisphenolic)

Glycidilated-o-cresol novolak resins CAS 37382-79-9
(Literature search found no data on its neurotoxicity)

Epoxy phenol-Novolak Resins CAS 9003-36-5
(Literature search found no data on its neurotoxicity)

Epoxy Novolak (Triphenolic) CAS 6602-38-6
(Literature search found no data on its neurotoxicity)

Tetraglycidyl ether of tetraphenolethane CAS 7328-97-4
(prepared from: Polyphenol 1 :1, 2 :2-(p-hydroxyphenol)ethane)
(Literature search found no data on its neurotoxicity)

Biphenol F-based resins (DGEBF) CAS 87139-40-0
(2,2’-methylene bisphenol, CAS 2467-02-9) (from formaldehyde + phenol)
(Literature search found no data on its neurotoxicity)

Diglycidyl ether of resorcinol CAS 101-90-6
(Bis (2,3-epoxycyclopentyl)ether (BECPE) 2386-90-5)
(Literature search found no data on its neurotoxicity)

**AROMATIC AND HETEROCYCLIC GLYCIDYL AMINE RESINS: THOSE COMMERCIAL SIGNIFICANT**

Cycloaliphatic and heterocyclic epoxy  
(FILAMENT WINDING FLEXIBLE:)
(Literature search found no data on its neurotoxicity)

Glycidyl amine epoxy  
(AEROSPACE COMPOSITS)
(Literature search found no data on its neurotoxicity)

Glycidyl ethers of aliphatic polyols  
(Literature search found no data on its neurotoxicity)

Tetraglycidylmethylenedianiline-Derived resins  
(Literature search found no data on its neurotoxicity)

(N,N,N,N’-Tetraglycidyl-4,4’-diaminodiphenylmethane CAS 28768-32-3)
(Literature search found no data on its neurotoxicity)

Triglycidyl p-aminophenol-Derived Resins  
(EXPLOSIVES, PROPELLANTS,
Triglycidyl p-aminophenol CAS 5026-74-7) MILITARY PLARES,
PYROTECHNICS
(Literature search found no data on its neurotoxicity)

Triazine-Based Resins  
(WEATHERABLE COATINGS, ELECTRONICS
Triazine isocyanurate CAS 2451-62-9) OPTICAL TRANSPARENCY
(Literature search found no data on its neurotoxicity)
WATERBORNE EPOXY RESINS: FOR NEW CONCRETE & METAL

Biphenol A or Novolac Resin emulsified w/:
Titanium Dioxide – surfactant (50% by volume)
(Please note: literature search found no data on its neurotoxicity)
Polyamide or polyamidoamine – Hardener (16% by volume)
(Please note: literature search found no data on its neurotoxicity)

EPOXY ACRYLATE RESINS

Vinyl ester resin—esterify epoxy resin via terminal group w/an unsaturated acid such as methacrylate acid derived from epoxy resin

Aromatic difunctional epoxy acrylates
(Please note: literature search found no data on its neurotoxicity)
Acrylated oil epoxy acrylates
(Please note: literature search found no data on its neurotoxicity)
Epoxy novolac acrylates
(Please note: literature search found no data on its neurotoxicity)
Aliphatic epoxy acrylates
(Please note: literature search found no data on its neurotoxicity)
Miscellaneous epoxy acrylates – used IN PIGMENTED COATINGS
oligomers w/fatty acid modification

EPOXY CURING AGENTS AND CATALYSTS (widely varying 5-20%,~ 10% typical)
COMMON POLYAMINES FOR CURING EPOXY RESINS:
(Please note: literature search found no data on its neurotoxicity)
Triethylenetetramine, (TETA)
Diethylenetriamine (DETA)
Poly(oxypropylene triamine)
Poly(glycol amine)
Isophorone Diamine (IPD) – sluggish cure rate, light color, chem. resist
1,2'-diaminocyclohexane (DAC)
n-aminohexylpiperazaine (AEP)
4,4'-diaminodiphenyl methane (MDA)
4,4'-diaminodiphenyl sulfone (DDS)
m-phenylenediamine

LESS COMMON
(Please note: literature search found no data on its neurotoxicity)
Triethylamine
diethylenetetramine
Triethylenepentamine
Tetraethylenepentamine
trimethylhexamethyldiamine
Triethylenetetramine phenol adduct
Cycloaliphatic polyamines
COMMONLY USED TERTIARY AMINE ACCELERATORS
aliphatic amines blush so these help avoid absorbing moisture, etc.
(Literature search found no data on its neurotoxicity)

Phenol
DMP 30 = o-(dimethylaminomethyl) phenol
Tris-(dimethylaminomethyl) phenol
DMP-10 = tris-(dimethylaminomethyl) phenol

Diethylaminopropylamine: (DEAPA) for curing epoxy adhesives where
low heat are required

Aminoethylpiperazone (AEP) used when toughness required

MODIFIED ALIPHATIC AMINES
(Literature search found no data on its neurotoxicity)
glycidyl adducts of aliphatic amines
N-Hydroxyethylethyleneetriamine
N,N'-Bis(hydroxyethyl)diethyleneetriamine
N-(2-Hydroxypropyl)ethylene diamine
N,N,N',N'-tetrahydroxypropylethylene diamine

POLYAMIDES – WIDELY USED in COATINGS & ADHESIVES
(Literature search found no data on its neurotoxicity)
Amidodiamines, adheres to POROUS CONCRETE, WOOD & Humidity

AROMATIC AMINES AND MODIFIED
(Literature search found no data on its neurotoxicity)
Metaphenylene diamine (MPDA) most common aromatic curing agents
Methylene Dianiline
Aromatic amine eutectics
Solvent solutions
Diaminodiphenylsulfone – best strength for elevated temperature exposure

ANHYDRIDES - casting compounds, encapsulates, molding compounds
MOST COMMON:
(Literature search found no data on its neurotoxicity)
Hexahydrophthalic anhydride (HHPA)
Phthalic Anhydride (PA)
Nadic Methyl Anhydride (NMA)
Pyromellitic Dianhydride (PMDA)
Dodecyl succinic anhydrides
Catalytic and latent hardeners – do not participate in the reaction homopolymerization of the resin

MOST POPULAR:
(Literature search found no data on its neurotoxicity)
Tertiary amines – a type of LEWIS ACID catalyst most widely used:
  
  DMP-10 = tris-(dimethylaminomethyl) phenol
  DMP-30 = o-(dimethylaminomethyl) phenol
  Benzylidimethylamine (BDMA)– mostly used as either sole catalyst or accelerator w/ anhydride and dicyanodiamide cured epoxy resins

Tertiary amine salts – good adhesion to metal
Boron trifluoride complexes – broad commercial use
Imidazoles – for metal, chem., temp resistance and lower exotherm than: dicyandiamide (dicy)
Polysulfides and mercaptans – low exotherm... e.g. Capcure

DILUENTS – higher molecular wt. than solvents, used to lower viscosity primarily and to modify processing conditions (varying~5-10% typical)

MONOFUNCTIONAL EPOXY REACTIVE DILUENTS
Butyl glycidyl ether CAS 2426-08-6
Phenyl Glycidyl ether CAS 12260-1
Diglycidyl ether CAS 30583-72-3
2-Ethylhexyl glycidyl ether
C8-10- Aliphatic monoglycidyl ether
C12-14- Aliphatic monoglycidyl ether
Cresyl glycidyl ether
Neopentyl glycol diglycidyl ether
Butanediol diglycidyl ether
(1,4-Butanediol diglycidyl ether CAS 2425-79-8)

DIFUNCTIONAL EPOXY DILUENTS
(Literature search found no data on its neurotoxicity)
Butadiene Dioxide
Vinyl cyclohexene dioxide
Diglycidyl ether of resorcinol CAS 101-90-6

OTHER REACTIVE DILUENTS
Diglycidyl ether of diphenylole propane
Glycidaledehyde

Glycidol:
The stereoisomers L- and D-glycidols were for their ability to cause neurotoxicity in male Sprague-Dawley rats (Abou-Donia, unpublished results). Daily intraperitoneal injection of each of the glycidol isomers, produced ataxia in treated rats, with the L-isomer being more neurotoxic than the D-isomer. These results suggest that glycidol isomers react stereo-specifically with target protein producing neurotoxicity.
Isooctyl glycidyl ether
1,2-epoxydodecane
Monoglycidyl ester of a synthetic fatty acid
Monoglycidyl ether of isomeric alcohols
Diglycidyl ether of butanediol
Diglycidyl ether of neopentylglycol

NON-EPOXY reactive diluents:
Triphenyl phosphate (react w/hydroxyl group in the resin)
Gamma-butyrolactone
Dibutyl Phthalate
Polymethyl acetal

SOLVENTS – sometimes used: higher concentrations in formulations for paint spraying but %s widely varying; purpose to lower viscosity of epoxy system to aid mixing, dispersing, wetting in formulation, to lower viscosity for easier mixing at application stage, or to liquefy solid resins and hardeners to apply as a film. They must be completely evaporated from the bond line prior to cure. (true solvents or those for which there chance of resin precipitation include: MEK, diacetone alcohol, methylcyclohexanone, glycol ethers and acetates) (Typical % mixture for others ~ 40%)

KETONES
Although ketone solvents on this list have not been shown to be neurotoxic, they are potent inducers of cytochrome P-450 mixed functions oxidase (MFO). This leads to interactions with other chemicals or medications, changing their action and could lead to neurotoxicity.

Acetone
MEK
Methyl Isobutyl Ketone
Diacetone alcohol
Isophorone

ESTERS
(Literature search found no data on its neurotoxicity)
Ethyl acetate
n-butyl acetate
cellosolve acetate

ETHER ALCOHOLS
(Literature search found no data on its neurotoxicity)
Methyl cellosolve
Ethyl cellosolve
Butyl cellosolve
Ethyl carbitol
Butyl “
CHLORINATED SOLVENTS:
These solvents are potent inducers of cytochrome P-450 mixed functions oxidase (MFO). This leads to interactions with other chemicals or medications, changing their action and could lead to neurotoxicity.

Trichloropropane
Chloroform

MIXED SOLVENTS

TOLUENE W/:
Toluene has been shown to produce neurobehavioral alterations following occupational exposure.
acetone
MEK
MIK
Diacetone alcohol
Isophorone
Isopropyl Alcohol
Cellosolve Acetate

TYPICAL w/DGEBA: Xylene, MIK, Cellosolve, Cyclohexanol

SUBSTITUTES: Citra-Safe, EP 921
Teksol EP, X-Caliber
Iso Prep
Safety Prep

Trend to water borne epoxies... rather than replace the solvents

MISCELANEOUS

Photoinitiator:
(4-Octylphenyl) pheyliodonium hexafluoroantimonate (OPPI) [or other aryl substituents] identified in e-beam curing at OR-LMES
II. Basis For Concern About Neurotoxicity In Epoxy Compounds

Epoxy compounds are defined as those containing one or more “oxirane” rings. Reaction of epichlorohydrin (C₃H₅OCl) with a diglycidyl ether (C₆H₁₀O₃) of bisphenol A type, that is formed from acetone and phenol, and a hardeners/curing agents (normally amines) yields epoxy resins. Epichlorohydrin is formed by the reaction of propylene and chlorine.

Residual epichlorohydrin level of less than 1 ppm (1 mg/kg) is present in almost all bisphenol A-based epoxy resins. Although the Threshold Limit Value/Permissible Exposure Limit-Time Weighted Average (TLV/PEL-TWA) epichlorohydrin is listed as 2 ppm (Dennis, 1992), exposure to it should be avoided because animal studies have shown that it as a probable human carcinogen (Group 2A; IARC, 1987). Epoxy resins have been reported to have low toxicity and cause slight to moderate skin irritation and skin sensitivity. Skin application of neopentylglycol diglycidyl ether to mice produced skin tumors (EPA, 1983). Long-term dermal exposure to epoxy resins with 340 molecular weight oligomer, is allergic dermal or respiratory sensitization (Fregert 1987).

This account of the neurotoxic effect of epoxy resins excludes the action of solvents. On the other hand, solvents especially ketone solvents such as acetone, methyl ethyl ketone and methyl n-butyl ketone would affect the action of epoxy resins. Ketone solvents are potent inducers of cytochrome P-450 mixed oxidase system. Thus, combined exposure to these chemicals results in increased toxicity of the epoxy resins.

III. Conclusions:

Although a thorough literature search was carried out to evaluate the neurotoxic effects of epoxy resins, no studies were found. Only glycidamide was reported to cause central-peripheral distal axonopathy. Also, we report unpublished results indicating the neurotoxicity of L-glycidol. Despite the paucity of reports on the neurotoxicity of epoxy compounds, these compounds are highly likely to be neurotoxic because of the presence of the very reactive “oxirane” ring that is capable of reacting with reactive hydrogen atoms present in hydroxyl, sulfhydryl, or amino groups in neuronal tissue proteins. Furthermore, combined exposure to epoxy resins and ketone solvents that are capable of inducing cytochrome P-450 activity, leads to their activation to more potent neurotoxic compounds.
Glycidamide References

4. Carrington, CD; Lapadula, DM; Dulak, L; Friedman, MA; Abou-Donia, MB: In vivo binding of $[^{14}C]$acrylamide to proteins in the mpuse nervous system; Neurochem. Int. 18:191-197; 1991.
9. Lapadula, DM; Bowe, M; Carrington, CD; Dulak, L; Friedman, MA; Abou-Donia, MB. In vitro binding of $[^{14}C]$acrylamide to neurofilament and microtubule proteins of rats. Brain. Res. 481:159-161; 1989.
15. Twaddle, NC; McDaniel, LP; da Costa, GG; Churchwell, MI; Beland, FA; Doerge, DR: Determination of acrylamide and glycidamide serum toxicokinetics in B6C3F1 mice using LC-ES/MS/MS; Cancer Lett. 207:9-17; 2004.


18. Doerge, DR; da Costa, GG; McDaniel, LP; Churchwell, MI; Twaddle, NC; Beland, FA: DNA adducts derived from administration of acrylamide and glycidamide to mice and rats; Mutat. Res. 580:131-141; 2005.

19. da Costa, GG; Churchwell, MI; Hamilton, LP; Von Tungein, LS; Beland, FA; Marques, MM; Doerge, DR: DNA adducts formation from acrylamide via conversion to glycidamide in adult and neonatal mice; Chem. Res.Toxicol 16: 1328-1337; 2003.
References

1. Lockey, MD, MS, James E; Bird, Jr., MD, MPH, Richard C; Freeman, MD, MS, Andrew G; Summary Report Of Findings; Oak Ridge, Tennessee, K-25 Worker Evaluations; July 31, 2000.


4. Ratner, Ph.D., Marsha; Boston University School of Medicine; Boston Medical Center, Occupational Neurology Program; Discussions

5. Abou-Donia, Ph.D., Mohammed B.; Duke University, Department of Pharmacology; Discussions

6. Petrie, Edward; Epoxy Adhesive Formulations, Mcgraw-Hill, 2006

7. Schiller, Julius; former Senior Engineer, Components Division, IBM and former Director of the Polymer Lab, Boca Raton, IBM; Discussions


9. Wooten, HD; Centrifuge Workers Study, PHASE II, Completion Report; September 1994; Prepared by Engineering Technology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee, ORNL – 6822

10. NIOSH; Organic Solvent Neurotoxicity, Current 48, March 31, 1987


12. Larsen MPH, Robert; Scheide MS, Ellen; Occupational Health Aspects Of Advanced Composite Manufacture And Use; Industrial Hygiene Services, 3m; (in: Conference on Occupational Health Aspects of Advanced Composite Technology in the Aerospace Industry, Editors: Raymond Kutzman, PhD. Lt. Col. Harvey J. Clewell, III, February 6-9 1989, Dayton, Ohio; Applied Industrial Hygiene, special issue, 12/89)


18. The Long and Short of Epoxy Resins, Shell Oil, Houston, Texas, 1992

19. Modern Plastics Encyclopedia, 1999 with buyers’ guide

20. Kantz, PhD FAIC, Melvin; Advanced Polymer Matrix Resins and Constituents: An Overview of Manufacturing, Composition, and Handling, Director of R & D Ferro corp. Composites Div; Applied Industrial Hygiene, pp 1-8; 12/89


22. Formisano, Jerry; Lt., MSC, USNR; Composite Fiber Field Study: Evaluation of Potential Personnel Exposures to Carbon Fibers during Investigation of a Military Aircraft Crash Site: Applied Industrial Hygiene, pp 54-56; 12/89.


78


30. Cross, Don L., MS; Engineering and Work Practice Controls for Working with Advanced Composites: Minimizing Workplace Exposures, Hexcel Corporation; Applied Industrial Hygiene; pp 50-51; 12/89.

31. J. Lindsey Chalk, MSPH, CIH; 4,4’-Methylenedianiline-Industrial Hygiene Experiences; McDonnel Aircraft Comp; Applied Industrial Hygiene; pp 60-63; 12/89

32. Faoro, Anthony; Composite Part Fabrication, Handling, and Machining: General Dynamics; Applied Industrial Hygiene; pp 9-13; 12/89


34. Larsen, MPH, Robert; Scheide, MS, Ellen; Occupational health Aspects of Advanced Composite Manufacture and Use: Industrial Hygiene Services, 3M; Applied Industrial Hygiene; pp 57-59; 12/89

35. 3M Technical Service Bulletin, Specialty Tapes and Adhesives; Regarding: Outgassing Information on Structural Adhesives; March 27, 1992

36. Hubbell, MS, Patricia; Hazard Communication and Composites, McDonnel Aircraft Comp., Applied Industrial Hygiene; pp 75-77; 12/89
37. Leibowitz, Alan, ITT Avionics, Material Safety Data Sheet Adequacy and Availability; Applied Industrial Hygiene; pp 73-74; 12/89

38. US Dept. of Health Education and Welfare, NIOSH, Current Intelligence Bulletin 47, 4,4’-Methylenedianiline (MDA) 10/12/78.


41. Confidential Worker Interviews and Information Provided.

42. Browning, E; Toxicity and metabolism of Industrial Solvents; Amsterdam, The Netherlands: Elsevier Publishing Comp. 1965.

43. Breysse, Peter, MS, MPH, CIH; Industrial Hygiene Problems Associated with Recognition and Assessment of Exposure to Composites; Univ. of Washington, Dept. of Environmental Health, School of Public Health and Community Medicine; Applied Industrial Hygiene; pp 80-84; 12/89

44. Daniell W.; Stebbins A, O’donnell J; Horstman, SW; Rosenstock L; Neuropsychological performance and solvent exposure among car body repair shop workers; British Journal of Indian Medicine, April 1993, 50 (4): 368-377.