



PolyOne Corporation
33587 Walker Road
Avon Lake, OH 44012
www.polyone.com

RECEIVED
OPPT CBIC
06 NOV 17 AM 10:44

November 13, 2006

Document Control Office (7407M)
Attention: TSCA Section 8(e) Coordinator
EPA East Building, Room 6428
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitutional Avenue, N.W.
Washington, DC 20460-0001
Phone: 202-564-8940

CONTAIN NO CBI



RE: TSCA 8(e) submission of a report of New Health Effects of Vinyl Chloride

Dear Sir or Madame:

PolyOne Corporation is submitting information in regards to previously unknown and previously unpublished research on vinyl chloride (CAS # 75-01-4) from the University of Louisville (U of L) pursuant to Section 8(e) of the Toxic Substance Control Act (TSCA).

The objectives of this submission are: 1) to confirm receipt of a Section 8(e) notification from Mr. Al Brightwell of Noveon, Inc. on October 12, 2006 on the same subject, 2) to quantify the study participants, and 3) to update certain information contained in that submission from Noveon.

Like the 8 (e) submission from Noveon, this submission is in regards to work by U of L investigators who have re-evaluated liver biopsy slides originally obtained in the 1970's from certain vinyl chloride workers employed at a BFGoodrich facility in Louisville, Kentucky. It would appear that most if not all of these workers had elevated workplace exposure to vinyl chloride substantially in excess of today's one part per million standard.

The U of L indicated to PolyOne that it has recently re-examined 20 to 30, of approximately 100 such slides. This corrects information previously supplied by Noveon indicating 100 liver biopsy slides had already been re-examined. The U of L



300199

investigators believe, as indicated in the study abstract, that in approximately 70% of those re-examined slides, the investigators have detected signs that the person may have suffered from non-alcoholic steatohepatitis (NASH).

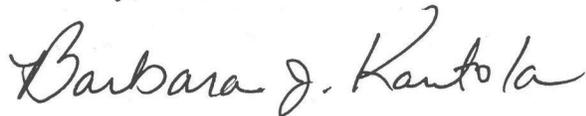
The principal investigator, Dr. Mathew Cave, or his colleague, Dr. Craig McClain, can be reached at 502-852-6181. A copy of the research grant proposal providing some details of the study is attached.

While the full significance of this preliminary report is not known, PolyOne corporation is submitting this information because it may be information that the EPA considers reportable under TSCA 8(e). A copy of the report will be provided if and when it is made available to PolyOne Corporation.

This submission does not contain any confidential business information.

If you have any questions, feel free to contact me directly by telephone at 440-930-1395 or by email at barbara.kantola@polyone.com.

Sincerely,

A handwritten signature in black ink that reads "Barbara J. Kantola". The signature is written in a cursive, flowing style.

Barbara J. Kantola
Corporate Manager, Product Stewardship and Regulatory Compliance
PolyOne Corporation

cc: John Gressler, Woody Ban

Attachments (1)

CAVE-FellowFacultyTransitionAward 2006-21

2007 AGA Fellowship/Faculty Transition Awards
Principal Investigator: Cave, Matthew

3. Scientific Abstract/Summary: In the space below, briefly describe the research project, technical approach and anticipated results. Describe how this award will advance your research career. (Do not use tab returns to create indentation or exceed the space provided below.)

Project: Obesity and the metabolic syndrome are rapidly increasing health problems, and non-alcoholic fatty liver disease (NAFLD) is the hepatic component of the metabolic syndrome and a frequent complication of obesity. Non-alcoholic steatohepatitis (NASH), a more serious form of NAFLD, is thought to occur through a two "hit" mechanism. This includes a baseline of steatosis, with multiple postulated second hits including oxidative stress, mitochondrial dysfunction, and cytokine dysregulation. Recently, industrial pollutants have been postulated to play a role in NASH, possibly even without the underlying, predisposing factor of obesity. We propose to utilize a large industrial database and specimen bank to determine the prevalence of NASH in workers chronically exposed to high amounts of vinyl chloride (VC) and to determine potential reversibility of this NASH following removal from the workplace. Next, in a rodent model, we will determine whether high carbohydrate feeding with subsequent hepatic steatosis sensitizes the liver to toxicity from the ubiquitous industrial pollutant acrolein with subsequent hepatic inflammation, injury, and NASH.

Technical Approach: We will use a unique specimen bank and database to evaluate whether high dose industrial exposure to VC leads to NASH and whether removal from the industrial exposure attenuates biomarkers for NASH. Liver biopsies will be graded by standard scoring system and markers of oxidative stress, liver fibrosis, cytokines and apoptosis will be determined. In the second aim, we will determine whether mice fed a high carbohydrate diet with subsequent mild steatosis are sensitized to hepatotoxicity from low-dose exposure of the industrial pollutant, acrolein. Acrolein adducts, liver histology and triglycerides, glutathione depletion, cytokines and adipokines, mitochondrial function, and markers of oxidative stress will be assayed to evaluate mechanisms for this industrial exposure-induced NASH.

Expected Results: We predict that there will be a high prevalence of NASH in subjects with high VC exposure and that markers of NASH will improve with removal from the workplace. Similarly, we predict that a high carbohydrate diet will sensitize to acrolein-induced NASH, and we postulate factors such as acrolein adduct formation and oxidative stress will play an etiologic role.

Career Development: This experience will provide me with the mentoring, industrial toxicology education, experience in trial design and statistics, laboratory skills, and preliminary data necessary to submit a K-type award to the NIH. During this period, I will begin a multidisciplinary Masters degree in Pharmacology and Toxicology, focusing on industrial pollutants and their hepatic effects.

CAVE-FellowFacultyTransitionAward 2006-21

4. Percent Effort: Please indicate below your current percent effort and projected percent effort should you receive this grant.

Current Percent Effort Projected Percent Effort Under Grant

30 Research 80
0 Administration 0
70 Clinical Activities 20
0 Teaching 0
100% Total 100%

3

†

2007 AGA Fellowship/Faculty Transition Awards

Principal Investigator: Cave, Matthew

10. Research Plan: Title: Environmental Toxins and Non-alcoholic Fatty Liver Disease

Specific Aims: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States (1). It is most often a disease of over-nutrition and is closely linked to the epidemic of obesity and the metabolic syndrome (1). Non-alcoholic steatohepatitis (NASH), a more serious form of NAFLD, can proceed to cirrhosis and even hepatocellular carcinoma (1). NASH is thought to occur through a "two hit" mechanism, with the first insult being over-nutrition with obesity and insulin resistance resulting in hepatic fat accumulation(2). A variety of "second hits" including oxidative stress, cytokine dysregulation and others have been proposed(2, 3). However, it is currently unknown why only some patients with simple steatosis progress to more advanced disease.

NASH also has been described in petrochemical workers in the absence of obesity (4). Similarly, our preliminary data demonstrate NASH with advanced fibrosis in a group of plant workers with high exposure to vinyl chloride (VC). These workers underwent liver biopsies in the mid 1970's as part of a large, unique screening project for hepatic angiosarcoma. Although high level occupational exposures appear to be sufficient to induce NASH in chemical workers, the hepatic effects of chronic low level exposure to environmental pollutants and the potential interaction between pollutants and nutrition have not been adequately evaluated.

Acrolein is a highly reactive aldehyde and a relevant environmental pollutant (5). It is a product of incomplete hydrocarbon combustion and is present in automobile exhaust and cigarette smoke, as well as in food and water (5). Our preliminary data show that mice treated with acrolein develop alterations in lipid and glucose metabolism associated with increased liver weights and hepatic fat accumulation. Furthermore, our preliminary data demonstrate that diet induced obesity can affect the liver's ability to safely metabolize xenobiotic compounds. Based on these and other novel initial observations by our group, we postulate that diet induced obesity and

hepatic steatosis will sensitize the liver to acrolein toxicity resulting in the development and accelerated progression of NASH.

Our central hypothesis is that (i) high level occupational chemical exposures are sufficient to produce NASH with advanced fibrosis in the absence of other risk factors, and (ii) chronic low level pollutant exposure on the background of diet induced simple steatosis is a novel "second hit" in the development and progression of NASH. These findings are relevant to all workers with chemical exposures, and the millions of overweight Americans exposed to urban pollutants. This hypothesis has not been tested, and is the objective of this grant.

The specific aims of this project are:

1) To evaluate for the presence / absence of NASH and to grade and to stage NASH in liver biopsies from

over 100 vinyl chloride workers with high industrial exposures who were later removed from the workplace

and followed clinically. Initially, the prevalence of NASH in this group will be determined. Next, using serial

serologic markers, as well as limited follow up biopsies, we will evaluate the potential reversibility of this

disease following removal from the workplace.

2) To examine in a rodent model how hepatic steatosis, induced by high carbohydrate feeding, sensitizes the

liver to acrolein toxicity resulting in increased liver injury and NASH. In this aim, examination of key

endpoints involving steatosis, inflammation, injury, fibrosis, and cell death will document the critical

pollutant-nutrient interaction in the genesis of some forms of NASH.

Background and Clinical Significance: More than 25% of Americans have non-alcoholic fatty liver disease (or

NAFLD) which is believed to be the hepatic manifestation of the metabolic syndrome(1). NAFLD represents a

spectrum of liver disease ranging from simple fat accumulation (steatosis), to inflammation and fibrosis (nonalcoholic steatohepatitis or NASH), to cirrhosis and even hepatocellular carcinoma(1). A "two hit" model has been proposed to explain why only some patients develop progressive liver disease (2, 3).

Hepatic steatosis develops as a result of the "first hit", largely regarded as over-nutrition with obesity and insulin resistance being the key

factors (2, 3). There are a variety of "second hits" that appear to mediate the transformation of simple steatosis

into NASH. These include: oxidative stress, cytokine and adipokine dysregulation, mitochondrial dysfunction, endoplasmic reticulum stress, and impaired hepatic trans-methylation (2, 3). It is unknown why these "second

hits" do not occur in all NAFLD patients, but differential pollutant exposure may play a key role.

Nutrient and pollutant interactions are relevant in the genesis of NASH, but are

under-studied (3). In NAFLD, high carbohydrate diets are associated with greater inflammation (6), and low carbohydrate diets may dramatically reduce intra-hepatic triglyceride content (7). Furthermore, NASH has been reported in petrochemical workers with high level chemical exposures even in the apparent absence of metabolic risk factors (4). Our group has found that rodents fed high carbohydrate diets develop hepatic steatosis and may have impaired ability to

21

♀
2007 AGA Fellowship/Faculty Transition Awards

Principal Investigator: Cave, Matthew

metabolize pollutants. Specifically, many glutathione-S-transferases (GST's), key enzymes involved in the hepatic conjugation of xenobiotic metabolites are down regulated (Table 1). The proposed study will provide supportive and mechanistic evidence for occupational NAFLD, and demonstrate that even low level chemical exposure may produce NASH on a background of hepatic steatosis due to a high carbohydrate diet.

Acrolein and VC monomer have been selected as relevant occupational and environmental pollutants which we believe have a role in the genesis of NASH (5, 8). High level occupational exposure still remains a significant problem, particularly in underdeveloped countries (8). In developed countries, VC monomer remains an important environmental contaminant which is present in air and water near petrochemical plants and landfills (8). Acrolein is a pollutant structurally related to 4-hydroxynonenal, an endogenous aldehyde associated with oxidative stress in NASH (9). Acrolein is present in fried foods and contaminated water, and it is estimated that the average human consumption is 1 to 2 mg / day (5). Inhalational exposure occurs most commonly with automobile exhaust and cigarette smoke (5). We have preliminary murine data for mice with both acute and chronic acrolein exposures. Acutely, C57B1/6 mice gavaged with a single 5 mg/kg dose of acrolein develop increased serum total cholesterol, triglycerides, and liver to body weight ratio at 24 hours (Table 2). Chronically, C57B1/6 ApoE-/- mice gavaged daily with acrolein (0.05 - 0.5 mg/kg) for 12 weeks develop, in a dose response fashion, increasing liver weights with hepatic fat accumulation along with increasing serum insulin and triglycerides (Table 3).

At the U of L, we have a unique experience in VC induced occupational liver disease. In 1942, a BF Goodrich chemical manufacturing plant began operations locally and produces VC monomer, PVC, and synthetic rubber. Until the adoption of OSHA regulations in 1976, chemical operators at this plant had significant exposure to approximately twenty chemicals. However, VC monomer exposures were often extraordinarily high. In the 1974, following the recognition of hepatic angiosarcoma in several workers, a liver cancer screening program was instituted by the plant in collaboration with our institution (10, 11). A quantitative method was developed to

determine cumulative chemical exposure for each employee. More than 100 chemical operators with exceptionally high VC exposure were identified and permanently removed from the workplace (high risk group). However, all 1183 employees were screened including office workers with minimal chemical exposure (low risk/control group). Upon entering the screening program (baseline) and yearly thereafter to the present, all employees receive clinical examinations and laboratory testing. Additional serum and urine specimens are collected at each visit, frozen, and archived. At each time-point, the following relevant data are collected: medical history, alcohol and tobacco use, BMI, AST, ALT, bilirubin, alkaline phosphatase, protein, albumin, cholesterol and glucose. All workers in the high risk group underwent liver biopsy at baseline, and some follow up biopsies were performed after they left the workplace. All these data, along with cell blocks and some frozen liver specimens, are available for retrospective analysis.

Recently, we have over-read the first 10 high risk group baseline liver biopsies with an expert liver pathologist at our institution, Makunda Ray, MD, Ph.D. Steatohepatitis with advanced fibrosis was observed in 7 out of 10 workers (figures I & II). VC exposure was the only risk factor for NASH in these employees, as all were non-drinkers with BMI's under 25. Since NASH was not described until six years after the initiation of the screening program, NASH was never reported in these VC workers.

Preliminary Results: Our preliminary results show previously unrecognized NASH in original 1973 biopsies from VC workers (Figures I,II), and steatosis on EM in a VC exposed rat (Figure III). Microarray data (table 1) show deleterious effects of a high carbohydrate diet on xenobiotic metabolizing enzymes, and tables 2 and 3 show acute and chronic effects of acrolein on lipids and liver weights. These preliminary data strongly support our work proposed.

22

Figure I.
H&E stain of
VC worker
showing
NASH
cirrhosis with
steatosis (1),
inflammatory
infiltrate and
fibrosis (2).
Figure II. H&E stain
of a second VC
worker with NASH
and steatosis (1),
inflammatory
infiltrate (2),
mallory's hyaline
(3), and hepatocyte
ballooning (4).

♀

Figure III. Electron microscopy of Sprague-Dawley rat hepatocytes following exposure to either ambient air (left) or 28,000 PPM VC monomer gas for 4 weeks (right). Steatosis is seen only in the treated group. L=lipid droplets, GL = glycogen, M = mitochondria, N= nucleus

Change (fold)

Gene name

Glutathione S-transferase mu 1

. 1.77

Glutathione S-transferase theta 3

. 2.01

Glutathione S-transferase mu 3

. 3.73

Glutathione S transferase, alpha 2 (Yc2)

. 8.01

Glutathione S-transferase alpha 4

. 3.44

Table 1. Down-regulation of glutathione S-transferases in the liver of mice fed a diet enriched in carbohydrates (sucrose, 67% by weight) for 16 weeks. Gene expression in terms of transcriptome, was assessed using MG430 Affymetrix cDNA chip.

Treatment	insulin (µg/L)	triglycerides (mg/dl)	Liver Weight (g)	Saline Control
97.9	1.30	Acrolein 0.05 mg/kg	.921 194	1.45
Acrolein 0.1 mg/kg	1.02	221	1.39	.550
Acrolein 0.5 mg/kg	.844	248	1.53	

Treatment	cholesterol (mg/dl)	triglycerides (mg/dl)	Liver to Body weight Ratio (% of control)
Saline	64.4	67.5	100 %
Acrolein 5 mg/kg	115.3	382	112 %

Table 2: Acute Acrolein Exposure. Serum total cholesterol, triglycerides and liver to body weight ratio were increased in C57Bl/6 mice at 24 hours following gavage with acrolein. Table 3: Chronic Acrolein Exposure. Serum total cholesterol, triglycerides, and liver weights were increased in C57Bl/6 ApoE-/- gavigated with acrolein a single high dose of acrolein. daily for 12 weeks.

Work Proposed:

Aim 1. Experimental Design and Methods. In the human component of this study (Aim 1), we will utilize the previously described specimen bank and database from our occupational health program at U of L that is directed by my mentor, Dr. McClain. We will compare clinical information (BMI, smoking, ethanol history, etc) from the >100 workers removed from the BF Goodrich plant because of high exposure to VC and other industrial toxins to

CAVE-FellowFacultyTransitionAward 2006-21

information on 30 co-workers (e.g., secretaries, security workers, executives, etc.) from the same plant with low exposure. Aim 1A. We will determine the prevalence and severity of NASH on liver biopsy from the high exposure workers using the Brunt scoring system(12); and Aim 1B compare potential markers for mechanisms and markers of severity of NASH in control plant workers vs. high risk workers with NASH, and in the high risk NASH group followed at 1, 5, and 10 years to determine potential reversibility of NASH following removal from the work place. Biochemical markers for mechanisms/progression include: 1) routine liver enzymes, 2) fasting plasma glucose, 3) plasma cytokines/adipokines thought to play a role in NASH (TNF, adiponectin, IL-6, IL-8, leptin (13)), 4) markers of fibrosis (NASH Fibrosure™ (14)) and a marker of endothelial cell dysfunction / fibrosis (hyaluronic acid (15, 16)), 5) markers of oxidative stress (serum thioredoxin, serum and urinary isoprostanes (17)), and 6) a marker of apoptosis (CK-18 (18)). Low risk controls will be age, sex, and BMI matched to the high risk group

removed from the plant. Blood and urine specimens from the same year as the plant removal date will be used from the low risk groups.

Time Group Variables Aim 1a. Removal from plant All High Risk (>100) Liver biopsy-Brunt score Aim 1b. Removal from plant (0) and 1,3,5 years later High Risk with NASH (unknown) + Low Risk Controls (30) LFTs, glucose, plasma cytokines/adipokines, fibrosis, oxidative stress, apoptosis markers

23

♀
2007 AGA Fellowship/Faculty Transition Awards
Principal Investigator: Cave, Matthew

All of the above assays from Aim 1 are ongoing in our laboratory and Dr. Makunda Ray, an expert liver pathologist and long-time collaborator with this group, will read and score all liver biopsies in Aim 1 and Aim 2.

Aim 2: Experimental Design and Methods. 80 C57/B16 mice will be divided into two equal groups receiving either a standard or a high carbohydrate (67% sucrose by weight) diet. At 16 weeks, a period sufficient to induce hepatic steatosis in the high carbohydrate group, equal numbers on each diet will then receive acute (5 mg / kg single gavage) or chronic (0.1 mg / kg daily gavage for 12 weeks) acrolein exposure vs. saline gavage control. The acute exposure group will be killed 24 hours after gavage and the chronic group will be killed at the end of the 12 week period. Mice will be maintained on their original diets throughout completion of the study. Livers, epidermal fat pads, and serum will be collected, processed and stored. Liver histopathology will be performed including H&E, Oil Red O, and trichrome stains, as well as immuno-histochemistry for acrolein-protein adducts.

CAVE-Fellow Faculty Transition Award 2006-21

Routine chemistries will be measured by standard methods. Western blot analysis will be performed to measure the abundance of hepatic GST's which were found to be down-regulated by the high carbohydrate diet. Likewise, western blot analysis will also be performed to measure hepatic acrolein-protein adducts (antibody from NOF Corporation, Japan). In acrolein treated animals, particularly on a high carbohydrate diet, we expect to find worsened hyperglycemia, hypertriglyceridemia, and hepatic histopathology with decreased hepatic GST's and increased acrolein-protein adducts.

(n=10) HC + vehicle
Acute (n=10) HC + acrolein Exposure at

(n=40)
(n=10) C + vehicle 16 weeks
(n=10) C + acrolein
16 weeks diet kill 24 hr after exposure
(n=10) HC + acrolein
Chronic

(n=40)
(n=10) HC + vehicle
(n=10) C + acrolein
(n=10) C + vehicle

16 weeks diet + 12 weeks exposure 28 week kill

Methods: Serum glucose, lipids and liver enzymes will be measured by our Liver Core Laboratory, and Dr. Ray will provide an overall liver histologic score (12). Mitochondrial dysfunction: Assay of glutathione S-transferases. Expression of GSTs that were found to be down-regulated by high carbohydrate diet will be examined by western blot procedure which is routinely performed in our laboratories. Appropriate antibodies for immunoblotting (Santa Cruz, CA) will be utilized.

Assay of mitochondrial fatty acid β -oxidation will be performed on isolated mitochondria and evaluating their oxygen consumption in the presence of long-chain fatty acyl-carnitines.

Additionally, we will also assess the expression of two enzymes, namely, acyl-CoA dehydrogenase and carnitine-palmitoyl-transferase, which play a key role in fatty acid β -oxidation.

Hepatic steatosis will be evaluated by histological Oil Red O staining. Hepatic fibrosis will be evaluated (i) histologically using Sirius red staining and (ii) immunohistochemically by staining by α -smooth muscle actin (19).

Hepatic and adipose tissue inflammation will be determined by examining tissue and serum expression of adipokines (adiponectin and leptin) and cytokines (TNF, IL-6, TGF β , MIP-2) by ELISA.

Hepatic injury/apoptosis will be assessed by (i) TUNEL assay, (ii) serum levels of cytokeratin 18 (M30 ELISA, DiaPharma, Westchester, OH), and (iii) liver enzymes (ALT, AST).

Hepatic oxidative stress will be determined by measuring (i) total hepatic GSH levels by HPLC, (ii) TBARS (Zeptomatrix, Buffalo, NY), and (iii) acrolein adducts by HPLC (20) and immunoblotting using appropriate antibodies.

Statistics: Repeated measures analysis will allow us to analyze the longitudinal data from the database (1, 5 and

CAVE-FellowFacultyTransitionAward 2006-21

10 year follow-up information). Other data will be analyzed by Analysis of Variance and Analysis of Co-variance.

We will use the biostatistical consulting group of the NIEHS P30 Center to help us in our analysis.

Predicted Outcomes, Alternative Strategies, and Future Goals. In Aim 1, we predict that there will be a high

prevalence of NASH in VC exposed patients and there will be improvement after removal from the work place. In

our animal studies (AIM 2) we predict that carbohydrate induced steatosis will sensitize to acrolein hepatotoxicity,

and in the future, we will study other diets (high-fat) and other pollutants. Concerning alternative strategies, we

have an outstanding "omics" facility at the University of Louisville NIEHS Core Laboratory directed at Occupational

Toxicology. We could evaluate stored liver specimens by proteomics to look for either unique proteins or

"signatures" that may identify industrial toxin related NASH. We have listed a Brunt histology grading score, but we

will select the final scoring system pending results from the upcoming AASLD Fatty Liver Symposium.

TIMELINE - Aim 1: Months 0 - 9; Aim 2: Months 6 - 24

24

♀

2007 AGA Fellowship/Faculty Transition Awards

Principal Investigator: Cave, Matthew

11. Plain Language Research Summary: This research project examines the role of occupational chemical exposure and environmental pollution on the development and progression of non-alcoholic fatty liver disease (NAFLD). As its name implies, NAFLD, is very similar to alcoholic liver disease. However, affected individuals do not drink. The central feature in NAFLD is the abnormal accumulation of fat within the liver. In some, but not all cases, fat accumulation may trigger an inflammatory reaction inside the liver. Some people can not properly adapt to this form of mild hepatitis, and develop scar tissue. If enough scar tissue forms within the liver, cirrhosis occurs. Patients with cirrhosis may die from chronic liver failure or even liver cancer. NAFLD usually has no symptoms, and it is possible for someone to develop cirrhosis without even knowing that they have fatty liver disease. NAFLD typically occurs during middle age in both men and women. It typically develops in patients with obesity, diabetes, and high cholesterol. Due to the epidemic of obesity in the United States, NAFLD is becoming more common. It is even occurring in overweight children. Currently, it is estimated that 1 in 4 Americans have NAFLD. Of these, the majority have mild fat accumulation without more advanced inflammatory or scarring disease. The outlook for these patients is good, and few will ever develop complications of their liver disease. However, approximately 10% of patients with NAFLD (or 5-10 million Americans), currently have an inflamed liver. These patients are at risk for developing scar tissue, cirrhosis, and cancer. There is no FDA approved medication for this condition. Weight loss is an effective, but difficult treatment. In some cases of advanced cirrhosis and cancer,

liver transplantation is the only possible treatment.

Currently, it is unknown why some, but not all, overweight individuals develop NAFLD. Likewise, it is unknown why only some patients with NAFLD develop progressive liver disease. Intense genetic and biochemical research has been conducted and a handful of clinical mechanisms have been proposed. However, the clinical relevance of these mechanisms is uncertain. We believe that pollution may be playing an important role in the development and progression of NAFLD. However, this area has been glaringly understudied. Pollution exposure differs between individuals. For example, it may be greater in cities, and especially near landfills and chemical plants. Some people are at increased risk due to their jobs, such as machine operators and chemical workers. Others are exposed to contaminated food and drinking water. Furthermore, some people may have an impaired ability to detoxify pollutants, making them more susceptible to liver injury. This could be due to dietary factors.

We have evidence to support these claims. In collaboration with local chemical companies, the University of Louisville has established an occupational health and liver disease program with over thirty years of data on more than 1000 chemical workers. This program is directed by my mentor, Dr. Craig McClain. Many of these workers were employed before government safety regulations were adopted, and they suffered tremendous chemical exposures. The most significant of these occurred at a single BF Goodrich rubber and plastics polymerization plant, and involved vinyl chloride (VC). In 1974, following the recognition of the rare liver cancer, angiosarcoma, in several workers at this plant, over 100 employees with high risk VC exposures were removed from their jobs and enrolled in a liver cancer screening project at our occupational health center. As a part of this program, workers received baseline liver biopsies and lab tests. They are followed with yearly physical exams and blood work. At each visit blood and urine samples were frozen and archived. We have recently begun to re-read the baseline liver biopsies from these employees. Out of the first 10 cases we have examined, 7 had advanced NAFLD. This novel finding was not initially noted because NAFLD was not described at the time the original work was performed. Furthermore, we have data on the development of fatty liver in mice exposed to acrolein, which is an environmental pollutant present in fried foods, contaminated water, automobile exhaust, and cigarette smoke. Additionally, we have identified that a specific family of protective liver enzymes responsible for detoxifying pollutants is diminished in mice that eat a diet rich in sugar.

The objectives for ongoing research are to complete the investigation of VC workers. We will determine how many of them had NAFLD, and if it resolved after removal from the plant. We will perform modern blood tests on frozen samples in an attempt to identify markers and mechanisms of this disease. Furthermore, in mice, we will study how a diet rich in sugar enhances acrolein toxicity resulting in advanced NAFLD. This research is relevant to all people with work related chemical exposures, and to the millions of Americans with a "sweet tooth" who are

CAVE-FellowFacultyTransitionAward 2006-21

also exposed to urban pollution.

25

♀