INDUSTRIAL HYGIENE/OCCUPATIONAL HEALTH ASSESSMENT:
Evaluating Potential Hazards Associated with Chemicals and Work Practices at the Ingenio San Antonio (Chichigalpa, Nicaragua)

FINAL REPORT - August 30, 2010

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I. INTRODUCTION

A. Objectives

The purpose of the industrial hygiene assessment was to evaluate the current work practices at the Ingenio San Antonio (ISA) during the 2009-2010 zafra (harvest), as well as the chemicals used at ISA both currently and in the past. Based on the results of currently available chemical and toxicological information and the ISA site visit, the ultimate goal of this task was to answer two key questions agreed to by the participants at the Dialogue Table in January 2010:

> 1. Is there evidence that current work practices or chemicals used by ISA currently or in the past cause CRI?
>
> 2. Is there evidence that current work practices or chemicals used by ISA currently or in the past are associated with CRI (e.g., have been shown to cause kidney damage in animals?)

We have interpreted Question 1 as intended to address whether particular practices or chemicals are "generally accepted" causes of chronic renal insufficiency (CKI). Therefore, we have addressed Question 1 based on our assessment of work practices at ISA and on information that is generally accessible from United States' government health and environment agencies such the Environmental Protection Agency (EPA), the National Institute of Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR), and other comparable international agencies.

We have interpreted Question 2 as actually having two subparts as follows:

> 2a. Is there evidence that current work practices or exposure to chemicals used by ISA currently or in the past are associated with CRI (defined by high creatinine/reduced kidney function)?
>
> 2b. Is there evidence that current work practices or exposure to chemicals used by ISA currently or in the past are associated with acute kidney damage in humans or animals?

We have addressed Question 2 based on our assessment of ISA work practices and on the results of an extensive literature review to consider whether activities and potential exposures at ISA could cause CRI specifically (Question 2a) and acute kidney damage (Question 2b).

The reasons for our interpretation of each question are addressed in Section V of the report.

B. Research Activities

As described in BU's contract for Phase II (Implementation) of the study, there were three main components of the Industrial Hygiene Assessment designed to address these questions: (1) a background appraisal of current ISA activities (prior to the site visit), (2) a site assessment at ISA, and (3) a toxicological review of current and past chemical use at ISA.

The background appraisal of current ISA activities was conducted as part of our preparation for the site visit and included a desk review of current best practice in agricultural industries (with particular emphasis on sugar cane operations), the collection of information about sugar cane operations and work practices at ISA (including a review of any ISA written work procedures), and the preparation and submission of human subjects research protocols for the site visit activities to the Institutional Review Boards at both the Boston University Medical Center (BUMC) and the Ministry of Health in Nicaragua (MINSA).

The site assessment at ISA was conducted from April 20-24, 2010, and included a walk-through of the facility (fields, factory, etc), interviews, records review, and worker observations. The assessment focused on evaluating all health and safety procedures, but with particular focus on hypotheses related to CRI.

The toxicological review of current and past chemical use at ISA included a determination of a list of chemicals for review, a review of information from government agencies and published scientific literature for these chemicals, and ultimately a determination regarding whether any of these chemicals have a known association with kidney damage or more specifically chronic kidney disease.

C. This Report

The purpose of this report is to summarize the results of the activities described above, to make recommendations that would improve the health and safety of workers at ISA, and to address the questions posed by the Dialogue participants. Following this introduction (Section I), Section II provides an overview of the participants, itinerary, and process by which the ISA site visit was conducted. Section III summarizes the overall health and safety administration at ISA, not with respect to any particular work area, but rather the overall program as a whole. Section IV provides an overview of each job that was observed during the site visit, which includes a description of the current work process, an evaluation of the hazards and controls associated with current work practices, and a description of how work processes or practices in the past may have been different from the current processes and practices. Section V addresses the questions posed by the Dialogue participants to determine whether there is evidence that exposure to chemicals or work practices at ISA are associated with CRI or acute kidney damage. Section VI provides recommendations that would improve the health and safety of workers at ISA, not necessarily restricted to work practices that may be associated with kidney damage, but rather to identify opportunities to improve the health and safety of ISA workers in general. And finally, Section VII summarizes the conclusions of the report.

There are two key limitations to this work that are important to note, but that do not change the basic conclusions presented in this report. First, the recommendations and conclusions of this report are based on information obtained during our Industrial Hygiene Assessment, which included a background appraisal of current ISA activities (prior to the site visit), a site assessment at ISA, and a review of the medical literature for chemicals used at ISA currently or in the past. Accordingly, we relied on documents provided to us by NSEL, our own observations during the site visit, information provided by walkthrough participants (representatives of NSEL, ASOCHIVIDA, and other organizations of retired workers), and information provided by current

workers at ISA, as well as toxicological and epidemiological data from government agencies, Material Safety Data Sheets, and the published scientific literature. Though we gathered and reviewed an extensive amount of information, we did not collect new exposure data or health data as part of this effort.

Second, we were only able to observe current work practices during the site visit and had only a limited ability to assess how past practices may have been different. The assessment of past work practices and potential exposures relied primarily on information provided by walkthrough participants (representatives of NSEL, ASOCHIVIDA, and other organizations of retired workers), and in part on information provided by current workers at ISA. In some cases, the different parties disagree. However, none of the areas of dispute would have affected our basic conclusions.

II. OVERVIEW OF PROCESS FOR ISA SITE VISIT

A. Description of BUSPH Site Visit Team

The ISA site visit was conducted by four members of the BUSPH research team: Dr. Michael McClean, Dr. Oriana Ramirez Rubio, Rebecca Laws, and Irving Gongora. Dr. McClean was responsible for overseeing all of the activities associated with the industrial hygiene assessment, which included preparation for the site visit, directing the site visit itself, and preparation of this report. He has an MS in Industrial Hygiene and Safety and a ScD in Exposure Assessment from the Harvard School of Public Health and is currently an Associate Professor in the Department of Environmental Health at BUSPH where he directs the Exposure Biology Research Laboratory. He has been investigating exposures in occupational populations for approximately 13 years.

Dr. Ramirez, who has an MPH from Harvard University School of Public Health and an MD from Universidad Autónoma de Madrid, served in the role of the project manager and played a key role in coordinating and conducting all aspects of the site visit. Rebecca Laws is a research assistant at BUSPH who worked closely with Dr. McClean during all phases of this effort, while Irving Gongora is a consultant on the project who served as the primary translator during the site visit and for this report.

B. Itinerary and Participants of the Site Visit

The ISA site visit was conducted from April 20-24, 2010. Table 1 provides an overview of the schedule for the week, which was designed to include a review of all major work processes involved in the production of sugar cane at ISA. The major categories of work processes included: field preparation and fertilization, agrichemical storage and application, cutting seed, planting seed, irrigation, burning cane, harvesting cane, and the factory. Each of these is described individually in the subparts of Section IV.

Table 1. Itinerary for ISA Site Visit

<table>
<tr><th>TIME</th><th>Tuesday</th><th>Wednesday</th><th>Thursday</th><th>Friday</th><th>Saturday</th></tr>
<tr><td>6:00 AM</td><td></td><td>Bus picked up participants</td><td></td><td></td><td rowspan="2"></td></tr>
<tr><td>6:30 AM</td><td>Bus picked up participants</td><td rowspan="2">Cutting of cane (manual and mechanized)</td><td>Bus picked up participants</td><td>Bus picked up participants</td></tr>
<tr><td>6:30 to 12:00</td><td>Agrichemicals: Application (manual and mechanized) and Storage/mixing</td><td>Cutting seed, Planting seed</td><td>Irrigation, Plague control (warehouse, fungus lab)</td><td rowspan="2">Debriefing meetings with walkthrough participants</td></tr>
<tr><td>12:00 to 1:30</td><td colspan="3">Lunch with entire walkthrough team at ISA</td><td>Lunch/Debriefing</td></tr>
<tr><td>1:30 to 4:30</td><td>Preparation of field, Fertilization</td><td>Factory</td><td>Human Resources Offices (record review meeting), ISA Hospital tour</td><td>Record/NAT review</td><td rowspan="4"></td></tr>
<tr><td>4:30 to 5:00</td><td>Debriefing</td><td>Debriefing</td><td>Debriefing</td><td>Meeting with union leaders</td></tr>
<tr><td>5:00 to 5:30</td><td>Meeting with union leaders</td><td></td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td>8:30 to 10:00</td><td></td><td>Burning of the cane</td></tr>
</table>

NAT: Work-related Accident Notification (Notificacion de Accidente de Trabajo)

Table 2 provides an overview of the participants by affiliation and day. The participants of the site visit included representatives from five organizations: BUSPH, Asociacion de Chichigalpa Por La Vida (ASOCHIVIDA), Nicaragua Sugar Estates Limited (NSEL), Independent Association of Retired Workers, and Amor y Servicio (also an association of retired workers).

From NSEL, Luis Enrique Martinez (Human Resources Manager) and Rafael Pavon (Chief of Hygiene and Security) participated throughout the entire week so that they could provide information and address questions about the overall health and safety administration at ISA. The participation of other NSEL representatives varied throughout the week so that the assessment of each work process could be conducted with the NSEL representative(s) who was most knowledgeable about the operation.

Table 2. Participants of ISA Site Visit by Affiliation and Day

AFFILIATION	Tuesday	Wednesday	Thursday	Friday (morning)
ASOCHIVIDA	Joaquin Quiroz Mendez (all day)	Jose Donald Cortez Castillo (all day)	Salvador Soto Ramirez (all day)	Ezequiel Ramirez Salgado
	Ezequiel Ramirez Salgado (all day)	Cecilio Jose Ferrufino (all day)	Ezequiel Ramirez Salgado (all day)	Vicente Espinales Guevara
	Jose Donald Cortez Castillo (all day)	Freddy Alvarado (M and A)	Castulo Ferrufino (all day)	Jose Donald Cortez Castillo
	Cecilio Jose Ferrufino (all day)	Eleodoro Cruz (M and A)		Cecilio Jose Ferrufino
	Vicente Espinales Guevara (A)	Vicente Espinales Guevara (M and A)		Santos Severo Calero
NSEL	Luis Enrique Martinez - Human Resources Manager (all day)	Luis Enrique Martinez (all day)	Luis Enrique Martinez (all day)	Luis Enrique Martinez
	Rafael Pavon - Hygiene and Security Chief (all day)	Rafael Pavon (all day)	Rafael Pavon (all day)	Rafael Pavon
	Ramon Sanchez - Chief of Agronomy (all day)	Ramon Sanchez (M)	Ramon Sanchez (M)	Ramon Sanchez
	Jaime Vega - Manager of Cane Production (M)	Walter Garcia (M and N)	Jaime Vega (M)	Luis Cepeda - Head of Irrigation
	Walter Garcia - Chief of Harvest (A)	Francisco Ortega (M and N)	Alejandro Marin - Director of Hospital (A)	Jaime Vega
	Francisco Ortega - Manager of Operations (A)	Jacinto Leal - Manager of Factory (A)	Felix Zelaya - Head of Social Medicine Program (A)	Rene Lecayo - Chief of Crop Protection
		Farley d'Leon - Chief of Sugar Production (A)		Francisco - Head of Warehouse
		Guillermo - Chief of Burning (N)		Gustavo Martinez - Lab Engineer
Independent Association of Retired Workers	Eliseo Velazquez (M)	Manuel Maltez (M and A)	Marvin Rivas (all day)	Marvin Rivas
	Manuel Maltez (A)			Jose Tomas Herias
Amor y Servicio	Santos Rocha (A)	Felix Bernardo Centeno (A)		

M: Morning, A: Afternoon, N: Night

From ASOCHIVIDA, the participants (3-5 each day) included both board members and non-board members. They were identified based on their work histories so that the assessment of each work process could be conducted with the ASOCHIVIDA representatives who were most knowledgeable about a particular operation.

Representatives from two other associations of retired workers were also included to capture information about past practices from retired workers with a range of perspectives. The number of representatives from each retired worker organization ranged from 0-2 participants each day and though an attempt was made to select representatives with the most appropriate work experience, our ability to do so was limited.

An important point is that the site visit was designed to include participants with a range of perspectives and experiences. Accordingly, we included representatives who were affiliated with different organizations and who worked at ISA during different time periods and in different jobs. Because of these differences, we expected that the information obtained from different participants would not always match, but we did not interpret that to mean that certain information was correct and other information was incorrect. Instead, in cases where there were differences, we simply interpreted those differences to reflect the intended range in perspectives and experiences of the participants.

C. Overview of Site Visit Procedures

At the start of each day, all participants gathered at the ISA human resources office and boarded the bus. All communication was translated between English and Spanish. Upon arriving at a particular work location, the appropriate NSEL manager provided an introductory overview and Dr. McClean followed with many questions for NSEL representatives about work processes and health and safety procedures. After the discussion with the NSEL representatives, Dr. McClean then asked ASOCHIVIDA representatives for their comments regarding anything that had been said, especially about how the current work process or health and safety procedures may be different than in the past. Finally, the representatives of the other two associations of retired workers were asked for their comments regarding anything that had been said, especially about how the current work process or health and safety procedures may be different than in the past. All of the above conversation typically occurred on the bus within view of the workers performing their tasks so that we could minimize the amount of time in the hot sun.

At this point, we got off of the bus and more closely observed current workers performing their normal tasks. Dr. McClean typically asked additional questions at this time. After all participants had the opportunity to contribute everything they wanted to say, the BUSPH team (McClean, Ramirez, Laws, Gongora) went into the field without the other participants and randomly selected two or three current workers to interview. These interviews were conducted individually and privately for approximately 20 minutes and no identifying information was obtained. At each job location, the BUSPH team took many pictures, obtained global positioning system (GPS) coordinates, and collected multiple heat stress measurements using a wet bulb globe thermometer (WBGT) which provides a composite of the dry bulb temperature (normal air temperature), the wet bulb temperature (humidity indicator), and the globe thermometer temperature (solar radiation). After boarding the bus, but before leaving each job location, we once again asked if any of the participants had anything that they would like to add. Finally, we ended each day of the site visit with a debriefing session so that participants could provide any additional information about the work processes observed during the day.

III. SUMMARY OF HEALTH & SAFETY ADMINISTRATION AT ISA

A. Hygiene and Security Overview

As the Hygiene and Security Chief at ISA, Rafael Pavon oversees all components of health and safety at ISA. ISA became ISO 9001 certified in April 2001 and re-certified in 2008. The International Organization for Standardization (ISO) is an international standard-setting body that defines and structures a company's management systems. Sugar production in the factory was HACCP-certified as of April 2007. The Hazard Analysis & Critical Control Points (HACCP) management system of the U.S. Food and Drug Administration addresses food safety "through the analysis and control of biological, chemical, and physical hazards from raw material production, procurement and handling, to manufacturing, distribution and consumption of the finished product (FDA, 2009)." These accreditations are intended to ensure that ISA processes are routinely monitored and that the company is adequately keeping records, regularly reviewing program effectiveness, and seeking continual improvements in their programs.

Field and factory workers at ISA receive both internal (provided by the company) and external (conducted by an outside group) formal trainings, some of which are voluntary and some of which are mandatory, that are coordinated by the area of Social and Health Responsibility in the Field. Every worker is supposed to receive training at the beginning of each zafra, even if the worker has performed the same job task in the past. It also appears that some trainings occur periodically throughout the zafra. Workers are trained on how to perform the job task(s), potential hazards associated with the job, necessary personal protective equipment (PPE) and how to use it properly, and how to avoid accidents and other occupational health issues. The area of Hygiene and Safety and the Director of Medical Services conduct these trainings in accordance with the Manual of Prevention of Labor Risks. ISA maintains records of all formal trainings including the title and date. Contractors also receive trainings regarding safety equipment, hydration, and first-aid kit maintenance. With respect to heat stress, it is unclear which workers receive formal training, whether it is mandatory, and what specifically is covered during the training session. In addition to formal training, social workers give informal talks to workers in the field about the importance of staying hydrated.

There are job-specific health and safety policies that dictate which types of PPE workers are supposed to use while working in the field or factory. For most jobs, supervisors who are on site for the duration of the shift monitor the use of PPE. If a worker is seen performing a job task without the appropriate equipment, the worker will first receive a verbal warning and will be reminded of their training; on the second offense, the worker may be put on probation from work for one to three days; and the third violation could result in termination of the worker's employment at ISA.

B. Addressing Workplace Injuries

Consistent with ISO-certification, there is a systematic process for defining, identifying, and reporting workplace injuries. Any work-related injury, no matter how minor, must be reported to the worker's supervisor. The supervisor first assesses the injury and addresses it to the best of his ability, often with the assistance of the first aid worker. The injured worker is then taken to the

ISA hospital, even if the injury was adequately addressed with the first aid kit in the field, and the supervisor must fill out the Primary Accident Report (which requires two witnesses). Then, a Work-related Accident Notification (Notificacion de Accidente de Trabajo), also referred to as "the NAT," must be filled out within 48 hours of the incident. The NAT has three copies: one copy goes to the worker, who brings it to the local delegation of the Nicaraguan Social Security Institute (INNS), which, in turn, sends a copy to Central INSS in Managua; a second copy is filed at the ISA Hospital; and the third copy is filed in the Human Resources offices. For subcontracted workers, the contractor (rather than an ISA Human Resources representative) is responsible for filling out the NAT. At the beginning of each month, ISA must prepare a summary of the previous month's accidents and send it to the Ministry of Labor (MITRAB).

Very serious or fatal accidents are handled somewhat differently but are still reported on the NAT forms. Such accidents must be reported to MITRAB within 24 hours and are formally investigated by a Mixed Commission, which is comprised of both company and union representatives. After the investigation, the Mixed Commission composes a report that describes the details of the accident, summarizes the findings of the investigation, and provides recommendations for minimizing the risk of future accidents. After receiving this report, MITRAB conducts its own independent investigation into the accident.

C. Social Medicine Program

Dr. Felix Zelaya coordinates the Social Medicine Program at ISA. With a team of social workers, he is responsible for overseeing the medical screening of subcontracted workers, which occurs in November just before the zafra starts and is required for workers to receive clearance to be hired. The screening includes a physical examination and the collection of a brief work history, and the worker must be deemed by the physician to not have any debilitating illnesses, hypertension, or any hernias. Since the late 1990s, the Labor Code has required tests to evaluate liver, lung, and kidney function during the screening, though it was reported that the measurement of creatinine has been a mandatory component for all ISA workers since 2003.To be cleared for hire, a worker must have a creatinine below 1.2 mg/dL, though if the level is higher than 1.2 mg/dL, the physician may recommend that the worker come back and repeat the test. There is a second creatinine screening in January that is voluntary and most workers seem to elect to undergo this second screening. For instance, it is estimated that 50-70% of workers received this screening in January 2010. Finally, workers receive training about the major health risks associated with fieldwork and how to avoid these hazards through proper use of PPE and hydration. These trainings may occur individually or in a large group of workers. Sometimes, the entire medical screening process may take place in the field if necessary, as there may be a large influx of new workers.

If the worker is deemed eligible to work and his registration papers are complete and correct (Social Security Number, National ID, etc), he receives a company ID and is allowed to start working the following day. If anything is missing (for example, if the worker does not have a Social Security Number), the company will provide him with a provisional ID, which is valid for one week. The worker may begin working but must obtain a permanent company ID within that week. If a contractor hires a worker who has not completed the necessary medical screening or was deemed ineligible to work, then the company policy is to intervene.

The use of social workers to monitor subcontracted workers and regulate practices in the field began approximately 8 years ago and has brought changes to the length of the workday and a greater consideration for worker hydration. As part of a hydration project that started a few years ago, "Boleros" pass out protein cookies and bolis (a 250mL electrolyte solution) three times a day while social workers record how much has been distributed to the workers. In addition to encouraging worker hydration, social workers ensure that workers properly use PPE, do not work past the designated time, and remain seated on the transport bus to reduce the risk of machete cuts. Each social worker is assigned to a particular contractor each day, and there may be as many as 12 social workers in a single field. The social workers are present 7 days per week and according to company policy, should remain in the fields until the last worker leaves. If someone becomes ill, the social worker and the supervisor coordinate the worker's transport to the hospital.

On a typical day, each social worker will select 20 workers to assess hydration. They record worker names and IDs and monitor how many bolis and how much water each worker has consumed. The social workers also give short informal talks to these workers about the importance of staying hydrated and wearing PPE. The company provides the bolis and cookies, but workers are required to bring their own drinking water. The contractors must have extra water available on the bus and are responsible for having a first aid kit accessible in the field.

D. Medical Care

ISA has its own hospital, which is directed by Dr. Alejandro Marin and employs eight general practitioners and 24 specialists. As part of its contract with the Social Security Institute, the hospital only provides care to ISA workers and their families (including subcontracted workers) except in emergencies. In the case of an emergency, any patient will be attended to, including residents of Chichigalpa who do not work for ISA. Workers who visit the hospital are brought to the emergency room and registered into the "black book." Hospital staff members record the date, name of the worker, Social Security number, age, sex, diagnosis, treatment, the number of days the worker should refrain from work, any additional observations, and the physician signature. The physician in charge of the Occupational Medicine department sees all workers who report with work-related injuries or illnesses, a social worker opens a file ("ficha") on the patient and fills out an "epicrisis" form, and a witness must confirm the injuries. The worker receives a copy of the epicrisis form, as well as the NAT form, and is responsible for taking these to the Social Security office to start any necessary paper work for pensions. In the special case of CRI, the epicrisis must be filled out by the hospital's nephrologist, Dr. Mauricio Jarquín, after three months of follow up.

The hospital is also in charge of providing the medications and medical supplies for the first aid kits used in fields where temporal ISA employees work. Contractors are responsible for maintaining first aid kits for jobs that are conducted by subcontracted workers. The first aid kits were designed in accordance with the "List of Basic Medicines Necessary in the First Aid Kit of a Company" as regulated by the Ministry of Labor; during the April 2010 site visit, these kits were observed to include: gauze, tape, and saline solution for cleaning and dressing wounds; acetaminophen for fever and headache; aluminum hydroxide for stomach pain; dorival and diclofenac for pain; pyridium (phenazopyridine) for pain during urination; loperamide for

diarrhea; loratadine for allergies; and oral rehydration powder for dehydration. First aid workers reported distributing medication for issues such as stomach pain, allergies, fever, and headache; however, the most commonly distributed medication was pyridium because urinary problems were the most common complaint among workers.

IV. SUMMARY OF CURRENT WORK PROCESSES AT ISA

A. Field Preparation and Fertilization

A.1. Overview of Current Process

Field preparation, which is done using machines, is required in areas where new cane (also known as plant cane) will be planted due to either a problem with pests/plagues or due to low production of ratoon cane after harvesting (ratoon cane is regrown from previously cut cane). The decision to plant new cane (and therefore prepare the soil) instead of allowing ratoon cane to grow is based on the production potential for the following zafra, as the yield from ratoon cane decreases each year of regrowth. A tractor is used to remove any debris remaining in the field and three rippers (approximately 25-30 inches deep) are then used to open the soil. In special cases (e.g. if the "blind chicken" or other pests are a particular problem), the soil is first turned over and left for 5-7 days so that the sun, birds, or other animals can kill the pests. This process is repeated until the pest/plague is minimized, typically after 25-30 days. Depending on soil conditions, the soil is tilled up to three times to turn over big pieces of soil and make it finer. Furrows are created, di-ammonium phosphate (18% nitrogen, 46% phosphate, 0% potassium) is applied to the bottom of the furrow, and the seeds are planted 3-4 days later.

The fertilization process is conducted approximately 12 hours per day, 7 days per week, during all months of the year and in all ISA fields. 95% of the fertilization process occurs between November and July, while the remaining 5% occurs during the non-zafra (between August and October). There are three primary jobs associated with fertilization: mixers, operators, and engineers. The mixers stand on a flatbed trailer and use shovels to mix 2 bags of di-ammonium phosphate (18% nitrogen, 46% phosphate, 0% potassium) and 3 bags of urea (46% nitrogen, 0% phosphate, 0% potassium). Next, an operator drives the tractor to the flatbed trailer, the mixers load the fertilizer into the machine using buckets, and the operator drives the tractor into the field to mechanically apply the fertilizer. The engineer supervises the operation and keeps track of where fertilizer has been applied. For plant cane, the di-ammonium phosphate is applied during field preparation prior to planting as a first step, and then the mixture described above is applied 35-45 days after planting as a second step. For ratoon cane, the only application is of the mixture described above, 40-60 days after harvesting. Though primarily applied mechanically, fertilizer is occasionally applied manually when conditions do not allow for machines to enter the fields, such as when the cane is too tall or when the fields are too wet.

A.2. Evaluation of Hazards and Controls

The two products described above are among the most commonly used fertilizers in the agricultural industry. The material safety data sheets (MSDS) for both products describe minimal ingestion hazard under normal use, possible eye irritation and mechanical aggravation to respiratory mucous membranes in dusty conditions, and the potential for slight dermal abrasion with prolonged contact. Accordingly, the recommended exposure controls include adequate ventilation and use of an approved dust respirator when necessary, normal clean work clothing, and potential use of eye protection in dusty conditions.

The fertilization workers wore boots, overalls, and gloves while working in this area. Given that the mixing is conducted outside in an open field, the ventilation was sufficient such that use of respirators and eye protection do not seem necessary. When fertilizer is applied manually, it was reported that in addition to the above-mentioned PPE, workers also wear face nets to prevent cuts on the face from sharp cane leaves. It was noted that manual application often causes blisters on the hands such that gloves should be worn during this task. The application of fertilizer occurs prior to the application of herbicides such that potential for herbicide exposure among fertilization workers appears to be minimal. There is potential for heat stress among these workers due to the high temperatures, strenuous activity, and long work shifts; however, due to the intermittent nature of the work (periods of rest throughout the work shift) and the fact that workers are not compensated per unit of production, the potential for heat stress among these workers is likely lower than among other field workers.

All workers in this area (mixers, operators, engineers) are employed directly by the company and not through outside contractors. Upon starting this job, workers receive training about the job process and required PPE but did not appear to receive training about heat stress. Workers bring their drinking water from home in wrapped containers (for insulation) and indicated that they do not consume water from sources in the field. Workers also bring lunch from home and eat in the field. Four bolis as well as protein cookies are provided to each operator every day. There is a first aid kit available in the field, but workers who feel sick can notify their supervisor and receive transportation to the ISA Hospital.

The field preparation is conducted using machines and was not directly observed during the site visit; however, it appears that most of the operators work in an air-conditioned cab and therefore have a relatively low risk of heat stress.

A.3. Consideration of Past Practices

It appears that the current field preparation and fertilization processes are quite similar to the processes that were used in the past. Regarding field preparation, there may have been slight differences in machinery (i.e. different blade configuration that opened the soil to shallower depths of 15-20 inches) and there was a perception that spitters (an insect pest) may have been a larger problem in the past due to production of corn by workers who lived at ISA, particularly in the 1960s and then again in the 1990s. The extent of spitter infestation would be assessed by visual inspection and other methods and the locations would then be marked. These areas were then controlled by a combination of mechanical, agricultural, biological, and chemical methods. In the case of chemical control, an insecticide (such as Cipermetrina, Imidacloprid, Furadan, etc.) would be applied in low levels to those specific locations. However, there was some confusion about which specific insecticides were used and whether they were applied manually (granulated form), using backpack sprayers (liquid form), or by aerial spraying (liquid form).

Regarding fertilization, the company previously purchased fertilizer that was already mixed but they no longer use this method. There were reports that occasionally during storage in the warehouse, the fertilizer would become wet and would then dry into a solid block, such that the mixers would have to break it apart manually. Also, when machines could not enter the fields, there were reports that fertilizer may have been applied using airplanes in addition to manual

application. It was also noted that while today workers perform only one job task, in the past most workers performed multiple jobs simultaneously since they were assigned to different jobs as they were needed.

B. Cutting Seed

B.1. Overview of Current Process

Seed cutters include both men and women who are hired through contractors and not employed directly by the company. A supervisor and social workers are also present in fields where seed is being cut. The amount of work to be done, and therefore the number of workers needed to cut seed on a typical day, depends on the planting needs and can vary throughout the year. Seed is needed to plant new fields and to replant specific areas in ratoon cane fields. The needs of private producers who purchase seeds directly from the company also affect the amount of cane that needs to be cut on a given day. Most days, there are approximately 400 workers who are divided into two to three groups of seed cutters. Each worker is usually assigned four furrows to cut, each approximately 7-8 meters long.

The cane used for seeding is cut at about six or seven months of age, always prior to germination. Using a machete with a straight blade, the worker first cuts at the base of the cane and then cuts off the very top. This leaves a long stick of cane, which is then cut into 3-4 pieces known as billets, each approximately 20-22 inches long and containing about four buds. Next, 40 billets are tied together with scrap cane leaves to form each package. Workers typically cut between 80 and 100 packages per day but can cut fewer if they wish. Seed cutters are paid by the package and therefore have an incentive to work as fast as possible.

Workers are transported to and from the field on a bus, which arrives between 6:00 and 6:30 am and leaves at 2:00 pm, though they may stop working any time before 2pm if they feel they have cut enough seed. When done for the day, workers have the option of walking home or waiting for the bus to leave, though no worker is allowed to stay past 2:00. Though seed cutting occurs seven days per week, most employees choose not to work every day.

B.2. Evaluation of Hazards and Controls

Seed cutters work under hot conditions, use sharp machetes, and are paid per unit of production. Accordingly, they are at risk for machete cuts and heat stress. Workers wore boots and most were observed to wear polainas (shin guards) to prevent machete cuts, though they did not wear gloves as this makes it more difficult to grasp the machete and the cane.

Social workers monitor water intake as well as consumption of bolis and cookies. They also check to ensure that drinking water containers are wrapped and speak with supervisors if it is discovered that workers are not drinking enough water. Finally, they make sure that all workers are seated on the transport bus to reduce the chance of cuts from machetes. Workers seemed to understand that staying hydrated and keeping their water containers wrapped is important, but they did not appear to receive training about heat stress specifically. Extra water was available on

the bus for those who ran out. Workers reported that when they feel sick from the heat they either sit down to rest or finish what they are doing and go home early.

95% of seed cutting occurs between November and July, and the other 5% occurs between August and October. Seed is cut when the cane is between 6 and 8 months old, which is several months after the second application of herbicides, so cutters have minimal risk of exposure to agrichemicals.. There is potential for heat stress among these workers due to the high temperatures, strenuous activity, and the incentive to work as fast as possible given that they are paid per unit of production. However, workers were observed to take breaks throughout the day and there is plenty of shade provided by the sugar cane given that it has not yet been burned.

B.3. Consideration of Past Practices

The current process of cutting seed is somewhat different than it was in the past. Previously, an entire cane stalk was transported to the planting field, placed in the furrow, and then cut into smaller pieces with a machete. Therefore, the two tasks of cutting and planting seed were combined. Now, the cane is cut into smaller pieces by the cutters and wrapped into packages before it is transported to the field to be planted. This new technique makes the task of planting much easier and safer. Because the planters do not need to use machetes, their risk of cuts and other injuries is reduced. This new process is more efficient for the planters because an entire step of their job has been eliminated.

Workers did not use PPE such as polainas in the past, and therefore had greater risk of cutting themselves with machetes. Although buses were used in the past, workers had the option of using them for transport. Some may have walked to the field alone, in which case they could work as long as they wished. Additionally, there were reports that workers may have come into the field the previous afternoon to start cutting seeds for the next day early. There were also reports of cutting as many as 10 to 20 furrows per day, though this may have been in rare cases. Although workers always brought their own water, in the past they may not have carried enough into the fields. It was also noted that while today, workers perform only one job task, in the past, most workers performed multiple jobs simultaneously since they were assigned to different jobs as they were needed.

C. Planting Seed

C.1. Overview of Current Process

Seed planters include both men and women who are hired through contractors and not employed directly by the company. They work from 6:00 am to 12:00 pm (and are not supposed to work later), though more skilled planters often finish between 11-11:30 am. Seed planters work between 5 and 7 days a week depending on demand. The seed packages produced by cutters are loaded onto a truck (by different workers), taken to the field to be planted, and distributed in each plot of land every 68 m. Planters are in charge of distributing the seeds throughout each furrow, though the trucks do the initial distribution of the packages. Each planter seeds between 2 and 4 furrows a day with most typically seeding 3, though they may plant as many as they wish until noon. Workers are paid per furrow planted such that they have an incentive to work as fast

as possible. The planters place the seeds at equal distances apart along the entire length of each 204-meter long furrow and use either a shovel or a hoe to cover them with soil. When done planting for the day, workers must remove the trash (ie cane leaves, etc) from the field. The company has purchased a $200,000 planting machine but currently all planting is conducted by hand while they continue to develop the methods for using machines.

C.2. Evaluation of Hazards and Controls

Workers receive training from supervisors on how to plant the seed, cover it, and remove the trash from the field. Planters are supposed to wear boots and bring either a shovel or a hoe, though it was unclear whether the company provides this equipment. Since there is high turnover in this job, the company has to regulate the provision of equipment because workers sometimes take these items and do not return.

There is potential for heat stress among these workers due to the high temperatures, strenuous activity, lack of shade, and the incentive to work as fast as possible given that they are paid per unit of production. Workers bring several liters of water and bolis with them into the fields and if they run out of either, they can get more on the transport bus. Workers typically drink between 4 and 8 bolis per day and many liters of water. The planting of seed occurs prior to the application of herbicides such that potential for herbicide exposure among planters is minimal.

C.3. Consideration of Past Practices

The primary change to this job is that the cane is now cut by the seed cutters and then delivered to the planters in packages, whereas in the past planters had to both cut the cane stalks and plant the seeds simultaneously. This change has made the planters' jobs less strenuous, reduced the number of accidents, and decreased the length of the workday. After experimentation with different techniques, the company has found that spacing the seeds in two rows approximately 10 cm apart seems to provide optimal germination (whereas they used to be planted together). Also, the furrows are now 1.75 m apart (whereas they were 1.5 m in the past), which allows the cane to receive more light, water, and nutrients and increases production. Also in the past, planters were hired directly by the company, instead of through a contractor, and provided their own footwear and shovel. It was also noted that while today, workers perform only one job task, in the past, most workers performed multiple jobs simultaneously since they were assigned to different jobs as they were needed.

D. Irrigation

D.1. Overview of Current Process

All irrigation workers are employed directly by the company. The irrigation process is primarily conducted during the zafra season, November to May, and sometimes from mid-July to mid-August. The irrigation cycle depends on soil type, irrigation phase, and developmental stage of the cane. Clay soil must be irrigated every 16-20 days and loose soil every 12-14 days. The first irrigation cycle requires more water and is more labor intensive, but during subsequent irrigation cycles more land can be irrigated with less time and water. In the rainy season, some of the

workers will continue to work in the fields to monitor drainage. There are four distinct types of irrigation that are used at the ISA: gravity irrigation (~9,000 manzanas), mechanized-pivot method (~5,400 manzanas), drip method (~2,200 manzanas), and sprinkler method (~1,300 manzanas). During the site visit, the gravity irrigation method and the sprinkler methods were observed.

Gravity irrigation is the most common method used at ISA, requiring approximately 400 workers per day. A typical workday lasts from 6:00 am to 3:00 pm, except on Sunday when the day ends at noon. At the beginning of each day, employees are picked up by a bus, dropped off in a central location, and given their daily task by the supervisor. Each worker controls the gravity irrigation for one field per day, and a supervisor oversees workers in multiple fields. Water is taken from a primary source, either a nearby lake or recycled water from the ISA factory, and diverted through a series of trenches that distribute the water throughout the cultivation fields. During field preparation, the topography of the field is assessed and the field is graded so that water flows from one side to the other. A main conductor (dug using a tractor) runs along the perimeter of the field where the water is allowed to flow into the furrows and throughout the field. The worker controls the flow of water on a field by opening or closing sections of the conductor using sticks and plastic, and by opening or closing connections between the conductor and the furrows through the removal or addition of soil. This process continues until the entire field has been irrigated. The amount of water handled by an irrigation worker is ~1000 gallons/manzana/day but depends on the total area of the plot, type of soil, first or second irrigation, and the growth stage of the cane.

Sprinkler irrigation is the least common method used at the ISA. This method uses the least amount of water and can cover a greater amount of land, but is the most expensive. There are typically two crews of workers on a field that work 12-hour shifts. A crew consists of three workers, and two crews are typically used to irrigate a field, one during a 12-hour day shift and the other during a 12-hour night shift. Water is diverted from a primary source, such as Tres Rios or the factory, pressurized through a mechanized pump, and then dispersed onto the fields through a series of aluminum pipes and sprinklers. As different areas of the field need to be irrigated, one worker moves the sprinklers while two other workers move the sections of pipe. When the pump needs to be relocated it is moved using a tractor. The number of sprinklers in a field is typically 6-8, but depends on the capacity of the engine and the pump.

D.2. Evaluation of Hazards and Controls

Irrigation workers are paid a daily rate and not by amount of land irrigated or water handled. Workers reportedly receive training about how to perform their job, the required PPE, and are instructed not to drink or bathe in the irrigation water. A gallon of drinking water, bolis, and cookies are distributed at the beginning of the work day, but given that workers spend most of the day working alone, it is unclear whether additional supplies continue to be available or provided throughout the day.

The supplies given to each gravity irrigation worker are reported to be: a shovel, machete, polaina, limas (sharpener), rubber boots, and hat with neck covering. Additionally, at the beginning of each workday, each worker is given a supply of water, bolis, and cookies. The

shovel is used to open/close the conductors and clear debris from the furrows. The machete is used to create wooden sticks, which hold the plastic in place for opening or closing a furrow. There is potential for heat stress among gravity irrigation workers due to the high temperatures; however, given the nature of the work environment (shade from cane that still has leaves, working close to water) and the fact that workers are not compensated per unit of production, the potential for heat stress among irrigation workers is likely lower than among other field workers.

For sprinkler irrigation, approximately five days is needed to completely irrigate a field with this method such that crews construct makeshift canvas shelters to provide shade. Current PPE observed includes pads for carrying pipes, gloves, boots, and hat with neck covering. Additional equipment includes: bolis, cookies, a 200 liter water tank ("rotoplast"), and antibacterial soap; and for the night shift: flashlights, 2 pairs of batteries every 7 days, sugar, and coffee. Despite the high temperatures, there appears to be a relatively low potential for heat stress among sprinkler irrigation workers due to the intermittent nature of the work (periods of rest throughout the work shift) and the consistent source of shade provided by the shelter.

The potential for exposure to herbicides or other agrichemicals was difficult to assess for gravity irrigation workers since it is unclear when they enter the fields in relation to the application of agrichemicals. Some irrigation is performed before agrichemical application while some is performed after application. For those irrigators working in the fields after an herbicide application, the reported minimum time before they may enter is 7 days. Though they may still be exposed to low levels of agrichemicals, this amount of time is consistent with the restricted entry intervals for the agrichemicals currently used at ISA.

D.3. Consideration of past practices

Current gravity irrigation practices appear to be similar to past practices. It was reported that in the past, workers used to work later in the day and that some would drink or bathe in irrigation water. Because the field preparation process resulted in poorly graded fields, workers used shovels to level the irregularities and ensure the water coverage was sufficient. The junctions between the conductor and furrow were previously closed using grass and dirt, but now it is more common to use plastic.

The current sprinkler irrigation methods are similar to past practices, except that a previous "crew" consisted of two workers (one to move sprinklers and one to move pipes) instead of the current three-worker team. Also, it appears that shoulder padding was not used when carrying pipes, and workers used to create shelters using their own materials whereas now the necessary materials are provided. It was also noted that while today, workers perform only one job task, in the past, most workers performed multiple jobs simultaneously since they were assigned to different jobs as they were needed.

E. Agrichemical Storage & Application

E.1. Overview of Current Process

A significant amount of work at ISA surrounds the storage, mixing, and application of agrichemicals. Herbicides account for approximately 95% of the agrichemicals used at ISA, as weeds pose the biggest risk to sugar cane production. The remaining 5% of chemicals applied at ISA consist of insecticides, fungicides, rodenticides, ripening agents, flowering inhibitors, and growth hormones.

Agrichemical storage and mixing. When agrichemicals and supplies first arrive at ISA, they are stored in bulk at a transitory warehouse, which is under the supervision of the Inventory, Supplies, and Logistics Office. Daily orders for chemicals and supplies are authorized and submitted to the warehouse at which point they are distributed to other areas such as El Piñal (discussed below). Two permanent workers at the warehouse fill the orders each day and also pick up the empty storage containers from previous orders. If an order is particularly large, other workers will come to assist in the delivery. Herbicides are stored in a locked cage area so that they will not be stolen.

When the levels of agrichemicals in the warehouse become low, more are ordered from the suppliers. First, an order must be sent to ISA's purchasing department, which will then place the order with the appropriate supplier. All ordering records are kept at the warehouse, in both electronic and paper form, and appear to be available back to 2004-2005, though these details are a bit unclear. Generally, deliveries received at the warehouse are large and occur approximately 4 times a year. Additional smaller purchases are made periodically as needs arise. At the time of the April 2010 site visit, it was noted that the supply in the warehouse would be sufficient for another 2 to 3 months.

One of the main areas to which agrichemicals are distributed from the main warehouse is a complex called El Piñal. This area consists of multiple buildings: one for the storage of application equipment, one for the storage and mixing of agrichemicals (received from the warehouse), several smaller buildings for the storage and cleaning of PPE, as well as one with showers, lockers, and toilets for use by workers who apply agrichemicals. Within the building where agrichemicals are stored and mixed, there is a contained rectangular area that is designated as the location for all mixing of agrichemicals.

After chemicals are mixed, they are taken outside and loaded into tanks that are half filled with water. The concentrations necessary for these mixtures are calculated according to the area over which they will be spread as well as the method of application that will be used. All agrichemical runoff is directed to a common area, where it is collected in one tank. Later, this mixture is redistributed in areas adjacent to the cane plots.

Agrichemical application. Agrichemicals at ISA are applied both manually and mechanically. Workers who apply chemicals manually typically work from 6:00 am to 10:00 am, 6 days a week. Manual application is done with backpack pumps, known as 'bombas de mochila.' These backpacks come in two main varieties: plastic mochilas and the metal mochilas, which are more

recent in their use at ISA. Plastic mochilas are the more common of the two and require manual force to create the pressure necessary for application. When using a plastic mochila, one hand pumps the backpack to maintain pressure while the other controls the sprayer. The metal mochilas do not require the applicator to apply pressure such that a sprayer can be operated in each hand. Herbicides, insecticides, and fungicides are all applied by backpack, while ripeners and flowering inhibitors are applied aerially using planes and pilots contracted by the company. All airplanes are filled at the nearby runway, and GPS is used to track where chemicals have been aerially applied.

While herbicides are applied in all months of the year, they are applied most often during the zafra and primarily at specific periods in the cane's life cycle. 95% of these applications occur between November and July, with the remaining 5% occurring between August and October. The first major application generally occurs between days 5-7 for plant cane (which consists of approximately 25% of the fields at ISA) and between days 10-20 for ratoon cane (which consists of approximately 75% of the fields at ISA). This pre-emergence application is always necessary for plant cane, but is only conducted for ratoon cane when there are particularly aggressive weeds. Typically, this pre-emergence application occurs in approximately 60-70% of ratoon cane areas, though it occurred in 100% of ratoon areas in the 2009-2010 zafra. The second major application generally occurs between days 100-120 for both plant and ratoon cane, and comprises 80% of overall herbicide application.

The most common application of herbicides is a mixture of 2,4-D, terbutrine, and ametrine with the amount of each chemical adjusted depending on the types of weeds. While 2,4-D is used in all areas, terbutrine is used mostly on ratoon cane and in areas with aggressive weeds, and ametrine is used in areas with grassy weeds and weeds with wide leaves. Additionally, pendimetalina is used for both plant and ratoon cane during pre-emergence application. Fields can receive a maximum of 2 applications per year and the herbicides are effective in soil for approximately 30-35 days. Company personnel stated that chemicals are applied in a manner consistent with manufacturer's recommendations at a concentration at or below the recommended dose.

Regarding the use of chemicals other than herbicides, insecticides are used rarely and applied to only 300-400 of ISA's 24,000 manzanas (<2%). Biotraps, which consist of yellow plastic bags that are coated with a sticky substance and hung in the fields to attract and kill insects, are also used as part of the integrated control of certain pests. In focus areas where rodents are a particular problem, rodenticides are applied and owl perches are erected. The rodenticides are solid cubes that are thrown into these areas for rats to consume. Flowering inhibitors are typically applied once the cane has reached a certain level of maturity (around day 170 for both plant and ratoon cane), since allowing sugar cane to flower would decrease production. It is only necessary to apply flowering inhibitors between July 25 and August 15. Ripening chemicals are only applied between October and January, approximately six weeks before the cane is cut.

Manual application is done in teams of 25-30 workers and can be divided into 3 distinct roles: applicators, engineers and a supervisor. Applicators walk through furrows and spray the ground and base of the cane. Generally 2 workers are assigned to 6 furrows at a time. On each team there are 2-3 engineers responsible for mixing the appropriate agrichemicals and filling the

backpacks, but applicators do not mix chemicals. Additionally, a supervisor tells the applicators which furrows to spray and keeps track of which furrows have been completed.

Mechanized application of agrichemicals is limited to terrain that will allow the entry of machines. Also, once cane reaches a certain height, the machines can no longer be used such that only manual application is feasible. Workers who apply chemicals mechanically start between 5-6:00 am and work between 5 and 12 hours per day, 7 days per week. Hours for this job are particularly variable because workers do not apply chemicals if it is too windy, in which case they are sent home early. Teams of 6-7 workers are used for the mechanized method and there are 3 distinct jobs: the driver, the worker responsible for refilling the tank, and the worker overseeing pesticide application from the top of the tractor. Herbicides are the only agrichemicals (other than fertilizer) that are applied using machines.

Because tractors are able to cover more area in less time than manual applicators, lower concentrations of chemicals are used in mechanical applications. For example, a typical mixture of herbicides will include 2 L of terbutrina, 2 L of ametrina, and 2 L of 2,4-D. This mixture will be dissolved in 200 L of water for mechanical application and in 100 L of water for manual application to reduce the time and effort of application.

Fungus production. In 1995, ISA started using a fungus purchased from a supplier in Venezuela as a biological insecticide that targets the "salivita" or "spitter." In 2000, the company decided to build a laboratory and produce the fungus for use at ISA and to sell it commercially. The company currently has the capacity to produce fungus for application on 86,000 manzanas; it also produces excess product to sell to colonos (independent suppliers of cane to ISA), other Ingenios in Nicaragua (such as Monte Rosa), and plantations in Honduras and El Salvador. The fungus can be applied directly to the soil or to the sugar cane crop in either a powder or liquid form and kills both the eggs and insect at anytime during development, therefore replacing insecticides such as cypermetrina. The lab is maintained as a sterile environment and lab workers shower before work to prevent contamination of the fungus, which is not toxic to humans.

E.2. Evaluation of Hazards and Controls

Table 3 provides a summary of agrichemicals currently used at ISA, all of which were confirmed by the company. The health effect information summarized in Table 3 is based on information obtained from Material Safety Data Sheets (MSDSs) and from United States government agencies such the Environmental Protection Agency (EPA), National Institutes for Occupational Safety and Health (NIOSH), Agency for Toxic Substances and Disease Registry (ATSDR), and other comparable international agencies. This table was intended to provide a summary of potential health effects from sources that should be readily accessible to anyone using these chemicals. For each chemical, we indicated whether any of the above mentioned sources noted any potential for kidney damage in humans or animals. In addition to potential health effects, the table also summarizes for each chemical: years in use at ISA, active ingredient, vapor pressure and boiling point, classification of chemical, and the source from which we learned of its use. After this initial research into understanding the toxicology and health effects of each chemical, a much more extensive literature review was conducted, upon which we based our final assessments (Section V). Of the chemicals that are currently used at ISA, the information

obtained during this initial review indicated that there is a potential for kidney damage associated with exposure to 2,4-D, glyphosate, cypermethrin, and captan.

All four of these chemicals are registered for agricultural use by the United States Environmental Protection Agency (U.S. EPA)[1]. In fact, the herbicide 2,4-D is the most widely used chemical at ISA and is also the most widely used home and garden and commercial agrichemical in the United States[2]. Glyphosate is also used extensively at ISA and is the second most commonly used home and garden and commercial agrichemical in the United States[2].

During manual application of agrichemicals, ISA follows the Ministerio del Trabajo de Nicaragua (MITRAB) requirements, in which chemical handlers must use certain types of PPE: long gloves, a respirator, rubber boots, overalls, a net for the face, and a cape/apron. Each worker is assigned a set of PPE, which he uses daily. Overalls and capes are turned in for cleaning at El Piñal but workers are responsible for cleaning and storing their own respirators, gloves, and boots. It was reported that this equipment is stored in lockers overnight and is not brought home. Workers are required to shower before going home. During the workday, workers' clean clothes are stored in their lockers, to be put back on after showering.

According to company representatives, respirator filters are changed upon request. Once workers are able to smell a chemical, they can alert their supervisor and have the cartridge changed. Respirators are not fit tested but rather are of a standard size, which workers learn how to adjust at training sessions. Facial hair is not allowed among agrichemical workers to ensure a good respirator fit. The filter cartridges being used at ISA are produced by 3M (NIOSH P100 7093C HF). However, after personal communication with the Technical Assistance department of Occupational Health & Environmental Safety at 3M, we learned that these cartridges are not recommended for use with agrichemicals. 3M provides the following information on this filter cartridge:

> *When properly fitted, use in a variety of applications including welding, brazing torch cutting, metal pouring, soldering and exposure to lead, asbestos, cadmium, arsenic, MDA and hydrogen fluoride (HF) for concentrations up to 10 times the Permissible Exposure Limit (PEL) with half face pieces or 50 times PEL with full face pieces. This filter also provides nuisance level protection against OV and AG exposures. Full-face pieces must be quantitatively fit tested to claim assigned protection factor above 10 in negative pressure mode. Do not use in environments that are Immediately Dangerous to Life or Health (IDLH).*
>
> *3M recommends these cartridges for relief against nuisance levels of organic vapor and acid gases. Nuisance level organic vapor and acid gas refers to concentrations not exceeding OSHA PEL or applicable government occupational exposure limits, whichever is lower. These cartridges are not NIOSH-approved for organic vapors or acid gases and should not be used for respiratory protection against organic vapors or acid gases (except HF).*

[1] http://www.cdpr.ca.gov/docs/label/labelque.htm
[2] http://www.epa.gov/pesticides/pestsales/01pestsales/usage2001_3.htm

Table 3: Summary of Agrichemicals Currently used at ISA and their Potential Health Effects

Agrichemical	Period of Use	Active Ingredient	Vapor Pressure	Boiling Point	Use	Health Hazards Reported by Government Agencies and MSDS's	Source
DIURON	1980-2010	Diuron	VP: 0.000000002 mmHg[3] White, odorless, crystalline solid[3]	BP: 365F (Decomposes)	Herbicide	• US EPA class D (not carcinogenic) IARC Class 2B1[1] • Irritation of eyes, skin, nose, throat[3] • Carcinogenic (category III)[5] • Endocrine disruptor[4]	NSEL
2-4-D	1980-2010	2,4-D	VP: <17 mmHg@20C 45% volatiles by volume[1], 0.4mmHg @(320F)[3]	BP: 214F[1], Decomposes[3] White to yellow crystalline, odorless powder[3]	Herbicide	• US EPA class D (not carcinogenic) IARC Class 2B1[1] • Liver, muscle damage, lassitude, stupor[3] • **Kidney damage in animals[3]** • Endocrine disruptor[4] • Neurotoxic (inespecific, level I) [6] • Sensitizers[8] • Associated with occupational disease-exposure to organoclorates[7] • **Prolonged overexposure causes kidney damage[3]**	NSEL
AMETRINA	1980-2010	Mesotrione	VP:4.3x10-8mmHg @20C	BP: not available[1]	Herbicide	• Skin sensitizer, irritant to mucous membranes/respiratory tract, chronic exposure leads to liver damage[1] • Endocrine disruptor [4] • Associated with occupational disease-exposure to aromatic amines- (bladder cancer)[7]	NSEL
PENDIMETALINA	1980-2010	Pendimethalin	VP: 23.4mbar	BP:85-100C (VP/BP info apply to solvent)[1]	Herbicide	• Orange-yellow colored urine, skin/eye irritant[1] • Endocrine disruptor[4] • Sensitizers[8]	NSEL
TERBUTRINA	1990-2010	Terbutryn			Herbicide	• Endocrine disruptor[4]	NSEL
METSULFURON METIL	2005-2010	Metsulfuron methyl			Herbicide	• None	NSEL
CLOMAZONE	2005-2010	Clomazone			Herbicide	• Low dermal, oral, inhalation toxicity[1]	NSEL

Table 3: Summary of Agrichemicals Currently used at ISA and their Potential Health Effects (Continued)

Agrichemical	Period of Use	Active Ingredient	Vapor Pressure	Boiling Point	Use	Health Hazards Reported by Government Agencies and MSDS's	Source
ATRAZINA	2009 - 2010	Atrazine	• VP:2.9x10^{-7} mmHg @20C[1] • Not very volatile or reactive[2] • Colorless or white, odorless, crystalline powder[3]	BP:Not applicable[1], decomposes[3]	Herbicide	• Reproductive/developmental effects[1] • IARC group 3 carcinogen[2] • Eye, skin irritation, skin sensitization, lassitude, dyspnea, incoordination, salivation, liver injury[3] • Carcinogenic (group 3)[5] • Endocrine disruptor[3] • Sensitizers[8]	NSEL
GLIFOSATO	1985-2010	Glyphosate, isopropylamine salt	VP: 1.75x10-7 mmHg	BP:113C	Herbicide	• Irritation to eyes, skin, respiratory, digestive system[1] • **Kidney damage with prolonged overexposure[1]**	NSEL
GLUFOSINATO DE AMONIO	2006-2010	Phosphinothricin			Herbicide	• Reproductive toxicant(category I+T(toxic))[5] • Use prohibited for pregnant women[8] • Associated with occupational diseases-exposure to organic esters and derivates, organofosforados and carbamatos[7]	NSEL
FLUAZIFOP-P-BUTYL	2010	Fluazifop-p-butyl	VP: 4.5x10-7mmHg @20C	BP: Not Available[1]	Herbicide	• Toxic if inhaled, respiratory tract/skin irritation, sensitization, drowsiness, dizziness[1]	NSEL
IMIDACLOPRID	2003-2010	Imidacloprid	VP: 1.9x10-9 Torr @20C	BP: >100C[1]	Insecticide	• Mildly toxic orally, non-toxic dermally[1]	NSEL
DIPEL	1990-2010	Bacillus thuringiensis (berliner), subsp. Kurstaki, strain SA-11	VP: N/A	BP: >400F[1]	Insecticide	• Lipoid pneumonia from inhalation, irritation of eyes, nose, throat[1]	NSEL
CYPERMETRINA	1990-2010	Cypermethrin, beta	Volatilization from soil and water occurs slowly[2]		Insecticide	• Dizziness, headache, nausea, muscle twitching, reduced energy, changes in awareness, convulsions, loss of consciousness. Occupational exposure leads to paresthesia, neurotoxicity[2] • **Decreased kidney weights and tubular degeneration in rats[2]**	NSEL
BEAUVERIA BASSIANA	1999-2010	Beauveria bassiana (fungus)	VP: Not Available	BP: Unknown[1]	Insecticide	• Skin, eye, respiratory irritant[1]	NSEL

Table 3: Summary of Agrichemicals Currently used at ISA and their Potential Health Effects (Continued)

Agrichemical	Period of Use	Active Ingredient	Vapor Pressure	Boiling Point	Use	Health Hazards Reported by Government Agencies and MSDS's	Source
METARHIZIUM ANISOPLIAE (METARHISA)	1995-2010	fungus			Insecticide	• None	NSEL
FIPRONIL	2009-2010	Fipronil	VP: negligible @ 20C		Insecticide	• CNS effects: convulsions, tremor, irritability[1] • Liver tissue lesions[1]	NSEL
BRODIFACOUM	1990-2010	Brodifacoum (bromfenacoum)	VP: 6x10-6mmHg @20C	BP: Not Applicable[1] Tendency to volatilize and Degrade in natural waters And soils[2]	Rodenticide	• Irritating to eyes[1,2] • Increased risk of cararacts, hemolytic anemia, nausea, vomiting, blood in urine, yellow skin, irritation/inflamation of nose/lungs[2] IARC-possibly carcinogenic, EPA group C[2]	NSEL
ETEPHON	1996-2010	Ethephon	VP: <0.013 hPa @25C	BP: no data available[1]	Hormone	• Irreversible eye damage, irritation, redness, swelling of skin on contact, respiratory tract irritation, burns to mouth and esophagus if inhaled[1]	NSEL
ACIDO GIBERELICO	2008-2010	Gibberellic acid	VP: 33mmHg @20C (Isopropanol)	BP: 82.5C (Isopropanol)[1]	Hormone	• Moderate eye irritant, slight to mild skin irritant, flushing, headache, dizziness, nausea, vomiting, drowsiness, mental depression, anesthesia, coma. Dryness or cracking of skin after prolonged contact[1]	NSEL
CARBOXIN + CAPTAN (VITAVAX)	2010	Carboxin, captan	Odorless, white crystalline Powder [3] VP: 0mmHg (approx)	BP: decomposes	Fungicide	• Toxicity to reproduction/fertility, A3 respirable fraction, sensitizer[1] • Irritation in eyes, skin upper respiratory system, blurred vision, dermatitis, skin sensitization, dyspnea, diarrhea, vomiting, potential occupational carcinogen[3] • **Kidney is a target organ of captan[3]**	NSEL

1. Material Safety Data Sheets (MSDS)
2. ATSDR Toxicological Profile Information Sheets
3. NIOSH Pocket Guide to Chemical Hazards
4. 'On the implementation of the European Community Strategy for Endocrine Disrupters - a range of substances suspected of interfering with the hormone systems of humans and wildlife'. June 2001, first progress report following the adoption of a Community Strategy for Endocrine Disrupters in December 1999.
5. Spanish National Institute of Work Safety and Hygiene (INSHT) Carcinogen, Reproductive, and Mutagen Classifications
6. Neurotoxicity classification (Vela, M.M., Laborda, R. y García, A.M., en Neurotóxicos en el ambiente laboral: criterios de clasificación y listado provisional.)
7. Ley General de Seguridad Social (Spain)
8. Spanish Royal Decree

Internal trainings at ISA include induction programs specific to applicators, in which workers learn which chemicals they will be using, how to apply these chemicals, necessary safety precautions to follow, and how to properly use PPE. External trainings are provided by both MINSA, which trains warehouse workers and applicators, as well as by agrichemical providers, which provide 4-5 different trainings each zafra. However, it seemed that workers do not always know what chemicals they are applying or what the associated hazards may be. Additionally, the Material Safety Data Sheets are not readily available for reference.

During manual application of agrichemicals, the risk of contact with chemicals varies with the type of equipment being used. The plastic mochilas are especially prone to leaking and breaking. Also, the lids come off easily such that when workers slip in the fields, the lids may open, spilling chemicals on the worker. The silver metal mochilas are heavier but reduce the occurrence of leaks and spills.

There is potential for heat stress among these workers due to the high temperatures, strenuous activity, and use of cumbersome PPE. The workers' coveralls were observed to be drenched with sweat, and there is little shade available. However, the intermittent nature of the work provides opportunity for regular breaks. Workers in the field bring drinking water in bottles from home.

During the mechanical application of pesticides, tractor drivers close the windows and use air conditioning. The drivers are required to wear gloves but only use a respirator occasionally while inside the cab. Because workers receive training specific to their job tasks, drivers are only trained in PPE use and machinery operation, but not in chemical hazards or issues related to heat stress. Workers responsible for filling the chemical tank and overseeing the agrichemical application are trained in PPE, and chemical hazards. It was unclear whether they received training about heat stress.

After fields are sprayed with agrichemicals, no signs are posted in the fields warning workers not to enter. It was noted that there is too much land for this to be feasible. MINSA requires a no-entry period of 72 hours after the application of agrichemicals.

E.3. Consideration of Past Practices

Table 4 provides a summary of the agrichemicals that may have been used at ISA in the past, based on information from ISA, information provided by former workers, and other sources. Health effect information summarized in Table 4 is based on information obtained from MSDSs and from U.S. government health agencies such EPA, NIOSH, ATSDR, and other comparable international agencies. This table was intended to provide a summary of potential health effects from sources that should be readily accessible to anyone using these chemicals. As in Table 3, for each chemical, we indicated whether any of the above mentioned sources noted any potential for kidney damage in humans or animals. In addition to potential health effects, the table also summarizes for each chemical: years in use at ISA (if available), active ingredient, vapor pressure and boiling point, classification of chemical, and the source from which we learned of its use. After this initial research into understanding the toxicology and health effects of each chemical, a much more extensive literature review was conducted, upon which we based our final assessments (Section V). Of these chemicals that may have been used at ISA in the past, the information obtained during this initial review indicated that there is a potential for kidney

damage associated with exposure to paraquat, MSMA, diazinon, warfarin, and DBCP (nemagon). However, of these five chemicals, NSEL representatives were only able to confirm the previous use of paraquat and warfarin. The remaining three chemicals have been implicated as being used by non-governmental organizations (DBCP or Nemagon as reported in the Exponent report) and by ASOCHIVIDA members (MSMA and diazinon). We do not currently have sufficient information to know whether these chemicals were used at ISA in the past.

In the past, for the manual application of chemicals, 2-3 workers were in charge of getting the appropriate chemicals, which were in powder form. It was reported that chemical applicators would mix the chemicals and refill the pumps themselves, with each applicator responsible for filling and applying approximately 14 backpacks of agrichemicals per day. Chemical contact was likely more common in the past due to the lack of PPE use. It was indicated that in about 1995 applicators began to use masks and gloves while working; prior to this, it was reported that only a net was worn on the face while applying chemicals to protect workers from being cut by the sharp leaves of the cane plant.

The mechanized application now uses a larger version of the same machine (Jackto) that was used in the past. Similar to manual application, it was reported that there was previously less distinction between the tasks of mixing and applying chemicals. Other chemicals for which records do not exist were also used in small quantities on an experimental basis. It was also reported that any chemicals leftover in tanks following application may have been dumped into rivers or onto the ground in the fields.

Practices surrounding eating, drinking, and smoking in the fields have also changed. Lunch was typically eaten in the field and workers' hands may have been dirty from having manually fixed pumps that had become stuck. It was also reported that workers may have smoked in the fields. There were no trainings in place, and workers were not familiar with safety measures that could be taken to prevent exposure to the agrichemicals they handled.

Showering at El Piñal before returning home has consistently occurred both in the past and the present, though shower facilities have been renovated. Additionally, PPE has always been stored and washed primarily at ISA, as it is currently. However, it has been suggested that PPE was not washed as thoroughly in the past, since washing used to occur manually. It was also noted that while today workers perform only one job task, in the past most workers performed multiple jobs simultaneously since they were assigned to different jobs as they were needed.

Table 4: Summary of Agrichemicals Potentially used at ISA in the Past and their Potential Health Effects

Agrichemical	Period of Use	Active Ingredient	Vapor Pressure	Boiling Point	Use	Health Hazards Reported by Government Agencies and MSDS's	Source
HEXAXINONA	1990-2009	Hexazinone			Herbicide	• Irreversible eye damage, skin irritant with discomfort or rash[1] • Associated with occupational disease-exposure to ketones[7]	NSEL
PARAQUAT	1984-1994	Paraquat dichloride	Yellow solid with a faint, ammonia-like odor[3] VP: <0.0000001 mmHg[3]	BP: Decomposes[3]	Herbicide	• Associated with occupational diseases-exposure to organoclorates and exogene fotosensitizers [7] • Irritation of eyes, skin, nose, throat, respiratory system, epistaxis, dermitits, finernail damage, irritation of GI tract, heart, liver, **kidney damage[3]**	NSEL
MSMA		Monosodium methanearsonate	VP: NI	BP: 212F[1]	Herbicide	• Irritating to skin, mucous membranes; may cause vomiting, diarrhea, pain in chest/abdomen; prolonged overexposure may affect liver**, kidneys[1]**	ASOCHIVIDA
TIOCICLAN HIDROGENOXALATO (EVISECT)	1996-2000	Thiocyclam hydrogen oxalate			Insecticide	• Harmful if swallowed, irritating to skin and eyes, skin sensitizer[1]	NSEL
LORSBAN		Chlorpyrifos	VP: <10mmHg @25C[1], 0.00002 mmHg[3]	BP:290F[1] 320F[3] Low volatility[2] Colorless to white, crystalline solid w/ mild, mercaptan-like odor. [3]	Insecticide	• Cholinesterase Inhibitor, skin irritant, moderate eye irritation/corneal injury[1,2]wheezing, laryngeal spasms, salivation; bluish lips, skin; miosis, blurred vision; nausea, vomiting, abdominal cramps, diarrhea[3]	ASOCHIVIDA
FURADAN		Carbofuran	Odorless, white or grayish, crystalline solid[3] VP: (77°F): 0.000003 mmHg[3]	BP: Not available[3]	Insecticide	• Reversible chonlinesterase inhibitor, toxic if swallowed[1] • Miosis, blurred vision; sweating, salivation, abdominal cramps, diarrhea, headache, nausea, vomiting; lassitude muscle twitching, incoordination, convulsions[3]	ASOCHIVIDA

Table 4: Summary of Agrichemicals Potentially used at ISA in the Past and their Potential Health Effects (Continued)

Agrichemical	Period of Use	Active Ingredient	Vapor Pressure	Boiling Point	Use	Health Hazards Reported by Government Agencies and MSDS's	Source
DIAZINON		Diazinon	VP: 1.20x10-2Pa @25C[1] 0.0001 mmHg[3]	BP: Not Established[1] Decomposes[3] Can volatilize from ground surfaces following aerial application[2] Low volatility-inhalation likely to be aerosols rather than vapor[2]	Insecticide	• Cholinesterase inhibitor[1,2,3] • Nervous system toxicant, slight neurological functional deficits,[2] • Irritation of eyes; miosis, blurred vision; dizziness, confusion, lassitude, convulsions; dyspnea salivation, abdominal cramps, nausea, vomiting[3] • **Kidney effects as a result of AChE inhibition[2]**	ASOCHIVIDA
NOVUCRON		Monocrotophos	VP: 0.000007 mmHg[3]	BP: >177C[1] Colorless to reddish-brown solid with a mild, ester odor.[3] BP: 257°F[3]	Insecticide	• Cholinesterase inhibitor[1] • Irritation of eyes, miosis, blurred vision; dizziness, convulsions; dyspnea, salivation, abdominal cramps, nausea, diarrhea, vomiting[3]	ASOCHIVIDA
PERMETRINA (PERMETHRIN)		Permethrin	VP: N/E	BP: N/E[1] Volatilization from soil and water surfaces occurs slowly[2]	Insecticide	• Dizziness, headache, nausea, muscle twitching, reduced energy, changes in awareness, convulsions, loss of consciousness[2] • Occupational esposure leads to paresthesia, neurotoxicity[2] • Endocrine disruptor[4] • Sensitizers[8]	Exponent report
TERBUGRAN		Terbufos	VP: 34.6mPa (a.i.)	BP:Not applicable[1]		• Acute cholinesterase depression evidenced by nausea, headache, vomiting, diarrhea, blurred vision[1]	Exponent report
BROMADIOLONA	2001-2009	Bromadiolone	VP: Not Applicable	BP: Not Applicable[1]	Rodenticide	• Reduced clotting ability, lethargy, loss of appetite, bleeding, internal bleeding leading to shock and coma[1]	NSEL

Table 4: Summary of Agrichemicals Potentially used at ISA in the Past and their Potential Health Effects (Continued)

Agrichemical	Period of Use	Active Ingredient	Vapor Pressure	Boiling Point	Use	Health Hazards Reported by Government Agencies and MSDS's	Source
COUMATETRALYL	2001-2009	Coumatetralyl	VP: 8.5x10-6mPa @20C	BP: Not Relevant[1]	Rodenticide	• Increased bleeding tendency, massive hemorrhage, hematuria, vomiting blood, cerebrovascular bleeding, bruisibility[1]	NSEL
WARFARINA	1980-1990	Warfarin	VP: Not Applicable[1] (71°F): 0.09 mmHg[3]	BP: Not Available[1] , Decomposes[3] Colorless, odorless, crystalline powder[3]	Rodenticide	• Possible teratogen, possible female reproductive effects, may be toxic to liver, kidneys[1]hematuria back pain; hematoma arms, legs; epistaxis , bleeding lips, mucous membrane hemorrhage; abdominal pain, vomiting, fecal blood; petechial rash; abnormal hematologic indices[3] • Reproductive toxicant (categoryI+T(toxic))[5] • **May be toxic to kidneys[1]**	NSEL
CHLOROCEL		Aluminum Oxide	VP: N/A	BP:N/A[1]		• Eye and skin irritation, drying, gastrointestinal disturbances[1]	Unknown
DBCP		Nemagon, 1,2-dibromo-3-chloropropane	Dense yellow or amber liquid with a pungent odor at high concentrations. [Note: A solid below 43°F.][3] VP: 0.8 mmHg	BP: 384°F[3]		• Damage to male reproductive system, skin and eye damage from contact, headache, nausea, lightheadedness, weakness[2] • Irritation eyes, skin, nose, throat; drowsiness; nausea, vomiting; pulmonary edema; liver, **kidney injury**; sterility; [potential occupational carcinogen][3]	Exponent report

1. Material Safety Data Sheets (MSDS)
2. ATSDR Toxicological Profile Information Sheets
3. NIOSH Pocket Guide to Chemical Hazards
4. 'On the implementation of the European Community Strategy for Endocrine Disrupters - a range of substances suspected of interfering with the hormone systems of humans and wildlife'. June 2001, first progress report following the adoption of a Community Strategy for Endocrine Disrupters in December 1999.
5. Spanish National Institute of Work Safety and Hygiene (INSHT) Carcinogen, Reproductive, and Mutagen Classifications
6. Neurotoxicity classification (Vela, M.M., Laborda, R. y García, A.M., en Neurotóxicos en el ambiente laboral: criterios de clasificación y listado provisional.)
7. Ley General de Seguridad Social (Spain)
8. Spanish Royal Decree

F. Burning Cane

F.1. Overview of Current Process

On the night before a cane field is to be harvested manually, the field is burned. This process removes most of the vegetation on the cane, which makes cutting easier but does not cause significant damage to the interior of the cane stalk. A group of workers called previsas (or "Ghostbusters") is responsible for burning the field. A previsa is made up of about 8 workers who work 12-hour shifts: 4 patrolmen, 2 burners, 1 truck driver, and 1 chief/supervisor. The night shift begins at 5:00 pm and the day shift starts at 5:00 am, with equal numbers of workers assigned to each shift. The intentional burning primarily occurs during the night shift, while the day shift primarily patrols the grounds to monitor and extinguish accidental fires. Up to five previsas may operate during the same shift but will work in different fields.

Each previsa will burn 1-3 fields each night. Before a field is burned, a machine is used to remove excess weeds around the perimeter of the field. A truck then drives around the entire perimeter just before burning to ensure that it is safe to begin the process. Also, the wind speed must be below 6 km/hr for burning to occur. The two burners start the fire using backpacks filled with kerosene and flamethrowers. Starting at the downwind corner of the field, the two burners walk in opposite directions and set the edge of the field on fire. The fires along the downwind edges are set as the counter fires, whereas the fires along the upwind edges spread through the field in the downwind direction. The four patrolmen monitor each edge of the field to ensure that the fire does not spread into adjacent fields. They control the field boundaries using backpacks filled with water, machetes, or by shoveling soil onto the fire. Four firemen work with the previsa in a truck filled with water, ready to extinguish fires that move into adjacent fields. After the cane leaves have burned, the fire extinguishes itself.

F.2. Evaluation of Hazards and Controls

Several steps must be taken before a field can be burned. When the Chief of Burning receives an order about which fields need to be burned, the patrol supervisor comes to the fields and makes notes about which areas could be problematic. This supervisor verifies the wind direction so that a counter fire can be planned accordingly. The patrol supervisor then calls the ranger in an observation tower to report where the fires are planned to occur. The ranger can spot any accidental fires that occur outside of the designated areas. Members of the previsa are required to use PPE, which consists of a hat with ear flaps, respirator, helmet, overalls, and face shield. They receive training from firemen or military personnel to learn how to set up and control fires. The most common injury for cane burners is reported to be minor burns. The most dangerous part of cane burning was reported to be controlling accidental fires, which occur 4-5 times per week. Workers bring water from home (usually about 2.5 gallons) and more water is available at their base should they need it.

F.3. Consideration of Past Practices

In the past, cane fields were burned in the morning as well as during the night-shift, which used to start at 3:00 pm instead of 5:00 pm. Though most of the PPE and work practices appeared to be

similar, previously workers did not use a face shield and helmet, and patrolmen primarily used a shovel to control fires since they did not have backpacks with water. Since firemen were not always present during burning, previsas would ask for help from anyone around. For instance, cane cutters could help by making a furrow to stop the fire, or heavy machinery operators could control fires by cutting cane or weeds. It was also noted that while today workers perform only one job task, in the past most workers performed multiple jobs simultaneously since they were assigned to different jobs as they were needed.

G. Harvesting Cane

G.1. Overview of Current Process

Sugar cane is cut when fully mature after about 10-12 months of growth. Cane is harvested only during the zafra (November through May) using either machines or manual labor. Though manual cutting better preserves the quality of the cane, mechanical cutting has production and cost advantages.

Manual cutters typically work from 5:30 am to 11:00 am or 12:00 pm and produce an average of 5-7 tons of cut cane per worker per day, depending on the condition of the cane and the skill level of the worker. Typically, 800-900 manual cutters work each day, producing an average of 4,000-5,000 tons of cut sugar cane per day. A crew of cutters (130-140 workers) is divided into different groups ("quadrillas") of 10-15 workers that are formed by the workers themselves. Each group is in charge of cutting one ruma (6 furrows), though experienced groups may be given more than one ruma to cut. Harvesters cut the cane just above ground level using machetes. Because sugar levels are highest in the base of the stalk, it is important for them to cut as low to the ground as possible. They then cut off the top of the cane stalk and stack the cane. After all workers have completed the day's task, the cane is collected by machines and brought to the factory for processing. These workers are hired by subcontractors and are paid according to the amount of cane they cut (cutting groups divide pay equally) such that they have an incentive to work as fast as possible.

Cane that is harvested mechanically is cut "green" and therefore not burned the previous night. All fields in close proximity to communities are now cut mechanically due to fire restrictions in these areas. All mechanical cane cutters are employed directly by ISA (not by subcontractors) and typically work 12-hour shifts. Mechanical workers assemble into teams, each of which includes the following: 3 supervisors, 4 harvest machine operators, 8 tractor drivers (with small trailers), 4-5 truck drivers (with large trailers), 4-6 workers who follow after the machines to make sure all cane is picked up, 1 person observing the quality of cut cane (to make sure the machine is not uprooting the plants), and 5 mechanics who maintain the machines. Each team operates in a single field where four machines cut together. ISA has a total of 5 teams of machines and presently owns and operates 20 harvesting machines. Approximately 10,000-10,500 tons of cane are cut using machines per day, depending on the capacity of the factory. The factory typically processes a total of 15,500–16,000 tons per day (including cane cut manually and mechanically), but if it is able to process a greater quantity, then more cane can be harvested mechanically.

G.2. Evaluation of Hazards and Controls

The minimum age for cane cutters is 18. Health and safety controls are enforced by social workers who monitor manual cane cutters as they work in the fields and also by supervisors who travel between fields on motorcycles. The social workers are responsible for enforcing the use of PPE in the fields, and they also monitor workers to ensure that they stay hydrated and do not work past noon. They also ensure that workers are seated on the bus to reduce the risk of cuts from machetes. There was some indication that social workers are not always present for the entire shift in which case workers sometimes cut cane until 2-3:00 pm. The required PPE for manual cane cutters includes polainas, which are shin guards to protect from machete injury, two shirts, two pairs of pants, a cap with a neck cover, and boots. Cane cutters use a curved machete, which is safer than the straight variety used in the past, and they also carry a lima (sharpener). At the beginning of every zafra, cane cutters attend a training that emphasizes proper PPE use, cane cutting technique, accident prevention, and the importance of staying hydrated. The amount of training received seems to vary among workers, with some workers only receiving information about how to perform their task.

Heat stress is a significant hazard for sugar cane workers. The zafra harvesting period occurs during the hottest months of the year, when temperatures reach over 38ºC (100ºF). Incidences of heat stress most commonly occur at the beginning of the zafra, when workers are not used to working long hours in the hot climate. There is currently no acclimatization plan for workers at the beginning of the zafra and the lack of breaks further increases the risk of heat stress. Though workers are allowed to take breaks, they are not required to. Workers have strong incentives to work continuously because they are paid according to how much they cut and more break time means less money for the entire quadrilla. To combat issues of heat stress, a hydration program has been put in place such that protein cookies and bolis are distributed to field workers throughout the shift. Workers must bring their own water from home, but additional water is also available to them on the buses. Workers typically consume several liters of water during a shift. Cutting machines, trucks and tractors are all outfitted with air-conditioned cabins.

There are not many options for shade cover such that workers often have their lunch and breaks in the field. Manual cane cutters are provided with a free hot lunch each day, and they typically eat once they have finished cutting or bring the meal home, though some may eat quickly in the field and return to work.

The most common injuries that occur during this task are cuts from the machete, either during use or during transportation on the bus. One fatal injury occurred this year when a worker on a mechanized cutting crew was crushed by a loading machine. Three other accidental deaths occurred the year before but we do not know the causes.

G.3. Consideration of Past Practices

Several changes to sugar cane cutting practices have occurred. The minimum working age is now 18, but it was widely reported that in the past, children began coming to the fields to work with their fathers as early as age 10. Manual cane cutters worked much longer days, on occasion up to 12-15 hour shifts, with reports that in some instances they worked into the night using the

headlights of cars for light. In the past, workers did not cut in groups of 12. Though workers may have worked in smaller teams, it was reported that two workers may be responsible for cutting one ruma, or one worker might even cut an entire ruma himself. Eight years ago, ISA began contracting sugar cane cutters instead of hiring them directly.

The use of social workers to regulate practices in the field also began about 8 years ago, which brought changes to the length of the workday and a greater consideration for worker hydration. The implementation of bolis and protein cookies is part of a hydration project that started a few years ago. Workers also did not use polainas (shin guards) in the past; it was reported that this practice began in the 1980s. Free lunch for cane cutters began 6 years ago and before that time workers could purchase lunch for three cordobas. Workers were required to bring their own water; it is unclear whether additional water was available to them if they ran out during the workday.

In the past, all sugar cane was burned before cutting, regardless of whether the cane was cut manually or by machine. The exception to this was if there was too much rain to start a fire, which sometimes happened at very beginning or end of the zafra. A few years ago, cane was almost entirely cut by machete, but the expansion of the factory and land has now made machines necessary to keep up with production. ISA had four harvest machines in 2002, purchased four more in 2003, and now owns twenty harvest machines. Originally, La Class machines were purchased from Germany, but these were only used for two or three years and were found to be expensive and inefficient. John Deere harvest machines are now used, which can cut the cane without burning it and also reduces the amount of trash produced. It was also noted that while today workers perform only one job task, in the past most workers performed multiple jobs simultaneously since they were assigned to different jobs as they were needed.

H. Factory

H.1. Overview of Current Process

Production of sugar is the primary function of the factory and occurs 24 hours per day, 7 days per week, during the zafra. The factory can typically process nearly 16,000 tons of sugar cane per day, though its capacity can vary from day to day. During the milling process, the sucrose-containing juice is extracted when the cane is ground and then goes through several filtration, evaporation, and crystallization steps to produce raw sugar. ISA does produce and sell crude sugar, but its primary market is for refined sugar. During the refining process, raw sugar is further purified by adding several elements and undergoing a series of centrifugation, filtration, absorption, and crystallization steps.

During the zafra, workers are employed in a number of different job tasks, primarily as operators, mechanics, and technicians, in all steps of the sugar processing and packaging as well as maintenance activities. Although sugar is not produced during the non-zafra season, a number of workers (far fewer than during the zafra) continue to work at the factory performing maintenance and preparation tasks. ISA also produces ethanol as a biofuel in the distillery and for consumption in the liquoria. Both the cane juice and molasses are used to create these products. The market determines how much of each product ISA will produce in any given zafra;

for example, due to comparative pricing of sugar, the distillery did not operate in the 2009-2010 zafra. Similar to the factory, the distillery and liquoria only operate during the zafra and employ workers in all steps of processing, packaging, and maintenance.

The factory also functions as a cogeneration power plant, as the waste biomass material from sugar cane can be used to create energy. Bagazo, the fibrous residue remaining after sugar cane is crushed to extract its juice, is burned to produce steam and generate energy. The cogeneration power plant consists of three high-pressure boilers with the capacity to produce 660,000 lb/h steam and three turbo generators with a capacity of 20 megawatts each. During the zafra, therefore, the plant is able to generate 60 megawatts of energy to power the factory, irrigation machines, and distillery; there is also excess energy after internal use which is sold to the public. During the non-zafra, the plant uses eucalyptus in a similar process to generate much less power, which is also used to operate irrigation machines and sold to the public. The cogeneration plant does not employ nearly as many workers as the factory, and most of the workers do maintenance tasks on the generators and boilers.

H.2. Evaluation of Hazards and Controls

The factory is a large facility and time constraints did not allow for a thorough assessment of all work processes. Accordingly, comments here will be of a general nature. Injuries in the factory are most commonly associated with maintenance work on the various machines. Likely the most significant potential hazards to workers are slips, trips, and falls; there are many levels to the factory, some of which are at great heights, and there is the potential for slippery or uneven surfaces in all areas. There is also the potential for overexposure to noise when working for long periods of time in close proximity to loud machinery. Eye injuries and head trauma are also possible when working in certain areas.

There is potential for heat stress among these workers due to the high temperatures in parts of the factory and long work shifts; however, because workers are not under the direct sun and are not compensated per unit of production, the potential for heat stress is likely lower than among most field workers. Additionally, workers reported that they are adequately hydrated and have access to both bolis and water, though they do not appear to receive any training regarding heat stress.

All factory workers are employed directly by the company and most appear to work 12 hour shifts, 7 days per week during the zafra. Workers are required to wear PPE (provided by the company) such as hearing and eye protection, hardhats, and dust masks appropriate for the area of work in the factory. At the beginning of each zafra, all factory workers receive training on general safety precautions and use of PPE. Additionally, those who work in loud areas receive hearing tests and the noise levels in these work areas are monitored, though the frequency of testing was not clear. Workers bring their own water from home but have access to additional water in the factory offices as well as bolis.

H.3. Consideration of Past Practices

The general process of sugar production in the factory is very similar to the past, though the amount of sugar produced has steadily increased over time, with the exception of the years 1976

to 1992, in which production was much lower than before. The distillery, where biofuels are produced, was added only five years ago, and the production of energy continues to increase. It appears that workers in the past performed similar job tasks as the factory workers today, though they may not have been required to wear all necessary personal protective equipment such as ear plugs or goggles. It was also noted that while today workers perform only one job task, in the past most workers performed multiple jobs simultaneously since they were assigned to different jobs as they were needed.

V. ADDRESSING THE QUESTIONS POSED BY DIALOGUE PARTICIPANTS

This section addresses the two key questions agreed to by the participants at the Dialogue Table in January 2010:

> 1. Is there evidence that current work practices or chemicals used by ISA currently or in the past cause CRI?
>
> 2. Is there evidence that current work practices or chemicals used by ISA currently or in the past are associated with CRI (e.g., have been shown to cause kidney damage in animals?)

The key difference in the wording of these two questions is in the use of the concept of "cause" (Question 1) and "association" (Question 2). There is no simple way to establish when a particular agent is a *cause* of a particular disease. Reasonable doubts can remain even after some evidence has been collected that demonstrates an association between agent and disease. Although there is no way to define the precise moment at which "association" becomes "causation", it is necessary to make decisions regarding when there is enough evidence to take action to protect the health of persons who may be exposed to such agents. In practice, agents are treated as causes of a particular disease when the scientific community and health authorities judge that the evidence is sufficient.

In order to address the issue of causation in Question 1, we have used the standard of whether particular practices or chemicals are "generally accepted" causes of CRI. Therefore, we have addressed Question 1 based on our assessment of work practices at ISA and on information that is generally accessible from United States government health and environment agencies such as the Environmental Protection Agency (EPA), the National Institute of Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR), and other comparable international agencies.

The focus of Question 2 is on the evidence for possible links between agents at ISA and CRI which aren't strong enough to support a causal relationship. Furthermore, we have interpreted Question 2 as actually having two subparts as follows:

> 2a. Is there evidence that work practices or exposure to chemicals used by ISA currently or in the past are associated with CRI (defined by high creatinine/reduced kidney function)?
>
> 2b. Is there evidence that work practices or exposure to chemicals used by ISA currently or in the past are associated with acute kidney damage in humans or animals?

Because of the distinction between CRI (questions 1 and 2a) and acute kidney damage (question 2b), we first define these terms and describe the difference between them. CRI, more commonly called chronic kidney disease (CKD) is defined by either:

1) Kidney damage for at least 3 months, as defined by structural or functional abnormalities of the kidneys with or without decreased glomerular filtration rate (GFR), manifest by either a) pathologic abnormalities or b) markers of kidney damage, including blood and/or urine markers, or abnormalities in imaging tests; or

2) GFR <60 mL/min per 1.73m^2 with or without kidney damage.

Acute kidney damage, more commonly referred to as acute kidney injury (AKI), is typically defined by an abrupt (within 48 hours) reduction in kidney function, currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/l), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours).

Acute kidney damage can be followed by recovery back to levels of prior function, although recent data suggest that acute kidney injury is associated with worse long term (chronic) kidney and mortality outcomes. This finding raises the possibility that, although clinical recovery has occurred, subclinical injury may remain unresolved and may predispose those affected by acute kidney damage to the progressive decline in kidney function known as CRI. In the absence of kidney biopsy data, this hypothesis remains difficult to prove. This reflects the remarkable kidney reserve, which is demonstrated when someone donates a kidney for organ transplantation. In these healthy individuals donating a kidney, their remaining kidney hypertrophies and the function of each of the functional units within the kidney (the nephron, approximately 1 million per kidney) increases such that, following adaptation, there is no significant difference in GFR pre- and post-kidney donation. Accordingly, while it is likely that acute injury to the kidney results in some chronic damage to individual nephrons, the remaining healthy nephrons are able to compensate assuming that there is sufficient healthy kidney remaining. Therefore, we are hindered by the lack of diagnostic tools for chronic kidney disease as 50% of nephrons can be eliminated before a rise in serum creatinine will even be seen. Accordingly, by the time an individual's creatinine actually rises, that individual has lost more than half of their kidney mass.

Chronic kidney disease can be broadly classified into conditions which affect the glomerulus (the filter) or the tubules of the kidney. The tubules are particularly vulnerable to dehydration and low perfusion, and, in chronic settings of low perfusion, may ultimately become fibrotic (scarred). Scarred portions of the kidney do not produce much urine; therefore, markers of kidney damage are less common with tubular kidney disease than glomerular kidney disease, making diagnosis more challenging. Ultimately and in the latest stage, kidneys with extensive scarring will look small on ultrasound imaging.

As can be appreciated from the definition above, acute kidney damage often is not a subtle presentation. However, among those without access to medical testing, acute kidney damage can go undiagnosed and 'recovery' can occur prior to the next blood test. This does not mean that there is no damage, but rather that the damage is subclinical (beyond our ability to diagnose). In theory, repeated kidney injury could lead to progressive kidney fibrosis and ultimately an elevated serum creatinine. This pattern of development of CRI has not been definitively proven.

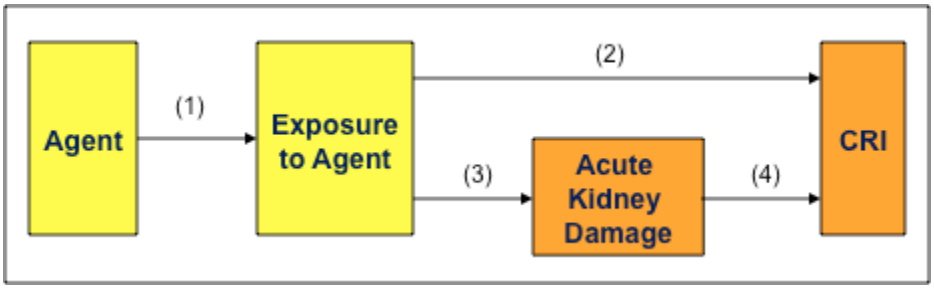
We have addressed Question 2 based on our assessment of ISA work practices and on the results of an extensive literature review to consider whether activities and potential exposures at ISA could cause CRI specifically (Question 2a) and acute kidney damage (Question 2b). While it is hypothesized that any agent causing acute kidney damage may ultimately result in CRI, it is unclear how frequently this may occur in the absence of clinical acute kidney damage. Accordingly, we did not consider evidence that an agent could cause acute kidney damage (Question 2b) to be evidence that it necessarily could cause CRI (Question 2a) under the working conditions at ISA. For an agent to be considered capable of causing CRI, we had to find direct evidence in our literature review.

The conclusions to Questions 1 and 2 are most helpfully interpreted as providing different levels of strength to the hypothesis that work practices or chemicals used by ISA are responsible for CRI. Question 1 addresses associations between an agent and CRI that would be generally accepted as causal based on current knowledge. Question 2 addresses relationships that are plausible but not established, and which would require new knowledge to make a causal connection. Within question 2, associations addressed in subpart (a) provide stronger evidence than associations in subpart (b).

We have addressed these questions for five categories of agents: Agrichemicals, Heat Stress, Metals, Infectious Agents, and Silica. While the 2009 Scoping Study Report identified a longer list of possible hypotheses for the epidemic of CRI in Nicaragua, the agents discussed in this report are the subset of that longer list that could be associated with occupational exposures. Silica is the one new agent that was not included in the 2009 Scoping Study Report; its inclusion grew out of our assessment of ISA work practices along with review of the literature. We have considered agents that might be naturally occurring (e.g., metals, infectious agents and silica) as potential occupational causes of CRI, because occupational activities frequently result in higher exposures than would typically occur in a non-occupational setting, thereby introducing a potential increased risk.

Figure 1 presents a conceptual model that describes the potential associations between agents of concern, possible exposure to those agents, acute kidney damage, and CRI. Our approach to addressing the questions posed by dialogue participants is best explained through a series of steps that correspond with the numbered arrows shown in this figure.

Figure 1. Conceptual model of the relation between agents, exposure and acute kidney damage and/or CRI



The simple presence of a hazardous agent does not mean the agent poses health risks to workers, because it is possible that the worker may not have any exposure to that agent. For this reason, our first step (1) was to consider the likelihood that work practices at ISA are associated with exposure to each agent of interest (e.g., agrichemicals, heavy metals, etc). So for each of the five agents, we commented on the likelihood of exposure among workers at ISA.

It is important to note that (with the exception of heat stress) quantitative exposure measurements were not available such that our assessment of the likelihood of exposure relies on qualitative information obtained during the site visit. This is an important limitation since the assessment of exposure to an agent is not simply a yes or no question. The mere fact that an agent may be present at ISA and even that workers have been exposed to that agent does not provide sufficient evidence to conclude that workers are experiencing exposures that are sufficiently high to cause health effects. We would ideally like to know the intensity of exposure (how much is a worker exposed), the frequency of exposure (how often a worker is exposed), and the duration of exposure (how long is a worker exposed), since all of these factors determine whether an exposure is sufficient to cause a health effect. The lack of quantitative exposure data is currently an important data gap that will be partly addressed by planned research activities.

The second step (2) was to consider whether exposure to the agent is specifically associated with CRI. So for each of the five agents, we commented on the likelihood of causing CRI. To characterize the likelihood that exposure to each agent of interest could be associated with CRI, we assigned a "Strength of Evidence" determination to each according to the following guidelines:

> The "**strong evidence**" category is reserved for agents where a causal association with CRI is well accepted by the scientific community. This category would be assigned to agents for which government agencies have determined that the agent is associated with CRI or for which epidemiologic studies have found clear associations between the agent and CRI.
>
> The "**good evidence**" category includes agents with some human evidence and strong corroborating animal evidence of an association between the agent and CRI.
>
> The "**limited evidence**" category contains agents for which evidence of an association with CRI in humans was limited to case reports or a small number of conflicting studies, even if the toxicological literature suggested an association. This category also contains agents for which there was no evidence or in which there were no available studies.

The third step (3) was to consider whether exposure to the agent is associated with acute kidney damage, which is essentially any type of kidney damage other than CRI. So for each of the five agents, we commented on the likelihood of causing acute kidney damage. The same "Strength of Evidence" options described above were used to characterize the likelihood that exposure to each agent of interest could cause acute kidney damage.

The fourth step (4) was not explored specifically but is important to address. It has been hypothesized that any insult causing acute kidney damage may ultimately result in CRI, but this

relationship has not been proven. Accordingly, our assessment of the possible relationship between exposure and CRI (as shown in step 2) is an assessment of evidence that the exposure is associated with CRI specifically, but does not consider the unproven hypothesis that any insult causing acute kidney damage may ultimately result in CRI (as shown in step 4).

This report represents an important first step toward evaluating if work practices at ISA are associated with CRI in workers, which requires us to have evidence that work practices at ISA are resulting in exposure to a certain agent (step 1) and have evidence that exposure to the agent at a certain intensity, frequency and duration can result in CRI and/or acute kidney damage (steps 2 and/or 3). Accordingly, the overall summary for each agent addressed the questions posed by the dialogue participants by considering what is known about both the likelihood of exposure (1) as well as the likelihood of causing CRI (2) and acute kidney damage (3).

The planned subsequent phases of this research program will focus on gathering additional exposure and outcome data in an effort to characterize the current gaps in our knowledge. After the summary for each agent, we list the activities proposed to increase our understanding of whether or not there may be a link between that agent and occurrence of CRI at ISA.

A. Agrichemicals

We evaluated the 21 agrichemicals identified by NSEL to be currently used at ISA (see Table 3). Regarding agrichemicals used in the past, we evaluated six identified by NSEL, five listed by ASOCHIVIDA and four listed by other sources (see Table 4). An extensive literature search was conducted using the United States National Library of Medicine's PubMed electronic database. This search was designed to be broad in scope (i.e. as inclusive as possible) and was carried out in a consistent manner for each of the 36 total agrichemicals. We focused our review on the articles that were identified by each search, in particular on studies of humans (epidemiological) and other mammals (toxicological). In other words, we did not review articles that focused on birds, amphibians, or fish since these were less relevant to human health. The methods used for conducting the search, as well as the detailed reviews for all 36 agrichemicals, are included in the Appendix.

A.1. Likelihood of Exposure

The potential for exposure to agrichemicals varies by job and by agrichemical. For instance, the manual applicators and mixers have the highest likelihood of exposure as compared to workers in other jobs, and 2,4-D appears to be the agrichemical that is used most often at ISA (based on information obtained during the site visit). Though the PPE used by these workers is designed to minimize exposures, there is still a high likelihood of exposure for these workers. This is particularly true given that the respirator cartridges used by applicators are not recommended for use with organic vapors and that the current procedures for decontamination and storage of some PPE could result in additional exposures (see Chapter IV, Section E.2). Exposure among field workers not directly involved with chemical application is likely lower given that they do not work directly with the chemicals and primarily work in fields weeks after chemicals were applied; however, these other workers still have some likelihood of lower exposures due to contact with agrichemicals in soil (inhalation of dust, incidental ingestion, dermal contact),

agrichemicals in irrigation water (incidental ingestion, dermal contact), or residues on the plant itself. It should be noted that incidental ingestion of water refers to ingestion that might occur from hand to mouth contact and not from use as drinking water, since it seems clear that workers currently bring their drinking water from home. It also appears that PPE use has improved over time and that in the past workers may have consumed water drawn from sources in the field, such that conditions in the past likely resulted in higher exposures than those experienced by current workers.

Overall, it seems likely that exposure to agrichemicals has decreased over time and that PPE is controlling exposure to agrichemicals to some extent, but the high frequency of agrichemical use, poor decontamination procedures, and the use of respirator cartridges not recommended for use with organic vapors likely result in exposures to agrichemicals that vary by job and chemical.

This assessment of the likelihood of exposure was limited to a qualitative assessment based on a review of work practices during the site visit. We do not currently have quantitative exposure data that allows us to estimate the intensity, duration and frequency of worker exposure to agrichemicals.

A.2. Likelihood of Causing Acute Kidney Damage and/or CRI

Regarding the potential for exposure to a given chemical to be associated with acute kidney damage, the results of the literature review indicated that two of the 36 agrichemicals (2,4-D and paraquat dichloride) have strong evidence of an association, four were determined to have good evidence of an association (captan, cypermethrin, glyphosate and DBCP), and the remaining 30 agrichemicals were determined to have limited or no evidence of an association.

Regarding the potential for an association with CRI specifically, we found only limited evidence (beyond the unproven hypothesis that any kidney damage may eventually result in CRI).

A.3. Summary

With respect to agrichemicals as an agent of interest, we have addressed the questions posed by dialogue participants based on the information that we obtained and reviewed as described in this report, and based on our interpretation of the questions as described above.

Regarding Question 1, our review of the medical literature did not find evidence that any of the 36 agrichemicals are generally accepted causes of CRI.

Regarding Question 2a, our review of the medical literature did not find evidence that any of the 36 agrichemicals are associated with CRI.

Regarding Question 2b, we found strong evidence in our review of the medical literature that chemicals used by ISA currently or in the past are associated with acute kidney damage in humans or animals under certain exposure scenarios. We have only limited, qualitative evidence from our field observations that current work practices are resulting in some exposure to agrichemicals, but we do not have quantitative information about the intensity, duration and

frequency of exposure. For instance, even though 2,4-D is commonly used by ISA, and there is strong evidence in the medical literature that exposure to 2,4-D under certain conditions is associated with acute kidney damage in humans or animals, we do not have any data about the intensity, duration and frequency of exposure among workers at ISA and therefore cannot evaluate whether exposures are sufficiently high among workers at ISA to result in acute kidney damage.

The primary activities that will address exposure to agrichemicals and whether agrichemicals are associated with CRI in workers at ISA are environmental testing, biological testing, and the retrospective cohort study. We may also gain additional insight from short-term intensive biomonitoring and medical record review.

B. Heat Stress (Volume Depletion and Muscle Damage)

Although heat stress is not a recognized cause of CRI, it is associated with volume depletion and muscle damage (rhabdomyolysis), both of which are recognized susceptibility factors for acute kidney damage. Available data suggests that CRI prevalence may be higher in occupations in which strenuous work is performed in high environmental temperatures (e.g., sugar cane workers, miners, etc.), conditions that would predispose to volume depletion and muscle damage (Torres, 2010).

B.1. Likelihood of Exposure

Field workers at ISA clearly perform strenuous tasks in a hot work environment such that heat stress is an important concern. Table 5 presents a summary of the temperature, humidity, and heat stress data collected during the site visit. The air temperature readings ranged from 28.6°C to 40.1°C (mean of 35.8°C), the humidity readings ranged from 26% to 74% (mean of 49%), and wet-bulb globe temperature (WBGT) readings ranged from 26.9°C to 33.2°C (mean of 30.6°C). The WBGT readings provide a composite measure used to estimate the effect of temperature, humidity, and solar radiation on humans.

For comparison, Table 6 provides a summary of the Permissible Heat Exposure Threshold Limit Values (TLVs) mandated by the United States Occupational Safety and Health Administration (OSHA). At the average WBGT readings of 30.6°C, OSHA would require workers performing heavy work (such as cutting sugar cane) to work for 15 minutes and rest for 45 minutes out of each hour. These TLV's apply to physically fit and acclimatized individuals wearing light summer clothing and are based on the assumption that nearly all acclimatized, fully clothed workers with adequate water and salt intake should be able to function effectively under the given working conditions without exceeding a deep body temperature of 38°C (100.4°F). Given the nature of the work and work environments at ISA, the workers with the greatest risk of heat stress are cane cutters, seed cutters, seed planters, and applicators.

The WBGT data and current work practices at ISA provide strong evidence that workers have a high risk of heat stress. Additionally, an unpublished study in ISA sugar cane workers found a weight loss of 2.6 kg, an increase in serum sodium to 145, an increase in serum osmolality to 301 mOsm/kg and an increase in urine specific gravity to 1.026 during the work day in a control

group, compared to a weight gain of 0.8 kg, an increase in serum sodium to 141, an increase in serum osmolality to 295 mOsm/kg, and an increase in urine specific gravity to 1.015 in a group educated about the need for adequate hydration. The results show clear evidence of volume depletion in the control group, while the group receiving the hydration education maintained adequate hydration during the workday (Solis Zepeda, 2007). There is no comparable evidence that muscle damage is occurring in workers at ISA.

Table 5. Summary of Heat Stress Data Collected During Site Visit

Field	Date	Time	Air Temperature (°C)	Humidity (%)	Wet Bulb Globe Temperature (°C)	Activity Observed
Morgan	4/20/2010	7:15	28.6	74.2%	26.9	Manual application of herbicides
Morgan	4/20/2010	8:55	35.1	55.6%	30.2	Manual application of herbicides
Bernard	4/20/2010	10:40	37.8	41.2%	31.2	Mechanized application of herbicides
El Pinal	4/20/2010	11:20	36.3	50.5%	31.2	Storage and mixing of herbicides
El Pinal	4/20/2010	12:40	37.4	43.1%	31.1	Storage and mixing of herbicides
Jerico	4/20/2010	14:53	34.6	60.9%	31.3	Fertilization mixture and storage
Jerico	4/20/2010	15:45	33.8	54.9%	30.0	Fertilization mixture and storage
El Socoro	4/21/2010	7:50	31.5	67.0%	28.6	Manual cutting of cane
El Socoro	4/21/2010	9:30	35.2	41.8%	29.2	Manual cutting of cane
El Socoro	4/21/2010	10:00	38.6	38.8%	31.1	Manual cutting of cane
Santa Rosa	4/21/2010	11:30	35.8	46.0%	31.2	Mechanized cutting of cane
Factory (inside)	4/21/2010	15:00	37.2	65.0%	32.4	Sugar processing
Factory (inside)	4/21/2010	16:30	38.2	51.9%	31.4	Sugar processing
Amallia	4/22/2010	8:00	34.4	46.6%	30.2	Cutting of seed
Amallia	4/22/2010	9:30	37.7	35.7%	30.2	Cutting of seed
San Francisco #4	4/22/2010	11:15	37.5	31.9%	29.7	Planting Seed
San Francisco #4	4/22/2010	11:45	40.1	25.8%	33.2	Planting Seed
Manchester	4/23/2010	8:50	33.9	58.6%	30.6	Gravity Irrigation
Pasondo	4/23/2010	10:30	37.4	35.8%	31.6	Sprinkler Irrigation

Table 6. Permissible Heat Exposure Threshold Limit Values – (OSHA)

	---------- Work Load* ----------		
Work/rest regimen	Light	Moderate	Heavy
Continuous work	30.0°C (86°F)	26.7°C (80°F)	25.0°C (77°F)
75% Work, 25% rest, each hour	30.6°C (87°F)	28.0°C (82°F)	25.9°C (78°F)
50% Work, 50% rest, each hour	31.4°C (89°F)	29.4°C (85°F)	27.9°C (82°F)
25% Work, 75% rest, each hour	32.2°C (90°F)	31.1°C (88°F)	30.0°C (86°F)
*Values are in °C and °F, WBGT.			

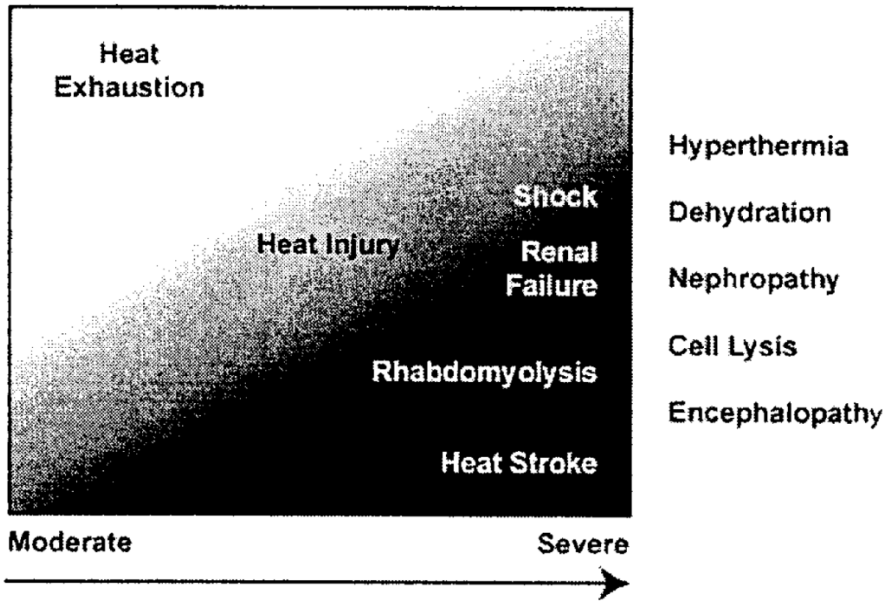
B.2. Likelihood of Causing Acute Kidney Damage and/or CRI

Thermoregulation is a complex process where human core body temperature remains constant at approximately 37°C despite wide variations in environmental temperatures and heat production by metabolism. A rise in the temperature of blood by less than 1°C activates peripheral and hypothalamic heat receptors that signal the hypothalamic thermoregulatory center, and the efferent response from this center increases the delivery of heated blood to the skin (the major heat dissipating organ), dilation of the peripheral venous system, and stimulation of sweat glands. Skin will dissipate heat through conduction, convection, radiation, and evaporation. The efficiency of evaporation as a mechanism of heat loss depends on the condition of the skin and sweat glands, the function of the lungs, ambient air temperature, humidity, air movement and whether or not the person is acclimated to high temperatures.

Figure 2 provides a summary of the heat illness spectrum. The acute-phase response to heat stress involves an upregulation of cytokines and heat shock proteins. Minor heat stress becomes more severe heat illness when internal organ temperatures rise to critical levels (approximately 40°C), at which point cell membranes are damaged, gene expression profiles significantly change, and cellular energy systems are disrupted. The progression to multisystem dysfunction is the result of a complex interplay among the acute physiological alterations of hyperthermia (circulatory failure, hypoxia, and increased metabolic demand), the direct cytotoxicity of heat, and the inflammatory and coagulation responses in the host.

Volume Depletion. Volume depletion is unlikely the primary cause of CRI, but it is a common and well-accepted susceptibility factor for kidney injury caused by other agents, particularly due to nephrotoxin exposure. In fact, the use of prophylactic volume expansion is the cornerstone for the prevention of acute kidney injury due to the administration of nephrotoxic agents such as radiographic contrast or chemotherapeutic drugs (Pannu, 2006). Furthermore several experimental models of nephrotoxic kidney injury require the use of diuretics and/or salt depletion for the nephrotoxin to cause kidney injury. These experimental models include aristolochic acid (Debelle, 2002), the likely cause of Balkan endemic nephropathy, as well as radiocontrast administration (Heyman, 1988).

Figure 2. Heat Illness spectrum from United States Air Force



Additionally, there is further evidence that adequate rehydration regimens can reduce the risk. The results from the unpublished study mentioned above show clear evidence of volume depletion in the control group, while the group receiving the hydration education maintained adequate hydration during the workday (Solis Zepeda, 2007).

Muscle Damage. Muscle damage is a well-recognized cause of acute renal failure, a severe form of acute kidney damage. Acute renal failure is thought to occur because of the release of the nephrotoxic muscle protein, myoglobin, from damaged muscle. Myoglobinuric acute renal failure has been reported after traumatic muscle damage (e.g., crush injury) and after non-traumatic muscle injury (e.g., resulting from statins). Though it is not typically considered to be a cause of CRI, there are isolated reports of chronic interstitial nephritis as a consequence of rhabdomyolysis. Kew et al. reported on 40 South African miners who developed heatstroke, all of whom also developed evidence for kidney damage during an acute heatstroke episode (Kew et al., 1970). Although the patients who survived the initial episode made complete clinical recoveries, four of the patients went on to develop chronic progressive tubulointerstial nephritis over a period of four years. There have been no subsequent reports of similar cases, but there has been a report of a patient with McCardle's disease who developed chronic tubulointerstitial nephritis (McCarron, 1980). McCardle's disease is a familial muscle enzyme deficiency characterized by recurrent episodes of rhabdomyolysis and myoglobinuria after exercise, rarely resulting in myoglobinuric acute kidney injury. The reported case had multiple episodes of myoglobinuria with a single episode of acute renal failure at age 42. A kidney biopsy done one month after the episode of acute renal failure, when the patient's serum creatinine was 1.2 mg/dl, showed marked chronic tubulointerstitial disease, which the authors attributed to recurrent episodes of myoglobinuria.

These two reports are important since they provide some histologic evidence for the development of CRI in response to myoglobinuria. The report of Kew et al. is particularly interesting, since the renal disease occurred in workers under similar environmental conditions to

those seen at ISA, specifically strenuous work in high environmental temperatures. However, this report only describes patients with heatstroke, the most severe manifestation of heat-induced injury. The report of the McCardle's patient suggests that chronic myoglobinuria may also be a cause of CRI.

B.3. Summary

With respect to heat stress as an agent of interest, we have addressed the questions posed by dialogue participants based on the information that we obtained and reviewed as described in this report, and based on our interpretation of the questions as described above.

Regarding Question 1, our review of the medical literature did not find evidence that heat stress, volume depletion, or muscle damage are generally accepted causes of CRI.

Regarding Question 2a, our review of the medical literature found very limited evidence that heat stress, volume depletion, or muscle damage are associated with CRI.

Regarding Question 2b, we have strong evidence from our field observations and available reports that current work practices at ISA could be associated with heat stress and volume depletion, and strong evidence from our review of the medical literature that volume depletion and muscle damage are associated with acute kidney damage in humans or animals; however, there are no data available to assess whether current work practices at ISA are resulting in acute kidney damage.

The primary activities that will address exposure to heat stress and whether heat stress is associated with CRI in workers at ISA are short-term intensive biomonitoring and the retrospective cohort study. We may also gain additional insight from biological testing and medical record review,

C. Systemic Infections

We identified in the scoping study that certain infectious diseases including leptospirosis, hantavirus, malaria, Chagas disease, yellow fever and schistosomiasis, are potential causes of CRI in Nicaragua. Here, we focus on leptospirosis and hantavirus since workers may have exposure to these infectious agents as the result of their activities at ISA.

C.1. Likelihood of Exposure

Leptospirosis is a zoonosis (a disease that can be transmitted from animals to humans) that can occur through direct or indirect transmission from a mammalian host such as rodents or dogs. Indirect transmission via contact with *Leptospira* contaminated water or soil is thought to be responsible for most cases. For this reason, workers in rice fields**,** sugar cane plantations and mines have been described as risk groups (Everard, 1992 and Cespedes, 2003). In Western Nicaragua, outbreaks following heavy rains have been described (Ashford, 2000).

Of particular relevance are the outbreaks that occurred in the municipalities of Achuapa and El Sauce (León) in 1995, in the Pacific Coast of Nicaragua in 1998 (post hurricane Mitch), in Rio San Juan in 1999 (rice fields), and in Chinandega, León and Managua in 2007 (post hurricane Felix) (Amador, 2008).

A cross-sectional survey immediately following the outbreak of 1995 found that 85 of 566 (15%) persons tested were IgM positive for leptospiral IgM antibody (Ashford, 2000). In the case-control study conducted to evaluate this outbreak, 23% of asymptomatic control subjects were seropositive by microscopic agglutination test (MAT), with antibodies reactive for serovars including Canicola (14.9%), Pyrogenes (10.6%), Bratislava (12.8%), and Icterohaemorrhagiae (8.5%). This high seropositive rate among controls suggests a high background rate of endemic disease, or alternatively a high rate of asymptomatic infections during the outbreak (Trevejo, 1998).

The CDC and MINSA conducted a baseline seroprevalence study in the Department of León (municipalities of El Sauce and Achuapa) in February 2007 (months prior to the October 2007 outbreak). They found a prevalence (single MAT antibody titer $\geq$100) of 42% (188 out of the 448 samples obtained). Eighty-two (32.3%) of females were seropositive with a MAT titer >100, compared to 106 (55.2%) of males ($p < 0.001$) (CDC, 2007).

Rodents are also the principal reservoir for hantavirus. Humans appear to be infected by aerosols or dust from rodent urine, droppings, or by direct contact with saliva through cuts or mucous membranes. People who come in direct contact with rodents and heavily rodent-contaminated areas are at risk, especially rural area residents and farmers (CDC disease fact sheet).

Due to the large number of rodents observed at ISA and the workers' potential exposure to these infectious agents in water (via incidental ingestion, dermal contact) and soil (via inhalation of dust, dermal contact, incidental ingestion), it is possible that workers have occupational exposure to leptospirosis and hantavirus. In particular, workers with high dust exposure (i.e., cane cutters and seed planters) or with extensive contact with water (i.e., irrigation workers) may have the highest likelihood of exposure. However, we have no data regarding the prevalence of these diseases in the ISA work environment and no exposure data to characterize the extent to which workers have occupational exposure to leptospirosis or hantavirus at ISA.

C.2. Likelihood of Causing Acute Kidney Damage and/or CRI

Leptospirosis can cause acute kidney injury; the lesion is typically consistent with a tubulointerstitial process and may also manifest with electrolyte abnormalities (potentially due to inhibition of the Na^+, K^+, $2Cl^-$ transporter in the ascending limb of the Loop of Henle). Interstitial nephritis with interstitial edema and mononuclear cellular infiltration are the usual findings. Clinically, non-oligouric acute renal failure, hypokalaemia and sodium wasting appear frequently in leptospirosis (Wu MS, 2004).

In general, recovery from renal failure after leptospirosis appears to be complete and leaves no lasting renal or other organ impairment, however, persistent tubular dysfunction after some months of follow up has been found in some studies (Abdulkader, 2008; Covic, 2003; Daher

2004, Visith, 2005). Progress to CRI has been described in the literature in one case in a patient with previous hypertension (Abdulkader, 2008).

Animals which have recovered from acute leptospirosis may develop a chronic carrier condition in which leptospires grow and may remain in the renal tubules and being excreted in the urine from periods of days to years. The kidneys of chronic carrier animals vary in appearance from normal (as frequently see in naturally infected rodents), to scarred, pale shrunken kidneys characteristic of chronic nephritis (as seen in some dogs) (Faine, 1999).

Several hantavirus species are known to cause hemorrhagic fever with renal syndrome (HFRS), one form of which is referred to as Nephropathia epidemica (NE). Kidney involvement is more common with Hantavirus infection in Europe and Asia and less common in endemic hantavirus in the Western Hemisphere. Usually the kidney disease presents with acute tubulointerstitial nephritis. Other common interstitial changes include congestion and dilatation of the medullary vessels, hemorrhage into the medullary tissues, interstitial edema, and tubular cell necrosis and degeneration. Histologic changes in the glomeruli are typically mild despite prominent proteinuria (Muranyi 2005, Papadimitriou, 1995, and Mustonen, 1994).
We found in the literature only one case in France of moderate CRI after 30 months of a Puumala hantavirus infection (Novo, 1999).

Accordingly, we found strong evidence that leptospirosis and hantavirus are associated with acute kidney damage in humans or animals but only limited evidence of a possible association with CRI specifically.

C.3. Summary

With respect to systemic infections as agents of interest, specifically leptospirosis and hantavirus, we have addressed the questions posed by the dialogue participants based on the information that we obtained and reviewed as described in this report, and based on our interpretation of the questions as described above.

Regarding Question 1, our review of the medical literature did not find evidence that leptospirosis or hantavirus are generally accepted causes of CRI.

Regarding Question 2a, we found very limited evidence in our review of the medical literature that leptospirosis or hantavirus are associated with CRI.

Regarding Question 2b, we found strong evidence in our review of the medical literature that leptospirosis and hantavirus are associated with acute kidney damage in humans or animals, but there are no exposure data available to characterize the extent to which workers may be exposed to leptospirosis or hantavirus at ISA.

The primary activity that will address exposure to infectious agents and whether infectious agents are associated with CRI in workers at ISA is biological testing. We may also gain additional insight from medical record review and the retrospective cohort study.

D. Heavy Metals

We identified in the scoping study that certain heavy metals including lead, cadmium, and uranium, are potential causes of CRI in Nicaragua. Here, we focus on the likelihood of occupational exposure to these metals at ISA and subsequently the likelihood that these metals may cause acute kidney damage and/or CRI among ISA workers.

D.1. Likelihood of Exposure

Lead, cadmium, and uranium may enter the environment through anthropogenic or natural activities. Occupational activities involving each of these metals may contaminate the ambient environment and cause them to be found in the air, soil, and water. Lead, in particular, may be deposited in environmental media from gasoline emissions and leaded paint (Romieu, 1994). A potentially major natural source of all three metals in the Nicaraguan environment is volcanic eruptions, which occur frequently in the area.

There is the potential for ISA workers to be exposed to lead, cadmium, and uranium through contact with soil (inhalation of dust, incidental ingestion, dermal contact) or water (incidental ingestion, dermal contact) while performing their jobs. The source of these metals would likely be volcanic activity, and work activities could result in exposure. In particular, workers in job tasks such as cane cutting and seed planting may have the highest likelihood of exposure, as working conditions tend to be dustier than those in other job tasks. However, there are currently limited exposure data to evaluate the extent to which workers may be exposed to lead, cadmium, and uranium at ISA.

Three studies have examined exposure to heavy metals among workers at ISA and its possible relation to CRI. A case-control study of 43 sick and 39 healthy ISA workers found that 28% of the sick workers and 2.5% of the healthy workers had a positive lead test (Odds Ratio: 18.9) (Marin, 2002). Another case-control study of 57 sick and 68 healthy ISA workers found high blood lead levels among patients in Leon and Chinandega (Zelaya FA, 2001). A third study of ISA workers found that cadmium levels were higher among 15 cases versus 15 controls (0.73 ug/day versus 0.42 ug/day) but found some evidence that the difference may be related to cigarette smoking, another important source of cadmium exposure (Uriarte Barrera, 2000). It is difficult to interpret these results due to the timing of the testing. The individuals with CRI were prevalent cases (i.e., had CRI at the time of testing), and therefore it is not possible to determine whether the higher levels of lead and cadmium among the cases were a cause or an effect of the disease.

D.2. Likelihood of Causing Acute Kidney Damage and/or CRI

Chronic exposure to heavy metals, most notably lead, cadmium, and uranium, is associated with chronic tubulointerstitial nephritis. These heavy metals may accumulate in proximal tubule cells, causing both functional and structural damage that results in reabsorptive and secretory defects. The mechanisms remain unknown but may involve local oxidative stress with associated lipid peroxidation, apoptosis, and necrosis as common phenomena in the course of nephrotoxicity of these metals (Sabolic, 2006).

Lead nephropathy has unique pathologic findings, including acid-fast intranuclear inclusions of proximal tubule cells; in chronic nephropathy, focal tubular atrophy, interstitial fibrosis, and minimal cellular infiltrates predominate (Sabolic, 2006). Most evidence supporting a causal role for lead in CRI comes from studies of occupationally exposed individuals who experienced high levels of exposure (Weeden, 1975). However, there is also evidence that lower exposure levels stemming from either occupational or environmental sources also have an adverse impact on renal function and may accelerate age-related impairment of renal function (Kim, 1996).

Cadmium has a well-established nephrotoxicity (U.S. Department of Health and Human Services, 2008), often following prolonged low-level exposure (Gonick, 2008). Damage is both tubular and glomerular, although tubular proteinuria appears more prominent than glomerular proteinuria. Other renal manifestations may include a Fanconi syndrome (proximal tubular wasting) as well as an immune-complex mediated glomerulonephritis. Chronic cadmium exposure is associated with progressive renal tubular dysfunction in humans, and the toxic effects on the kidney appear to be dose-related (Gonick, 2008). Even very low levels of cadmium exposure may have adverse effects on the kidney, although the lowest dose that induces renal damage is currently unknown.

Animal studies, as well as studies of occupationally exposed persons, have shown that the major health effect of uranium is chemical kidney toxicity, rather than a radiation hazard (Wrenn, 1985; Leggett, 1989; Taylor, 1997). Both functional and histologic damage to the proximal tubules has been demonstrated (Haley, 1982; Diamond, 1989; Gilman, 1998).

Accordingly, we found strong evidence that heavy metals are not only associated with acute kidney damage in humans or animals, but also associated with CRI specifically.

D.3. Summary

With respect to heavy metals as agents of interest, we have addressed the questions posed by the dialogue participants based on the information that we obtained and reviewed as described in this report, and based on our interpretation of the questions as described above.

Regarding Question 1, we found strong evidence in our review of the medical literature that heavy metals are a generally accepted cause of CRI, but currently lack the exposure data that would be necessary to evaluate whether exposure to metals among workers is sufficiently high to cause health effects.

Regarding Question 2a, we found strong evidence in our review of the medical literature that heavy metals are associated with CRI, but currently lack the exposure data that would be necessary to evaluate whether exposure to metals among workers is sufficiently high to cause health effects.

Regarding Question 2b, we found strong evidence in our review of the medical literature that heavy metals are associated with acute kidney damage in humans or animals, but currently lack

the exposure data that would be necessary to evaluate whether exposure to metals among workers is sufficiently high to cause health effects.

The primary activities that will address exposure to heavy metals and whether heavy metals are associated with CRI in workers at ISA are environmental testing and biological testing. We may also gain additional insight from medical record review and the retrospective cohort study.

E. Silica

The hypothesis that silica may be associated with CRI in this region was developed as a result of the high dust exposures observed during the site visit. The silica content in the soil in this region is particularly high, there is selective uptake of silica by the sugar cane plant, and the silica content of bagazo (the fibrous residue remaining after sugar cane is crushed to extract its juice) is similarly high, as is the silica content of bagazo ash (the residue resulting from the burning of bagazo to produce energy).

E.1. Likelihood of Exposure

Cristobalite, a form of crystalline silica, forms during volcanic eruptions in locations such as Nicaragua where eruptions are explosive. These explosions produce ash that is deposited in environmental media throughout the region (LeBlond, 2008). The Ring of Fire, a chain of volcanoes that spans the western coast of North and South America, as well as the eastern coast of Asia and Australia, includes Nicaragua's volcanic chain and has an especially high level of silica.

In addition to the high likelihood that silica is present in environmental media in the region, it is also known that the Poaceae (grass) family (of which sugar cane is a part) accumulates large amounts of silica in its tissue as it is an enriching nutrient for the plant. The sugar cane plant contains particularly high levels of silica, deposited as amorphous hydrated silica. The burning of sugar cane has been shown to form cristobalite due to the very high temperatures (LeBlond, 2008). A case-control study of lung cancer among sugar cane farmers in India also determined that cristobalite forms after the burning of sugar cane (Amre, 1999). Additionally, there is high silica content in bagazo and bagazo ash.

Currently, we have no information about the levels of silica exposure among ISA workers. However, due to the high possibility that silica exists in environmental media, ISA workers may be occupationally exposed via inhalation of dust. In particular, workers in job tasks such as cane cutting and seed planting may have a high likelihood of exposure, as these conditions tend to be dustier than other jobs. Though previous studies have found that sugar cane workers do experience occupational exposure to silica (Boeniger, 1988; LeBlond, 2008), there are currently no exposure data to characterize the extent to which workers may be exposed to silica at ISA.

E.2. Likelihood of Causing Acute Kidney Damage and/or CRI

The United States Silica Company identifies the following as potential health effects of exposure to respirable silica: silicosis, lung cancer, tuberculosis, autoimmune and chronic kidney diseases

(including end stage renal disease) and other non-malignant respiratory diseases (U.S. Silica Company, 2006). The United States Centers for Disease Control (CDC) states that recent epidemiologic studies of occupational exposure to crystalline silica dust have also reported increased incidence of or mortality from extrapulmonary diseases such as scleroderma, rheumatoid arthritis, other autoimmune disorders, and renal disease (NIOSH, 2002). Additionally, the World Health Organization has stated that recent epidemiological studies have found statistically significant associations between occupational exposure to crystalline silica dust and renal diseases and subclinical renal changes (WHO, 2000).

Several other studies have examined the association between silica and kidney damage. Kidney dysfunction was analyzed following short silica exposure (average 1.5 years) in workers who did not suffer from silicosis. An increase in urine excretion of several proteins was found in exposed workers, which led researchers to strongly suggest that occupational silica exposure may lead to subclinical renal dysfunction in less than two years in the absence of silicosis (Hotz, 1995). In Lazio Italy, ceramic workers exposed to silica had a significantly higher risk of developing end-stage renal disease (Rapiti, 1999). End-stage renal disease was found to be significantly elevated in a retrospective cohort of gold mine workers who were exposed to crystalline silica between 1945 and 1965 (Calvert, 1997). Another cohort study followed cases with silicosis and found a significant association between silica exposure and kidney disease, stating that kidney disease should be considered a complication of silicosis (Rosenman, 2000).

Accordingly, we found strong evidence in our review of the medical literature that silica is not only associated with acute kidney damage in humans or animals, but also associated with CRI specifically; however, there is some question as to whether the type of CRI caused by silica is the same as the disease that is occurring in Nicaragua. Silica exposure typically results in a glomerular disease and consequent proteinuria, while the CRI in Nicaragua appears to have characteristics of a tubulointerstitial disease, but the data are not sufficient to rule out silica as an agent of interest.

E.3. Summary

With respect to silica as an agent of interest, we have addressed the questions posed by the dialogue participants based on the information that we obtained and reviewed as described in this report, and based on our interpretation of the questions as described above.

Regarding Question 1, we found strong evidence in our review of the medical literature that silica is a generally accepted cause of CRI; however, there is some question as to whether the type of CRI caused by silica is the same as the disease that is occurring in Nicaragua, and there are no exposure data to evaluate the extent to which workers may be exposed to silica at ISA.

Regarding Question 2a, we found strong evidence in our review of the medical literature that silica exposure is associated with CRI under certain exposure scenarios.

Regarding Question 2b, we found strong evidence in our review of the medical literature that silica exposure is associated with kidney damage in humans or animals under certain exposure scenarios.

One additional consideration is that silica exposure more commonly results in pulmonary pathology (silicosis) rather than kidney disease, and therefore we might expect that frequent occurrence of silica-associated CRI would also be accompanied by cases of silicosis. At this time, we have no evidence that there have been any cases of silicosis among ISA workers, which casts some doubt on the hypothesis that exposure to silica could be causing CRI at ISA. However, the lack of evidence of silicosis is not sufficient to discard the silica hypothesis for the following reasons. First, we do not know whether silicosis has been underdiagnosed among ISA workers. Second, there are multiple forms of silica, and only one type has been clearly associated with silicosis; we do not currently know what type of silica might be the predominant form at ISA. Finally, the combination of silica exposure and volume depletion could theoretically lead to CRI at a lower dose than if silica were the only agent, which could also potentially explain a frequent occurrence of CRI without a similar occurrence of silicosis.

The primary activity that will address exposure to silica and whether silica is associated with CRI in workers at ISA is short-term intensive biomonitoring of workers. We also may gain additional insight from medical record review and the retrospective cohort study.

VI. HEALTH AND SAFETY RECOMMENDATIONS

This section summarizes recommendations that we feel would improve the health and safety program at ISA. These recommendations are not made due to any connection between work practices at ISA with kidney damage, but rather to simply identify opportunities to improve the health and safety procedures at ISA in general. These recommendations are based on our current understanding of ISA operations, which we acknowledge may not be complete. Of note, because the factory is so large and the evaluation focused more on field workers, time constraints did not allow for a thorough assessment of all work processes. Accordingly, we have not made recommendations regarding work practices in the factory.

A. Improve Training Program

The current training program appears to be formal for some topics and informal for other topics. We recommend a simplified approach to worker training in which job-specific training sessions are required for all employees, both temporal and subcontracted. One comprehensive training session should be designed for each job and required of all workers before they are allowed to perform that job. This single training session would at least include the following:

- Technical information about how to perform the job properly
- How to safely operate necessary equipment
- All potential exposures and other hazards associated with performing the job (including heat stress)
- Proper use and maintenance of PPE and why it is required
- Explanation of who is responsible for obtaining, cleaning, and storing PPE (worker versus company)
- Explanation of policies for PPE enforcement
- Procedures for accidents and other emergencies

We recommend that a worker be allowed to perform a particular job only after receiving this job-specific training. We recommend that workers be required to attend this training annually or prior to switching to a new job, and that these trainings are recorded in a consistent manner for all workers. The current method of record keeping is by 'type of training' and is kept on paper, but it would be preferable to keep training records electronically and by worker. This approach would make it easier to quickly determine whether a worker has had the training session required to perform a particular job.

B. Improve Handling and Storage of Agrichemicals

There are several aspects of agrichemicals handling and storage that could be improved at ISA:

- Each container or package of agrichemical needs to be properly labeled with the chemical name and relevant warnings. Many of the containers in the chemical storage area at El Piñal were not properly labeled such that there was no way to know the contents of the container.

- The Material Safety Data Sheet (MSDS) for each agrichemical should be readily available to workers in the areas where the chemicals are handled. For instance, a binder containing all relevant MSDSs should be kept in a readily accessible location at El Piñal.

- Agrichemical workers should receive more comprehensive training regarding the proper handling and potential hazards of agrichemicals. In addition to the core training elements described above, the training session developed for agrichemical workers should include an explanation of:

    - How to use and understand the labels and MSDSs
    - How workers can be exposed to agrichemicals
    - Symptoms as well as long term hazards associated with exposure to each agrichemical with which they will have contact
    - Safety and decontamination procedures
    - How to properly use and maintain PPE, with a particular focus on respirators
    - How to avoid unintentionally taking agrichemicals home

  This annual training should be supplemented by daily debriefing sessions (~5 minutes) at the beginning of each workday in which workers are told what chemicals they are applying, reminded of the health and safety procedures, and provided any additional information that is relevant to that day's work.

- The decontamination procedures should be improved. Workers should not remove their contaminated clothing in the same area where they transfer into their clean clothes. All clothing, PPE, and boots used while working with agrichemicals should be cleaned and stored at ISA and should not go home with the worker, but workers should not store their work clothing, PPE, and boots in the same location where they store their clean clothes since there is a high likelihood that their locker is contaminated with agrichemicals.

- As described in Section IV, the filter cartridges that are currently being used (NIOSH P100 7093C HF) are not recommended for use with organic vapors. For agrichemical applicators, 3M typically recommends a 6001 organic vapor cartridge along with a 5P71 pre-filter, both of which fit into a 501 filter container. However, given the wide range of agrichemicals that are used at ISA, it is possible that one configuration will not be appropriate in all cases. Furthermore, we recommend that the respirators be fit-tested to each worker and that the cartridges be changed regularly based on the manufacturers 'service life' guidelines, rather than the current practice of only being changed when the worker smells the chemical.

- The spilled agrichemicals that are collected in the drainage tank at El Piñal should be disposed of properly as hazardous waste and not applied to areas within ISA, for at least two reasons: one is that it is impossible to know the composition of the mixture since one tank collects spillage of many chemicals in varying amounts, and the other is that there are no procedures in place to control access to areas where the agrichemicals are disposed. Furthermore, some of the labeled containers were observed to be past the date of expiration. Such products should similarly be disposed of as hazardous waste.

C. Reduce Risk of Heat Stress

During the site visit, we observed that workers at ISA perform strenuous tasks in severe heat. Though earlier sections of this report evaluate the potential role of heat stress and CRI, heat stress is a health concern even beyond a potential role in the development of CRI. To reduce the risk of heat stress, we recommend the following:

- An acclimatization program should be developed and utilized at the beginning of each zafra, in which workers work fewer hours initially and gradually increase their work load so that they may become acclimated to the hot conditions. Non-acclimated individuals can only produce 1 L of sweat per hour (which only dispels 580 kcal of heat per hour) whereas acclimated individuals can produce 2-3 L of sweat per hour and can dissipate as much as 1740 kcal of heat per hour through evaporation. Acclimatization to hot environments usually occurs over 7-10 days and enables individuals to reduce the threshold at which sweating begins, increase sweat production, and increase the capacity of the sweat glands to reabsorb sweat sodium, thereby increasing the efficiency of heat dissipation. The fact that incidents of heat stress were reported to be highest at the beginning of each zafra provides further evidence of the need for such a program at ISA.

- At least three breaks per day should be required for cane cutters, seed cutters, and seed planters, in which the workers must come out of the field and rest in the shade. When working in fields where nearby shade is not available, temporary tents or other structures should be used to provide the necessary shade during breaks, though long-term it could be more efficient to build permanent structures at the intersections of several fields. As shown in Table 6, workers performing such tasks should work ~25% of the time and rest ~75% of the time; however, we recognize that this may not be feasible. Instead, we recommend that workers performing such tasks should work ~75% of the time and rest ~25% of the time by taking a 30-minute break approximately every 1.5 hours. For instance, a worker might work from 6-7:30, break for 30 minutes, work from 8-9:30, break for 30 minutes, work from 10-11:30, break for 30 minutes and eat lunch at this time (not in the field), and then work from 12-1:30. Such breaks could be coordinated through the social workers, who should remain in the field for the entire duration of each workday. Although this results in a longer workday (finishing at ~1:30 instead of ~12), we believe that this system will significantly reduce the risk of heat stress and improve worker health.

- We recommend that heat stress training be incorporated into the job-specific training session received by all workers, both temporal and subcontracted. This training should include information about the symptoms of heat stress, how to avoid heat stress with breaks and hydration, the health effects of heat stress, and what to do in case a worker is feeling ill from heat. The informal talks in the field provided by social workers are valuable reminders, but by themselves do not provide workers with sufficient information about heat stress.

D. Enhance Recordkeeping to Improve Surveillance

For the purpose of monitoring the occurrence of CRI as well as for the general health and safety of workers, we have the following recommendations:

- We recommend maintaining a recordkeeping system for contracted workers ("contratados"). Currently, there is almost no employment and limited medical information on this group of workers who constitute a substantial proportion of the workforce. Responsibility for employment recordkeeping appears to be left to the contractors ("contratistas"), but it is not clear what information is maintained and none of this information appears to be provided to ISA. As a result, it is difficult, if not impossible, to conduct basic surveillance of the health of all people working at ISA. ISA already has a good tracking system for its employees. It would be best if contracted workers could be brought into a single integrated system, but if this is not possible, an easily accessible parallel system would be the next best solution. It should be as simple to access the employment history of a contracted worker as it currently is for ISA employees.

- We recommend that social workers record the administration of any medications in the field and save this information in an electronic database organized by worker, regardless of whether the worker is a contractor or an employee. Given the concerns about CRI, it is important to monitor the use of medications distributed to workers while they are at ISA.

- We recommend that the ISA hospital be equipped with an electronic system to aid in basic surveillance of the health of workers. This could aid in detecting an increase or decrease in the occurrence of kidney disease among workers, as well as other outcomes, such as heat stress, infectious disease, chemical overexposure, etc. By tracking patterns of disease over time, surveillance would help identify potential problems which may otherwise be missed and allow ISA to address them.

VII. CONCLUSIONS

The purpose of the industrial hygiene assessment was to evaluate the current work practices at ISA during the 2009-2010 zafra (harvest), as well as the chemicals used at ISA both currently and in the past. We have addressed the questions posed by dialogue participants based on the information that we obtained and reviewed as described in this report, and based on our interpretation of the questions as described in Chapter V.

Based on the investigation described in this report, we found no evidence to conclude that work practices and chemicals used by ISA are causing CRI in ISA workers. Establishing whether there is in fact an association will require the creation of new scientific knowledge.

Our specific responses to the questions posed by dialogue participants consider both the likelihood of exposure to the agents evaluated as well as the likelihood of causing CRI and/or acute kidney damage:

> **1. We found no evidence that the current work practices or the chemicals used by ISA currently or in the past are generally accepted causes of CRI.**
>
> **2a. We found very limited evidence that current work practices or exposure to chemicals used by ISA currently or in the past might be associated with CRI. This association is plausible but not established.**
>
> **2b. We found evidence that agents evaluated at ISA might be associated with acute kidney damage, but we do not have the information that would allow us to determine if exposure levels are sufficient to result in acute kidney damage. In theory, even repeated subclinical acute kidney damage could lead to CRI, but this mechanism has not been proven.**

The specific relation of each of the five agents considered in this report to CRI and/or acute kidney damage is summarized below:

- We found no evidence in our review of the medical literature that any of the 36 agrichemicals evaluated in this report are generally accepted causes of CRI and found no evidence that any of these 36 agrichemicals are associated with CRI.
- We found no evidence in our review of the medical literature that heat stress (volume depletion and muscle damage) and systemic infections (leptospirosis and hantavirus) are generally accepted causes of CRI, and we found only very limited evidence that exposure to these agents is associated with CRI.
- We found evidence in our review of the medical literature that heavy metals and silica cause CRI. However, we do not know the extent of worker exposure to these agents at ISA.
- All five agents could cause acute kidney damage in humans or animals under certain exposure scenarios. However, we do not currently have evidence that exposures at ISA have caused acute kidney damage or whether acute kidney damage might have led to CRI.

The participants of the dialogue table posed questions that focus on the work practices of ISA and we responded to these questions based the current scientific information available. We have concluded that none of the current work practices or the chemicals used by ISA are generally accepted causes of CRI. This conclusion does not rule out the possibility that one or more of these agents might in fact cause CRI, but new scientific knowledge and insights will be necessary to establish whether any link actually exists. To develop this new knowledge, subsequent phases of our work will focus on gathering additional exposure and health data and investigating their possible connection to CRI both within ISA and in other areas of Western Nicaragua.

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APPENDIX

TOXICOLOGICAL REVIEW OF AGRICHEMICALS USED AT ISA

METHODS

We evaluated the 21 agrichemicals that are currently being used at ISA, as well as an additional 15 agrichemicals that may be have been used at ISA in the past.

The literature search was conducted using PubMed, was designed to be broad in scope (i.e. as inclusive as possible), and was carried out in a consistent manner for each agrichemical. There were two components of each search: the terms used to capture the agrichemical of interest and the terms used to capture kidney damage.

For each agrichemical, multiple terms (separated by 'or' statements) were used to ensure that all relevant articles were captured. These terms included the name of the product (eg karmex), the name of the active ingredient (eg diuron), and the CAS number of the active ingredient (eg 330-54-1).

Similarly, multiple terms (separated by 'or' statements) were used to capture all articles that focused on kidney effects. The terms "kidney" and "renal" were included as general search terms. The wildcard search term "nephro*" was included as well, to retrieve any article containing any word with the prefix "nephro." But because PubMed limits its search to the first 600 variations of a wildcard search term (and because "nephro*" has more than 600 variations), the additional wildcard terms "nephrotox*" and "nephropath*" were included to ensure that the most relevant variants of the prefix "nephro" were included.

The search terms relating to each agrichemical were combined with the kidney search terms using Boolean operators as shown in this example for the agrichemical diuron:

(diuron OR karmex OR 330-54-1)
AND
(kidney OR renal OR nephrotox* OR nephropath* OR nephro*)

A search similar to this example was conducted for each of the 36 agrichemicals. We focused our review on the articles that were identified by each search, in particular on studies of humans (epidemiological) and other mammals (toxicological). In other words, we did not review articles that focused on birds, amphibians, or fish since these were less relevant to human health.

AGRICHEMICALS CURRENTLY USED AT ISA

2,4-D

1) Active Ingredient: 2,4-Dichlorophenoxyacetic Acid, CAS #: 94-75-7

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
The MSDS states that 2,4-D exposure is associated with kidney damage in humans with prolonged overexposure. It is classified as US EPA class D (not carcinogenic), IARC Class 2B1. Information on animal studies was not included.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for 2,4-D.

National Institute on Occupational Safety and Health (NIOSH)
The NIOSH Pocket Guide to Chemical Hazards profile considers 2,4-D to be associated with kidney damage in animals. The following are recognized as symptoms of exposure; lassitude (weakness, exhaustion), stupor, hyporeflexia, muscle twitching; convulsions; dermatitis. The target organs identified are: skin, central nervous system, liver, kidneys.

Occupational Safety and Health Organization (OSHA)
Human exposure to 2,4-D has been associated with central and peripheral nervous system effects, liver and kidney damage, and death [NLM 1995; Hathaway et al. 1991; ACGIH 1991]. Acute exposure to 2,4-D has caused irritation of the skin, eyes, throat, and chest; nausea, vomiting, and diarrhea; muscle twitching and weakness; swelling or aching of the extremities; numbness; flaccid paralysis; hyporeflexia and hyperflexia; malaise, headache, and dizziness; low blood pressure; increased body temperature; loss of appetite and weight; malaise; stupor, convulsions, and death [Hathaway et al. 1991; Parmeggiani 1983]. Protein in the urine has also been reported following acute exposure [ACGIH 1991]. OSHA identified one, 2,4-D exposure study in dogs and two studies in rats that resulted in kidney effects. The kidney effects identified were changes in tubules including acute renal failure and acute tubular necrosis.

3) Literature

The scientific literature review resulted in a total retrieval of 105 citations. Of the 105 citations reviewed, the following pertinent articles are summarized below: 2 human epidemiological studies, 7 toxicological studies in humans, and 15 toxicological studies in animals published between 1990 and 2010.

Epidemiological Studies
A study published in 2002 reviewed 2,4-dichlorophenoxyacetic acid (2,4-D) and the current knowledge of the epidemiology and toxicology. The scientific evidence in humans and animals relevant to cancer risks, neurologic disease, reproductive risks, and immunotoxicity of 2,4-D was reviewed. Authors found no experimental evidence exists supporting the theory that 2,4-D or any of its salts and esters damages DNA under physiologic conditions. Overall, the available evidence from epidemiologic studies was not adequate to conclude that any form of cancer is

causally associated with 2,4-D exposure. There is no human evidence of adverse reproductive outcomes related to 2,4-D. The available data from animal studies of acute, subchronic, and chronic exposure to 2,4-D, its salts, and esters show an unequivocal lack of systemic toxicity at doses that do not exceed renal clearance mechanisms. There is no evidence that 2,4-D in any of its forms activates or transforms the immune system in animals at any dose. The one conclusion found is that at high doses, 2,4-D damages the liver and kidney and irritates mucous membranes. (1)

One study investigated renal dysfunction in chemical plant workers. The study group included 24 men, aged 29-54 years, employed directly in the production, and 22 women, aged 31-52 years, comprising a control group and performing auxiliary jobs and handling only closed packages. Renal function was assessed in the workers by determining the concentrations of serum creatinine and uric acid, and urinary protein, albumin and alpha 1-microglobulin concentration, as well as the activity of alkaline phosphatase (AP) and N-acetyl-beta-glucosaminidase (NAG). The active substances with concentrations ranging from 10 to 75% in the final product were as follows: triazines, dithiocarbamates, carbendazim and thiophanate-methyl, captan, phenylureas, cupric oxychloride and occasionally also carbamates, dodine and 2,4-D. As compared to the results in the control group, a significantly higher serum creatinine concentration (in none of the subjects creatinine concentration exceeded the upper normal limit) and higher urinary protein, albumin and alpha1-microglobulin concentrations, and higher enzyme activity were found in men,while in women only urine enzyme activity was significantly increased. The results show possible discreet subclinical kidney impairment in the chemical plant workers. (2)

Toxicology - Humans

One study noted that the toxicity of phenoxyacetic acids (group of herbicides that includes 2, 4-D) is debated, but high-level exposure has been shown to be hepatotoxic as well as nephrotoxic in animal studies. (3) This study validated the use of measurements of urinary phenoxyacetic acids as biomarkers of exposure to the herbicides. Two healthy volunteers received 200 mcg of each phenoxyacetic acid (MCPA, 2,4-D and 2,4,5-T) in a single oral dose followed by urine sampling for 72 h post-exposure. (4) After exposure, between 90 and 100% of the dose was recovered in the urine. In the female subject, 23%, and in the male subject 17%, of MCPA was excreted as HMCPA. (3)

In this paper, 2, 4-D is noted to have moderate mammalian toxicity but human poisoning has rarely been reported except following ingestion with suicidal intent. Between January 1962 and January 1999, 66 cases of chlorophenoxy herbicide poisoning following ingestion were reported in the literature. Two young adults who ingested it with suicidal intent, developed neurological, cardiac, hepatic and renal toxicity and died. (4)

One review paper investigated the mechanisms of toxicity, clinical features, and management of acute chlorophenoxy herbicide poisoning. Between January 1962 and January 1999, 66 cases of chlorophenoxy herbicide poisoning following ingestion were reported in the literature. Twenty-two of 66 patients died. Following an injestion the early effects were vomiting, abdominal pain, diarrhea, and, occasionally, gastrointestinal hemorrhage. Hypotension, if present, was predominantly due to intravascular volume loss, although vasodilation and direct myocardial toxicity may have contributed in some cases. Neurotoxic features included coma, hypertonia,

hyperreflexia, ataxia, nystagmus, miosis, hallucinations, convulsions, fasciculation, and paralysis. Hypoventilation occurred not infrequently, usually in association with central nervous system depression, but respiratory muscle weakness was a factor in the development of respiratory failure in some patients. Myopathic symptoms including limb muscle weakness, loss of tendon reflexes, and myotonia were observed and increased creatine kinase activity was noted in some cases. Other clinical features reported included metabolic acidosis, rhabdomyolysis, renal failure, increased aminotransferase activities, pyrexia, and hyperventilation. It also states that substantial dermal or inhalational 2,4-dichlorophenoxyacetic acid exposure has occasionally led to systemic features but no such reports have been published in the last 20 years and no fatalities have been reported at any time. Substantial dermal exposure has been reported to cause mild gastrointestinal irritation after a latent period followed by progressive mixed sensory-motor peripheral neuropathy. (5)

Toxicology – Animals

2,4-D is considered moderately toxic to animals. There were 16 published reports from 1990 to 2010 on animal exposure to 2,4-D. A primary finding included reports that exposure was associated with kidney impairment and/or nephrotoxicity.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that 2,4-D is associated with chronic kidney disease in humans. OSHA considers human exposure to 2,4-D to be associated with kidney damage. Additionally, NIOSH identifies exposure to 2,4-D to be associated with kidney damage in animals, specifically changes in tubules including acute renal failure and acute tubular necrosis. We found that an extensive body of literature has been published concerning the toxicological profile of 2,4-D as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is strong evidence that 2,4-D is associated with kidney damage in humans or animals.

5) References

1. Garabrant DH, Philbert MA. Review of 2,4-dichlorophenoxyacetic acid (2,4-D) epidemiology and toxicology. Crit Rev Toxicol. 2002 Jul;32(4):233-57. Review. PubMed PMID: 12184504.

2. Kossmann S, Tustanowski J, Kołodziej B. [Renal dysfunction in chemical plant workers producing dust pesticides]. Med Pr. 2001;52(4):253-6. Polish. PubMed PMID: 11761670.

3. Lindh CH, Littorin M, Amilon A, Jönsson BA. Analysis of phenoxyacetic acid herbicides as biomarkers in human urine using liquid chromatography/triple quadrupole mass spectrometry. Rapid Commun Mass Spectrom. 2008;22(2):143-50. PubMed PMID: 18059043.

4. Singh S, Yadav S, Sharma N, Malhotra P, Bambery P. Fatal 2,4-D (ethyl ester) ingestion. J Assoc Physicians India. 2003 Jun;51:609-10. PubMed PMID: 15266931.

5. Bradberry SM, Watt BE, Proudfoot AT, Vale JA. Mechanisms of toxicity, clinical features, and management of acute chlorophenoxy herbicide poisoning: a review. J Toxicol Clin Toxicol. 2000;38(2):111-22. Review. PubMed PMID: 10778907.

ACIDO GIBERELICO

1) Active Ingredient: Gibberellic Acid, CAS #: 77-06-5

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Gibberellic Acid is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for gibberellic acid.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for gibberellic acid.

3) Literature

The scientific literature review resulted in a total retrieval of 8 citations. Of the 8 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 0 toxicological studies in humans, and 4 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between gibberellic acid exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that showed an association between gibberellic acid exposure and kidney damage.

Toxicology - Animals
One study examined the health effects of subacute treatment of combinations of gibberellic acid and ethephon (2-chloroethylphosphonic acid) in mice. Treated groups showed statistically significant increases in mean liver, kidney and spleen weights. All treatments caused significant dose dependent increases in serum creatinine compared to the control group (1).

Two studies examined the effect of two plant plant growth regulators (PGRs) [Abcisic acid (ABA) and Gibberellic acid (GA3)] on antioxidant defense systems [reduced glutathione (GSH), glutathione reductase (GR), superoxide dismutase (SOD), glutathione-S-transferase (GST) and catalase (CAT)] and lipid peroxidation level in various tissues in rats. The lipid peroxidation end product MDA significantly increased in the lungs, heart and kidney of rats treated with GA3 without significant change in the spleen. (2) The GSH levels significantly increased in the kidneys of rats treated with GA3. (2) SOD significantly increased in the kidney of rats treated with GA (3). Additionally, the ancillary enzyme GR activity decreased in the spleen and increased in the kidney with GA3 treatment. (3) These data suggest that PGRs produced

substantial systemic organ toxicity in the spleen, lungs, stomach, heart and kidney during a 50-day period of subchronic exposure. (2,3)

A fourth study investigated effects of injecting rats with several classes of plant growth-promoting hormones and positive plant growth regulators (auxins, gibberellins, and cytokinins), as plant growth-promoting hormones are known to increase RNA and protein synthesis in not only plants, but animals as well. All of these chemicals increased rat lung, small intestine, liver, and renal cortex guanylate cyclase activity 2-to 4-fold at the 1 mM concentration. (4)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that gibberellic acid exposure is associated with chronic kidney disease in humans. We found that a limited body of literature has been published concerning the toxicological profile of gibberellic acid as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that gibberellic acid exposure is associated with kidney damage in humans or animals.

5) References

1) El-Okazy AM. The Effects of Combination of Gibberellic Acid - 3 (GA3) and Ethephon (2-Chloroethyl Phosphonic Acid) (Plant Growth Regulators) on Some Physiological Parameters in Mice. J Egypt Public Health Assoc. 2008;83(1-2):67-86. PubMed PMID: 18992204.

2) Celik I, Tuluce Y, Isik I. Evalution of toxicity of abcisic acid and gibberellic acid in rats: 50 days drinking water study. J Enzyme Inhib Med Chem. 2007 Apr;22(2):219-26. PubMed PMID: 17518349.

3) Celik I, Turker M, Tuluce Y. Abcisic acid and gibberellic acid cause increased lipid peroxidation and fluctuated antioxidant defense systems of various tissues in rats. J Hazard Mater. 2007 Sep 30;148(3):623-9. Epub 2007 Mar 12. PubMed PMID:17418944.

4) Vesely DL, Hudson JL, Pipkin JL Jr, Pack LD, Meiners SE. Plant growth-promoting hormones activate mammalian guanylate cyclase activity. Endocrinology. 1985 May;116(5):1887-92. PubMed PMID: 2859192.

AMETRINA

1) Active Ingredient: Mesotrione CAS #: 104206-82-8

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Ametrina is associated with kidney damage in humans. Animal studies showed evidence of reduced body weight gain, increased liver and kidney weights, hematologic effects (polycythemia, reduced white blood cell count) and eye effects (cataract formation, keratitis).

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for mesotrione.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for mesotrione.

3) Literature
The scientific literature review resulted in a total retrieval of 1 citation. Of the 1 citation reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 1 toxicological study in humans, and 0 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between mesotrione exposure and kidney damage.

Toxicology - Humans
There is one case of fatal intoxication caused by the ingestion of the herbicide Gesapax (an emulsion type), which consists of 25% ametryn (ametryne, ametrin, ametrine, and ametrina), and 75% other components (xylene and cyclohexanone). Forensic autopsy revealed no remarkable injury or morphological changes. The amount of ametryn (microg/g) extract from each body fluid or organ tissue is as follows: 6.69 (heart blood), 3.50 (peripheral blood), 0.085 (urine), 17.2 (brain frontal lobe), 71.9 (right lung), 23.9 (liver), 19.1 (right kidney), and 74,200 (stomach contents). (1)

Toxicology - Animals
There were no toxicological studies in animals found that showed an association between mesotrione exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that mesotrione is associated with chronic kidney disease in humans. We found that a limited amount of literature has been published concerning the toxicological profile of mesotrione as it relates to the kidney. These references, in addition to the chemical MSDS and

health organization statements, suggest that there is limited evidence that mesotrione is associated with kidney damage in humans or animals.

5) References

1) Takayasu T, Ishida Y, Kimura A, Nosaka M, Kawaguchi M, Kondo T. Postmortem distribution of ametryn in the blood and organ tissues of an herbicide-poisoning victim. J Anal Toxicol. 2010;34(5):287-91. PubMed PMID: 20529463.

ATRAZINA

1) Active Ingredient: Atrazine, CAS #: 1912-24-9

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that atrazine is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no information on the ATSDR Toxicological Profile stating that atrazine is associated with kidney damage in humans. The profile states that atrazine has been shown to cause liver, kidney, and heart damage in animal studies.

National Institute on Occupational Safety and Health (NIOSH)
There is no information on the NIOSH Pocket Guide to Chemical Hazards stating that atrazine is associated with kidney damage in humans.

3) Literature

The scientific literature review resulted in a total retrieval of 34 citations. Of the 34 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 1 case study in humans, and 2 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between atrazine exposure and kidney damage.

Toxicology - Humans
One case study of a human fatality was identified as being caused by the ingestion of an herbicide mix containing atrazine, aminotriazole, ethylene glycol and formaldehyde. On autopsy, the kidney showed the highest concentration of atrazine (97.62 micrograms/g-1 wet tissue) with lesser concentrations in the lung, small intestine and liver, and the lowest concentration in the heart. (1)

Toxicology - Animals
One study looked at female Wistar rats and the amount of atrazine retained in the animal tissues. The atrazine concentrations measured in the liver were higher than those found in the kidney, but both can be ranked as low compared with the amount of the administered doses. These data confirm that tissue retention is minimal. (2)

One study investigated the biochemical and toxicological studies on the mixtures of three commonly-used herbicides in mice. They found that kidney/body weights were significantly higher experimental group as compared with the control group. (3)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that atrazine is associated with chronic kidney disease in humans. We found that a limited amount of literature has been published concerning the toxicological profile of atrazine as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that atrazine is associated with kidney damage in humans or animals.

5) References

1. Pommery J, Mathieu M, Mathieu D, Lhermitte M. Atrazine in plasma and tissue following atrazine-aminotriazole-ethylene glycol-formaldehyde poisoning. J Toxicol Clin Toxicol. 1993;31(2):323-31. PubMed PMID: 8492345.

2. Scutaru B, Giersch T, Cozmei C, Hock B. Immunoenzymatic determination of atrazine in rat tissue samples. Toxicology. 1998 May 15;127(1-3):11-6. PubMed PMID: 9699789.

3. Chaturvedi AK. Biochemical and toxicological studies on the mixtures of three commonly-used herbicides in mice. Arch Environ Contam Toxicol. 1993 May;24(4):449-54. PubMed PMID: 8507100.

BEAUVERIA BASSIANA

1) Active Ingredient: Beauveria Bassiana, CAS #: N/A

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that beauveria bassiana is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for beauveria bassiana.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for beauveria bassiana.

3) Literature

The scientific literature review resulted in a total retrieval of 0 citations.

Epidemiological Studies
There were no human epidemiological studies found that show an association between beauveria bassiana exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between beauveria bassiana exposure and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that show an association between beauveria bassiana exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that beauveria bassiana exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of beauveria bassiana as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between beauveria bassiana exposure and kidney damage in humans or animals.

5) References

None.

BRODIFACOUM

1) Active Ingredient: Brodifacoum, CAS #: 56073-10-0

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that brodifacoum is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for brodifacoum.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for brodifacoum.

3) Literature

The scientific literature review resulted in a total retrieval of 26 citations. Of the 26 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 1 toxicological study in humans, and 1 toxicological study in animals.

Epidemiological Studies
There were no human epidemiological studies found that show an association between brodifacoum exposure and kidney damage.

Toxicology - Humans
One case report was published on self-ingestion of brodifacoum. The subject suffered spontaneous intra-abdominal hemorrhage, circulatory shock, rhabdomyolysis, and acute renal failure. (2)

Toxicology - Animals
Brodifacoum was detected in the liver of a female dog that had suffered an acute death. Upon postmortem examination, it was discovered that the dog had suffered hemorrhages in the thoracic and peritoneal cavities, as well as a large subcapsular renal hematoma. To the authors' knowledge, this was the first report of a brodifacoum-associated renal subcapsular hematoma in a non-human species. (1)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that brodifacoum exposure is associated with chronic kidney disease in humans. We found that a moderate amount of literature has been published concerning the toxicological profile of brodifacoum as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that brodifacoum exposure is associated with kidney damage in humans or animals.

5) References

1) Radi ZA, Thompson LJ. Renal subcapsular hematoma associated with brodifacoum toxicosis in a dog. Vet Hum Toxicol. 2004 Apr;46(2):83-4. PubMed PMID: 15080210.

2) Corke PJ. Superwarfarin (brodifacoum) poisoning. Anaesth Intensive Care. 1997 Dec; 25(6):707-9. PubMed PMID: 9452861.

CARBOXIN + CAPTAN (VITAVAX)

1) Active Ingredient: Carboxin, CAS #: 5234-68-4 (12.5% by weight)
Active Ingredient: Captan, CAS #: 133-06-2 (25% by weight)

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that either carboxin or captan is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for carboxin or captan.

National Institute on Occupational Safety and Health (NIOSH)
The NIOSH Pocket Guide to Chemical Hazards states that the kidneys, along with the eyes, skin, respiratory system, gastrointestinal tract, and liver are a target organ of captan, though it does not further explain the extent or method of kidney damage due to exposure. There is no NIOSH Pocket Guide to Chemical Hazards profile available for carboxin.

3) Literature

The scientific literature review resulted in a total retrieval of 15 citations. Of the 15 citations reviewed, the following pertinent articles are summarized below: 2 human epidemiological studies, 0 toxicological studies in humans, and 9 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that show an association between carboxin and kidney damage. Of the 2 epidemiological studies examining the association between captan and kidney damage (summarized below), one showed an association and one did not.

The first study addressed the health risk for workers using pesticides in the flower-bulb culture in Holland. 137 workers who applied pesticides for more than 10 years (average 20 years) in bulb disinfection and crop protection were compared to 73 controls. No effects were found on liver and renal function and no difference in the prevalence of symptoms that might be ascribed to the usage of pesticides. (1)

A second study examined renal dysfunction among chemical plant workers producing dust pesticides, including captan. The study group included 24 men, aged 29-54 years, employed directly in the production, and 22 women, aged 31-52 years, performing auxiliary jobs and handling only closed packages; the control group consisted of 31 healthy men and 22 women, free from occupational exposure. In order to assess the renal function in the workers, the concentrations of serum creatinine and uric acid, urinary protein, albumin and alpha 1-microglobulin concentration, as well as the activity of alkaline phosphatase (AP) and N-acetyl-beta-glucosaminidase (NAG) in urine were determined. As compared to the control groups, a significantly higher serum creatinine concentration and higher urinary protein, albumin and alpha

1-microglobulin concentrations, and higher enzyme activity were found in men, while in women only urine enzyme activity was significantly increased. The results support subclinical kidney damage due to exposure to these chemicals. (2)

Toxicology - Humans
There were no human toxicological studies found that show an association between carboxin or captan and kidney damage.

Toxicology – Animals
There were no toxicological studies in animals found that show an association between carboxin and kidney damage. We found 9 toxicological studies in animals (summarized below) that show an association between captan and kidney damage.

One study investigated whether exposure to captan impairs CYP-catalyzed drug metabolism in murine liver, kidney and lung of mice. Daily doses of captan were administered to different groups of Swiss Albino CD1 mice of both sexes for 1 or 3 consecutive days. While a single dose of this fungicide did not affect CYP-machinery, repeated treatment significantly impaired the microsomal metabolism. In the kidney, both CYP3A- and CYP1A2-linked monooxygenases were significantly induced (2-fold) by this pesticide. The adverse outcomes associated to CYP changes (e.g. cotoxicity, comutagenicity and promotion) may have harmful consequences. (3)

A second study examined the carcinogenic potential of 5 pesticides, including captan, in multi-organ bioassays in male F344 rats. For captan, neoplastic and pre-neoplastic lesions were found in the forestomach, kidney and thyroid. These results are in concordance with reported long-term carcinogenicity for this chemical. (4) A similar study also examined the carcinogenic potential of four fungicides including captan. All of the fungicides were categorized as Group B2 (probable human) carcinogens based upon findings of an increased incidence of malignant tumors, or combined malignant and benign tumors, in multiple experiments involving different strains of mice and rats. For captan, the main sites of tumor formation in rats of one or both sexes (CR CD, Wistar, or F344 strains) were the kidney and uterus. (5)

A fourth study reviewed two studies on the carcinogenicity of captan in animals and concluded that this fungicide is highly carcinogenic in rats and mice. It found that neoplasms at all sites, as well as malignant neoplasms, were increased in both low and high dose captan-treated male and female rats. More specifically, captan-treated male rats were more susceptible to the induction of chronic renal disease than were female rats. (6)

Several studies examined the effects of a very similar chemical to captan called captafol, which is also a phthalimide fungicide. The first of these studies acknowledged that this chemical is known to induce kidney tumors in rats. (7) Another study examined the enhancing effects of captafol on the expression of proliferating cell nuclear antigen (PCNA) in the kidney and found that the PCNA-labelling indices of renal tubule cells were elevated in rats treated with captafol alone. (8) Two similar studies examined the effects of captafol in F344/DuCrj rats. The first fed both sexes of captafol at concentrations of 0, 0.075, 0.15, 0.3, and 0.6% and found that the liver- and kidney-to-body weight ratios were increased in both male and female rats, and histopathological changes were observed in the forestomach, liver, and kidney. Additionally,

multifocal appearance of karyocytomegaly and tubular cell atypia in the proximal tubules of the kidney was found in the 0.3 and 0.6% groups of both sexes. (9) The second administered captafol at dietary levels of 0 (control), 750 and 1,500 parts per million (ppm) to groups of 50 male and 50 female F344/DuCrj rats for 104 weeks. Renal cell carcinoma was found in eight of 50 male rats treated with 1,500 ppm and in one of 50 male rats treated with 750 ppm of captafol. The incidences of renal adenomas, including micro-adenomas, and basophilic altered cell tubules were significantly higher in both sexes treated with captafol than in controls, and the increases were apparently dose-dependent except that of adenomas in females. The incidences of neoplastic and preneoplastic lesions of the kidney in captafol-treated animals were higher in males than in females. (10)

Finally, one study examined the renal carcinogenic effect of Merpafol, also a phthalimide fungicide very similar to captan and captafol, and found that a range of nonneoplastic and neoplastic lesions were observed in the kidneys of Fischer 344 rats fed Merpafol. (11)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that carboxin exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of carboxin as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between carboxin exposure and kidney damage in humans or animals.

We found limited evidence that captan exposure is associated with chronic kidney disease in humans. We found that a limited body of literature has been published concerning the toxicological profile of captan as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is good evidence that captan exposure is associated with kidney damage in humans or animals.

5) References

1) Verberk MM, Brouwer DH, Brouwer EJ, Bruyzeel DP, Emmen HH, Van Hemmen JJ, Hooisma J, Jonkman EJ, Ruijten MW, Sallé HJ, et al. Health effects of pesticides in the flower-bulb culture in Holland. Med Lav. 1990 Nov-Dec;81(6):530-41. PubMed PMID: 2100770.

2) Kossmann S, Tustanowski J, Kołodziej B. [Renal dysfunction in chemical plant workers producing dust pesticides]. Med Pr. 2001;52(4):253-6. Polish. PubMed PMID: 11761670.

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Cancer. 1993 May 28;54(3):489-93. Erratum in: Int J Cancer 1993 Sep 30;55(3):528. PubMed PMID: 8509224.

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6) Reuber MD. Carcinogenicity of captan. J Environ Pathol Toxicol Oncol. 1989 Mar-Apr;9(2):127-43. PubMed PMID: 2732908.

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CLOMAZONE

1) Active Ingredient: Clomazone, CAS #: 81777-89-1

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that clomazone is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for clomazone.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile for clomazone.

3) Literature

The scientific literature review resulted in a total retrieval of 0 citations.

Epidemiological Studies
There were no human epidemiological studies found that show an association between clomazone exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between clomazone exposure and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that show an association between clomazone exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that clomazone exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of clomazone as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between clomazone exposure and kidney damage in humans or animals.

5) References

None.

CYPERMETRINA

1) Active Ingredient: Cypermethrin, CAS #: 52315-07-8

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
The appropriate MSDS could not be located.

ATSDR Toxicological Profile Information Sheets
The ATSDR Toxicological Profile for cypermethrin stated that no studies were located regarding renal effects in humans following oral exposure to pyrethrins or pyrethroids (a class of chemicals of which cypermethrin is a part). Available information regarding renal effects in animals is limited to a report of decreased kidney weights and tubular degeneration in rats consuming pyrethrins in their diet. It was noted that the magnitude and statistical significance of these renal changes were not presented in these reports. Another study reported increased absolute and relative kidney weights observed in male (but not female) rats fed fenpropathrin (another chemical in this class).

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for cypermethrin.

3) Literature

The scientific literature review resulted in a total retrieval of 25 citations. Of the 25 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 0 toxicological studies in humans, and 12 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between cypermethrin exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that showed an association between cypermethrin exposure and kidney damage.

Toxicology - Animals
One study looked for residues of zeta-cypermethrin in bovine tissues and milk following pour-on and spray application formulation of 2.5 and 5.0 mg zeta-cypermethrin per kg-1 body weight. It was found that muscle, liver and kidney residue concentrations were generally less than the limit of detection (LOD = 0.01 mg kg-1). However, residues in renal-fat and back-fat samples from animals treated with 2.5 mg kg-1 all exceeded the limit of quantitation (LOQ = 0.05 mg kg-1), peaking at 10 days after treatment. (1)

A study investigated 30 male dwarf goats (Capra hircus) and the effects of cypermethrin on some clinico-hemato-biochemical and pathological parameters. Microscopically kidneys showed

congestion of parenchyma and condensation of epithelial cells of tubules along with deposition of casts in tubules. Shrinkage of glomerular capillaries and increased urinary spaces were pronounced in the high-dose group. (2)

A study on the biochemical investigation of cypermethrin toxicity in rabbits lead investigators to believe that cypermethrin is moderately toxic to animals. In this study the pyrethroid cypermethrin Sherpa 25% (active substance 250 g/l cypermethrin) was used and rabbits were gavaged by 1/20 LD50 for 3 weeks (one dose every week). Rabbits showed depression, decrease in feed intake, body weight and loose feces. Livers exhibited fatty change, necrosis, lesions in kidney included tubular necrosis and pink homogeneous tubular casts. (3)

In four studies investigating exposure to cypermethrin in rats via oral dosing or dermal application, the exposure was associated with mild to moderate histological alterations in the kidney. (4, 5, 6, 7) Another study hypothesized that the oxidative stress and lipid peroxidation that is induced in exposure to cypermethrin is the mechanism behind the hepatotoxicology in rats to the compound. (8)

One rat study looked at the influence of neonatal treatment with the pyrethroid insecticide cypermethrin on the development of dopamine receptors in the rat kidney. The findings indicated indicate that neonatal treatment with the pyrethroid insecticide cypermethrin induces long-lasting impairment of renal dopamine D1- and D2-like receptors. Additionally, they conclude that the kidney is a target of the toxic action of the compound. Renal dopamine receptor changes caused by cypermethrin are consistent with possible alterations of renal tubular function and of sympathetic neuroeffector modulation. (9)

Three studies investigated toxic effects of Cypermethrin in mice. In one study it was found that there was a congestion of vessels and marked lymphocytic infiltration (more than 50 lymphocytes/HPF) in the kidneys of the experimental group receiving 30 mg/kg body weight of cypermethrin. They did not find abnormality in the animals receiving 15 mg/kg body weight of cypermethrin and in the animals of the control group. They conclude that nephrotoxicity is present after repeated exposure to cypermethrin. (10) A second study found a statistically significant ($p<0.05$) dose-dependent increase in DNA damage was observed in all the organs vital organs like brain, liver, kidney. (11) A third study investigated subacute toxicity of orally applied alpha-cypermethrin in Swiss mice. In mice administered 1/5 LD(50) or1/2 LD(50) of the preparation examined, histopathologic and ultrastructural changes were observed in the liver and kidneys. (12)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that cypermethrin is associated with chronic kidney disease in humans. We found that a moderate amount of literature has been published concerning the toxicological profile of cypermethrin as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is good evidence that cypermethrin is associated with kidney damage in humans or animals.

5) References

1. Rothwell JT, Burnett TJ, Hacket K, Chevis R, Lowe LB. Residues of zeta-cypermethrin in bovine tissues and milk following pour-on and spray application. Pest Manag Sci. 2001 Nov;57(11):993-9. PubMed PMID: 11721528.

2. Khan A, Faridi HA, Ali M, Khan MZ, Siddique M, Hussain I, Ahmad M. Effects of cypermethrin on some clinico-hemato-biochemical and pathological parameters in male dwarf goats (Capra hircus). Exp Toxicol Pathol. 2009 Mar;61(2):151-60. Epub 2008 Sep 7. PubMed PMID: 18778926.

3. Dahamna S, Harzallah D, Guemache A, Sekfali N. Biochemical investigation of cypermethrin toxicity in rabbits. Commun Agric Appl Biol Sci. 2009;74(1):149-53. PubMed PMID: 20218522

4. Hussain S, Khan MZ, Khan A, Javed I, Asi MR. Toxico-pathological effects in rats induced by concurrent exposure to aflatoxin and cypermethrin. Toxicon. 2009 Jan;53(1):33-41. Epub 2008 Nov 1. PubMed PMID: 18977377

5. Manna S, Bhattacharyya D, Mandal TK, Das S. Repeated dose toxicity of alfa-cypermethrin in rats. J Vet Sci. 2004 Sep;5(3):241-5. PubMed PMID: 15365239.

6. Latuszyńska J, Luty S, Halliop J, Przylepa E, Tochman A, Obuchowska D, Korczak E. Studies of toxicity of dermally-absorbed nurelle D 550 EC preparations. Ann Agric Environ Med. 1999;6(2):151-9. PubMed PMID: 10607997.

7. Luty S, Latuszyńska J, Halliop J, Tochman A, Obuchowska D, Przylepa E, Korczak E. Toxicity of dermally applied alpha-cypermethrin in rats. Ann Agric Environ Med. 1998;5(2):109-16. PubMed PMID: 9860811.

8. Sushma N, Devasena T. Aqueous extract of Trigonella foenum graecum (fenugreek) prevents cypermethrin-induced hepatotoxicity and nephrotoxicity. Hum Exp Toxicol. 2010 Apr;29(4):311-9. Epub 2010 Feb 10. PubMed PMID: 20147568.

9. Cantalamessa F, Barili P, Cavagna R, Sabbatini M, Tenore G, Amenta F. Influence of neonatal treatment with the pyrethroid insecticide cypermethrin on the development of dopamine receptors in the rat kidney. Mech Ageing Dev. 1998 Jun 15;103(2):165-78. PubMed PMID: 9701769.

10. Inayat Q, Ilahi M, Khan J. A morphometric and histological study of the kidney of mice after dermal application of cypermethrin. J Pak Med Assoc. 2007 Dec;57(12):587-91. PubMed PMID: 18173040

11. Patel S, Pandey AK, Bajpayee M, Parmar D, Dhawan A. Cypermethrin-induced DNA damage in organs and tissues of the mouse: evidence from the comet assay. Mutat Res. 2006 Sep 5;607(2):176-83. Epub 2006 Jun 12. PubMed PMID: 16765632.

12. Luty S, Latuszynska J, Obuchowska-Przebirowska D, Tokarska M, Haratym-Maj A. Subacute toxicity of orally applied alpha-cypermethrin in Swiss mice. Ann Agric Environ Med. 2000;7(1):33-41. PubMed PMID: 10865243

DIPEL

1) Active Ingredient: Bacillus thuringiensis CAS #: N/A

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Dipel is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for bacillus thuringiensis.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for bacillus thuringiensis.

3) Literature

The scientific literature review resulted in a total retrieval of 27 citations. Of the 27 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 0 toxicological studies in humans, and 2 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between bacillus thuringiensis exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that showed an association between bacillus thuringiensis exposure and kidney damage.

Toxicology - Animals
One study was conducted to investigate the haematological, biochemical and histopathological alterations induced by abamectin and *Bacillus thuringiensis* in male albino rats. Male albino rats were administered dietary doses each equivalent to 1/10 or 1/100 of the LD50 values of each toxicant for 30 consecutive days. Abamectin was found to pose risks of renal- and hepato-toxicity in rats, since the biochemical parameters of liver function (i.e. aspartate aminotransferase activity, alanine aminotransferase activity, acid phosphatase activity, albumin, and total protein levels) and kidney function (uric acid and creatinine concentration) were severely affected. (1)

One study investigated the elimination of the thermostable exotoxin from *Bacillus thuringiensis* after ingestion in the mouse. They found that after ingestion, the thermostable exotoxin was quickly eliminated in the feces without fixation on the liver, heart, spleen or kidneys. The quantitative study utilizing radio-active tritium-labelled exotoxin, this elimination is shown to be almost complete in 24 hours. (2)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that bacillus thuringiensis is associated with chronic kidney disease in humans. We found that a moderate amount of literature has been published concerning the toxicological profile of bacillus thuringiensis and as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that bacillus thuringiensis is associated with kidney damage in humans or animals.

5) References

1) Eissa FI, Zidan NA. Haematological, biochemical and histopathological alterations induced by abamectin and Bacillus thuringiensis in male albino rats. Acta Biol Hung. 2010 Mar;61(1):33-44. PubMed PMID: 20194097.

2) de Barjac H, Lecadet MM. [Elimination of the thermostable exotoxin from B. thuringiensis after ingestion in the mouse]. C R Acad Sci Hebd Seances Acad Sci D. 1975 Feb 3;280(5):677-9. French. PubMed PMID: 809165.

DIURON

1) Active Ingredient: Diuron, CAS #: 330-54-1

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Diuron is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for diuron.

National Institute on Occupational Safety and Health (NIOSH)
There is no information on the NIOSH Pocket Guide to Chemical Hazards stating that diuron is associated with kidney damage in humans.

3) Literature

The scientific literature review resulted in a total retrieval of 10 citations. Of the 10 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 0 toxicological studies in humans, and 3 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between diuron and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that showed an association between diuron and kidney damage.

Toxicology - Animals
Two studies identified that manufacturing processes and environmental degradation by photolysis and biolysis of diuron can lead to the unwanted byproduct, 3,3',4,4' Tetrachloroazobenzene. This contaminant has been shown to produce renal tubule hyaline droplet accumulation in the cytoplasm of renal cortical epithelial cells and chronic nephropathy which was observed microscopically in male rats at dosing rates of 80, 200, and 500 mg/kg. (1, 2)

Another study found that in the synthesis of diuron, 1,2-dichlorobenzene is used as an intermediate. Exposure to 1,2-dichlorobenzene leads to renal tubular degeneration in male rats at 500 mg/kg, and multifocal mineralization of the myocardial fibers of the heart and skeletal muscle were seen in mice. (3)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that diuron is associated with chronic kidney disease in humans. We found that limited literature has been published concerning the toxicological profile of diuron as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that diuron is associated with kidney damage in humans or animals.

5) References

1) NTP Technical Report on the Toxicity Studies of 3,3',4,4'-Tetrachloroazoxybenzene (CAS No. 21232-47-3) Administered by Gavage to F344/N Rats and B6C3F1 Mice. Toxic Rep Ser. 1998 Nov;66:1-G4. PubMed PMID: 11986683.

2) NTP Technical Report on the Toxicity Studies of 3,3',4,4'-Tetrachloroazobenzene (CAS No. 14047-09-7) Administered by Gavage to F344/N Rats and B6C3F1 Mice. Toxic Rep Ser. 1998 Nov;65:1-F6. PubMed PMID: 11986682.

3) National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of 1,2-Dichlorobenzene (o-Dichlorobenzene) (CAS No. 95-50-1) in F344/N Rats and B6C3F1 Mice (Gavage Studies). Natl Toxicol Program Tech Rep Ser. 1985 Oct;255:1-195. PubMed PMID: 12748691.

ETEPHON

1) Active Ingredient: Ethephon, CAS #: 16672-87-0

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Etephon is associated with kidney damage in humans. The MSDS does state that Etephon causes organ effects in the thyroid, liver, and kidney in chronic toxicity studies of rats.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for ethephon.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for ethephon.

3) Literature

The scientific literature review resulted in a total retrieval of 3 citations. Of the 3 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 0 toxicological studies in humans, and 1 toxicological study in animals.

Epidemiological Studies
There were no human epidemiological studies found that show an association between ethephon exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between ethephon exposure and kidney damage.

Toxicology - Animals
One study analyzed the ultrastructure of the epithelial cells of the proximal tubules of the kidneys of rats treated with water solutions of Ethrel, which is comprised of ethephon. An increase of thickness of the basic epithelial membranes and smoothing of the folds of the capsule at its base were observed in this study, as well as an increase in the number of apical vesicles, lisosomes and microbodies present. The authors state that there were no toxic injuries to the epithelial cells of the proximal tubules of the kidneys which might be caused by Ethrel. (1)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that ethephon exposure is associated with chronic kidney disease in humans. We found that a limited body of literature has been published concerning the toxicological profile of ethephon as it relates to the kidney. The information presented in the chemical MSDS,

health organization statements, and in the literature suggest that there is limited evidence that diuron is associated with kidney damage in humans or animals.

5) References

1) Latalski M, Lipecki J, Sokolowska J. [Effect of Ethrel on the ultrastructure of some internal organs in rats. II. Kidneys]. Pol Arch Weter. 1975;17(4):675-81. Polish. PubMed PMID: 1178546.

FIPRONIL

1) Active Ingredient: Fipronil, CAS #: 120068-37-3

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Fipronil is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for fipronil.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for fipronil.

3) Literature

The scientific literature review resulted in a total retrieval of 0 citations.

Epidemiological Studies
There were no human epidemiological studies found that show an association between fipronil exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between fipronil exposure and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that show an association between fipronil exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that fipronil exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of fipronil as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between fipronil exposure and kidney damage in humans or animals.

5) References

None.

FLUAZIFOP-P-BUTYL

1) Active Ingredient: Fluazifop-p-butyl, CAS #: 79241-46-6 (24.5% by weight)
Inactive Ingredient: Naphthalene, CAS #: 91-20-3 (<4% by weight)

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that the active ingredient, fluazifop-P-butyl, is associated with kidney damage in humans or animals. The MSDS does state that the kidneys are a target organ of the inactive ingredient, naphthalene, and that exposure to naphthalene can cause kidney failure, in addition to cataracts, liver damage, respiratory failure, hematuria, anemia, damage to red blood cells, leukocytosis, or coma. (Note: the inactive ingredient comprises less than 4% by weight of the chemical compound).

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for fluazifop-p-butyl.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for fluazifop-p-butyl.

3) Literature

The scientific literature review resulted in a total retrieval of 0 citations.

Epidemiological Studies
There were no human epidemiological studies found that show an association between fluazifop-p-butyl exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between fluazifop-p-butyl exposure and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that show an association between fluazifop-p-butyl exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that fluazifop-p-butyl exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of fluazifop-p-butyl as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between fluazifop-p-butyl exposure and kidney damage in humans or animals.

5) References

None.

GLIFOSATO

1) Active Ingredient: Glyphosate, CAS #: 1071-83-6

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
The MSDS states that glyphosate may cause kidney damage in an overview of the health effects to humans. The MSDS also states that with prolonged overexposure glyphosate may cause kidney effects in humans.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for glyphosate.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for glyphosate.

3) Literature

The scientific literature review resulted in a total retrieval of 25 citations. Of the 25 citations reviewed, the following pertinent articles are summarized below: 3 human epidemiological studies, 5 toxicological studies in humans, and 2 toxicological studies in animals.

Epidemiological Studies
A case-control study with 58 participants was conducted using data from 2 hospitals in Taiwan. Glyphosate-surfectant herbicide (GlySH) intoxicated patients were observed, and it was concluded that GlySH poisoning has multiorgan toxicity. Additionally, pulmonary toxicity and renal toxicity seem to be responsible for its mortality. (1)

A retrospective study of 131 patients conducted by the same research group a few years earlier investigated prognostic predictors of mortality upon GlySH ingestion, and found that renal failure necessitating hemodialysis and hyperkalemia were among predictors highly associated with poor outcomes and mortality. This study concluded that in managing patients who have larger amount of GlySH ingestion prevention of further renal damage appear to be of critical importance. (2)

A third study reviewed 93 hospital cases of GlySH poisoning, and found that the kidney was affected in 14% of cases. (3)

Toxicology - Humans
One study stated that the clinical picture of severe glyphosate-surfactant poisoning is manifested by renal failure, among other outcomes. A single case report of a 56-year old woman ingested about 500 mL of herbicide containing glyphosate isopropylamine salt followed. The most prominent manifestation of poisoning included hypotension, coma, hyperkalemia, respiratory and renal failure. (4)

Numerous other case studies following accidental or intentional ingestion among humans were found, and many discussed hemodialysis as an approach for treatment, to assist in intoxicant clearance, which would normally be accomplished by the kidney. (5, 6, 7) One case study reported development of acute renal failure with oliguria and severe hypoxia. (5) Another noted two separate patients that experienced complicated renal failure upon poisoning. (6) A third described four cases of self-poisoning associated with renal failure. (8)

Two studies noted that human poisoning with this herbicide is not with the active ingredient alone but with complex and variable mixtures including surfactants. Experimental studies suggest that the toxicity of the surfactant used can significantly affect overall toxicity. (7, 8) One of these studies stated that renal and hepatic impairment are also frequent and usually reflect reduced organ perfusion. Among other symptoms, the study stated that renal failure requiring hemodialysis and hyperkalaemia may supervene in severe cases. (7)

Toxicology - Animals

One study conducted trials with rats fed commercialized genetically modified (GM) maize, including NK 603, which has been modified to be tolerant to the broad spectrum herbicide Roundup and thus contains residues of this formulation. The analysis following this trial revealed new side effects linked with GM maize consumption, which were sex- and often dose-dependent. Effects were mostly associated with the kidney and liver, the dietary detoxifying organs. The authors concluded that these data highlight signs of hepatorenal toxicity, possibly due to the new pesticides specific to the GM corn. (9)

Another study noted that contradictory data that exists surrounding genotoxicity of glyphosate and glyphosate-containing herbicide formulations (GCHF). Some data reported includes findings of mouse liver and kidney DNA adducts and damage following intraperitoneal (ip) injection. Results from ip and oral exposures were compared, and exposure by ip injection indeed produced marked hepatic and renal toxicity, but oral administration did not. The results suggest that ip injection of GCHF may induce secondary effects mediated by local toxicity rather than genotoxicity. Furthermore, these results continue to support the conclusion that glyphosate and GCHF are not genotoxic under exposure conditions that are relevant to animals and humans. (10)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that glyphosate is associated with chronic kidney disease in humans. We found that moderate literature has been published concerning the toxicological profile of chemical name and as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is good evidence that glyphosate is associated with kidney damage in humans or animals.

5) References

1. Lee CH, Shih CP, Hsu KH, Hung DZ, Lin CC. The early prognostic factors of glyphosate-surfactant intoxication. Am J Emerg Med. 2008 Mar;26(3):275-81. PubMed PMID: 18358936.

2. Lee HL, Chen KW, Chi CH, Huang JJ, Tsai LM. Clinical presentations and prognostic factors of a glyphosate-surfactant herbicide intoxication: a review of 131 cases. Acad Emerg Med. 2000 Aug;7(8):906-10. PubMed PMID: 10958131.

3. Talbot AR, Shiaw MH, Huang JS, Yang SF, Goo TS, Wang SH, Chen CL, Sanford TR. Acute poisoning with a glyphosate-surfactant herbicide ('Roundup'): a review of 93 cases. Hum Exp Toxicol. 1991 Jan;10(1):1-8. PubMed PMID: 1673618.

4. Potrebić O, Jović-Stosić J, Vucinić S, Tadić J, Radulac M. [Acute glyphosate-surfactant poisoning with neurological sequels and fatal outcome]. Vojnosanit Pregl. 2009 Sep;66(9):758-62. Serbian. PubMed PMID: 19877558.

5. Sampogna RV, Cunard R. Roundup intoxication and a rationale for treatment. Clin Nephrol. 2007 Sep;68(3):190-6. PubMed PMID: 17915625.

6. Moon JM, Min YI, Chun BJ. Can early hemodialysis affect the outcome of the ingestion of glyphosate herbicide? Clin Toxicol (Phila). 2006;44(3):329-32. PubMed PMID: 16749554.

7. Bradberry SM, Proudfoot AT, Vale JA. Glyphosate poisoning. Toxicol Rev. 2004;23(3):159-67. Review. PubMed PMID: 15862083.

8. Menkes DB, Temple WA, Edwards IR. Intentional self-poisoning with glyphosate-containing herbicides. Hum Exp Toxicol. 1991 Mar;10(2):103-7. PubMed PMID: 1675099.

9. de Vendômois JS, Roullier F, Cellier D, Séralini GE. A comparison of the effects of three GM corn varieties on mammalian health. Int J Biol Sci. 2009 Dec 10;5(7):706-26. PubMed PMID: 20011136; PubMed Central PMCID: PMC2793308.

10. Heydens WF, Healy CE, Hotz KJ, Kier LD, Martens MA, Wilson AG, Farmer DR. Genotoxic potential of glyphosate formulations: mode-of-action investigations. J Agric Food Chem. 2008 Feb 27;56(4):1517-23. Epub 2008 Jan 16. PubMed PMID: 18197620.

GLUFOSINATO DE AMONIO

1) Active Ingredient: Glufosinate ammonium (phosphinothricin), CAS #: 51276-47-2

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
The appropriate MSDS could not be located.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for glufosinate ammonium.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for glufosinate ammonium.

3) Literature

The scientific literature review resulted in a total retrieval of 6 citations. Of the 6 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 3 toxicological studies in humans, and 0 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between glufosinate ammonium exposure and kidney damage.

Toxicology - Humans
Two human toxicological studies found that glufosinate ammonium is excreted rapidly through the renal route. (1, 3) A case report of a poisoning with an herbicide containing 20% glufosinate ammonium described the transient development of central diabetes insipidus resulting from the acute oral poisoning; this condition typically reflects damage to the pituitary gland and not to the kidney. (2)

Toxicology - Animals
There were no toxicological studies in animals found that showed an association between glufosinate ammonium and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that glufosinate ammonium exposure is associated with chronic kidney disease in humans. We found that limited literature has been published concerning the toxicological profile of glufosinate ammonium as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that glufosinate ammonium exposure is associated with kidney damage in humans or animals.

5) References

1. Hori Y, Koyama K, Fujisawa M, Nakajima M, Shimada K, Hirose Y, Kohda Y, Akuzawa H. Protein binding of glufosinate and factors affecting it revealed by an equilibrium dialysis technique. J Anal Toxicol. 2001 Sep;25(6):439-42. PubMed PMID: 11550817.

2. Takahashi H, Toya T, Matsumiya N, Koyama K. A case of transient diabetes insipidus associated with poisoning by a herbicide containing glufosinate. J Toxicol Clin Toxicol. 2000;38(2):153-6. PubMed PMID: 10778913.

3. Hirose Y, Kobayashi M, Koyama K, Kohda Y, Tanaka T, Honda H, Hori Y, Yoshida K, Kikuchi M. A toxicokinetic analysis in a patient with acute glufosinate poisoning. Hum Exp Toxicol. 1999 May;18(5):305-8. PubMed PMID: 10372751.

IMIDACLOPRID

1) Active Ingredient: Imidacloprid, CAS #:105827-78-9

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Imidacloprid is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for imidacloprid.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for imidacloprid.

3) Literature

The scientific literature review resulted in a total retrieval of 5 citations. Of the 5 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 1 toxicological study in humans, and 1 toxicological study in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between imidacloprid exposure and kidney damage.

Toxicology - Humans
One case report was published on the acute multiple organ failure with imidacloprid and alcohol ingestion. The pathology included oliguric kidney injury, acute lung injury, hypotension, and metabolic acidosis that developed within hours of ingestion. Renal replacement therapy, including intermittent, hemodialysis and continuous venovenous hemodialysis, quickly corrected the metabolic acidosis with better blood pressure. The authors concluded that despite the original belief that imidacloprid has low mammalian toxicity, there is increasing evidence that imidacloprid may cause heart, kidney, and other organ damages and even death in addition to gastrointestinal irritation and neurological symptoms. (1)

Toxicology - Animals
One study analyzed the morphological, biochemical and histopathological evaluations of a 90-day oral toxicity of imidacloprid in female rats. The brain, liver and kidney of rats exposed to a high dose of imidacloprid had showed mild pathological changes. (2)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that imidacloprid is associated with chronic kidney disease in humans. We found that limited literature has been published concerning the toxicological profile of

imidacloprid as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that imidacloprid is associated with kidney damage in humans or animals.

5) References

1. Yeh IJ, Lin TJ, Hwang DY. Acute multiple organ failure with imidacloprid and alcohol ingestion. Am J Emerg Med. 2010 Feb;28(2):255.e1-3. PubMed PMID: 20159407.

2. Bhardwaj S, Srivastava MK, Kapoor U, Srivastava LP. A 90 days oral toxicity of imidacloprid in female rats: morphological, biochemical and histopathological evaluations. Food Chem Toxicol. 2010 May;48(5):1185-90. Epub 2010 Feb 8. PubMed PMID: 20146932.

METARHIZIUM ANISOPLIAE (METARHISA)

1) Active Ingredient: fungus, CAS #: N/A

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
We were unable to locate the MSDS for Metarhisa. Metarhisa is a fungus produced at ISA and used as an insecticide.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for Metarhisa.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for Metarhisa.

3) Literature

The scientific literature review resulted in a total retrieval of 0 citations.

Epidemiologic Studies
There were no human epidemiological studies found that show an association between Metarhisa exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between Metarhisa exposure and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that show an association between Metarhisa exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that Metarhisa exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of Metarhisa as it relates to the kidney. The absence of information available on Metarhisa from chemical MSDS, health organization statements, and literature does not allow us to draw a conclusion on the association between Metarhisa exposure and kidney damage in humans or animals.

5) References

None.

METSULFURON METIL

1) Active Ingredient: Metsulfuron methyl, CAS #: 74223-64-6

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Metsulfuron Methyl is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for metsulfuron methyl.

National Institute on Occupational Safety and Health (NIOSH)
There is no information in the NIOSH Pocket Guide to Chemical Hazards stating that metsulfuron methyl is associated with kidney damage in humans.

3) Literature

The scientific literature review resulted in a total retrieval of 0 citations.

Epidemiological Studies
There were no human epidemiological studies found that show an association between metsulfuron methyl exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between metsulfuron methyl exposure and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that show an association between metsulfuron methyl exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that metsulfuron methyl exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of metsulfuron methyl as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between metsulfuron methyl exposure and kidney damage in humans or animals.

5) References

None.

PENDIMETALINA

1) Active Ingredient: Pendimethalin, CAS #: 40487-42-1

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Pendimethalin is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for pendimethalin.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for pendimethalin.

3) Literature

The scientific literature review resulted in a total retrieval of 1 citation. Of the 1 citation reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 1 toxicological study in humans, and 0 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between pendimethalin exposure and kidney damage.

Toxicology - Humans
One study evaluated five dinitroaniline herbicides including pendimethalin for anticryptosporidial activity in an in vitro cultivation model of Cryptosporidium parvum. Pendimethalin exhibited significant anticryptosporidial activities with no corresponding evidence of toxicity. (1)

Toxicology - Animals
There were no toxicological studies in animals found that showed an association between pendimethalin and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that pendimethalin is associated with chronic kidney disease in humans. We found that limited literature has been published concerning the toxicological profile of pendimethalin as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statement, and in the literature does not allow us to draw a conclusion on the association between pendimethalin and kidney damage in humans or animals.

5) References

1. Arrowood MJ, Mead JR, Xie L, You X. In vitro anticryptosporidial activity of dinitroaniline herbicides. FEMS Microbiol Lett. 1996 Mar 1;136(3):245-9. PubMed PMID: 8867379.

TERBUTRINA

1) Active Ingredient: Terbutryn, CAS #: 886-50-0

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
The appropriate MSDS could not be located.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for terbutryn.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for terbutryn.

3) Literature

The scientific literature review resulted in a total retrieval of 2 citations. Of the 2 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 0 toxicological studies in humans, and 0 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between terbutryn exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that showed an association between terbutryn and kidney damage.

Toxicology - Animals
There were no toxicological studies on animals found that showed an association between terbutryn and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that terbutryn is associated with chronic kidney disease in humans. We found that limited literature has been published concerning the toxicological profile of terbutryn as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between terbutryn and kidney damage in humans or animals.

5) References

None.

AGRICHEMICALS POTENTIALLY USED AT ISA IN THE PAST

BROMADIOLONA

1) Active Ingredient: Bromadiolone, CAS #: 28772-56-7

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that bromadiolone is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for bromadiolone.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for bromadiolone.

3) Literature

The scientific literature review resulted in a total retrieval of 4 citations. Of the 4 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 0 toxicological studies in humans, and 2 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between bromadiolone exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that showed an association between bromadiolone and kidney damage.

Toxicology - Animals
The effects of bromadiolone on the organs and tissue of coypu (Myocastor coypus) were the subject of one study. It was found that bromadiolone damaged the erythrocytes, resulting in a probable saturation of transferrin, a deposit of iron in the connective tissue and in a few cells of the proximal tubules of the kidneys and an increased storage of ferritin in the spleen. (1)

In another study, rats (rattus norvegicus) were dosed orally with the rodenticide bromadiolone, and it was found that the compound disappeared slowly from the organism. Bromadiolone levels in kidney were slightly higher than those observed in plasma, with a longer half-life, though lower than those observed in the liver. (2)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that bromadiolone is associated with chronic kidney disease in humans. We found that limited literature has been published concerning the toxicological profile of

bromadiolone as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that bromadiolone is associated with kidney damage in humans or animals.

5) References

1. Jeantet AY, Truchet M, Naulleau G, Martoja R. [Effects of bromadiolone on some organs and tissues (liver, kidney, spleen, blood) of coypu (Myocastor coypus)]. C R Acad Sci III. 1991;312(4):149-56. French. PubMed PMID: 1901755.

2. Kamil N. Kinetics of bromadiolone, anticoagulant rodenticide, in the Norway rat (Rattus norvegicus). Pharmacol Res Commun. 1987 Nov;19(11):767-75. PubMed PMID: 3444841.

CHLOROCEL

1) Active Ingredient: Aluminum oxide (alumina), CAS #: 1344-28-1

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Chlorocel is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for aluminum oxide.

National Institute on Occupational Safety and Health (NIOSH)
There is no information on the NIOSH Pocket Guide to Chemical Hazards profile stating that aluminum oxide exposure is associated with kidney damage in humans.

3) Literature

The scientific literature review resulted in a total retrieval of 122 citations. Of the 122 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 0 toxicological studies in humans, and 1 toxicological study in animals.

Epidemiological Studies
There were no human epidemiological studies found that show an association between aluminum oxide exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between aluminum oxide exposure and kidney damage.

Toxicology - Animals
In one study, plasma-sprayed alumina on 316L stainless steel discs was implanted in Sprague-Dawley rats for six months, after which the liver, testes, and kidneys were examined and found to exhibit significant increases in aluminum ion concentration. The study did not state any conclusions make about the toxicity of aluminum oxide. (1)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that aluminum oxide exposure is associated with chronic kidney disease in humans. A limited body of literature has been published concerning the toxicological profile of aluminum oxide as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between aluminum oxide exposure and kidney damage in humans or animals.

5) References

1) Drummond JL, Simon MR, Woodman JL, Brown SD. Aluminum ion deposition in rat tissues following implantation of a ceramic-metal disc. Biomater Med Devices Artif Organs. 1983; 11(2-3):147-59. PubMed PMID: 6667321.

COUMATETRALYL

1) Active Ingredient: Coumatetralyl, CAS #: 5836-29-3

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that coumatetralyl is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for coumatetralyl.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for coumatetralyl.

3) Literature

The scientific literature review resulted in a total retrieval of 1 citation. Of the 1 citation reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 0 toxicological studies in humans, and 0 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between coumatetralyl exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that showed an association between coumatetralyl and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that showed an association between coumatetralyl and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that coumatetralyl is associated with chronic kidney disease in humans. Limited literature has been published concerning the toxicological profile of coumatetralyl as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statement, and in the literature does not allow us to draw a conclusion on the association between coumatetralyl and kidney damage in humans or animals.

5) References

None.

DBCP

1) Active Ingredient: 1,2-dibromo-3-chloropropane, CAS #: 96-12-8

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
The appropriate MSDS could not be located.

ATSDR Toxicological Profile Information Sheets
The toxicological profile states that the kidney is a target organ for DBCP. Breakdown products of DBCP can cause harmful effects in the liver, kidneys, or male reproductive organs. Rats or mice that ingested large amounts of DBCP had damaged stomachs, livers, and kidneys, and cancer of the stomach and kidneys was seen in animals that were fed DBCP for long periods of time. Following high exposures, study animals developed scarring of the kidneys, nephritis, and lesions in their kidneys.

National Institute on Occupational Safety and Health (NIOSH)
NIOSH considers the kidney to be a target organ for DBCP and also states that DBCP causes kidney injury, though it does not specify the extent.

3) Literature

The scientific literature review resulted in a total retrieval of 48 citations. Of the 48 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 2 toxicological studies in humans, and 16 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that show an association between DBCP exposure and kidney damage.

Toxicology - Humans
One article reviewed the data demonstrating the reproductive toxicity of DBCP. The article states that DBCP has been widely used as a nematocide in the United States and is still currently used in some other countries. It has spermatogenic effects, and is also a CNS depressant, a liver and kidney toxin, and a skin, eye, and respiratory irritant, as well as a probable carcinogen. (1)

One experiment studied the effects of DBCP on HL-60 and LLCPK1 cells. DBCP (30-300 micromol/L) caused a concentration-dependednt increase in the levels of DNA single-strand breaks in both cell lines, as well as in cultured human renal proximal tubular cells. These in vitro findings may be important for the development of DBCP-induced toxicity in vivo. (2)

Toxicology - Animals
Multiple articles investigated the effects of subcutaneous injection of DBCP on the urogenital system of the male rat. Major findings showed that following subcutaneous injection of DBCP,

subject animals experienced; among other symptoms, general damage to the kidneys (3,4, 5, 6), toxic lesions of the kidneys (7, 8, 9), or renal necrosis (10, 11, 12).
Another study examined carcinogenesis of vapors. The authors stated that DBCP vapor was associated with toxic tubular neropathy in both male and female rats and mice. (13) Several in vivo studies concluded that DBCP is genotoxic and can induce DNA damage in the kidney. (22, 23, 24, 16, 25) Multiple articles investigating a variety of subjects note that DBCP is toxic or detrimental to the kidney (14, 15, 16, 17, 18, 19, 20, 21).

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that DBCP is associated with chronic kidney disease in humans. We found that a moderate body of literature has been published concerning the toxicological profile of DBCP as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is good evidence that DBCP is associated with kidney damage in humans or animals.

5) References

1) Teitelbaum DT. The toxicology of 1,2-dibromo-3-chloropropane (DBCP): a brief review. Int J Occup Environ Health. 1999 Apr-Jun;5(2):122-6. Review. PubMed PMID:10330513.

2) Wiger R, Holme JA, Hongslo JK, Brunborg G, Haug K, Rodilla V, Dybing E, Søderlund EJ. Single-strand breaks, cell cycle arrest and apoptosis in HL-60 and LLCPK1 cells exposed to 1,2-dibromo-3-chloropropane. Cell Biol Toxicol. 1998 Aug;14(4):267-82. PubMed PMID: 9733282.

3) Låg M, Søderlund EJ, Omichinski JG, Brunborg G, Holme JA, Dahl JE, Nelson SD, Dybing E. Effect of bromine and chlorine positioning in the induction of renal and testicular toxicity by halogenated propanes. Chem Res Toxicol. 1991 Sep-Oct;4(5):528-34. PubMed PMID: 1793801.

4) Saegusa J. Age-related susceptibility to dibromochloropropane. Toxicol Lett. 1987 Mar;36(1):45-50. PubMed PMID: 3564068.

5) Kluwe WM. Chemical modulation of 1,2-dibromo-3-chloropropane toxicity. Toxicology. 1983 Jul-Aug;27(3-4):287-99. PubMed PMID: 6623477.

6) Jones AR, Fakhouri G, Gadiel P. The metabolism of the soil fumigant 1,2-dibromo-3-chloropropane in the rat. Experientia. 1979 Nov 15;35(11):1432-4. PubMed PMID: 510467.

7) Saegusa J. Cumulative effects of 1,2-dibromo-3-chloropropane (DBCP) on kidney and testis. Ind Health. 1989;27(2):49-58. PubMed PMID: 2745161.

8) Kluwe WM, Greenwell A, Harrington F. Relationship of tissue nonprotein/sulfhydryls to the acute toxic effects of 1,2-dibromo-3-chloropropane. J Pharmacol Exp Ther. 1982 Feb;220(2):399-405. PubMed PMID: 7057399.

9) Reznik G, Stinson SF, Ward JM. Respiratory pathology in rats and mice after inhalation of 1,2-dibromo-3-chloropropane or 1,2 dibromoethane for 13 weeks. Arch Toxicol. 1980 Dec;46(3-4):233-40. PubMed PMID: 7016076.

10) Søderlund EJ, Låg M, Holme JA, Brunborg G, Omichinski JG, Dahl JE, Nelson SD, Dybing E. Species differences in kidney necrosis and DNA damage, distribution and glutathione-dependent metabolism of 1,2-dibromo-3-chloropropane (DBCP). Pharmacol Toxicol. 1990 Apr;66(4):287-93. PubMed PMID: 2371234.

11) Kluwe WM, Weber H, Greenwell A, Harrington F. Initial and residual toxicity following acute exposure of developing male rats to dibromochloropropane. Toxicol Appl Pharmacol. 1985 Jun 15;79(1):54-68. PubMed PMID: 4049407.

12) Kluwe WM, Gupta BN, Lamb JC 4th. The comparative effects of 1,2-dibromo-3-chloropropane (DBCP) and its metabolites, 3-chloro-1,2-propaneoxide (epichlorohydrin), 3-chloro-1,2-propanediol (alphachlorohydrin), and oxalic acid, on the urogenital system of male rats. Toxicol Appl Pharmacol. 1983 Aug;70(1):67-86. PubMed PMID: 6612740.

13) National Toxicology Program. Carcinogenesis Bioassay of 1,2-Dibromo-3-chloropropane (CAS No. 96-12-8) in F344 Rats and B6C3F1 Mice (Inhalation Study). Natl Toxicol Program Tech Rep Ser. 1982 Mar;206:1-174. PubMed PMID: 12778229.

14) Weber GL, Steenwyk RC, Nelson SD, Pearson PG. Identification of N-acetylcysteine conjugates of 1,2-dibromo-3-chloropropane: evidence for cytochrome P450 and glutathione mediated bioactivation pathways. Chem Res Toxicol. 1995 Jun;8(4):560-73. PubMed PMID: 7548736.

15) Humphreys WG, Kim DH, Guengerich FP. Isolation and characterization of N7-guanyl adducts derived from 1,2-dibromo-3-chloropropane. Chem Res Toxicol. 1991 Jul-Aug;4(4):445-53. PubMed PMID: 1912332.

16) Låg M, Omichinski JG, Søderlund EJ, Brunborg G, Holme JA, Dahl JE, Nelson SD, Dybing E. Role of P-450 activity and glutathione levels in 1,2-dibromo-3-chloropropane tissue distribution, renal necrosis and in vivo DNA damage. Toxicology. 1989 Jun 16;56(3):273-88. PubMed PMID: 2734806.

17) Russell LA. 1,2-Dibromo-3-chloropropane (DBCP)-induced nuclear atypia in rat kidney. J Environ Pathol Toxicol Oncol. 1989 Mar-Apr;9(2):145-57. PubMed PMID: 2732909.

18) Låg M, Søderlund EJ, Omichinski JG, Nelson SD, Dybing E. Metabolism of selectively methylated and deuterated analogs of 1,2-dibromo-3-chloropropane: role in organ toxicity and mutagenicity. Chem Biol Interact. 1989;69(1):33-44.
PubMed PMID: 2914329.

19) Brunborg G, Holme JA, Søderlund EJ, Omichinski JG, Dybing E. An automated alkaline elution system: DNA damage induced by 1,2-dibromo-3-chloropropane in vivo and in vitro. Anal Biochem. 1988 Nov 1;174(2):522-36. PubMed PMID: 3239754.

20) Kluwe WM. Effects of partial hepatectomy on organ-specific toxic response to 1,2-dibromo-3-chloropropane (DBCP). J Appl Toxicol. 1983 Aug;3(4):167-74. PubMed PMID: 6643914.

21) Pearson PG, Soderlund EJ, Dybing E, Nelson SD. Metabolic activation of 1,2-dibromo-3-chloropropane: evidence for the formation of reactive episulfonium ion intermediates. Biochemistry. 1990 May 22;29(20):4971-81. PubMed PMID: 2364069.

22) Sasaki YF, Saga A, Akasaka M, Ishibashi S, Yoshida K, Su YQ, Matsusaka N, Tsuda S. Detection of in vivo genotoxicity of haloalkanes and haloalkenes carcinogenic to rodents by the alkaline single cell gel electrophoresis (comet) assay in multiple mouse organs. Mutat Res. 1998 Nov 9;419(1-3):13-20. PubMed PMID: 9804871.

23) Brunborg G, Søderlund EJ, Holme JA, Dybing E. Organ-specific and transplacental DNA damage and its repair in rats treated with 1,2-dibromo-3-chloropropane. Chem Biol Interact. 1996 Jun;101(1):33-48. PubMed PMID: 8665617.

24) Holme JA, Søderlund J, Låg M, Brunborg G, Dybing E. Prevention of 1,2-dibromo-3-chloropropane (DBCP)-induced kidney necrosis and testicular atrophy by 3-aminobenzamide. Toxicol Appl Pharmacol. 1991 Aug;110(1):118-28. PubMed PMID: 1908144.

25) Heindel JJ, Berkowitz AS, Kyle G, Luthra R, Bruckner JV. Assessment in rats of the gonadotoxic and hepatorenal toxic potential of dibromochloropropane (DBCP) in drinking water. Fundam Appl Toxicol. 1989 Nov;13(4):804-15. PubMed PMID: 2620797.

DIAZINON

1) Active Ingredient: Diazinon, CAS #: 333-41-5

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Diazinon is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
The toxicological profile of diazinon states that the systemic toxicity of diazinon exposure is mostly attributable to its effects on the nervous system and as a result of AChE inhibition. In acute exposures, kidney damage was observed. The profile references a human toxicological study of acute diazinon poisoning in which kidney and rare renal tract and kidney cortex submucosal petechiae and ecchymoses were observed in autopsies.

The profile also mentions animal studies of single dose diazinon exposure resulting in oliguria, aciduria, and humaturia in rats among other renal effects such as tubular swelling, capillary loop congestion, glycosuria, proteinuria, and hematuria.

Beagle dogs treated with 5 mg/kg for 8 months showed kidney corticomedullary congestion and capsular adhesions. One dog that died from exposure to 10 mg/kg/day diazinon exhibited localized chronic nephritis, tubular atrophy, and glomeruli with fibrous infiltrations.

However, the profile also notes that other animal studies (rabbits, Sprague-Dawley rats, beagle dogs) suggest that there is no gross or histological evidence of treatment-related damage to the kidneys after oral exposure to diazinon.

National Institute on Occupational Safety and Health (NIOSH)
There is no information in the NIOSH Pocket Guide to Chemical Hazards stating that diazinon is associated with kidney damage in humans.

3) Literature

The scientific literature review resulted in a total retrieval of 19 citations. Of the 19 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 2 toxicological studies in humans, and 7 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that show an association between diazinon exposure and kidney damage.

Toxicology - Humans
One study looked at the symptoms of farmers exposed to pesticide residues and found that exposed persons complained about liver and kidney dysfunctions and RTI, suggesting prolonged

exposure to multiple pesticides may be related to kidney effects such as a burning sensation in urine. (2) Another study from 1994 suggests that renal failure from organophosphate intoxication is very rare. (4)

Toxicology - Animals

One study looked at the histopathological and histochemical effects of high and low diazinon exposures in rabbits. Kidney effects, such as increased glycogen content in the Bowman's capsule and increased AChE activity in glomerular cells, were more pronounced at the higher exposure level. (1) Three other studies in which rats were given diazinon doses orally found the highest concentration of diazinon after administration in the kidneys, when comparing to liver, kidney, brain tissues. (3, 6, 7) One study observed that kidney concentrations were 500 times that in the liver and 11 times that in the brain at 8 h after dosing rats with 100 mg/kg body wt of diazinon. (7)

In a study of calves, the toxicity of diazinon was enhanced in calves with renal tubular lesions induced by exposure to mercuric chloride. (5) However, in an early study in rats, mild structural and functional changes were observed in liver and testes of rats after a single intraperitoneal administration of diazinon (21.6 mg/kg), but the kidney, showed no pathological lesion. (8)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that diazinon is associated with chronic kidney disease in humans. A limited body of literature has been published concerning the toxicological profile of diazinon as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that diazinon is associated with kidney damage in humans or animals. Although this chemical was initially flagged as potentially causing kidney damage, a more thorough literature review has demonstrated only limited evidence of a causal relationship.

5) References

1) Yehia MA, El-Banna SG, Okab AB.Diazinon toxicity affects histophysiological and biochemical parameters in rabbits. Exp Toxicol Pathol. 2007 Nov;59(3-4):215-25. Epub 2007 Oct 22. PMID: 17933502

2) Azmi MA, Naqvi SN, Azmi MA, Aslam M. Effect of pesticide residues on health and different enzyme levels in the blood of farm workers from Gadap (rural area) Karachi-Pakistan. Chemosphere. 2006 Sep;64(10):1739-44. Epub 2006 Feb 20.PMID: 16487989

3) Wu HX, Evreux-Gros C, Descotes J.Diazinon toxicokinetics, tissue distribution and anticholinesterase activity in the rat. Biomed Environ Sci. 1996 Dec;9(4):359-69.PMID: 8988804

4) Abend Y, Goland S, Evron E, Sthoeger ZM, Geltner D.Acute renal failure complicating organophosphate intoxication. Ren Fail. 1994;16(3):415-7. Review.PMID: 8059024

5) Abdelsalam EB, Ford EJ. The effect of induced liver, kidney and lung lesions on the toxicity of levamisole and diazinon in calves. J Comp Pathol. 1987 Nov;97(6):619-27.PMID: 3443686

6) Tomokuni K, Hasegawa T, Hirai Y, Koga N.The tissue distribution of diazinon and the inhibition of blood cholinesterase activities in rats and mice receiving a single intraperitoneal dose of diazinon. Toxicology. 1985 Oct;37(1-2):91-8.PMID: 4060172

7) Tomokuni K, Hasegawa T. Diazinon concentrations and blood cholinesterase activities in rats exposed to diazinon. Toxicol Lett. 1985 Apr;25(1):7-10.PMID: 3992605

8) Dikshith TS, Behari JR, Datta KK, Mathur AK. Effect of diazinon in male rats. Histopathological and biochemical studies. Environ Physiol Biochem. 1975;5(5):293-9.PMID: 1193042 [PubMed - indexed for MEDLINE]

FURADAN

1) Active Ingredient: Carbofuran, CAS #: 1563-66-2 (44% by weight)
Inactive Ingredient: Propylene Glycol, CAS #: 57-55-6 (5% by weight)

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that the active ingredient, carbofuran, is associated with kidney damage in humans or animals. The MSDS does state that in laboratory animals, repeated overexposure to propylene glycol, the inactive ingredient, can produce central nervous system depression, hemolysis and minimal kidney damage. There is no mention of kidney damage in humans due to exposure to propylene glycol. (Note: the inactive ingredient propylene glycol comprises only 5% by weight of the chemical compound).

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for carbofuran.

National Institute on Occupational Safety and Health (NIOSH)
There is no information on the NIOSH Pocket Guide to Chemical Hazards profile stating that carbofuran exposure is associated with kidney damage in humans.

3) Literature

The scientific literature review resulted in a total retrieval of 20 citations. Of the 20 citations reviewed, the following pertinent articles are summarized below: 1 human epidemiological study, 0 toxicological studies in humans, and 2 toxicological studies in animals.

Epidemiological Studies
One study aimed to determine health effects of exposure to several pesticides (including carbofuran) among factory workers in Pakistan by measuring biomarkers in the blood, liver, and kidney. Plasma cypermethrin, endosulfan, imidacloprid, thiodicarb, carbofuran, and methamidophos levels were found to be higher than allowable daily intake. Serum AST, ALT, creatinine, GGT, malondialdehyde, total antioxidant, and CRP were significantly raised among the workers of small and medium pesticide formulation factories as compared to large industrial unit workers and controls ($p < 0.001$). This study revealed that unsafe practices among small- and medium-sized pesticides industrial workers cause significant increase in pesticide exposure, oxidative stress, and derangement of hepatic and renal function. (1)

Toxicology - Humans
There were no human toxicological studies found that show an association between carbofuran exposure and kidney damage.

Toxicology - Animals
In one toxicological study, rats were fed fava bean-bound residues of carbofuran. Metabolites carbofuran phenol and 3-hydroxy carbofuran were found to be excreted in the urine. Serum

transaminases and blood urea nitrogen were significantly elevated, indicating injury to hepatic and renal structures. (2)

Another study examined dermal penetration of carbofuran in Fischer rats. In both young and adult rats, the kidney showed the highest tissue-to-blood concentration ratio. (3)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that carbofuran exposure is associated with chronic kidney disease in humans. We found that a limited body of literature has been published concerning the toxicological profile of carbofuran as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that carbofuran exposure is associated with kidney damage in humans or animals.

5) References

1) Khan DA, Hashmi I, Mahjabeen W, Naqvi TA. Monitoring health implications of pesticide exposure in factory workers in Pakistan. Environ Monit Assess. 2009 Aug 8. [Epub ahead of print] PubMed PMID: 19669582.

2) Mostafa IY, Zayed SM, Farghaly M, Mahdy F. Bioavailability to rats and toxicity in mice of carbofuran residues bound to faba beans. J Environ Sci Health B. 1992 Aug;27(4):399-405. PubMed PMID: 1527362.

3) Shah PV, Fisher HL, Month NJ, Sumler MR, Hall LL. Dermal penetration of carbofuran in young and adult Fischer 344 rats. J Toxicol Environ Health. 1987;22(2):207-23. PubMed PMID: 3669102.

HEXAXINONA

1) Active Ingredient: Hexazinone, CAS #: 51235-04-2

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Hexaxinona is associated with kidney damage in humans or animals

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for hexazinone.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile for hexazinone.

3) Literature

The scientific literature review resulted in a total retrieval of 0 citations.

Epidemiological Studies
There were no human epidemiological studies found that show an association between hexazinone exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between hexazinone exposure and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that show an association between hexazinone exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that hexazinone exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of hexazinone as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between hexazinone exposure and kidney damage in humans or animals.

5) References

None.

LORSBAN

1) Active Ingredient: Chlorpyrifos, CAS #: 2921-88-2

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Lorsban is associated with kidney damage in humans.

ATSDR Toxicological Profile Information Sheets
The toxicological profile states that changes in urinary frequency have been observed in humans exposed to chlorpyrifos but no statistically significant differences in the prevalence of renal illnesses were found in the exposed groups compared to matched controls. In rats exposed to 0, 0.075, 0.148, or 0.295 mg/m^3 chlorpyrifos for 6 hours a day, 5 days a week for 13 weeks, there was no difference in urine chemistry or changes in kidney weight or histopathology compared to a control group. No data were located for renal effects in animals following acute- or chronic-duration exposure to chlorpyrifos.

National Institute on Occupational Safety and Health (NIOSH)
There is no information in the NIOSH Pocket Guide to Chemical Hazards stating that chlorpyrifos is associated with kidney damage in humans.

3) Literature

The scientific literature review resulted in a total retrieval of 33 citations. Of the 33 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 2 toxicological studies in humans, and 6 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that show an association between chlorpyrifos exposure and kidney damage.

Toxicology - Humans
In an instance of organophosphate poisoning, concentrations in the kidney were higher than in other tissues. (3) Another study examined a patient with end-stage renal disease (ESRD) who had attempted suicide with a chlorpyrifos overdose and showed signs of intermediate syndrome (IMS) 45 hours later. (4)

Toxicology - Animals
One study that looked at Wistar rats given either daily doses of 5 mg/kg b wt or 10 mg/kg b wt of chlorpyrifos for up to 8 weeks. The changes noticed were mainly the shrinkage of the glomerulus at initial stage of treatment, tubular dilation, glomerular hypercellularity, hypertrophy of tubular epithelium, degeneration of glomerulus and renal tubules, deposition of eosin-positive substances in the glomerulus and renal tubules and infiltration of leucocytes. (1) Other studies confirm observable symptoms of nephrotoxicity in rats exposed to chlorpyrifos. (5, 6) In one of these

studies, rats fed soybeans contaminated with chlorpyrifos displayed lower blood picture, liver and kidney function. (5) In another, albino rats showed necrosis of some of the seminiferous tubules of the testes and cloudy swelling of the convoluted tubules of the kidney. (8)

In a study of 344 male Fischer rats, chlorpyrifos was found to increase the expression of P-glycoprotein, a protein believed to be involved in the detoxification of xenobiotics, in the large bile ducts of the liver and the proximal tubule region of the kidney. (7)

However, in another study of rats treated with Chlorpyrifos (CPF) and carbaryl (CAR) alone or in combination no histopathological changes were observed in the liver and kidney tissues. (2)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that chlorpyrifos exposure is associated with chronic kidney disease in humans. Moderate literature has been published concerning the toxicological profile of chlorpyrifos as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that chlorpyrifos is associated with kidney damage in humans or animals.

5) References

1) Tripathi S, Srivastav AK. Nephrotoxicity induced by long-term oral administration of different doses of chlorpyrifos. Toxicol Ind Health. 2010 May 26. [Epub ahead of print]PMID: 20504822 [PubMed - as supplied by publisher]

2) Wang HP, Liang YJ, Long DX, Chen JX, Hou WY, Wu YJ. Metabolic profiles of serum from rats after subchronic exposure to chlorpyrifos and carbaryl. Chem Res Toxicol. 2009 Jun;22(6):1026-33.PMID: 19522548 [PubMed - indexed for MEDLINE]

3) Tarbah FA, Shaheen AM, Benomran FA, Hassan AI, Daldrup T. Distribution of dimethoate in the body after a fatal organophosphate intoxication. Forensic Sci Int. 2007 Aug 6;170(2-3):129-32. Epub 2007 Jul 23.PMID: 17643882 [PubMed - indexed for MEDLINE]

4) Lee F, Lin JL. Intermediate syndrome after organophosphate intoxication in patient with end-stage renal disease. Ren Fail. 2006;28(2):197-200.PMID: 16538982 [PubMed - indexed for MEDLINE]

5) Zayed SM, Farghaly M, El-Maghraby S. Fate of 14C-chlorpyrifos in stored soybeans and its toxicological potential to mice. Food Chem Toxicol. 2003 Jun;41(6):767-72.PMID: 12738182 [PubMed - indexed for MEDLINE]

6) Oncu M, Gultekin F, Karaöz E, Altuntas I, Delibas N. Nephrotoxicity in rats induced by chlorpryfos-ethyl and ameliorating effects of antioxidants. Hum Exp Toxicol. 2002 Apr;21(4):223-30.PMID: 12099624 [PubMed - indexed for MEDLINE]

7) Lanning CL, Fine RL, Sachs CW, Rao US, Corcoran JJ, Abou-Donia MB. Chlorpyrifos oxon interacts with the mammalian multidrug resistance protein, P-glycoprotein. J Toxicol Environ Health. 1996 Mar;47(4):395-407.PMID: 8600291 [PubMed - indexed for MEDLINE]

8) Mikhail TH, Aggour N, Awadallah R, Boulos MN, El-Dessoukey EA, Karima AI. Acute toxicity of organophosphorus and organochlorine insecticides in laboratory animals. Z Ernahrungswiss. 1979 Dec;18(4):258-68.PMID: 95070 [PubMed - indexed for MEDLINE]

MSMA

1) Active Ingredient: Monosodium Methanearsonate (MSMA), CAS #: 2163-80-6

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
The MSDS states that prolonged overexposure to MSMA may affect kidneys but does not specify the extent of damage.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for MSMA.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for MSMA.

3) Literature

The scientific literature review resulted in a total retrieval of 24 citations. Of the 24 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 1 toxicological study in humans, and 1 toxicological study in animals.

Epidemiologic Studies
There were no human epidemiological studies found that show an association between MSMA exposure and kidney damage.

Toxicology - Humans
A case study identified a 20 year-old male attempting suicide by drinking approximately 500 ml of a 16% monosodium methanearsenate (MSMA) solution. He vomited 10 or more times and was admitted to the intensive care unit with impending shock and early liver and renal involvement. (1)

Toxicology - Animals
MSMA was administered orally to adult male New Zealand white rabbits weighing 2.5-3kg over a period of 40 days to monitor potential histopathological effects. Doses were given in 5, 10 or 20mg/kg amounts of MSMA. Primary lesions included hepatic cellular degeneration, periportal inflammation, renal tubular nephrosis, interstitial nephritis and vascular hyperemia, with severity of lesions varying by dose. (2)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that MSMA exposure is associated with chronic kidney disease in humans. Limited literature has been published concerning the toxicological profile of MSMA as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that MSMA exposure is associated

with kidney damage in humans or animals. Although this chemical was initially flagged as potentially causing kidney damage, a more thorough literature review has demonstrated only limited evidence of a causal relationship.

5) References

1) Shum S, Whitehead J, Vaughn L, Shum S, Hale T. Chelation of organoarsenate with dimercaptosuccinic acid. Vet Hum Toxicol. 1995 Jun;37(3):239-42. PubMed PMID: 7571355.

2) Jaghabir MT, Abdelghani AA, Anderson AC. Histopathological effects of monosodium methanearsonate (MSMA) on New Zealand white rabbits (Oryctalagus cuniculus). Bull Environ Contam Toxicol. 1989 Feb;42(2):289-93. PubMed PMID: 2920237.

NOVUCRON

1) Active Ingredient: Monocrotophos, CAS #: 6923-22-4

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Novucron is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for monocrotophos.

National Institute on Occupational Safety and Health (NIOSH)
There is no information on the NIOSH Pocket Guide to Chemical Hazards profile stating that monocrotophos is associated with kidney damage in humans.

3) Literature

The scientific literature review resulted in a total retrieval of 23 citations. Of the 23 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 2 toxicological studies in humans, and 10 toxicological studies in animals.

Epidemiological Studies
There were no human epidemiological studies found that showed an association between monocrotophos exposure and kidney damage.

Toxicology - Humans
One study of the effect of pesticide residues, including monocrotophos, on health and enzyme levels in farm workers from Pakistan found that exposed persons complained about liver and kidney dysfunctions. The study concluded that exposure of the pesticides in question for prolonged periods affects the normal functioning of different organ systems and possibly produced characteristics clinical effects such as hepatitis, dyspnea and burning sensation in urine. (1)

Another study noted that organophosphate intoxication is an extremely uncommon cause of rhabdomyolysis. However, the article went on to describe two cases with rhabdomyolysis induced acute renal failure complicated by monocrotophos, an organophosphate compound. The first patient discussed had rhabdomyolysis induced acute renal failure and subarachnoid hemorrhage. The second patient described had rhabdomyolysis induced acute renal failure after organophosphate overdose. (2)

Toxicology - Animals
One study observed histopathological changes in the liver, kidney and muscles of normal, protein-malnourished, diabetic as well as both protein-malnourished and diabetic albino rats when exposed to a mixture of monocrotophos, hexachlorocyclohexane and endosulfan at varying

intervals. The examination revealed hepatotoxic, nephrotoxic and muscular necrotic effects in pesticides exposed rats. Toxicity was aggravated in protein-malnourished and diabetic animals and more so, if the animals were both diabetic and protein-malnourished. (3)

Another study investigated the impact of monocrotophos on protein and carbohydrate metabolism in different tissues of albino rats. The monocrotophos (0.25 mg/ml) was given orally into an experimental group of rats. The protein content decreased in muscle and kidney, and overall the free sugar level decreased in all tissues after treatment with monocrotophos. The glycogen content increased in muscle, serum and kidney after treatment with monocrotophos. (4)

In another study, the metabolism of monocrotophos was studied. The study found that monocrotophos and/or its metabolites are evenly distributed between the tissues and organs of the animals; the highest concentrations are typically found in organs involved in the elimination process, i.e., liver and kidney. There were no indications for any organ-specific retention. (5)

Multiple articles also discussed the effects of novel thion analogues of monocrotophos, primarily developed at the Indian Institute of Chemical Technology, on the activity of various enzymes and cytochromes in rats. Some of the enzymes of interest included detoxifying enzymes of the liver and kidney, whose activities were affected by exposure to these novel organophosphorous chemicals. (6, 7, 8, 9, 10, 11, 12, 13)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that monocrotophos is associated with chronic kidney disease in humans. We found that limited literature has been published concerning the toxicological profile of monocrotophos as it relates to the kidney. These references, in addition to the chemical MSDS and health organization statements, suggest that there is limited evidence that monocrotophos is associated with kidney damage in humans or animals.

5) References

1. Azmi MA, Naqvi SN, Azmi MA, Aslam M. Effect of pesticide residues on health and different enzyme levels in the blood of farm workers from Gadap (rural area) Karachi-Pakistan. Chemosphere. 2006 Sep;64(10):1739-44. Epub 2006 Feb 20. PubMed PMID: 16487989.

2. Gokel Y. Subarachnoid hemorrhage and rhabdomyolysis induced acute renal failure complicating organophosphate intoxication. Ren Fail. 2002 Nov;24(6):867-71. PubMed PMID: 12472209.

3. Benjamin N, Kushwah A, Sharma RK, Katiyar AK. Histopathological changes in liver, kidney and muscles of pesticides exposed malnourished and diabetic rats. Indian J Exp Biol. 2006 Mar;44(3):228-32. PubMed PMID: 16538862.

4. Elumalai M, Jayakumar R, Balasubramanian MP. Impact of monocrotophos on protein and carbohydrate metabolism in different tissues of albino rats. Cytobios. 1999;98(389):131-6. PubMed PMID: 10533267.

5. Mücke W. Metabolism of monocrotophos in animals. Rev Environ Contam Toxicol. 1994;139:59-65. Review. PubMed PMID: 7809421.

6. Mahboob M, Kaleem M, Siddiqui J. Effects of a novel organophosphorus pesticide (RPR-V) on extra hepatic detoxifying enzymes after repeated oral doses in rats. Toxicology. 2004 Oct 1;202(3):159-64. PubMed PMID: 15337579.

7. Rahman MF, Siddiqui MK. Biochemical enzyme activity in different tissues of rats exposed to a novel phosphorothionate (RPR-V). J Environ Sci Health B. 2003 Jan;38(1):59-71. PubMed PMID: 12602824.

8. Mahboob M, Siddiqui MK. Long-term effects of a novel phosphorothionate (RPR-II) on detoxifying enzymes in brain, lung, and kidney rats. Ecotoxicol Environ Saf. 2002 Nov;53(3):355-60. PubMed PMID: 12485578.

9. Mahboob M, Siddiqui MK, Jamil K. Subacute effects of a phosphorothionate pesticide on mixed function oxidases of Wistar rats. J Environ Sci Health B. 2000 Nov;35(6):739-49. PubMed PMID: 11069016.

10. Rahman MF, Siddiqui MK, Jamil K. Acid and alkaline phosphatase activities in a novel phosphorothionate (RPR-11) treated male and female rats. Evidence of dose and time-dependent response. Drug Chem Toxicol. 2000 Aug;23(3):497-509. PubMed PMID: 10959550.

11. Rahman MF, Siddiqui MK, Jamil K. Biochemical alterations induced by a new phosphorothionate (RPR-II) in tissues of male and female rats. Indian J Exp Biol. 1999 Jun;37(6):546-52. PubMed PMID: 10641186.

12. Siddiqui MK, Mahboob M, Mustafa M. Interaction of monocrotophos and its novel thion analogues with microsomal cytochrome P-450: in vivo and in vitro studies in rat. Toxicology. 1992 Nov 30;76(2):133-9. PubMed PMID: 1462357.

13. Swamy KV, Srinivas T, Mohan PM. Effect of monocrotophos on mono amine oxidase activity in albino rats. Biochem Int. 1991 Jul;24(4):785-92. PubMed PMID: 1799376.

PARAQUAT

1) Active Ingredient: Paraquat Dichloride CAS #: 4685-14-7

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
The appropriate MSDS could not be located.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for paraquat dichloride.

National Institute on Occupational Safety and Health (NIOSH)
NIOSH considers a symptom of Paraquat exposure to be kidney damage. The target organs identified by NIOSH are the eyes, skin, respiratory system, heart, liver, kidneys, and gastrointestinal tract.

3) Literature

The scientific literature review resulted in a total retrieval of 395 citations. Of the 395 citations reviewed, the following pertinent articles are summarized below: 5 human epidemiological studies, 4 toxicological studies in humans, and 0 toxicological studies in animals.

Epidemiological Studies
A review of pesticide poisoning identified acute poisoning with pesticides to be a global public health problem and accounts for as many as 300,000 deaths worldwide every year. The report identified ingestion of paraquat to cause severe inflammation of the throat, corrosive injury to the gastrointestinal tract, renal tubular necrosis, hepatic necrosis and pulmonary fibrosis. (1)

A retrospective study executed in the emergency department of a university hospital in the UK enrolled one hundred three consecutive patients poisoned with Paraquat (PQ) between January 1999 and December 2004. Urine PQ concentration, electrolyte and renal function, detailed history, and Acute Physiology and Chronic Health Evaluation II were extracted from medical records. The outcome measure was 30-day mortality. The crude 30-day mortality was 67.9% (70 of 103). Independent predictors of death were acute renal failure (hazard ratio, 3.53; 95% confidence interval, 1.97-6.32), hypokalemia (2.07, 1.21-3.51), hypothermia (2.91, 1.67-5.07), suicide (2.11, 1.04-4.29), and self-reported ingested dose (2.06, 1.38-3.06). (2)

A prospective study investigated changes in urinary kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) in acute PQ intoxication. From May 2008 to September 2008, 20 patients were included. Urine KIM-1, NGAL, and 8-hydroxy-2-deoxyguanosine (8-OH-dG) were measured at 6, 12, 24, 48, 72, and 120 h after ingestion. The serum creatinine was measured also at the same intervals. (3) Acute kidney injury (AKI) was diagnosed in 11 out of 20 patients. There was a significant difference in the creatinine at 12 h between patients with AKI and those without AKI (0.50 +/- 0.15 vs. 1.04 +/- 0.53 mg/dL, p=

0.01). (3) PQ is a very potent stimulant of NGAL-1 and KIM-1. Therefore, the NGAL might reflect reactive oxygen species-induced kidney injury. (3)

One case series report describes a series of unsuspected paraquat poisonings presenting as an outbreak of fatal acute pneumonitis. Exposure to paraquat occurred during the widespread practice of adding substances to alter the taste or potency of illicit alcohol. The diagnosis was suspected only after autopsy findings suggestive of paraquat toxicity were seen in the first fatality. An estimated 50 persons were exposed. Of these, 5 presented with progressive dyspnea, and died 9-30 days after exposure. Autopsy revealed widespread renal and hepatic necrosis in the early deaths, and prominent pulmonary fibrosis in those dying later. (4)

One study investigated AKI in patients with acute paraquat poisoning. The study attempted to provide a model for the clinical features of ROS-induced AKI. From January 2007 to December 2007, 278 patients with acute PQ intoxication were included in the study. An initial serum Cr >1.2 mg/dL was a significant predictor of mortality [odds ratio 9.00, 95% C.I. (4.747, 17.061), P < 0.01]. The incidence of AKI was 51.4% among the 173 patients who had an initial serum Cr ≤1.2 mg/dL. Among them, 34.7% were the failure group and oliguric AKI was observed in 10 patients. The average peak serum Cr level, among the 13 survivors in the failure group, was 4.38 mg/dL at the fifth day, after ingestion, and their Cr level normalized within 3 weeks. They found that none of the 13 survivors had permanent loss of renal function. They estimated amount of PQ ingestion was a predictor of the incidence of AKI. The mortality risk was significantly higher in the AKI group than in the group without AKI. The clinical course was characterized by fully developed AKI at the fifth day after PQ ingestion and normalized within 3 weeks without exception. (5)

Toxicology - Humans

One study noted that the ingestion of paraquat, a non-selective herbicide, can be fatal in humans. Paraquat is toxic to multiple organs, including the kidney, heart, gastrointestinal tract and central nervous system. Although paraquat has been established as one cause of acute tubular necrosis, Fanconi syndrome presenting as severe hypophosphataemia after paraquat intoxication has not been reported. This report is on the case of a 44-year-old Korean woman who presented with generalized proximal tubular dysfunction including aminoaciduria, phosphaturia and glycosuria after paraquat intoxication. Renal biopsy findings indicated the presence of acute tubular necrosis. (6)

A review from 2003 investigating toxic nephropathy and environmental chemicals identified compounds such as paraquat or diquat to damage the kidney via the production of reactive oxygen species. (7)

One study stated that paraquat is an herbicide that is highly toxic to humans and pediatric ingestion has become uncommon in the United States because of preventative efforts. This case report concerns an unintentional, fatal paraquat ingestion by an 8-year-old child. The pathological findings of childhood paraquat poisoning are the development of skin and mucous membrane burns, gastrointestinal symptoms, acute kidney injury, and respiratory failure.(8)

There was one report of fetal poisoning after maternal paraquat ingestion during third trimester of pregnancy. A 17-year-old female in 36 weeks of gestation attempted suicide by ingesting 1/2 a glass of Gramozonetrade mark (paraquat 27.6 % w/v) She developed mild renal insufficiency 63 hours after the ingestion. The infant developed tachypnea immediately after birth that self-resolved but then developed tachypnea again on day 6 of life. A chest x-ray of the infant revealed right lower lobe infiltration that progressed to diffuse interstitial pattern; subsequent chest x-rays showed evidence of fibrosis. Both mother and infant survived and upon follow up at 10 months of age, he still had evidence of chronic lung disease clinically and on chest x-ray. (9)

Toxicology - Animals
No studies were summarized on paraquat exposure in animals.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that paraquat dichloride is associated with chronic kidney disease in humans. NIOSH considers a symptom of Paraquat exposure to be kidney damage and identifies the kidney as one of the target organs. We found that extensive literature has been published concerning the toxicological profile of paraquat dichloride as it relates to the kidney. Experimental studies have shown that Paraquat will accumulate in the lung and kidney epithelial cells, leading eventually to pulmonary fibrosis and acute renal failure. (10) These references, in addition to the chemical MSDS and health organization statements, suggest that there is strong evidence that paraquat dichloride is associated with kidney damage in humans or animals.

5) References

1. Goel A, Aggarwal P. Pesticide poisoning. Natl Med J India. 2007 Jul-Aug;20(4):182-91. Review. PubMed PMID: 18085124

2. Chang MW, Chang SS, Lee CC, Sheu BF, Young YR. Hypokalemia and hypothermia are associated with 30-day mortality in patients with acute paraquat poisoning. Am J Med Sci. 2008 Jun;335(6):451-6. PubMed PMID: 18552575

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PERMETRINA (PERMETHRIN)

1) Active Ingredient: Permethrin, CAS #: 52645-53-1

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Permethrin is associated with kidney damage in humans. In long term feeding studies in animals, Permethrin ingestion resulted in increased liver and kidney weights.

ATSDR Toxicological Profile Information Sheets
The ATSDR Toxicological Profile for permethrin stated that no studies were located regarding renal effects in humans following oral exposure to pyrethrins or pyrethroids (a class of chemicals of which permethrin is a part). Available information regarding renal effects in animals is limited to a report of decreased kidney weights and tubular degeneration in rats consuming pyrethrins in their diet. It was noted that the magnitude and statistical significance of these renal changes were not presented in these reports. Another study reported increased absolute and relative kidney weights observed in male (but not female) rats fed fenpropathrin (another chemical in this class).

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for permethrin.

3) Literature

The scientific literature review resulted in a total retrieval of 6 citations. Of the 6 citations reviewed, the following pertinent articles are summarized below: 0 human epidemiological studies, 1 toxicological study in humans, and 1 toxicological study in animals.

Epidemiological Studies
There were no human epidemiological studies found that show an association between permethrin exposure and kidney damage.

Toxicology - Humans
In a study of 48 patients poisoned with insecticide formulations containing permethrin (a Type I pyrethroid insecticide), xylene, and surfactants, mild renal dysfunction was found in 10% of patients. However, the relative contributions of the 20% permethrin, 70% xylene, and 10% surfactant to these toxic symptoms were unclear. (1)

Toxicology – Animals
One study administered permethrin to mice infested with Myobia musculi (Schrank) using four different methods of dose delivery. The study found no significant differences between treated and untreated groups in either body weight or histopathology of the liver, lung, or kidney. (2)

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that permethrin is associated with chronic kidney disease in humans. We found that limited literature has been published concerning the toxicological profile of permethrin as it relates to the kidney. The absence of or limited information presented in the chemical MSDS, health organization statement, and in the literature does not allow us to draw a conclusion on the association between permethrin and kidney damage in humans or animals.

5) References

1) Acute ingestion poisoning with insecticide formulations containing the pyrethroid permethrin, xylene, and surfactant: a review of 48 cases.Yang PY, Lin JL, Hall AH, Tsao TC, Chern MS. J Toxicol Clin Toxicol. 2002;40(2):107-13.PMID: 12126181 [PubMed - indexed for MEDLINE]

2) Evaluation of the control of Myobia musculi infestations on laboratory mice with permethrin. Bean-Knudsen DE, Wagner JE, Hall RD. Lab Anim Sci. 1986 Jun;36(3):268-70.PMID: 3724052 [PubMed - indexed for MEDLINE]

TERBUGRAN

1) Active Ingredient: Terbufos, CAS #: 13071-79-9

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that terbufos is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for terbufos.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for terbufos.

3) Literature

The scientific literature review resulted in a total retrieval of 0 citations.

Epidemiological Studies
There were no human epidemiological studies found that show an association between terbufos exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between terbufos exposure and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that show an association between terbufos exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that terbufos exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of terbufos as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between terbufos exposure and kidney damage in humans or animals.

5) References

None.

TIOCICLAN HIDROGENOXALATO (EVISECT)

1) Active Ingredient: Thiocyclam hydrogen oxalate, CAS #: N/A

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
There is no information on the MSDS stating that Evisect is associated with kidney damage in humans or animals.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for thiocyclam hydrogen oxalate.

National Institute on Occupational Safety and Health (NIOSH)
There is no NIOSH Pocket Guide to Chemical Hazards profile available for thiocyclam hydrogen oxalate.

3) Literature

The scientific literature review resulted in a total retrieval of 0 citations.

Epidemiological Studies
There were no human epidemiological studies found that show an association between thiocyclam hydrogen oxalate exposure and kidney damage.

Toxicology - Humans
There were no human toxicological studies found that show an association between thiocyclam hydrogen oxalate exposure and kidney damage.

Toxicology - Animals
There were no toxicological studies in animals found that show an association between thiocyclam hydrogen oxalate exposure and kidney damage.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found no evidence that thiocyclam hydrogen oxalate exposure is associated with chronic kidney disease in humans. No literature has been published concerning the toxicological profile of thiocyclam hydrogen oxalate as it relates to the kidney. The absence of information presented in the chemical MSDS, health organization statements, and in the literature does not allow us to draw a conclusion on the association between thiocyclam hydrogen oxalate exposure and kidney damage in humans or animals.

5) References

None.

WARFARINA

1) Active Ingredient: Warfarin, CAS #: 81-81-2

2) Health Organizations/Agencies

Material Safety Data Sheet (MSDS)
The MSDS indicates that Warfarin may be toxic to kidneys.

ATSDR Toxicological Profile Information Sheets
There is no ATSDR Toxicological Profile available for warfarin.

National Institute on Occupational Safety and Health (NIOSH)
There is no information on the NIOSH Pocket Guide to Chemical Hazards stating that warfarin is associated with kidney damage in humans or animals.

3) Literature

The scientific literature review resulted in a total retrieval of 906 citations. The search was narrowed to focus on the adverse effects of warfarin, and 110 citations remained. Of the 110 citations reviewed, the following pertinent articles are summarized below: 2 human epidemiological studies, 10 toxicological studies in humans, and 0 toxicological studies in animals.

Epidemiological Studies
One prospective, observational study aimed to evaluate the roles of hypoalbuminemia and renal impairment as independent predictors of bleeding in patients receiving anticoagulation therapy with warfarin. Hypoalbuminemia and renal impairment were identified as patient-related predictive factors for bleeding. (1)

In another analysis of a prospective cohort, the influence of kidney function on warfarin responsiveness and hemorrhagic complications was evaluated. The study concluded that patients with reduced kidney function require lower dosages of warfarin, have poorer control of anticoagulation, and are at a higher risk for major hemorrhage. It was suggested that warfarin may need to be initiated at a lower dosage and monitored more closely in patients with moderate or severe CKD compared with the general population. Diminished renal function may have implications for a larger proportion of warfarin users than previously estimated. (2)

Toxicology - Humans
One study reported pathological findings in kidney biopsy specimens from 9 patients with warfarin overdose, hematuria, and acute kidney injury (AKI). Each biopsy specimen showed chronic kidney injury. Six of 9 patients did not recover from AKI. The authors suggested that warfarin therapy can result in AKI by causing glomerular hemorrhage and renal tubular obstruction by RBC casts. It was also suggested that this may be a potentially serious complication of warfarin therapy, especially in older patients with underlying chronic kidney injury. (3)

Another case study discussed a 48-year-old man who was on warfarin sodium for 2 months and presented with acute renal failure. Kidney biopsy showed allergic interstitial nephritis. The biopsy also showed high eosinophil count, highly suggestive of a drug-induced reaction. After a negative comprehensive work-up and the absence of other recent medication changes, the patient was determined to have allergic interstitial nephritis secondary to warfarin sodium. (4)

Another case study discussed late-onset warfarin necrosis. A 43-year-old woman developed tenderness and induration of her thighs and lower abdomen, 56 days after commencing warfarin for aortic and mitral valve replacements. Investigations showed, among other symptoms, mild renal impairment. (5)

Another paper described a case of rhabdomyolysis and acute renal failure associated with concomitant use of simvastatin and warfarin. Rhabdomyolysis and renal failure occurred 7 days after warfarin was added to a chronic stable dose of simvastatin and resolved abruptly after discontinuation of simvastatin. Careful monitoring was recommended when warfarin is given to patients receiving simvastatin. (6)

Many of the articles retrieved discussed the appropriateness of warfarin use for patients on hemodialysis, and its associated risks. In particular, one article noted that patients with end-stage renal disease (ESRD) who are undergoing hemodialysis are already 3 to 10 times more likely than the general population to experience stroke and bleeding, which warfarin can exacerbate. (7) Multiple other studies also noted the substantially increased risk of bleeding in patients on dialysis who use warfarin. (8, 9) Acute renal failure and chronic kidney disease have also been shown to increase the risk of hemorrhage during warfarin treatment. (10) When warfarin-induced renal hemorrhaging does occur, hematuria and abdominal pain are the most common complaints. (11) One other study reported on a case of acute renal failure due to retroperitoneal hematoma in which warfarin treatment was considered a complicating factor. (12)

Toxicology - Animals

No studies were summarized on warfarin exposure in animals.

4) Summary

Based on our cumulative review of health organization statements and scientific literature, we found limited evidence that warfarin is associated with chronic kidney disease in humans. We found that extensive literature has been published concerning the toxicological profile of warfarin as it relates to the kidney. However, the literature review suggests that warfarin is not directly toxic to the kidneys, but rather causes kidney damage as a secondary effect due to hemorrhaging. For instance, an individual who has excessive exposure to warfarin would experience hemorrhaging before they would experience kidney damage. Therefore, in the context of this toxicological review and assessment, we have concluded that there is limited evidence of an association between warfarin and kidney damage in humans or animals.

5) References

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