

# NIOSH 2013 Pesticide Handler Personal Protective Technology Stakeholders Meeting



**Michael Alavanja, DrPH**



**Elaine Cullen, PhD**

**Maryann D'Alessandro, PhD**

**Kim Faulkner, PhD, MPH**

**Xuemei Huang, MD, PhD**



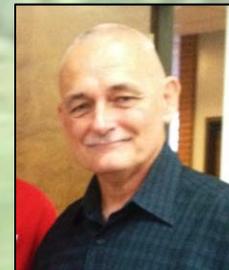
**Ron Jester, MS, PE**

**Kevin Keaney**

**Chuck Urban**

**March 26, 2013**

**Washington D.C.**



**This meeting is being recorded**

# Using “Stories” to Motivate Correct Personal Protective Equipment Practices

---



Kim Faulkner, PhD, MPH

Epidemiologist, NIOSH Personal Protective Technology Laboratory

This meeting is being recorded

# Getting Compliance Through Motivation and 'Stories'

---



Maryann D'Alessandro, PhD  
Director, NIOSH Personal Protective Technology Laboratory

This meeting is being recorded

# NIOSH National Personal Protective Equipment Surveillance and Intervention Project among Pesticide Handlers

## Objectives:

### 1. Determine the extent to which handlers use correct PPE practices

- Correct type of PPE
- Proper use of PPE



PPE = personal protective equipment

# NIOSH National Personal Protective Equipment Surveillance and Intervention Project among Pesticide Handlers, *cont.*

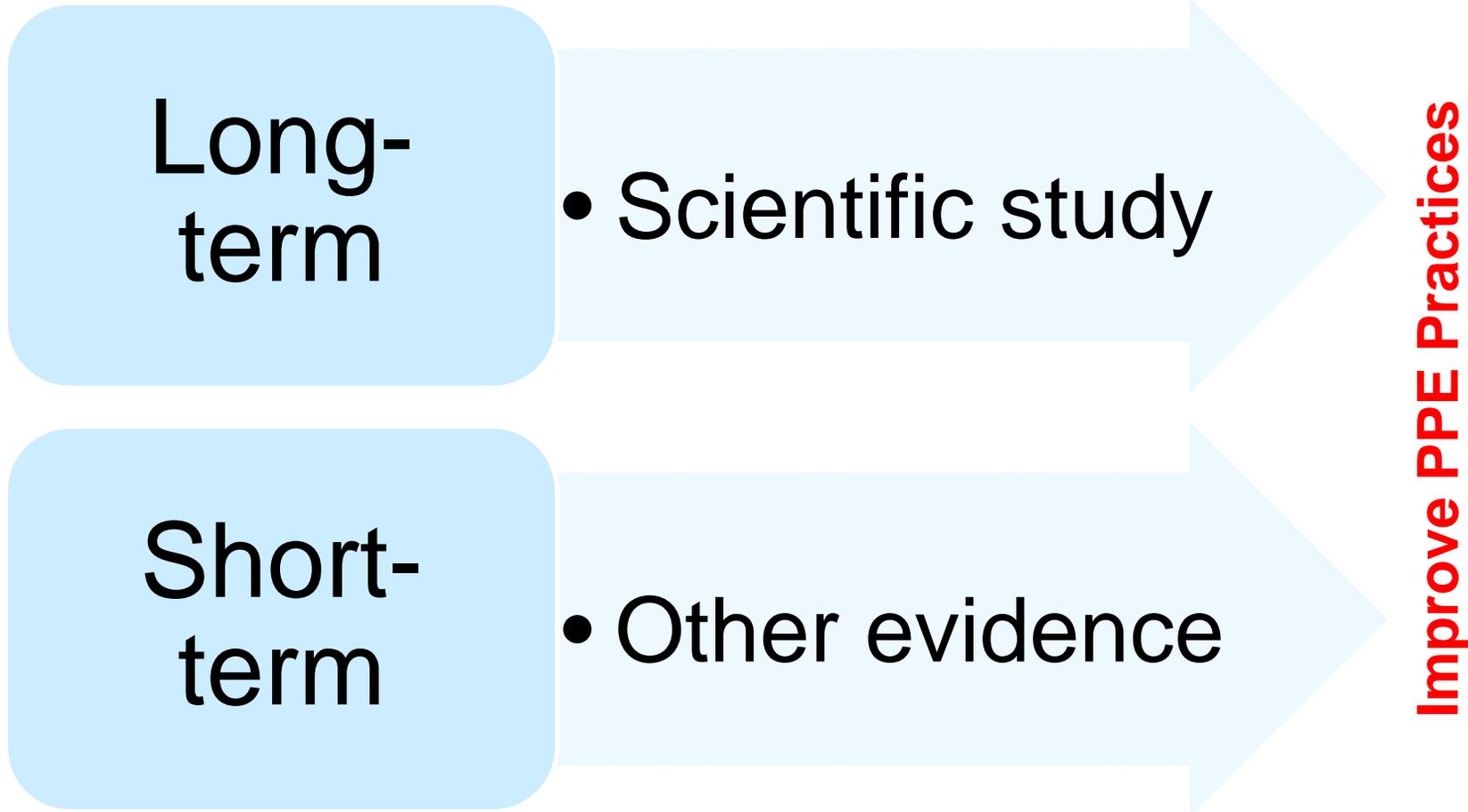
---

## **Objectives:**

- 1. Determine the correctness of PPE practices**
- 2. Identify barriers and motivating factors**
- 3. Develop, implement, and evaluate interventions**

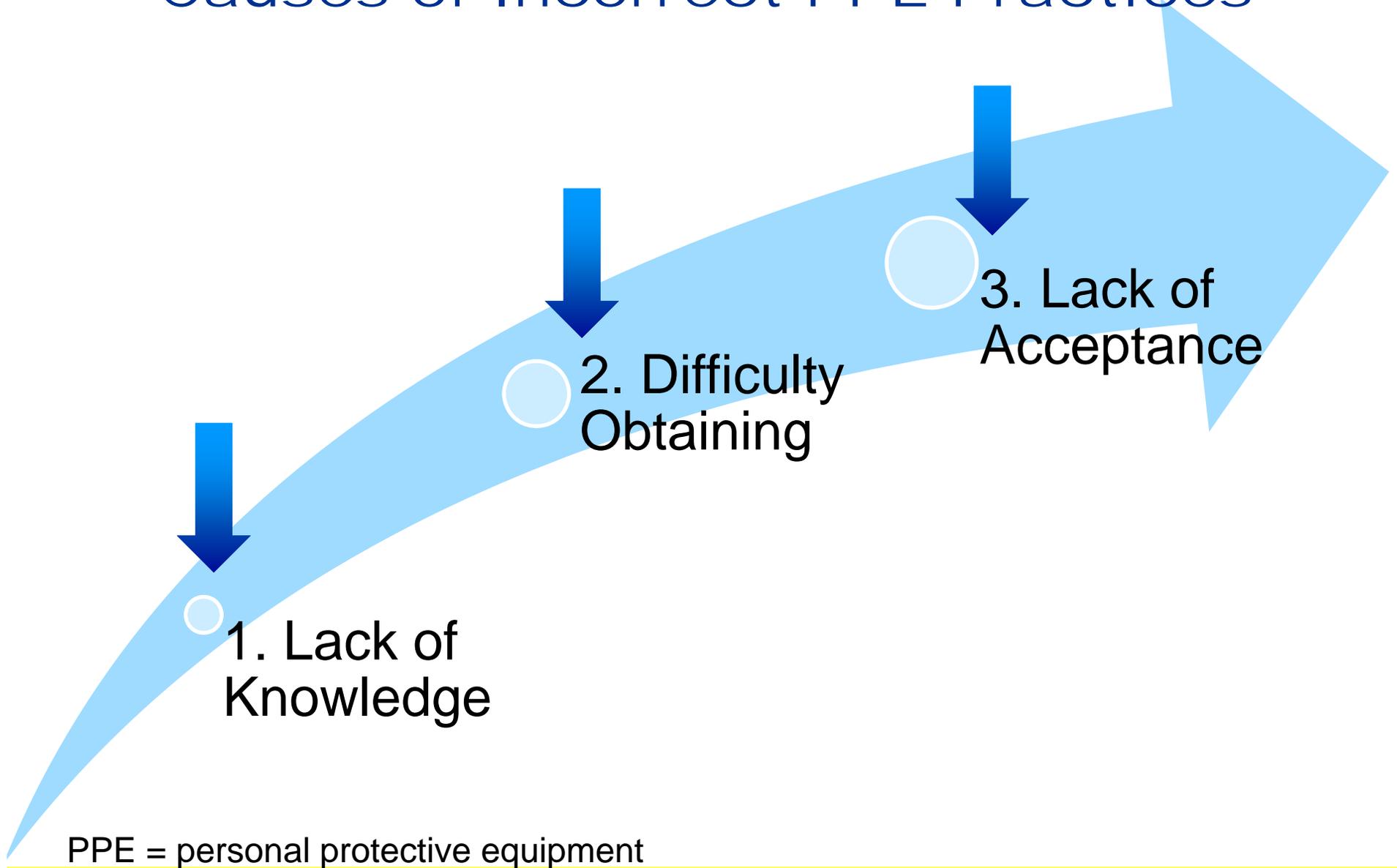
PPE = personal protective equipment

## Two-Pronged Approach



PPE = personal protective equipment

# Causes of Incorrect PPE Practices



# NIOSH Stakeholders Meetings Address Barriers to Correct PPE Practices

---

- **2011 – Lack of Knowledge**
  - National Training Solutions Committee
  - Pesticide PPE Exhibit
- **2012 – Difficulty Obtaining (Correct PPE)**
  - Enhanced PPE sales
  - PPE Kiosk
- **2013 – Lack of Acceptance (Handler Preference)**
  - Storytelling

PPE = personal protective equipment

This meeting is being recorded

# Virginia Slims Campaign from the 1960's

---

*“You’ve Come A Long Way, Baby”*

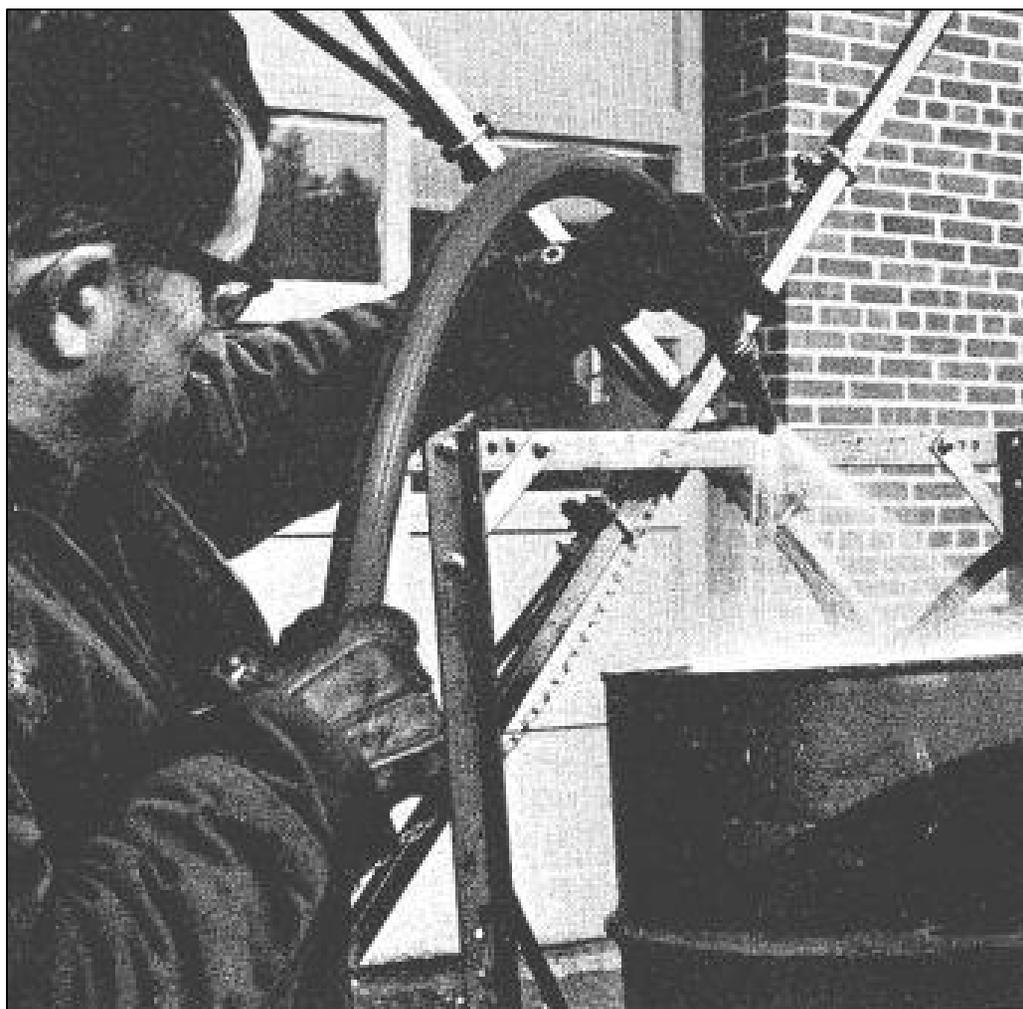
This meeting is being recorded

## Pesticide Training from the 1960's



This meeting is being recorded

# Pesticide Training from the 1960's



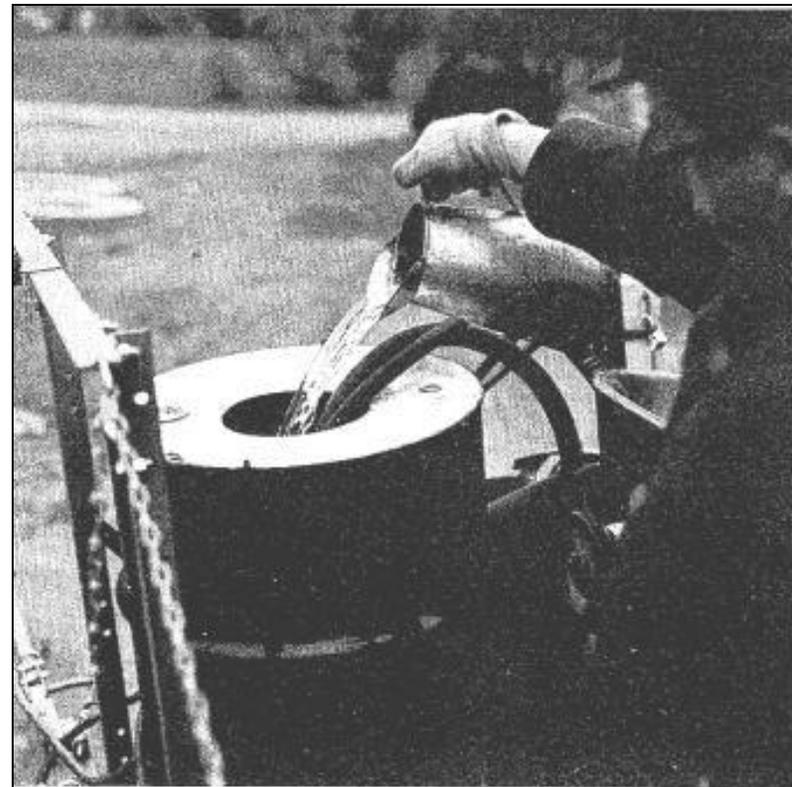
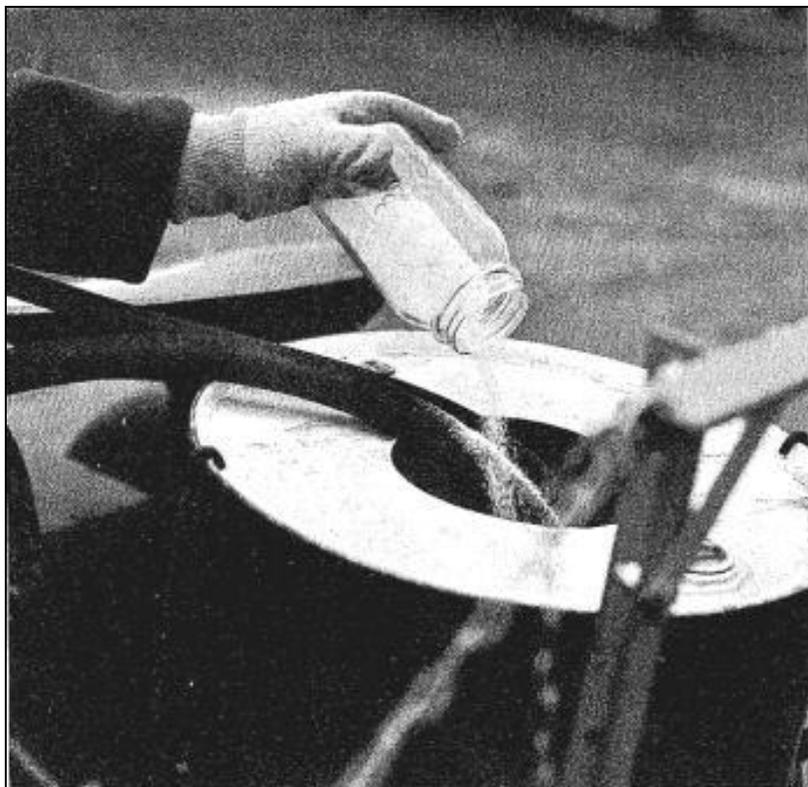
This meeting is being recorded

# Pesticide Training from the 1960's



This meeting is being recorded

# Pesticide Training from the 1960's



This meeting is being recorded

# Are regulations and policies enough?



This meeting is being recorded

# Some handlers don't read PPE requirements

## Precautionary Statements

### Hazards to Humans and Domestic Animals

# CAUTION

Harmful If Swallowed • Causes Moderate Eye Irritation • Prolonged Or Frequently Repeated Skin Contact May Cause Allergic Reactions In Some Individuals

Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking chewing gum, or using tobacco.

**Personal Protective Equipment (PPE)**  
Some materials that are chemical-resistant to this product are made of barrier laminate, nitrile rubber, neoprene rubber, and viton. If you want more options, follow the instructions for category E on an EPA chemical resistance category selection chart.

All mixers, loaders, applicators, flaggers, and other handlers must wear:

- Long-sleeved shirt and long pants
- Shoes plus socks
- Chemical-resistant gloves made of any waterproof material such as barrier laminate, nitrile rubber, neoprene rubber, and viton
- Protective eyewear
- Chemical resistant apron when mixing or loading, cleaning up spills or equipment, or otherwise exposed to the concentrate

See engineering controls for additional requirements

Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables exist, use detergent and hot water. Keep and wash PPE separately from other laundry.

**Engineering Controls**  
When handlers use closed systems or enclosed cabs in a manner that meets the requirements listed in the Worker Protections Standard (WPS) for agricultural pesticides [40 CFR 170.240 (d) (4-6)], the handler PPE requirements may be reduced or modified as specified in the WPS.

Pilots must use an enclosed cockpit that meets the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides [40 CFR 170.240(d)(4-6)].

**User Safety Recommendations**  
Users should:  
• Wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.  
• Remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.  
• Remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

**First Aid**  
If swallowed: Immediately call a poison control center or doctor. Do not induce vomiting unless told to do so by a poison control center or doctor. Do not give any liquid to the person. Do not give anything by mouth to an unconscious person.

**First Aid (Cont.)**  
If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor, or you may also contact 1-800-992-5994 for treatment information.

**Note to Physician:** This product may be a respiratory hazard. Contains petroleum.

**Environmental Hazards**  
This pesticide is toxic to fish and may injure invertebrates. Do not apply directly to surface water is present, or to intertidal high water mark. Drift or runoff may injure nontarget plants. Drift and runoff may contaminate water when disposing of

This chemical has properties and characteristics associated with chemicals detected in groundwater. The use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination.

**Physical or Chemical Hazards**  
**Combustible.** Do not use or store near heat or open flame.

**Directions for Use**  
It is a violation of Federal law to use this product in a manner inconsistent with its labeling.  
Read all Directions for Use carefully before applying.

**Storage and Disposal**  
Do not contaminate water, food or feed by storage or disposal.  
**Pesticide Storage:** Store above 10°F or agitate before use.  
**Pesticide Disposal:** Pesticide wastes are toxic. Improper disposal of excess pesticide, spray mixture, or rinsate is a violation of federal law. If these wastes cannot be disposed of by use according to the label instructions, contact your State Pesticide or Environmental Control Agency, or the hazardous waste representative at the nearest EPA Regional Office for guidance.  
**Container Handling:** Nonrefillable container. Do not reuse or refill this container.  
Triple rinse or pressure rinse container (or equivalent) promptly after emptying. **Triple rinse** as follows: Empty the remaining contents into application equipment or a mix tank and drain for 10 seconds after the flow begins to drip. Fill the container 1/4 full with water and recap. Shake for 10 seconds. Pour rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times.  
**Pressure rinse** as follows: Empty the remaining contents into application equipment or a mix tank and continue to drain for 10 seconds after the flow begins to drip. Hold container upside down over application equipment or mix tank or collect rinsate for later use or disposal. Insert pressure rinsing nozzle in the side of the container, and rinse at about 40 psi for at least 30 seconds. Drain for 10 seconds after the flow begins to drip.

**The Label is the Law!**  
When using pesticide products, the requirements for PPE on the product label are your main source of information.

PPE = personal protective equipment



# Some handlers don't wear the required PPE



PPE = personal protective equipment

Some handlers don't wear the required gloves



Some handlers don't want to be told what to wear



# Using “Stories” to Motivate Correct Personal Protective Equipment Practices

---

- **Raise awareness of potential risks**
- **Change attitude and beliefs**
- **Improving PPE practices**

PPE = personal protective equipment

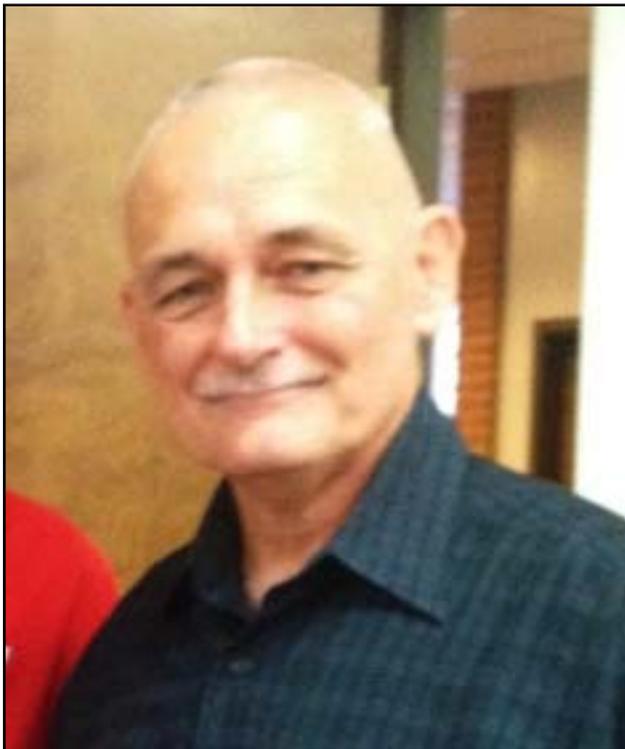
**This meeting is being recorded**

# Attitudes, Beliefs and Behaviors



# Chuck Urban NIOSH Video Specialist

---



- **Productions of Video  
“Stories”**

- Coal Miners: “Faces of Black Lung”
- Electricians: “Arc Flash Awareness”

This meeting is being recorded

# Using “Stories” to Motivate Correct PPE Practices

- **8:00-8:45 - Introduction** D’Alessandro, Faulkner, Urban
- **8:45-10:05 - Cancer and Neurological Issues** Alavanja, Huang
- **10:20-10:45 - Agricultural Safety Culture** Jester
- **10:45-11:45 - Storytelling to Motivate Safety** Cullen
- **1:15-1:45 - US EPA Updates** Keaney
- **1:45-3:00 - Innovative Studies to Improve PPE** Calvert, Gonzalez De Del Pilar, Proctor, Tutor-Marcom, Walker
- **3:15-5:30 – Video ‘Stories’ to Improve PPE** Harrington, Hamilton, Faulkner, Advisory Panel, and Participants
- **5:30-6:00 - Closing**

# Diverse Partners Participating

---

- **Federal and state regulators**
- **Educators/Extension**
- **Researchers**
- **Growers**
- **Commercial Applicator Companies**
- **Pesticide handlers**
- **Equipment , PPE, and Pesticide Manufacturers**
- **Equipment , PPE and Pesticide Suppliers**

PPE = personal protective equipment

**This meeting is being recorded**

# Logistics

---

- **Interactive sessions**
- **Demonstration -- Live Meeting question/comment**
- **Recorded and archived sessions**
- **Restrooms, Lunch, Water**
- **Support Team**

**This meeting is being recorded**

## DISCLAIMER

*The findings and conclusions in this presentation have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.*

This meeting is being recorded

# Pesticides, Cancer, and Neurological Issues



**Michael Alavanja, DrPH**  
**Xuemei Huang, MD, PhD**  
**March 26, 2013**  
**Washington D.C.**



**This meeting is being recorded**

# Pesticides and Cancer



Michael Alavanja, DrPH  
National Cancer Institute

National Cancer Institute

# CANCER RISK AMONG FARMERS AND THEIR SPOUSES

(AGRICULTURAL HEALTH STUDY [AHS] & OTHER  
SOURCES)

MICHAEL ALAVANJA, DR.P.H.  
SENIOR INVESTIGATOR  
OCCUPATIONAL & ENVIRONMENTAL EPIDEMIOLOGY BRANCH,  
DCEG, NCI

MARCH, 2013  
PESTICIDE HANDLER PERSONAL PROTECTIVE TECHNOLOGY,  
STAKEHOLDERS MEETING  
PATRIOT PLAZA 1  
395 E STREET, S.W., ROOM 9000  
WASHINGTON D.C. 20201



# Agricultural Health Study Research Team

- **National Cancer Institute:**

- Michael Alavanja Co-PI
- Laura Beane Freeman Co-PI
- Francesco Barone Adesi
- Gabriella Andreotti
- Kathryn Hughes Barry
- Sonja Berndt
- Aaron Blair
- Neil Caporaso
- Curt Dellavalle
- Nicole Deziel
- Jonathan Hofmann
- Sarah Karami
- Stella Koutros
- Ola Landgren
- Sarah Locke
- Jay Lubin
- Sharon Savage
- Rashmi Sinha
- Mary Ward
- Shelia Zahm

- **NIEHS**

- Jane Hoppin Co-PI
- Dale Sandler Co-PI
- Donna Baird
- John Beard
- Honglei Chen
- Freya Kamel
- Stephanie London
- Sharon Myers
- Christine Parks
- Jessica Rinsky
- Anne Starling
- David Umbach
- Jenna Waggoner

- **NIOSH**

- Cynthia Hines Co-PI
- Brian Curwin
- Paul Henneberger
- Amy Mobley

- **USEPA**

- Kent Thomas Co-PI
- Carol Christensen

# Background: Diseases and Farming

- ❑ Disease and injury patterns among agricultural populations distinct from other populations for **cancer**, respiratory disease, neurological symptoms and injury patterns and others conditions.
- ❑ Farmers live where they work.
- ❑ Family members exposed to pesticides and other potential hazards.
- ❑ Inadequate exposure assessment, reduces our ability to identify agents responsible for disease (**Zahm et al., 1997, Kromhout and Heedrick 2005**).
- ❑ Case-control studies (case-recall bias)
- ❑ Factory-based pesticide studies—too small

# Cancer

- ▣ Known medically as a malignant neoplasm.
- ▣ Cancer is a broad group of various diseases, all involving unregulated cell growth.
- ▣ In cancer, cells divide and grow uncontrollably and invade nearby parts of the body.
- ▣ The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream.
- ▣ Not all tumors are cancerous.
- ▣ Benign tumors, do not spread throughout the body.
- ▣ Determining what causes cancer is complex!
  
- *Cancer Epidemiology and Prevention 3rd edition. Oxford University Press ed. Schottenfeld & Fraumeni*

# Known and Suspected Causes of Cancer

- ▣ Tobacco use
- ▣ Certain infectious diseases.
- ▣ Radiation.
- ▣ Lack of physical activity.
- ▣ Obesity.
- ▣ Occupational and environmental pollutants.
- ▣ Diet
- ▣ Approximately 5 % of cancers are entirely hereditary.
- ▣ Susceptibility gene and environment interaction.

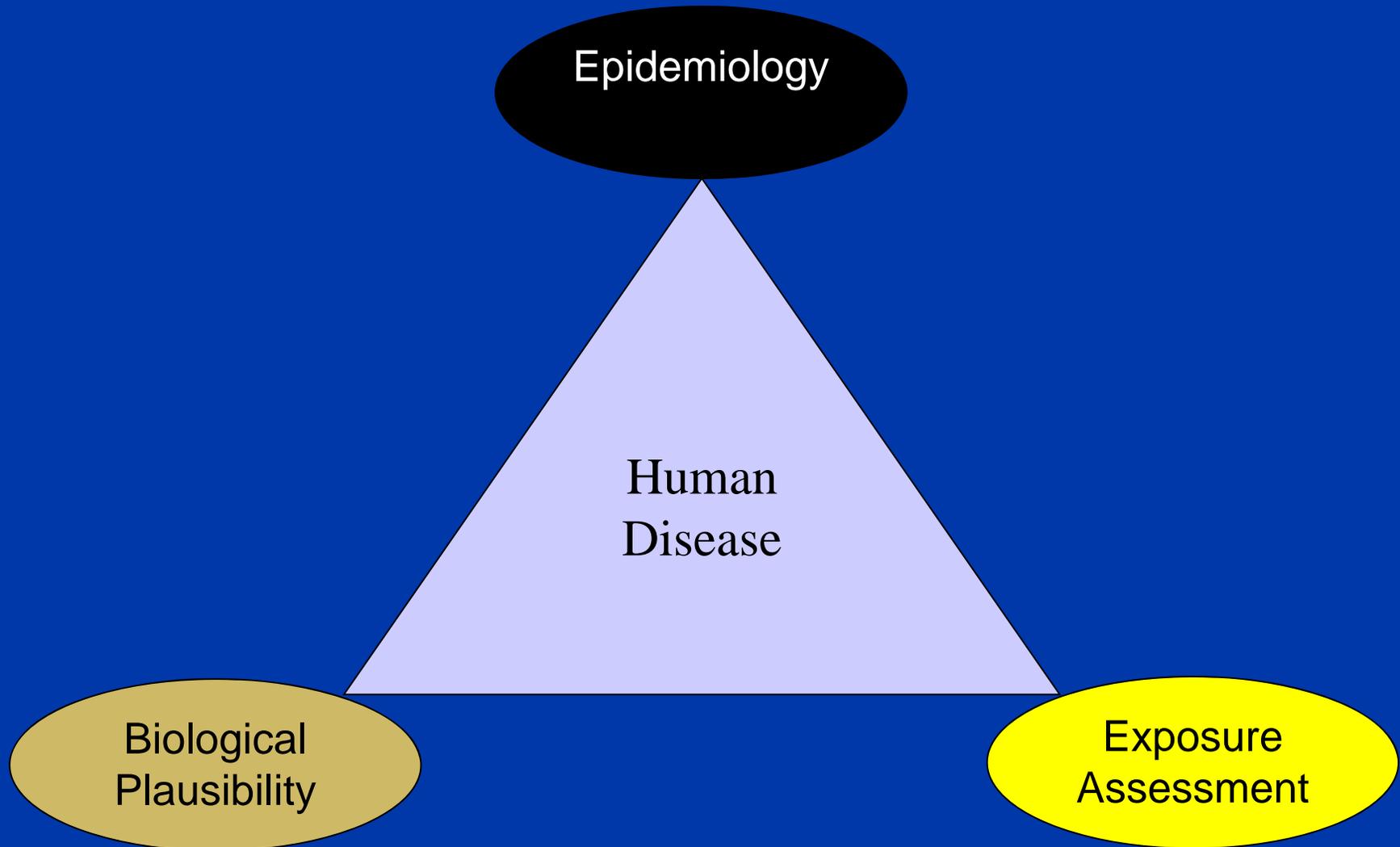
*Cancer Epidemiology and Prevention* 3rd edition. Oxford University Press ed.  
*Schottenfeld & Fraumeni*

# Cells and Cell replication

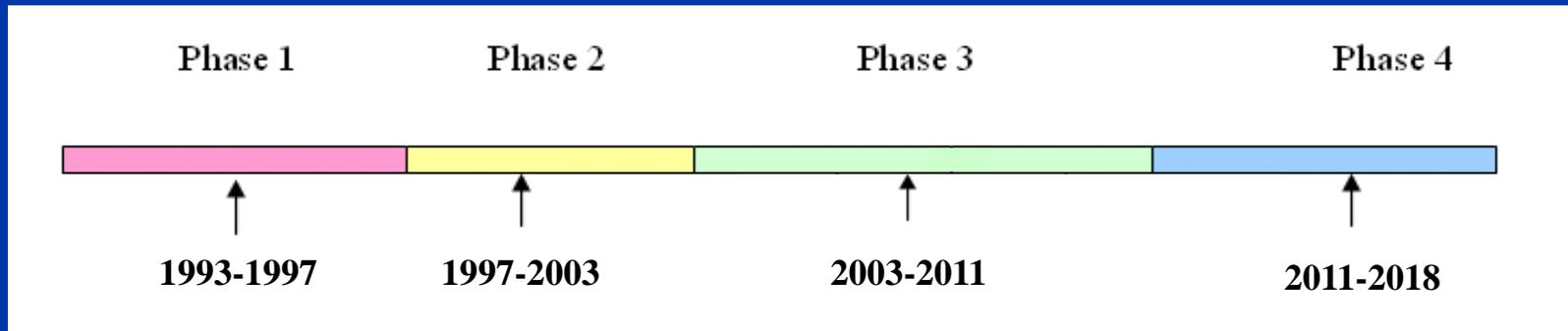
- ▣ Cells ( latin: small room) are the basic structural and functional unit of a living organism. It is the smallest unit of life that is classified as a living thing.
- ▣ Genes within the cell contain the information necessary for the cell to develop, function and reproduce.
- ▣ DNA (deoxyribonucleic acid) is a molecule that encodes the genetic instructions used for the development and functioning of all known living organisms and many viruses.

*Cancer Epidemiology and Prevention 3 edition. Oxford University Press ed. Schottenfeld & Fraumeni*

# Logic to Establish Human Disease Associations



# AHS Timeline 1993 to 2018 (and beyond)



Exposure Assessment

Disease follow-up, Mortality follow-up, Address follow-up

- **Phase 1**- Enrollment questionnaire (82% of target population of private pesticide applicators enrolled)
- **Phase 2**- Follow-up questionnaire, field validation of pesticide exposures, buccal cell collection for DNA, dietary questionnaire
- **Phase 3**- Second follow-up, blood collection in sub-studies, disease etiology, begin DNA evaluation. Disease etiology.
- **Phase 4**- Disease etiology and molecular mechanisms studies

# Other Agricultural Health Study Design Issues

- ▣ Cohort is linked annually to Death and Cancer Registries
- ▣ Proposing linkage to:
  - Medicare
  - End stage renal disease registry
- ▣ Validation of exposure estimation through field monitoring
- ▣ Add-on studies by both intramural and extramural investigators

# AHS follow-up

- ▣ Over one-million person-years of follow-up.
- ▣ Essentially no loss to mortality follow-up, National Death Index (NDI) [n=4].
- ▣ Determine address, state of residence, marital status (IRS address records)
- ▣ Little loss to cancer incidence follow-up (2.2%)
  - Population-based cancer registries in both states

Question 1: Are farmers and other pesticide applicators exposed to pesticides?

Question 2: Are farmers and other pesticide applicators at an increased risk of cancer?

Question 3: Are some people who use pesticides at greater risk of cancer than others?

Question 4: If farmers are at increased cancer risk from occupational exposures, what can be done to reduce the risk and protect the farmer (and other workers)?

Question 5: What role can PPE play in reducing exposure to pesticides?

Question 1: Are farmers and other pesticide applicators exposed to pesticides?

# AHS Exposure Assessment

1. Too expensive to measure pesticides on all 89,000 participants even once.
2. Need a lifetime pesticide exposure history on everyone , all 89,000 participants.

# Exposure Assessment Algorithm

$$\text{Intensity Score} = (\text{Mix} + \text{Application Method} + \text{Repair}) * \text{PPE}$$

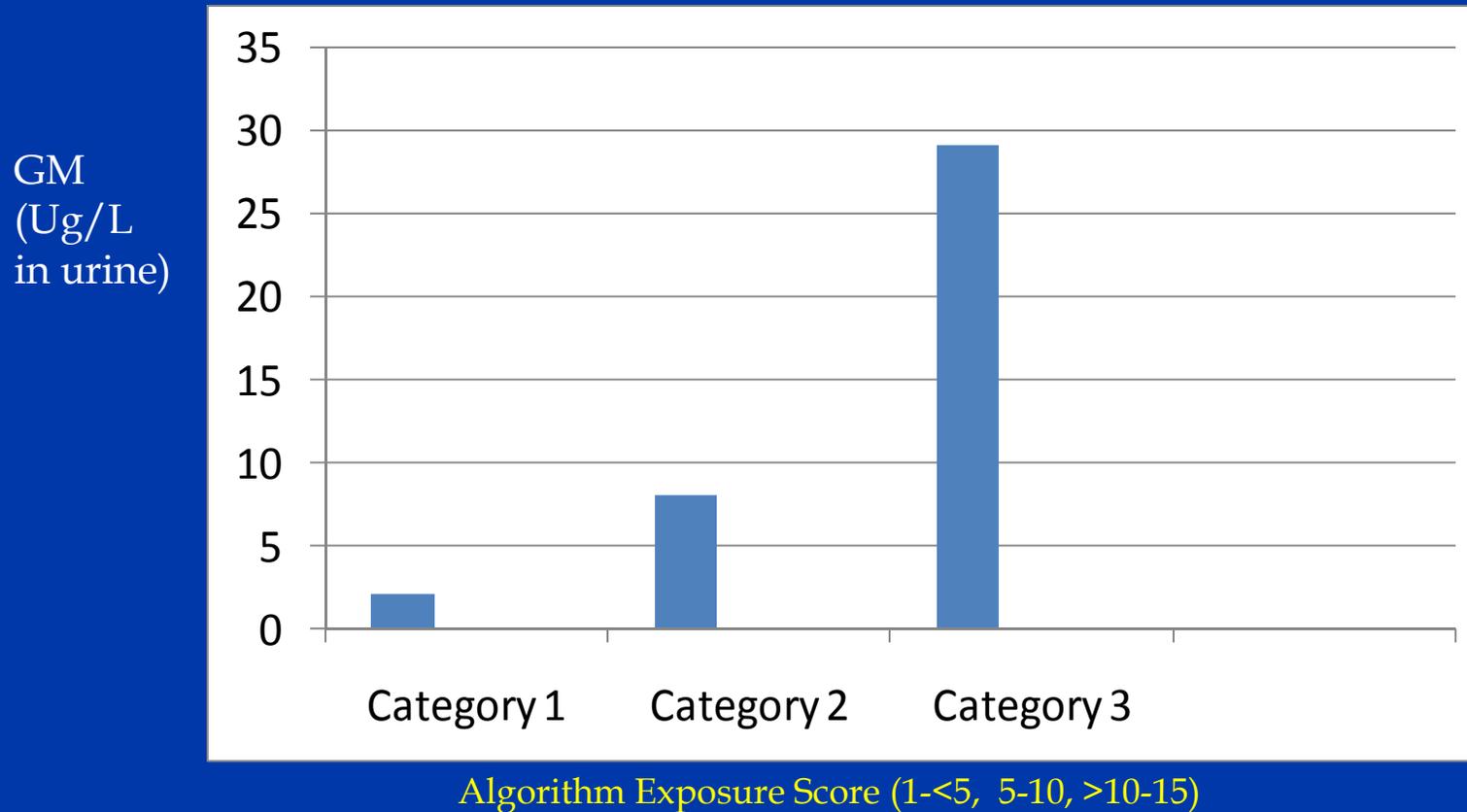
1. Mixed (yes) = 9
2. Application method (Hand spray) = 9
3. Repair (yes) = 2
4. PPE (chem. resistant gloves & boots) = 0.4

$$\text{Intensity Score} = (9 + 8 + 2) * 0.4 = 7.6$$

*Dosemeci M, et al. (2002) Ann Occup Hyg. Vol 46 (2), 245-260.*

*Coble J, et al. (2011) Int J Environ Public Health. 8(12):4608-4622.*

## Pesticide concentrations measured in urine samples (in ug/L) for applicators grouped by algorithm exposure score (2,4-D)



*Coble J. et al. (2005) J of Occupational and Environmental Hygiene. 2: 194-201.*

# Lessons learned

- ▣ Exposure estimates from AHS questionnaires correlate well with field measurements of pesticide exposure.
- ▣ A major determinant of pesticide exposure is the proper use of PPE (personal protective equipment).
- ▣ Chemically resistant gloves are very effective PPE for many pesticides and pesticide applications.
- ▣ Other PPE should be used as per label instructions.
- ▣ *Thomas K. et al., J exposure Sci. Environ Epidemiol. 2010;20:559-569*
- ▣ *Coble J. et al., Int J Environ med 2011;8(12);4608-4622.*

Question 2: Are farmers and other pesticide applicators at an increased risk of cancer?

# Some Signs and Symptoms of Cancer (potential)

- Cancerous tumor mass of breast or testicles may be easily felt.
- Coughing up blood or persistent cough (respiratory cancer).
- Rectal bleeding or change in bowel habits (colon or rectal cancer).
- Blood in urine or change in bladder habits (bladder cancer).
- Persistent Fever of unknown origin (leukemia, liver, kidney)
- Changes to skin (freckles [nevi] enlarge & new colors)

# Some Signs and Symptoms of Cancer

- Unintentional weight loss.
- Being excessively tired.
- Build up of fluids within the chest or abdomen.
  
- *<http://www.mayoclinic.com/health/cancer/D501076/DSECTION-Symptoms>*

## Cancer Risk among Private and Commercial Pesticide Applicators in the AHS

- Total cancer rates among private applicators only 80% of the general population in Iowa and 92 % of the general population in North Carolina. (adjusted for difference in age)
- But some cancers were significantly elevated among pesticide applicators
  - The prostate cancer excess was 19% among private.
  - The prostate cancer excess was 28 % among commercial applicators
  - The lip cancer excess was 97 % among private applicators.
  - Ovarian Cancer 145% excess among private applicators
  - The multiple myeloma excess was 42 % among private applicators from NC .

## Cancer Risk among spouse of private applicators in the AHS

- ▣ Spouses from both states had significant deficits for all cancers combined.
  - IA spouse had only 80% of the cancer rate compared to other women in IA.
  - In North Carolina spouses had only 87% of the cancer rate as other women in North Carolina.

# Cancer risk observed to be associated with pesticide exposure in the AHS ([www.aghealth.org](http://www.aghealth.org))

- ▣ **Aggressive Prostate Cancer** ( Fonofos, Malathion, Terbufos, Koutros et al, 2012)
- ▣ **Leukemia** (Chlordane, Purdue et al, 2007 ; Diazinon Beane Freeman, 2005)
- ▣ **Non-Hodgkin Lymphoma** (Lindane, Purdue et al, 2007).
- ▣ **Multiple Myeloma** (Permethrin, Rusiecki et al., 2009).
- ▣ **Melanoma** (Carbaryl, Maneb, Parathion, Dennis et al., 2010, Toxaphene, Purdue et al., 2007)

# Cancer risk observed to be associated with pesticide exposure in the AHS ([www.aghealth.org](http://www.aghealth.org))

- ▣ **Lung Cancer** (Dieldrin, Purdue et al 2007; Diazinon, Bean Freeman et al, 2005)
- ▣ **Colon Cancer** (Imazethapyr, Koutros et al, 2009; Trifluralin, Kang et al, 2008)
- ▣ **Rectal Cancer** (Chlordane, Purdue et al 2007; Pendimethalin, Hou et al, 2006)
- ▣ **Pancreatic Cancer** (EPTC, Pendimethalin, Andreotti et al, 2009) .
- ▣ **Bladder Cancer** (Imazethapyr, Koutros et al, 2009)

# Lessons learned

- ▣ Pesticides in every functional class of pesticides (i.e., insecticides, herbicides, fungicides and fumigants) are associated with an array of cancer sites in the AHS.
- ▣ Specific pesticides in every chemical class (i.e., chlorinated, organophosphate and carbamate insecticides, phenoxy acid and triazine herbicides) have been associated with specific cancers in the AHS.
- ▣ Not every pesticide in a chemical class has been associated with a cancer in the AHS.

Question 3: Are some people who use pesticides at greater risk of cancer than others?

Terminology: *Relative Risk* (approximately=*odds ratio*)= Rate of disease in exposed population/ Rate of disease in the unexposed population.

Odds ratio=1 (no extra risk due to exposure)

Odds ratio=2 (twice the risk due to exposure)

Odds ratio=3 (three time the risk due to exposure)

# Risk of Prostate Cancer by Fonofos Exposure With and Without a Family History of Prostate Cancer in the AHS

| Pesticide | PC risk, no family history of PC |            |          | PC risk, family history of PC |            |          | Statistical interaction, PC history & Pesticide Exposure |
|-----------|----------------------------------|------------|----------|-------------------------------|------------|----------|--|
|           | Lifetime exposure days           | Odds Ratio | 95% C.I. | Cases                         | Odds Ratio | 95% C.I. |  |
| 0         | 1.00                             | Ref.       | 534      | 1.00                          | Ref.       | 100      | 1.28 (1.07-1.54)   |
| >0-20     | 1.08                             | 0.82-1.41  | 58       | 1.42                          | 0.84-2.41  | 16       |  |
| >20-56    | 0.93                             | 0.70-1.35  | 51       | 1.57                          | 0.95-2.60  | 18       |  |
| >56       | 0.86                             | 0.60-1.24  | 30       | 1.77                          | 1.03-3.05  | 15       |  |
| P trend   | P=0.37                           |            |          | P=0.02                        |            |          |  |

Mahajan R et al. *Environ Health Perspect.* (2006); 114 (12): 1838-1842

# Follow-up prostate cancer study

## Chromosome 8q24 , terbufos exposure and prostate cancer risk

|            | No terbufos exposure | Low terbufos exposure | High terbufos exposure |
|------------|----------------------|-----------------------|------------------------|
| Odds Ratio | 1.13                 | 1.71                  | 2.15                   |
| 95% C.I.   | 0.87-1.47            | 1.07-2.74             | 1.32-3.52              |

-Koutros, et al., *Cancer Research* 2010; 70(22):9224-9233

-previously identified variant rs4242382

-adjusted *P*-interaction=0.02

-similar effect modification for *fonofos*, *coumaphos*, *phorate*, *permethrin*

-*fonofos*, *phorate* and *terbufos* are phosphorodithioates

## Growing list of Susceptibility Genes identified in the AHS

- ▣ Susceptibility genes (*replication necessary*):
  - Base-excision repair (BER)-
  - Nucleotide excision repair (NER)-
  - Xenobiotic metabolizing enzymes (XME)-
  - Lipid Metabolizing Genes (LME)
  - Others genes/pathways from prostate etiology literature will be examined (e.g., telomere length control genes)

# Lessons learned

- ❑ Common difference in gene type (genetic polymorphisms) causes some pesticide applicators to be at greater cancer risk than others using the same pesticides.
- ❑ Genetic testing is not the answer.
- ❑ Minimizing exposure to all pesticides by using appropriate PPE according to label instructions and wise health practices!

❑ *Alavanja M et al., CA: A Cancer Journal for Clinicians 2013:63(2)120-142.*

❑ *Centers for Disease Control and Prevention 4<sup>th</sup> National Report.*

❑ *[cdc.gov/exposure\\_report/pdf/fourthreport.pdf](http://cdc.gov/exposure_report/pdf/fourthreport.pdf)*

Question 4: If farmers are at increased cancer risk from occupational exposures, what can be done to reduce the risk and protect the farmer (and other workers)?

# Lessons learned

- ▣ Particularly hazardous pesticides should be identified and use should be highly regulated/restricted.
- ▣ Develop engineering controls that reduce applicators exposure.
- ▣ Good work practices reduce exposure.
- ▣ Chemically resistant gloves and other PPE should be used per label instructions.
- ▣ Washing, showering, laundering soon after application.
- ▣ *Alavanja M et al., CA: A Cancer Journal for Clinicians 2013:63(2)120-142.*

Question 5: What role can PPE play in reducing exposure to pesticides?

This meeting will encourage correct PPE practice.

**Thank you.**

➤ **Questions?**

## References for Pesticides and Cancer:

1. Alavanja and Bonner. Occupational pesticide exposure and cancer risk: A Review. J. of Toxicology and Environ. Health (part B); 2012; 15:238-263.
2. Alavanja et al., Increased cancer burden among pesticide applicators and others due to pesticide exposure. CA : Cancer J Clin 2013; 63(3):120-142.

## DISCLAIMER

*The findings and conclusions in this presentation have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.*

This meeting is being recorded

# Pesticides and Neurological Issues



Xuemei Huang, MD, PhD  
Hershey Medical Center/The Penn State University

PENNS<sup>T</sup>ATE



Milton S. Hershey Medical Center

# Pesticides and Brain Disorders

*March 26, 2013*

**Xuemei Huang, M.D., Ph.D.**

*Vice Chair, Department of Neurology,  
Associate Professor of Neurology, Pharmacology, Neurosurgery,  
Radiology, Pharmacology & Kinesiology*

*Director, Hershey Brain Analysis Research Laboratory for  
Neurodegenerative Diseases (“Hershey BAR”)*

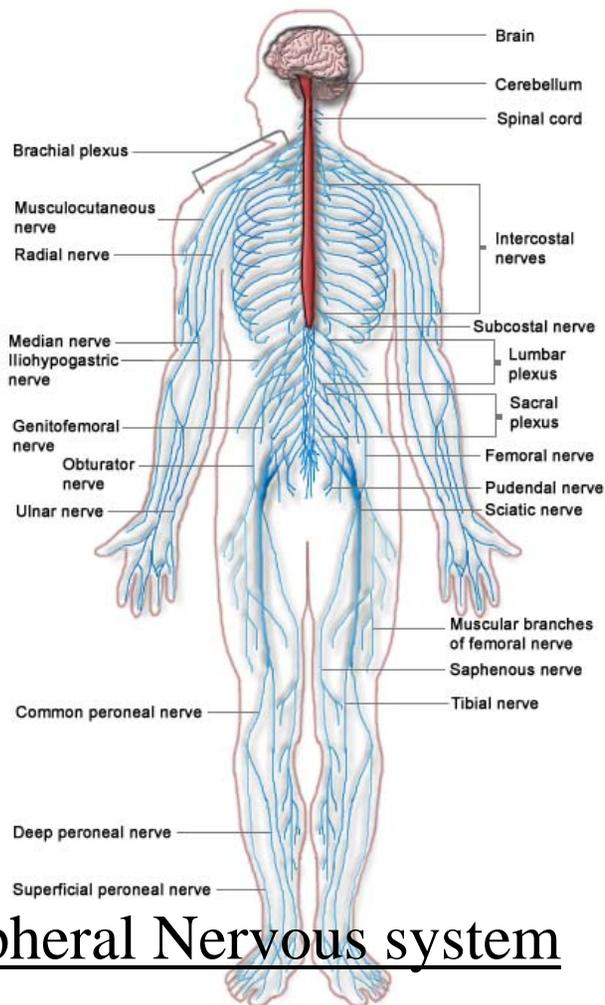
PENNS<sup>T</sup>ATE



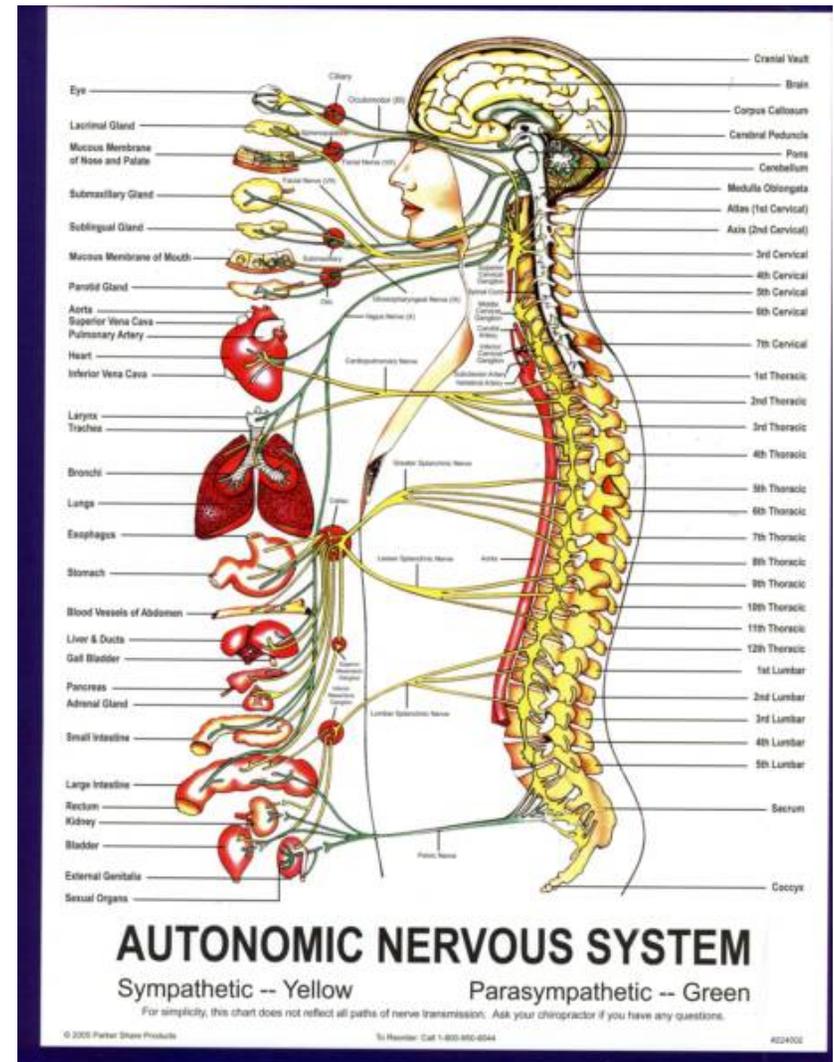
Milton S. Hershey Medical Center

# The nervous system and its functions

## Central Nervous system



## Peripheral Nervous system



# Pesticides

- A major part of the agricultural revolution
  - *dramatically increased per capita food production*
  - *helps sustain the growth of the world's population*
- **Pesticides are toxic and design to kill!!**
  - *developed to be more toxic to target species than to humans.*

# Nervous system can be vulnerable to a number of pesticides

- Some pesticides are designed to poison the nervous system
  - *Organophosphates & carbamates*
    - soman and sarin (Nerve Gas)
    - parathion; malathion; carbamyl
    - ziram
  - *Cyclodienes:*
    - aldrin, dieldrin; chlordane
  - *Pyrethroids*
  - *Organochlorines*
    - DDT
  - *Rotenone*
- Some pesticides poison the nervous system as side effects
  - *Lead arsenate*
  - *Ethylmercury*
- Some may have long-term effects on the nervous system
  - *Paraquat*
    - Linked to PD
  - *Maneb*
    - Linked to PD
  - *Benomyl*
    - Linked to PD

***These are just some examples!!!***

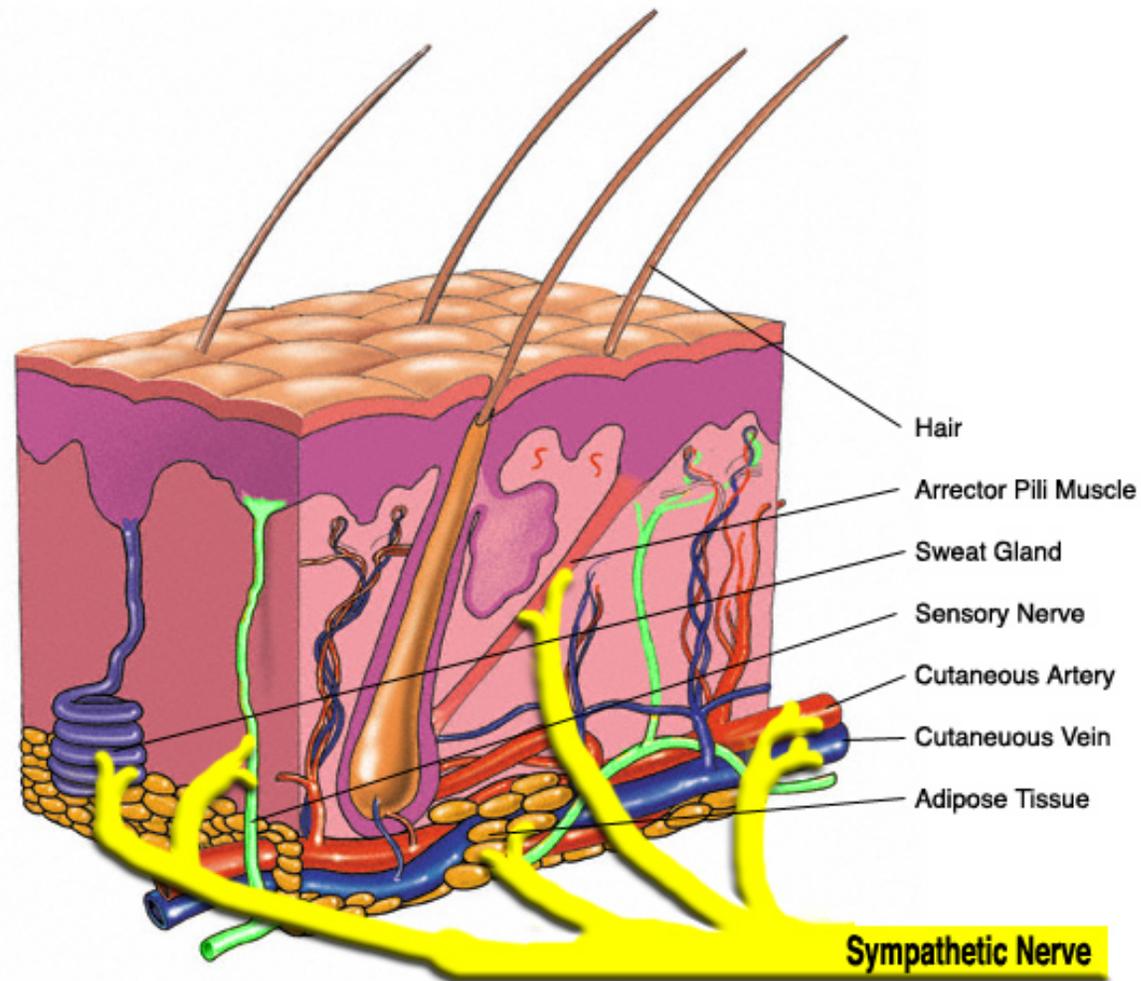
# Symptoms of the nervous system dysfunction

- Higher functions
  - *Memory & cognitive changes*
  - *Mood disorders*
  - *Lack of concentration*
  - *Irritable*
  - *Hallucination/confusion*
  - *Convulsion-Coma*
- Motor
  - *Tremor,*
  - *Loss of balance (ataxia)*
  - *Weakness and in-coordination*
- Sensory
  - *Headache*
  - *Numbness/tingling*
  - *Pain*
- Cardiovascular
  - *Palpitation*
- Respiratory
  - *Shortness of breath*
- Gastrointestinal functions
  - *Diarrhea/Vomiting*
- Autonomic dysfunctions
  - *Drooling/dry mouth*
  - *Dizziness*
  - *Urination problem*
  - *Sexual dysfunction*

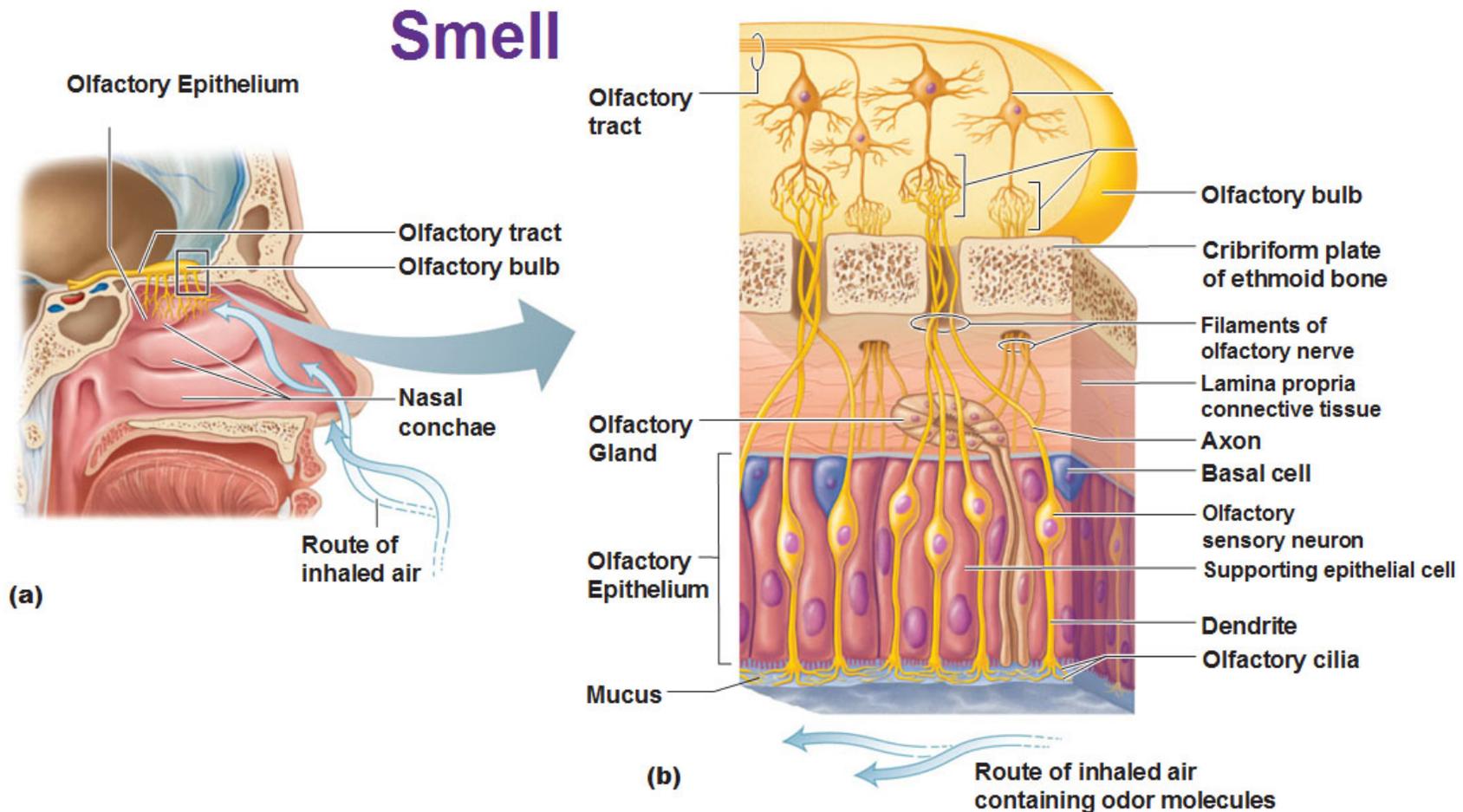
# Routes of toxicant entry into nervous system



# Touch → Skin → Toxicant entry



# Smell → Nose → Toxicant entry



# Food → Mouth → Gut → Toxicant entry

## The Brain in Your Gut

The gut's brain, known as the enteric nervous system, is located in sheaths of tissue lining the esophagus, stomach, small intestine and colon.

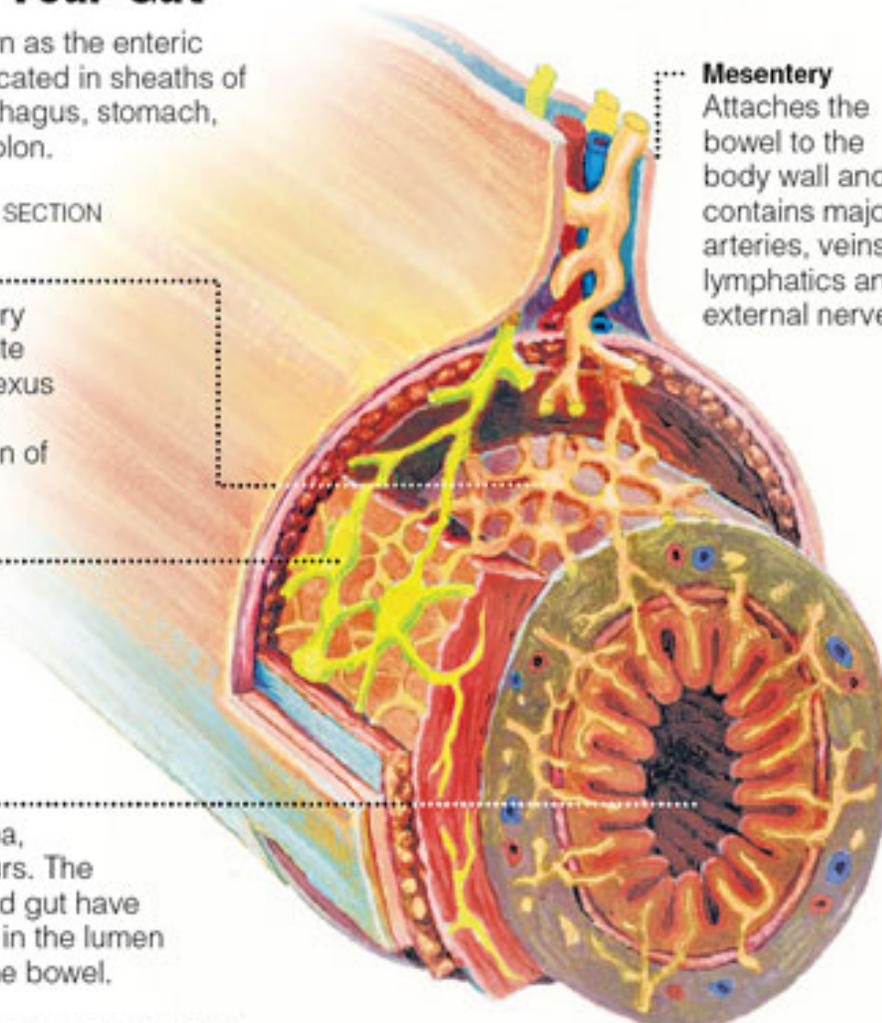
SMALL INTESTINE CROSS SECTION

**Submucosal plexus** .....  
Layer contains sensory cells that communicate with the myenteric plexus and motor fibers that stimulate the secretion of fluids into the lumen.

**Myenteric plexus** .....  
Layer contains the neurons responsible for regulating the enzyme output of adjacent organs.

**Lumen** No nerves .....  
actually enter this area, where digestion occurs. The brains in the head and gut have to monitor conditions in the lumen across the lining of the bowel.

**Mesentery**  
Attaches the bowel to the body wall and contains major arteries, veins, lymphatics and external nerves.



Source: Dr. Michael D. Gershon, Columbia University



# Basic principles of toxicology-1

- **Everything is toxic at a high enough dose!!!**
- Safety is the relationship between a dose that is toxic to humans and the exposure that someone receives.
- Toxicity can be minimized by controlling exposure.

# Basic principles of toxicology-2

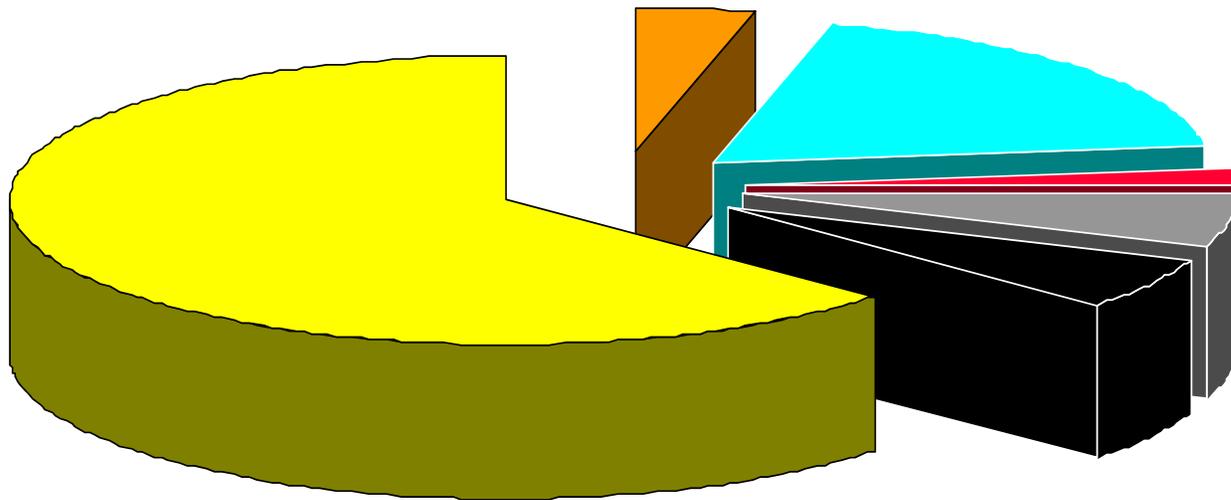
- Acute
  - *Generally higher dosage*
  - *More easily recognized and regulated*
  - *Progression often stops with exposure cessation; symptoms may be reversible to varying degrees*
- Chronic exposure
  - *Lower dosage (every day exposure)*
  - *Harder to recognize and regulate*
  - *Often irreversible*
  - *Can relate to developmental neurotoxicity*
    - e.g., lead, methylmercury

# There are many brain disorders for which the cause is often not known

- Dementia
  - *Alzheimer's disease*
- Amyotrophic Lateral Sclerosis (ALS)
  - *Lou Gehrig (1903-1941)*
- Psychiatric disorders
- Developmental disorders
- Gait disorder
- Neuropathy



# Many factors may contribute to these brain disorders of unknown cause



- Single Gene
- Multiple Genes
- Single Chemical
- Single gene & chemical
- Multiple Chemicals
- Complex interactions

*– Detecting long-term effects that do not cause  
– immediate illness is often difficult.*

# Parkinson's disease

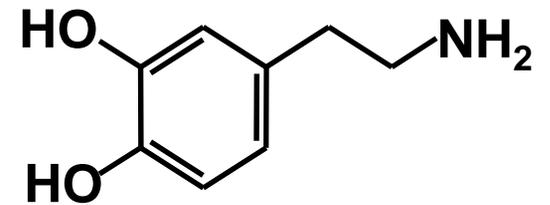
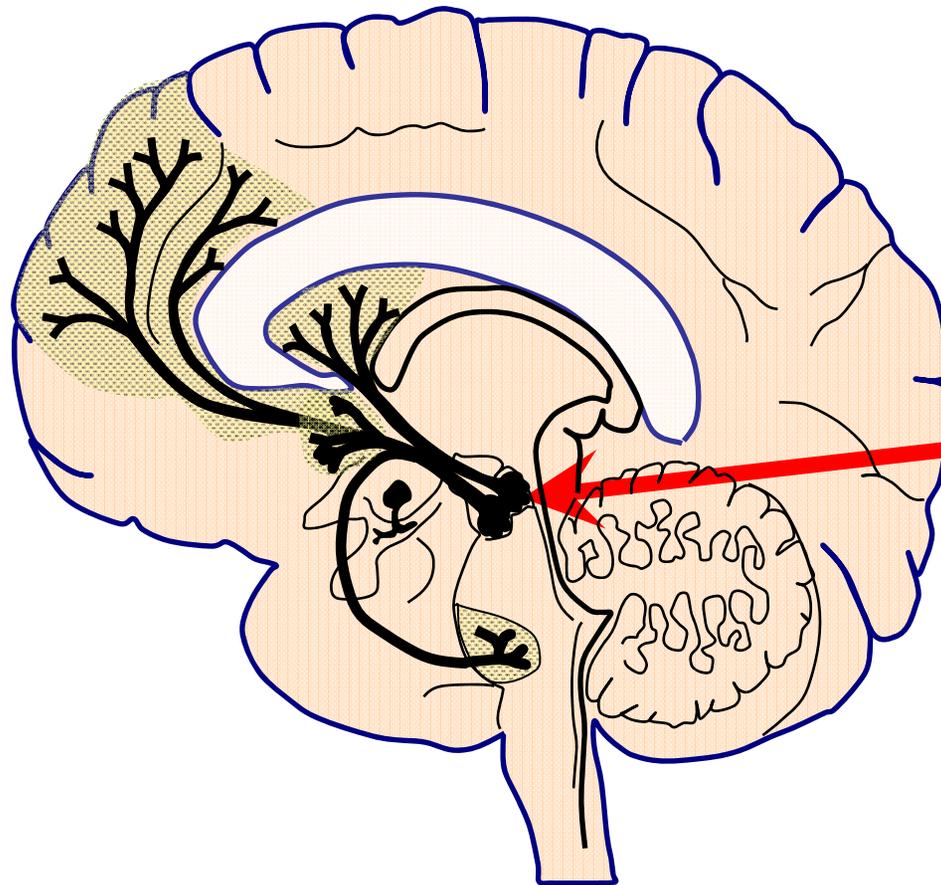


- First described in 1817 by James Parkinson as “Shaking Palsy.”
- Affects about 1 million Americans currently
  - *Number projected to triple or quadruple over the next decades*
- Risk factors
  - *Older*
  - *Male > Female*

# Clinical signs of Parkinson's disease

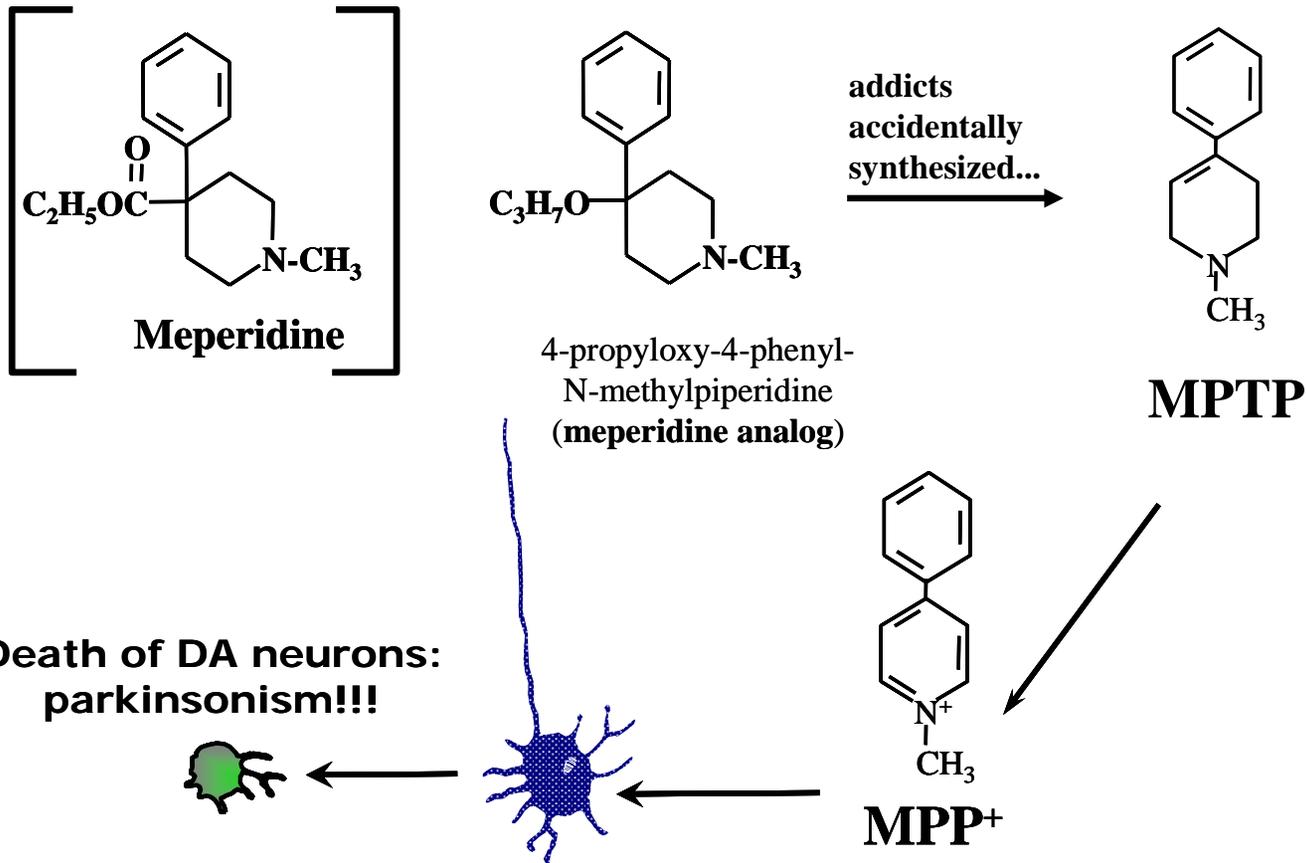
- At Diagnosis
  - *Resting tremor*
  - *Slowness-  
Bradykinesia*
  - *Stiffness--Rigidity*
  - *Gait and postural disorders*
- Early symptoms
  - *Lack expression*
  - *Difficulty to get out from car or chair*
  - *Hunch over*
  - *Small steps*
  - *Ache and pain*
  - *Depression*
  - *Sleep disorders*
  - *Loss smell*
  - *Constipation*

# Nigrostriatal dopamine degeneration



**Substantia  
Nigra**

# The tragic human MPTP experiment!



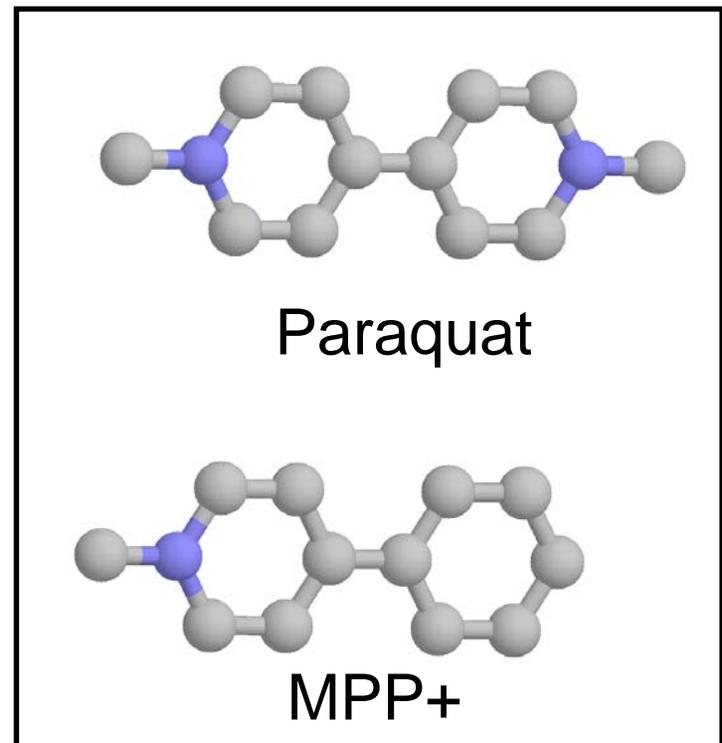
- Frozen addicts in the Emergency Room
  - *Davis et al., Psych. Res 1979; 1:249-254*
  - *Ballard et al. Neurology 1985; 35:949-956*

# Environmental toxicants linked to Parkinson's disease

- Pesticides (herbicides, insecticides, fungicides)
  - *Rotenone (mitochondrial complex inhibitor)*
  - *Paraquat (increases oxidative stress)*
    - Herzman et al., 1990
    - Kamel et al., 2007
    - Dhillon et al, 2008;
    - Tanner et al., 2009; 2011

# Paraquat (1,1'-dimethyl-4,4'-bipyridinium)

- Paraquat is one of the most widely used (> 120 countries) broad-spectrum herbicides.
- It is structurally similar to the active species of MPTP.



PENNSYLVANIA



Milton S. Hershey Medical Center

# Paraquat has been used to induce Parkinson's-like pathology in animals

- Selective nigrostriatal dopamine cell loss
  - *McCormack et al., 2002*
- Present of Lewy pathology
  - *Manning-Bog et al., 2002*
- Cause chronic neuroinflammation and impose oxidative stress
  - *Franco et al., 2010 review*

*... yet the animal research has been challenged as being irrelevant to humans.*

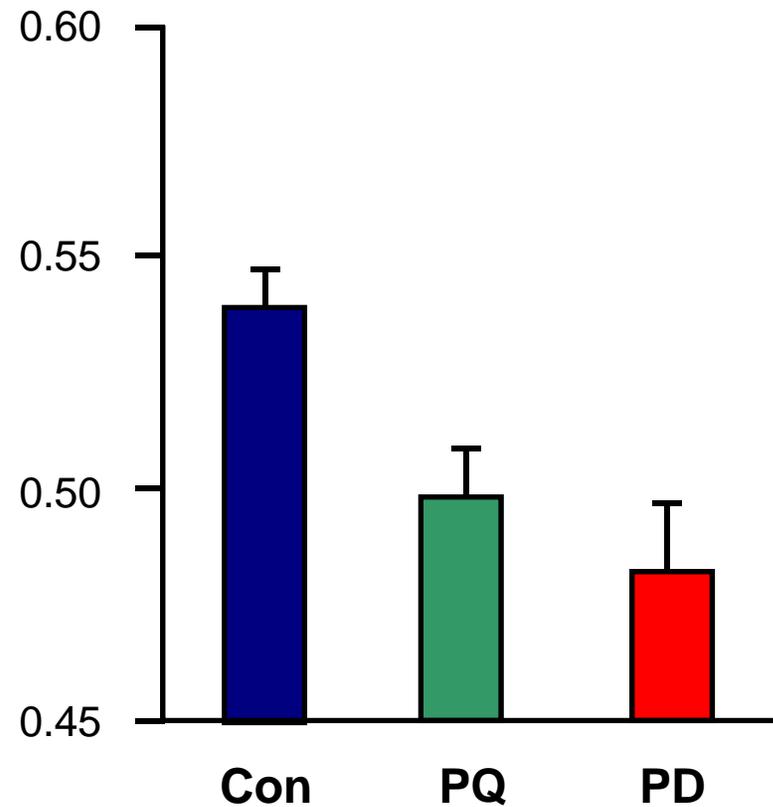
# What is missing to link PQ to PD?

- There is no direct evidence that chronic, subtoxic exposure of PQ can cause damage to the SN in humans.
- MRI may provide us a unique opportunity to test for such a link.
- This would provide direct evidence for toxicants playing a role in neurodegenerative disorders.

# A pilot study of PQ-exposed subjects

|                        | <b>Controls</b> | <b>PQ-exposed</b> | <b>PD subjects</b> |
|------------------------|-----------------|-------------------|--------------------|
| <b>N</b>               | 12              | 12                | 12                 |
| <b>Average Age</b>     | 53.9            | 55.8              | 57.1               |
| <b>Gender</b>          | Male            | Male              | Male               |
| <b>Years of PQ use</b> | 0               | 18.6              | n/a                |

# Chronic paraquat users seem to have brain changes similar to Parkinson's disease





# Study conclusions

- Chronic subtoxic PQ exposure leads to microstructural changes in the midbrain
- These changes are similar to those seen in PD subjects.
- Provides another piece of evidence that some pesticides may sometimes cause harmful effects on the brain at current levels of exposure.

# Take-home message

- There is a need to continue research on potential links between chronic exposure of pesticides and brain disorders.
- There is a new array of technology that can assist in making such assessments.
- There should be increase consideration for decreasing the exposure to agents for which there is some evidence of long term effects.

# Acknowledgements

- My patients and their families
- Many volunteers and their families
- National Institutes of Health
  - *NIA (K23: 2003-2008);*
  - *NINDS (R01: 2009-2014; U01: 2012-2016),*
  - *NIEHS (R01: 2011-2015)*
- Pennsylvania Tobacco Settlement Fund
- Personal gifts from many donors to our program.
- .. *and of course*
  - my staff and collaborators

## DISCLAIMER

*The findings and conclusions in this presentation have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.*

This meeting is being recorded

# Fifteen-Minute Break



**Michael Alavanja**  
National Cancer Institute



**Elaine Cullen**  
Prima Consulting  
Services



**Maryann D'Alessandro**  
NIOSH/NPPTL



**Kim Faulkner**  
NIOSH/NPPTL



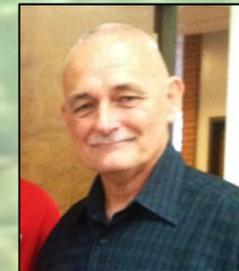
**Xuemei Huang**  
Hershey Medical Center



**Ron Jester**  
University of Delaware  
Extension



**Kevin Keaney**  
U.S. EPA



**Chuck Urban**  
NIOSH

**This meeting is being recorded**