Registration of Enlist Duo™ Herbicide

October 15, 2014

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Technical Briefing Outline

- Introduction
- Background
- Health Effects Assessments
- Ecological and Endangered Species Risk Assessments
- Usage of 2,4-D and Resistance Management
- Final Decision
- Questions and Answers
  - Submit any questions regarding this presentation to: enlistduoquestions@epa.gov
  - Questions will be answered live at the completion of the webinar until 3:15 PM EST.

Enlist Duo™

- End-use herbicide product
- Developed by Dow AgroSciences LLC
- Contains:
  - 24.4% 2,4-D choline salt
  - 22.1% glyphosate
- To be used on Genetically Engineered (GE) crops:
  - Enlist™ Corn
  - Enlist™ Soybean

Multiple Agency Regulatory Decisions

USDA

Evaluates GE Seeds

(Enlist Corn and Soybeans)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Evaluates Pesticides

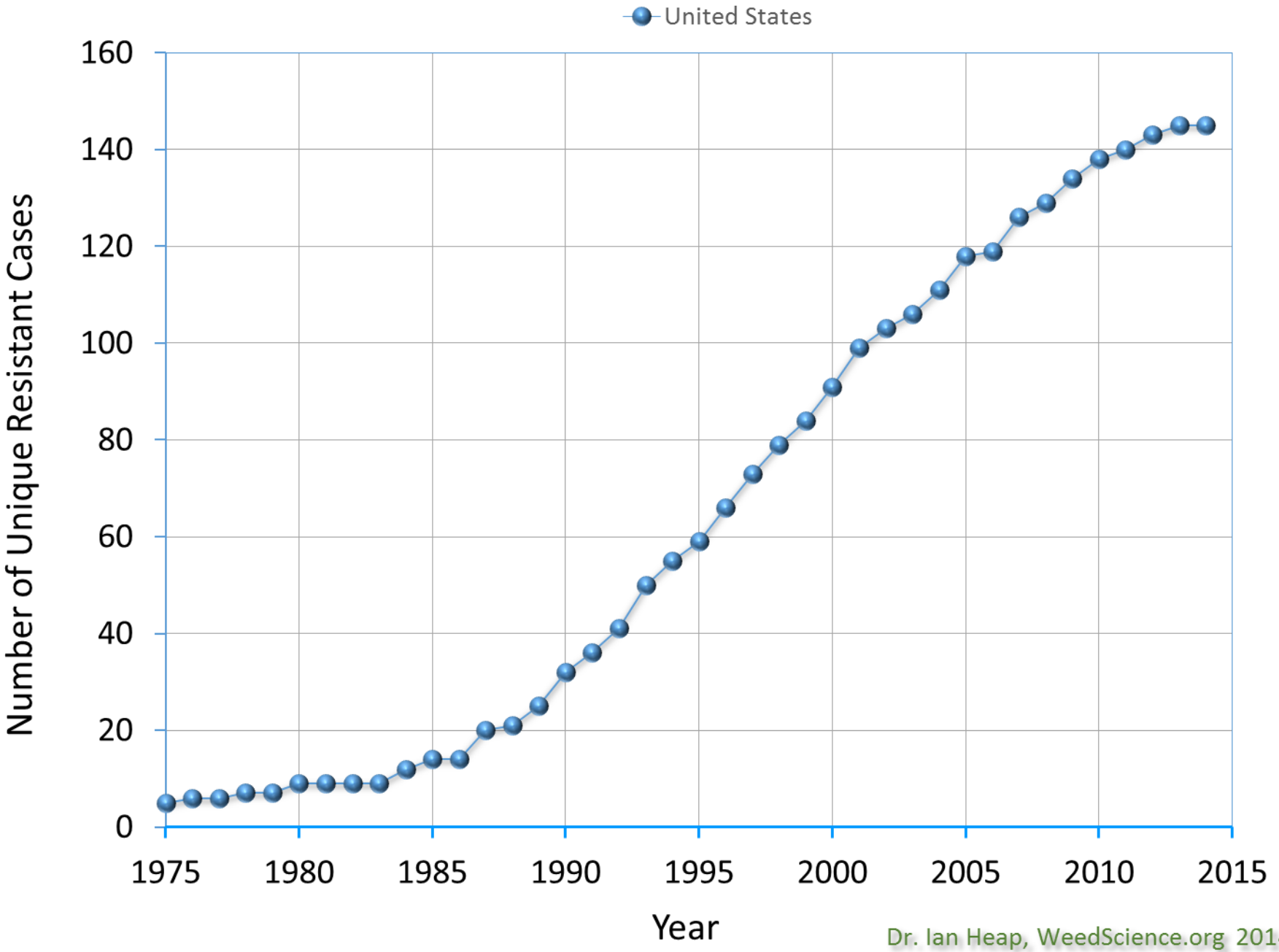
(Enlist Duo Herbicide)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Weed Resistance Management

- Herbicide resistant weeds are an increasing problem
  - Glyphosate is an important tool that is becoming less effective
  - Significant economic issue for growers
  - Millions of acres affected across the US
- Additional management tools are needed
  - Enlist Duo adds another herbicidal mode of action to control resistant weeds

Increase in Unique Resistant Weed Cases for the USA



Dr. Ian Heap, WeedScience.org 2014

Glyphosate: No Change in Use Pattern

- No new use or exposures to consider with this decision
- No new assessment is needed for glyphosate for this product
  - The current risk assessments show that glyphosate is safe for use on corn and soybeans

Expanded Use Pattern for 2,4-D

- A revised use pattern for corn and soybeans
- Issuing a registration to expand the timing (application window) of current use pattern
- Choline salt formulation only

2,4-D Use Patterns

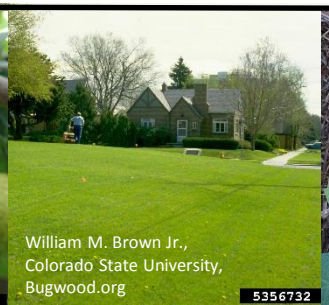
	Current Use		Amended Use	
	Application	Maximum Seasonal Rate	Application	Maximum Seasonal Rate
Soybean	Pre-plant applications only	1 lb ae/A	Over-the-top applications to GE soy	3 lb ae/A
Corn	Over-the-top up to 8 inches tall	3 lb ae/A	Over-the-top to GE corn up to 48 inches tall	3 lb ae/A

What is 2,4-D?

- Selective herbicide
  - Effective on a wide variety of terrestrial and aquatic broadleaf weeds
- Formulations:
  - Acids
  - Esters
  - Salts
    - ➢Choline Salt

2,4-D

- Registered in the US for over 60 years
- Current uses:
  - Agriculture: Field, fruit, and vegetable crops
  - Turf and lawns
  - Rights-of-way
  - Aquatic sites
  - Forestry
  - **Corn**: over-the-top applications up to 8 inches tall
  - **Soybeans**: pre-plant applications



2,4-D

- One of the most widely studied and well understood pesticides
- Registered in dozens of countries
  - Canada, Mexico, Japan, 26 European Union Members, and many member countries of the Organisation for Economic Co-operation and Development (OECD)

2,4-D Choline Salt

- A herbicidal tool expected to be a useful aid in weed resistance management
- Less spray drift potential and less volatile than other forms of 2,4-D
- Part of an Integrated Weed Management Plan
  - In combination with GE herbicide resistant crops and other weed management practices

Decision Process

- Amended use pattern
  - Not the first use for corn and soybeans
- EPA is treating this action like a major new use
- Exceptionally robust assessment using the latest data and scientific tools
- For this review:
  - Aggregate exposure assessment
  - 100% crop treated
  - Bystander exposure
  - Endangered Species Assessment
  - Resistance management stewardship

Decision Process

- Developed and Published a Proposed Decision
  - Discussed findings in risk assessments
  - Introduced proposed risk mitigation strategies
  - Addressed comments from published NOR
  - Allowed 30-day public comment period
  - Granted 30-day extension to comment period
- EPA received and read 417,301 comments on the proposed decision to register Enlist Duo
  - Comments were evaluated and used in developing the final decision

Health Effects Assessments

Road Map

- Introduction to risk assessment
- Introduction to hazard identification/ dose response assessment
- 2,4-D specific hazard identification

What is Risk?

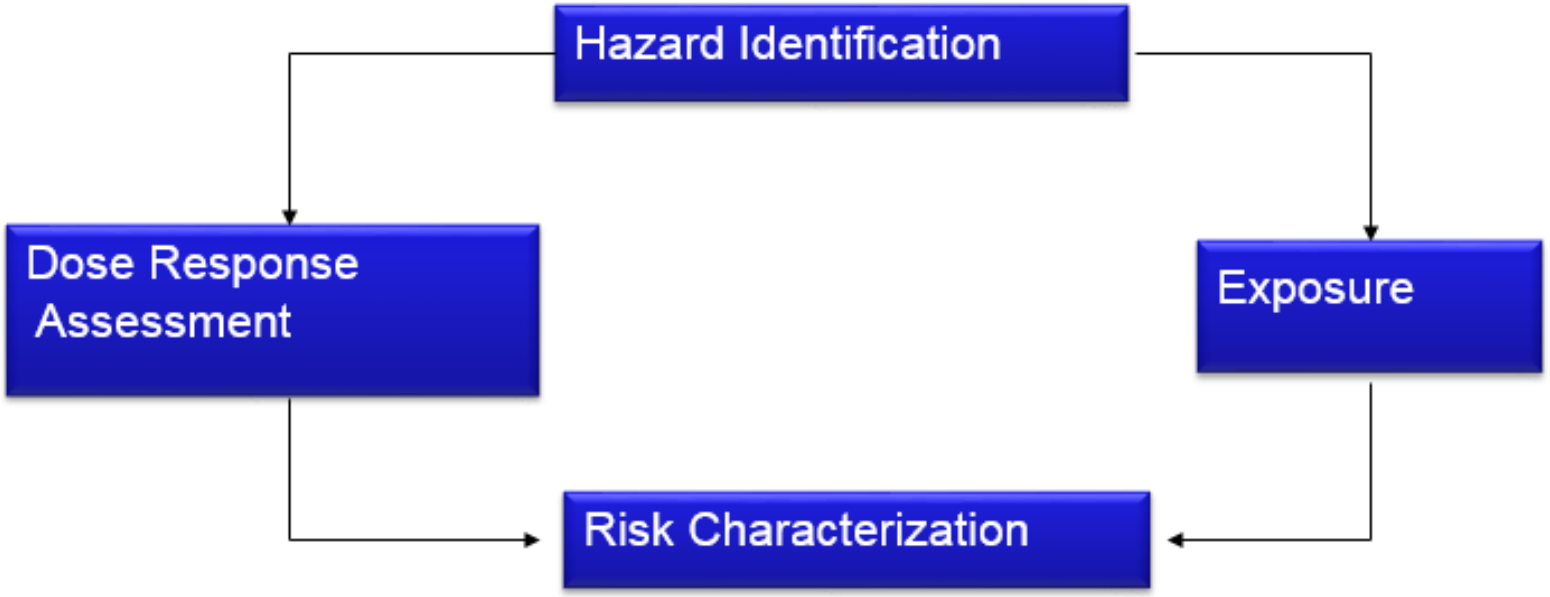
"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."

Paracelsus (1493-1541)

Risk is a function of hazard (toxicity) and exposure.

How Do We Assess Risk?

Follow the National Academy of Sciences (NAS) four-step risk assessment paradigm*:



*From the National Research Council's *Risk Assessment in the Federal Government: Managing the Process,* 1983.

Expressing Risk

- Risks in OPP are generally expressed in the following ways:
  - % Population Adjusted Dose (%PAD)
  - Margin of Exposure (MOE)

Hazard Identification/ Dose Response Assessment

Hazard Identification

Process of identifying the potential health effects as a result of various types of chemical exposure

Basic Concepts

- Battery of toxicology studies are required for pesticide registration
- Toxicity studies are conducted in a variety of laboratory animals – mice, rats, rabbits, dogs, etc.
- Treatment of animals in these studies range from single (acute) exposure to repeated (chronic or long term) exposures for up to 2 years

Toxicology Data Requirements

Acute Toxicity Testing
Acute Oral – Rat
Acute Dermal – Rat or Rabbit
Acute Inhalation – Rat
Primary Eye Irritation - Rabbit
Primary Dermal Irritation – Rabbit
Dermal Sensitization – Guinea Pig

Toxicology Data Requirements

Subchronic Toxicity Testing
90-day Oral – Rodent
90-day Oral – Non-rodent
21/28-day Dermal (Rat or Rabbit)
90-day Dermal (Rat or Rabbit)
90-day Inhalation - Rat

Toxicology Data Requirements

Chronic Toxicity Testing
Chronic Oral – Rodent
Carcinogenicity – Mouse & Rat

Developmental / Reproductive Toxicity Testing
Prenatal toxicity – Rat & Rabbit
Multi-generation Reproduction - Rat

Toxicology Data Requirements

Mutagenicity Testing
Reverse mutation assay – bacteria
Mammalian cell assay – *in vitro*
Mammalian cell assay – *in vivo*
Cytogenetics assay – *in vivo*

Toxicology Data Requirements

Neurotoxicity Testing
Acute Neurotoxicity – Rat
Subchronic Neurotoxicity – Rat
Developmental Neurotoxicity - Rat

Toxicology Data Requirements

Other Studies
Metabolism & Pharmacokinetics
Dermal Penetration
Comparative Thyroid Assay
Immunotoxicity
Open Literature Studies

Dose Response Assessment

Hazard Identification and Endpoint Selection

- Provides a quantitative description of the hazard potential which can be used to assess the degree of concern for effects to people who may be exposed
  - **Point of Departure (POD):** Any dose level used to quantify risk (generic)
    - Usually the dose where no adverse effects were seen

Endpoint Selection

- Dose and endpoints selected for 11 exposure scenarios
  - Considers exposure pathways, routes, and durations
    - Dietary exposures
    - Occupational and residential exposures (ORE)

Pathways and Routes of Exposure

- Oral exposure
  - Food supply
  - Drinking water
  - Incidental ingestion
- Dermal exposure
  - Applying pesticide
  - Harvesting crops
  - Spray drift
  - Turf contact
- Inhalation exposure
  - Applying pesticide
  - Bystander

Duration of exposure

From one dose to a lifetime of exposure

Review Process

- Toxicology study reports submitted
  - Conducted in accordance to EPA's OCSPP Harmonized Guidelines http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm
  - Include summary **and** individual animal data
- EPA's OPP scientists independently review these studies

Quantifying Toxicity

Considers toxicity profile, duration of exposure, use pattern, life stage sensitivity

Dietary Hazard Assessment

- Acute – effects due to a single exposure
  - Protective of all populations
    - Protective of the general population including infants & children
    - Protective of women of childbearing age
- Chronic – effects due to repeated exposures
  - Protective of all populations

Occupational and Residential Exposure Assessments

- Incidental oral exposures
  - Primarily for infants and children
    - Assess potential hazard resulting from oral exposure due to specific behaviors associated with small children (e.g. hand-to-mouth)
- Dermal exposures
  - Assess potential hazard due to dermal exposures
- Inhalation assessments
  - Assess potential hazard due to inhalation exposures

Uncertainty Factors

- 10 X Uncertainty Factor (UF) for using an animal study in human risk assessment (inter species factor) (UF_A)
- 10 X UF because some people may be more sensitive than others (intra species factor) (UF_H)
- 10 X FQPA Safety Factor
  - Enhanced sensitivity in the young if not accounted for through endpoint selection

2,4-D Specific Hazard Identification

Available Studies for 2,4-D

- Subchronic:
  - 21-day dermal toxicity (rabbit)
  - 90-day oral toxicity (rat)
  - 90-day oral (diet) toxicity (dog)
  - 90-day oral (capsule) toxicity (dog)
  - 28-day inhalation toxicity (rat)
- Developmental toxicity:
  - Developmental toxicity (rat)
  - Developmental toxicity (rabbit)
- Reproduction:
  - 2-generation reproduction study (rat)
  - Extended 1-generation reproductive toxicity study (rat)
    - Includes developmental neurotoxicity, immunotoxicity, and thyroid assessment

Available Studies for 2,4-D

- Chronic:
  - Combined oral chronic toxicity/carcinogenicity (rat)
  - Carcinogenicity (mouse)
  - Chronic oral toxicity (dog)
- Neurotoxicity:
  - Acute neurotoxicity (rat)
  - Subchronic neurotoxicity (rat)
- Other:
  - Mutagenicity battery
  - Metabolism (rat)

Available Studies for 2,4-D

Data from open literature

- Screened entire database

- ~150 studies met the standards and were looked at closely
- In general, open literature studies are designed to investigate a mode of action usually at one dose level
- Guideline studies (those listed in previous slides) are designed to investigate a chemical's dose response relationship across a wide range of doses.
  - At least 3 doses in addition to vehicle control
  - Data should be sufficient to produce a dose-effect curve

Available Studies for 2,4-D

- Available toxicity studies provide a comprehensive database, with routes of administration that are consistent with potential exposure scenarios
- Available 2,4-D studies are of high quality
- Studies were conducted under GLP

2,4-D Hazard Identification for Risk Assessment

Duration/ Route/ Population	Study	Lowest Dose where Effect Seen	Dose where no effect seen
Acute Dietary: General Population	Acute Neurotoxicity	227 mg/kg/day	67 mg/kg/day
Acute Dietary: Females 13 – 49	Developmental Toxicity	75 mg/kg/day	25 mg/kg/day
Chronic Dietary: All Populations	Extended one generation reproductive toxicity study	47 mg/kg/day	21 mg/kg/day
Incidental Oral : All durations		47 mg/kg/day	21 mg/kg/day
Inhalation: All durations	Subchronic Inhalation	0.05 mg/L/day	Not identified
Dermal: All Durations	No hazard via the dermal route		

PODs based on most sensitive effects for the appropriate duration and route of exposure

2,4-D and Renal Clearance

- Once 2,4-D enters the body, it is quickly removed by the kidney virtually unchanged
- 2,4-D is rapidly excreted until renal saturation is reached

Renal saturation = kidney's ability to clear 2,4-D from the body is overwhelmed

- Occurs at dose levels of approximately 50 mg/kg/day and above (rat)
- 2,4-D builds up in the body resulting in toxic effects

All the adverse effects attributed to 2,4-D are associated with exposure levels that exceed the body's ability to excrete 2,4-D (above ~50 mg/kg/day), except for inhalation.

EPA regulated 2,4-D to ensure that exposures are more than 100X lower than where renal saturation occurs.

Public Comments

Questions regarding toxic effects:

- Effects on hormone systems (thyroid)
- Reproductive system
  - Sperm effects
- Immune system
- Neurological effects
- Liver and kidney effects
- Cancer

Extended One Generation Reproductive Toxicity Study

- The extended one generation reproductive toxicity study (EOGRTS) is a detailed, high quality, comprehensive toxicity study
  - Guideline drafted by an international expert group of developmental/reproductive toxicologists
  - Unanimously adopted by OECD member countries

EOGRTS: Comprehensive Assessment of Toxicity

- Evaluation of potential effects of chemical exposure across multiple age groups and organ systems
  - Fetal/infant (pre- and post-natal) development
  - Pregnant females
  - Lactating females
  - Nursing young
  - Young
  - Adult
  - Offspring

From conception through adulthood

Parameters of EOGRTS

- Reproductive health
  - Menstrual cycle, sperm motility, sperm count, mating, conception, lactation
- Developmental neurotoxicity
- Developmental immunotoxicity
- All organ systems including but not limited to:
  - Liver
  - Kidney
  - Thyroid
    - Hormones and structure
- Hematology, clinical chemistry, urinalysis
- Toxicokinetics

EOGRTS: Thyroid assessment

- Adult and offspring (from birth to adulthood)
  - Assesses for changes in hormones, weights and histopathology
    - Sporadic
    - Non-statistically significant
    - Non dose related
  - This means no thyroid concerns
- Thyroid toxicity manifested as:
  - Decrease in T3 and T4 accompanied by increase in Thyroid Stimulating Hormone (TSH)
  - Consistent changes in weights and histopathology

EOGRTS: Reproductive Effects

- Adults
  - Organ weights
    - Very slight changes
      - Within range of normal variability
      - Not statistically significant
      - No dose response
      - Not considered adverse
  - No histopathological effects
  - No effects on reproductive function

EOGRTS: Reproductive Effects

- Offspring
  - Organ Weights
    - Slight changes
      - Non statistically significant
  - No changes in ano-genital distance
  - No effects on nipple retention
  - Puberty onset unaffected
  - Estrous cyclicity unaffected
  - Ovarian follicle counts unaffected
  - Sperm motility, morphology, and count unaffected

EOGRTS: Immunotoxicity

- 2 functional measures of immunotoxicity
  - Neither affected
- Decreased thymus weights in the young
  - No dose response, not statistically significant, no histopathological changes in thymus
  - Not considered adverse in isolation

EOGRTS: Developmental Neurotoxicity

- For animals dosed from conception through adulthood
  - No changes in any of the parameters evaluated:
    - Temperature, grip strength, landing foot splay, urination
    - Motor activity
    - Acoustic startle response
    - Brain weights
    - Gross measurements of brain regions
    - Neuropathological or morphometric measures

EOGRTS: Liver Effects

No effects were observed for any age group and any parameter measured:

- Adult animal (both sexes), young animal (both sexes), pregnant female
- Liver weight
- Clinical chemistry (liver enzymes)
- Microscopic examination of the liver

EOGRTS: Kidney Effects

- Adult:
  - Increase kidney weights and degenerative lesions in kidney structure – regulating on this effect
- Offspring:
  - Same effect as in adults and beginning at approximately same dose
    - No sensitivity

No Indication of Cancer

- Full battery of mutagenicity studies
  - Not a mutagen
- 2 carcinogenicity studies– negative
- No reliable toxicity studies indicate carcinogenicity
- Epidemiology studies
  - SAP in 1994
  - Reassessed by EPA in 1996 and 2004
  - Assessed by EU and PMRA (2013)
  - Data do not support cause-and-effect relationship with 2,4-D exposure

Neurotoxicity

- Extended One Generation Reproductive Toxicity Study
  - Animals dosed from conception through adulthood
  - No evidence of developmental neurotoxicity
- Acute Neurotoxicity Study
  - Effects (gait abnormalities, decreased motor activity) seen at doses 4-5 fold above renal saturation
- Subchronic Neurotoxicity Study
  - Effects (decreased grip strength) at doses ≈ 3-fold above renal saturation
- Epidemiology data
  - Parkinson's disease
    - No cause-effect relationship identified

Oral Uncertainty/Safety Factors for 2,4-D

- 10 X for intraspecies variability
- 10 X for interspecies extrapolation
- 10 X FQPA Safety Factor reduced to 1 X
  - Complete database for toxicity and exposure

- Level of Concern = 100 X

Inhalation Uncertainty/Safety Factors for 2,4-D

- Inhalation Toxicity Study
  - NOAEL not identified
  - Effects at all exposure concentrations
    - Point of contact effects
- Uncertainty Factors
  - 3 X for interspecies extrapolation (since using human equivalent dose/concentrations)
  - 10 X for intraspecies variability
  - 10 X FQPA factor for extrapolation from LOAEL to NOAEL
- Level of Concern = 300 X

Toxicity of Salts and Mixtures

- Toxicity of mixtures
  - Acute toxicity data of single chemical versus mixture shows no increase in toxicity of mixture of 2,4-D and glyphosate
- Toxicity of salts
  - 90-day oral toxicity (dog and rat), 21-day dermal toxicity (rabbit), developmental toxicity (rat and rabbit) studies available on the amine salts and esters of 2,4-D, which show a similar toxicity profile as that following exposure to 2,4-D
  - Acute toxicity data of 2,4-D choline shows no increase in toxicity compared to 2,4-D

2,4-D Hazard Summary

- Robust toxicology database – we know what happens at high doses
  - Toxic effects occur at doses that overwhelm the body's ability to excrete 2,4-D
- Kidney is main target organ for 2,4-D
  - Effects on the kidney occur first
  - When the kidney's ability to eliminate 2,4-D is compromised, effects on various other organ systems can occur
- EOGRTS specifically designed to identify what happens at levels that approach/slightly exceed ability to excrete 2,4-D
  - All systems (endocrine, reproduction, thyroid, hormonal, sperm, kidney, etc) were monitored in all lifestages (fetal, infant, young, pregnant and nursing female, and adults)
- Endpoint Selection
  - At highest dose tested, kidney effects were beginning to occur (defined as the Lowest Observed Adverse Effect Level; LOAEL)
  - At the next lower dose (defined as the No Observed Adverse Effect Level; NOAEL = 21 mg/kg/day) no adverse effects were observed
  - The NOAEL was divided by 10X for interspecies variability and again divided by 10X for intraspecies sensitivity to determine the maximum safe exposure level
- We are regulating at a level that is 100-fold lower than the dose level where NO effects occurred

Road Map

- Exposure assessment of 2,4-D
  - Dietary exposure assessment
  - Residential exposure assessment
    - Spray drift and volatility
  - Aggregate exposure assessment
  - Occupational exposure assessment
- Dioxins risk assessment
- International risk assessment of 2,4-D

Dietary Exposure Assessment

Residue Chemistry

Major areas include – but not limited to:

- Metabolism (plant and livestock)
  - Identifies potential metabolites of concern
- Residue field trials
  - Measures pesticide and metabolites in crops under a variety of field conditions
  - Nationally representative
- Food processing studies
  - Measures how the pesticide and metabolites move into processed foods

These studies are used to determine tolerances and residues for dietary risk assessment

Tolerances

- EPA sets tolerances on food or feed crops (maximum residue levels)
  - It is the amount of the pesticide that can legally remain in or on foods
- Based on results from field trials designed to identify the highest concentrations expected on crops
  - Use maximum application rates
  - Maximum number of applications
  - Shortest application to harvest interval
- Generally, tolerance is higher than the highest measured residue
- Generally, actual measured residues in food are 10-100 times lower than tolerances
  - Due to degradation during storage or washing

2,4-D Residue Chemistry: HT Corn and Soy

- Existing 2,4-D tolerances do not need to be changed
- 2,4-D breaks down to metabolite (2,4-DCP) to a greater extent in HT corn and soy
- Parent and metabolite are considered in dietary risk assessment
- 2,4-DCP is less toxic than 2,4-D

Dietary Exposure Assessment

- Evaluate food and water consumption patterns and residue concentrations that lead to highest potential for exposure
- Exposure algorithm:
  - Consumption x residue = dietary exposure
- DEEM model
  - Uses nationally representative consumption information for adults and children of all ages
    - Protective of pregnant women, infants, etc.

Dietary Exposure Assessment

Acute Dietary:

- Risk resulting from 1-day dietary exposure
- Residue level, food and drinking water consumption, and toxicological endpoint all must represent 1-day exposure or dosing

Chronic Dietary:

- Risks resulting from 6 months to lifetime exposure
- Residue levels, consumption: use average values
- Chronic toxicological endpoint

2,4-D Acute and Chronic Dietary Assessment

- Used tolerance level residues and 100% crop treated for all registered and proposed crops
  - Assumes all registered foods are treated with 2,4-D
  - All treated foods have residues present at tolerance level concentrations
- Combined 2,4-D and 2,4-DCP residue values for corn and soy
- Used modeled drinking water value
  - Designed to not underestimate exposure in comparison to actual water monitoring data
- **No acute or chronic dietary risk of concern**

Residential Exposure Assessment

Residential Exposure Assessment

- Handler Exposure
  - Exposures occurring only as a result of non-occupational application activities (e.g., spraying weeds in the backyard)
  - Adult exposure only
  - Dermal and inhalation routes of exposure assessed

- Post-application Exposure
  - Exposures that occur after direct applications in residential settings (e.g., homes, parks, schools, etc.)
  - Exposures from indirect applications on neighboring fields (bystander exposure)
  - Adults and children assessed
  - Dermal, inhalation and oral routes of exposure

2,4-D Residential Exposure Assessment – Direct Applications

- New use does not change the residential exposure from direct applications to residential settings
- However, these exposures were reassessed using updated exposure assessment policies
  - Used the 2012 Residential SOPs
- Used maximum application rates from registered uses
- Handlers making application to turf
  - **No risks of concern for residential handlers**
- Post-application exposure to treated turf
  - Assumed children played on turf immediately after an application was made
  - Assumed exposed for 30 consecutive days
  - **No residential post-application risks of concern**

Spray Drift Assessment

2,4-D Spray Drift Exposure

- During application to corn or soy field, assumes spray drifts onto a residential lawn adjacent to the agricultural field
- Assessment assumes that children play on lawn adjacent to the treated field directly after the application
- Resulting residue from direct application to turf at the rate of 1.5 lb/acre would be greater than any potential residue resulting from drift from adjacent field where 2,4-D was applied at 1 lb/acre
- Therefore, the residential turf assessment is protective of any potential spray drift onto neighboring lawns
- **No risks of concern**

Volatilization Assessment

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2,4-D Volatilization Assessment

- Volatilization assessment completed assuming adults and children inhale off-gases from a neighboring treated field
  - PERFUM Model used
  - 2,4-D choline specific flux (volatilization) data used
  - Maximum application rate assessed
  - Day of application assessed (worst case)
- **No risks of concern at the edge of treated field**

http://www.epa.gov/scipoly/sap/meetings/2009/120109meeting.html

Aggregate Exposure Assessment

Aggregate Exposure

Aggregate Exposure:

- The total exposure a person has to a chemical from all likely sources and routes

Residential Exposure (oral, dermal, and inhalation)

Food

Drinking Water

2,4-D Aggregate Assessment

- Acute and chronic aggregate assessments include food and drinking water exposure only
  - **No risks of concern**
- A short-term aggregate assessment was completed that includes food, water and residential exposure
  - **No risks of concern for adults or children**
  - For children, the aggregate exposure is 3 X lower than the level determined to be safe

2,4-D Assessment based on Public Comments

- Additional assessments completed using a 3 fold lower POD and retained the FQPA factor to address specific comments on EOGRTS
- Chronic dietary assessment
  - Used anticipated residues (more realistic values) for some commodities and tolerance level residues, 100% crop treated, and modeled drinking water values
  - **No chronic dietary risks of concern**
- Spray Drift
  - Used Agdrift model
  - Assesses children playing on lawn adjacent to treated field directly after an application
  - **No risks of concern at the edge of the treated field**
- Volatilization
  - **No risks of concern with the FQPA factor**

Occupational Exposure Assessment

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Occupational Exposure Assessment

- Handlers: professional applicators/farmers who may be exposed while mixing, loading, and/or applying pesticide products to crops, lawns, etc.
  - Dermal and inhalation routes
- Post-application workers: professionals who enter previously treated fields to tend/ harvest crops that have been previously treated with a pesticide product
  - Typically only dermal route quantitatively assessed

2,4-D Occupational Assessment

- Occupational mixer/loader and applicator assessed for groundboom application of 2,4-D to corn and soy
- Maximum application rate assessed
- **No risks of concern for occupational handlers**
- **No dermal hazard for post-application workers**

Dioxins Assessment

Dioxins

- Dioxins are a byproduct of some 2,4-D manufacturing processes
- 2,4-D choline salt products contained no detectable measures of dioxins
  - Non-measurable levels at very sensitive limit of detection (LOD)
- Screen of occupational and dietary exposure and risk completed using LOD residue values
  - **No risks of concern**
- **No ecological risk concern from dioxins** for 2,4-D choline salt based on 2005 assessment of dioxins at higher concentrations

Agent Orange

- 2,4-D is not the same as Agent Orange
- Agent Orange also contained 2,4,5-T
  - 2,4,5-T was determined to be a severe developmental toxicant
  - Contained higher levels of dioxins
    - Older formulations had higher dioxin levels
  - 2,4,5-T was banned for use because of these risks
- Modern manufacturing processes have reduced dioxin levels in 2,4-D to non-detectible levels

International Review of 2,4-D

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International Review

- EU and Canada also assessed 2,4-D
- Risk conclusions are the same as EPA

No risks of concern

Ecological and Endangered Species Risk Assessments

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Role of Environmental Fate and Effects Division

- Assess risks from pesticide use to non-target organisms such as birds, mammals, fish, plants, etc.

- Meet obligations under:
  - Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
  - Endangered Species Act (ESA)
  - Migratory Bird Treaty Act (MBTA)

- Ecological and endangered species risk assessments

- Typically conduct assessments:
  - Based on “worst case” scenarios
  - Determines where risk concerns lie

Public Comments

- Concerns raised about:
  - Volatility and spray drift
    - Buffer distance
  - Synergy of glyphosate and 2,4-D choline
  - Toxicity to plants and animals
  - 2,4-D in water
  - Degradate 2,4-DCP
  - Endangered species
- Addressed in risk assessments


Photo courtesy of EPA


Photo courtesy of EPA

Ecological Risk Assessment

Enlist Duo Applications

- Contains 2,4-D choline salt (and glyphosate)
  - Reduced spray drift and volatility properties compared with other 2,4-D forms – especially esters

- Ground boom spray only; no aerial applications

- Corn and Soybeans
  - 3 applications at 1 lb/A
  - Pre-plant (1)
  - Post-plant (2)
  - 12-day application interval

- Application timing is later
  - Corn – up to 48 inches
  - Soybean – during flowering

2,4-D Toxicity to Non-Target Organisms


Photo courtesy of EPA


Photo courtesy of EPA


Photo courtesy of EPA

- Some toxicity to aquatic plants
- Toxic to terrestrial plants (herbicide!)
- Effects based on acute exposure:
  - Practically non-toxic to terrestrial invertebrates
  - Slightly toxic to fish and aquatic invertebrates
  - Moderately toxic to birds and mammals at higher doses
- Effects based on chronic exposure:
  - Mortality at higher doses
    - Fish, aquatic invertebrates
  - Reduced size and reproduction capacity
    - Fish, aquatic invertebrates, mammals

Risk Assessment Basics

Hazard (Toxicity) x Exposure = Risk

- How much risk is too much?
  - Risk assessment thresholds (levels of concern) help define which taxa have risk concerns

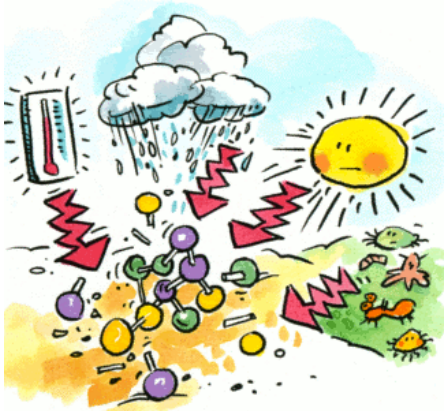
Risk Concerns ≠ Bad Outcome

- Detailed information can refine risk conclusions
  - Species biology
  - Species location
  - Pesticide use patterns
  - Incidents
  - Monitoring data

Physico-Chemical Properties of 2,4-D

- 2,4-D choline is a derivative of 2,4-D acid, which dissociates rapidly (6 seconds) in water, thus the properties are based on 2,4-D acid

- Physico-chemical properties
  - Highly soluble in water
  - Low volatility from soil and water
  - Low potential to bioaccumulate



http://npic.orst.edu/envir/efate.html

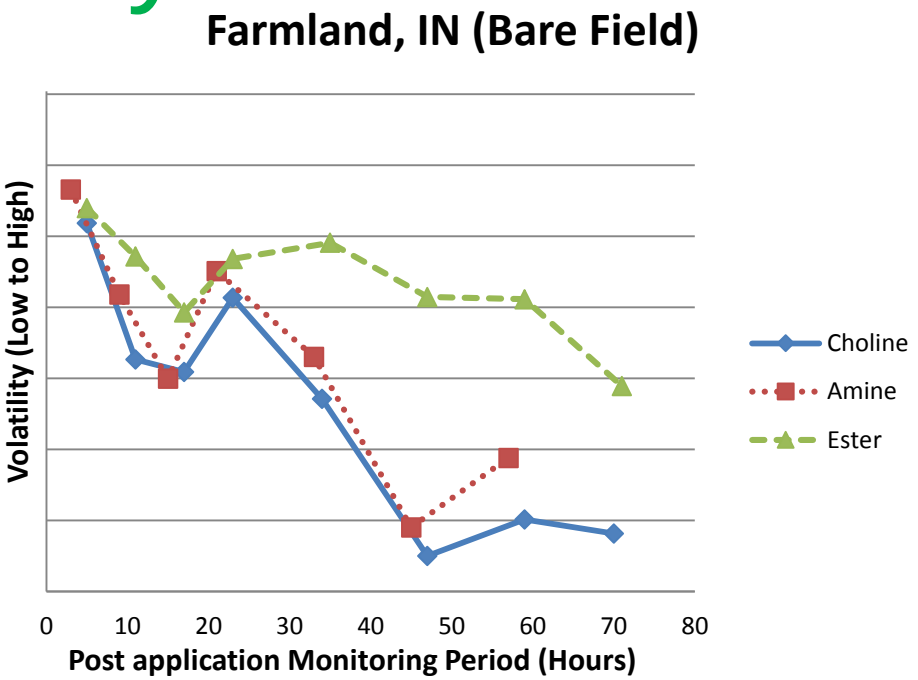
- Environmental fate and transport properties
  - Not persistent in soil and water in natural environment
  - Rapid to moderately rapid dissipation from application sites
  - Mobile in the environment
  - Major degradate - 2,4-DCP

Special Considerations - Volatility

- Field volatilization of 2,4-D choline is lower than esters

- Laboratory Plant Data
  - Grapes were most sensitive followed by cotton, tomato and soybean

- Field Terrestrial Plant Data
  - Peer-reviewed literature
    - Grape was most sensitive
  - Field volatility study
    - **No effects to grape and cotton plants ~15 ft from field**



Special Considerations – Spray Drift

- Enlist Duo reduces drift
  - Spray drift field study verified at least 46% reduction
- 32 additional nozzles were tested
  - 75 nozzle/pressure combinations found acceptable
- **Label requires use of specific nozzles to ensure reduced spray drift**


Photo courtesy of EPA


M.G. Radtke, EPA, personal collection

Special Considerations - Synergy

- Enlist Duo = 2,4-D Choline + Glyphosate
  - Two herbicides with different modes of action

- Is synergy a concern?
  - Rat 2,4-D and Enlist Duo toxicity is similar
  - Channel catfish, bluegill sunfish and crawfish study
  - **No indication of synergy**


M.G. Radtke, EPA, personal collection


Photo courtesy of EPA

Modeling Terrestrial Exposure

- Terrestrial Residue Exposure (T-REX)
  - Mammals, birds, reptiles, land-phase amphibians, honeybees
  - Exposure via diet
  - Predicts concentration of 2,4-D on leaves, grass, fruit, seeds, and arthropods


Photo courtesy of EPA

- TerrPlant
  - Terrestrial plants
  - Exposure via spray drift and runoff
  - Predicts concentration of 2,4-D contacting plant via spray drift and available for root uptake via runoff

Modeling Aquatic Exposure

- Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS)
  - Aquatic plants, freshwater/saltwater fish and invertebrates, aquatic-phase amphibians
  - Exposure through spray drift and runoff
  - Predicts concentration of 2,4-D and degradate 2,4-DCP in water


Photo courtesy of EPA


Photo courtesy of EPA

- 2,4-DCP
  - Major aquatic degradate
  - Potentially more toxic to some species

Aquatic Exposure – Monitoring Data

- Surface water
  - 2,4-D detected in 47% of samples (931 total)
  - Max. concentrations from 0.008 µg/l to 8.7 µg/L
- Groundwater
  - 2,4-D detected in 1% of samples (1184 total)
  - Max. concentrations from 0.008 µg/L to 1.4 µg/L

- Established MCL (Maximum Contaminant Level)
  - 70 µg/L
- Concentrations of 2,4-D from monitoring data are lower than the modeled exposures for various scenarios (8.7 µg/L vs. 58 µg/L)
- Monitoring data may not necessarily reflect major 2,4-D use area and application timing to detect maximum environmental concentrations

Modeling Atmospheric Exposure

- Screening-level air quality model (AERSCREEN)
  - Exposure from wet and dry deposition of volatilized 2,4-D
  - Predicts potential deposition of 2,4-D (in pounds) that lands off the field during a 24 hour time period
    - **No risk concerns from re-deposited 2,4-D**

- Refined air quality model (PERFUM - Probabilistic Exposure and Risk Model for Fumigants)
  - Exposure from 2,4-D vapor
  - Predicts air concentrations of volatilized 2,4-D at edge of the field
    - **No risk concerns from volatilized 2,4-D**

Estimating Risk

- Risk Quotients (RQ)
  - Exposure divided by hazard (toxicity value)

- Risk Thresholds (levels of concern)
  - If RQ is below threshold, there is no risk concern

Taxa	Acute	Chronic	Other
Terrestrial animals	0.1 (listed spp.) 0.5 (non-listed spp.)	1.0 (listed and non-listed spp.)	N/A
Aquatic animals	0.05 (listed spp.) 0.50 (non-listed spp.)	1.0 (listed and non-listed spp.)	N/A
Terrestrial and aquatic plants	N/A	N/A	1.0 (listed and non-listed spp.)

Ecological Risk Assessment Conclusions

- No direct risk concerns for:
  - Aquatic plants and invertebrates, fish, aquatic-phase amphibians, and terrestrial invertebrates
- Potential direct risk concerns for:
  - Birds (reptiles and land-phase amphibians)
  - Mammals
  - Terrestrial plants
- Indirect risk concerns for species that depend on birds, reptiles, amphibians, mammals or terrestrial plants
- Next step is to refine analysis with an endangered species risk assessment

Risk Mitigation

Keeping Enlist Duo on the Field

Corn field

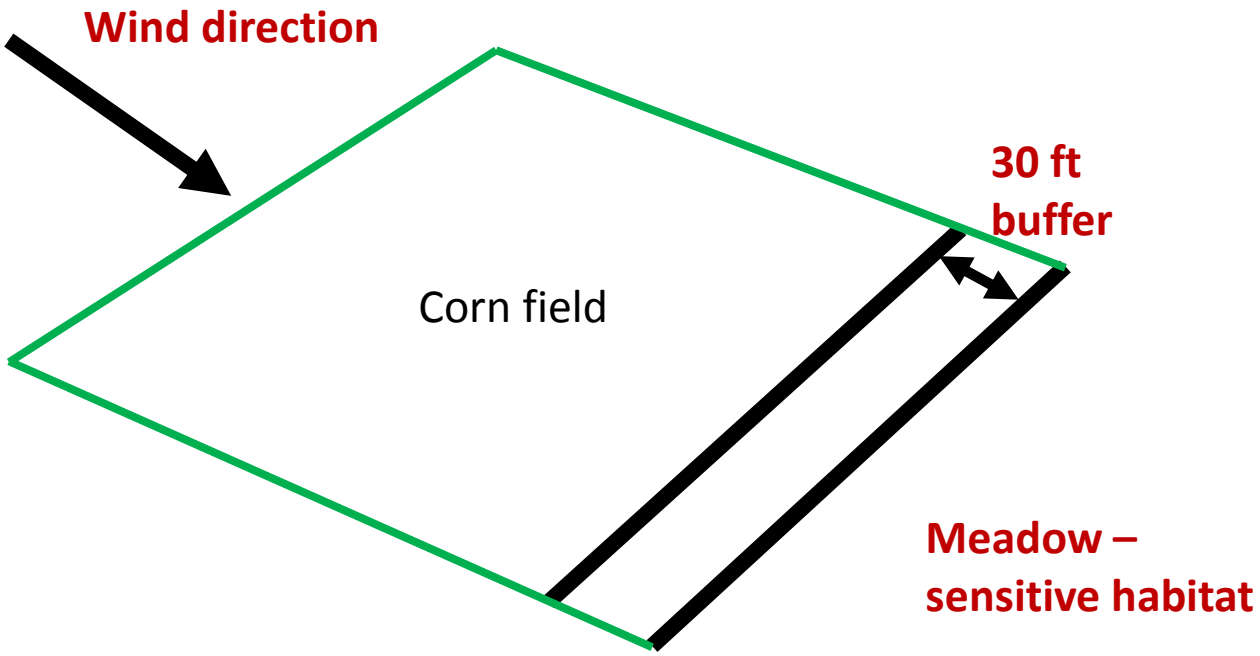
Area of concern

Adjacent wetland

No concerns

Wind Direction and Buffers

- 30 ft in-field buffer required when wind blows towards sensitive habitat
- "Sensitive habitat" is anything but field (in crop), pavement, or a building
  - Protects everything off the field from spray drift

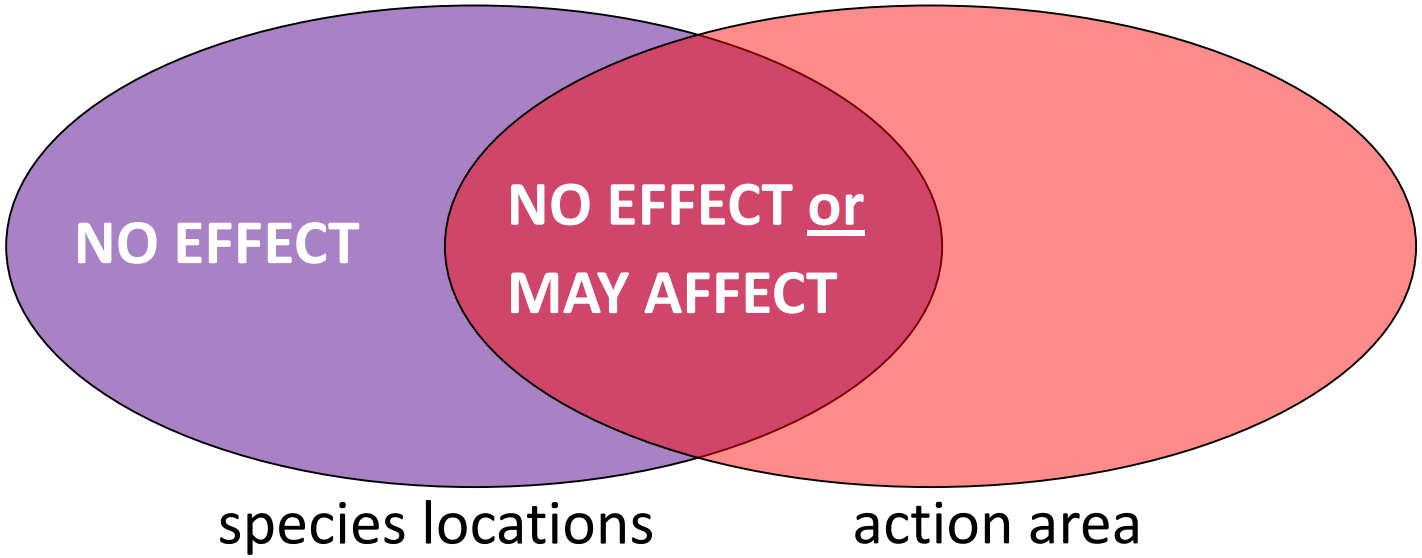


2,4-D Choline Endangered Species Risk Assessment

Refined Assessment

Making an Effects Determination

- Legal requirement of the Endangered Species Act
  - "No Effect"
  - "May Affect, Not Likely to Adversely Affect"
  - "May Affect, Likely to Adversely Affect"



Geographical Scope

- Assessment limited to 6 states
  - Indiana
  - Illinois
  - Iowa
  - Ohio
  - South Dakota
  - Wisconsin


Photo courtesy of EPA

- 53 endangered/threatened species

Species on Corn/Soybean Fields

- Action area is limited to corn and soybean fields

- Only 4 species out of 53!
  - American burying beetle (insect)
  - Canada lynx (mammal)
  - Indiana bat (mammal)
  - Whooping crane (bird)


Photo courtesy of EPA


Eric Kilby, Flickr User, Mentalfloss.com


Brian E. Small, Focusing on Wildlife, Focusingonwildlife.com

American Burying Beetle

- Food item (carrion and live insects) may be found on fields

- Concern (indirect)
  - Beetle requires vegetative cover
  - Indirect effects from adversely affected vegetation
- Determination
  - Beetle tolerates a wide variety of vegetative covers (generalist)
  - "**No Effect**"

Canada Lynx

- May pass through agricultural fields as it moves between patches of boreal forest

- Concern (direct)
  - Dietary exposure - prey items may contain 2,4-D choline residues
  - Direct effects from consumption of prey

- Determination
  - Primary food source is snowshoe hare, found in boreal forests
  - **“No Effect”**


Susi Von Oettingen, U.S. Fish and Wildlife Service, commons.wikimedia.org

Indiana Bat

- Have been observed foraging above corn and soybean fields

- Concern (direct)
  - Dietary exposure – consumption of flying insects containing 2,4-D choline residues
  - Direct effects from consumption of prey

- Determination
  - Performed acute and chronic dietary analysis using species weight and diet information
    - Daily consumption of 2,4-D choline residues not expected to reach toxicity threshold
  - **“No Effect”**

Whooping Crane

- Annual migration places whooping cranes in 2,4-D choline use areas (March – May)

- Concern (direct)
  - Dietary exposure – consumption of insects containing 2,4-D choline residues
  - Direct effects from consumption of prey

- Determination
  - Dietary analysis with whooping crane-specific body weight yielded RQ of 0.065 (below risk threshold of 0.1)
  - **“No Effect”**

Summary

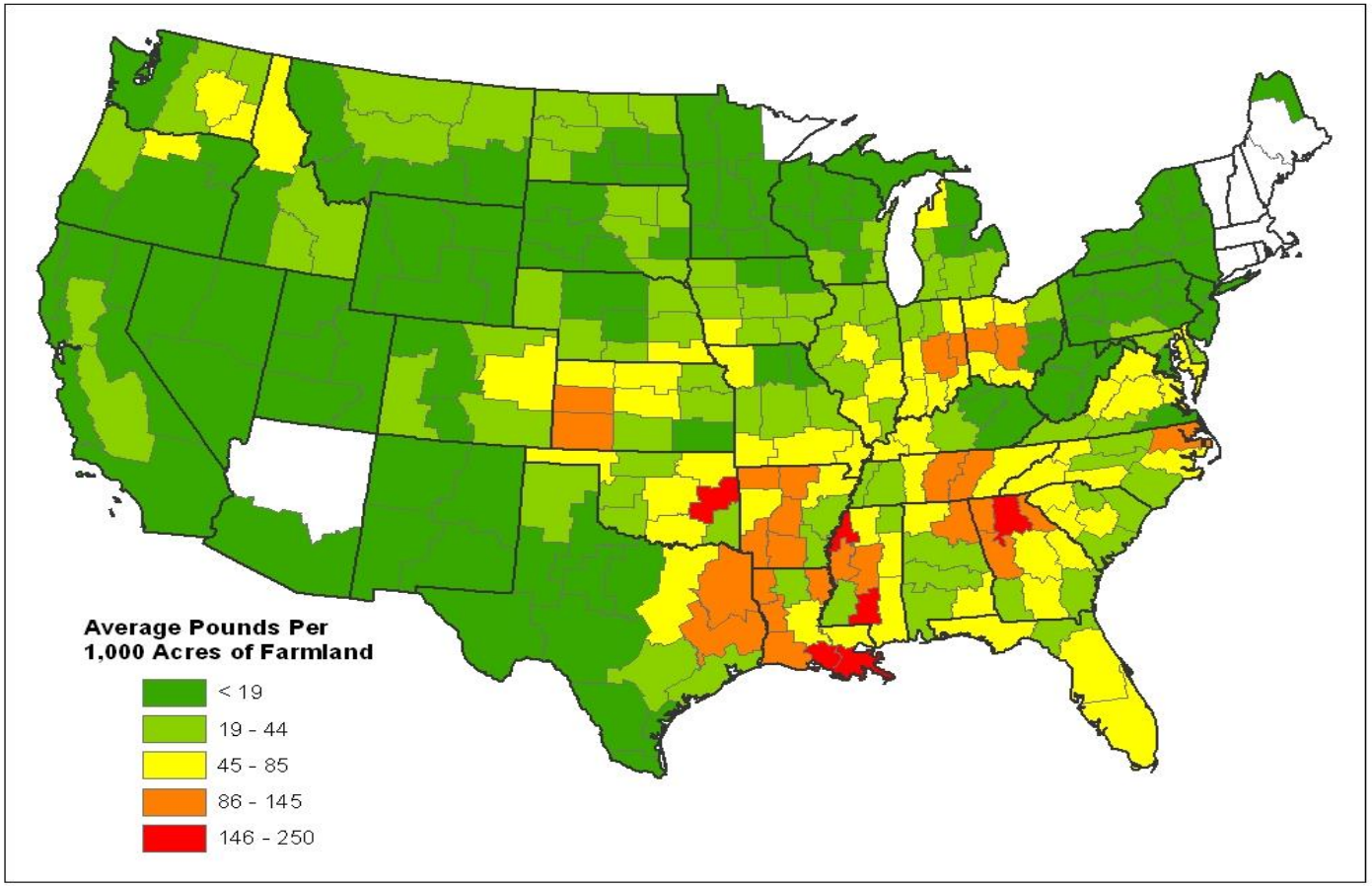
- Exposure and toxicity determine risk
- Ecological risk assessment
  - Risks for birds (reptiles and land-phase amphibians), mammals, and terrestrial plants

- Mitigation refinements
  - 30ft in-field spray drift buffer based on wind direction

- Endangered species assessment
  - 53 species
    - Most eliminated by geographical considerations
    - 4 eliminated by species-specific information
  - **"No Effects" determination for all species**

Usage of 2,4-D and Resistance Management

2,4-D Agricultural Usage by Crop Reporting District (2006-2010)



Benefits of Enlist Duo to Corn and Soybean Growers

- Increased flexibility in weed control in corn and soybean
- A new tool for in season broadleaf weed control in herbicide-resistant soybean
- Improved ability to manage broadleaf weeds resistant to glyphosate or other herbicides; may extend viability of glyphosate
- An active stewardship program is needed to preserve benefits
- The measures needed to preserve the benefits to growers of Enlist Duo will be clearly outlined in the stewardship plan and education and outreach programs

Herbicide Resistance

- Herbicide resistance is the acquired ability of a weed population to survive a herbicide application that previously was known to control the population. *
- Impacts of Resistance *
  - Requires changes in crop and weed management
  - Increases the cost of weed management
  - Reduces viable herbicide options
  - Loss of yield potential and income

- EPA's overall goal is to extend the useful life of chemicals used for pest control by slowing the development of resistance to fungicides, herbicides, and insecticides and extend the life of the technology.

  - Weed Science Society of America training modules available online at http://wssa.net/2011/12/wssa-lesson-module-herbicide-resistant-weeds/

Picture source. B. Hanson. UC Davis. Http://ucanr.edu/blogs/blogcore/postdetail.cfm?postnum=3973

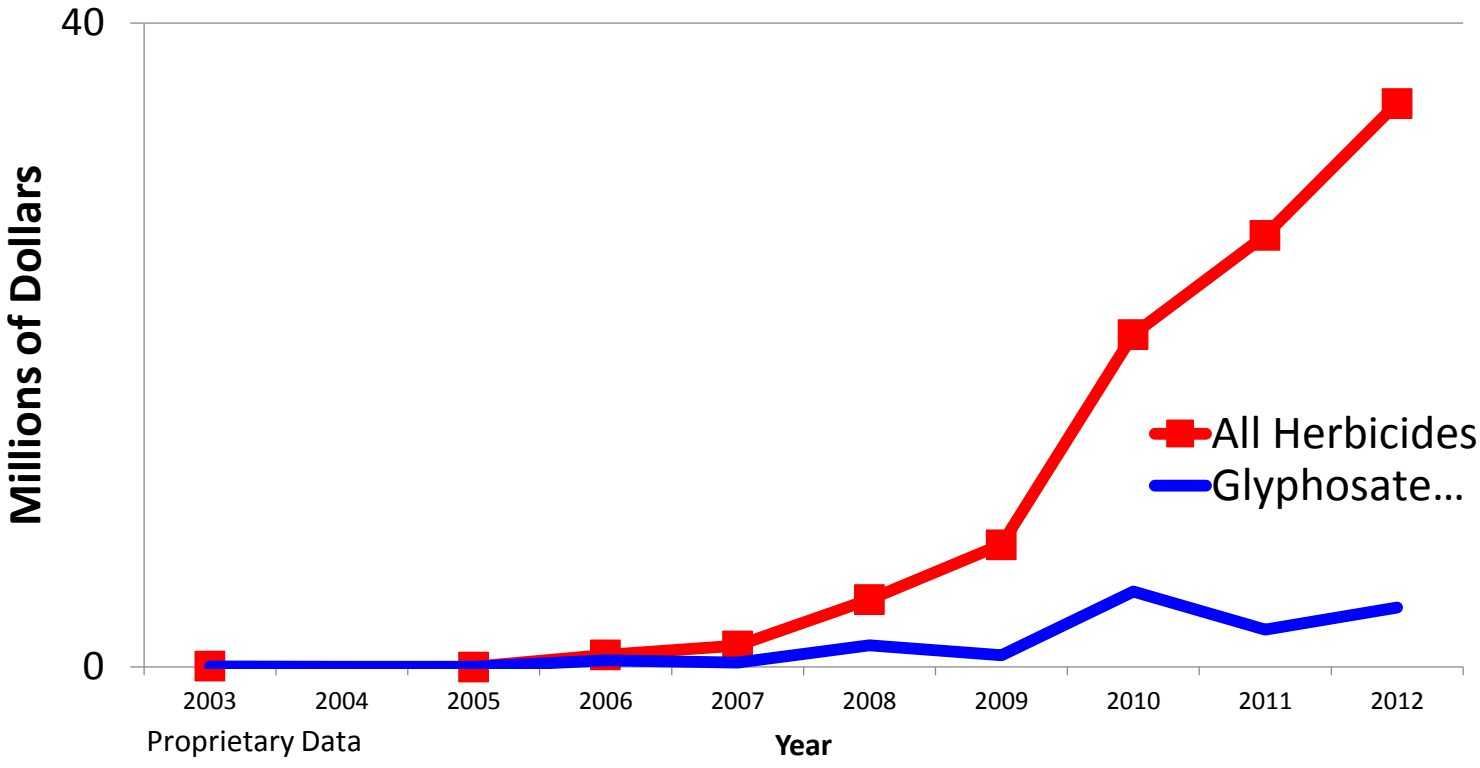
Example - Herbicide Resistance Is Not Unique to Genetically Engineered Crops

Palmer amaranth (*Amaranthus palmerii*) is resistant to glyphosate and AcetoLactate Synthase herbicides

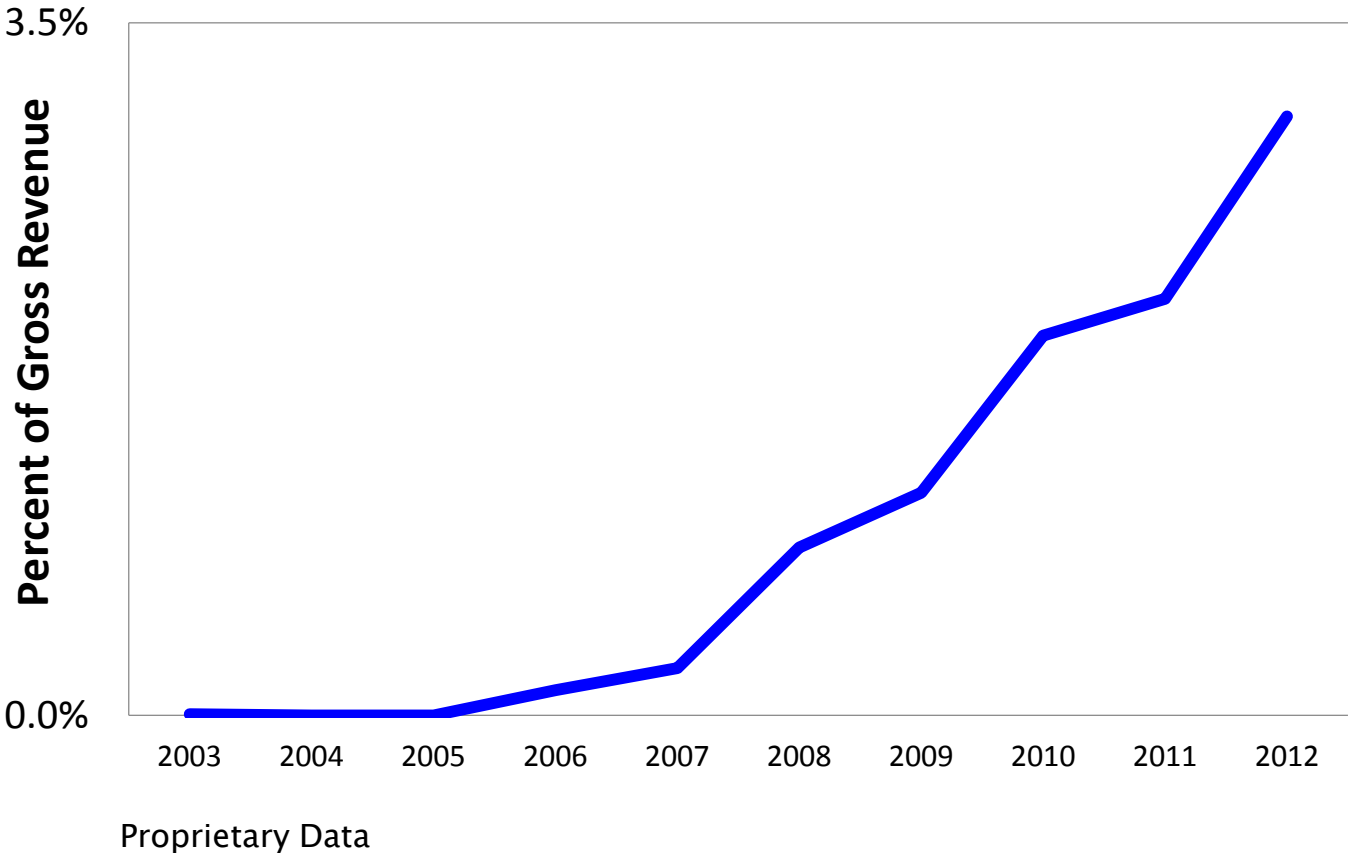
- Biology of Palmer amaranth
  - Able to grow several inches per day
  - Deep tap root
  - Under optimal conditions, a single female Palmer amaranth plant can produce up to 1 million seed
- Increase in herbicide use
- Increase in cultivation and plowing (increased erosion)

Picture Source: Extension, Univ. of Georgia http://extension.uga.edu/publications/detail.cfm?number=C1000

Control of Palmer Amaranth in Georgia Cotton
Increased Cost of Herbicides

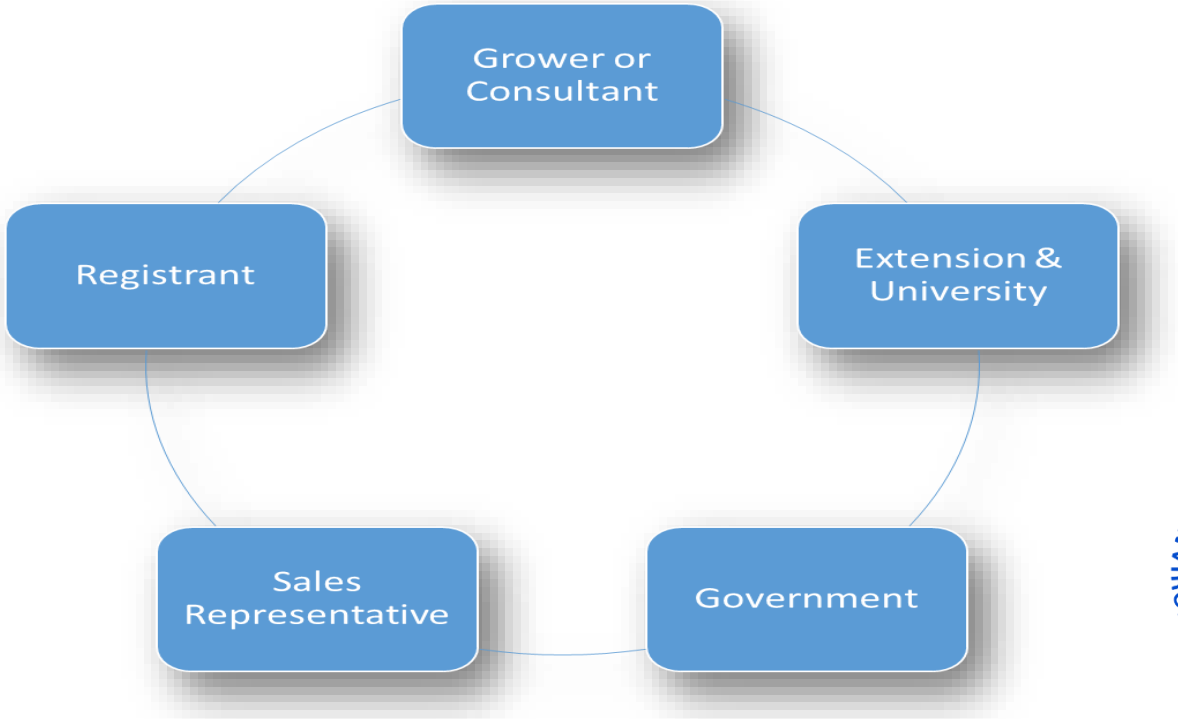


Control of Palmer Amaranth in Georgia Cotton Herbicide Costs as Share of Gross Revenue Expenditures



Managing Weed Resistance

- EPA considers resistance a risk
  - EPA will require measures to address weed resistance on all new herbicide resistant crops
- Requires a common understanding of resistance and its causes
- Managing resistance and slowing the development of resistance involves all stakeholders



Label – Resistance Management Elements

- Label must contain
  - Mechanism of Action (MoA)
  - Best Management Practices to control resistance, e.g. those developed by Weed Science Society of America (WSSA) and Herbicide Resistance Action Committee (HRAC)
- Because early identification of problems is critical to managing herbicide resistance, the following items will be placed with the directions for use so that they are clearly visible
- User or consultant should:
  - Scout before application to identify weed and size
  - Scout after application to determine if application was effective
  - Report poor performance / likely resistance to registrant or their representative

Terms of Registration - Resistance Management Elements

- Develop a Stewardship Program
- Develop Training and Education materials
- Investigate cases of non-performance
  - Use Norsworthy et al. 2012 criteria for determining likely herbicide resistance
- Develop a Remediation Plan for use if resistance is suspected
  - Registrant must take steps to control and prevent the spread of likely resistant weeds
  - Thorough follow up to make sure problem is addressed
- Annual reporting of likely and confirmed resistance to EPA
  - Enough information to describe nature and extent of infestation
  - Early notification is important to allow time to respond to the problem
- Continued registration of Enlist will depend on successfully controlling herbicide resistant weeds

Final Decision

Enlist Duo

- EPA recognizes the need for this important tool as part of an integrated pest management program.
- EPA has determined that this use is safe for humans and the environment when used according to the label.

Terms of Registration

- Six States for initial registration:
  - Illinois, Indiana, Iowa, Ohio, South Dakota, Wisconsin
- Resistance Management Stewardship program
  - Training and education
  - Use monitoring and investigation
  - Remediation and reporting
- Regulatory control held by EPA

Labeling

- Mitigation
  - Prevent off-site movement from spray drift
    - Buffers/wind direction
    - Nozzles/PSI requirements
    - Formulation restrictions
    - Ground application only
- Stewardship
  - Resistance management
    - Scout for potential problems
    - Report “likely resistance”
    - Follow Best Management Practices from WSSA

Moving Forward

- EPA will continue to conduct Endangered Species Assessments for additional states.
- EPA will continue to evaluate additional nozzles to provide greater flexibility for growers.
- EPA will retain control to easily and quickly modify or stop the use and sale of Enlist Duo as necessary.
- EPA will use the resistance management plan developed for Enlist Duo for future products to be used on GE crops

Questions?

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Email: enlistduoquestions@epa.gov

For More Information:

www.regulations.gov

Docket ID: EPA-HQ-OPP-2014-0195


UNITED STATES
ENVIRONMENTAL PROTECTION AGENCY

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