Background on Risk Assessment at DPR

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California Department of Pesticide Regulation

DPR Brown Bag Lunch Series
www.cdpr.ca.gov
March 23, 2016

Human Health Assessment Branch

Data Review Section	Risk Assessment Section	Exposure Assessment Section
Review data submitted in support of pesticide registration Identify potential acute, sub-chronic, and chronic health effects	Determine doses below which health impacts are not expected Compare these doses with estimated exposures to determine risk	Identify situations when exposure to pesticides can occur Estimate exposures associated with legal uses of pesticides

DPR Mission

Our mission is to protect human health and the environment by regulating pesticide sales and use, and by fostering reduced-risk pest management.

Protect Human Health

- Need to determine, when pesticides are used…
  - What health impacts may occur
  - Circumstances when adverse effects could happen
- Can take measures if needed to decrease exposures
  - May require changes in how pesticide products are used
  - May cancel certain uses

(Photo from visitcalifornia.com)

(Photo from NPR.org)

What Is Risk Assessment?

- Risk assessment is a process regulators use to evaluate the safety of pesticide uses
- Risk includes both toxicity and exposure
  - If there is no exposure, then no risk
  - Low (or practically no) toxicity, low risk
- Risk assessment compares the exposure to the dose where no effects were seen or to a negligible risk level
  - Include safety and uncertainty factors

(DPR Photo)

When Is Risk Assessment Done?

- Before pesticides are registered
  - DPR required by law to have complete toxicity database and to review for adverse health effects
  - In some cases, DPR conducts a formal risk assessment to determine potential risks of proposed new uses
- Pesticides already in use
  - Determine if new regulations or use restrictions are needed
- Risks are assessed when needed
  - Can be triggered by new data, changes in uses, etc.

California is the only state that conducts risk assessments

Risk Assessment Goal

- Realistic, health protective estimates of risk
  - Protect individuals from injury when pesticide is properly used
  - Improper uses are handled in the enforcement process
  - Balance protective assumptions with best available scientific information

(USDA Photo)

How Are People Exposed?

- Can be exposed directly when pesticides are applied
  - Individuals involved in pesticide applications
  - Airborne exposures to others
- Can be exposed to residues on crops or in the environment
  - Entering area where pesticide was applied
  - Dietary from eating treated crops
  - Drinking water

(Photo from UFL)

Sources for Data

- Data used in assessments come from many sources
  - Pesticide registrants must submit certain data
  - Scientific papers by university and other researchers
  - DPR sometimes conducts studies
- Required studies for registration include several types
  - For example, chemistry and environmental fate studies
  - Toxicity studies to indicate potential health hazards
- Exposure studies are not necessarily required
  - Measure pesticides on skin and clothing, in blood and other body fluids, or in the environment (air, water, food, soil, etc.)

New Kinds of Data

- Traditional toxicity and exposure studies use methods developed in 1970s through 1990s (and earlier)
- 21st Century Toxicology
  - Understand toxicity without use of animals
- Models to better characterize exposure

Incorporating New Methods into the Risk Assessment Process

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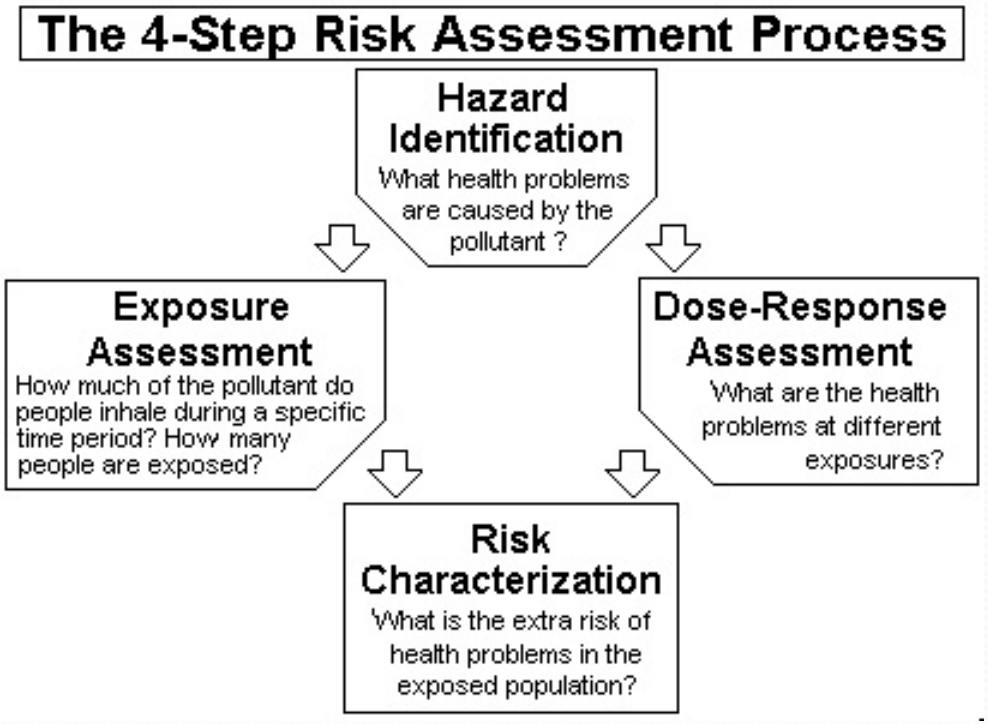
DPR Brown Bag Lunch Series
March 23, 2016

Human Health Risk Assessment

- Estimates the risk to humans from exposure to pesticides
  - Based on scientific data
- Predicts:
  - Type of health effects
  - Magnitude of the effects
- Uses of conventions, extrapolations and uncertainties
- Toxicologically-based risk assessments are valid within their assumptions

Risk Assessment Process



(Figure from U.S. EPA)

- California 1807 and SB950 Acts:
  - adverse effects to pesticides are determined through the risk assessment process
- 1983 National Academy of Sciences (NAS) Framework:
  - 4-step process

Risk Assessment Section

- Typically, the DPR's Risk Assessments are about 100-200 pages
- The best available scientific information is used to estimate the risk to humans
  I. Hazard Identification
  II. Dose Response Evaluation
  III. Exposure Assessment
  IV. Risk Characterization

Hazard Identification

- Hazard Identification is about half of the risk assessment
- This part summarizes available studies
  - Studies submitted by registrants: follow Federal Fungicide, Insecticide and Rodenticide Act (FIFRA) guidelines
  - Published studies: not following specific guidelines

HHAB Reviewing Studies

Dose-Response Evaluation

- Non-cancer effects: determines critical No-Observed Effect Level (NOEL) for toxic effects (e.g., body weight reductions, liver or brain pathology)
- Cancer: estimates potency based on tumor incidence in animal studies
- Approaches: mathematical models (e.g. Benchmark Dose Analysis) are used to estimate NOELs and cancer potency

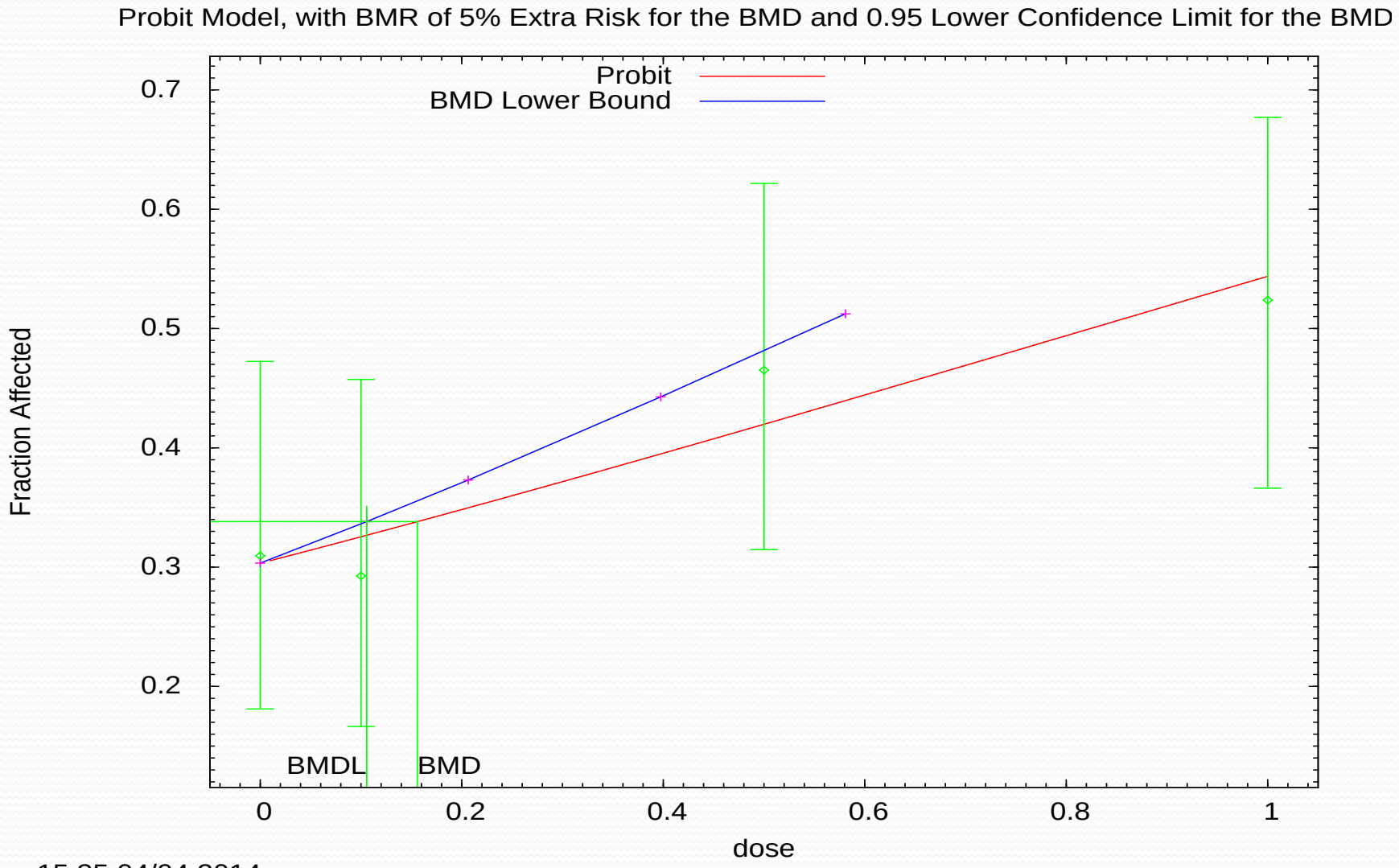
Hazard Identification

Table 1. Acute/Short term Effects of Chemical X and Respective NOELs

Species	Exposure	NOEL mg/kg	Critical Effects
Rat[a]	Single, gavage	1.0	↓ ChE in cortex of males
Mouse	7 days, diet	5.0	Decreased body weight
Rabbit[b]	9 days, gavage	1.0	Maternal: Cholinergic signs Fetal: decreased birth weight
Rat[b]	9 days, gavage	2.5	Maternal: Cholinergic signs
Rat[a]	**14 days, diet**	**0.18**	**↓ ChE in cortex of males**

a Neurotoxicity study
b Developmental toxicity study

Benchmark Dose Analysis



Exposure Assessment Section

- Typically, the DPR's Risk Assessments are about 100-200 pages
- The best available scientific information is used to estimate the risk to humans
    I. Hazard Identification
    II. Dose Response Evaluation
    III. Exposure Assessment
    IV. Risk Characterization

How to Evaluate Pesticide Risk Computer Modeling Plus Laboratory and Fieldwork to Build Understanding

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Senior Toxicologist
Exposure Assessment Section
Human Health Assessment Branch

Equation for Exposure Calculation

$$\text{Exposure} = \int \left(\begin{matrix} \text{Concentration} \times \\ \text{Exposure Factors} \end{matrix} \right) dt$$

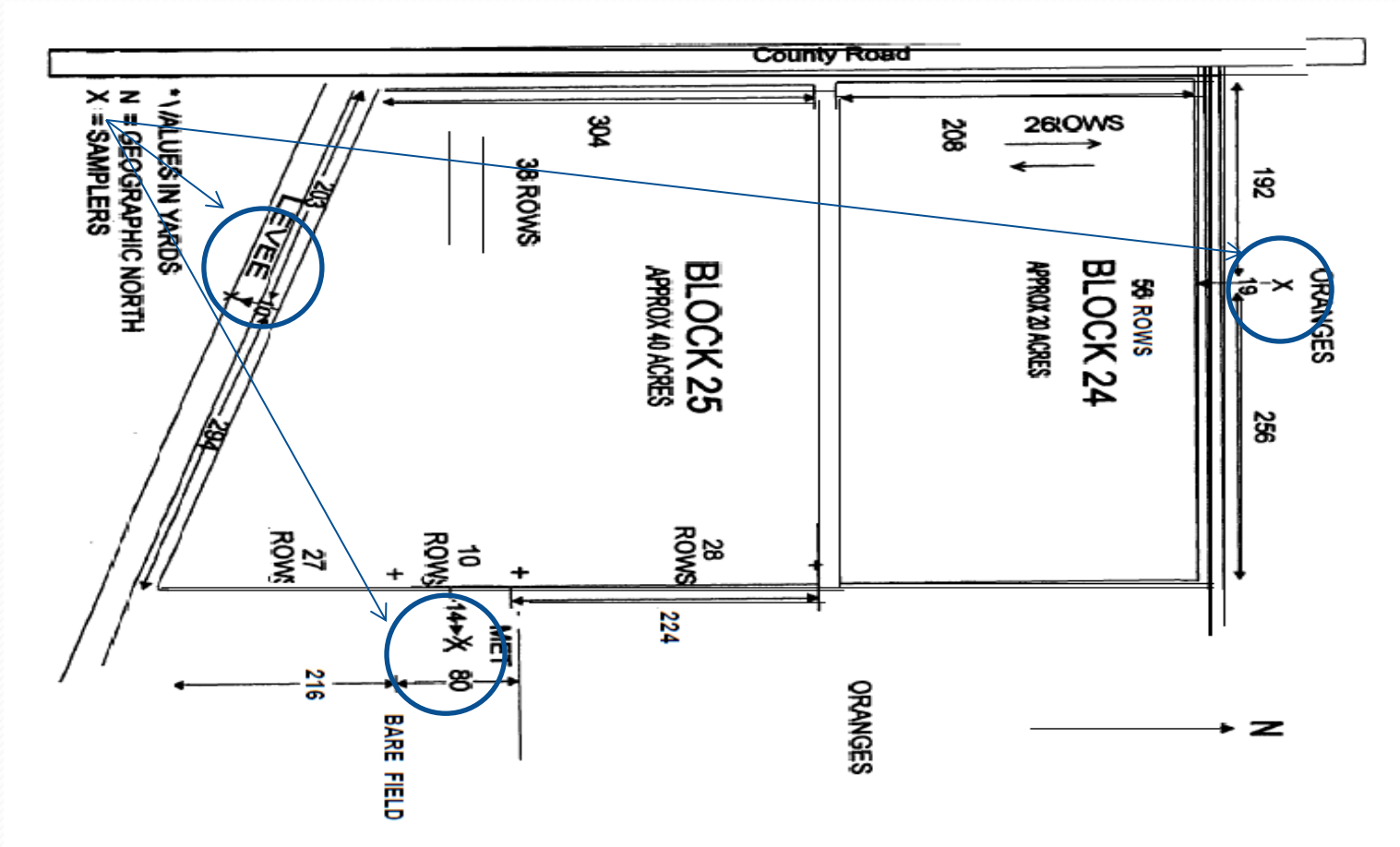
Two Questions for Determining Exposure:

1. What are the concentrations?
2. What are the exposure factors?

Sources and Releases
Example: Escape of Pesticide from Field to Air

Monitoring at Application Site

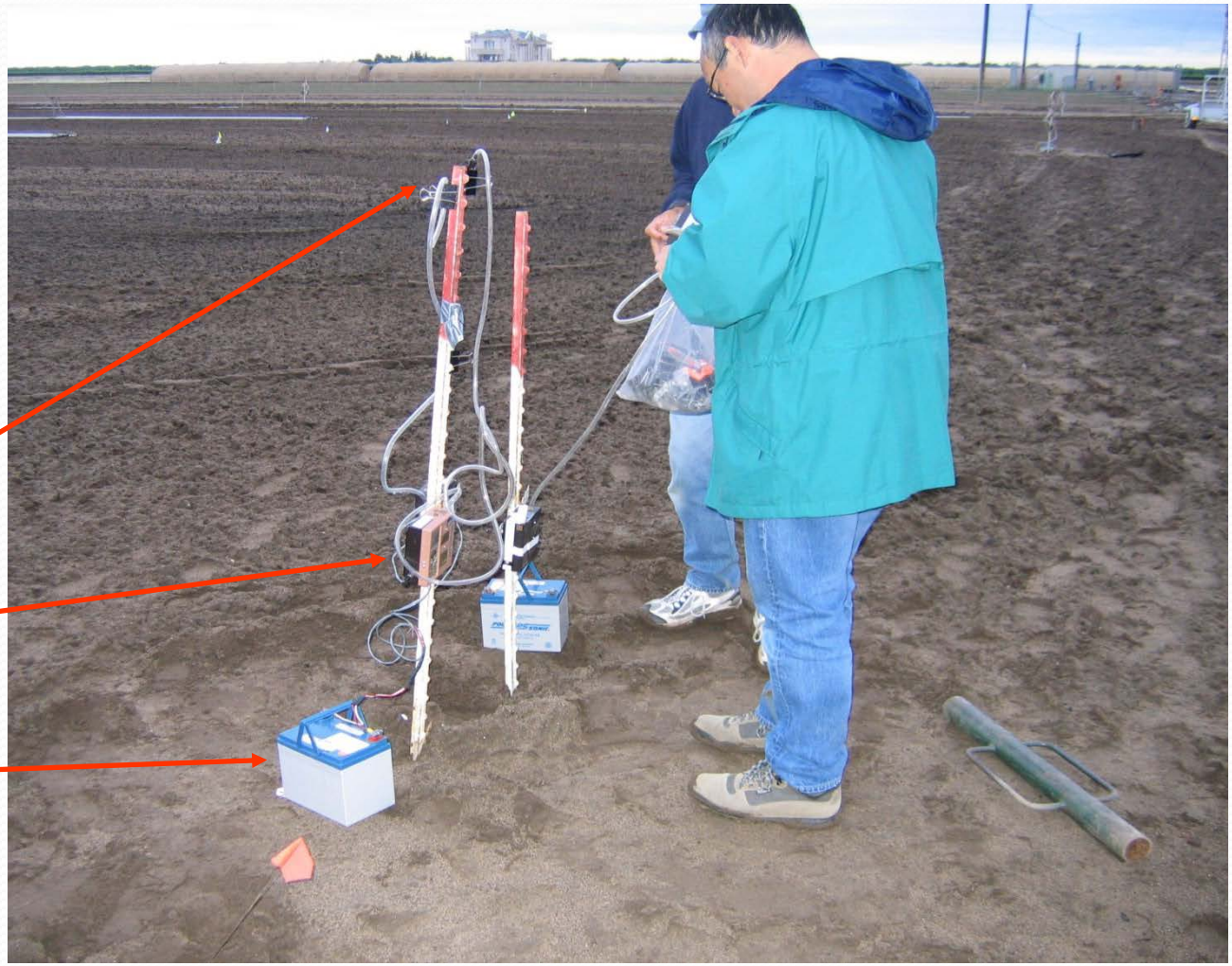
Example: Ground-Rig Blower to 60-Acre Orange Orchard



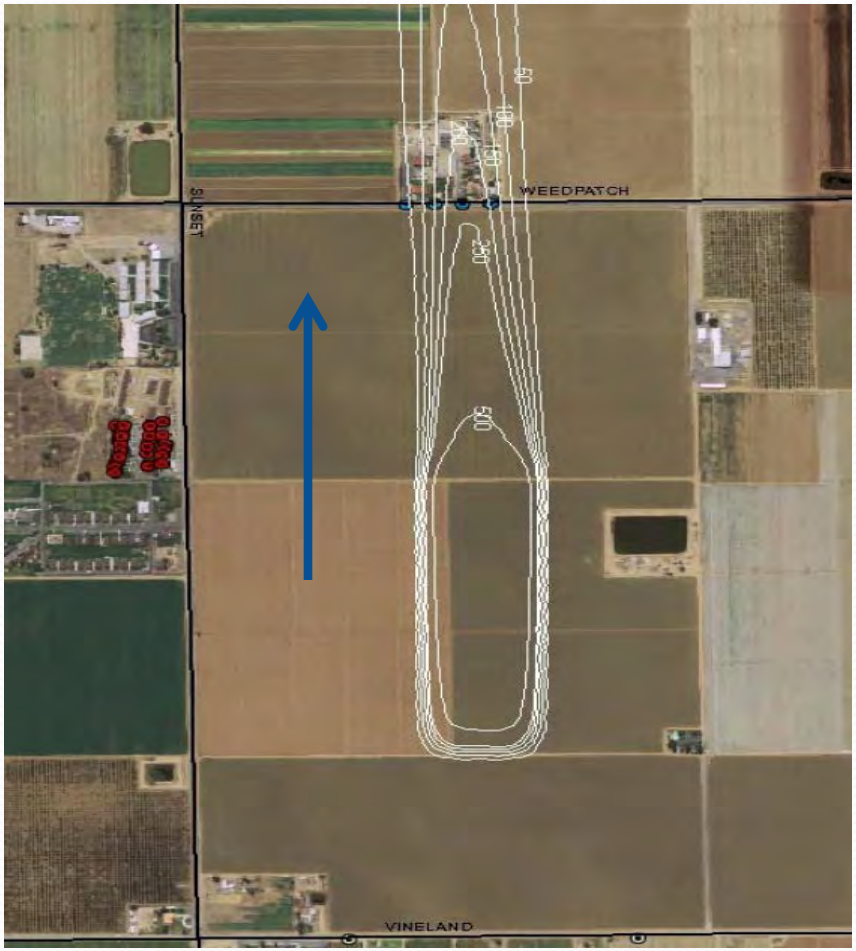
Source: ARB, 1998. Report for the Application and Ambient Air Monitoring of Chlorpyrifos (and the oxon analogue) in Tulare County During Spring/Summer, 1996, pp.170

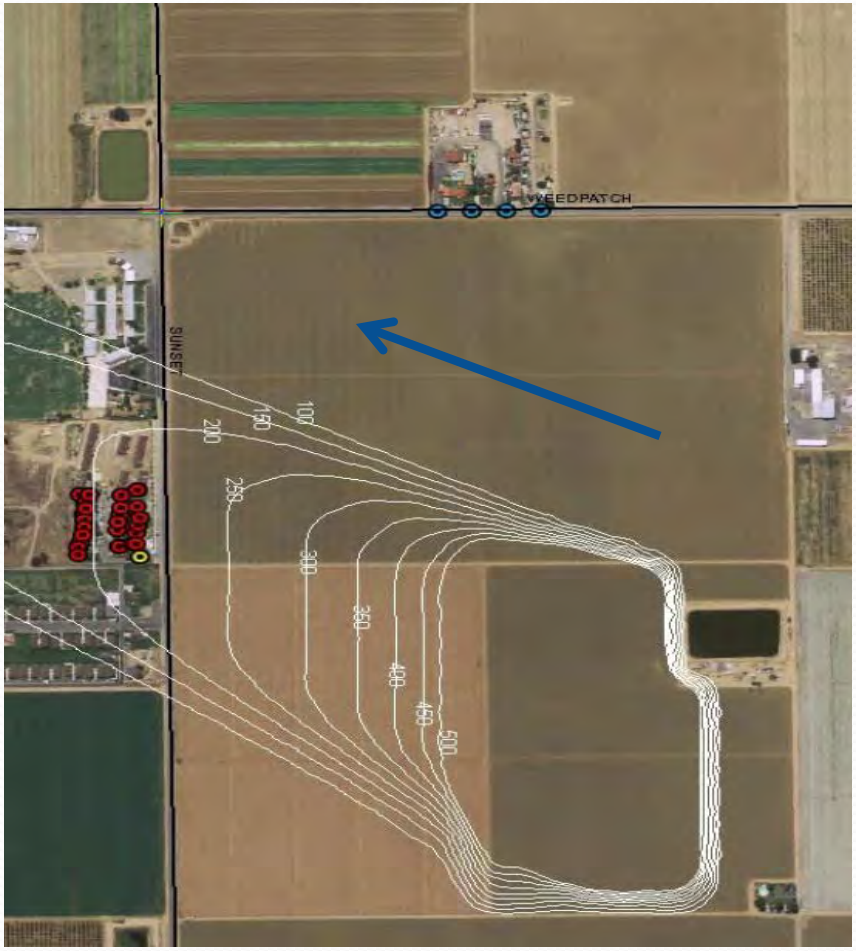
CDPR Sampler

Example of low-volume samplers with personal sample pumps



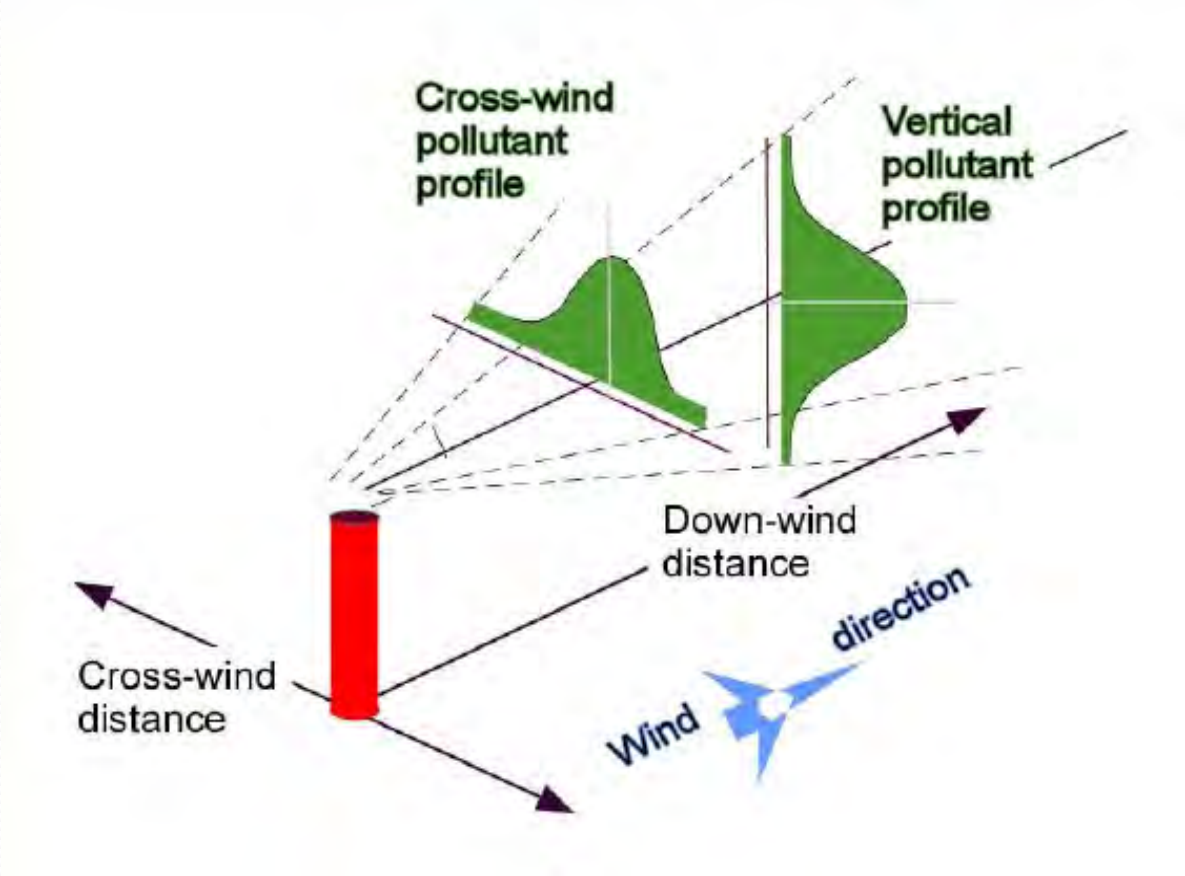
Pesticide Transport Through the Environment
Example: Air dispersion





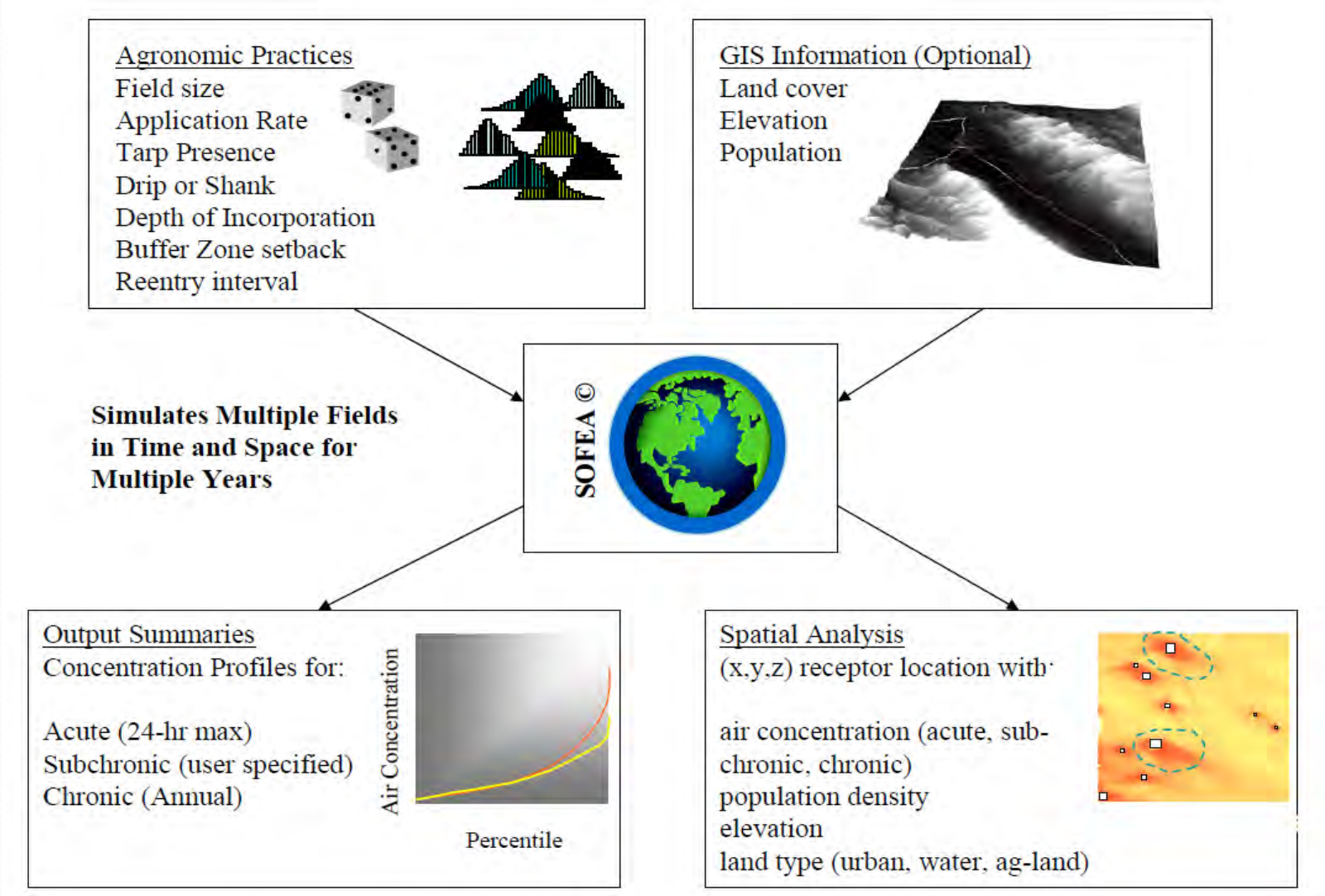
Source: Barry and Johnson, 2011

Air Dispersion Model
Example: Industrial Sources Complex Short Term Version 3 (ISCST3 Model)

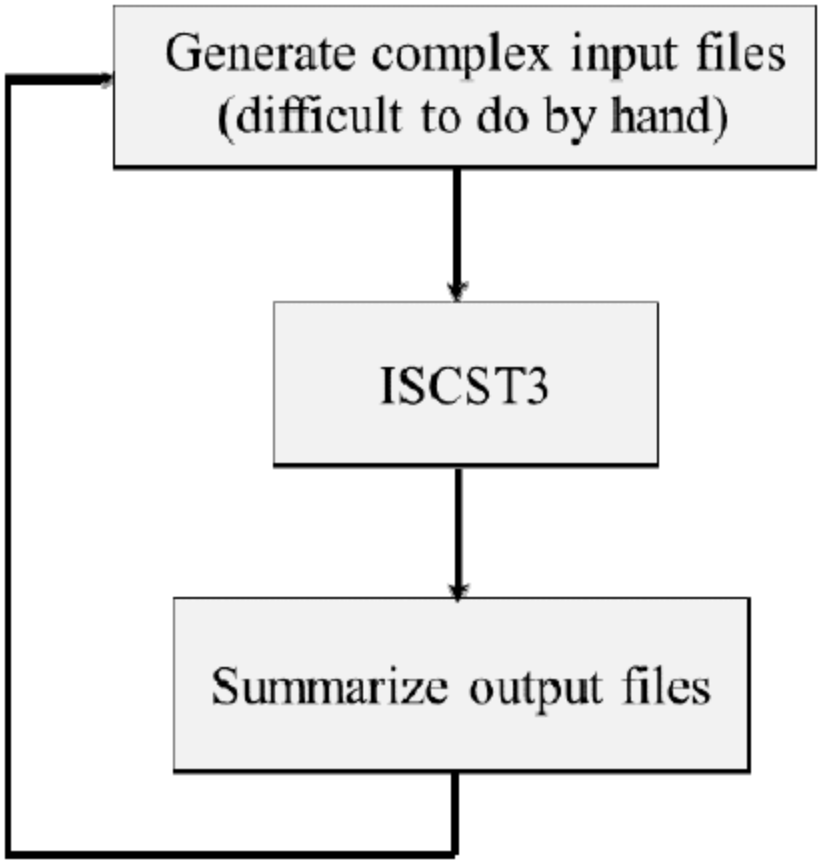


Source: Barry and Johnson, 2011

Soil Fumigant Exposure Assessment System (SOFEA)

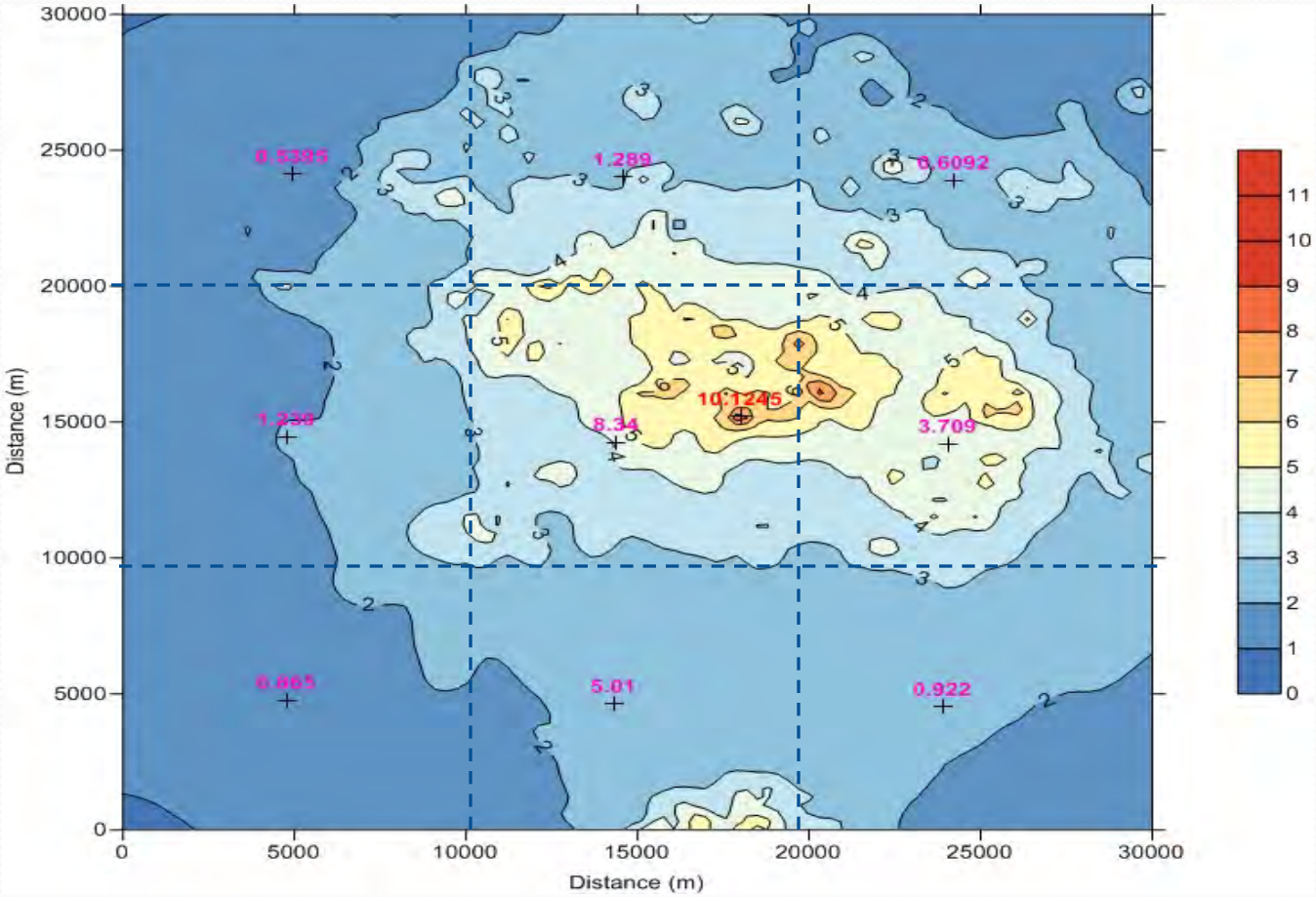


Source: Cryer and van Wesenbeeck, 2015



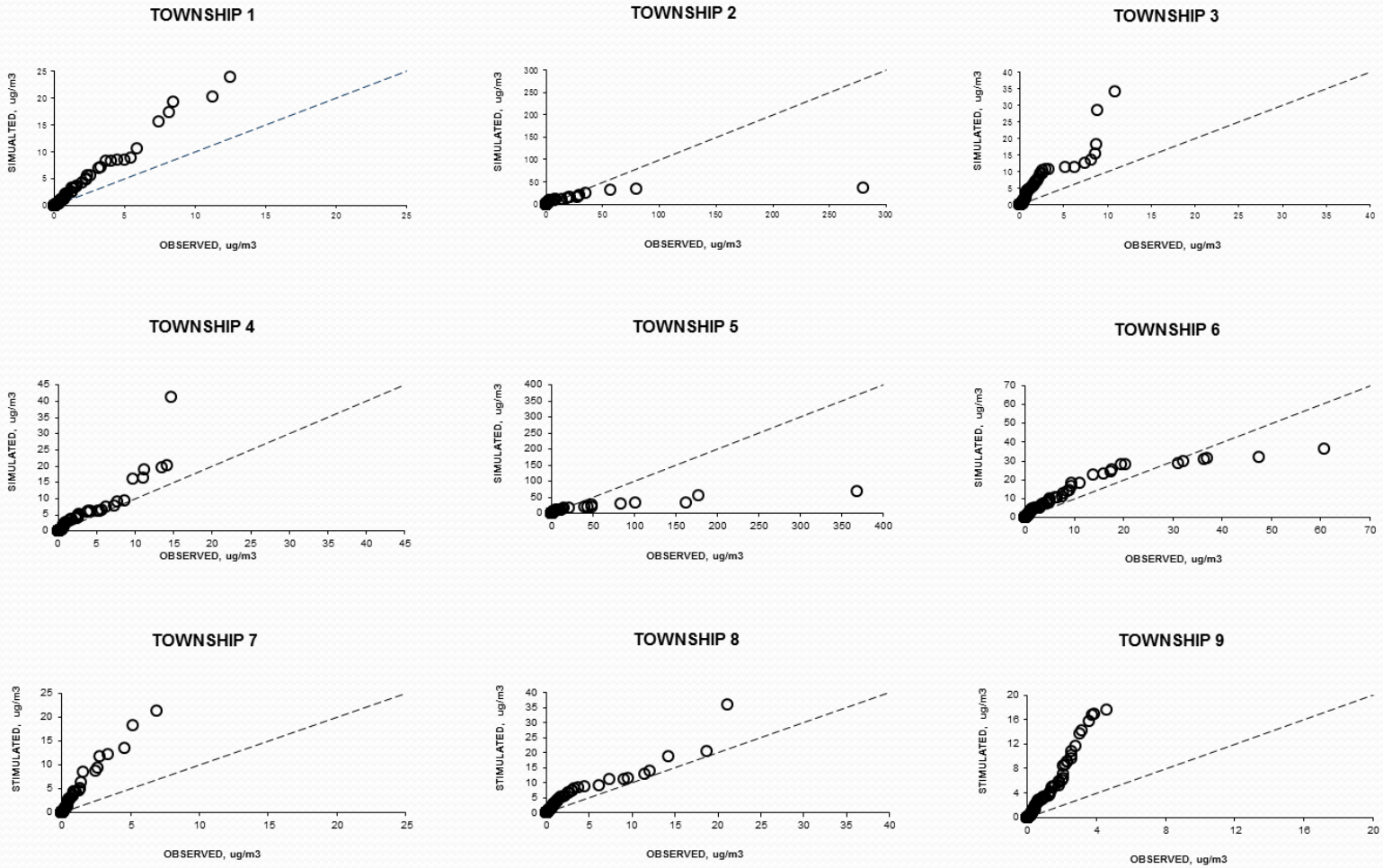
SOFEA is an intelligent input file generator and output repository for agronomic use of the Gaussian plume model ISCST3

Source: Cryer and van Wesenbeeck, 2015



Contour plot of ISCST modeled average 1,3-D air concentrations (μg/m³). Black crosses are the locations of the monitored air concentrations. Purple text are the measured 14.5 month 1,3-D air concentrations (μg/m³).

Source: Barry, 2015

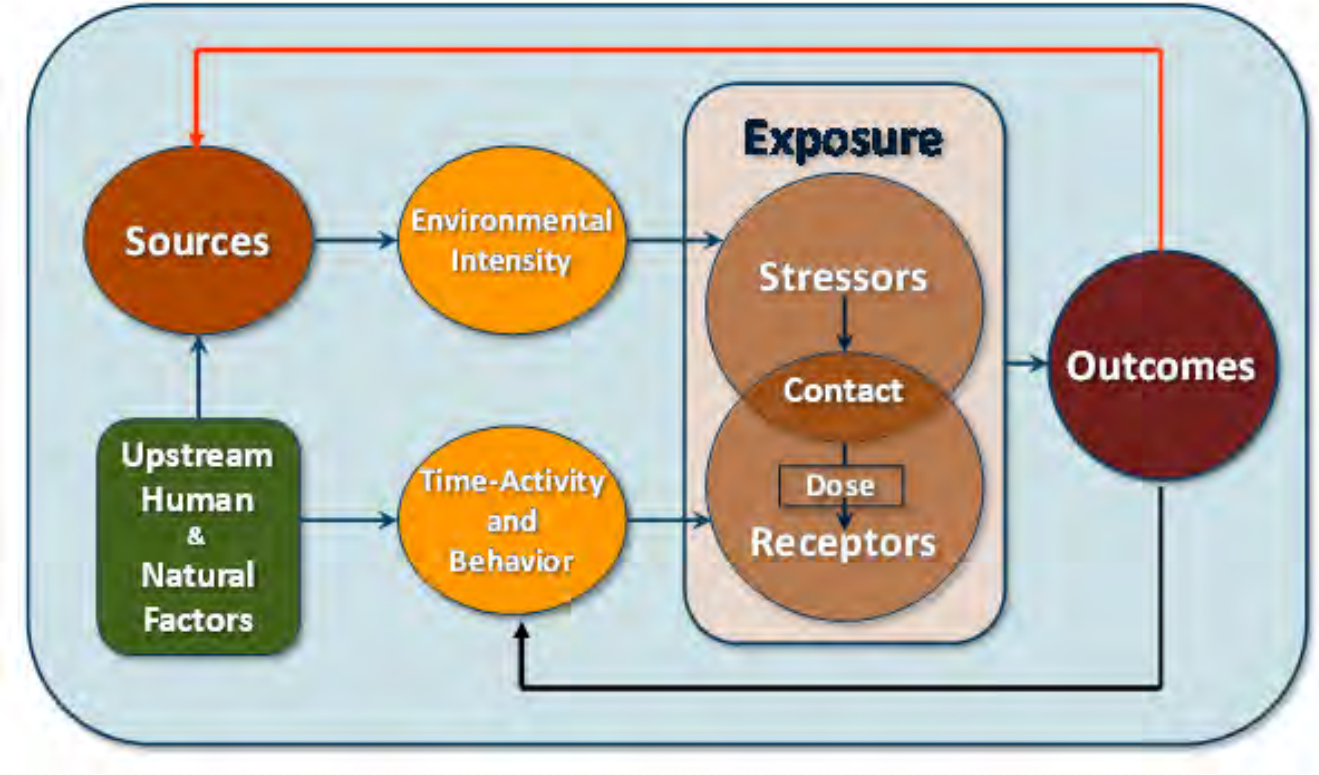


Empirical quantile-quantile plots of the simulated versus observed 72-hour values of 1,3-D concentrations in air at 9 contiguous townships of Merced County, CA.

Exposed Population

Infants, Children, and Adults

Core Elements of Exposure Science

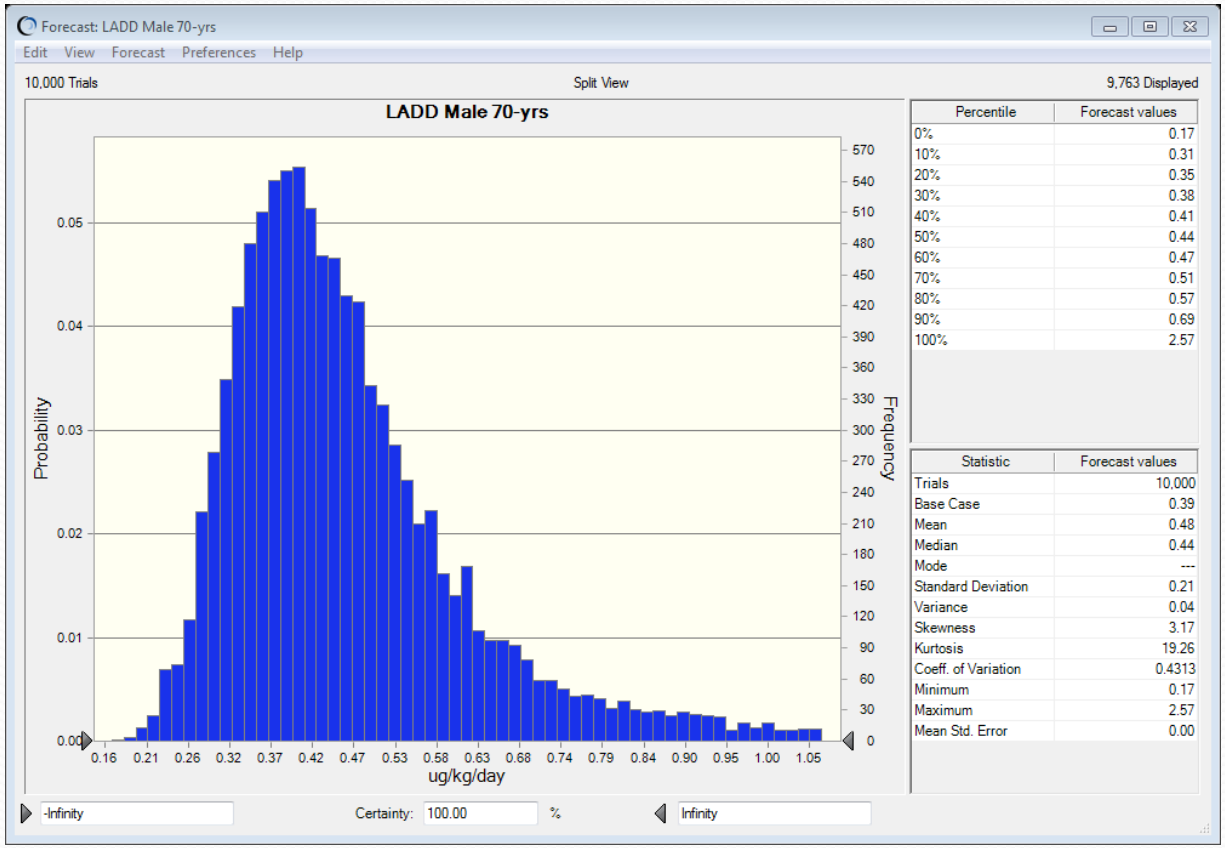


Source: NRC 2012. Exposure science in the 21st century : a vision and a strategy. Washington, D.C.: National Academies Press. pp. xiv, 195 p.

Population-Based Exposure Models

Examples:

1. High End Exposure Version 5 Crystal Ball (HEE5CB) Model
2. Monte Carlo Annual Based estimate of Lifetime Exposure (MCABLE) Model



Percentile	Forecast values
0%	0.17
10%	0.31
20%	0.35
30%	0.38
40%	0.41
50%	0.44
60%	0.47
70%	0.51
80%	0.57
90%	0.69
100%	2.57

Statistic	Forecast values
Trials	10,000
Base Case	0.39
Mean	0.48
Median	0.44
Mode	---
Standard Deviation	0.21
Variance	0.04
Skewness	3.17
Kurtosis	19.26
Coeff. of Variation	0.4313
Minimum	0.17
Maximum	2.57
Mean Std. Error	0.00

Population-Based Exposure Model

$$LADD = \left(\sum_{i=1}^{10} RT_i \left[\frac{Conc_i \times BR_i}{BW_i} \right] \right) \times \frac{1}{70}$$

where the summation is over 10 age intervals,

RT_i = number of years in age interval *i* that the person resides in the high 1,3-D use area,

$Conc_i$ = annual average of air concentrations ($\mu g/m^3$) in 5 locations weighted by the proportion of time spent in each location in interval *i* ,

BR_i = average breathing rate (m^3/day) at each of 4 activity levels weighted by proportion of time spent at each level in interval *i*,

BW_i = body weight (kg) in interval *i*, and 70 years is the assumed lifetime.

Risk Characterization

- Final step: used by the risk manager to develop control or mitigation strategies
- Combines the exposure and the dose response assessment
- For effects other than cancer:
  - Risk is calculated as Margin of Exposures: MOE = NOEL/exposure
  - Estimated MOEs are compared to a target MOE
- For cancer effects:
  - Risk is expressed as the probability of an individual to develop cancer over a life time exposure (e.g., one individual in a million)

Human Studies

- Human Studies
  - Human studies are most useful in risk assessment
  - Rarely available
  - DPR prefers studies that have been approved by USEPA's Human Studies Review Board
- Epidemiology studies, human case reports human illness reports
  - Informative
  - Exposure level is uncertain

Laboratory Animal Studies

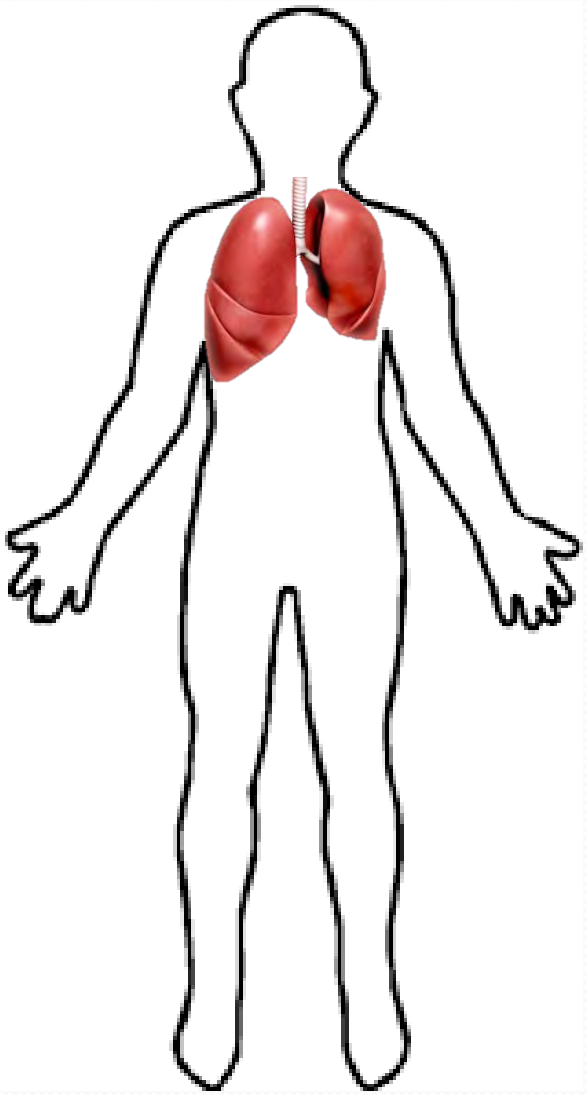
- Required studies for pesticides include dosing by oral, dermal and inhalation routes
  - Routes by which people can be exposed
  - Multiple laboratory animal species
  - Both short and long-term studies
- Look for most sensitive animals and the lowest dose at which health effects appear
- Uncertainties in moving from animals to people
  - High doses in lab *vs.* low exposures in field or from food

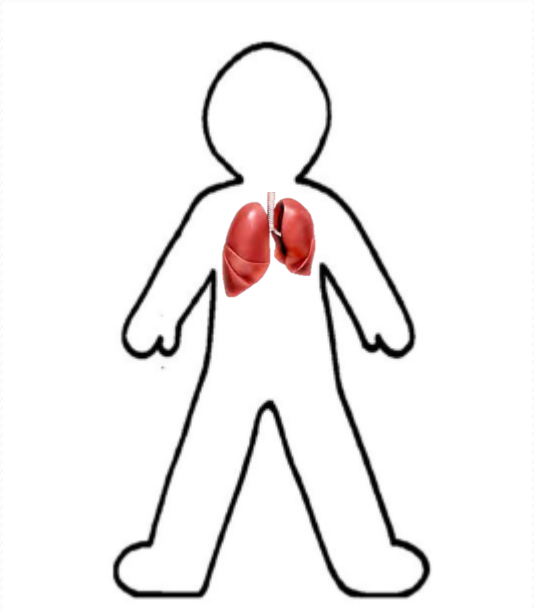
(Photos from National Cancer Institute)

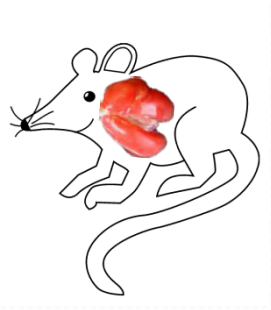
Extrapolating the Dose from Animals to Humans

- Scaling of the dose among and within species:
  - Body weight-based scaling: extrapolating the animal dose to the equivalent human dose based on differences in body weight
  - Target tissue-based scaling: new science allows extrapolation of the animal dose to the equivalent human dose based on the dose at the target organ (e.g., lung)
  - DPR recently employed a target-tissue scaling called Regional Gas Dose Ratio (RGDR) in a fumigant risk assessment

Extrapolating the Dose







Pressures Against Animal Testing

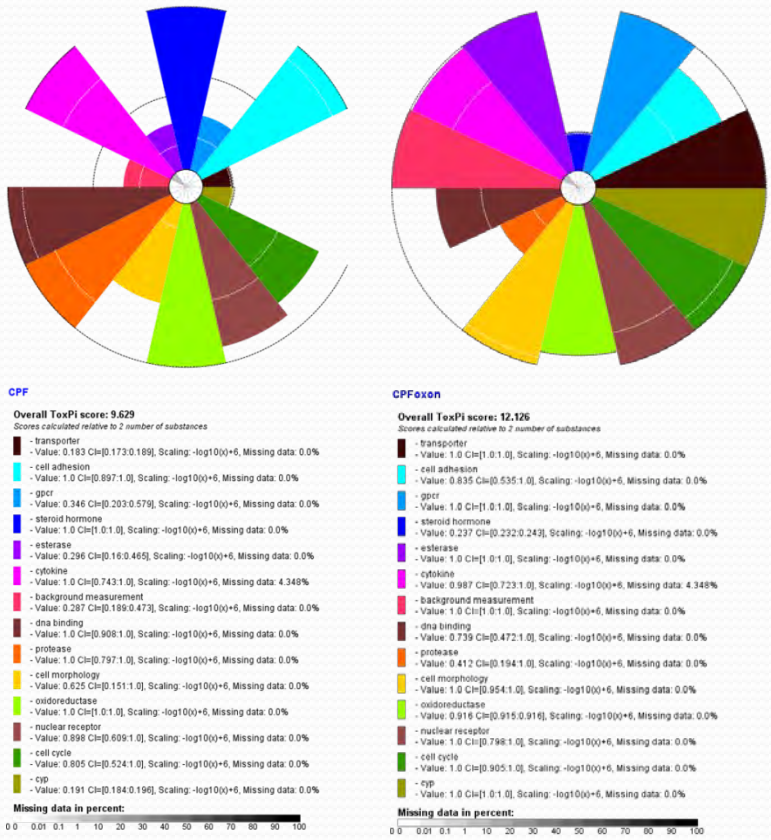
- Animal welfare concerns
- Relevance of animal tests to humans
- Number of chemicals needing risk decisions
  - too many chemicals and not enough data
  - Over 65,000
  - No tox data = 46,000
- Cost of animal studies
  - $2-4 million and 3-5 years for a life time rodent study

New Types of Toxicity Data

- In 2007, NAS published a report on the future of toxicity testing
- Toxicology in the 21st Century (Tox21)
  - Federal program that includes government, universities and industry
  - Develops better toxicity assessment methods; to reduces animal tests
  - Focus is on mechanisms of toxicity
  - Uses cell cultures and biochemical reactions in test tubes (*in vitro*)
  - Automated methods
  - Fast, can test many chemicals
  - Can run many tests on each plate

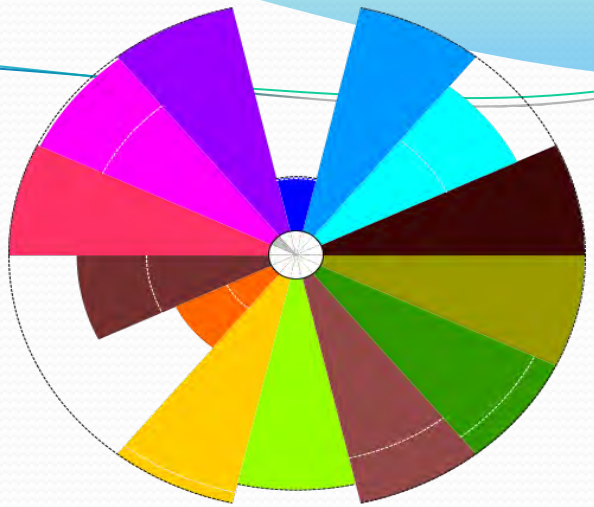
Use of New Toxicity Data

- DPR now receives some *in vitro* toxicity data for pesticides
  - Submitted by the registrants to supplement current toxicity screening procedures
- DPR utilized Tox21 approaches in its three most recent risk assessments



(Image from 2015 Chlorpyrifos Risk Assessment)

Tox21



CPFoxon

Overall ToxPi score: 12.126

Scores calculated relative to 2 number of substances

- transporter
  - Value: 1.0 CI=[1.0:1.0], Scaling: -log10(x)+6, Missing data: 0.0%
- cell adhesion
  - Value: 0.835 CI=[0.535:1.0], Scaling: -log10(x)+6, Missing data: 0.0%
- gpcr
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- steroid hormone
  - Value: 0.237 CI=[0.232:0.243], Scaling: -log10(x)+6, Missing data: 0.0%
- esterase
  - Value: 1.0 CI=[1.0:1.0], Scaling: -log10(x)+6, Missing data: 0.0%
- cytokine
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- background measurement
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- dna binding
  - Value: 0.739 CI=[0.472:1.0], Scaling: -log10(x)+6, Missing data: 0.0%
- protease
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- cell morphology
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- oxidoreductase
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- cell cycle
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- cyp
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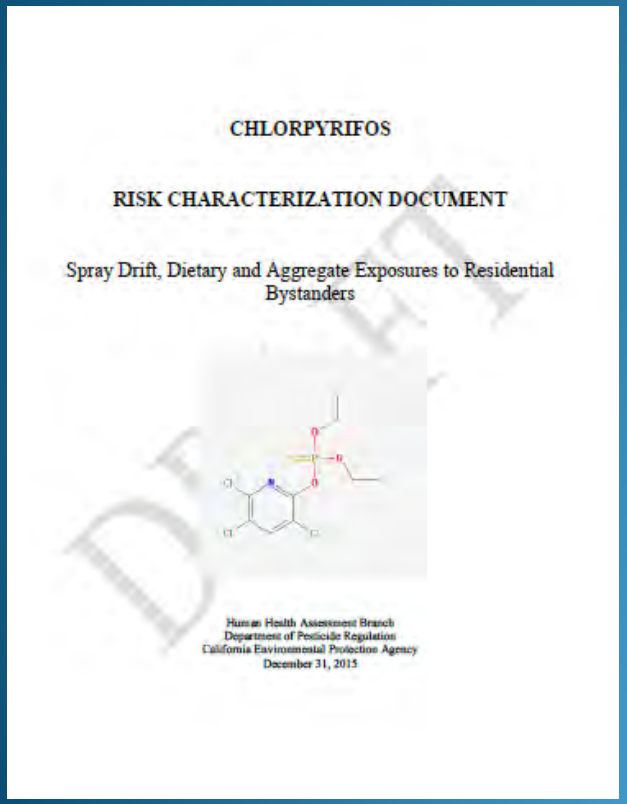
Missing data in percent:

0 0 0.01 0.1 1 10 20 30 40 50 60 70 80 90 100

DPR Latest Risk Assessments

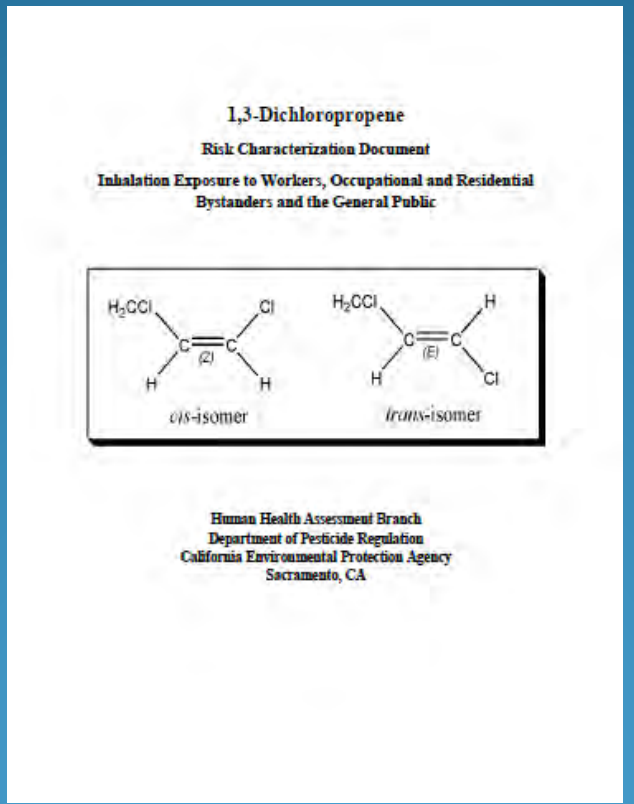


CHLORPYRIFOS

RISK CHARACTERIZATION DOCUMENT

Spray Drift, Dietary and Aggregate Exposures to Residential Bystanders

Human Health Assessment Branch
Department of Pesticide Regulation
California Environmental Protection Agency
December 31, 2015



1,3-Dichloropropene

Risk Characterization Document

Inhalation Exposure to Workers, Occupational and Residential Bystanders and the General Public

cis-isomer *trans*-isomer

Human Health Assessment Branch
Department of Pesticide Regulation
California Environmental Protection Agency
Sacramento, CA

DICROTOPHOS

RISK CHARACTERIZATION DOCUMENT

Occupational and Residential Bystander Exposures
Special Local Need (24c) Registration: Use on Cotton

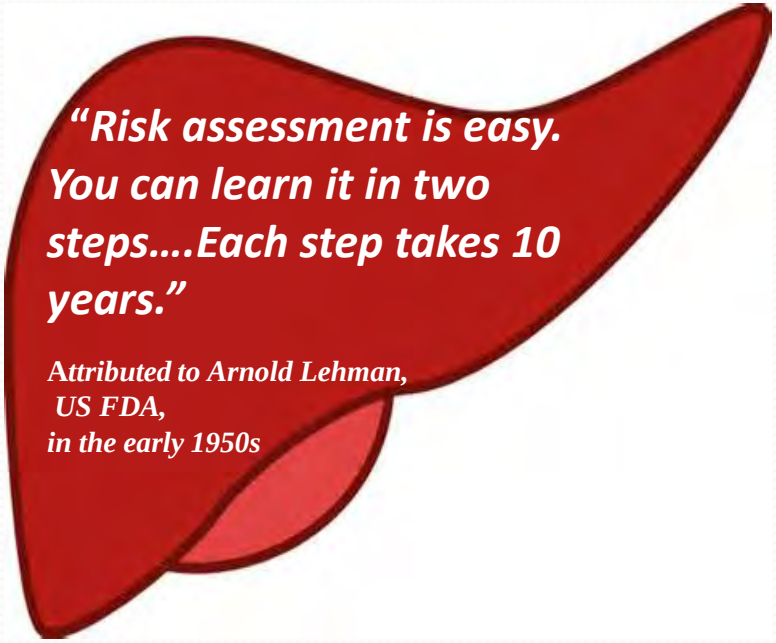
Human Health Assessment Branch
Department of Pesticide Regulation
California Environmental Protection Agency

December 30, 2015

http://www.cdpr.ca.gov/docs/risk/rcd.htm

Conclusions

- New techniques are promising and give us useful information
- A lot of work is still needed before we can rely completely on non-animal methods in risk assessment
- Linkages between old and new are being developed



DPR Scientists win 2016 James G. Wilson Award

A team led by DPR scientists won this year's prestigious James G. Wilson Publication Award for research on use of in vitro cell-based assays, systems toxicity models and computational approaches in predicting pesticide-induced toxic effects, including birth defects