Ecological risk assessment and decision-making: making effective use of data to reduce uncertainty

Alan Raybould, Environmental Safety, Syngenta
"The complexity of ecological systems presents considerable challenges for experiments to assess the risks and benefits and inevitable uncertainties of genetically engineered plants”

...so we need lots of data...
...to improve our decision-making
More data = better decision-making

● This analysis is wrong
  - Risk assessment doesn’t have to be complex
  - Scientific uncertainties are often irrelevant
  - Many data are superfluous or even detrimental to decision-making

● Technical reasons
  - The scientific method: data are only valuable as tests of hypotheses
  - Confusion between risk assessment and basic research: test hypotheses about risk, not about fundamental truths

● Non-technical reasons
  - Decision-making requires judgement
  - Policy uncertainties are more important than scientific uncertainties
  - Scientific analysis cannot replace judgement or policy
Categorisation by harm helps to define the problem

- Risk = seriousness of harm x probability of harm
- ERA need not characterise every possible effect following an action
  - What is the probability that this activity will cause ecological harm? ✓
  - What will happen following this activity? ×
Accurate categorisation often better than precise quantification

Scientific Research

All possible effects

A B C D E F

Risk Assessment

Harmless effects

C E F

Harmful effects

A B D

Probabilities of A, B, C, D, E & F?

Probability of A?
Application to ERA for cultivation of GM crops – composition

● Assessment of unintended changes that might result from transformation
  - Includes compositional analysis

● Adopt a “targeted approach”, not profiling (i.e., don’t measure everything)
  - Measure only compounds that plausibly indicate potential harm
    • e.g., gossypol in cotton
  - Measure as precisely as necessary to make a decision
    • No higher than the isoline? Within range of similar varieties?
    • Below the concentration known to be harmful?

● If potentially harmful unintended changes are identified, assess the risk

Uncertainty about the concentration of a compound does not imply uncertainty about risk
Use existing knowledge to reduce data requirements

- Event-specific data also test generic hypotheses
- Event-specific hypothesis:
  - This particular transformation event has not led to potentially harmful unintended effects
- Generic hypothesis about plant transformation and event selection:
  - Transformation and event selection is no more likely to lead to crops with potentially harmful unintended effects than are other methods of introducing, combining and selecting genetic variation
- Unless metabolic pathways are the target of genetic engineering, do we need to keep testing for unintended effects of transformation?

Case-by-case risk assessment does not imply identical study requirements
Adapt (including reduce/waive) requirements as knowledge accumulates
A risk assessment is a test of a hypothesis not a set of new studies
Application to ERA for cultivation of GM crops – management

● Assessment of potentially harmful unintended effects that might result from altered management of a GM crop
  - For example, ecological changes in response to different herbicide use

● As with composition, adopt a targeted approach, not profiling
  - Compare species abundance under GM and non-GM management
  - Measure (or predict) species for which change is, or may indicate, harm
  - Measure as precisely as necessary to estimate the probability of harm
  - Don’t measure every species that can be measured

● If potentially harmful unintended changes are identified, assess the risk
A real example of problems when harm is not defined

- Introduction of GM glyphosate-tolerant maize
- Continual use of glyphosate is likely to change weed populations
Interpretation

● First question: are we measuring something important to ERA?
  - Do we regard changes in weed abundance as potentially harmful?

● Decisions following the FSEs suggest that weeds are seen as important
  - Changes in weed abundance may drive the population dynamics of farmland birds
  - Reduced abundance of farmland birds is regarded as ecological harm

● Second question: what about changes in weed species composition?
  - Are the predicted changes harmful, beneficial or neutral?
  - This depends on the value we place on the various species
  - Sources or bird food, intrinsic value, other considerations…?
Changes in weed composition

- To make progress in the risk assessment of GMHT maize, we need an indication of what changes are regarded as harmful
  - Reduce policy uncertainty (a wider problem than GM crop regulation)
  - Not more research to reduce scientific uncertainty
Disputes about “scientific justification” often concern uncertainty about the reliability of ecotoxicology studies that have detected an adverse effect.

Is this the only source of uncertainty?

Ought an adverse effect in an ecotoxicology study lead directly to a decision not to allow cultivation of a GM crop?

- Would such a decision be “scientifically justified”?
Interpreting ecotoxicology results for decision-making

- Is the result an artefact?
- Studies must be reliable
  - Minimise false positives
    - Good controls
  - Maximise interpretability
    - Purified proteins: reduce confounding effects of other substances
  - Sufficient ability to detect effects
    - Statistical power: regulatory guidelines; historical data; +ve control
    - “Biological power”: test exposure ≥ highest field exposure

Minimise uncertainty through good experimental design: science
Interpreting ecotoxicology results for decision-making

- What is the probability that the adverse effect in the laboratory indicates an adverse effect in the field?
- Well-known in ecology that laboratory experiments overestimate effects
- Exposure is often lower in the field
- Adverse effects on individuals may not adversely affect populations
  - e.g., density-dependence; recovery

Minimise uncertainty through refined exposure assessments, higher tier effects tests and models of population dynamics: science
Interpreting ecotoxicology results for decision-making

- What is the probability that the adverse effect on populations is ecologically relevant?

![Bar chart showing measures of population size or ecological function for GM crop, Non-GM near isolate, Variety A, Variety B, and Variety C.]

Minimise uncertainty through better knowledge of existing effects: science
Interpreting ecotoxicology results for decision-making

- Is the ecologically relevant effect harmful?

Minimise uncertainty through clear definitions of harm: policy
Interpreting ecotoxicology results for decision-making

- Is the harmful effect unacceptable?

Minimise uncertainty through clear decision-making criteria: policy
Adverse effects in studies

Is the effect real?

Does it indicate an adverse effect in the field?

Is the effect in the field ecologically relevant?

Is the ecologically relevant effect harmful?

Is the harmful effect unacceptable (and cannot be managed)?

Ban cultivation of the GM crop

Science

Policy

Regulatory decisions are not solely scientific
Potentially misleading to talk of scientific justification for decisions
A famous example – Cry1Ab maize and the monarch butterfly

- Losey et al. 1999
  - *Nature* 399: 214
Is the result an artefact?

- Unlikely given what is known about Cry1Ab
  - Toxic to Lepidoptera

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**Monarch larvae sensitivity to Bacillus thuringiensis-purified proteins and pollen**

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**Table 1. Comparative toxicity of the four Bt endotoxins tested against D. plexippus larvae on artificial diet**

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Instar</th>
<th>n</th>
<th>LC_{50} (95% FL)*</th>
<th>EC_{50} (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cry1Ab</td>
<td>1st</td>
<td>318</td>
<td>3.3 (2.2–4.8)</td>
<td>0.8 (0.6–0.9)</td>
</tr>
<tr>
<td></td>
<td>2nd–3rd</td>
<td>141</td>
<td>35.1 (30–100)</td>
<td>9.6 (6.0–15)</td>
</tr>
<tr>
<td></td>
<td>3rd–4th</td>
<td>125</td>
<td>&gt;100‡</td>
<td>18.3 (9.4–40)</td>
</tr>
<tr>
<td>Cry1Ac</td>
<td>1st</td>
<td>192</td>
<td>13.8 (3.0–26)</td>
<td>0.9 (0.9–1.0)</td>
</tr>
<tr>
<td>Cry9C</td>
<td>1st</td>
<td>164</td>
<td>316 (203–428)</td>
<td>34.9 (22–55)</td>
</tr>
<tr>
<td>Cry1F</td>
<td>1st</td>
<td>62</td>
<td>&gt;30,000‡</td>
<td>5,220 (2930–8520)</td>
</tr>
</tbody>
</table>

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* Nanograms of Cry1Ab per milliliter treated artificial diet. FL, fiducial limit.
† Concentration of Cry1Ab that produces 50% growth inhibition relative to untreated controls. Calculated by nonlinear regression fitted to a probit model. CI, confidence interval.
‡ Highest concentration tested.
What is the probability of an adverse effect in the field?

● Characterise the adverse effect:
  - Relationship between maize pollen density and reduced survival and growth

● Characterise exposure:
  - Density of maize pollen on milkweed – the monarch’s food plant
What is the probability of an adverse effect in the field?

Impact of \textit{Bt} corn pollen on monarch butterfly populations: A risk assessment

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- “Risk” (\(R\)) is the probability of exposure of the final generation of monarch larvae to amounts of \textit{Bt} pollen that have an adverse effect on individuals
- At highest predicted adoption rates, \(R = 0.0041\) for all \textit{Bt} maize events at the time of the assessment
- Up to 0.41\% of monarch larvae will suffer an adverse effect from \textit{Bt} pollen
  - Mortality or reduced growth
What is the probability of an adverse effect in the field?

- Not clear that the population size of monarchs will be reduced
  - For example, density dependence may mean that there is compensation for reduced survival and growth of larvae near maize.

- However, to be conservative, we could assume that reduced larval growth and survival will cause reduced population size
  - (Or we could decide that reduced larval growth and survival are ecologically adverse effects in themselves)

- Likely that $Bt$ maize causes ecologically adverse effects to monarchs

- Are those adverse effects ecologically relevant?
  - *i.e.*, outside the range prior to the introduction of $Bt$ maize
Is the adverse effect ecologically relevant?

- If conventional pesticides have adverse effects on monarchs, and *Bt* maize reduces pesticide use, the adverse effect of *Bt* maize vs untreated conventional maize may not be ecologically relevant.
Would an ecologically relevant effect on monarchs be harmful?

- The monarch is not a threatened or endangered species
  - Therefore it is not explicitly protected under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
  - The US EPA regulates *Bt* maize because *Bt* toxins produced in GM crops are regarded as pesticides under FIFRA

- The US EPA refers to “risks to monarchs”
  - Risk could mean “the probability of adverse effects on monarchs”
  - Or it could mean that “the US EPA regards ecologically relevant adverse effects to monarchs as being ecologically harmful”

- Not entirely clear that ecologically relevant adverse effects to monarch populations is ecological harm
Would ecological harm to monarchs be unacceptable?

- Ecological harm to monarchs would not necessarily be unacceptable
  - Opportunities may be considered to outweigh the risks
Inferred US EPA decision-making

Is the effect real?

\[ \downarrow \]

Does it indicate an adverse effect in the field?

\[ \downarrow \]

Would that adverse effect be ecologically relevant?

\[ \downarrow \]

Would an ecologically relevant effect be harmful?

\[ \downarrow \]

Would a harmful effect be unacceptable?

\[ \downarrow \]

Ban cultivation of the GM crop?

\[ \downarrow \]

Yes

\[ \downarrow \]

Yes, but it’s likely to be small

\[ \downarrow \]

Probably not

\[ \downarrow \]

Not necessarily

\[ \downarrow \]

Not necessarily

\[ \downarrow \]

No
Relevance for the EU

- The monarch is *highly* sensitive to Cry1Ab
- 50% of its breeding habitat is in the corn belt
- Its food plant occurs in and adjacent to maize fields
- Yet still any adverse effect of Cry1Ab maize on monarchs is almost certainly minimal (compared with conventional maize managed identically) and is unlikely to be ecologically relevant
- Any ecologically relevant adverse effects to monarch populations may not be regarded as ecologically harmful, nor harmful effects unacceptable

Does the monarch risk assessment protect European butterflies and moths?
Relevance of the monarch risk assessment for the EU

European butterflies sensitive to Cry1Ab?
  ↓
Does sensitivity indicate an adverse effect in the field?
  ↓
Is the adverse effect in the field ecologically relevant?
  ↓
Would an ecologically relevant adverse effect be regarded as harmful?
  ↓
Would harmful effects be unacceptable?
  ↓
Make a decision using monarch data, or ask for more research?
  ↓
Yes, but most (all?) less so than monarchs
  ↓
Perhaps, but it’s likely to be small unless toxicity and/or exposure >> monarch
  ↓
Highly unlikely unless toxicity and/or exposure >> monarch
  ↓
A policy question: which butterflies are valued at least as much as monarchs?
  ↓
A policy question: how to trade-off opportunities and risks?
  ↓
Not solely a scientific question
Conclusions

● There are two main sources of sources of uncertainty in ERA
  - Scientific uncertainty: the likelihood and magnitude of effects
  - Policy uncertainty: definitions of harm and decision-making criteria

● Definitions of harm are essential to focus the ERA and decision-making
  - Some scientific uncertainties are irrelevant to the ERA
  - If no plausible mechanism by which a factor may cause harm, uncertainty about its value does not imply uncertainty about risk
  - If a factor may cause harm, accurate categorisation of its likely effect into harmful or harmless may be sufficient

● Uncertainty about policy objectives cannot be reduced by science
  - Don’t use quantitative risk assessment as a displacement activity for setting policy objectives and decision-making criteria

More scientific research is not necessarily the right response to uncertainty