# Pesticide Risk Mitigation Engine

## Avian Acute Risk Index

### White Paper

## Summary

This index measures the probability that a pesticide application will provide conditions conducive to a bird kill here defined as the finding of any compound-related mortality. It makes use of an unbiased measure of pesticide toxicity derived from laboratory acute gavage studies, principles of species-sensitivity distributions and scaling of toxicity to body mass. This toxicity measure and the application rate are used as a joint predictor in a logistic model based on a large sample of agricultural field studies where avian carcass searching was carried out.

## Data Sources

A detailed description of procedures to develop a standard toxicity value representative of all bird species is given in Mineau *et al.* (2001). Avian risk assessment of pesticides depends for the most part on two laboratory-derived measures of lethality:

- The median Lethal Dose ($LD_{50}$), a statistically derived single oral dose of a compound which will cause 50% mortality of the test population;
- The median Lethal Concentration ($LC_{50}$) which similarly derives the concentration of a substance in the diet which is expected to lead to 50% mortality of the test population.

Mineau *et al.* (1994a) have argued against the continued use of $LC_{50}$ endpoints in avian risk assessment of pesticides. The test, as currently designed, was found to provide unreliable results due in part to the difficulty of properly determining exposure during the test. The $LC_{50}$ test is typically conducted on very young birds and is greatly influenced by the age and condition of the test population. Also, the correlation of $LC_{50}$ values among test species is weak thus casting further doubt on the value of these endpoints for extrapolation purposes. Finally comparison of test results with field evidence (e.g. the extensive kill record with the insecticide diazinon despite high $LC_{50}$ values in same-aged birds - Mineau et al. op.cit.) suggests that lab-derived $LC_{50}$s are poor predictors of risk. Until the $LC_{50}$ test is redesigned to address these weaknesses, avian risk assessment will depend almost entirely on the results of the $LD_{50}$ test.

New pesticides are customarily tested against no more than one to three bird species; however, for some older products, many more species have been tested. The goal is to maximise the use of this older information while not biasing the comparison of these older products with newer ones. A distribution-based method is used, fitting available toxicity endpoints to a mathematically-defined distribution, typically a log normal distribution (Posthuma *et al.* 2002). Two modifications of this technique were applied: 1) Introducing a scaling factor for body weight to improve cross-species comparisons of toxicological susceptibility (Mineau *et al.* 1996); and 2) Developing a small sample strategy to deal with chemicals for which there are insufficient data. The database of avian acute reference values in Mineau *et al.* (2001) is already available on the web at:

http://www.abcbirds.org/abcprograms/policy/pesticides/aims/aims/toxicity.cfm

More recent pesticides were assessed on a case by case basis. It is unlikely for these newer compounds to have data from a large number of species. A small sample approach is therefore the norm. Factors are applied to either single $LD_{50}$ values or geometric means of several values to obtain an estimated $HD_5$ (Hazardous Dose 5 - the $LD_{50}$ value at the 5% tail of the species sensitivity distribution) in line with the scaled values given in Mineau *et al.* (2001). The factors are reproduced from Mineau *et al.* 2001 in the following table.

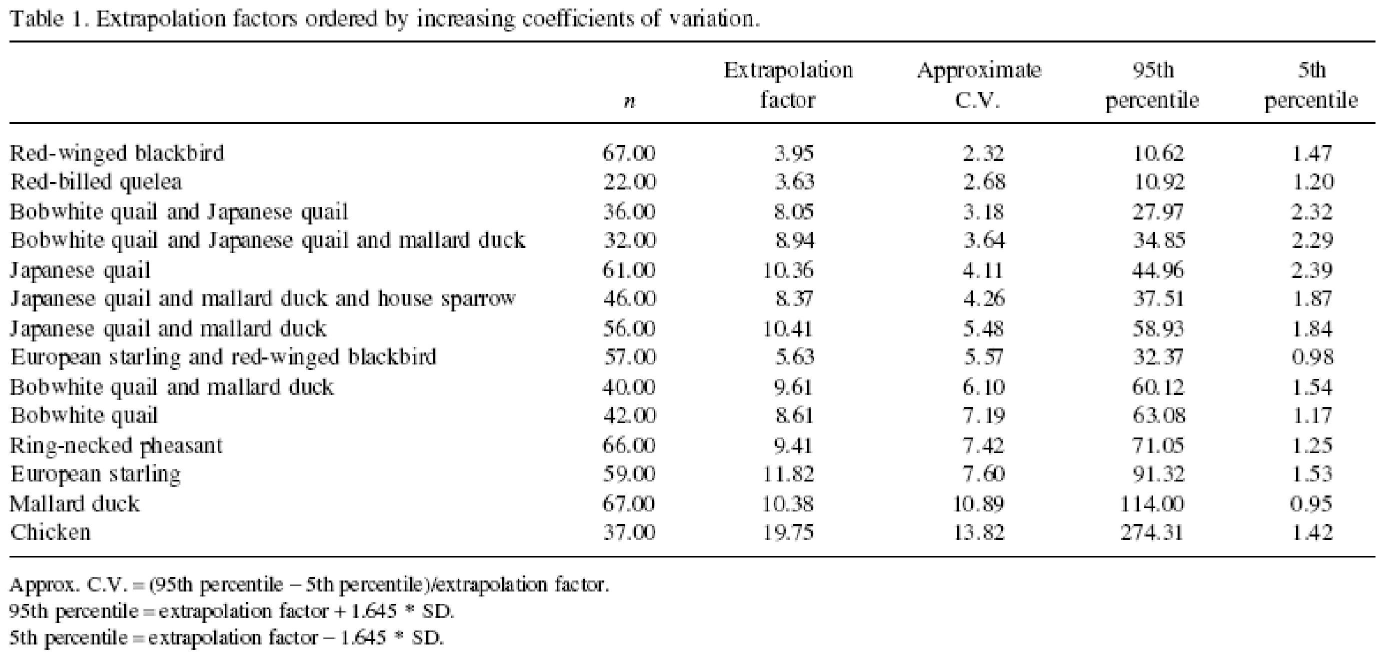


Table 1. Extrapolation factors ordered by increasing coefficients of variation.

| | *n* | Extrapolation factor | Approximate C.V. | 95th percentile | 5th percentile |
|---|---|---|---|---|---|
| Red-winged blackbird | 67.00 | 3.95 | 2.32 | 10.62 | 1.47 |
| Red-billed quelea | 22.00 | 3.63 | 2.68 | 10.92 | 1.20 |
| Bobwhite quail and Japanese quail | 36.00 | 8.05 | 3.18 | 27.97 | 2.32 |
| Bobwhite quail and Japanese quail and mallard duck | 32.00 | 8.94 | 3.64 | 34.85 | 2.29 |
| Japanese quail | 61.00 | 10.36 | 4.11 | 44.96 | 2.39 |
| Japanese quail and mallard duck and house sparrow | 46.00 | 8.37 | 4.26 | 37.51 | 1.87 |
| Japanese quail and mallard duck | 56.00 | 10.41 | 5.48 | 58.93 | 1.84 |
| European starling and red-winged blackbird | 57.00 | 5.63 | 5.57 | 32.37 | 0.98 |
| Bobwhite quail and mallard duck | 40.00 | 9.61 | 6.10 | 60.12 | 1.54 |
| Bobwhite quail | 42.00 | 8.61 | 7.19 | 63.08 | 1.17 |
| Ring-necked pheasant | 66.00 | 9.41 | 7.42 | 71.05 | 1.25 |
| European starling | 59.00 | 11.82 | 7.60 | 91.32 | 1.53 |
| Mallard duck | 67.00 | 10.38 | 10.89 | 114.00 | 0.95 |
| Chicken | 37.00 | 19.75 | 13.82 | 274.31 | 1.42 |

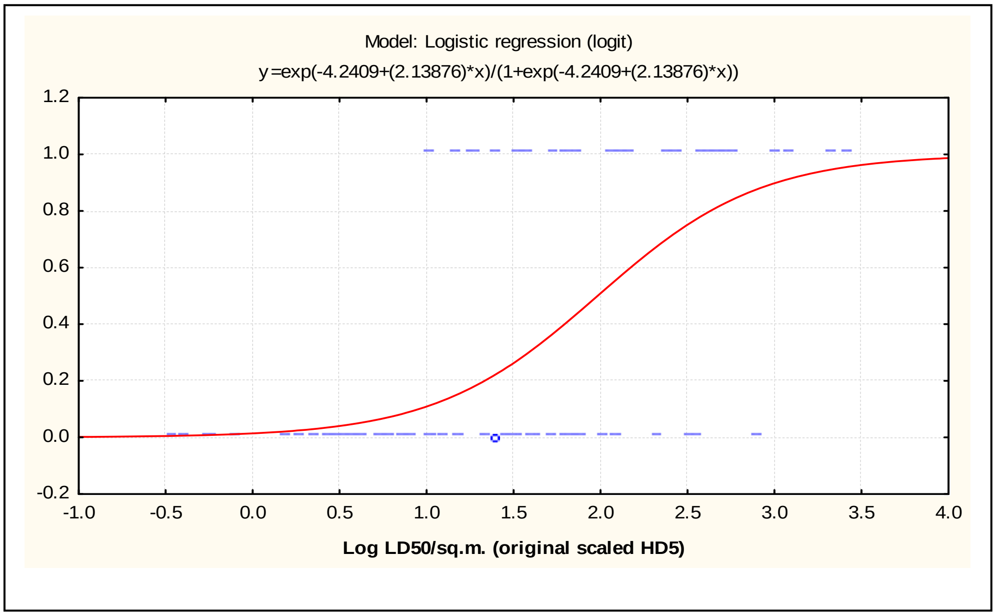
Approx. C.V. = (95th percentile – 5th percentile)/extrapolation factor.
95th percentile = extrapolation factor + 1.645 * SD.
5th percentile = extrapolation factor – 1.645 * SD.

**Index Structure**

Whereas it is customary to have some form of Toxicity/Exposure Ratio (TER) or Risk Quotient (RQ) at the core of most indicators for avian risk assessment, this ignores the fact that we now have a reasonable sample of field studies on which to base a standard for avian acute effects. The first analysis of that body of work was published by Mineau (2002). Insecticides (invariably cholinesterase-inhibiting compounds) were applied to various crops or on forests and the impact on birds measured through a combination of carcass searches and/or cholinesterase inhibition measurements. Several risk models were developed incorporating a toxicity component and application rate as well as other predictors built-up from several physico-chemical measures. All models were based on a logistic regression – a probability of impact was given based on toxicity and application rate, sometimes aided by a physico-chemical constant that appeared to better define non-dietary sources of exposure. Because the models were based on empirical data – actual field studies – there is much less uncertainty with the results than there is with the more standard approach to risk assessment.

**Details and Algorithms**

Models developed in Mineau (2002) were modified to take into account the addition of a few more field studies and a recent re-evaluation of all the component agricultural studies by a panel of four evaluators mandated by the European Food Safety Authority (EFSA 2008). Mineau (2002) argued for the importance of dermal exposure when assessing the field data; however, because of the uncertainty surrounding dermal exposure to non-cholinesterase-inhibiting pesticides (EFSA op. cit.), the algorithm used for our indicator considered only the toxicity of the various pesticides to birds (here the $HD_5$) in arriving at a probability of kill. The data used to generate the final algorithm are shown here:



… where studies scoring 0 are those where pesticide-related avian mortality was not deemed to have taken place and 1 where some (unquantified) mortality had taken place.

The final algorithm proposed for our avian indicator gives P as the probability that an application will give rise to avian mortality as follows:

$$\boxed{p = \left( \frac{e^{a+bx)}}{1 + e^{a+bx)}} \right)}$$

…where x is the number of TUs (Toxic Units expressed as the base 10 logarithm of the number of $HD_5$ equivalents applied per meter square of field).

- TUs = $\log_{10} [(AR/10)/HD_5]$ (The factor of 10 is merely there to ensure the TUs are expressed as the number per meter square)
- AR = Application rate in g a.i./ha
- HD5 is in mg/kg bw
- a = -4.2409
- b = 2.13876

For example, a probability of 0.20 indicates that, given the existing corpus of avian field studies (over 100 such studies conducted in agricultural landscapes – combining orchard and field crop studies - were compiled for assessment), we would expect to find avian mortality approximately in 1 in 5 applications. It was recently argued (Mineau *et al.* 2009), based on a comparison of these risk ratings with poisoning incidents that a probability of kill of greater than 10% is associated with incidents; probabilities of kill calculated to fall below 10% will be considered to be *de minimus* and not carry any real risk of mortality. On the other hand, probabilities of mortality of 50% or more are typically associated with products having extensive kill records; this threshold will denote products carrying an extreme risk.

The same algorithm was applied to both liquid and granular applications with the addition of Use Pattern Adjustment Factors (UPAFs). These factors were developed through expert opinion in the context of the PEAS indicator (Mineau 2004) and are meant to be multipliers of $p$. At this stage, seed treatments are not considered – they combine an extremely low application rate per hectare with a very high risk per seed placing them outside of the models developed.

## UPAFs for Avian acute risk index

| Pre-Plant or Pre-Emergence | | | Post-Emergence | | Either |
|---|---|---|---|---|---|
| Soil Applied: Liquid | Soil Applied: Granular | Soil Applied:<br>Unspecified | Ground Foliar Applied | Soil Applied: Liquid | Aerial Application |
| 0.5 (surface)<br>0.1 (sub-surface)<br>0 (application followed by tarping) | See below | 0.5 | 1 | 0.5 (surface)<br>0.1 (sub-surface) | 1 |

| Silica granules | Corn cob (organic) granules | Heat treated montmorillonite and other non friable clays, cellulose | Friable granule bases: bentonite and gypsum | Tarping follows granular application |
|---|---|---|---|---|
| 2.0 | 1.0 | 0.2 | 0.1 | 0 |

**Literature cited ( Note : Author's articles and reports available upon request)**

EFSA. 2008. Scientific Opinion of the Panel on Plant protection products and their residues on a request from the EFSA PRAPeR Unit on risk assessment for birds and mammals. The EFSA Journal (2008) 734, 1-181.

Mineau, P., B. Jobin, A. Baril. 1994. A critique of the avian 5-day dietary test (LC50) as the basis of avian risk assessment. Technical Report Series. No. 215. Environment Canada, Canadian Wildlife Service, Ottawa. 23 pp.

Mineau, P., B.T. Collins and A. Baril. 1996. On the use of scaling factors to improve interspecies extrapolation of acute toxicity in birds. Regulatory Toxicology and Pharmacology 24:24-29.

Mineau, P., A. Baril, B.T. Collins , J. Duffe, G. Joerman, R. Luttik. 2001. Reference values for comparing the acute toxicity of pesticides to birds. Reviews of Environmental Contamination and Toxicology 170:13-74.

Mineau, P. 2002. Estimating the probability of bird mortality from pesticide sprays on the basis of the field study record. Environmental Toxicology and Chemistry 24(7):1497-1506.

Mineau, P. 2004. PEAS-AR: An index of pesticide acute risks to birds. Version 2004.2. Unpublished Report to Benbrook Consulting, dated 24 August 2004. 9 pp.

Mineau, P., T. Dawson, M. Whiteside, C. Morrison, K. Harding, L. Singh, T. Längle, and D.A.R. McQueen. 2009. Environmental Risk-Based Standards for Pesticide Use in Canada. National Agri-Environmental Standards Initiative Synthesis Report No. 7. Environment Canada. Gatineau, Quebec. 94 p.

Posthuma, L., G.W. Suter II, T.P. Traas. 2002. Species Sensitivity Distributions in Ecotoxicology. Lewis Publishers, Boca Raton, Florida. 587 pp.

**Appendix 1.** Comparison of proposed avian acute scores calculated with a sample of in use pesticides in apples and the NASS-determined national average application rate. Scores are given in decreasing order of risk. This is for illustration purposes only since actual scores will depend on actual application rates entered into PRiME. Also, these are raw scores without any mitigating UPAF.

| AI Accepted Name | NASS Average Application Rate (g ai/ha) | Acute Risk to Avian Species |
|---|---:|---:|
| Diazinon | 1685.98 | 0.73 |
| Phosmet | 1803.69 | 0.60 |
| Chlorpyrifos | 1683.74 | 0.33 |
| Azinphos-methyl | 932.67 | 0.31 |
| Oxamyl | 236.53 | 0.26 |
| Dimethoate | 1268.97 | 0.20 |
| Endosulfan | 1634.42 | 0.17 |
| Formetanate HCL | 858.69 | 0.16 |
| Captan | 2228.55 | 0.10 |
| Methomyl | 589.65 | 0.08 |
| Copper oxychloride | 2831.65 | 0.07 |
| Carbaryl | 1249.92 | 0.05 |
| 2,4-D, dimeth salt | 1095.22 | 0.04 |
| Paraquat | 1338.47 | 0.04 |
| Malathion | 3021.10 | 0.03 |
| Copper sulfate | 884.47 | 0.03 |
| Sulfur | 7051.09 | 0.02 |
| Copper hydroxide | 2933.66 | 0.02 |
| Pendimethalin | 1617.60 | 0.02 |
| Metiram | 2898.91 | 0.02 |
| Imidacloprid | 96.41 | 0.02 |
| Diuron | 1663.56 | 0.01 |
| Dodine | 896.80 | 0.01 |
| Acetamiprid | 164.79 | 0.01 |
| Glyphosate iso salt | 1337.35 | 0.01 |
| Chlorothalonil | 1460.66 | 0.01 |
| Mancozeb | 2999.80 | 0.01 |
| 2,4-D | 508.93 | 0.01 |
| Terbacil | 925.95 | 0.01 |
| Fosetyl-al | 2738.60 | 0.01 |
| Glufosinate-ammonium | 832.90 | 0.01 |
| Myclobutanil | 143.49 | 0.00 |
| Oxyfluorfen | 1256.64 | 0.00 |
| Simazine | 1592.94 | 0.00 |
| Ethephon | 543.69 | 0.00 |
| Pyridaben | 278.01 | 0.00 |

| | | |
|---|---|---|
| Cyprodinil | 205.14 | 0.00 |
| Spinosad | 116.58 | 0.00 |
| Clofentezine | 232.05 | 0.00 |
| Trifloxystrobin | 73.99 | 0.00 |
| Fenbuconazole | 68.38 | 0.00 |
| Kresoxim-methyl | 124.43 | 0.00 |
| Benzyladenine | 38.11 | 0.00 |
| Pyrethrins | 143.49 | 0.00 |
| Lambda-cyhalothrin | 34.75 | 0.00 |
| NAD | 65.02 | 0.00 |
| NAA | 22.42 | 0.00 |
| Permethrin | 190.57 | 0.00 |
| NAA, Sodium | 13.45 | 0.00 |
| Pyraclostrobin | 1.12 | 0.00 |
| Boscalid | 15.69 | 0.00 |

**Appendix 2: Peer Review Comments**

This white paper was reviewed by the following independent experts. Below are their comments, listed anonymously, along with the author's responses.

- **Rick Bennett,** wildlife toxicologist, US EPA
- **Anne Fairbrother**, senior managing scientist, Exponent
- **Rich Marovich**, staff environmental scientist, California DPR

**General comments:**

- This white paper does a good job of describing the acute risk index which has a solid foundation in the previously published papers.
- I can envision great utility for this approach as a comparative tool for assessing risks among pesticides or between different organism classes. I'm not sure that this tool will necessarily replace any others, but I do think it will be very useful when conducting comparative risk analyses, either among chemicals or between classes of organisms for individual chemicals. It also is a very good communication tool for these types of assessments.
- I find the indexes to be well presented, and that they represent a significant advancement in applied science. I support the design of the avian acute risk index. Strongly agree with reliance on observed avian mortality in the field; strongly agree with statistical comparisons of toxicity and preference for LD50 data.

**Detailed comments and responses:**

**Comment 1:** Page 3, Data Sources section – Do you have reference(s) for the sentence "Finally comparison of test results with field evidence suggests that lab-derived LC50s are poor predictors of risk"? One study that directly compared the lab LC50 results to a comparable field scenario is Matz et al. (1998) Effects of azinphos-methyl on northern bobwhite: A comparison of laboratory and field results. ET&C 17:1364-1370.

> **Response:** *Done but without the added complication of describing the Matz paper.*

**Comment 2:** I agree with Mineau that the LC50 test is an unreliable indicator of risk and concur with using the LD50 values instead. This is a highly repeatable test and is a good measure of relative risk (i.e., comparison of one chemical with another).

**Comment 3:** I like the use of the species sensitivity distribution (SSD) to determine the HC5 as the effect level. However, I disagree with scaling by body weight, despite Mineau's analysis (dose sensitivity is not related to body weight, but rather to metabolic rate and species-specific metabolic processes; I think Mineau's analysis showed how highly variable the relationship of effective dose with body weight is, and I submit that he actually proved why this type of adjustment should not be done). However, because the LD50 is already expressed on a mg/kg-body weight basis, any adjustments based on total body weight will not be necessary. The adjustment for small sample size (using pooled variability) by Luttik et al. is a reasonable approach for approximating a SSD when only a few species have been tested.

> **Response:** *This statement is incorrect. There is a need to distinguish between acute and chronic toxicity endpoints. Looking at several toxicity predictors to see which ones provided the best fit with the 144 field studies tallied in my database, the scaled toxicity predictor did fare slightly*

*better than the unscaled one - although a more substantial model improvement came from using an HD5.*

| Toxicity predictor | AIC | Likelihood ratio Chi 2 |
|---|---|---|
| **Scaled HD5 (Mineau et al. 2001)** | **127.8** | **76.3** |
| **Unscaled HD5 (ETx)** | **128.7** | **75.5** |
| **Geomean all species** | **139.6** | **64.5** |
| **Lowest of BWQ or Mallard** | **144.7** | **59.4** |
| **Mallard** | **171.6** | **32.5** |

**Comment 4:** Field exposure / kills – the important underlying assumption here is that all pesticides have the same "kill" relationships as the cholinesterase inhibitors (OPs and carbamates), since the only field studies that were used were from these chemicals. For the purpose of this (current) model, it appears that the original data from the ET&C paper (Mineau 2002) were combined such that any mortality (groups 3 and 4 in the cited paper) were characterized as an "effect." This seems appropriate for the current model. However, there should be some note that it is likely that the model over estimates effects from other classes of chemicals, such as pyrethroids.

**Response:** *I agree that it will be more difficult to find evidence of field kills with pesticides that take longer to kill. However, given that the model is based on a lethality threshold (HD5) established from laboratory data, it should be as accurate with other chemistries. The reviewer mentions pyrethroids but, surely, the main difference with the latter is their much reduced acute toxicity. In fact no pyrethroids to date return any probability of mortality in the model. I will go further and put forward an opinion diametrically opposite to the reviewer comment. Because there is more likely to be a cumulative toxicity issue with more recently developed pesticides (they tend now to be less acutely toxic but more persistent - both in vivo and in vitro), I believe that the model will more often underestimate effects from classes of pesticides other than OPs and carbamates.*

**Comment 5:** Toxic units are defined as a function of application rate (AR) and the toxicity index. This returns a value with units of # of HD5's per hectare (or acre):

$$\text{TUs} = \text{Log10}\ [(\text{AR}/10)/\text{HD5}]$$

As a relative scale (one pesticide to another), this is reasonable, as it provides a measure of the fraction of the normal application rate that would kill a bird within a specified area (assuming the bird foraged only in that area), adjusted to the relative potency of the pesticide. However, it is not clear (and no explanation is provided) for why the AR is divided by 10.

**Response:** *This is merely to ensure the units come out as stated. A small text was added.*

**Comment 6:** The equation describing the probability of risk is appropriate.

**Comment 7:** I suggest deleting the following: "It was recently argued (Mineau et al. 2009), based on a comparison of these risk ratings with poisoning incidents that a probability of kill of greater than 10% is worthy of concern; probabilities of mortality of 50% or more indicate a critical risk that most probably cannot be mitigated." This support document should provide information only on how the algorithms are derived; it is not appropriate to argue risk management policy here.

> **Response:** *The wording was improved.*

**Comment 7:** I am uncomfortable with the Use Pattern Adjustment Factors without being able to review the analysis in detail. Since this was based on Best Professional Judgment of those involved, it will by its very nature be subjective. Perhaps it would be best if the model itself provided for the user to input a UPAF – the table shown here with the associated reference can be included with the model to provide default values; but the user could change these values if they had better information or a different bias.

> **Response:** *It was decided by the steering group that this would not be appropriate for all users. It would lead to different scores being generated for the same conditions.*

**Comment 8:** Some crops such as rice that are very attractive to birds pose much greater risks than other crops (e.g. cotton).

> **Response:** *Crop attractiveness is currently not a factor in the model. It has been shown that even unattractive crops (e.g. cotton) will have a complement of bird species. This may be grounds for a UPAF-type of correction in the future.*

**Comment 9:** Some mitigation methods such as incorporation of granules reduced mortalities from thousands of birds per year to zero with carbofuran, even as monitoring increased and with advance notice of sites of application.

> **Response:** *Available evidence suggests that rice may be a special case. Attempts to mitigate risk through better granule incorporation have largely failed in field crops.*