Australian Government
Australian Pesticides and Veterinary Medicines Authority

Adverse Experience Reporting Program (AERP)

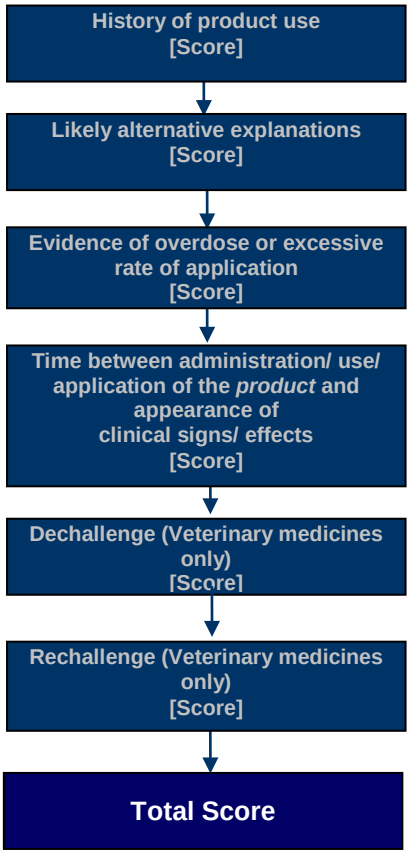
The Causality Assessment Algorithm

GL_AER05

Each registrant should conduct a causality assessment for each adverse experience report (AER). The following algorithm has been adapted from published information and may be used as a guide by registrants to conduct causality assessments of adverse experience reports. If registrants wish to conduct causality assessment using another method, then the results of the assessment must be consistent with the APVMA's requirements.

The APVMA will validate the registrant's assessments using statistical random sampling techniques.

CAUSALITY ASSESSMENT ALGORITHM - FOR VETERINARY MEDICINES



1. Previous experience with product

Assessment	Score
Clinical signs generally recognised to occur in this species at the dose used	+1
Clinical signs are not generally recognised to occur in this species at the dose used, but has been previously reported in veterinary and/or human medicine	0
Product has limited accumulated clinical experience	0
Clinical signs previously unreported and product has substantial accumulated clinical experience	-1

2. Alternative aetiological candidates

Assessment	Score
There is no good alternative that can explain the clinical signs exclusive of product administration	+2
An alternative exists, but does not explain the clinical signs well	0

The clinical signs commonly occur spontaneously in this type of patient and situation, usually in the absence of any recognisable alternative	0
There is a good alternative explanation for the clinical signs exclusive of product administration	-1

3. Evidence of overdose

Assessment	Score
The clinical signs are clearly dose-related and there is unequivocal evidence that the amount of product used was an overdose for this animal	+1
The clinical signs are not dose-related or there is no evidence of an overdose	0

4. Timing of events

Assessment	Score
Timing was consistent and as expected for these types of clinical signs to this product	+1
Do not know what timing to expect	0
Timing was inconsistent for these types of clinical signs to this product	-2

5. Dechallenge

Assessment	Score
Clinical signs diminished or disappear after discontinuation of suspect product or administration of a specific antidote	+1
Clinical signs are known to be dose-related and they diminish after dosage reduction	+1
Dechallenge difficult, impossible or inappropriate to assess	0
A non-specific agent or manoeuvre (non-antidotal was administered that was directed against the clinical sign and that usually produces the degree and rate of improvement observed in this case)	0
Clinical signs characteristically transient and episodic and there is no established pattern episode (regardless of what occurs after discontinuing the product)	0
Clinical signs known to be dose-related and did not diminish or disappear after dosage was reduced	0
Clinical signs did not diminish or disappear after discontinuing suspect product or administration of a specific antidote	-1
Clinical signs improved without dechallenge and the improvement cannot be attributed to the development of tolerance	-1

6. Rechallenge

Assessment	Score
Clinical signs unequivocally recurred or exacerbated after rechallenge	+1
There was no rechallenge	0
A non-specific agent or manoeuvre (non-antidotal) was administered that obscured the response of the clinical signs	0
Clinical signs failed to recur or exacerbate on rechallenge, but the dosage or duration of product administration on rechallenge was substantially less than that suspected of causing the original clinical signs	0
Recurrence or exacerbation of clinical signs was impossible to assess because it was progressing or was at a level of severity that any further increase would be difficult to appreciate	0
Clinical signs failed to recur or exacerbate on rechallenge	-1

Causality Assessment - Veterinary Medicines

The relationship between the use of the veterinary chemical product and the reported clinical signs, assessed after investigation of the incident has been carried out. The relationship is expressed in terms of:

Probable

(Algorithm score 3 to 7)

For inclusion in the category 'probable' all of the following minimum criteria should be met:

- there should be a reasonable association between the administration of the product and onset and duration of the reported adverse experience,
- the description of the clinical signs should be consistent with or at least plausible given the known pharmacology and toxicology of the product, and
- there should be no other equally plausible explanation (or contributing factors) for the clinical signs.

When any of the above criteria cannot be satisfied (due to lack of sufficient information or conflicting data) then the association cannot be assessed as 'probable'.

Probable/Off-label

(Algorithm score 3 to 7)

As per the classification of 'probable' and where there is obvious evidence of off-label use (including use in species not listed on the product label, over-dosing or under-dosing). It is acknowledged that depending on State and Territory legislation, veterinary prescribing

privileges, APVMA Permits and other legal exemptions may allow off-label use in some situations.

Possible

(Algorithm score 0 to 2)

For inclusion in the category 'possible' association of the adverse experience with administration of the primary suspect product is one of other possible and equally plausible explanations (or contributing factors) for the described adverse experience.

Possible/Off-label

(Algorithm score 0 to 2)

As per the classification 'possible' and where there is obvious evidence of off-label use (including use in species not listed on the product label, over-dosing or under-dosing). It is acknowledged that depending on State and Territory legislation, veterinary prescribing privileges, APVMA Permits and other legal exemptions may allow off-label use in some situations.

Unlikely

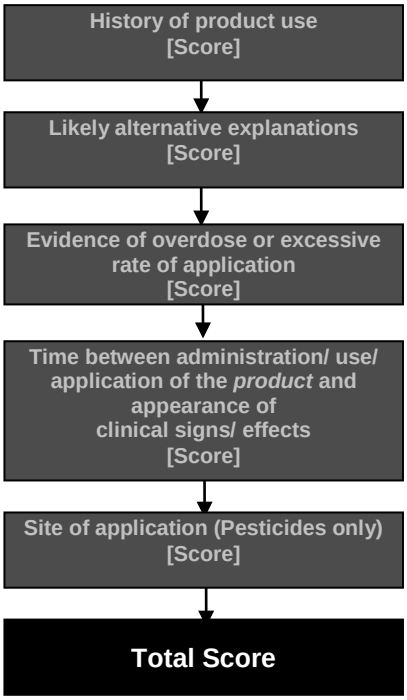
(Algorithm score –1 to –6)

Where sufficient information exists to establish that the described adverse experience was not likely to have been associated with administration of the product(s), or other more plausible explanations exist, the assessment should be categorised as 'unlikely'.

Unknown

All adverse experiences where reliable data is either unavailable or is insufficient to make an assessment should be categorised as 'unknown'.

CAUSALITY ASSESSMENT ALGORITHM - FOR AGRICULTURAL CHEMICALS



1. History of product use

Assessment	Score
Effect is generally known to occur in this crop/situation at the rate/method used	+1
Effect is not known to occur in this crop/situation at the rate/method used, but has been previously reported in other crops/situations	0
Product has limited accumulated information	0
Effect previously unreported and product has substantial accumulated information	-1

2. Likely alternative explanations

Assessment	Score
There is no likely alternative that can explain the effect	+2
An alternative exists, but does not explain the effect well	0
The effect commonly occurs in this crop/plant/situation	0
There is a likely alternative explanation for the effect	-1

3. Evidence of excessive rate of application

Assessment	Score
The effect is clearly rate-related and there is evidence that the amount of product used was an overdose for this crop/plant/situation	+1
The effect is not rate-related or there is no evidence of an overdose	0

4. Time between application and effect

Assessment	Score
Timing was consistent and as expected for this type of effect to this product	+1
Do not know what timing to expect	0
Timing was inconsistent for this type of effect to this product	-2

5. Site of application

Assessment	Score
Effect is uniform over the entire area treated	+1
Effect only in areas treated (eg only in paddocks treated)	+1
No pattern to the effect is apparent	0
Effect is not uniform in area treated (eg is in strips or specific areas)	-1

Causality Assessment – Agricultural Chemicals

Once the relationship between the use of the product and the reported effect has been assessed after investigation of the incident it is expressed in terms of:

Probable

(Algorithm score 3 to 6)

For inclusion in the category 'probable' all of the following minimum criteria should be met:

- there should be a reasonable association between the use of the product and onset and duration of the reported adverse experience,
- the description of the effect should be consistent with or at least plausible given the known mode of action, toxicology and metabolism of the product, and
- there should be no other equally plausible explanation (or contributing factors) for the clinical signs.

When any of the above criteria cannot be satisfied (due to lack of sufficient information or conflicting data) then the association cannot be assessed as 'probable'.

Probable/Off-label

(Algorithm score 3 to 6)

As per the classification of 'probable' and where there is obvious evidence of off-label use (including use in crops/plants/situations not listed on the product label, excessive rates etc).

Possible

(Algorithm score 0 to 2)

For inclusion in the category 'possible' association of the adverse experience with use of the product is one of other possible and equally plausible explanations (or contributing factors) for the described adverse experience.

Possible/Off-label

(Algorithm score 0 to 2)

As per the classification 'possible' and where there is obvious evidence of off-label use (including use in crops/plants/situations not listed on the product label, excessive rates etc).

Unlikely

(Algorithm score –1 to –5)

Where sufficient information exists to establish that the described adverse experience was not likely to have been associated with use of the product(s), or other more plausible explanations exist, the assessment should be categorised as 'unlikely'.

Unknown

All adverse experiences where reliable data is either unavailable or is insufficient to make an assessment should be categorised as 'unknown'.