anses
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Investigate, evaluate, protect

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Definition of a serious adverse event in intensive food animal production

Pharmacovigilance (PV) is defined by WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

In this context, the collection and assessment of serious adverse reactions is ANSES-ANMV's principal objective in order to quickly take appropriate measures in cases where public health is at risk.

French regulations are above all geared to the management of serious adverse reactions. In particular:

- veterinarians must report all serious adverse reactions they observe (as well as any unexpected reactions)
- pharmaceutical companies must inform ANSES-ANMV of all serious adverse reactions within 15 days of them being brought to their attention

Article R. 5141-92 3 of the French Public Health Code, which transposes into French law Article 1 (paragraph 12) of Directive 2001/82/EC, as amended, defines a serious adverse reaction as "An adverse reaction which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or which results in permanent or prolonged signs in the animals treated". "

In 2007, the French Veterinary Pharmacovigilance Commission, then in 2013 the French Veterinary Drug Commission, worked on this definition by providing clarifications with regard to non-lethal cases (see the ANSES website, https://www.anses.fr/fr/system/files/Avis-CNMV-classification-cas-graves-052013_1.pdf (In French))

However, the legal definition of a serious adverse reaction applies first and foremost to an individualised type of medicine. When treatments are administered to production animals managed in groups, it is recommended to take clinical signs into consideration at the level of the treatment group. They also note that reduced zootechnical performance can be considered a serious adverse reaction.

Since these zootechnical criteria can vary from one species to another, a review of the subject was conducted by ANSES-ANMV and its partners in the pig, poultry and rabbit sectors in order to define objective, quantifiable criteria for evaluating whether a given adverse reaction in

intensive food animal production should be considered serious. The two goals of this review were:

- to promote reporting in the various intensive food animal production sectors and at the same time help veterinarians to fulfil their reporting obligations;
- to harmonise the classification practices of the authorities and MA holders.

With regard to mortality and reproductive problems, levels were set, by sector and by the animals' physiological stages, beyond which an event should be considered as serious.

Potentially life-threatening individual clinical signs that are permanent or prolonged, or which result in significant incapacity, are difficult to observe in large groups of animals. These signs however often have an indirect effect on water and/or feed consumption, with repercussions on growth and zootechnical performance.

In addition to the fatal cases, it was decided that these indirect criteria would also be taken into account by setting, for each sector, specific levels for reduced water consumption, feed consumption and/or growth beyond which the consequences of the adverse reactions should be considered as serious, and should therefore lead to reporting.

The following annexes provide the sector-based seriousness criteria chosen to describe a serious adverse event in intensive food animal production sectors.

Annex 1: Seriousness criteria for pig farming

Mortality

	Mortality rate	Calculation reference
Sows	X 4 during 1 month	Average annual rate for farm*
Suckers	X 2	Average of the 3 previous batches
Post-weaning	X 1.5	
Fattening	X 1.5	

* Example for sows
6% annual mortality in a farm with 100 sows represents an average of 0.5 deaths/month. A loss of 2 sows over a one-month period would therefore be considered a serious event.

Reproduction

	Criteria	Calculation reference
Late-term abortions	≥ 10% of the animals in the batch, or ≥ 10% of the animals in several batches over a month with a minimum of 4 sows	Average of the 3 previous batches
Artificial Insemination success rate	20% decrease	
Perinatal mortality	2X the average rate	
Live births	20% decrease of the average number	

Consumption

	Daily decrease	Calculation reference
Feed	≥ 30%	Previous days
Water	≥ 50%	

Growth

	Growth rate	Calculation reference
Post-weaning	20% decrease	Average of the 3 previous batches
Fattening	20% decrease	

Annex 2: Seriousness criteria for poultry farming

Mortality

		% mortality over a single day	% mortality per day over two consecutive days	
			D	D + 1
TURKEYS*	Confined broilers	≥ 4	≥ 1	≥ 1
	Free-range broilers	≥ 4	≥ 0.5	≥ 0.5
	Future Breeders	≥ 4	≥ 0.25	≥ 0.25
	Layer breeders	≥ 4	≥ 0.25	≥ 0.25
BROILER CHICKEN SECTOR	Confined broilers	≥ 4	≥ 1	≥ 1
	Free-range broilers	≥ 4	≥ 0.5	≥ 0.5
	Future Breeders	≥ 4	≥ 0.25	≥ 0.25
	Layer breeders	≥ 4	≥ 0.25	≥ 0.25
TABLE EGG SECTOR	Pullets	≥ 4	≥ 0.5	≥ 0.5
	Laying hen	≥ 4	≥ 0.5	≥ 0.5
	Future Breeders	≥ 4	≥ 0.25	≥ 0.25
	Layer breeders	≥ 4	≥ 0.25	≥ 0.25
GUINEA FOWL	Confined broilers	≥ 4	≥ 0.5	≥ 0.5
	Free-range broilers	≥ 4	≥ 0.25	≥ 0.25
	Future Breeders	≥ 4	≥ 0.25	≥ 0.25
	Layer breeders	≥ 4	≥ 0.25	≥ 0.25
QUAILS	Confined broilers	≥ 4	≥ 0.5	≥ 0.5
	Free-range broilers	≥ 4	≥ 0.25	≥ 0.25
	Future Breeders	≥ 4	≥ 0.25	≥ 0.25
	Layer breeders	≥ 4	≥ 0.25	≥ 0.25
DUCKS	Broilers	≥ 2	≥ 0.5	≥ 0.5
	Ready-for-gavage	≥ 2	≥ 0.25	≥ 0.25
	Future Breeders	≥ 2	≥ 0.25	≥ 0.25
	Layer breeders	≥ 2	≥ 0.5	≥ 0.5
GEESE	Broilers	≥ 2	≥ 0.5	≥ 0.5
	Ready-for-gavage	≥ 2	≥ 0.25	≥ 0.25
	Future Breeders	≥ 2	≥ 0.25	≥ 0.25
	Layer breeders	≥ 2	≥ 1	≥ 1
PHEASANTS	Any stage	≥ 4	≥ 0.25	≥ 0.25
Red-legged PARTRIDGES	Any stage	≥ 4	≥ 0.25	≥ 0.25
Grey PARTRIDGES	Any stage	≥ 4	≥ 0.25	≥ 0.25
MALLARDS	Reproduction and breeding	≥ 4	≥ 0.25	≥ 0.25

PIGEONS	Future Breeders	≥ 4	≥ 1	≥ 1
	Breeders	≥ 4	≥ 0.25	≥ 0.25

* Example for a confined broiler turkey farm:
With a mortality rate equal to or higher than 4% over a one-day period, or a mortality rate of between 1% and 4% the first day and remaining at between 1% and 4% for 2 days or more, the veterinarian who was called in, after having excluded any pathological cause or a farming or feed accident, concluded that there was a possible connection between the administration of a veterinary medicinal product and the signs observed, and therefore filed a serious adverse event report.

Reproduction/Laying

	Decrease in laying over a single day	Decrease over 3 successive days			Calculation reference
		D0	D1	D2	
Laying	≥ 15%	≥ 5%	≥ 5%	≥ 5%	Previous days

Consumption

	Daily decrease over a single day	Decrease over 3 successive days			Calculation reference
		D0	D1	D2	
Feed	≥ 50%	≥ 25%	≥ 25%	≥ 25%	Previous days
Water	≥ 50%	≥ 25%	≥ 25%	≥ 25%	

Example for water or feed consumption:
With a reduction equal to or higher than 50% over a one-day period, or between 25% and 50% the first day (D0) and remaining at between 25% and 50% D1 and D2, the veterinarian who was called in, after having excluded any pathological cause or a farming or feed accident, concluded that there was a possible connection between the administration of a veterinary medicinal product and the signs observed, and therefore filed a serious adverse event report.

Annex 3: Seriousness criteria for rabbitry

Mortality

	Mortality over a single day	Total mortality/batch
Does	≥ 4%	≥ 2%/average mortalities of the 3 previous batches X% + 2% With X = average mortalities of the 3 previous batches
Unweaned young	≥ 5%	
Fattening rabbits	≥ 5%	
Future breeder rabbits	≥ 4%	

* Examples for does
- If the mortality rate for does over a single day is 4% or more, the event is considered serious.

- If the average mortality rate for does is 3.5% in the 3 previous batches and the rate is 5.5% in the following batch, the event is considered serious.

Reproduction

	Decrease	Calculation reference
Birth/palpation difference	≥ 20%	Average of the 3 previous batches
Parturition rate	≥ 20%	
Still births	≥ 50%	
Live births	≥ 30%	

Consumption

	Daily decrease	Calculation reference
Feed	≥ 30%	Previous days
Water	≥ 50%	

Annex 4: Seriousness criteria for beekeeping

Given the wide diversity of beekeepers in terms of bee stock and production, thresholds have been established to characterise the seriousness criteria for adverse reactions at the apiary level.

The adverse reactions presented in this annex may therefore be regarded as serious if observations reach the following thresholds in terms of symptomatic colonies/treated colonies within the same apiary:

Total number of colonies treated in the apiary	Number of colonies expressing the symptom(s) in the apiary
1-5	≥ 1 (100-25%)
6-10	≥ 2 (33-20%)
11-20	≥ 3 (27-15%)
21-40	≥ 4 (19-10%)
> 40	≥ 10%

List of serious events in the beekeeping sector

Mortality

	Criteria	Reference
Bees	Massive acute mortality of adult bees	> 3000 bees (1 litre of bees) suddenly found dead in the form of a carpet in front of or inside the hive
Colony	Colony mortality during the season	Colony regarded as dead if residual population < 500 bees
	Winter mortality	Colony found empty or with residual population < 500 bees at the end of winter

Impaired reproduction

	Criteria	Reference
Queen	Mortality or disappearance	Queen found dead, or not found and with absence of sustainable egg-laying (> 15d) during the season
	Prolonged pause in egg-laying	No eggs in the hive, observed on at least two visits at 15-day intervals
	Requeening or supersedure	The bees have changed the queen by themselves (without the population leaving): strong population but no queen and queen cells in development
	Drone colony	Exclusively male brood and workers replaced by drones
Brood	Mosaic (spotty) brood	Appearance of empty cells or cells containing dead larvae/pupae over more than 10% of the total surface area of the brood
	Abnormal evacuation of larvae and/or pupae	Dead larvae and/or pupae found inside or in front of the hive, in a quantity corresponding to more than 10% of the total surface area of the brood

Growth disorders

	Criteria	Reference
Population	Weakening/Die-off	Gradual decrease in population density, hive activity and honey production
	Depopulation/Collapse	Disappearance of a large proportion of adult bees with only a very limited population of bees remaining in the hive, despite there being brood, honey reserves and pollen supplies
Bees	Malformations of adult bees	Observation of malformed bees in the hive (deformed wings, shortened abdomen, etc.) in a proportion exceeding six malformed bees for a population of 10,000 individuals

Level of parasitic infestation

	Criteria	Reference
Varroa population at the start/end of winter	Detection of > 1 *Varroa*/300 worker bees	Monitoring of the infestation rate by counting *Varroa* on a sample of 300 worker bees after flushing with alcohol, detergent or icing sugar, or after gassing with CO_2
	Falls of > 0.5 *Varroa*/day	Monitoring of the infestation rate by counting natural falls of *Varroa* onto greased or glued sheets placed under a wire-mesh floor
Population of *Varroa* during the season	Detection of > 15 *Varroa*/300 worker bees	Monitoring of the infestation rate by counting *Varroa* on a sample of 300 worker bees after flushing with alcohol, detergent or icing sugar, or after gassing with CO_2
	Falls of > 8 *Varroa*/day	Monitoring of the infestation rate by counting natural falls of *Varroa* onto greased or glued sheets placed under a wire-mesh floor
	> 5% brood infestation of males in early spring	*Varroa* count in cells or on larvae/pupae after uncapping 200 male brood cells