European Food Safety Authority

EFSA Journal 2012;10(1):2539

SCIENTIFIC OPINION

Guidance on studies concerning the safety of use of the additive for users/workers[1†]

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

This document provides guidance on how to conduct studies concerning safety for the user/workers.

Users/workers are defined as the persons who may be exposed to the additive while handling it, when incorporating it into premixtures or feedingstuffs or using a feedingstuff supplemented with the additive.

An assessment of risk to users/workers should be included based on toxicological studies relevant to the nature of the additive. Experience in the manufacturing plant may be an important source of information in evaluating the risks to workers from exposure to the additive itself by both airborne and topical routes.

1. Toxicological risk assessment for user/worker safety

Risks to users/workers should be assessed in a series of studies using the additive in all forms of the final product for which the application has been submitted. Any other available toxicological data should be used to assess the potential systemic toxicity of the additive. All these should be assessed, if necessary, by direct measurement and specific studies.

The use of *in vitro* studies is encouraged, wherever possible. In case of *in vivo* studies, classifications should follow Regulation (EC) No 1272/2008.

1.1. Effects on the respiratory system

Standardised methods are currently not available for respiratory sensitization. If the product is demonstrated to be a dermal sensitizer then it is assumed, on a precautionary basis and in the absence of other information, that it is also a respiratory sensitizer. If the product is proteinaceous in nature then it is assumed to be a respiratory sensitizer.

---

[1] On request from EFSA, Question No EFSA-Q-2010-01162, adopted on 15 December 2011.

[†] This guidance document replaces the previous EFSA Technical Guidance: Studies concerning the safety of use of the additive for users/workers, adopted in September 2008 (EFSA-Q-2008-407). Sections 1 and 2 have been modified and appendixes added.

[2] Panel members: Gabriele Aquilina, Georges Bories, Andrew Chesson, Pier Sandro Cocconcelli, Joop de Knecht, Noël Albert Dierick, Mikolaj Antoni Gralak, Jürgen Gropp, Ingrid Halle, Christer Hogstrand, Reinhard Kroker, Lubomir Leng, Secundino López Puente, Anne-Katrine Lundebye Haldorsen, Alberto Mantovani, Giovanna Martelli, Miklós Mézes, Derek Renshaw, Maria Saarela, Kristen Sejrsen and Johannes Westendorf. Correspondence: FEEDAP@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Guidance, including Paul Brantom, for the preparatory work on this scientific opinion.

Suggested citation: EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP); Guidance on studies concerning the safety of use of the additive for users/workers. EFSA Journal 2012;10(1):2539. [5 pp.] doi:10.2903/j.efsa.2012.2539. Available online: www.efsa.europa.eu/efsajournal

Particle size should be measured, preferably by laser diffraction, means or medians should be expressed in relation to volume. Dusting potential should be measured following recognised methods (e.g., Stauber-Heubach,[4] EN 15051[5]) and expressed in mg/m^3.

For enzymes and microorganisms, where a sensitization hazard is presumed, these data will be used to estimate the likelihood of exposure and hence, risk. For additives other than enzymes and microorganisms, dusting potential, and, when relevant, particle size of dust and the concentration of the active substance in the dust fraction, will be used to calculate/estimate inhalation exposure which can be related to data on systemic and inhalation toxicity.

For substances with a potential for serious adverse effects at low levels of exposure, an estimate of worker exposure by inhalation will be required. Particle size distribution and the content of the active substance(s) should be determined in dust following the measurement of the dusting potential. From these data, a daily exposure of workers in a premixture plant to the active substance can be calculated as shown in Appendix 1. Using the data in Appendix 2, the amount of active substance which reaches the different parts of the respiratory tract can be calculated.

Protocols for inhalation toxicity studies should comply with OECD Guidelines 403 (Acute Inhalation Toxicity), 412 (Repeated Dose Inhalation Toxicity: 28-day or 14-day study) or 413 (Sub-chronic Inhalation Toxicity: 90-day study).

1.2. Effects on the eyes and skin

Tests for skin and eye irritation and for skin sensitisation potential should be performed using the appropriate form of the additive.

Protocols for these studies should comply with OECD Guidelines 404 (Dermal Irritation/Corrosion), 439 (*In vitro* skin irritation), 430 (*In Vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test (TER)), 431 (*In vitro* skin corrosion), 405 (Eye Irritation/Corrosion), 437 (Bovine Corneal Opacity and Permeability Test), 406 (Skin Sensitisation) and 429 (Skin Sensitisation - local lymph-node assay). Studies on skin irritancy should be performed first, and only if these give negative results, mucous membrane (e.g., eye) irritancy should be assessed.

Where available, data on irritancy and/or sensitisation from known human situations should be provided.

Dermal toxicity must be considered if there is likely to be significant systemic exposure resulting from this route. Studies must comply with OECD Guideline 402 (Acute Dermal Toxicity).

1.3. Systemic toxicity

All available toxicity data, including those generated to meet consumer safety (e.g., repeated dose toxicity, mutagenicity, carcinogenicity and reproductive testing and metabolic fate) should be used to assess systemic toxicity.

1.4. Exposure assessment

Information should be provided on how the use of the additive is likely to give rise to exposure by all routes (inhalation, through the skin or by ingestion). This information should ideally include a quantitative assessment, and may be based on elements such as typical airborne concentration, dermal contamination or extent of ingestion.

[4] Stauber D and Beutel R. (1984). Bestimmung und Kontrolle des Staubpotentials von Futtermittelvormischungen. Fresenius' Journal of Analytical Chemistry 318(7), 522-524.

[5] Workplace atmospheres—measurement of the dustiness of bulk materials—requirements and reference test methods. 2006. Berlin: Beauth Verlag.

Where exposure of consumers is expected to be near to the acceptable daily intake (ADI) or tolerable upper intake level (UL) additional exposure of the user/worker should be avoided.

2. Measures to control exposure

Using the information from the toxicology and exposure assessment, a conclusion should be drawn about the risks to health of the users/workers (inhalation, irritancy, sensitisation and systemic toxicity). Precautionary measures may be proposed to reduce or eliminate exposure. All measures used to minimise exposure should be documented. However, use of personal protective devices should only be regarded as a measure of last resort to protect against any residual risk once other control measures are in place. It is preferable, for example, to consider reformulation of the product.

APPENDIX 1

Calculation of inhalation exposure to an additive in a premixture factory

Assumptions

There are different operations in a premixture factory during which the worker could be exposed to dust:

- Taking the additive from its bag for weighing in the dispensary
- Emptying bags of previously weighed material in the hopper or mixers
- Packing the final premixture

Default values/positions:

- A factory with a large throughput can prepare 40 premixture batches per day (8 hours per shift)
- The maximum time for weighing/emptying is 20 seconds
- A total breathed air per worker of 10 m^3 per 8 hours = 1.25 m^3 per hour
- All dust comes from the additive
- All air available for inspiration contains the additive's dust

Factors related to the feed additive:

- Percentage of premixtures which contain the additive
- Dusting potential measured (g/m^3)
- Concentration of the active substance in dust

Estimate of risk mitigation

- Estimated reduction (%) of exposure due to the use of personal protection equipment (coverall, goggles, gloves and masks of the type P2 or P3).

Calculation of exposure by inhalation during a working day

Batches with potential exposure (**N**)	40 batches × fraction of batches containing additive = **N** batches
Time of exposure (**Te**)	**N** × 20 sec = **Te** sec an uncertainty factor of 2 should be introduced
Inhaled air during exposure (**Ia**)	1.25 m^3 per hour × **2Te** in hours = **Ia** m^3
Active substance in air (**Asa**)	dust g/m^3 × **X** (% active substance in dust) = **Asa** g/m^3
Active substance inhaled (**Asi**)	**Asa** g/m^3 × **Ia** m^3 = **Asi** g
Reduction by filter mask (**Asir**)	**Asi** g × factor (depending on filter mask) = **Asir** g

APPENDIX 2

Numerical values of the separation curve following DIN EN 481[6] to compile the aerosol fraction relevant for occupational health, related to the whole air transported aerosol.

Aerodynamic diameter (µm)	Breathable (inhalable) fraction (%)	Thoracic fraction (%)	Alveolar (respirable) fraction (%)
0	100	100	100
1	97.1	97.1	97.1
2	94.3	94.3	91.4
3	91.7	91.7	73.9
4	89.3	89	50
5	87	85.4	30
6	84.9	80.5	16.8
7	82.9	74.2	9
8	80.9	66.6	4.8
9	79.1	58.3	2.5
10	77.4	50	1.3
11	75.8	42.1	0.7
12	74.3	34.9	0.4
13	72.9	28.6	0.2
14	71.6	23.2	0.2
15	70.3	18.7	0.1
16	69.1	15	0
18	67	9.5	
20	65.1	5.9	
25	61.2	1.8	
30	58.3	0.6	
35	56.1	0.2	
40	54.5	0.1	
50	52.5	0	
60	51.4		
80	50.4		
100	50.1		

- Inhalable fraction: the separation curve corresponds to the average probability of inhalation
- Thoracic fraction: the separation curve corresponds to the average probability for particles entering the tracheo-bronchial-tree and the alveolar area
- Alveolar (respirable) fraction: That fraction is part of a thoracic fraction. The separation curve corresponds to the average probability for particles entering the alveolar area

[6] DIN EN 481, Festlegung der Teilchengrößenverteilung zur Messung luftgetragener Partikel, Beuth Verlag, Berlin, 1993.