GMP+ International

READER
FACT SHEETS
UNDESIRABLE SUBSTANCES

Version EN: 10 July 2010

Index

1. Introduction

The HACCP system is accepted as an effective tool to assess and control the haz-ards to safe levels present in this food chain. In the feed chain, being part of the food chain, the HACCP system is also widely accepted and even compulsory within the GMP+ system of GMP+ International.

Handing the feed industry a tool in founding their HACCP analysis, GMP+ Interna-tional has published several fact sheets of undesirable substances. This scientific information can be used to found the occurrence and severity, being part of the HACCP analysis. This information can be used in phase 7.2, the risk assessement, of the HACCP manual as published by GMP+ Interantional.
Also other information like toxicokinetics, method of analysis and control measures for each part of the feed chain can be found in the fact sheets.

The undesirable substances addressed to in the fact sheets are present in EU di-rective 2002/32/EC, and its amendments, and in GMP+ Appendix 1, stating maxi-mum levels of undesirable substances in feed materials and animal feed.

The fact sheets are intended for any entity involved, either directly or indirectly, in the production of feed materials and animal feed.

In this reader the chapters which are addressed to in the fact sheets and their scope are explained, creating a clear frame work for the reader.

2. Format of fact sheets

The format of the fact sheets is fixed as shown in table 1. For some undesirable substances this format was not suitable and another format was used (e.g. pesticides and biocides), derived from the fixed format.

Table 1. Format fact sheet

General summary Summary of GMP+ product standards for the animal feed sector More facts 1. Nature, history and prevalence 2. Transmission and likelihood of occurrence 3. Diagnose of poisoning 4. Potential adverse effects 5. Severity of potential adverse effects 6. Legislation and standards 7. Methods of analysis 8. Possible control measures 9. References 10. Websites APPENDICES

3. General summary

This chapter contains information about the name, the code as used in Appendix GMP+ BA1 of the GMP+ Feed Safety Scheme, a short description, type of hazard (Chemical, Microbiological or physical), the severity (low, medium or high) and a list of control measures as mentioned in the Feed Support Products.

4. Summary of GMP+ product standards for the animal feed sector

GMP+ standards as in Appendix GMP+ BA1 . Including EU standards as laid down in Directive 2002/32/EC and its amendments.

5. General information

The **chemical name** of the undesirable substance or product used in the fact sheet is, when available, the name given by the International Union of Pure and Applied Chemistry (IUPAC).

The **CAS-number** is the unique identifier of a substance and is given by the Chemical Abstracts Service (CAS). In the fact sheets of processing aids, this information can be found in the appendix.

Undesirable substances and product often have **synonyms**. These synonyms are included in the fact sheet. The list is non exhaustive.

6. Nature, history and prevalence

This chapter contains the following information:

- Chemical information about the undesirable substance or product, like what kind of a substance is it, reactivity, solubility;
- Its presence in nature, e.g. as elemental substance or as part of a compound (e.g. salts) and where does it originate from;
- Possible co-occurrence with other undesirable substances;
- How and under what conditions is the undesirable substance or product produced (in case of heavy metals: mining or in case of mycotoxins: by fungi). A flow chart of processing can be included in the appendix.
- When applicable: what are former and present applications.

7. Transmission and likelihood of occurrence

Information in this chapter is used to determine the ***likelihood of occurrence*** of the undesirable substance or product.
This chapter is divided into five paragraphs:

- Environment:
    - How is the undesirable substance or product transmitted into the environment (natural and anthropogenic sources);
    - Transmission in various media (air, water, soil);
    - Likelihood of occurrence in products of non-animal and non-vegetal origin (e.g. minerals);
    - When available data concerning levels in products of non-animal and non-vegetal origin.

- Plants:
  - How is the undesirable substance or product taken up by the plant;
  - Likelihood of occurrence in products of vegetal origin. When available, information about forages is included;
  - When available data concerning levels in products of vegetal origin;
  - Effect of processing (e.g. heating, drying) on the presence of the undesirable substance or product.
- Animals:
  - Animals referred to is food producing animals, excluding fish. In case no or limited livestock data is available, laboratory animals (e.g. rodents) data will be included;
  - Animal exposure (oral):
    For the majority of non-ruminant livestock (pigs and poultry) in the EU, feed is provided as compounded feed, consisting of a mixture of individual feed components, to which additives and/or mineral supplements are added. Intake of cadmium may therefore be estimated by multiplying the concentrations of each compound by the estimated intake of the compound for the particular class of livestock.
    Estimating intake by ruminants is less straightforward. For cattle and sheep, the daily ration usually consists of forage (or mixture of forages), either fresh or conserved, together with complementary feeds or individual feed materials as necessary to achieve the required the level of production (growth rate, milk yield). The ratio of concentrate feeds to forage in the diet is also influenced by the digestibility of the forage.
  - Toxicokinetics: absorption, distribution (incl. placental transfer), metabolism, excretion (incl. excretion via milk). When available species information is included (e.g. toxicokinetics of ruminants can be different form monogastric animals).
- Humans via animal products:
  - Likelihood of occurrence in products of animal origin;
  - When available data concerning levels in products of animal origin are included;
  - Effect of processing (e.g. heating, drying) on the presence of the undesirable substance or product;
- Humans:
  - Human exposure (oral) by food (incl. vegetal and animal origin);
  - Toxicokinetics: absorption, distribution (incl. placental transfer), metabolism, excretion (incl. excretion via milk).
    When no information about human toxicokinetics is available and in literature is cited that animals can be used as a model for humans, then is referred to toxicokinetics of animals. When no scientific data are available for this assumption no information will be included in the fact sheet.
    When information about human toxicokinetics is available, but no scientific data are available to assume that animals can be used as a model for humans, the information about human toxicokinetics is included separately in the fact sheet, even when the toxicokinetics seem to be similar to animals.

8. Diagnose of poisoning

This chapter is divided into two paragraphs: animals and humans.
With diagnosing of poisoning or toxicosis is meant the analytical part of determining the toxicosis. In general these are called biomarkers, like blood, urine and hair. Also autopsy finding might be included (like renal effects). Symptoms of living animals and humans or other adverse effects or not included, but are included in the chapter "Potential hazards and adverse effects".
When no information about human or animals diagnostics is available and in literature is cited that similar biomarkers of animals or humans can be used, then this is referred to. When no scientific prove is available for this assumption and no information is available, no information will be included in the fact sheet. In case no or limited livestock data is available, laboratory animals (e.g. rodents) data will be included.
When information about human and animal diagnostics are available and no scientific data are available to assume that similar biomarkers can be used, the information about human and animal diagnostics are included separately in the fact sheet, even when the diagnostics seem to be similar to each other.

9. Potential adverse effects

Elemental undesirable substances or products and compounds are included (e.g. elemental mercury, but also mercury salts).
Information in this chapter is used to determine the ***severity*** of the undesirable substance or product and is non-exhaustive.
This chapter is divided into three paragraphs:

- Environment: effects on plants, micro-organisms;
- Animals:
  Route of exposure is oral. Duration of exposure is (ATSDR[1], 2009):
  - Chronic : > 3 months;
  - Sub-chronic : 1 to 3 months;
  - Sub-acute : 24 hours and less than 1 month.

  These durations of exposure reflect the length of life of livestock, with dairy cattle, sows and horses have the longest length of life, of several years. Broilers however has the shortest length of live, of several weeks.
  Acute exposure is not taken into account in the fact sheets because, in general, acute exposure does not reflect the actual situation in animal husbandry.

Additionally acute exposure data are, in general, high levels of exposure. As a consequence, any substance at acute exposure can be classified as being of high severity.
    - Animals referred to are food producing animals, excluding. In case no or limited livestock data is available, laboratory animals (e.g. rodents) data will be included;
    - Sensitive animals (e.g. carrying, weaned animals);
    - Description of potential adverse effects, when available per animal species;
    - Toxicity data is not included in the chapter, but is included in the appendix (e.g. LD50, NOAEL) as is an overview of the potential adverse effects in animals.
- Humans:
  As in animals route of exposure is oral. Duration of exposure is (ATSDR[1], 2009):
    - Chronic : > 3 months;
    - Sub-chronic : 1 to 3 months;
    - Sub-acute : 24 hours and less than 1 month.

  Acute exposure is not taken into account in the fact sheets because, in general, acute exposure, does not reflect the actual exposure of humans to the undesirable substance in animal products. Additionally acute exposure data are, in general, high levels of exposure. As a consequence, any substance at acute exposure can be classified as being of high severity.
    - Sensitive humans (e.g. children, pregnant women, elderly);
    - Description of potential adverse effects;
    - Toxicity data is not included in the chapter, but is included in the appendix (e.g. ADI, LD50, NOAEL) when human data is available.

Adverse effects in animals and humans are classified in groups of effects, being:
- Lethal
- Carcinogen
- Mutagen
- Reproductive effects
- Internal injury (by physical contamination)
- Neurotoxic
- Immunological effects
- Effects on organs (e.g. liver, kidney)
- Dermal and ocular effects (e.g. skin, eye)
- Respiratory effects
- Musculo-skeletal effects
- Cardiovascular effects
- Gastrointestinal effects
- Hematological effects
- Endocrine effects
- Body weight effects

In Annex I a list of definitions is included of the above mentioned potential adverse effects.

An overview of the groups of potential adverse effects in animals and humans is included in the appendix of the fact sheet.

Mind that in case certain potential adverse effects are not mentioned, this does not mean that these do not occur. In some cases these effects were not / have not been studied or no data has been found.

10. Severity of the potential adverse effects

Using information in the chapter "Potential adverse effects" the ***severity*** of the undesirable substance is determined for animals and humans. Severity is the effect on the target animal's health as well as the consequential damage for humans when products of animal origin are consumed.
In the HACCP manual of GMP+ International (2010) there are three classes of severity as shown in table 2.

Table 2. Severity classes (GMP+, 2010).

Severity class	Definition
High	Serious diseases, harmful effects and/or wounds, both occurring immediately and long-term effects, possibly with fatal consequences.
Medium	Substantial diseases, harmful effects and/or wounds, both occurring immediately and long-term effects.
Low	Minor diseases, harmful effects and/or wounds, not or hardly occurring, or only long-term effects after extremely high doses.

The severity for **animals** is classified as high when scientific data is present that the undesirable substance (oral exposure) is / has / causes:

- Lethal;
- Carcinogen;
- Mutagen;
- Reproductive effects;
- Internal injury (by physical contamination).

See also Annex 1.

The severity for **humans** is classified as high when scientific data is present that the undesirable substance (oral exposure) is / has / causes (Cnossen et al., 2009):

- Causing effects on physiological systems that may show only later after a longer period (including carcinogenicity, mutagenicity, teratogenicity (as part of reproductive effects) etc.);
- Lethal;
- Causing internal injury (by physical contamination);
- Causing actual disease, curable but disabling for more than a few days;
- Causing longer term illness;
- Causing effects on organs that may show only later after a longer period.

See also Annex 1.

No assessment has been made of the severity within a group of potential adverse effects (e.g. dermal and ocular effects) which, as a group, has been classified as high severity. It is possible that within a group of potential adverse effect with a high severity, the actual effect is of medium severity. The same goes or medium and low severity classes and specific adverse effects within these classes. Severity classification is based on groups of potential adverse effects and not on effects within such groups.

In case the potential adverse effects of an undesirable substance or product cannot be assigned to an effect which is classified as high severity, it will be classified as medium or low severity.

The reader is free to make use of a different degree of seriousness such as when a specific estimate of seriousness is made within the group of food-producing animals for each type of animal: dairy cattle, pigs, laying hens, etc., as not all undesirable substances or products have the same effect on specific types of animal. This should, however, be demonstrably supported with reasons.

The severity classification is based on the worst case scenario (e.g. for the most sensitive species) and is stated as severity for animals in general.
An overview, as displayed in the fact sheet, of the severity classification is given in table 3.

Table 3. Severity classification

	Severity		
	Low	**Medium**	**High**
Food producing Animals			
Humans			

11. Legislation and standards

Other legislation and standards, not being EU legislation and standards of GMP+ International.

12. Method of analysis

For certain undesirable substances or products the method of analysis is laid down in standards. For other undesirable substances or products this is not the case. A general description of the method of analysis, either laid down by authorities or by other bodies (e.g. the EFSA) in the feed or food industry, is described in this chapter.

13. Possible control measures

- Listing of products of risk, including processing aids and additives;
- Listing of sensitive species;
- Possible control measures per part of the food chain, e.g. cultivation / mining, production of feed or food material, storage and transport and production of animal feed / compound feed.

14. References in fact sheets

List of literature cited.

15. Websites

List of interesting websites.

16. Appendices in fact sheets

- Tables with a categorized overview of potential adverse effects in humans and animals.
- Toxicity data
  Table with several oral toxicity data, like:
  - LD50 = **L**ethal **D**ose of a undesirable substance that has been calculated to cause death in 50% of a defined experimental animal population;
  - NOAEL = **No** **A**dverse **E**ffect **L**evel is the highest concentration or amount of a substance, found by experiment or observation, that causes no detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure. Alterations of morphology, functional capacity, growth, development or life span of the target organism may be detected that are not judged to be adverse (WHO, 2006).
- CAS-numbers and synonyms (only in fact sheets of processing aids):
  - The **CAS-number** is the unique identifier of a substance and is given by the Chemical Abstracts Service (CAS);
  - Undesirable substances and product often have many **synonyms**. These synonyms are included in the fact sheet. The list is non exhaustive.
- Flow chart of processing from which the undesirable substance or product originates (in some fact sheets);

17. References

1 ATSDR[1], Toxicology Curriculum for Communities Trainers Manuals, 2009

2 ATSDR[2], Draft toxicological profile for cadmium, 2008

3 Cnossen et al. (TNO Quality of Life), Vulnerabilities in the Food Chain: A stakeholders' guide, 2009

4 GMP+, Guideline HACCP GMP+: Supporting document of GMP+ FSA scheme, GMP+ D.2.1, January 2010

5 Scheepers et al., Dossier Carcinogene, mutagene en reproductietoxische stoffen (CMR-stoffen), Arbokennisnet, 2009

6 WHO, Principles for Evaluating Health Risks in Children, Environmental Health Criteria 237, 2006

Websites

1 http://www.atsdr.cdc.gov/training/toxmanual/index.html

ANNEX I Definitions of groups of potential adverse effects

Name group of adverse effect	Definition
Lethal[1,2]	Causing death. Either directly or via irreversible effects ultimately leading to death.
Carcinogen[1, 2]	Induces cancer either genotoxic (causing DNA damage) or non-genotoxic (not causing DNA damage) (Scheepers et al., 2009).
Mutagen[1,2]	Causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer (ATSDR[2], 2008)**.** It initiates cancer, however these substances need the presence of other substances for further promotion and progression of cancer (Scheepers et al., 2009).
Reproductive effects[1,2] **(incl. teratogenic effects)**	The occurrence of adverse effects on the reproductive system. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behaviour, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system (ATSDR[2], 2008). This includes the sexual maturation, formation of spermatozoids and ova, fertilization, full term of pregnancy / gestation, embryonic / foetal development (teratogenic), birth, postnatal adaptation, growth and development. Teratogenic effects are a part of reproductive effects, being effects on the development occurring in utero (before birth).
Internal injury[1,2]	Injury caused by physical contamination with e.g. glass, wood, metal.
Neurological effects[2]	The occurrence of adverse effects on the nervous system.
Immunological effects[2]	The occurrence of adverse effects on the immune system.
Effects on organs[2]	The occurrence of adverse effects on organs (e.g. liver, kidney).
Dermal and ocular effects[2]	The occurrence of adverse effects on the skin and eyes.
Respiratory effects[2]	The occurrence of adverse effects on the lungs.
Musculo-skeletal effects[2]	The occurrence of adverse effects on the skeleton and muscles .

[1] This potential adverse effect is classified as high severity for animals
[2] This potential adverse effect is classified as high severity for humans

Name group of adverse effect	Definition
Cardiovascular effects[2]	The occurrence of adverse effects on the heart and veins (e.g. blood pressure).
Hematological effect[2]	The occurrence of adverse effects on the blood and blood forming organs.
Endocrine effects[2]	The occurrence of adverse effects on the secretion of hormones.
Gastrointestinal effects	The occurrence of adverse effects on the gastrointestinal tract (e.g. from mouth to colon).
Bodyweight effects	The occurrence of adverse effects on bodyweight

GMP+ International

GMP+ International
Braillelaan 9
2289 CL Rijswijk
The Netherlands
t. +31 (0)70 – 307 41 20 (Office)
+31 (0)70 – 307 41 44 (Help Desk)
e. info@gmpplus.org