

# Justification for guidelines

In the field of veterinary medicine, practice staff, owners, and livestock farmers are all regularly exposed to medical products. Working with these substances is so natural to us that we rarely stop to consider their properties and the potential risks they may pose. Though we may indeed consider that an accident, such as self-injection or oral ingestion of a medicine, may pose a risk to us as humans, we can easily overlook the fact that exposure during normal day-to-day handling can also be a potential risk to our health. The database on this website is a tool for easy identification of the risks of active substances. Careful use of these resources helps reduce potential risks. What follows is an explanation of what hazardous substances are and how the assessment of active substances used in the practice was arrived at.

## Risks to safety or health

Hazardous substances are substances or mixtures that pose a risk to safety or health. Exposure to hazardous substances can have serious health consequences. Often the consequences are only visible in the longer term, which is why it is important to handle (potentially) hazardous substances with great care.

Hazard pictograms may appear on the packaging of substances, indicating the hazardous nature of the product. However, if there are no hazard signs on a product, this does not always mean that a product is indeed safe. Whether health effects actually occur depends on the **hazard properties** of an active substance and on the **degree of exposure**.

## Hazardous properties of a substance

To achieve greater unity in the designation of the hazards of substances, the UN has designed the GHS.<sup>1</sup> The GHS (globally harmonized system of classification and labelling of chemicals) is a set of criteria for classifying the hazard properties of substances.

The classification system has 9 hazard pictograms; standardized hazard statements (H-phrases) and precautionary statements (P-phrases).

Information about the hazards (H-phrases) and the protective measures to be taken for humans and the environment are contained in a product's safety data sheet (SDS).<sup>2</sup>

A supplier or manufacturer is required to provide an SDS of a hazardous substance to the customer - this is included in the European REACH regulation (1907/2006). This regulation also includes the requirements that an SDS must meet. However, there is no independent organisation that monitors the quality of an SDS. The content of an SDS can therefore vary. A study by the LNA showed that comparing three sources gives a good indication of the hazard properties.<sup>2</sup>

The following sources were used for the information on this website:

- Information known to ECHA (European chemicals agency), which is a European database of properties/risks of raw materials.
- SDS belonging to the reference standards of the European Pharmacopoeia
- SDS belonging to the reference standards of the American Pharmacopoeia
- SDS from the raw material supplier Sigma Aldrich
- SDS of specific products
- Assessment of active substances by the RIFAS.
- List of veterinary medicines with additional risks from the Faculty of Veterinary Medicine (Veterinary Pharmacy).

The risk associated with each active substance was considered on the basis of the H-phrases. Using a RIFAS (Risk Instrument for Pharmaceutical Substances) the substances were classified into hazard classes (1 to 5) based on the H-phrases.<sup>3</sup>

That ultimately results in the following classification:



**A = Hazard class 1 and 2**

No or limited (reversible) health effect



**B = Hazard class 3**

Potentially hazardous substance that may cause a hypersensitivity reaction



**C = Hazard class 4 and 5\***

Acute toxicity, carcinogenic, mutagenic, reprotoxic, risk of respiratory allergy

\*There has been a minor adjustment to the RIFAS classification: H362 (may be harmful to breastfeeding) has been added to hazard category 4. And based on the VTGM opinions of the RIFAS, it has been decided to place H334 in hazard category C.

Initially, all active substances were evaluated on the basis of 100% by weight percentage. After this, the active ingredients were divided into smaller groups based on form of administration, including the percentages by weight of active ingredients present in the products. This is important because the H-phrases may change or expire if the concentration is below a certain concentration limit (Table 1). The risk from the product may then be lower than from the pure (100%) substance. <sup>4</sup>

Some examples (Table 1):

Category H-phrases	H-phrases	Not applicable at concentration	Additional information
CMR	H340 and H350	< 0,1 %	
	H341 and H351	< 1 %	
	H360 and H362	< 0,3 %	
	H361	< 3 %	
Sensitising substances	H317 and H334	< 1 %	
Eye	H318	< 3 %	>1 % and < 3 % becomes H319
	H319	< 10 %	

The ATE formula was used to assess the H-phrases of acute toxicity. <sup>2</sup>

## Limit

The limit for a hazardous substance is an established limit that indicates how much of a particular substance may be present in the air of a workplace (in the form of aerosol, particle, gas, vapour, or fibre) without harming the health of workers and their children. This also applies to repeated exposure and over a prolonged period of time. The limit applies to exposure during a reference period (usually 8 hours and/or 15 minutes). Limits are established based on toxicological studies. The goal is to limit exposure to hazardous substances and ensure worker safety.

There are 2 types of limits in the Netherlands:

- Public limits
  - › > The EU imposes a limit for these substances.
  - › > Substances for which there is a special reason to establish limits as public.
- Private limits

Information on public limits can be found in the Working Conditions Regulation Annex XIII. More detailed information can be found at [www.ser.nl](http://www.ser.nl).



If no public limits are known, the employer is required to have the limits of a hazardous substance established (Health and Safety Decree Art. 4.3.2). The degree of exposure must be tested against this limit. In this way, it can be determined whether there is a risk of harm to employees.

For carcinogenic and mutagenic substances and substances that can cause respiratory allergies, safe limits are often not known. And accordingly, no limits can be set. The same applies to many active substances used in veterinary medicine. This means that exposure to these substances always poses a risk, even if this is only a one-time event.

## CMR substances

Substances with additional risks are the CMR substances (carcinogenic, mutagenic, or reprotoxic substances). These can respectively be carcinogenic, damage DNA, or be detrimental to fertility (for both men and women) or the unborn child and/or breastfeeding. The H-phrases corresponding to the substances are shown in Table 2; depending on the coding, there is a proven risk, or they are suspected of causing harm.

The government has made a list (SZW list) of CMR substances, which is revised twice a year. Some substances on this list are ethanol, formaldehyde, dexamethasone, and metronidazole. However, the list is not complete, and some substances used in veterinary medicine are omitted.

In connection with the increased risk, additional rules have been included in the occupational health and safety legislation with regard to working with CMR substances. This applies even more to pregnant employees. There is also an additional registration requirement.

Table 2:

	Proven	Suspected
Mutagenic	H340	H341
Carcinogenic	H350	H351
Reprotoxic	H360	H361
Possibly harmful through breastfeeding		H362

It is important to also alert owners to the risks posed by these substances.

## Sensitising substances

Sensitising substances are substances that can cause hypersensitivity (allergy).

2 phases can be distinguished:

1. Sensitisation phase; the immune system becomes hypersensitive (sensitised) as a result of contact with the substance.
2. With repeated contact with the same substance, an abnormally strong reaction of the immune system occurs (allergic inflammatory reaction).

Sensitisation and subsequent allergic reaction can occur as early as a few weeks after initial exposure, but it can also take years. Dermal exposure provides the greatest chance of sensitisation. However, after sensitisation, a person cannot tolerate the substance at all, and an allergic reaction will occur regardless of concentration or route of exposure.

**H317:** may cause an allergic skin reaction

**H334:** may cause allergy or asthma symptoms or breathing difficulties if inhaled

**EUH208:** this is sensitising substance. May cause an allergic reaction.

## The degree of exposure

The degree of exposure is determined by:

- The **concentration** of the veterinary medicine.
  - › At a low concentration, a hazardous substance is more dilute.
- The possible **absorption route** of the veterinary medicine
  - › Through the skin, through inhalation, through ingestion (directly or indirectly) or through the eye.
- The **action** being performed.
  - › Breaking or pulverising tablets, aspirating an injection fluid.
- The **care** with which the action is performed.
  - › Is careful practice maintained or not.
- The **frequency** of contact with the veterinary medicine per operative.
  - › Several times a day or sporadically
  - › Daily for extended periods of time or 3x daily for 5 days.
- **Precautions** taken to control exposure.
  - › Using an extractor hood or wearing gloves.
- **Enforcement of hygienic measures**
  - › Hands must always be washed after preparing or administering a veterinary medicine.

Table 3

	Through the skin	Through the airways	Hand-mouth contact	Splash accident (through the eye)
Tablets and capsule (in whole form)	+	-	+	-
Pulverised tablets for solution	+	+	+	-
Powder	+	+	+	-
Oral solutions	+	-	+	+
Infusion fluid	+	-	+	+
Injection fluid	+	-	+	+
Skin ointment	+	-	+	-
Medicated shampoo	+	-	+	+
Spot on/Pour on	+	-	+	+
Ear drops/ointment	+	-	+	+
Eye drops/ointment	+	-	+	+
Implant	+	-	-	-
Skin spray	+	+	+	+
Nebuliser	+	+	+	+
Medicated collar	+	-	+	-
Intramammary administration	+	-	+	+
Intrauterine tablet	+	-	+	-

As shown in Table 3, with any form of administration there is a potential for exposure through the skin - hence the recommendation to wear gloves. This is a requirement for products in a higher (B or C) hazard category.

At the request of the professional association of pharmacists (KNMP), TNO has investigated the inhalation exposure of various VTGM (preparing for administration) procedures <sup>5</sup>. This investigation showed that all operations cause exposure, but the degree of exposure varies greatly. Exposure occurs, for example, when pulping tablets in a mortar; breaking tablets; when opening capsules and spreading the contents (with the same being true when preparing feed with powder) and when transferring tablets from one jar to another.

## Database

The method by which the database was compiled:

1. List of FIDIN with all active substances used in veterinary medicine.
2. List supplemented with active substances of human medicines also used in veterinary medicine.
3. SZW list, for determining the active substances listed on the government's SZW list.
4. CBG-MEB website.
  - a. For each active ingredient, the registered dosage forms, and the concentration of the active ingredient per dosage form have been determined
  - b. Combinations of active ingredients have been identified.
5. Determine on SER.nl whether a Dutch limit is known for the substance
  - a. Yes, then the value for internal exposure is calculated from this and this leads directly to a hazard class allocation.
  - b. No, consult VIBs for limits.
6. If no limit is known, the hazard class is assigned based on the H-phrases.
7. For each active ingredient, it is noted which H-phrases are mentioned in the different safety sheets of the active ingredient.
8. Assign H-phrases to an active substance:
  - a. H-phrases from the SZW list are always adopted
  - b. H-phrases named in 3 SDS are always adopted
  - c. The H-phrases H360 and H361 are checked (if available) against the information in the Informatorium Medicamentorum (IM), where the minimum therapeutic dosage (human) is examined. If this is more than 1 mg/day, then the H-phrases H360 or H361 are not adopted, unless a CM H-phrase (H340, H341, H350 and/or H351) also applies or other information in the IM shows that the substance is indeed reprotoxic.
  - d. For veterinary raw materials, the information under item 8c is not available, and in this case item 8b applies.
  - e. If available, the RIFAS assessment will be included.
  - f. All H-phrases are reviewed against the GHS classification on Pubchem.
  - g. For a number of veterinary active substances, point 8b cannot be complied with because there are not enough MSDSs available. In these cases, information from the package insert is also used. The document: Converting P-phrases and toxicological information into H-phrases (RIFAS) is used for this purpose. If there are 2 MSDSs available, which describe similar risks, these are always used. However, if only 1 MSDS is available, the reliability of the assessment of this substance is lower and this is mentioned on the page.
9. H-phrases are corrected for the concentration of the active ingredient by form of administration. The ATE formula was used to assess acute toxicity. <sup>2</sup>
10. The hazard category of an active substance is determined by the highest score applicable to a form of administration.
11. For each administration form, the hazard category for that administration form is indicated.
  - a. The hazard category may differ for each form of administration, as it depends on the concentration of active substance(s).
  - b. The first exception is products with antibiotics in them. These products always receive at least a B regardless of the H-phrases associated with a form of administration. With these products, resistance is always a risk. Careful handling is accordingly necessary to prevent exposure.
  - c. A second exception is single (human) products which do not contain H-phrases but are still assigned a higher hazard class by RIFAS. These products may still pose a risk and careful handling is thus required.
12. It is also always indicated at the bottom of the page which H-phrases apply to the 100% active ingredient.



## Alerts

### CMR alert

This involves an active substance that is carcinogenic, mutagenic, or reprotoxic. The alert will always be shown as soon as the 100% active substance possesses one of these properties. It is possible that the active substance may be assigned a hazard category A, because a very low concentration of the substance is present in all administrations, but there is still a CMR alert associated with the substance. In such a case, be extra vigilant against self-injection or accidental ingestion. H340, H341, H350. H351, H360D, H360F, H361d, H361

### Eye alert

This alert is displayed when there is a risk of serious eye damage or eye irritation if the product containing this active ingredient enters the eye. The alert is displayed only when H314, H318 or H319 applies to at least one of the forms of administration. Ensure eye protection.

### Skin alert

This alert is displayed as soon as the active ingredient:

- Causes damage to the skin itself (e.g. H312 = Harmful on contact with skin).
- May cause an allergic skin reaction (H317)
- Can be absorbed through the skin and cause systemic exposure of the body to the substance (e.g. CMR H-phrases or H373 = May cause organ damage with prolonged or repeated exposure).
- Or with contact through hand/mouth (H302 = Harmful if swallowed).

The alert is displayed only when one of the following H-phrases apply to a form of administration: H300, H301, H302, H310, H311, H312, H314, H315, H317, H330, H331, H332, H336, H340, H341, H350, H351, H360 D, H360F, H361d, H361f, H362, H370, H371, H372, H373. Always wear gloves after a skin alert.

### Risk of inhalation allergy

This alert is displayed if the active substance could be sensitising to the respiratory tract. The alert is displayed only when H334 applies to one of the forms of administration. Active substances with an H334 alert are in hazard category C. There are often no known safe thresholds, so even a single exposure constitutes a risk.

Table 3 shows which forms of administration pose a risk (respiratory exposure). Check the database to see what precautions are needed to prevent the risk of inhalation allergy.

## Excipients

For the preparation of this website, it was decided to work on the basis of the active substance. This means that for products with an active substance in category C, you can say with certainty that it is a high-risk substance, and precautions are required to prevent exposure to it.

To fully evaluate a product with an active ingredient in category A or B, the product's safety data sheet must be viewed. However, it is not always available. Excipients may be present in a product (in a high concentration), which also pose risks.

Two major high-risk excipients are ethanol and N-methylpyrrolidone.

- Ethanol is on the SZW list and is a carcinogenic and reprotoxic substance. It mainly concerns spot-on products, some injection liquids and disinfectants. A product containing ethanol falls into hazard category C if > 0.1% ethanol is present in a product.
- N-methylpyrrolidone is a reprotoxic agent (see database). This excipient is present mainly in spot-on and pour-on products and some injection liquids. A product containing N-methylpyrrolidone falls into hazard category C if > 0.3% N-methylpyrrolidone is present in a product.

This website shows the risk of the active ingredient. Thus, if a product is rated A or B on this basis, the hazard category may be higher if excipients are included. There may also be physical hazards (risk of fire or explosion) associated with an excipient-based product.



## Guidelines

Guidelines are given for each form of administration and for each hazard category. These have been drawn up on the basis of the recommendations from the Health and Safety Catalogue for Working Safely with Medicines and the TNO study: Carrying out exposure measurements in VTGM operations - Final report. <sup>5</sup>

## Accidental exposure

### Accidental exposure

In normal use, exposure to the active substances can be prevented with suitable measures. However, there is always a chance of the occurrence of an accident (oral ingestion; self-injection or breaking a bottle of injection fluid or isoflurane), by which the user is exposed to a relatively large amount of active substance, which could involve other (additional) risks. For some groups of people, working with specific substances can be especially risky (e.g., anaesthetic agents). Always consider the properties of the substance being worked with. There are active substances that are risky in accidental self-injection or oral exposure for e.g. pregnant women, women after childbirth and breastfeeding women. Take great care in these cases.

### Guidelines in the event of accidental ingestion

To reduce the risk of accidental ingestion (especially by children or through confusing tablets), it is important to remove the tablet from the blister only when it is administered to the animal. Always store unused tablet portions in the blister, in the original packaging. In the event of accidental ingestion, consult a physician immediately and show the package insert or label. DO NOT drive a vehicle in the event of accidental oral ingestion of anaesthetics.

### Guidelines for accidental self-injection

In the event of accidental self-injection, consider the properties of the substance. In the event of accidental injection, consult a physician immediately and show the package insert or label. DO NOT drive a vehicle in the event of accidental self-injection of anaesthetics. Be alert with use of injection fluids (e.g., vaccines) containing mineral oil. Accidental (self) injection can result in severe pain and swelling, especially in the case of injection into a joint or finger. Without prompt medical intervention, in rare cases this can lead to loss of the affected finger.

## Statutory framework

The Working Conditions Decree (especially chapter 4) [wetten.nl - Regeling - Arbeidsomstandighedenbesluit - BWBR0008498](https://wetten.nl/Regeling-Arbeidsomstandighedenbesluit-BWBR0008498) ([overheid.nl](https://overheid.nl)) describes how to deal with hazardous substances at work, paying specific attention to so-called CMR substances and special groups (such as pregnant women). The employer has a duty of care towards his employees.

To help companies, the government has set up the self-inspection website "Working with Hazardous Substances", and with this tool you as a practice can get a better understanding of the risks of hazardous substances and this will help you to discharge the registration and assessment duty you have as an employer in good order. In addition, you will be able to see what measures you need to take to protect your employees.

[Working with hazardous substances | Self-inspection by the Dutch Labour Inspectorate](#)



## References

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