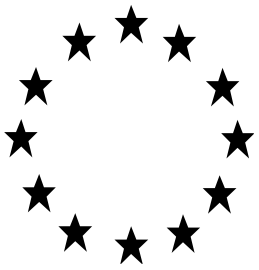
# Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

***Evaluation of active substances***

Assessment Report



# Cyanamide

Product-types 3 and 18
(Use in Veterinary Hygiene Biocidal Products and use in Insecticides, Acaricides and Products to control other Athropods)

(January 2022)

eCA: Germany

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# 1. STATEMENT OF SUBJECT MATTER AND PURPOSE

## 1.1. Procedure followed

This assessment report has been established as a result of the evaluation of the active substance cyanamide as product-types 3 and 18 (Veterinary Hygiene and Insecticides, Acaricides and Products to control other Athropods), carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

Cyanamide (CAS no. 420-04-2) was notified as an existing active substance, by AlzChem GmbH, hereafter referred to as the applicant, in product-types 3 and 18.

Commission Regulation (EC) No 1062/2014 of of 4 August 2014[1] lays down the detailed rules for the evaluation of dossiers and for the decision-making process.

On 4 July 2007, the German Competent authority received a dossier from AlzChem GmbH for PT3. The evaluating Competent Authority accepted the dossier as complete for the purpose of the evaluation on 31 October 2007. On 27 April 2006, the Germany Competent Authority received a dossier from AlzChem GmbH for PT18 which was accepted as complete on 8 February 2007.

On 30 July 2013, the evaluating Competent Authority submitted to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. As the CAR was submitted before 1 September 2013, the decision on the approval of cyanamide has to be taken based on the principles of the Directive[2].

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the the "Agency" (ECHA ). Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

## 1.2. Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of cyanamide for product types 3 and 18, and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web-site shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

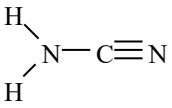
[1] COMMISSION DELEGATED REGULATION (EU) No 1062/2014 of 4 August 2014 on the work programme for the systematic examination of all existing active substances contained in biocidal products referred to in Regulation (EU) No 528/2012 of the European Parliament and of the Council. OJ L 294, 10.10.2014, p. 1

[2] CA-March14-Doc.4.1 - Final - Principles for substance approval.doc

# 2. OVERALL SUMMARY AND CONCLUSIONS

## 2.1. Presentation of the Active Substance

### *2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis*

| | |
|---|---|
| **CAS-No.** | 420-04-2 |
| **EINECS-No.** | 206-992-3 |
| **Other No. (CIPAC, ELINCS)** | CIPAC-No.: 685 |
| **IUPAC Name** | Cyanamide |
| **CAS Name** | Cyanamide |
| **Common name, synonyma** | - |
| **Molecular formula** | $CH_2N_2$ |
| **Structural formula** |  |
| **Molecular weight (g/mol)** | 42.05 g/mol |
| **Typical concentration or concentration range (% w/w)** | 96.8% w/w (dry weight)<br>50.5 %w/w (aqueous solution) |

Purified cyanamide is a colourless and odourless solid with a melting point of 46.1 °C which decomposes before boiling. The vapour pressure is determined to 0.51 Pa at 20 °C. At higher temperatures (> 46 °C) fast dimerisation occurs of the pure solid active ingredient cyanamide which may lead to explosion.

In demineralised water cyanamide is readily soluble with no dependence on the pH. The solubility in organic solvents differs from almost insoluble in nonpolar solvents like n-hexane (2.4 mg/L) and the solvents dichloromethane respectively toluene (410 and 670 mg/L) to high soluble in polar solvents like isopropanol, acetone, methanol and ethylacetate (> 210 g/L). The pure cyanamide is hydrolytically stable, but degradation, i. e. dimerisation occurs slowly even at room temperature. The $\log_{Pow}$ is -0.72, indicating a low risk of bioaccumulation.

The result of the manufacturing process is cyanamide as a ca. 50 % aqueous solution. Cyanamide is not isolated at any stage of the production process. It is stressed by the company that all cyanamide products are not produced from a concentrated technical active substance by dilution but from enrichment of the cyanamide content in solutions.

The analytical method for cyanamide in the aqueous solution is based on a potentiometric titration with silver nitrate solution and a silver ion-selective electrode for the end-point determination. The specificity of the potentiometric method was proven by an independent HPLC method.
The analytic methods of the impurities and additives are mentioned in the confidential part.

The methods of analysis for the active substance and for the determination of the impurities and additives in the technical cyanamide have been validated and shown to be sufficiently specific, linear, accurate and precise.

**Residue Analysis**

Acceptable primary methods are available for determination of cyanamide residues in soil, air, drinking and surface water, body fluids and body tissues. An acceptable confirmatory method is presented for surface water. The method is successfully validated for the determination of cyanamide residues in surface water at the limit for drinking water of 0.1 µg/L. The study is considered to be acceptable for drinking and surface

water.
Since the application of the biocidal product is restricted to professional operators inside pig stables, secondary exposure of the general public is not expected. Therefore, the proposed method for the determination of cyanamide in air is considered to be appropriate for enforcement of a concentration of 2 µg/m³. This method is accepted.
Reliable confirmatory methods are available for determination of cyanamide residues in soil, body fluids and body tissues.

**Identity, Physico-chemical Properties and Method of Analysis of ALZOGUR®**

ALZOGUR®, as it is produced, differs from the active substance only by small amounts of additional constituents. ALZOGUR® is a blue and odourless soluble concentrate. The persistence of foam is determined to 0 ml.

**Residue Analytical Methods**

Additional analytical methods for determination of ALZOGUR residues in soil, air and water, animal and human body fluids and tissues as well as food / feeding stuffs are not required.

### *2.1.2. Intended Uses and Efficacy*

**PT 3:**

The intended use of the biocidal product "ALZOGUR®" is the disinfection against *Brachyspira hyodysenteriae* of the liquid manure stored underneath the slatted floor in pig stables in order to protect fattening pigs against the pig disease dysenteria. The product is for application by professional users only.
ALZOGUR® is rinsed from the treated surfaces (slatted floor) into the liquid manure where it exerts its effects. ALZOGUR® remains in the treated medium with a half-life of about 45 days.
The performed tests provide reliable results for efficacy assessment.
The key study showing the bactericidal activity against *Brachyspira hyodysenteriae* was performed using cyanamide L 500. Cyanamide L 500 is an aqueous solution containing approximately 50 % (w/w) cyanamide. ALZOGUR® differs in its composition to cyanamide L 500 by small amounts of additional contituents not influencing the efficacy of the product. The content of the active substance is equal in both products. Therefore it is possible to draw conclusions regarding the efficacy of ALZOGUR® based on the results achieved using cyanamide L 500.
Thus, the following results could be derived from the study:
Cyanamide L 500 exhibits a basic bactericidal activity against *Brachyspira hyodysenteriae* at a concentration of 5% after 24 h; at 0.6% after 48-96 h and at 0.3% after 144 h.

Although the quantitative test was not performed according to a guideline and the criteria of the corresponding study DIN EN 1040 were not fulfilled, the test is accepted in the frame of Annex I-inclusion of the active substance because the test method was developed considering the specific requirements of the test organism. It seems to be reliable that the efficacy achieved is sufficient for the in use situations. Nevertheless, in the frame of product authorisation further studies have to be provided.

Cyanamide is regarded to be a multi-site inhibitor interfering with the respiratory metabolism. It is known to inhibit the activity of the enzymes catalase and dehydrogenase leading to accumulation of Hydrogen peroxide in treated organisms.

Cyanamide is regarded to be a multi-site inhibitor. It is not expected that resistance to cyanamide develops from its use in pig stables under PT 3.

**PT 18:**

Cyanamide is to be used as an insecticide (PT 18). The intended use of the representative biocidal product ALZOGUR®, a 50 % aqueous solution of cyanamide, is to control fly larvae (*Musca domestica*) in liquid manure in animal housings (pig stables). The product is for application by professional users only.

The assessment of the biocidal activity of cyanamide demonstrates that it has a sufficient level of efficacy against larvae of dung breeding house flies, while no data on its ovicidal activity had been submitted. Owing to its multi-site nature of action, the development of resistance in target organisms against cyanamide is considered to be of low risk.

Acceptable laboratory studies have been provided, indicating a sufficient efficacy of the product in reducing the number of larvae of dung breeding insects. However, simulated-use, semi-field or field tests have not been provided. Therefore, it could only be anticipated that the product would be efficacious at real use conditions – but the obligation rests with the applicant to demonstrate – at product authorisation stage - the effectiveness of the larvicidal action of the product in a simulated-use test.

The intended uses of the substance, as identified during the evaluation process, are listed in APPENDIX II.

### *2.1.3. Classification and Labelling*

**Classification and Labelling of cyanamide**

The classification and labelling for cyanamide according to regulation (EC) No 1272/2008 (CLP Regulation, 10th ATP) is:

**Table 2-1 Classification of cyanamide based on Regulation (EC) No 1272/2008**

| | Classification | Wording |
|---|---|---|
| Hazard classes, Hazard categories | Acute Tox. 3<br>Acute Tox. 3<br>Skin Corr. 1<br>Skin sens. 1<br>Eye Dam. 1<br>Carc. 2<br>STOT RE 2<br>Repr. 2<br>Aquatic Chronic 3 | |
| Hazard statements | H301<br>H311<br>H314<br><br>H317<br>H318[1]<br>H351<br>H373<br><br><br>H361fd<br><br><br>H412 | Toxic if swallowed.<br>Toxic in contact with skin.<br>Causes severe skin burns and eye damage.<br>May cause an allergic skin reaction.<br>Causes serious eye damage.<br>Suspect of causing cancer.<br>May cause damage to organs (thyroid gland) through prolonged or repeated exposure.<br>Suspected of damaging fertility;<br>Suspected of damaging the unborn child.<br>Harmful to aquatic life with longlasting effects. |

[1] H318 does not need to be indicated on the label for corrosive substances and mixtures to avoid redundancy.

**Table 2-2 Labelling of cyanamide based on Regulation (EC) No 1272/2008**

| | Labelling | **Wording** |
|---|---|---|
| Pictograms | GHS05<br>GHS06<br>GHS08 | |
| Signal Word | Danger | |
| Hazard statements | H301<br>H311<br>H314<br><br>H317<br>H351<br>H373<br><br><br>H361fd<br><br><br>H412 | Toxic if swallowed<br>Toxic in contact with skin<br>Causes severe skin burns and eye damage<br>May cause an allergic skin reaction<br>Suspected of causing cancer<br>Causes damage to organs through prolonged or repeated exposure (thyroid gland)<br>Suspected of damaging fertility<br>Suspected of damaging the unborn child<br>Harmful to aquatic life with long lasting effects |
| Suppl. Hazard statements | - | - |
| Precautionary statements | None listed in Annex VI | |

**Classification and Labelling of ALZOGUR**

As the biocidal product contains a considerable amount of pure cyanamide it should be classified and labelled nearly in the same way as the active substance.

**Table 2-3 Proposed classification of ALZOGUR® based on Regulation (EC) No 1272/2008 (in accordance with CLP Regulation):**

| | Classification | **Wording** |
|---|---|---|
| Hazard classes, Hazard categories | Carc. 2<br>Repr. 2<br>Acute Tox. 3<br>Acute Tox. 3<br>Skin Corr. 1<br>Eye Dam. 1<br>Skin Sens. 1<br>STOT RE 2<br>Aquatic chronic 3 | |
| Hazard statements | H351<br>H361fd<br><br><br>H301<br>H311<br>H314<br><br>H317<br>H318<br>H373<br><br><br>H412 | Suspected of causing cancer.<br>Suspected of damaging fertility.<br>Suspected of damaging the unborn child.<br>Toxic if swallowed.<br>Toxic in contact with skin.<br>Causes severe skin burns and eye damage.<br>May cause an allergic skin reaction.<br>Causes serious eye damage.<br>May cause damage to organs (thyroid gland) through prolonged or repeated exposure.<br>Harmful to aquatic life with long |

| | Classification | **Wording** |
|---|---|---|
| | | lasting effects. |

**Table 2-4 Proposed labelling of ALZOGUR® based on Regulation (EC) No 1272/2008 (in accordance with CLP Regulation):**

| | Labelling | **Wording** |
|---|---|---|
| Pictograms | GHS05<br>GHS06<br>GHS08 | |
| Signal Word | Danger | |
| Hazard statements | H351<br>H361fd<br><br><br>H301<br>H311<br>H314<br><br>H317<br>H373<br><br><br>H412 | Suspected of causing cancer.<br>Suspected of damaging fertility;<br>Suspected of damaging the unborn child.<br>Toxic if swallowed.<br>Toxic in contact with skin.<br>Causes severe skin burns and eye damage.<br>May cause an allergic skin reaction.<br>May cause damage to organs (thyroid gland) through prolonged or repeated exposure.<br>Harmful to aquatic life with long lasting effects. |
| Suppl. Hazard statements | - | - |
| Precautionary statements | P101<br><br>P102<br>P201+202<br><br><br><br>P260<br><br>P261<br><br>P264<br>P270<br><br>P271<br><br>P272<br><br>P273<br>P280<br><br><br>P310<br><br>P321<br><br>P301+310<br><br>P302+352 | If medical advice is needed, have product container or label at hand<br>Keep out of reach of children<br>Obtain special instructions before use. Do not handle until all safety precautions have been read and understood.<br>Do not breathe dust/fume/ gas/mist/vapours/spray.<br>Avoid breathing dust/fume/gas/mist/vapours/spray.<br>Wash … thoroughly after handling.<br>Do no eat, drink or smoke when using this product.<br>Use only outdoors or in a well-ventilated area.<br>Contaminated work clothing should not be allowed out of the workplace.<br>Avoid release to the environment.<br>Wear protective gloves/protective clothing/eye protection/face protection.<br>Immediately call a POISON CENTER/doctor/…<br>Specific treatment (see … on this label).<br>IF SWALLOWED: Immediately call a POISON CENTER/doctor/….<br>IF ON SKIN: Wash with plenty of |

| | Labelling | **Wording** |
|---|---|---|
| | | water/… |
| | P304+340 | IF INHALED: Remove person to fresh air and keep comfortable for breathing. |
| | P308+313 | IF exposed or concerned: Get medical advice/attention. |
| | P361+364 | Take off immediately all contaminated clothing and wash it before reuse. |
| | P305+351+338 | IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. |
| | P405 | Store locked up. |
| | P501 | Dispose of contents/container to …. |

**Remark:**

According to the Guidance on the Biocidal Products Regulation – Volume III Human Health – Part B Risk Assessment (version 2.0, October 2015), this classification of Alzogur results in a hazard category "high" for local effects.
For application, the concentrated biocidal product is diluted with water (3 parts Alzogur + 7 parts water = 153.6 g/L cyanamide). According to skin irritation study (*in vivo* rabbit, tested ALZODEF dilutions with a cyanamide content of 1; 5 and 25 %), no classification for skin irritation or corrosivity is considered necessary for dilutions up to 25 % cyanamide (cf. skin irritation study described in Doc. II-3.3, Doc. IIIA-6.1.4/03).

Precautionary statements are selected in accordance with the rules of the Regulation (EC) No 1272/2008 and the recommendations given in the Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures (IHCP, DG Joint Research Centre, European Commission, 2009). Although the biocidal product is not used by the general public the biocidal product should be labelled with P101, P102 and P405: The biocidal product is used on farms. Thus, it is possible that children on these farms may get eased access to repositories of this biocidal product.

In addition, cyanamide meets the specific scientific criteria for endocrine disruption as set out in Regulation (EU) 2017/2100 (please refer to section 2.2.3). Thus, the product is considered to meet the criteria for endocrine disruption, too.

## 2.2. Summary of the Risk Assessment

### *2.2.1. Human Health Risk Assessment*

2.2.1.1. Hazard identification and effects assessment

In humans, cyanamide was rapidly absorbed after oral ingestion. At a dose level of 0.3 mg/kg bw (corresponding to a low dose used in human alcohol aversion therapy), the amount of substance in the systemic circulation was restricted to about 45 % of dose, which was seen as indicative of a saturable first-pass effect. The bioavailability increased with higher doses, reaching > 80 % at a dose of 1.5 mg/kg bw. Judging from the volume of distribution, cyanamide was widely distributed into tissues. Elimination from plasma proceeded with a half-life of about 40 min at the low dose and about 1 h at higher doses.

In the rat, hydrogen cyanamide was apparently completely absorbed after oral administration, with a slightly higher bioavailability in fasted animals, had a plasma half-

life of about 1 h, and was rapidly excreted, regardless of the route of administration. Total amounts of 67-92 % were eliminated within the first 24 hours post-dose in urine (the main route of excretion), faeces and expired air. The amount excreted in the urine after oral administration ranged from approximately 79.0 % to 97.7 % at 168 hours post-dose. Biliary excretion was not an important mechanism after oral dosing, however, as evidenced by faecal excretion following i.v. administration (ca. 15 % vs. ca. 3 % after oral administration), it may become relevant after intravenous or other parenteral exposure. Dose and sex-specific differences were noted in the amount of radioactivity eliminated in exhaled air, in the faeces or remaining as residues in the liver. It appears that the metabolic pathway leading to elimination as $CO_2$ is saturable in both sexes. Moreover, it is less active in females. After 168 h, residues were detected mainly in blood, liver, and kidney. No potential for accumulation was noted.
The major pathway for cyanamide metabolism after oral and intravenous dosing was acetylation of the nitrogen, resulting in the formation of N-acetylcyanamide. This pathway has been described for rats, rabbits, dogs, and humans. N-acetylcyanamide was the major metabolite in both urine and faeces and accounted for at least 40-65 % of the administered dose in rats, 85 % in dogs, and 28-58 % in humans. Other unidentified radioactive metabolites were present in rat urine and faeces, but represented less than 10 % of the administered dose in each case. Metabolism of cyanamide by mitochondrial catalase has been described as a minor pathway (DeMaster, E. et al. 1982 and 1998) resulting in the formation of cyanide and nitroxyl, but the extent of this reaction has not been quantified. Although cyanide and the cyanide metabolite thiocyanate have not been found in significant amounts in human blood and urine, respectively, nitroxyl has been identified as the active metabolite responsible for the inhibition of aldehyde dehydrogenases and is generated in humans in relevant concentrations at therapeutic dose levels (0.3 mg/kg bw/day) of cyanamide in alcohol aversion therapy.

Based on urinary excretion of the main metabolite N-acetylcyanamide after oral and dermal exposure in humans, maximum dermal absorption from a 1 % aqueous cyanamide solution following a 6 h exposure period was found to be 3.5 %. Compared to the oral absorption, dermal absorption was considerably delayed. For rats, reasonable worst case dermal absorption calculations result in 14.3 % for a 10 %, 9.5 % for a 1 % and 8.2 % for a 0.1 % solution at the 10 h exposure and sacrifice timepoint. The high dose level in this study was in the same order of magnitude (800 vs. 625 µg/cm$^2$) as the amount of test substance administered in the human experiment; a 4-fold higher absorption rate in rats (which can be explained with physiological differences, e.g. the higher number of hair follicles present in rat skin) is in good agreement with common toxicological experience.

The BPC WG-I-2016 concluded the following dermal absorption values due to corrosivity of cyanamide: Where exposure to corrosive concentrations takes place, dermal absorption of 100 % should be used.

For concentrations above 10 %: when irritant or corrosive effects can be excluded 25 % dermal absorption should be used.

Therefore a dermal absorption value of 100 % should be used for the concentrate (50 % cyanamide) and 25 % for the in use dilution (15.4 % cyanamide).

For calculation of dermal risks for the worker the dermal absorption value of 25 % is used because a distinction of using the concentrate (mixing and loading phase) and the in use dilution (application phase) is not possible and not appropriate for the following reasons:

Measurement data was available to assess the whole process of mixing and loading, application and rinsing off of treated surfaces. Actual dermal hand exposure, actual body exposure (without hands) and air concentration were determined over one working day without differentiation of the described working steps. The mixing and loading is immediately performed before the pouring on the stable floor and it is not possible to distinguish the phases. The use of only hand exposure data to assess the mixing and

loading phase is not reasonable since hand exposure also occurred during the pouring phase. In addition, measured data is also available for the movable cart application. These values are in the same order of magnitude as for the watering can application even though for the movable cart only 2 mixing and loading steps are necessary. Therefore, it seems that the exposure relevant step is the application to the stable floor. Moreover, the use of the corrosive product in mixing and loading phase is assessed qualitatively in a local risk assessment.

**Acute Toxicity**

In rats, cyanamide was toxic after acute oral exposure: LD50 values of 223 and 142 mg/kg bw were obtained in two key studies, but values < 200 mg/kg bw were also established in some of the additional/supplementary studies. Following acute dermal exposure, toxicity was less pronounced (LD50 = 848 mg/kg bw), while some toxicity, but no mortalities were noted after inhalation of up to 1.0 mg cyanamide/L air for 4 h, the highest attainable concentration.

Additional studies in rats demonstrated an increase in toxicity, if ethanol was administered orally shortly after oral or inhalative exposure to cyanamide.

**Classification and labelling according to Regulation (EC) No 1272/2008 (RAC opinion adopted 5th June 2015):**

Acute toxicity, cat. 3; H301 - Toxic if swallowed
Acute toxicity, cat. 3; H311 - Toxic in contact with skin

**Skin / Eye Irritation; Sensitisation**

While tests in rabbits clearly proved cyanamide to be an eye irritant, equivocal data on skin irritation was obtained from three skin irritation tests. However, in line with observations in humans, according to an in vitro skin corrosion test with cyanamide L 500 using EpiDerm reconstructed skin membranes and with Regulation (EC) No. 1272/2008, the RAC decided that cyanamide should also be considered skin corrosive.
As cyanamide is skin corrosive (cat. 1, H314 according to CLP criteria), specific classification as an eye irritant is not necessary, because it is already included implicitly in the classification as skin corrosive. Therefore, no classification and labeling for eye irritation are necessary. In the guinea pig maximisation test, cyanamide demonstrated sensitising properties.

**Classification and labelling according to Regulation (EC) No 1272/2008 (RAC opinion adopted 5th June 2015):**

Skin Corr. 1, H314 - Causes severe skin burns and eye damage
Skin Sens. 1, H317 - May cause an allergic skin reaction

**Medium-term Toxicity**

The main target organs following repeated oral administration of cyanamide were red blood cells, the thyroid gland and the testes. The most sensitive effect occurred in the testes of dogs. Dose-dependent decreases in spermatogenesis in young dogs were noted from the low dose group onwards (0.6, 2 and 6 mg/kg bw/d) of the 90-d study. However, the low dose of 0.6 mg/kg bw/day was free of effect when tested in a group of mature male dogs in a supplementary 90-d study. Also, in the 1-yr study, similar effects were only observed at a 10-fold higher dose in older animals. Based on published data on the maturation of spermatogenesis in dogs it must be concluded that the young dogs were still immature at the end of the study so that the findings at the low dose cannot be ascribed to treatment unequivocally. Thus, a substance related effect in the cyanamide treated animals concerning a delay in sexual maturation can not be excluded.

The impairment of spermatogenesis in adult dogs may be related to a depletion of retinoic acid in testicular tissues following the inhibition of (retin)aldehyde dehydrogenase activity by cyanamide treatment. In this case, dietary intake of vitamin A can be expected to modulate the effect on the testis.
In rats and dogs, anaemia or reduced red blood cell counts were associated with decreases in haemoglobin and haematocrit, pigmentation of spleen and liver, or extramedullary haematopoiesis. Decreases in $T_4$ plasma levels and histological changes in the thyroid gland indicated thyroid hormone depletion; $T_3$ values remained in the normal range.
The oral NOAEL in rats was 1.5 mg/kg bw/d based on thyroid gland changes (small follicular lumen without colloid) at 4.5 mg/kg bw/d in the 90-d study. The inhalative NOAEL in rats was < 0.15 mg/L air based on a decrease in body weight gain in the 14-d study (6 h exposure/day). The oral NOAEL in dogs was 1 mg/kg bw/d based on testicular findings in the 90-d and 1-yr studies in sexually mature dogs. The dermal (local) NOAEL in rabbits was 12.5 mg/kg bw/d, based on the results of the 21-d study; it should be noted that this study was considered by the RMS as not acceptable with respect to assessment of systemic effects, and therefore should not be used for estimation of the rate of dermal absorption of cyanamide.

**Classification and labelling according to Regulation (EC) No 1272/2008 (RAC opinion adopted 5th June 2015):**
STOT-RE 2, H373 – May cause damage to organs through prolonged or repeated exposure (thyroid gland)

**Genotoxicity**

Hydrogen cyanamide was clastogenic *in vitro,* inducing structural chromosome aberrations in cultured human lymphocytes. The *in vivo* micronucleus assay provided no evidence for a genotoxic or clastogenic potential of cyanamide. In summary, the available data indicate that cyanamide is unlikely to be genotoxic *in vivo*.

**Classification and labelling according to Regulation (EC) No 1272/2008 (RAC opinion adopted 5th June 2015):**

None

**Chronic Toxicity/ Carcinogenicity**

Long-term dietary toxicity studies were conducted in rats and mice. In the chronic toxicity study in Sprague-Dawley rats, hydrogen cyanamide was administered via oral gavage for 91 weeks. In the high dose group, clinical observations demonstrated effects of general health reduction. Due to these observations, the dose levels have been reduced after 16 weeks of treatment. Significant depressions in body weight and body weight gain values were obtained in intermediate and high dose males and females in the first weeks. A decrease in mean food consumption was observed in the high dose group. Compound-related clinical pathology changes were found in males and females of the high dose group and in males of the intermediate dose group, histopathological changes (reduced colloid) were noted in the thyroid gland of intermediate and high dose males and in high dose females. The NOAEL of this study was 1 mg/kg/day active substance cyanamide based on the histopathological effects in the thyroid gland obtained in the intermediate dose.
In a carcinogenicity study, calcium cyanamide was administered to F344 (Fischer) rats orally in the diet for 107, and to B6C3F1 mice for 100 weeks. In rats, no tumour at any site could be related to test substance administration. In male mice, a significant test substance-related increase in mortality was found and mean body weight of high and intermediate dose males as well as high-dose females was slightly lower than those of the corresponding controls. With regard to neoplasms, increased incidences of haemangiosarcoma (M) and malignant lymphoma (F) were observed in mice of the

highest dose group; however statistical significance could either not be established and/or incidences were not clearly outside the range of historical controls.
In another carcinogenicity study, [Crl:CD-1 (ICR) BR] mice were administered hydrogen cyanamide via the drinking water in concentrations of 70, 200, and 600 ppm. A slight increase in morbidity and mortality in the female intermediate and high dose groups was obtained. In the first weeks of the study body weight gain, food and water consumption were reduced in the intermediate and high dose groups. Substance-related histopathological effects were observed in the form of dose-related chronic cystitis in the urinary bladder in the medium and high dose groups and atrophic basophilic tubules in the kidney in the high dose group. At the high dose in females, a slight increase in granulosa-theca tumours was found. The Maximum Tolerable Dose (MTD) was exceeded at this dose level. There were no treatment-related changes in the tumour profile at 200 ppm referring to approximately 12.2 mg/kg bw/day active substance cyanamide. The non-neoplastic NOAEL was 70 ppm or approximately 4.2 mg/kg bw/day, based on increased mortality, reduction in body weight gain, food consumption and histopathological effects at higher dose levels.

**Classification and labelling according to Regulation (EC) No 1272/2008 (RAC opinion adopted 5th June 2015):**

Carc. 2, H351

**Developmental / Reproduction Toxicity**

**Developmental Toxicity:**

In the developmental toxicity studies, the main effect of cyanamide on maternal animals was decreased body weight gain (rats) or body weight loss (rabbits). The maternal NOAEL was < 5 mg/kg bw/d in rats and 6 mg/kg bw/d in rabbits. Body weight was also the most sensitive endpoint for the rat foetus. A reduction in foetal weight, associated with a reduction in skeletal ossification, was observed at the dose of 15 mg/kg bw/d, while a specific malformation (Bochdalek-type diaphragmatic hernia) was found in 20 % of the litters at 45 mg/kg bw/d. These anomalies may relate to an interference of cyanamide metabolites with retinoic acid production. In addition, skeletal malformations, mainly of the vertebrae, were noted in a few foetuses of this group. Variations related to a less advanced state of general ossification and to possible interference with the process of rib ossification were present to a greater extent in the high dose group and correspond to the reduction in foetal weight. These variations included unossified hyoid body, incomplete ossification of the skull, bipartite vertebral centra, incomplete ossification of vertebral arches, less than four caudal vertebrae ossified, unossified sternebrae, incomplete ossification of the sternebrae, $14^{th}$ rudimentary ribs, wavy or bent ribs and unossified pubes. No external abnormalities of the foetuses were observed.
Malformations (diaphragmatic hernia and vertebral malformations) were observed at 45 mg/kg bw/day, a dose with considerable maternal toxicity.

Rabbit foetuses did not exhibit substance-related malformations. Prenatal developmental toxicity in the high dose group presented as embryo- and foetolethality and a higher prevalence of small foetuses. An increased foetal incidence of a specific eye abnormality (folded retina) was considered a fixation artefact based on new data regarding the frequency of such fixation-related findings in rabbit foetuses.
The developmental NOAEL of cyanamide therefore is 5 mg/kg bw/d in rats and 6 mg/kg bw/d in rabbits under the conditions of the studies described here, but could be modulated, presumably, by the vitamin A intake of the mothers.

**Reproduction Toxicity:**

In a rat two-generation study with gavage treatment, effects on the parental generations (P, F1) included reduced body weight gain and food consumption during the pre-mating period. Low fertility and an increase in complete prenatal litter losses were observed in

the high dose P animals. Although this may be related to the compromised state of health of these animals which necessitated dose reduction prior to mating, the finding was also present, although less notable, in the F1 generation. No substance-induced morphological abnormalities were found in the offspring. Neonatal survival of the F1 and the F2 pups, however, was significantly lower in all treated groups compared to the control group. Similar results on F2 offspring viability have been obtained from a feeding study with comparable dose levels of cyanamide. In this study, the concomitant increase in the number of neonates with pale or bluish skin could indicate that respiration problems may have been involved. In addition, testicular histopathology of adult F1 males indicated dose-dependent effects on spermatogenesis but of insufficient magnitude to impair fertility in these rats. The discrepancy for testicular findings in the F1 generation between oral gavage and feeding studies might be explained by low milk excretion of the active substance leading to a relative lack of exposure of the pups during lactation when the mother is treated by gavage.
For parental and reproductive toxicity, the NOAEL was 3.75 mg/kg bw/d, based on the reduced body weight gain and the fertility impairment observed in the gavage study. For offspring toxicity, the NOAEL was < 1.25 mg/kg bw/d, based on neonate mortality.

Overall, in several repeat-dose studies there were single indications for adverse effects on fertility and reproduction (rat, rabbit) and on the testes (dogs), however neither a consistent pattern could be observed, nor could the findings be reproduced in the respective other studies. Additionally, some methodological limitations in the studies need to be taken into account. Overall, the RMS sees "some evidence" but not a "clear evidence" for adverse effects on reproduction and therefore, proposes a classification with category 2 (H361f, CLP regulation).

In the study of [redacted] (1989), diaphragmatic hernias occurred with an incidence rate of about 4.3 % (7/163 pups, in 5 out of 24 litters) in the rat offspring of the high dose group (45 mg/kg bw/d). Maternal toxicity in the high and medium dose group (15 and 45 mg/kg bw/d) was considered significant. There were no deaths, but hypoactivity was seen in 8 dams of each dose group during the first two exposure days, and the corrected body weight gain was reduced by 29 % and 71 %, respectively, compared to the control. Mean food consumption was reduced by 8-11 % in the mid dose group and by 23-24 % in the high dose group during gestation days 6-20.
In addition, there was clear evidence from other studies that repeated daily doses of 4.5-40 mg/kg bw/day caused significant systemic toxicity in rats. At these dose levels, consistent and marked effects on thyroid gland morphology (increased number of small follicles, reduction of colloid content) were observed in the 28-day study ([redacted], 1988), in the 90-day study ([redacted]., 1975) and in the two-generation reproduction study ([redacted]., 1986). Furthermore, repeated daily doses of 45 mg/kg bw/day are expected to produce marked systemic toxicity in rats since this dose level is only about 3-fold lower than the doses causing mortality following a single oral administration ([redacted], 1973; [redacted], 1994).

Diaphragmatic hernias are considered as life-threatening malformation.
There is evidence that cyanamide might induce fetal diaphragmatic hernias via the following mechanism of action: 1) Cyanamide enters the maternal blood circulation and is metabolised to the active metabolite nitroxyl (HNO). 2) HNO enters the fetal blood circulation and reaches the tissue of the developing diaphragm. 3) HNO inhibits retinaldehyde dehydrogenase genes (Raldh2/ALDH1A2) of the diaphragmatic tissue, thereby reducing the concentration of retinoic acid in the tissue. 4) Decrease of retinoic acid during the retinoic acid-dependent diaphragm formation disrupts normal tissue development and leads to diaphragmatic hernias.
Metabolic activity leading to malformations (e.g. conversion of cyanamide to nitroxyl postulated to be responsible for the aldehyde dehydrogenase (ALDH)-inhibitory properties of cyanamide) significantly takes place in the maternal liver (see 4.12.1.5

Species-specific differences in cyanamide-induced toxicities). The foetal liver does not have acquired sufficient metabolic capacity to bioactivate cyanamide. Thus, a specific maternally-mediated mechanism leading to malformations can be demonstrated.
Since developmental effects relevant for classification (i.e. diaphragmatic hernia) were observed only in one species at a high dose level associated with significant maternal toxicity or marked systemic toxicity, classification concerning effects on development in Category 2 (H361d, CLP criteria) is considered appropriate.

**Classification and labelling according to Regulation (EC) No 1272/2008 (RAC opinion adopted 5th June 2015):**

Repr. 2, H361fd - Suspected of damaging fertility; Suspected of damaging the unborn child

**Neurotoxicity**

Special neurotoxicity studies were not performed. There is no evidence of a neurotoxic effect from other studies. An investigation of delayed neurotoxicity is not required, as the cyanamide molecule is unrelated to substances with known delayed neurotoxic properties such as organophosphates. Therefore submission of acute or repeat-dose neurotoxicity studies was not considered necessary by the RMS.

**Classification and labelling according to Regulation (EC) No 1272/2008 (RAC opinion adopted 5th June 2015):**
None

**Mechanistic Studies**

The inhibitory action of cyanamide on ethanol metabolism, resulting in increased acetaldehyde levels in blood, has been exploited in alcohol aversion therapy. Cyanamide itself is not active *in vitro* and has to be activated by the mitochondrial catalase enzyme. This results in the formation of an unstable N-hydroxycyanamide intermediate that decomposes to release nitroxyl (HNO) and cyanide (CN). It has been proposed that nitroxyl interacts in a partially irreversible fashion with sulfhydryl groups in the catalytic center of $NAD^+$-dependent aldehyde dehydrogenases (cytoplasmic ALDH1 and mitochondrial ALDH2) and thus interferes with the conversion of their aldehyde substrates to the respective acids. *In vitro*, a predominantly irreversible inhibition is elicited in the pH range of 7.0 to 6.0, while more than 50 % of the inhibition at pH 8.5 can be reversed by the addition of thiols. Inhibition of ALDH family enzymes has been observed in liver and brain, but can be expected to occur in other tissues as well, due to the wide distribution of the active substance. The $ED_{50}$ of cyanamide for an increase of acetaldehyde concentration in blood has been estimated to be 0.11 mmol/kg in male rats (equivalent to 4.6 mg/kg bw).
Few studies to characterise the mechanism(s) of cyanamide toxicity have been conducted. Activation of the hypothalamo-pituitary-adrenal axis by cyanamide resulting in an increase of circulating glucocorticoids has been reported. The involvement of ALDH enzymes in this action has not yet been elucidated; however, ALDH activity in the paraventricular nucleus is high, and this suggests that cyanamide may alter the HPA axis at the hypothalamic level. Changes in the activity of pituitary thyrotrophic, lactotrophic and gonadotrophic cells may have played a role in cyanamide effects on thyroid gland and testis function noted in rats and dogs, as well as in the reduction of fertility observed in the two-generation study in rats. In addition, cyanamide exposure might have a direct influence on the testis through inhibition of ALDH enzymes and induction of a local tissue deficiency of the morphogen retinoic acid (RA). Spermatogenesis ceases in male rats when vitamin A stores in the liver are depleted, an effect, which is rescued within a few hours of RA application. An inhibition of RA synthesis during cyanamide exposure, therefore, may have similar effects on the testis as the lack of retinol esters, the starting material for ALDH-mediated RA production.

The malformations of the diaphragm observed in the rat study are considered to be a consequence of ALDH inhibition, as this type of diaphragmatic hernia can also be elicited in mice by genetic interference with RA-mediated transcription pathways. Moreover, the lesions are identical in location (dorsolateral area of diaphragm, near oesophagus) to those observed with another ALDH inhibitor, nitrofen. Rats exposed to this substance *in utero* also displayed an increase in neonatal mortality, similar to the offspring in the two-generation studies with cyanamide. For nitrofen, this effect could be attributed to a maturational delay in pulmonary function, associated with smaller lungs and decreased surfactant. As the nitrofen-induced diaphragmatic hernia can be rescued by increasing the maternal supply of retinol or RA, it is expected that vitamin A intake will also serve to modulate the embryotoxicity of cyanamide.

**Medical Data**

With the exception of minor skin irritation leading to dermatitis, no signs of diseases or health impairments caused by cyanamide were found during medical surveillance of manufacturing plant personnel. Medical examinations also included special investigations of functional disorders regarding the testes and the thyroid gland, and potential sensitising properties. Hypersensitivity to alcohol as a measure of a pharmacologically relevant inhibition of aldehyde dehydrogenases could be diagnosed in workers handling calcium cyanamide or calcium cyanamide-containing products. Under prevailing workplace conditions, exposure may have occurred by inhalation or by dermal absorption. Alcohol sensitisation and urinary excretion of the metabolite N-acetylcyanamide indicated that 60-70 % of workers experience internal exposure on a regular basis. The effective dose range for humans with respect to aldehyde dehydrogenase inhibition can be estimated from the daily doses used in alcohol aversion therapy (10-200 mg/person/d).

While the toxic potential under manufacturing conditions appears to be low, a number of acute reactions related to the spraying of hydrogen cyanamide in agriculture and presenting mostly as erythema and dermatitis but also as neurological signs, cardiovascular symptoms, nausea and eye irritation, have recently been reported from Italy. Effects occurred with a latency ranging from 30 minutes to 30 hours. The majority (66 %) of the persons affected apparently used insufficient or no protective equipment. Similar findings are reported from India where vineyard workers without protective equipment developed skin lesions, in some cases involving destruction of the upper skin layers, after mixing and/or spraying a 49 % hydrogen cyanamide solution.

Cases of allergic contact dermatitis are also reported among nurses handling cyanamide solutions intended to be administered to patients. Adverse drug reactions in the form of lichen planus-like skin eruptions were observed in a number of patients ingesting cyanamide as an alcohol deterrent.

No specific antidote is known, and symptomatic treatment is recommended. In case of skin/eye contact, immediate decontamination should be performed. In case of ingestion and if the amount ingested is small, use of activated charcoal for gastrointestinal decontamination, sodium sulfate, and drinking of several glasses of water is recommended. The ingestion of large amounts may lead to a fall in blood pressure and to unconsciousness, and the patient will require professional medical care. Intake of alcoholic beverages must be avoided in any case.

**Summary & Conclusion**

Cyanamide is rapidly absorbed after oral ingestion and widely distributed into tissues; systemic bioavailability of the parent substance to organs other than the liver increases with dose due to a saturable first-pass metabolism. Excretion is rapid, mainly via urine, with minor amounts being eliminated via faeces and expired air. N-acetylcyanamide was identified as the main metabolite but appears to be of no toxicological concern, whereas nitroxyl, generated through a minor metabolism pathway, has toxicological relevance due to its inhibitory effect on aldehyde dehydrogenases. Dermal absorption in humans is

estimated to reach 3.5 % of dose following exposure to a 1 % aqueous solution. For rats, realistic worst case dermal absorption calculations result in 14.3 % for a 10 %, 9.5 % for a 1 % and 8.2 % for a 0.1 % solution.

The BPC WG-I-2016 concluded the following dermal absorption values due to corrosivity of cyanamide: Where exposure to corrosive concentrations takes place, dermal absorption of 100 % should be used.
For concentrations above 10 %: when irritant or corrosive effects can be excluded 25 % dermal absorption should be used.
Therefore a dermal absorption value of 100 % should be used for the concentrate and 25 % for the in use dilution (15.4 % cyanamide).

For calculation of dermal risks for the worker the dermal absorption value of 25 % is used for the concentrate as well as for the dilution as the mixing and loading phase cannot be distinguished from the application phase (explanation see above).

Acute toxicity of cyanamide was moderate after oral, and lower, but measurable after dermal exposure. Inhalative uptake did not result in toxic signs but increased the sensitivity towards ethanol. Cyanamide is considered irritating to eyes, corrosive to skin and to be a sensitiser via the skin.

There was no evidence for a genotoxic or a carcinogenic potential of cyanamide in humans *in vivo*. In repeat-dose studies, red blood cells, thyroid gland, and testes were identified as toxicological targets. In addition, fertility was impaired in the two-generation study. In rats, teratogenic effects on the diaphragm were presumably related to the inhibition of aldehyde dehydrogenases and a reduction in retinoic acid signalling resulting from a decrease in enzyme activity. Based on the data from other ALDH inhibitors, the nutritional supply of vitamin A at the time of exposure can be expected to modulate teratogenic risk.

The relevant medium-term overall NOAEL of 1 mg/kg bw/d (1-yr study in dogs, supported by 90-d study in mature dogs) was used as the starting point for risk characterisation of both medium- and long-term exposure, based on the nature of the effect observed on the testes, indicating that spermatogenesis can be impaired in males. By using a combined assessment factor of 100 and assuming 100 % oral absorption, a

**Systemic Acceptable Exposure Level ($AEL_{medium-/long-term}$) of 0.01 mg/kg bw/d**

is proposed for repeated medium-/long-term exposure towards cyanamide of the general population, including sensitive sub-populations. This AEL is well below the minimum daily dose used for alcohol aversion therapy in humans (0.4 mg/kg bw/day).
Acute maternal effects (hypoactivity in 20 % of the dams) were observed in the embryotoxicity/ teratogenicity study in rats on the first 1-2 days of treatment with 15 or 45 mg/kg bw/day. Diaphragmatic hernia was seen in rats at the top dose level (45 mg/kg bw/day). The NOAEL of 5 mg/kg bw/day for hypoactivity following the first two applications is regarded as the relevant starting point for setting a systemic reference dose for acute exposure. By using a standard combined assessment factor of 100 and assuming 100 % oral absorption, a

**Systemic acute Acceptable Exposure Level ($AEL_{acute}$) of 0.05 mg/kg bw/d**

is proposed for cyanamide.
Although no residues in food or feed are expected to arise from the intended use of the exemplary product submitted for this dossier, they cannot be excluded with certainty for further applications with other product types. Therefore, an **ADI of 0.01 mg/kg bw** and an **ARfD of 0.05 mg/kg bw** are derived, which were also established during the resubmission assessment of the a.s. cyanamide for inclusion in Annex I of Directive 91/414/EC. They are based on the same considerations to establish the $AEL_{medium-/long-term}$ and $AEL_{acute}$ reference values in this CA-report, respectively.

**Classification/labelling according to Regulation (EC) No 1272/2008 as in the RAC opinion from 5th June 2015:**

Acute Tox 3, H301, H311
Skin Corr 1, H314
Skin Sens. 1, H317
STOT-RE 2, H373 (thyroid gland)
Repr. 2, H361fd
Carc. 2, H351

2.2.1.2. Exposure assessment

**Exposure of Professionals**

**PT 3:**

The active substance cyanamide is produced in the EU, the biocidal product ALZOGUR® is manufactured within the EU.

For exposure of professionals the application by watering can or half-automated movable cart ("Dosierwagen") (scenario 1) and also secondary exposure to cyanamide (scenario 2) is considered.
Purified cyanamide is a colourless and odourless solid, the formulated product ALZOGUR® (concentration of 49 - 51 % cyanamide) is a blue, odourless water soluble concentrate. ALZOGUR® is diluted on site with water to the desired application concentration (10 L application solution contains 3 parts ALZOGUR and 7 parts water, as worst case if the remaining slurry is 10 cm high). ALZOGUR® is applied by means of a watering can equipped with a sprinkler head onto the slatted floor in downward direction in empty pig stables. Alternatively, ALZOGUR® can be applied by means of a half-automated movable cart ("Dosierwagen"). For both application methods, the solution drains into the liquid manure, i.e. into the canal under the floor. The application solution remaining on the surface of the slatted floor is finally rinsed with a watering hose into the liquid manure canal.
Since no applicable models are available to assess an application by watering can, the participant accepted to perform an operator exposure study. The operator exposure study was conducted as a higher tier study to determine realistic occupational exposure to ALZOGUR® containing 50 % w/w cyanamide during typical application by watering can in piggeries. The study was performed in the west of Germany (North Rhine-Westphalia) in the years 2010 - 2011. Additionally in a former field trial the application with a movable cart was reviewed. The results showed that this application form is comparable with the watering can application.
The total inhalation exposure based on the maximum determined value. The resulting inhalation exposure during all phases of application using a watering can or movable cart is **0.035 mg/m³** as 8 h time weighted average (8-h TWA). Respiratory protective equipment was not used during the working period. Due to local risk assessment respiratory protective equipment (full face mask or half face mask with safety goggles) is mandatory. The resulting inhalation exposure by use of RPE (AF 10) is **0.0035 mg/m³** cyanamide as 8 h time weighted average (8-h TWA).

Dermal exposure was measured by means of a whole-body inner dosimeter. In the study a Pro-Chem® I"C" Typ3 coverall, and Camatril® 732 gloves are used as suitable protective clothing. The total actual dermal exposure during the application of the biocidal product ALZOGUR® is based on the maximum determined value. The resulting actual dermal exposure during all phases of application using a watering can or movable cart is **1.5 mg cyanamide/person/day**.

After application and post-application, residues of ALZOGUR® are present in the liquid

manure below the slatted floor area of the pig stable (scenario 2). ALZOGUR® has been further diluted by rinsing with water and washing into the liquid manure, an estimate of the in-use solution attenuation leads to a dilution factor of approximately 1000 (1 L ALZOGUR® per $m^3$ of liquid manure). Taking this into account, the inhalation exposure is assessed as negligible. Also the direct contact with the ALZOGUR® residues in the manure canal is not possible, dermal exposure inside the pig stable is highly unlikely and assessed as negligible.

**PT 18:**

For exposure of professionals the application by watering can or half-automated movable cart ("Dosierwagen") (scenario 1) and also secondary exposure to cyanamide (scenario 2) is considered.
Purified cyanamide is a colourless and odourless solid, the formulated product ALZOGUR® (concentration of 49 - 51 % cyanamide) is a blue, odourless water soluble concentrate. ALZOGUR® is diluted on site with water to the desired application concentration (10 L application solution contains 1 part ALZOGUR® and 9 parts water, as worst case if the remaining slurry is 10 cm high). ALZOGUR® is applied by means of a watering can equipped with a sprinkler head onto the slatted floor in downward direction in empty pig stables. Alternatively, ALZOGUR® can be applied by means of a half-automated movable cart ("Dosierwagen"). For both application methods, the solution drains into the liquid manure, i.e. into the canal under the floor. The application solution remaining on the surface of the slatted floor is finally rinsed with a watering hose into the liquid manure canal.
Since no applicable models are available to assess an application by watering can, the participant accepted to perform an operator exposure study. The operator exposure study (2010-2011) was conducted as a higher tier study to determine realistic occupational exposure to ALZOGUR® containing 50 % w/w cyanamide during typical application by watering can in piggeries for disinfection (PT 03). Though the concentration of cyanamide is higher for PT 03 (3 parts ALZOGUR® and 7 parts water) than for PT 18 (1 part ALZOGUR® and 9 parts water) it is expected that the exposure during mixing and loading phase is comparable since the operator handles the concentrate of the product. For the application phase it is assumed that the exposure is lower in PT 18 due to the lower concentration. Therefore the values determined for PT 03 used also for PT 18 but representing a worst case assessment. Additionally in a former field trial the application with a movable cart was reviewed (PT 03). The results showed that this application form is comparable with the watering can application.
The total inhalation exposure based on the maximum determined value. The resulting inhalation exposure during all phases of application using a watering can or movable cart is **0.035 mg/m³** as 8 h time weighted average (8-h TWA). Respiratory protective equipment was not used during the working period. Due to local risk assessment respiratory protective equipment (full face mask or half face mask with safety goggles) is mandatory. The resulting inhalation exposure by use of RPE (AF 10) is **0.0035 mg/m³** cyanamide as 8 h time weighted average (8-h TWA).
Dermal exposure was measured by means of a whole-body inner dosimeter. In the study a Pro-Chem® I"C" Typ3 coverall, and Camatril® 732 gloves are used as suitable protective clothing. The total actual dermal exposure during the application of the biocidal product ALZOGUR® is based on the maximum determined value. The resulting actual dermal exposure during all phases of application using a watering can or movable cart is **1.5 mg cyanamide/person/day**.

After application and post-application, residues of ALZOGUR® are present in the liquid manure below the slatted floor area of the pig stable (scenario 2). ALZOGUR® has been further diluted by rinsing with water and washing into the liquid manure, an estimate of the in-use solution attenuation leads to a dilution factor of approximately 330 or 1000 (1 L or 3 L ALZOGUR® per $m^3$ of liquid manure in PT 18 or PT 3 respectively). Taking this into account, the inhalation exposure is assessed as negligible.Also the direct contact with ALZOGUR® residues in the manure canal is not possible, dermal exposure inside the

pig stable is highly unlikely and assessed as negligible.

**Exposure of Non-Professionals and the general public**

For the biocidal product ALZOGUR, only professional use is intended. Therefore, non-professional primary exposure is not expected.
Secondary exposure by production is not expected for the general public if the biocidal product is produced as described by the applicant. The production takes place in closed systems and the general public does not have access to production plants.
The product is intended to be used inside empty pig stables. Residues in food or feed are therefore not expected to occur and it is assumed that the general public does not have access to such buildings.

In the frame of considering the questions mandated to ECHA in the Art.75(1)(g) request, the potential exposure of the general public to liquid manure was assessed. Cyanamide is considered to have endocrine disrupting properties with respect to humans. However, there is currently no agreed methodology for undertaking a risk assessment for ED properties.

The exposure of the general public via liquid manure is considered relevant according to the current standards of assessment. As there are no models for the application of liquid manure and the exposure of the general public, the description of the exposure for the general public regarding the qualitative assessment is based on exposure scenarios developed for the application of plant protection products, i.e. bystander and resident exposure as well as recreational exposure. For details please refer to APPENDIX V.
Considering the exposure description (APPENDIX V, section 2.1) an exposure to the active substance due to the contact during and after the application of liquid manure cannot be excluded for the general public. There is only the possibility of reducing the exposure of the general public by potential risk mitigation measures, e.g.: i) prolonged storage of liquid manure, ii) warning signs or other measures to restrict access to treated areas and iii) incorporation into soil as additional consideration. A detailed description is included in APPENDIX V.
Based on the given description of the exposure for the general public and the description of potential risk mitigation measures, there are uncertainties about the magnitude of exposure-reducing measures. These measures may lead to a reduction of exposure of the general public, but the WG did not consider them suitable and concluded that the exposure to the general public cannot be generally excluded. This is one reason why it cannot be concluded whether these measures are sufficient to ensure an acceptable risk with regard to the ED properties of the active substance as requested in the mandate. Furthermore, all presented RMM have already been considered unsuitable in a regulatory framework by the ENV WG.

Following the e-consultation about the qualitative assessment for the general public and the WG discussion it was concluded that the exposure of the general public cannot be excluded. Further, it was not possible to conclude on the risk assessment at the WG.

With regard to the e-consultation on dietary exposure, the WG confirmed the conclusion that consumer exposure via residues is not expected.
Due to the fact that application takes place in empty piggeries as intended (treatment of liquid manure stored underneath the slatted floor) and product is rinsed from the treated surfaces (slatted floor) into the liquid manure, no exposure assessment is considered necessary for animals after application and post-application. Secondary exposure of animals is considered very low. Therefore the product should only be authorised for the application in empty piggeries which need to be taken into consideration at national authorisation stage.

2.2.1.3. Risk characterisation

**Risk Assessment for Professionals**

The risk characterisation for systemic effects of cyanamide is performed with the AEL approach. In this approach total internal body burden is compared either to the $AEL_{short-term}$ of 0.05 mg/kg bw/d or to the $AEL_{long-term}$ of 0.01 mg/kg bw/d. Both AELs are used because the frequency of exposure to cyanamide is different for farmers (short-term exposure) and for pest control operators (short-term and long-term exposure).
The $AEL_{short-term}$ (an internal reference value) is based upon the oral NOAEL of 5 mg/kg bw/day (acute maternal effects, hypoactivity) from an embryotoxicity / teratogenicity study in rats, and the assumption of 100 % oral absorption. By using a default assessment factor of 100 an $AEL_{short-term}$ of 0.05 mg/kg bw/day is derived for short term exposure towards cyanamide.
The $AEL_{long-term}$ (an internal reference value) is based upon the oral NOAEL of 1 mg/kg bw/day (effects on the testes) from a 1-yr study in dogs supported by 90-d study in mature dogs, and the assumption of 100 % oral absorption. By using a default assessment factor of 100 an $AEL_{long-term}$ of 0.01 mg/kg bw/day is derived for long term exposure towards cyanamide.

If the total internal body burden is lower than the reference dose, health risks leading to concern are not anticipated.

For pest control operators the total actual exposure in tier 2a exceeds the long-term AEL by a factor of 1.18 in scenario 1 (application by watering can or half automated movable cart).
It cannot be excluded that the high exposure levels of cyanamide from this exposure scenario will result in toxic effects in workers. Therefore no safe use is identified for this scenario in the risk characterization for systemic effects.
Based on these results and conclusions on systemic health risks in tier 2a, further refinement of the risk characterisation (starting with the refinement of the exposure estimate) is considered obligatory for scenario 1 (see tier 2b).
If risk mitigation measures (gloves, coverall and RPE) are taken into account (tier 2b) for scenario 1 (application by watering can or half automated movable cart), the estimated exposure is below the reference value.

For the other professional exposure scenario for farmers (application by watering can or half automated movable cart) the estimated uptake / reference value is below 100 % and thus a safe use is identified if risk mitigation measures (gloves and coverall) are taken into account (tier 2a).

Due to the skin corrosive properties of cyanamide, a qualitative risk assessment for local effects is necessary. Based on the Guidance for Human Health Risk Assessment, Volume III – Part B, a local risk assessment taking into account contact to skin, respiratory tract and eyes has been carried out in addition to the quantitative risk characterisations for systemic effects. The local dermal risk assessment was carried out for exposure to the concentrated biocidal product during mixing and loading phase.

Considering scenario 1 (application by watering can or half automated movable cart) the reduction of contact to skin, respiratory tract and eyes with the proposed safety protection measures (effective chemically protective gloves like Camatril 732, a protective coverall like Pro-Chem I "C" according to the study of Rath, 2011, respiratory protective equipment including full face mask or half face mask with safety goggles, and chemically protective boots) minimizes the anticipated health risks to an acceptable level for professional users (farmers and pest control operators).

| Scenario | Conclusion risk assessment systemic effects | Conclusion risk assessment local dermal effects | Conclusion ED risk assessment | Overall conclusion | Included RMM |
|---|---|---|---|---|---|
| 1 - application by watering can or half automated movable cart – farmers, short-term exposure | acceptable | acceptable | acceptable | acceptable | effective chemically protective gloves like Camatril 732, a protective coverall like Pro-Chem I "C" according to the study of Rath, 2011, respiratory protective equipment including full face mask or half face mask with safety goggles, and chemically protective boots |
| 1 - application by watering can or half automated movable cart – pest control operators, long-term exposure | acceptable | acceptable | acceptable | acceptable | effective chemically protective gloves like Camatril 732, a protective coverall like Pro-Chem I "C" according to the study of Rath, 2011, respiratory pretective equipment including full face mask or half face mask with safety goggles, and chemically protective boots |

For the following exposure scenarios the risk assessment does not indicate a concern taking into account the described protection measures: scenario 1 (application by watering can or half automated movable cart – farmers (small-size farm), **short-term exposure**) and scenario 1 (application by watering can or half automated movable cart – pest control operators or farmers, **long-term exposure**). For detailed description of the required measures please refer to chapter 15.1.2. Regarding these scenarios, the risk characterisation is considered to be sufficiently comprehensive and reliable for the purpose of inclusion of cyanamide in the Union List. It is essential to indicate, that the conclusion only applies to the active substance in the biocidal product (and not to other ingredients).

**Safety Measures for Professionals**

Risk mitigation measures (RMM) necessary are

- chemically protective gloves (EN 374), coverall (type 3, EN 14605), and boots (EN 13832), due to systemic and local risks, as well as
- respiratory protection measures (full face mask plus adequate gas filter or self-contained breathing apparatus, SCBA) and eye protection (goggles if no full face mask is possible) due to local risks during the mixing and loading-phase, at least.

Concerning respiratory protection, it should be specified on the label and in the SDS that the product shall only be used in well-ventilated areas. If aerosols or mists are formed, P2-filter shall be indicated on the label and in the SDS. For use of the representative biocidal product the formation of aerosols is not expected.

Based on the results of the study of Rath 2011 the following specific personal protective equipment proved to be suitable to reduce the dermal exposure to an acceptable level:

- chemically protective gloves (Camatril 732, Cat.III, EN 374 AJL, thickness ca. 0,40 mm, length ca. 400 mm),
- chemically protective suit, Cat. III, Type 3 (Pro-Chem I "C" has proven to be suitable to reduce the exposure to an acceptable level according to the study of Rath, 2011).

It is noted that the above specifications are an example of appropriate personal protective equipment to be worn when handling the product. However, if different PPE are proposed at product authorisation stage material test have to be provided demonstrating the same level of protection.
In general, personal protective equipment (PPE) should be replaced by engineering and/or technical and/or procedural measures, if possible. According to the Chemical Agent Directive 98/24/EC, article 6, paragraph 2 – it should be ensured that technical and organisational measures are applied by preference, and that only the remaining risks are mitigated by PPE.

**Qualitative exposure and risk assessment of the professional user regarding ED assessment PT 3 and PT 18 (75(1) (g) request)**

**Background:**

In the working group Human Health II/2021, the eCA presented a quantitative risk assessment for the ED properties taking into account a threshold. Based on this quantitative assessment the risk regarding ED properties of cyanamide for professional users was considered acceptable by the eCA. However, in the HH WG meeting a majority of the commenting members supported a qualitative risk assessment for professionals. In the following section the qualitative assessment is presented:

**Description of the exposure**

The quantitative systemic risk assessment is based on an operator exposure study performed by the applicant valid for PT 3 and PT 18. The operator exposure study was conducted as a higher tier study to determine realistic occupational exposure to ALZOGUR® containing 50 % w/w cyanamide during typical application by watering can or movable cart in piggeries. The actual dermal exposure during all phases of application using a watering can or movable cart is 1.5 mg cyanamide/person/day. The inhalation exposure by use of RPE (AF 10) is 0.0035 mg/m$^3$ cyanamide as 8 h time weighted average (8-h TWA). The exposure duration is assumed to be 2 - 3 h lasted for all work steps by using the watering can or the movable cart, for a treated area of 400 m$^2$ (information from the operator exposure study, CAR PT 3 and 18, chapter 8.2.2.3.1).

Based on the observation in the study inhalation and dermal exposure of hands and body occurs during mixing and loading (for PT 3 three parts ALZOGUR® and 7 parts water, and for PT 18 one part ALZOGUR® and 9 parts water), pouring of in-use solutions onto slatted floors, and rinsing of slatted floors and equipment with water. Also exposure to the eyes via splashes might be possible.

The biocidal product has been further diluted by rinsing with water into the liquid manure, an estimate of the in-use solution attenuation leads to a dilution factor of approximately 330 or 1000. After the rinsing, residues of the biocidal product are only present in the liquid manure below the slatted floor area of the pig stable. The colour of the applied product is blue and the successful rinsing step can be controlled by the discolouring of the rinsing water. Taking into account the further dilution, it is assumed that the inhalation exposure, dermal exposure inside the pig stable and the direct contact with residues in the manure is highly unlikely. The manure is further stored in slurry tank and afterwards pumped into the slurry tanker of a tractor. The usual application on the field is via tractor. Exposure of the farmer during application with a tractor is highly unlikely/not assumed.

**Risk mitigation measures**

The following risk mitigation measures were already reported for PT 3 and PT 18 based on the local and systemic risk assessment. These RMMs are also considered to mitigate the risk from ED:

- Chemically protective gloves (EN 374),
- Protective coverall (type 3, EN 14605),
- Boots (EN 13832)
- Respiratory protective equipment (full face mask plus adequate gas filter or self-contained breathing apparatus, SCBA)
- Eye protection (goggles if no full face mask is possible)
- Rinsing with water after application
- Use in well-ventilated areas

**Conclusion**

Professional users represent a defined subpopulation that is con-sidered to not comprise sensitive sub-groups. As appropriate risk mitigation measures are in place to ensure minimised exposure the **risk regarding ED properties of cyanamide for**

**professional users is considered acceptable.**

**Risk Assessment for Non-Professionals and general public**

The biocidal product ALZOGUR is only used by professionals. Primary exposure by non-professional use is not expected. Thus, a risk characterisation is not required for non-professional primary exposure.

The production takes place in closed systems. The general public does not have access to production plants. Thus, secondary exposure by production is not expected for the general public if the production process runs as described by the applicant.

The biocidal product ALZOGUR is applied only by professionals inside empty pig stables. Deposits are diluted and rinsed into the liquid manure. The general public has no access to these buildings. Therefore, in general no exposure inside stables is expected.

**Safety Measures for Non-Professionals and the general public**

The product will only be used by professionals in empty pig stables. The general public has no access to pig stables.

Considering the exposure description (APPENDIX V, section 2.1) an exposure to the active substance due to the contact during and after the application of liquid manure cannot be excluded for the general public. There is only the possibility of reducing the exposure of the general public by potential risk mitigation measures, e.g.: i) prolonged storage of liquid manure, ii) warning signs or other measures to restrict access to treated areas and iii) incorporation into soil as additional consideration. A detailed description is included in APPENDIX V.
These measures may lead to a reduction of exposure of the general public, but the WG did not consider them suitable and concluded that the exposure to the general public cannot be generally excluded. Furthermore, all presented RMM have already been considered unsuitable in a regulatory framework by the ENV WG.

Following the e-consultation about the qualitative assessment for the general public and the WG discussion it was concluded that the exposure of the general public cannot be excluded. Further, it was not possible to conclude on the risk assessment at the WG.

For preventive consumer protection and particularly to prevent uptake of the biocidal product by animals via feedingstuffs, it is suggested to add S13 - Keep away from food, drink and animal feedingstuffs.

### *2.2.2. Environmental Risk Assessment*

An environmental risk assessment is performed for the active substance cyanamide and the metabolite thiourea. In the study on biodegradation of cyanamide in liquid manure the metabolite thiourea was detected with maximum amounts of 4.7% at day 71. Normally it is not necessary to assess a metabolite with an amount < 10% because of the minor relevance for the environment. For thiourea the applicant has submitted effect data and data for PEC calculations and furthermore thiourea can reach the environmental compartments via application of slurry onto agricultural land. Thus, an environmental risk assessment was carried out for this metabolite.

2.2.2.1. Hazard identification and effects assessment

**Biodegradation**

According to a ready biodegradability test cyanamide was shown to be not readily biodegradable.

**Water-sediment systems**

In water-sediment systems cyanamide showed a rapid degradation under aerobic conditions with $DT_{50}$ values (12°C) of 4.4 and 8.2 days in the water phase of the river and pond system, respectively, and 4.7 and 9.1 days in the total system. Cyanamide was mainly mineralised to carbon dioxide, that reached maximum amounts of 86.1% of the applied radioactivity (AR) in the river and 83.5% of AR in the pond test system after 28 days of incubation. The maximum of non-extractable radioactivity amounted to 11% (day 28) in the river and 7.8% (day 21) in the pond system.

In the overall assessment considering the three assessment-relevant parameters primary and ultimate degradation together with the extent of bound residues in the sediment, cyanamide can be considered to have a low persistence in aquatic systems.
The only relevant metabolite (>10% of applied radioactivity) detected was urea (max. 13.4% AR, day 1). Estimated $DT_{50}$ values (12°C) of urea were 14.2 days in the water phase and 15.2 days in the total pond system as well as 5.1 days in the water phase and 5.5 days in the total river system. Thus, urea will not persist in aquatic environments.
In the simulation study on degradation of cyanamide in liquid manure the metabolite thiourea was detected. For thiourea only literature data on degradation in water-sediment systems (Elbe estuary and Baltic Sea) are available. The available information shows that thiourea is degradable in water-sediment systems. The mineralisation rates indicate that thiourea may show a moderate to rapid degradation for some water-sediment systems. However, as for some water-sediment systems degradation seems to be slow and as additionally no half-lives exist, based on the available information thiourea should be regarded as persistent in the environmental assessment of water-sediment systems (marine and fresh water).

**Soil**

Route and rate of degradation in soil were investigated in an aerobic laboratory study with a sandy loam soil. The first order half-life was determined to be 2.81 days (12°C, 100% field capacity). Mineralisation ($CO_2$) was almost complete, accounting for a maximum of 94.6% after 14 days.
The amount of bound residues reached a maximum of 9.46% after 4 hours.
In the overall assessment considering the three assessment-relevant parameters primary and ultimate degradation together with the extent of bound residues, cyanamide can be considered to have a low persistence in soil under aerobic conditions.
Further, the degradation of cyanamide in a sandy loam soil under anaerobic conditions

was investigated. The $DT_{50}$ value was calculated to be 80.17 days (12°C, 100% field capacity). Mineralisation ($CO_2$) accounted for a maximum of 53.1% after 60 days. The amount of bound residues reached a maximum of 9.55 % after 12 hours.
In the overall assessment considering the three assessment-relevant parameters primary and ultimate degradation together with the extent of bound residues, cyanamide can be considered to have a moderate persistence in soil under anaerobic conditions.

Under aerobic as well as under anaerobic conditions no relevant metabolites (>10% of applied radioactivity) were detected. However, in the simulation study on degradation of cyanamide in liquid manure the metabolite thiourea was detected. According to the available literature data a half-life of 17.8 days (12°C, 100% field capacity) can be assumed for degradation of thiourea in soil. This indicates that under aerobic conditions thiourea will not be persistent in soil.

**Liquid Manure**

Degradation rate and route of cyanamide was investigated under anaerobic laboratory conditions in liquid pig manure at 20±2°C in the dark for 105 days. The $DT_{50}$ value was calculated to be 45.4 days (20°C). The mineralisation rate ($CO_2$ evolution) was low to moderate, reaching a maximum of 25.1% after 105 days. The percentage of bound residues was with a maximum of 2.7% of applied radioactivity (day 59) very low. Two metabolites, dicyandiamide and guanidine, were detected with rates above 10% of the applied radioactivity. Hence, data on the biodegradation rates of these two degradates are required. However, the concentration of guanidine declined towards the end of the incubation period and the concentration of dicyandiamide did not increase after 71 days of incubation in spite of continued cyanamide degradation and $CO_2$ production. A continued degradation of both metabolites can be therefore expected. In addition, there is an indication from the aerobic biodegradation study in soil, on which the liquid manure is applied after storage, that dicyandiamide is quickly degraded under aerobic conditions in soil. The metabolite guanidine showed no inhibitory effects in a test on microbial inhibition, it naturally occurs in biological metabolic processes, such as the urea cycle, and many natural substances, e.g. the amino acid arginine, are derivates of guanidine. Therefore, further studies on the biodegradation of dicyandiamide and guanidine deemed not necessary. The metabolite thiourea was found with a maximum concentration of 4.7% (day 71).

**Abiotic Degradation**

Cyanamide is hydrolytic stable at all investigated pH-values. Cyanamide is directly photolytically degraded in Xenon light exposed samples (Xenon lamp 290 - 400 nm) with half-lives of 28.9 d and 38.5 d at pH 5 and pH 7, respectively. Urea was detected as major degradation product in these light-exposed samples. The adsorption coefficient at 290 nm is below 10 in UV-VIS spectra. Therefore, it can be concluded that in contrary to the laboratory conditions natural irradiation in Central Europe does not cause relevant direct photolytic degradation.
A photodegradation study of cyanamide in one soil provides an indication that cyanamide is rapidly degraded on the soil surface with a photolytic half-life of 2.75 days (converted to an average EU outdoor temperature of 12°C).
According to Atkinson calculation, cyanamide is stable in the atmosphere.

**Distribution and Mobility**

Based on the adsorption study, cyanamide can be classified as being very mobile in soil. The substance will not be adsorbed in soils (arithmetic mean $K_{oc}$: 4.38 mL/g).

**Bioaccumulation**

A $BCF_{fish}$ of 0.049 $L*kg_{wet\ fish}^{-1}$ and a $BCF_{earthworm}$ of 0.84 $L*kg_{wet\ earthworm}^{-1}$ were estimated for cyanamide. For the metabolite thiourea $BCF_{fish}$ values between 0.033 and 0.0085 $L*kg_{wet\ fish}^{-1}$ and a $BCF_{earthworm}$ of 0.84 $L*kg_{wet\ earthworm}^{-1}$ were calculated. Due to these results the aquatic as well as the terrestrial bioaccumulation potential can be classified as low for cyanamide and its metabolite thiourea.

2.2.2.2. Effects Assessment

**Aquatic Compartment**

Short-term tests with fish, daphnids and algae are available for cyanamide. The lowest acute toxicity was found for daphnids ($EC_{50}$ = 3.2 mg a.s./L). Long-term tests are available for daphnids (NOEC = 0.1044 mg a.s./L) and algae ($NOE_rC$ = 2.6 mg a.s./L) and aquatic plants ($NOE_rC$ = 0.43 mg a.s./L), the prolonged toxicity study with fish cannot be used as long-term test since it does not examine a sensitive stage in the fish life cycle and no sublethal endpoints. According to TGD normally an assessment factor of 50 would be applied on the lowest NOEC, because there are two long term NOECs from species representing two trophic levels available. However, as in the short-term tests fish were about a factor of 10 less sensitive to cyanamide than the most sensitive species *Daphnia magna*, it can be concluded that the NOEC from a long-term fish test would not be lower than the NOEC for *Daphnia* (NOEC = 0.1044 mg a.s./L). Thus, according to the TGD, the assessment factor is reduced to 10 and a $PNEC_{aqua}$ for cyanamide 0.01044 mg a.s./L = 10.44 µg a.s./L was derived.
Results from short-term tests with three trophic levels and long-term tests with 2 trophic levels (invertebrates and aquatic plants) are available for the metabolite thiourea. The lowest acute toxicity was found for daphnids ($EC_{50}$ = 5.6 mg /L), also in long-term tests daphnids exhibit the lowest valid effect value (21d-NOEC = 1 mg/L). According to TGD normally an assessment factor of 50 would be applied on the lowest NOEC, because there are two long term NOECs from species representing two trophic levels are available. However, as in the short-term tests fish were about a factor of 100 less sensitive to thiourea than the most sensitive species *Daphnia magna*, it can be concluded that the NOEC from a long-term fish test would not be lower than the NOEC for *Daphnia*. Thus, according to the TGD, the assessment factor is reduced to 10 and a $PNEC_{aqua}$ = 100 µg/L was derived.

**Sediment**

The $PNEC_{sediment}$ for cyanamide is derived from the $PNEC_{aqua}$ using the equilibrium partitioning method according to the TGD resulting in $PNEC_{sediment}$ of 9.16 µg a.s./kg ww.
Also the $PNEC_{sediment}$ for thiourea is derived from the $PNEC_{aqua}$ using the equilibrium partitioning method according to the TGD resulting in a $PNEC_{sediment}$ of 144.96 µg a.s./kg ww.

**Inhibition of microbial activity (STP)**

In a test on the growth inhibition of *Pseudomonas putida* an $EC_{50}$ of 283 mg a.s./L (nominal) was calculated for 100 % cyanamide. The NOEC was determined being 88 mg/L (nominal). Considering an assessment factor of 10 on the $EC_{50}$ a $PNEC_{microorganisms,\ STP}$ of 28.3 mg/L was derived.

For the metabolite guanidine in a test on the growth inhibition of *Pseudomonas putida* a toxicity threshold of 831.8 mg guanidine/L was determined, which is adopted to be equivalent to the NOEC. No $EC_{50}$ was derived from the data. As a worst case an $EC_{50}$ of 831.8 mg/L can be assumed. Considering an assessment factor of 10 on the $EC_{50}$ a $PNEC_{microorganisms,\ STP}$ of 83.18 mg/L was derived.

**Atmosphere**

Cyanamide is not considered to be used as fumigant. The vapour pressure is 5.1 x $10^{-1}$ Pa at 20 °C, the Henry's constant equals to 3.83 x $10^{-5}$ Pa.$m^3$.$Mol^{-1}$. Direct evaporation is not expected and no potential of volatility from water is considered. According to the Atkinson calculation, cyanamide is stable in the atmosphere. It is, however, questionable whether the Atkinson calculation allows for an adequate estimation of the photochemical degradation of cyanamide. Due to the limited application of cyanamide as biocide in stables it is not expected that the a. s. will accumulate in the atmosphere.

**Terrestrial Compartment**

For cyanamide tests with plants (short-term and long-term), earthworms (short-term), collembolans (long-term) and soil-microorganisms are provided. In short-term tests the plant species *Allium cepa* was most sensitive to cyanamide. The lowest long-term effect was found in a reproduction study with the collembolan *Folsomia candida* ($EC_{10}$ = 1.5 mg a.s./kg soil dw). Therefore, this value is used for the derivation of the $PNEC_{soil}$. As long-term tests with species from three trophic levels are available, an assessment factor of 10 can be used according to the TGD, so the $PNEC_{soil}$ for cyanamide = 0.15 mg a.s./kg soil dw = 0.133 mg a.s./kg soil ww = 133 µg a.s./kg soil ww.

For thiourea short-term tests with terrestrial plants and earthworms are available, long-term tests are provided by the applicant for plants and microorganisms. Microorganisms are the most sensitive organisms in long-term tests and so an AF of 50 would be applied on the NOEC (28d-NOEC ≥ 53.3 mg/kg dw) from this test. Therefore, the $PNEC_{soil}$ for thiourea = 1.06 mg/kg soil dw = 0.94 mg/kg soil ww = 940 µg/kg soil ww.

**Secondary poisoning**

Due to its physico-chemical properties cyanamide is not expected to accumulate in terrestrial or aquatic species. Therefore, no assessment of secondary poisoning was made.

2.2.2.3. PBT, vPvB Assessment

**P/vP Criteria:**

Cyanamide
According to the results of the water-sediment simulation studies the half-lives (12°C) for the river and pond system amounted to 4.4 and 8.2 days, respectively, in the water phase and 4.7 and 9.1 days for the entire system.
The degradation of cyanamide in soil was investigated in a laboratory study resulting in half-lives of 2.81 days (12°C, 100% FC) under aerobic conditions and 80.17 days (12°C, 100% FC) under anaerobic conditions.
Therefore, the P and the vP criterion is not fulfilled.

Metabolites
Estimated half-lives (12°C) for urea in the pond system are 14.2 days in the water phase and 15.2 days in the total system as well as 5.1 days in the water phase and 5.5 days in the total river system.
Microbial degradability of the metabolite thiourea was investigated in two water-sediment systems (Elbe estuary and Baltic Sea). Half-lives for water-sediment systems were not determined. Due to the available information thiourea should be regarded as persistent in the environmental assessment of water-sediment systems (marine and fresh water).
The degradation of the metabolite thiourea in soil was investigated in aerobic laboratory studies resulting in $DT_{50}$ values (12°C, 100% field capacity) of 25.7 days in sandy loam and to 17.8 days in sandy silt loam. As the determined confidence limits indicate higher validity of the results obtained for the sandy silt loam ($r^2$ = 0.86) than for the sandy loam ($r^2$ = 0.45), the half-life determined for the sandy silt loam should be used for

further environmental assessments of thiourea.
Therefore, the P and the vP criterion is fulfilled for the metabolite thiourea.

**B/vB criteria:**

Cyanamide
For cyanamide the calculated bioconcentration factor in fish is 0.049 $L*kg_{wet\ fish}^{-1}$ and the estimation on terrestrial bioconcentration leads to a value of 0.84 $L*kg_{wet\ earthworm}^{-1}$ for earthworm.
Therefore, the B and the vB criteria are not fulfilled.

Metabolites
As thiourea has to be regarded as persistent in water-sediment systems the bioaccumulation behaviour has to be assessed. The calculated bioconcentration factors in fish are between 0.033 and 0.0085 $L*kg_{wet\ fish}^{-1}$ and the estimation on terrestrial bioconcentration leads to a value of 0.84 $L*kg_{wet\ earthworm}^{-1}$ for earthworm.
Therefore, the B and the vB criteria are not fulfilled.

**T criterion:**

Cyanamide
For cyanamide the 21d-NOEC for daphnids (*D. magna*), the most sensitive aquatic species, is 0.1044 mg a.s./L thus the T criterion is not fulfilled in relation to ecotoxicological studies. However, according to RAC opinion from 5 June 2015, cyanamide has to be classified as STOT RE2, Repr. 2 and Carc. 2. Therefore, the T criterion is fulfilled for cyanamide.

Metabolites
For thiourea the 21d-NOEC for daphnids (*D. magna*), the most sensitive aquatic species, is 1.0 mg a.s.

Therefore the T criterion is not fulfilled.

Conclusion:
The active substance cyanamide with its metabolite thiourea is neither PBT - nor vP/vB – candidate.

2.2.2.4. Exposure assessment

For the assessment of the representative biocidal product (b.p.) ALZOGUR® as veterinary hygiene biocidal product, the following life cycle stages are selected as relevant:

- production of a.s.
- formulation of b.p.
- product use as aqueous solution applied to the liquid manure in empty pig houses by professionals.

The environmental release estimation is not performed for life cycle stages "production of a.s." and "formulation of b.p." because, according to the applicant, no releases to the environment occur in these life-cycle steps.

Exposure estimation has been performed for the life cycle stage "product use by professionals" of the biocidal product indoors in pig housings. ALZOGUR® is normally applied against dysenteria once to twice a year (ref. to Doc. II-B, chapter 8.3.1.3) after the end of a fattening cycle (after the pigs have been housed out); ALZOGUR® is not used after every fattening cycle but merely if an application is indicated. The application of the b.p. is performed to the liquid manure stored underneath the slatted floor in

piggeries. The likely concentration at which the b.p. will be used is 3 L ALZOGUR® per m³ liquid manure (PT 03). This corresponds to 1.536 kg a.s. per m³ liquid manure.

The b.p. ALZOGUR® can also be used for fly control (PT 18) in pig housings. The way of application of ALZOGUR® is the same in both PTs. The only difference is the concentration of the application solution, which is for the PT 03 threefold higher than the concentration for the PT 18 use. Thus, the environmental exposure assessment in this CAR is carried out on the basis of application of ALZOGUR® as b.p. used in PT 03.

However, if the b.p. is already applied against dysenteria (PT 03) a further application for fly control (PT 18) is not required in the calendar year. An overlapping of local product application in the different PTs can be excluded, as the product is always applied after the end of a fattening cycle, independent of product type / intended use. Thus, an aggregated exposure assessment is not necessary.

The releases of b.p. ALZOGUR® to the environment are assessed by applying emission models to soil after slurry applications on grassland and arable land followed by emission models to groundwater and to surface water. The environmental exposures are assessed applying the EU Technical Guidance Document (TGD) on Risk Assessment (2003) and the EU Emission Scenario Document for PT 3: Veterinary hygiene biocidal products (EUR 25116 EN, 2011).

2.2.2.5. Risk characterisation

The environmental risk characterisation is based on the concept of releases of active substance to the environment taking into account all relevant life cycle stages. Details on the emission scenarios and PEC estimation for different application areas and environmental compartments are described in the document Doc II, chapter 8.3. The derivation of predicted no effect concentrations (PNECs) for different environmental compartments is described in detail in Doc II A, chapter 4.

**Aquatic Compartment including sediment**

Due to the specific applications of the product by professional operators, indoors in pig barns/facilities a release via a municipal sewage treatment plant and/or surface water is not relevant. The risk assessment for the aquatic compartment comprises the application of contaminated manure to grassland / arable land and the subsequent translocation of cyanamide and the metabolite thiourea to surface water (run off). The estimated concentrations of cyanamide in the aquatic compartment according to EU TGD Part II (2003) indicated potential concern for this environmental compartment. Therefore, the surface water assessment is refined with the FOCUS surface water model. The refined risk assessment for sediment was carried out according to a decision at TM III/2011 (ref. to Doc. II-B, chapter 8.3.3.2). All the estimated PEC/PNEC values for surface water as well as for sediment were found to be below the trigger value of 1. Thus, the intended use of ALZOGUR® as a disinfectant in animal housings (pig barns) indicates no unacceptable risk for the aquatic compartment by cyanamide.
In the aquatic and the sediment compartment, a risk characterisation was also carried out for the metabolite thiourea. No unacceptable risk for the aquatic compartment by thiourea was identicated.
In summary, no unacceptable risks for the aquatic compartment including the sediment were identified for the use of ALZOGUR® containing cyanamide is indicated.

**Terrestrial Compartment including Groundwater**

In view of the intended use of ALZOGUR® for disinfection in pig barns / facilities a direct exposure to the soil compartment does not occur. The releases of b.p. are due to slurry application on grassland / arable land and subsequent translocation to the groundwater. The calculated PEC/PNEC values for soil indicate no unacceptable risk to this

compartment whereas for groundwater the quality standard of 0.1 µg/l for pesticides and biocidal products according to Directive 2006/118/EC for drinking water was exceeded in a tier one assessment. As a second tier $PEC_{groundwater}$ calculation applying FOCUS PEARL (version 3.3.3) was performed, which considers potential mobility of cyanamide in soils and the leaching behaviour to groundwater. It could be demonstrated that the average concentration of cyanamide closest to the 80$^{th}$ percentile is below the threshold criteria of 0.1 µg**.**$L^{-1}$ for all agricultural scenarios.
In the terrestrial compartment, a risk characterisation was carried out for the metabolite thiourea. For that purpose, the assumption was made, that the metabolite is formed in manure/slurry at a quantity of 3.8 % in regard to cyanamide. No unacceptable risk for soil was identified. The calculation of $PEC_{groundwater}$ for thiourea was refined by use of FOCUS model PEARL (transport and fate simulation tool). The predicted concentrations of thiourea in groundwater are below the threshold criteria of 0.1 µg.$L^{-1}$ for more than one FOCUS-scenario, both for grassland and arable land situations. At the 47$^{th}$ CA-Meeting (July 2012) it was decided that one safe use scenario in FOCUS PEARL both for grassland and arable land is sufficient for active substance approval. Thus, according to this decision a sufficient number of safe use scenarios is available to conclude that during the use of cyanamide as active substance in product ALZOGUR® in animal houses (pig stables) no unacceptable risk of the metabolite thiourea is indicated for the terrestrial compartment including groundwater.
In summary, no unacceptable risk for the terrestrial compartment including groundwater is identified for the use of ALZOGUR® containing cyanamide.

**Atmosphere**

Due to the intended uses of the b.p. for product type PT 03 and PT 18 which are limited to indoor application and on basis of the available substance information the environmental risk of cyanamide for the atmosphere can be assumed as negligible.

### *2.2.3. Assessment of endocrine disruptor properties*

Evaluation was performed according to Regulation (EU) 2017/2100.

**Assessment according to section A of Regulation (EU) 2017/2100: ED properties with respect to humans**

In the result of the analysis of available information related to human health hazard identification, observed adverse effects in endocrine organs as well as relevant mechanistic information can be summarized as follows:

Evidence for T-mediated adversity:

1. In the 6 day investigative gavage study in female rats ([redacted] 2016), a single dose of 45 mg/kg bw/d of cyanamide was tested in pregnant dams. Cyanamide administration between gestational day and 12 led to an increase in relative thyroid weight (+31 %, $p<0.05$), and a statistically non-significant increase in absolute organ weight (+16 %, no stat.sign). Minimal or slight follicular cell hypertrophy was observed in all treated animals (12/12). In this study the MTD in dams was reached (12 % decrease in body weight and 24 % decrease in food consumption). An increase in liver weight (rel. +9 %, $p<0.05$, abs. +3 %, $p>0.05$) with no concomitant histopathological findings were reported.
2. In the 28 day study in rat ([redacted] 1988), slight histopathological changes in thyroids were observed in males starting from the lowest tested dose of 5 mg/kg bw/d, such as incidences of small and closely packed follicles (2/5) and reduced colloid content (1/5). Starting from 10 mg/kg bw/d, all treated males were affected (follicular cell hyperplasia (5/5), reduced colloid content (5/5), small and closely packed follicles (5/5)). Histopathological changes in thyroids of female rats occurred from the dose of 20 mg/kg bw/d (follicular cell hyperplasia (1/5),

reduced colloid content (1/5), small and closely packed follicles (2/5). A relative thyroid weight increase was observed for males in the high dose group (+49 %, p<0.05). At this dose level, some signs of general toxicity, such as reduction in mean body weight (-15 %, p<0.05 in males and -12 %, no stat. sign. in females) and food consumption (-13 %, p<0.05 in males and -12.7 %, not stat. sign. in females) occurred. Additionally, at 20 mg/kg bw and above, an increase in rel. liver weight (+22 % and +62 % at 20 and 40 mg/kg bw/d, p<0.05) and biliary hyperplasia (2/5 and 5/5) were reported for males. Relative liver weight increase in females occurred first at 40 mg/kg bw/d (+19%, p<0.05).

3. In the 90 day rat feed study, ( 1975) reduced colloid content was observed in males and females at 4.5 mg/kg bw/d (3/10 and 2/10 respectively), while in the lower dose of 1.5 mg/kg bw/d1/10 males was affected. In this study, no changes in body weight were observed. Changes in liver weight were mild: rel. liver weight increase was observed in males (+6 % at 4.5 mg/kg bw/d, p<0.05).
4. In the chronic (91 week) rat gavage study ( 1991), an increase in relative thyroid weight was demonstrated in the high dose rats of both sexes. Histopathological observations included reduced colloid content (and small follicles in males) starting from 2.5/7.5 mg/kg bw/d with an incidence of 7/20 and 5/20 in males and females respectively. In this study, the MTD was exceeded leading to a change in dosing at week 17. At 2.5/7.5 mg/kg bw/d, body weight decrease was reaching statistical significance during weeks 4-16 in males (7-16 %) and at week 4 and week 16 in females (6-7 %). A decrease in food consumption was observed at the higher dose (-26.7 % week 1-16 and -10 % week16-88 in males, -12 % week 1-16 and -9.1 % week 16-88 in females, p<0.05 at 7.5/30 mg/kg bw/d).
5. In the sub-chronic arm (7 weeks) of the study in rats ( 1979, also referred to as 1979), designed to determine the MTD for the chronic study, thyroid size was increased macroscopically 2-3 fold at a dose exceeding the MTD (4000 ppm). At the lower doses, a dose dependent increase in incidences of thyroid hyperplasia and pale-stained colloid indicative of goitre was reported. At the lower dose of 400 ppm, cases of hyperplasia with excess colloid formation (M: 3/5, F: 1/ 5) were found.
6. In the oral reproductive study in rat ( 1986), with 70 days of exposure via feed prior to mating, in the high dose group of 7.55 mg/kg bw/d activated appearance in thyroid was reported for males and females: 8/24 and 15/24 in F0 and 18/24 and 6/24 in F1 respectively, p<0.05. Additionally, absolute and relative thyroid weight increase was reported (+19 % (abs.) and +39% (rel.), p<0.05 in males and +8 % (abs.), p>0.05 and +19 % (rel.), p<0.05 in females). At the same dose level, statistically significant reduced food consumption and body weight gain were reported for both males and females (in males (F0-F1): 9-14 % / 15-21%; in females (F0-F1): 8-13 % / 7-20 %. In spite of the changes in food consumption and body weight gains, the effects on thyroid are considered adverse. Additionally, a decrease in absolute liver weight in females (-8 %, p<0.05 in F0 at 7.5 mg/kg bw/d) and an increase in liver weight in males (+11 %, p<0.05 in F0 males at 0.81 mg/kg bw/d, +11 %, p<0.05 in F1 in males at 7.5 mg/kg bw/d) were reported in the same study. Of note, in this study the diet was additionally supplemented with Vitamin A (6339 IU/kg).
7. In the oral gavage reproductive study in rat ( 1990), with 14 weeks of exposure prior to mating, enlarged thyroid was observed in males (1/26) at 2.5/1.25 and 7.5/3.75 mg/kg bw/d. In this study, the change of dosing regime was done at week 12 due to the exceeded MTD at the top dose of 30/15 mg/kg bw/d. Histopathology of thyroid was not conducted in this study (as it is not foreseen by the OECD TG 416).
8. In the rat reproductive gavage study ( 1987), thyroid was not investigated.

9. In the oral (drinking water) chronic (100/104 weeks for males and females) study in mouse ([redacted] 1990), where cyanamide was administered in drinking water, no effects on thyroid were reported.
10. In the sub-chronic arm of the dietary study in mice ([redacted] 1979, also referred to as [redacted] 1979), the thyroid was not affected.
11. In dogs, in the 90 day feed study, ([redacted] 1982), no histopathological changes in thyroids were observed.
12. In the other available 90-day study in male dogs ([redacted] 1986), only reproductive organs were microscopically investigated.
13. In dogs, in the 1 year-long gavage study ([redacted] 1989), rel. thyroid/parathyroid weight was increased in females in the high dose group of 5 (2.5) mg/kg bw/d (+56 %, $p<0.05$). Chronic inflammation in thyroids occurred at an incidence comparable to the control group. Food consumption was comparable in all animals in the study. Changes in body weight gains were profound at this dose (-100 %, $p<0.05$ in females and -67 %, $p<0.05$ in males). Clinical signs were observed with salivation in all high dose animals and in one medium-dosed female and tremors in 3/4 males and 2/4 females at 5 (2.5) mg/kg bw/d. An increase in cholesterol level was noted in both males and females of the highest dose group (+51 %, $p<0.05$ in males and +41 %, $p<0.05$ in females) and suppression of the hepatic markers of AST (-39 %, $p<0.05$) and ALT (-60 %, $p<0.05$) at week 13 in females and AST (-43 %, $p<0.05$), ALT (-52 %, $p<0.05$) at week13 in males. Histopathological examination revealed accumulation of brown pigment in Kupfer cells in liver (3/4 in males and 4/4 in females), however with no changes in liver weight.

Evidence for T-mediated activity:

An endocrine mechanism based on TPO-inhibition was established in the following studies:

1. The high-throughput ToxCast assay NCCT_TPO_AUR_dn, with rat TPO was positive (iCSSToxCast Dashboard v2, https://actor.epa.gov/dashboard/#chemical/420-04-2 accessed on 28.11.2018) at the AC50=2.42 µM. This assay is conducted in excess of H2O2 (Paul K.B. et al 2014), in order to test metabolites of cyanamide that are expected to be formed in vivo upon activation via mitochondrial catalase.
2. In vitro TPO inhibition tests (guaiacol assays) with rat, dog and human thyroid microsomes (Haines 2018a, Hines 2018b) as well as with porcine TPO preparation (Davidson et al, 1979) demonstrated activity of cyanamide in the range of 2.2 –7 µM.
3. In the in vitro test with rat microsomes, the reaction of iodination was inhibited (Davidson et al, 1979). This confirms the positive results of the guaiacol-based TPO assays, as not only the guiaicol oxidation, but as well organification of iodine, mediated by the TPO, is inhibited.
4. Further, in support of the observations made in vitro, an available in vivo TPO test was positive, inducing 30 % inhibition of TPO within 30 minutes of i.p. exposure to cyanamide ([redacted] 1979).
5. In the same test, upon 30 min of exposure to the cyanamide in vivo, 97-99 % of iodination was inhibited ([redacted] 1979).

Thyroid hormone measurements were performed in the following studies:

1. In the 6 day investigative gavage study in female rats ([redacted] 2016), 45 mg/kg

bw/d of cyanamide led to an increase in TSH (+68 %, p<0.05), with no concomitant changes in T3 and T4. The last can probably be explained by the buffering capacity of rat thyroid gland capable of storing thyroxin to respond to potential increase in demand in circulating hormone over a short period of stress. Thus, its suggested that administration of cyanamide in this case was not affecting pool of readily available hormone precursors. In this study the MTD in dams was reached (see in details above).

2. In the 28 day study in rat ([redacted] 1988), in both males (n=5) and females (n=5) a decrease in T4 (28%, p>0.05) and an increase in TSH (100%, p>0.05) occurred at the highest dose groups of 40 mg/kg bw/d (gavage). Changes in T3 were approx. 10 % and non-concomitant in two sexes (an increase in males and a decrease in females). The changes in the T4 and TSH cannot be disregarded based on the absence of statistical significance.
3. In the chronic rat gavage study ([redacted] 1991), TSH, T3 and T4 were measured. Upon 91 week of exposure to cyanamide in the high dose group, T4 and T3 were decreased in males (-30 % and -50 % respectively, p<0.05) at high dose group (7.5/30 mg/kg bw/d). In females at the same dose, a slight decrease in circulating T4 (-13 %, p>0.05) and a decrease in T3 (-24 %, p<0.05) were measured. In the mid-dose group, in females decrease in T3 (-33 %, p<0.05), but not T4 was demonstrated.
4. In dogs, in the 90 day feed study, ([redacted] 1982), in males (n=4) a statistically non-significant decrease in T4 (38 %, p>0.05) was observed at 2 mg/kg bw/d. At 6 mg/kg bw/d, T4 was decreased by 47 % vs Ctrl. (p>0.05) and T3 concentration was as well suppressed (-37 % vs Ctrl and –21 % vs baseline at day 0 at 6 mg/kg bw/d, p>0.05). In females (n=4), only T3 was potentially affected in the high dose group (-36 % vs Ctrl and –29 % vs baseline at day 0 at 6 mg/kg bw/d, p>0.05). Similarly to the findings in rat, the changes in the thyroid hormones cannot be disregarded due to the absence of statistical significance. Body weight was affected in females (-13 % at 6 mg/kg bw/d, p<0.05), but not in males in this study.
5. In dogs, in the 1-year gavage study ([redacted] 1989), thyroid hormones were affected in the high dose group (5 (2.5) mg/kg bw/d). In males (n=4), a decrease in T4 was measured at the end of the study (-45 %, p<0.05) and at week 13 (-44 %, p>0.05). In females (n=4), a decrease in T4 was measured at the end of the study (-41 %, p>0.05). T3 was reduced in high dose groups in both males and females (p>0.05). TSH was not measured in this study.
6. In the 90 day rat study, ([redacted] 1975) TSH, T3, T4 were not measured.
7. In the other available 90-day study in male dogs ([redacted] 1986), thyroid hormones were not measured.

Conclusion on T-modality: Overall, all available TPO assays with cyanamide were positive. This includes one high-throughput ToxCast assay and 4 in vitro TPO assays with rat, human and dog thyroid microsomes and a study with porcine TPO preparations. The available dedicated thyroid mechanistic in vivo study further confirms the plausibility of the TPO-inhibition-mediated mechanism of thyroid toxicity, which was observed in the repeated dose studies with cyanamide and was not considered secondary to systemic / liver toxicity. Depression of the thyroid hormones can be considered biologically relevant in spite of the absence of statistical significance. This conclusion is made based on the 1) repetitive observations of the repressed circulating thyroid hormones, 2) the magnitude of thyroid hormone changes observed and the consideration that 3) measurements were performed mainly in statistically underpowered experiments.

Evidence for EAS-mediated adversity:

1. In the 28 day study in rat ([redacted] 1988), no effects on female reproductive organs were described. A depression of absolute testis weight (- 14 % at 20 mg/kg bw/d and-15 % at 40 mg/kg bw/d, $p<0.05$) was reported for male rats. As described above, starting from 20 mg/kg bw/d, a reduction in mean body weight (-15 %, $p<0.05$ in males) occurred, notably at the comparable level to the reduction in absolute testis weight. No histopathological effects in testis were observed.
2. In the 90 day rat feed study ([redacted]., 1975), gonads weight and histopathology was not affected.
3. In the 91-week-long study in rat ([redacted] 1991), no effects in female reproductive organs were described. In males, organ-to-terminal body weight values of testis with epididymides were increased in the high dose group, related to the profound suppression in the body weight (25-32 % in males, $p<0.05$).
4. Reduced fertility was observed in the male and female rat reproductive gavage study ([redacted]., 1987), in the high dose group (25 mg/ kg bw/d), with a stronger effect attributed to dosing of males: fertility was reduced by 48 % when both males and females were treated with 25 mg/kg bw/d cyanamide, by 41.2 % when only males were receiving cyanamide and by 22.2 % when only females were treated. No changes in relative weight in uterus and ovaries were reported. In males, testicular atrophy was observed in 4/20 males in F0 and 1/6 males in F1 vs 1/18 in control F1 group. In the high dose group, reduced number of corpora lutea, a decrease in number of live embryos and live born pups as well as an increase in pre- and post-implantation loss was described in F0. In F1 the reliable assessment of these parameters was not possible, due to the low number of embryos in F0 and consequently pregnant dams from F1 (6 vs 20 in Ctrl). Reduced body weight gain was reported in the dams in high dose group (15.35 % vs 23.02 % in control, $p<0.05$)
5. In the oral reproductive study in rat ([redacted]., 1986), with 70 days of exposure via feed prior to mating, no effects on fertility were reported up to 7.55 mg/kg bw/d. A decrease in litter size at birth in F1 (8.2 vs 9.8 in Ctrl., $p<0.05$) and at postnatal day 4 in F0 (8.1 vs 10.2 in Ctrl., $p<0.05$) was observed. In males, an increase in tubular atrophy in testis were observed starting from the lowest dose of 0.81 mg/kg bw/d (2/24 vs 0/24 in Ctrl., $p<0.05$). A decrease in spermatogenesis was reported for the low dose males (2/24 vs 0/24 in Ctrl.) and an increased interstitial cell proliferation was reported for mid and high dose males. In this study for the high dose group, reduced body weight gain (-21 %, $p<0.05$ in F0 males and -15 %, $p<0.05$ in males F1 during pre-mating) and food consumption (-9 %, $p<0.05$ in F0 and -14 %, $p<0.05$ F1 males during pre-mating) were reported.
6. In the oral gavage reproductive study in rat ([redacted] 1990), with 14 weeks of exposure prior to mating, observations in ovaries were limited to cysts (1/26) and unequally sized ovaries (1/26) in high dose (30/15 mg/kg bw/d) and a small ovary (1/26) in mid dose (7.5/3.75 mg/kg bw/d) group. In the low dose group, cysts in ovaries were observed in 3 out of 25 females. In males, observations in testis were limited to observations made in high dose group, such as small (1/26) and soft testis (1/26) in F1 and small testis (1/26) in F0. Microscopically, tubular degeneration was observed in F0 (2/26 vs 0/25 in Ctrl.) and in comparable to the control levels in F1 (3/26 vs 3/26 in Ctrl). No histopathological effects in epididymides were reported. Notably, during pre-mating and prior to change in dosing at week 12, body weight gain in parental animals were reduced (-55 %, $p<0.05$ for males and -48 %, $p<0.05$ for females at 30/15 mg/kg bw/d) accompanied by reduced food consumption (-20 %, $p<0.05$ in F0 males and 8-16 %, $p<0.05$ in F0 females).

7. In the 107 weeks carcinogenicity study ([redacted], 1979 also referred to as [redacted] 1979) an increase in incidences of dilation of ducts in male mammary gland (7/50 vs 0/20) and diffuse hyperplasia (9/50 vs 0/20) in the highest dose group (200 ppm). Mean body weights of the high dose male rats were slightly lower than in controls, but are considered not to be compound related. In spite of the limitations of the study (for example, low number of animals in control group), it is still used in the overall weight of evidence.
8. In the CD-1 mice, ovarian granulosa-thecal cell tumours were significantly increased at 600 ppm (39 mg/kg bw/d), at the dose that exceeded MTD. ([redacted], 1990).
9. In dogs, in the 90 day feed study ([redacted], 1982), no effects on spermatogenesis were described for control males. In the test groups, atrophic seminiferous tubules (1/4), slight to moderate reduced spermatogenesis (2/4), reduced number of sperms in epididymides (2/4), absent number of sperms in epididymides (2/4) were described for the lowest dose group (0.6 mg/kg bw/d). In the mid dose (2 mg/kg bw/d), atrophic seminiferous tubules (2/4), absent spermatogenesis (1/4), slight to moderate reduced spermatogenesis (1/4), reduced number of sperms in epididymides (2/4), absent number of sperms in epididymides (2/4) were observed. In the high dose group (6 mg/kg bw/d), unilateral testis atrophy (1/4), bilateral testes atrophy (1/4), absent spermatogenesis (3/4), absent number of sperms in epididymides (3/4) were described. Additionally, changes in testis weight were reported (rel. -35 % and abs. -39 %, no stat. sign.). In the clinical chemistry investigations, reduced red blood cells count (-10 % at 6 mg/kg bw/d, $p<0.05$) in males was reported. Body weight was affected in females, but not in males in this study.
10. In the other available 90-day study in male dogs ([redacted] 1986), observations of histopathological changes in male reproductive organs were restricted to the highest dose group and comprised atrophy of germinal epithelium (2/4), reduced spermatogenesis in testes (2/4), reduced number of spermatocytes in epididymides (1/4). Histopathological observations were accompanied by the reduction in relative absolute weight of testes in two dogs (for the whole group $p>0.05$). Macroscopically observations of small testes (2/4 vs 0/4 in Ctrl) and small prostate gland (2/4 vs 1/4 in Ctrl) were reported. No statistically significant change in body weight were reported (2 dogs in high dose gained weight and two lost). Re-analysis by Weber and Creasy (2009), submitted for pesticide assessment, claims that effects may not be substance-related for one of two affected animals of the high dose group.
11. In dogs, in the 1-year gavage study ([redacted]1989), males were affected in the high dose group (5/2.5 mg/kg bw/d) with chronic active inflammation in testis (2/4), reduced spermatogenesis (bilateral hypospermatogenesis (2/4) and bilateral aspermatogenesis (1/4)), hypospermia (2/4) and immature sperm (1/4) in epididymidis. While changes in body weight gains were profound at this dose (-67 %, $p<0.05$ in males), body weight changes were no statistically significant (-6 % at week 13 and -14 % at week 52). Food consumption was comparable in all animals in the study.

Evidence for EAS-mediated activity:

1. ER Bioactivity Model: negative for estrogenic and anti-estrogenic activity. However, the acceptability of the prediction is questionable, based on the knowledge of the metabolism of cyanamide, which requires activation via the addition of $H_2O_2$ or partially purified enzyme preparations from beef or rat liver ([redacted]. 1982).
2. AR Bioactivity Model: negative for androgenic and anti-androgenic activity. The same cautious interpretation of the predictions of the model is applied as in case

of the ER Model.

3. Measurements of "in vivo mechanistic" parameters (e.g. oestrodiol, testosterone, LH, FSH levels) for EAS modalities were not performed in the toxicological studies.

Assessment of the weight of evidence for non-EATS-mediated adversity (i.e. HPA and RA pathway) and endocrine activity:

1. In the acute i.v. study ( 2000a) in rats with duration up to 2 hours in the dose up to 50 mg/kg, a dose-dependent increase in plasma corticosterone in circulation was observed. Together with the observation of increase in the mRNA expression of corticotrophin releasing factor and arginine vasopressin in paraventricular nucleus and proopiomelanocortin in anterior pituitary, authors came to the conclusion that HPA axis was activated upon i.v. exposure to cyanamide.
2. In the long-term studies with cyanamide, upon dietary administration of of cyanamide, pituitary was not identified as a target organ. Of note, no histopathological investigation of pituitary was conducted in 90 day rat study ( . 1975).
3. In the reproductive study in rats, ( 1990) the findings were limited to macroscopic observation of a small adrenal (n=1) at the dose 7.5/3.75 mg/kg bw/d. This effect was not considered as adverse.
4. In the dietary carcinogenicity study with calcium cyanamide ( 1979, Doc. No. 592-009 also referred to as 1979), an increase in incidences in benign pheochromocytoma in male and cortical adenoma in female rats (not statistically significant) was reported. The carcinogenicity is discussed in chapter 2.2.1.1.
5. In the teratogenicity study in rats, ( 1989), an increase in incidences of diaphragmatic hernia (5 litters/7 foetuses vs 0 in Ctrl) was observed in the foetuses of the high dose group (45 mg/kg bw/d). Dosing occurred between gestation days 6 and 15. In this study, food consumption was affected starting from a lower dose of 15 mg/kg bw/d and changes in body weight were observed at gestation days 6-20 for all treated groups
6. In the second teratogenicity gavage study in rats ( 2014), 45 mg/kg bw/d of cyanamide dosed from gestation day 6-19 again led to an increase in incidences of diaphragmatic hernia (7 litters/10 foetuses vs 0 in Ctrl). Similarly, to the previous study, food consumption and body weight was affected in dams starting from a lower dose of from 15 mg/kg bw/d.

**Conclusion on EAS and non-EATS modalities:**
Considering developmental findings (e.g. diaphragm hernia) together with the above mentioned findings in testes, it may be suggested that inhibition of retinaldehyde dehydrogenases leading to the retinoic acid deficiency might be the initial step of the endocrine mechanism contributing to these observed adverse effects as described in chapter 2.2.1.1. However, no further studies to elucidate this hypothesized MoA were submitted. Similarly, no conclusion could be drawn on the relevance of effects on adrenals with regard to the identification of endocrine disrupting properties.

**Overall conclusion on ED (human health)**
Cyanamide meets the specific scientific criteria for endocrine disruption as set out in Regulation (EU) 2017/2100. Based on the multiple observations of thyroid toxicity, the eCA concludes that cyanamide exhibits thyroid-disruptive effect caused by the direct endocrine mechanism of TPO inhibition. Relevance of this finding to humans is supported by the provided TPO inhibition studies in which cyanamide was shown to be a potent

inhibitor of human TPO activity. It was concluded that the adverse effects on the thyroid cannot be considered as secondary to systemic / liver toxicity.

**Summary on the Article 75(1)(g)-mandate of the European Commission "Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18"**

As cyanamide is considered to have endocrine disrupting properties, the European Commission initiated a mandate according to Article 75(1)(g) of the BPR as the initial BPC opinions on cyanamide for PT 3 and PT 18 did not provide a clear conclusion on the level of the risks associated with the use of cyanamide in relation to its ED properties. The concern was mainly based on the following paragraph, which was included in the BPC opinion after discussion of cyanamide at the 33rd BPC-meeting in December 2019: "(…) *With regards to the fact that cyanamide is considered to have endocrine disrupting properties, there is no currently agreed methodology for undertaking a risk assessment based on such properties and no agreed methodology available on how to consider the data used for the identification of whether this substance is an endocrine disruptor in risk assessment for the environment.* ***Given the exposure of cyanamide to humans and the environment, a risk related to the ED properties cannot be excluded.****"*

Therefore, the eCA was asked to clarify the following aspects with regard to human health:

1. Based on available information, clarify whether a safe level (threshold) can be determined for the ED properties of cyanamide for human health, and if such threshold can be established, what would be this level.
2. Clarify the level of the risks to human health by:
   - Assessing the level of risk for human health, either by a quantitative assessment or by a qualitative assessment
   - Providing an opinion whether the risks can be considered acceptable or not.

In order to answer the above-mentioned questions, the eCA was assigned to consider the following aspects in its assessment:

- All the data submitted in the application, as well as the conclusions of the discussions in the BPC and its Working Groups.
- Any further information submitted by the applicant or other interested parties within the scope of this request and the timeline specified by the eCA or ECHA as appropriate.
- The data submitted during the public consultations on this substance organised by ECHA from 22 February to 21 April 2016 and from 26 June 2019 to 25 August 2019, including those submitted by the applicant.

In order to be able to answer the questions of the mandate with respect to human health, the following steps were taken:

A quantitative risk assessment on the ED properties of cyanamide based on the available information was provided by the eCA and an e-consultation was launched to address the mandate of the European Commission from 29. March - 26 April. Based on subsequent discussions and conclusions of the WG-II-2021, a qualitative approach regarding the assessment of the general public was presented in a second e-consultation launched from 15 July to 6 August 2021 and subsequently discussed at the WG-III-2021.

Regarding the identification of a threshold for the ED properties of cyanamide, the HH-WG II/2021 concluded, that due to several uncertainties (missing DNT-Study, no conclusion on EAS modalities, no Guidance on ED risk assessment), the values proposed by the eCA could not be supported and that the available data would not allow defining a threshold. The majority of the commenting members supported performing a qualitative assessment. With regard to the qualitative risk assessment of the ED properties for cyanamide, the HH-WG III/2021 concluded, that no final conclusion can be drawn at the scientific level.

The details of the risk assessment of the ED properties for cyanamide are presented in Appendix V. There, the background of the mandate is given, followed by the two approaches for the risk assessment: first the quantitative and secondly the qualitative approach. Since this is a precedent for the risk assessment of ED properties, the approaches are presented in detail, by including the documents of the two e-consultations, and enclosing the summary of the e-consultations and the BPC-WG discussions, respectively.

The following table gives an overview on the different aspects, which were discussed during the HH-WG II/2021 with regard to the quantitative risk assessment (Points 1-3) and the HH-WG III/2021 with regard to the qualitative risk assessment (Points 4-18).

| # | Question | WG conclusion | Reference |
|---|---|---|---|
| 1 | Do you agree with the eCA on the identified threshold(s) for the ED properties? | The majority of the commenting members:<br>• did not support the values proposed by the eCA<br>considered that the available data would not allow defining a threshold | HH WG II/2021 |
| 2 | Do you agree with the eCA proposal for assessing the level of risk for human health by a MoE approach? And do you agree, that the proposed MoE of 100 is sufficiently safe for all populations? | There was no conclusion due to not having an agreement in point 1 above. | HH WG II/2021 |
| 3 | Do you agree with the eCA, that the risk resulting from the intended use can be considered acceptable? | There was no conclusion due to not having an agreement in point 1 above. The majority of the commenting members supported performing a qualitative assessment for professionals. | HH WG II/2021 |
| 4 | Do you agree with the eCA proposal on the described scenarios and that they have to be taken into account in the current assessment? | The WG agreed on the scenarios presented by the eCA. | HH WG III/2021 |
| 5 | Do you agree that the qualitative assessment takes | The WG agreed that all relevant scenarios are included. | HH WG III/2021 |

| | | | |
|---|---|---|---|
| | into account all relevant scenarios of general public exposure? | | |
| 6 | Do you agree that none of the described RMMs are suitable to reduce the exposure to the general public?<br><br>Do you consider other RMMs or alternative approaches for a qualitative assessment suitable for reducing risks after the application of cyanamide? | The WG did not consider any of the described RMMs suitable for reducing the exposure of the general public, while some members suggested that they might not be necessary either. | HH WG III/2021 |
| 7 | Do you agree that no conclusions can be drawn about the magnitude of exposure reduction and feasibility? | No conclusions can be drawn regarding the magnitude of exposure reduction. | HH WG III/2021 |
| 8 | Do you agree that the exposure of the general public cannot be excluded by any RMM? | The WG agreed that the exposure of the general public cannot be excluded. | HH WG III/2021 |
| 9 | Do you agree that it is not possible to conclude on the risk assessment for ED properties, as requested by the mandate? | The WG considered that concluding on the risk assessment was not possible at the WG. | HH WG III/2021 |
| 10 | Do you agree that an update of the dietary risk assessment in the existing CAR is not required? | The WG agreed that the dietary risk assessment does not need to be updated.<br>The proposed RMM was not supported. | HH WG III/2021 |

With respect to the documents submitted by the applicant prior to the WG III/21 concerning the degradation rate of cyanamide in liquid pig manure, the HH-WG III/21 concluded that the degradation rate is considered in the human health assessment and the degradation rate had already been set by the ENV WG that had earlier concluded that further information on the degradation rate is not needed. The ENV-WG III/21 concluded again that there was no need to revise the current degradation assessment in the context of the current mandate.
The details of the assessment are summarised in APPENDIX V.

Based on the discussions with the member states in the context of the HH WG, the questions of the COM's mandate can be answered as follows:

1. **Based on available information, clarify whether a safe level (threshold) can be determined for the ED properties of cyanamide for human health, and if such threshold can be established, what would be this level.**

   *A threshold for biological adversity through TPO inhibition by cyanamide was proposed. The WG did not support the suggested safe level or threshold for the ED properties due to a variety of uncertainties (*missing DNT-Study, no conclusion on EAS modalities, no Guidance on ED risk assessment*).*

2. **Clarify the level of the risks for human health by:**

- **Assessing the level of risk for the human health, either by a quantitative assessment or by a qualitative assessment**

  *Based on available information, a quantitative risk assessment on the ED properties of cyanamide was conducted. Although there are several uncertainties within the current database, a threshold for the ED effects of cyanamide as well as a risk assessment approach using the margin of exposure approach was proposed. The WG did not support the approach.*

- *A qualitative risk assessment was based on the description of scenarios available for plant protection products due to lack of harmonised exposure scenarios for the application of liquid manure for the general public. In addition to the exposure of professionals, the exposure of general public including bystanders, residents and during recreational exposure was considered. None of the suggested RMMs allowed to exclude the exposure of the general public. The level of risk could not be determined in the scope of the qualitative assessment for the general public.*
  *A qualitative risk assessment for the professional user was performed on the basis of the already agreed exposure pathways from the quantitative exposure assessment. The level of risk were determined taking into account the suggested RMM and the assumption that the professional users represent a defined subpopulation that is considered to not comprise sensitive sub-groups.*

- **Providing an opinion whether the risks can be considered acceptable or not.**

  *Regarding the acceptability of the risk, no final conclusion is possible. The WG concluded that given the uncertainties of the assessment and lack of methodology, it is currently not possible to determine whether the risk is acceptable or not for the general public.*

For the details of the assessment, please refer to APPENDIX V.

**Assessment according to section B of Regulation (EU) 2017/2100: ED properties with respect to non-target organisms**

According to the Commission Delegated Regulation (EU) 2017/2100 and as further specified in the EFSA/ECHA Guidance for the identification of endocrine disruptors (ED) in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 a conclusion on whether the ED criteria are met needs to be drawn separately with respect to humans and non-target organisms. It is recommended to strive for a conclusion on the ED properties with regard to humans and in parallel, using the same data base, to strive for a consluion on mammals as non-target organisms. Only where, based on this assessment the ED criteria are not met for mammals as non-target organisms, a further assessment of non-mammalian non-target organisms in the environment (e.g. fish and/or amphibians) would be required.
The EDEG in June 2019 agreed that based on the mammalian data set cyanamide fulfills the ED criteria according to Regulation 2017/2100 for the T-modality for human health.
For the assessment of the ED-criteria for non-target organisms the EFSA/ECHA ED guidance requires the assessment of the population relevance of the observed effects. In this respect, effects on growth, development and reproduction are generally regarded relevant for the maintenance of wild populations and the relevance of such effects at population level should be assumed when determining the adversity in the absence of appropriate data demonstrating non-relevance. According to the guidance thyroid histopathological findings observed in isolation - i.e. without an impairment of growth and development and/or reproduction are likely not relevant at population level.
In the mammalian data set effects on thyroid, T3- and T4-levels, testis, spermatogenesis and fertility as well as on growth and development are reported. According to the ECHA/EFSA ED guidance at least the effects on testis, spermatogenesis, fertility as well as on growth and development should be considered as being relevant for populations of environmental mammalian non-target organisms.

The observed effects in mammals were reported in a similar way also for the metabolite thiourea in fish and amphibians, respectively. There have been reports on histopathological changes in the thyroid as well as reduced T3- as well as T4-levels or an impaired development of ovarian follicles and spermatozoa. Furthermore, also adverse effects on growth and development as well as reproduction of the exposed organisms via the HPT - as well as via the HPG –axis such as an influence on metamorphosis as well effects on the development of secondary sex characteristics have been reported.

Furthermore, based on the available mammalian data set also an interference of cyanamide and its metabolites with retinoid system seems to be likely. This signaling pathway is essential for the vertebrate embryonic development and reproduction of several environmental non-target species.

In addition, three AOPs are currently under development, which strengthen the hypothesis that the overserved effects in mammals are also relevant for populations non-mammalian non-target species in the environment: AOP 175: Thyroperoxidase inhibition leading to altered amphibian metamorphosis, AOP 271: Inhibition of thyroid peroxidase leading to impaired fertility in fish and AOP 297: Inhibition of retinaldehyde dehydrogenase leads to population decline (fish).

Overall, from the available data it can be concluded that wild populations will be affected by cyanamide and its metabolites via endocrine-mediated modes of action.

**Overall conclusion on ED related to non-target organisms:** Based on the available data it can be concluded that cyanamide meets the specific scientific criteria for endocrine disruption as set out in Regulation (EU) 2017/2100 with respect to environmental non-target organisms.

**Summary on the Article 75(1)(g)-mandate of the European Commission "Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18"**

As cyanamide is considered to have endocrine disrupting properties, the European Commission initiated a mandate according to Article 75(1)(g) of the BPR as the initial BPC opinions on cyanamide for PT 3 and PT 18 did not provide a clear conclusion on the level of the risks associated with the use of cyanamide in relation to its ED properties. The concern was mainly based on the following paragraph, which was included in the BPC opinion after discussion of cyanamide at the 33rd BPC-meeting in December 2019: "(…) *With regards to the fact that cyanamide is considered to have endocrine disrupting properties, there is no currently agreed methodology for undertaking a risk assessment based on such properties and no agreed methodology available on how to consider the data used for the identification of whether this substance is an endocrine disruptor in risk assessment for the environment.* ***Given the exposure of cyanamide to humans and the environment, a risk related to the ED properties cannot be excluded.***"

Therefore, the eCA was asked to clarify the following aspects with regard to environment:

3. Based on available information, clarify whether a safe level (threshold) can be determined for the ED properties of cyanamide for the environment, and if such threshold can be established, what would be this level.
4. Clarify the level of the risks to the environment by:
   - Assessing the level of risk for the environment, either by a quantitative assessment or by a qualitative assessment
   - Providing an opinion whether the risks can be considered acceptable or not.

In order to answer the above-mentioned questions, the eCA was assigned to consider the following aspects in its assessment:

- All the data submitted in the application, as well as the conclusions of the discussions in the BPC and its Working Groups.
- Any further information submitted by the applicant or other interested parties within the scope of this request and the timeline specified by the eCA or ECHA as appropriate.
- The data submitted during the public consultations on this substance organised by ECHA from 22 February to 21 April 2016 and from 26 June 2019 to 25 August 2019, including those submitted by the applicant.

In order to be able to answer the questions of the mandate with respect to the environmental risk assessment, the following steps were taken:

In the light of the available data, the eCA provided an opinion on the risks for the environment that integrated the hazard caused by the ED properties of cyanamide as well as a series of general questions on the ED risk assessment that first needed to be addressed before the questions of the mandate could be answered accordingly. This document underwent an e-consultation from 29 March until 26 April 2021 during which six member states, NO, CH and ECHA as well as the applicant submitted comments. The first discussion on the proposal took place at WG-II-2021, where the majority of the commenting WG members supported the eCA evaluation and considered that the available data would not allow defining a safe threshold with regard to environmental

non-target organisms. However, several questions remained open, also concerning the data submitted by the applicant on the natural occurrence of cyanamide, so a further e-consultation was initiated.
This e-consultation took place from 12 July until 6 August 2021 and four member states and NO as well as the applicant commented on the eCA's evaluation of the additional data. The final WG discussion on the COM's mandate on cyanamide took place at WG-III-2021 where all open questions could be closed accordingly.

The following questions were addressed by the ENV WG:

| # | Question | WG conclusion | Reference |
|---|---|---|---|
| 1 | Does the WG agree that currently no thresholds/safe concentration limits can be derived for EDs with regard to environmental non-target organisms for cyanamide? | The WG agreed that currently no thresholds/safe concentration limits can be derived with regard to environmental non-target organisms for cyanamide. | ENV WG II/2021 |
| 2 | Does the WG agree that no further (ecotox-) tests for cyanamide are necessary? | The WG agreed that no further tests on ED for NTO[3] should be requested at this point in time. The lack of guidance to derive a threshold makes it impossible for the MSCA[4]s to indicate which test would be required. | ENV WG II/2021 |
| 3a | Does the WG agree that the data submitted by the applicant does not allow to assess reliably the environmental background levels and distribution of cyanamide? | The WG agreed that the data submitted by the applicant does not allow to assess reliably the environmental background levels and distribution of cyanamide. | ENV WG III/2021 |
| 3b | Does the WG agree that as a consequence the data submitted by the applicant is not sufficient to show the biocidal contribution relative to the existing background concentrations can be considered negligible? | The WG agreed that with the available information exposure to the environment from biocidal uses cannot be excluded. | ENV WG III/2021 |
| 4 | Does the WG agree that since exposure from the biocidal use of cyanamide cannot be excluded, neither can the risk, even though the substance might occur naturally due to certain plant species? | The WG agreed that, since exposure cannot be excluded, also risk coming from this exposure cannot be excluded. | ENV WG III/2021 |
| 5 | Does the WG agree that a quantitative risk assessment is not possible for EDs with regard to non-target organisms for cyanamide at this point in time? | The WG agreed that a quantitative risk assessment is not possible for ED with regard to non-target organisms for cyanamide at this point in time. | ENV WG II/2021 |

[3] NTO: non-target organisms
[4] MSCA: member states competent authority

| | | | |
|---|---|---|---|
| 6 | Does the WG agree that a qualitative risk assessment is currently not possible for cyanamide? | The WG agreed that the current environmental background concentrations are unclear. Since there is unclear background concentration and the absence of a safe level no qualitative risk assessment can be carried out. Nevertheless, a qualitative assessment for the exposure is possible. | ENV WG II/ 2021; ENV WG III/2021 |
| 7 | Does the WG agree that the available data does not show that the risk from exposure is negligible? | The WG agreed that, since exposure from biocidal uses cannot be excluded, also risk coming from this exposure cannot be excluded. | ENV WG II/ 2021; ENV WG III/2021 |
| 8 | Does the WG see a need for further testing with regard to the degradation of cyanamide in liquid manure and/or for monitoring data from field applications as proposed by the applicant? | The WG didn´t see the need to perform new studies on degradation or monitoring. The already agreed CAR contains degradation studies which can enable qualitative assessment for the purpose of the COM Mandate. | ENV WG II/ 2021; ENV WG III/2021 |
| 9a | Does the WG agree that it is currently impossible to decide whether the risk is acceptable or not? | The WG agreed that, given the uncertainties *(of the assessment, addition of the eCA)* and lack of methodology, it is currently not possible to determine whether the risk is acceptable. | ENV WG III/2021 |
| 9b | If so, does the WG agree that currently it is not possible to demonstrate that the risk is acceptable (as requested by the mandate)? | The WG agreed that currently it is not possible to demonstrate that the risk is acceptable. Nevertheless, the WG agreed that, since exposure cannot be excluded, also risk coming from this exposure cannot be excluded. | ENV WG III/2021 |

The details of the assessment are summarised in APPENDIX VI.

Based on the discussions with the member states in the context of the ENV WG, the questions of the COM's mandate can be answered as follows:

1. **Based on available information, clarify whether a safe level (threshold) can be determined for the ED properties of cyanamide for the environment, and if such threshold can be established, what would be this level.**

   *Currently no thresholds/safe concentration limits with regard to environmental non-target organisms can be derived for the ED properties of cyanamide due to a variety of uncertainties associated with such an approach.*

2. **Clarify the level of the risks to the environment by:**

- **Assessing the level of risk for the environment, either by a quantitative assessment or by a qualitative assessment with particular focus on**

**whether the exposure can be considered negligible, like for non-threshold carcinogen/mutagen substances or PBTs.**

*A risk assessment in the strict sense, i.e. comparing "PEC/PNEC" or "exposure and effect", is not possible for cyanamide at this point in time. Neither a quantitative nor a qualitative risk assessment can be conducted as no safe threshold can be derived with which the exposure can be compared to. The only option is an assessment of the exposure situation with particular focus on whether the exposure can be considered negligible or not. However, it needs to be considered in this context, that the term "negligible" is not yet defined within the frame of the BPR. Although* the final interpretation of the term 'negligble' is outside the scope of the WG*, the MS agreed that the term "negligible risk from exposure" as used in the BPR should be finally understood as "no releases from biocidal uses into the environment".*
*The conclusions of the qualitative assessment of the exposure situation are: i) the data submitted by the applicant on the natural occurrence of cyanamide in certain plant species does not allow to assess reliably the environmental background levels and distribution of cyanamide in the environment and ii) releases to the environment from the intended uses of cyanamide cannot be excluded.*

- **Providing an opinion whether the risks can be considered acceptable or not.**
  *Regarding the acceptability of the risk no final conclusion is possible. It was agreed between the MS that, given the uncertainties of the assessment and lack of methodology, it is currently not possible to determine whether the risk is acceptable. The MS also agreed that currently it is not possible to demonstrate that the risk is acceptable. Nevertheless, the MS agreed that, since exposure cannot be excluded, also the risk coming from this exposure cannot be excluded.*

For the details of the assessment please refer to the APPENDIX VI.

## 2.3. Overall conclusions

The outcome of the assessment for cyanamide in product-types 3 and 18 is specified in the BPC opinion following discussions at the 16$^{th}$, 33$^{rd}$ and 41$^{st}$ meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA web-site.

## 2.4. List of endpoints

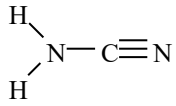
The most important endpoints, as identified during the evaluation process, are listed in APPENDIX I.

# APPENDIX I: List of endpoints

## Chapter 1:Identity, Physical and Chemical Properties, Classification and Labelling

| | |
|---|---|
| Active substance (ISO Name) | Cyanamide |
| Product-type | 03 and 18 |

**Identity**

| | |
|---|---|
| Chemical name (IUPAC) | Cyanamide |
| Chemical name (CA) | |
| CAS No | 420-04-2 |
| EC No | 206-992-3 |
| Other substance No. | CIPAC No:: 685 |
| Minimum purity of the active substance as manufactured (g/kg or g/l) | 96.8 % w/w (dry weight)<br>50.5 %w/w (aqueous solution |
| Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg) | No relevant impurities and additives (substances of concern) |
| Molecular formula | $CH_2N_2$ |
| Molecular mass | 42.05 g/mol |
| Structural formula |  |

**Physical and chemical properties**

| | |
|---|---|
| Melting point (state purity) | 46.1 °C (99.7 % w/w pure Cyanamide F 1000) |
| Boiling point (state purity) | decomposition before boiling (99.7 % w/w pure Cyanamide F 1000) |
| Temperature of decomposition | > 141 °C |
| Appearance (state purity) | solid, colourless, odourless (purity > 96 % Cyanamide F 1000)<br>The ca. 50 % technical solution is a blue liquid. |
| Relative density (state purity) | $d_4^{20} = 1.23 (21.4°C)$<br>(purity: 101.2 % pure Cyanamide F 1000) |
| Surface tension | 86 mN/m (20 °C) (99.7 % (w/w) cyanamide F1000, tested at a concentration of 1 g/l |

| | |
|---|---|
| Vapour pressure (in Pa, state temperature) | 0.51 Pa (T = 20 °C) (purity: > 99.6 % pure Cyanamide F 1000)<br>1.0 Pa (T = 25 °C) (purity: > 99.6 % pure Cyanamide F 1000)) |
| Henry's law constant (Pa m3 mol -1) | < 3.83 * 10-5 Pa m3 mol-1 ((at 20 °C) |
| Solubility in water (g/l or mg/l, state temperature) | pH__7____: > 560 g/l (buffered, preliminary test, T = 20 °C) |
| Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1) | n-Hexane: 2,4 mg/l (at 20 °C) |
| | Dichloromethane: 410 mg/l (at 20 °C) |
| | Toluene: 670 mg/l (at 20 °C) |
| | Isopropanol: > 210 g/l (at 20 °C) |
| | Methanol: > 210 g/l (at 20 °C) |
| | Ethylacetate: > 210 g/l (at 20 °C) |
| | Acetone: > 210 g/l (at 20 °C) |
| Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2) | No organic solvent included |
| Partition coefficient (log POW) (state temperature) | pH___6,8___: -0.72 (T = 20 °C) |
| Hydrolytic stability (DT50) (state pH and temperature) (point VII.7.6.2.1) | T = 285 K calculated by Arrhenius equation<br>pH___5___: 4458 d |
| | pH___7___: 8444 d |
| | pH___9___: 4456 d |
| Dissociation constant (not stated in Annex IIA or IIIA; additional data requirement from TNsG) | Cyanamide does not dissociate in water, pH = 6 – 9 |
| UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength) | No absorption maximum |
| Photostability (DT50) (aqueous, sunlight, state pH)<br>(point VII.7.6.2.2) | DT50: 28.9 d at pH 5<br>38.5 d at pH 7 |
| Quantum yield of direct phototransformation in water at Σ > 290 nm (point VII.7.6.2.2) | not reported due to adsorption coefficient at 290 nm is below 10 in UV-VIS spectra |
| Flammability | not highly flammable, self-ignition > 600 °C |
| Explosive properties | non-explosive |

**Classification and proposed labelling**

**with regard to human health hazards**

The classification and labelling for cyanamide according to regulation (EC) No 1272/2008 (CLP Regulation, 10th ATP) is:

| | Classification | Wording |
|---|---|---|
| Hazard classes, Hazard categories | Acute Tox. 3<br>Acute Tox. 3<br>Skin Corr 1<br>Eye Dam. 1<br>Skin Sens. 1<br>Carc. 2<br>STOT RE 2<br>Repr. 2 | |
| Hazard statements | H301<br>H311<br>H314<br><br>H318[1]<br>H317<br>H351<br>H373<br><br><br>H361fd | Toxic if swallowed<br>Toxic in contact with skin<br>Causes severe skin burns and eye damage<br>Causes serious eye damage<br>May cause an allergic skin reaction<br>Suspected of causing cancer<br>Causes damage to organs through prolonged or repeated exposure (thyroid gland)<br>Suspected of damaging fertility.<br>Suspected of damaging the unborn child |

[1] H318 does not need to be indicated on the label for corrosive substances and mixtures to avoid redundancy.

Labelling of cyanamide based on Regulation (EC) No 1272/2008

| | Labelling | Wording |
|---|---|---|
| Pictograms | GHS05<br>GHS06<br>GHS08 | |
| Signal Word | Danger | |
| Hazard statements | H301<br>H311<br>H314<br><br>H317<br>H351<br>H373<br><br><br>H361fd | Toxic if swallowed<br>Toxic in contact with skin<br>Causes severe skin burns and eye damage<br>May cause an allergic skin reaction<br>Suspected of causing cancer<br>Causes damage to organs through prolonged or repeated exposure (thyroid gland)<br>Suspected of damaging fertility.<br>Suspected of damaging the unborn child |
| Suppl. Hazard statements | - | - |
| Precautionary statements | (P102)<br>P201<br><br>P202 | (Keep out of reach of children)<br>Obtain special instructions before use.<br>Do not handle until all safety precautions have been read and |

| | | |
|---|---|---|
| | | understood. |
| | P280 | Wear protective gloves/protective clothing/eye protection/face protection. |
| | P301 + P330 + P331 | IF SWALLOWED: rinse mouth. Do NOT induce vomiting. |
| | P303 + P361 + P353 | IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower. |
| | P305 + P351 + P338 | IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. |
| | P308 + P310 | IF exposed or concerned: Immediately call a POISON CENTER or doctor/physician. |
| | P405 | Store locked up. |
| | P501 | Dispose of contents/container to … |

**with regard to ecotoxicological data**

The classification and labelling for cyanamide according to regulation (EC) No 1272/2008 (CLP Regulation, 10th ATP) is:

| | Classification | Wording |
|---|---|---|
| Hazard classes, Hazard categories | Aquatic chronic 3 | |
| Hazard statements | H412 | Harmful to aquatic life with long lasting effects. |

Labelling of cyanamide based on Regulation (EC) No 1272/2008

| | Labelling | Wording |
|---|---|---|
| Pictograms | - | |
| Signal Word | - | |
| Hazard statements | H412 | Harmful to aquatic life with long lasting effects. |
| M-factor | - | |
| Precautionary statements | P273<br>P391<br>P501 | Avoid release to the environment.<br>Collect spillage.<br>Dispose of contents/container to... |

## Chapter 2:Methods of Analysis

### Analytical methods for the active substance

| | |
|---|---|
| Technical active substance (principle of method) | The analytical method for the active substance is based on a potentiometric titration method |
| Impurities in technical active substance (principle of method) | Analytical methods for the determination of the impurities in cyanamide solutions as manufactured are described in detail in Document IIIA Section 4.1/02-09 in the "Confidential Data" file. |

### Analytical methods for residues

| | |
|---|---|
| Soil (principle of method and LOQ) (Annex IIA, point 4.2) | residue definition: cyanamide<br>RP-HPLC-UV<br>LOQ = 0.05 mg/kg |
| Air (principle of method and LOQ) (Annex IIA, point 4.2) | residue definition: cyanamide<br>RP-HPLC-UV<br>LOQ = 2 µg/m³ |
| Water (principle of method and LOQ) (Annex IIA, point 4.2) | residue definition : cyanamide<br>Ion-HPLC-UV<br>LOQ = 0.1 µg/L (drinking water)<br>LOQ = 0.5 µg/L (surface water)<br>HPLC-MS/MS<br>LOQ = 0.1 µg/L (surface water, also acceptable for drinking water) |
| Body fluids and tissues (principle of method and LOQ) (Annex IIA, point 4.2) | residue definition: cyanamide<br>RP-HPLC-UV<br>LOQ = 0.05 mg/L (blood)<br>LOQ = 0.05 mg/kg (muscle) |
| Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1) | not required |
| Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1) | not required |

## Chapter 3:Impact on Human Health

**Absorption, distribution, metabolism and excretion in mammals**

| | |
|---|---|
| Rate and extent of oral absorption: | > 90 % (based on urine, expired $CO_2$ excretion over 7 d) |
| Rate and extent of dermal absorption*: | 14.3 % for a 10 %, 9.5 % for a 1 % and 8.2 % for a 0.1 % aqueous dilution, based on rat *in vivo*:<br>According to Agreement of BPC-WG I-2016:<br>exposure to corrosive concentrations: dermal absorption of 100 %;<br>concentrations above 10 %: 25 % dermal absorption when irritant or corrosive effects can be excluded. |
| Distribution: | Widely distributed |
| Potential for accumulation: | No evidence for accumulation |
| Rate and extent of excretion: | Rapid (> 67 % first 24 hours post-dose); 79 % via urine, 4.2 % via faeces, 10 % as $CO_2$ over 7 d for single low dose in rats |
| Toxicologically significant metabolite(s) | Nitroxyl (CAS 14332-28-6). Toxicity of other metabolites not specified. |

* the dermal absorption value is applicable for the active substance and might not be usable in product authorization

**Acute toxicity**

| | |
|---|---|
| Rat $LD_{50}$ oral | 142 - 223 mg/kg bw |
| Rat $LD_{50}$ dermal | 848 mg/kg bw |
| Rat $LC_{50}$ inhalation | > 1 mg/L (4 h; highest attainable concentration, aerosol) |

| | |
|---|---|
| **Skin corrosion/irritation** | Corrosive |
| **Eye irritation** | Irritant |
| **Respiratory tract irritation** | Presumed (based on skin corrosive and eye irritant properties) |
| **Skin sensitisation (test method used and result)** | Sensitising (Magnusson & Kligman) |
| **Respiratory sensitisation (test method used and result)** | No data |

**Repeated dose toxicity**

**Short term**

| | |
|---|---|
| Species / target / critical effect | Rat, dog: thyroid gland (hypothyroidism), testes (decreased spermatogenesis), anaemia<br>Rat: thyroid gland (decreased colloid) and reduced body weight/body weight gain<br>Mouse: urinary bladder (chronic cystitis), kidney (atrophic basophilic tubules), morbidity/mortality |
| Relevant oral NOAEL / LOAEL | 90-d rat: 1.5 mg/kg bw/d<br>90-d dog: 0.6 mg/kg bw/d<br>1-yr dog: 1 mg/kg bw/d<br>91-wk rat: 1 mg/kg bw/d<br>100-/104-wk mouse: 4.2 mg/kg bw/d |
| Relevant dermal NOAEL / LOAEL | Local: 12.5 mg/kg bw/d (21-d rabbit)<br>Systemic: no data, accepted |
| Relevant inhalation NOAEL / LOAEL | 14-d rat: < 0.15 mg/L air |

**Subchronic**

| | |
|---|---|
| Species/ target / critical effect | See above |
| Relevant oral NOAEL / LOAEL | |
| Relevant dermal NOAEL / LOAEL | |
| Relevant inhalation NOAEL / LOAEL | |

**Long term**

| | |
|---|---|
| Species/ target / critical effect | See above |
| Relevant oral NOAEL / LOAEL | |
| Relevant dermal NOAEL / LOAEL | |
| Relevant inhalation NOAEL / LOAEL | |

| | |
|---|---|
| **Genotoxicity** | Clastogenic *in vitro*, no evidence for genotoxicity *in vivo* |

**Carcinogenicity**

| | |
|---|---|
| Species/type of tumour | 100-/104-wk mouse [Crl:CD-1 (ICR) BR]: increased incidence of ovarian granulosa-theca tumours at dose level > MTD, not observed in B6C3F1 mice or rats |
| Relevant NOAEL/LOAEL | 39.0 mg/kg bw/d (600 ppm) |

**Reproductive toxicity**

*Developmental toxicity*

| | |
|---|---|
| Species/ Reproduction target / critical effect | Rat: reduced fertility, testicular degeneration and atrophy, decreased pup weights and neonatal viability |
| Lowest relevant reproductive NOAEL | 3.75 mg/kg bw/d (parental)<br>3.75 mg/kg bw/d (fertility)<br>< 1.25 mg/kg bw/d (offspring, gavage study)<br>1.66 mg/kg bw/d (offspring, dietary study)) |
| Species/Developmental target / critical effect | Rat: decreased foetal bw; diaphragmatic hernia at maternally toxic dose level<br>Rabbit: decreased foetal bw at maternally toxic dose level |
| Lowest relevant developmental NOAEL | |

| | |
|---|---|
| Species/ Reproduction target / critical effect | Rat: reduced fertility, testicular degeneration and atrophy, decreased pup weights and neonatal viability |
| Lowest relevant reproductive NOAEL | 3.75 mg/kg bw/d (parental)<br>3.75 mg/kg bw/d (fertility)<br>< 1.25 mg/kg bw/d (offspring, gavage study)<br>1.66 mg/kg bw/d (offspring, dietary study)) |
| Species/Developmental target / critical effect | Rat: decreased foetal bw; diaphragmatic hernia at maternally toxic dose level<br>Rabbit: decreased foetal bw at maternally toxic dose level |
| Lowest relevant developmental NOAEL | Rat: 5 mg/kg bw/d<br>Rabbit: 6 mg/kg bw/d |

**Neurotoxicity**

| | |
|---|---|
| Species/ target/critical effect | No data, no evidence for neurotoxic potential in other studies |

**Developmental Neurotoxicity**

| | |
|---|---|
| Species/ target/critical effect | No data, effects on thyroid hormone levels represent potential reason for concern |

**Immunotoxicity**

| | |
|---|---|
| Species/ target/critical effect | No data |

**Developmental Immunotoxicity**

| | |
|---|---|
| Species/ target/critical effect | No data |

**Other toxicological studies**

**Conclusion on endocrine system disruption:** Based on the multiple observations of thyroid toxicity, it is concluded that cyanamide exhibits thyroid-disruptive effect caused by the direct endocrine mechanism of TPO inhibition. Relevance of this finding to humans is supported by the provided TPO inhibition studies in which cyanamide was shown to be a potent inhibitor of human TPO activity.

**Other toxicological studies:**

N-acetylcyanamide was identified as major metabolite in several species, including man; an instable minor metabolite (hydroxycyanamide) decomposes to cyanide and nitroxyl; cyanide content in the blood of male human volunteers is not affected by cyanamide intake; nitroxyl is the active metabolite responsible for ALDH inhibition.

Acetylcystein increases acute oral toxicity of cyanamide in male rats whereas cystein leads to a reduction; cyanamide preparation (Alzodef) in combination with ethanol resulted in lower oral and inhalative $LD_{50}$.

No indication for cyanamide-induced hepatic inclusion bodies in rats after long-term administration but abnormal liver histology ("ground glass hepatocytes") reported after treatment of chronic alcoholics.

Reproductive toxicity observed with cyanamide in rats and rabbits could be a consequence of inhibition of tissue-specific aldehyde dehydrogenases.

The test substance cyanamide L 500 was examined for its in vitro skin corrosion potential using EpiDerm™ reconstructed skin membranes and was classified as corrosive.

**Medical data**

Cyanamide is used as a deterrent to alcohol consumption (> 20 mg/person/day). Cyanamide ingestion or inhalation alone or more pronounced in combination with alcohol consumption induces vasomotoric reactions, known as "Cyanamide Flush"; including symptoms, such as facial flushing, tachycardia, dyspnea, hypotension, headache, nausea, vomiting, tightness in the chest and sensation of coldness in the extremities. In general these symptoms disappear with no residual effects on general health without specific treatment. In the cases of exposure to larger quantities (gram range/day) severe irrritating properties of hydrogen cyanamide to the mucous membranes were also observed. Additional effects such as trembling, convulsion, salivation, danger of aspiration, pains behind the sternum and in the epigastrum, unconsciousness and final exitus can occur.

No signs of diseases or health impairments caused by cyanamide were found during medical surveillance on manufactoring plant personnel. Medical examinations also included special investigations of functional disorders regarding the testes and the thyroid gland and potential sensitising properties

**Summary**

| | Value | Study | Safety factor |
|---|---|---|---|
| $AEL_{acute}$ | 0.05 mg/kg bw | Developmental toxicity, rat (maternal effect), supported by human experience | 100 |
| $AEL_{medium-/long-term}$ | 0.01 mg/kg bw | 90-d & 1-yr, dog (overall NOAEL) | 100 |

| | | | |
|---|---|---|---|
| ADI[5] | 0.01 mg/kg bw | 90-d & 1-yr, dog (overall NOAEL) | 100 |
| ARfD | 0.05 mg/kg bw | Developmental toxicity, rat (maternal effect), supported by human experience | 100 |

**MRLs**

| | |
|---|---|
| Relevant commodities | Reg. (EC) No. 149/2008<br>Food of plant origin: variable values in the range of 0.05* to 0.2 mg/kg,<br>no EU values set for food of animal origin<br><br>Note: Since drafting the CAR MRLs were updated according to<br>Reg. (EU) No. 1126/2014:<br>Food of plant and animal origin:<br>0.01* mg/kg<br>(*MRL set at LOQ)<br><br>The values from Reg. (EC) No. 149/2008 were used during preparation of the CAR. Since then, new values were set in Reg. (EU) No. 1126/2014, however the HH WG III 2021 agreed that the dietary risk assessment does not need to be updated at this point. Therefore, both values are listed here. |

**Reference value for groundwater**

| | |
|---|---|
| According to BPR Annex VI, point 68 | |

**Dermal absorption**

| | |
|---|---|
| Study (*in vitro/vivo*), species tested | n.a. |
| Formulation (formulation type and including concentration(s) tested, vehicle) | n.a. |
| Dermal absorption values used in risk assessment | According to agreement of BPC-WG I-2016:<br>exposure to corrosive concentrations: dermal absorption of 100 %;<br>concentrations above 10 %: 25 % dermal absorption when irritant or corrosive effects can be excluded. |

[5] If residues in food or feed.

## Chapter 4: Fate and Behaviour in the Environment

### Route and rate of degradation in water

| | |
|---|---|
| Hydrolysis of active substance and relevant metabolites ($DT_{50}$) (state pH and temperature) | T = 285 K calculated by Arrhenius equation<br>pH___5___: 4458 d<br>pH___7___: 8444 d<br>pH___9___: 4456 d |
| | |
| Photolytic / photo-oxidative degradation of active substance and resulting metabolites | Half-life: 28.9 d at pH 5<br>38.5 d at pH 7<br>Degradation product: urea (12.2 %) at pH 7; 42.4 % at pH 5 |
| Readily biodegradable (yes/no) | No |
| Inherent biodegradable (yes/no) | |
| Biodegradation in freshwater | |
| Biodegradation in seawater | No study conducted, not relevant |
| Non-extractable residues | River: max. 11% (day 28, end of study)<br>Pond: max. 7.8% (day 21) |
| Distribution in water / sediment systems (active substance) | Mineralisation:<br>River: max. 86.1% (day 28)<br>Pond: max. 83.5% (day 28) |
| | $DT_{50}$ total systems (20°C, aerobic):<br>2.5 d (River); 4.8 d (Pond) |
| | $DT_{50}$ water (20°C, aerobic):<br>2.3 d (River); 4.3 d (Pond) |
| | $DT_{50}$ total systems (converted to 12°C, aerobic):<br>4.7 d (River); 9.1 d (Pond) |
| | $DT_{50}$ water (converted to 12°C, aerobic):<br>4.4 d (River); 8.2 d (Pond) |
| | Radioactivity in the water phases:<br>River: 101.2% (day 0), decline to 0.1% (day 12), thereafter not detectable<br>Pond: 96.7% (day 0), decline to 0.1% (day 28, end of study) |
| | Radioactivity in the sediment (extractable):<br>River: max. of 4.9% (day 2), decline to 0.7% (day 28, end of study)<br>Pond: max. of 8.2% (day 6), decline to 1.2% (day 28, end of study) |

| | |
|---|---|
| Distribution in water / sediment systems (metabolites) | River: Up to 8 metabolites were detected, non exceeding 10% of the applied radioactivity. |
| | Pond: At least 4 metabolites were detected, non exceeding 10% of the applied radioactivity, except for Urea. |
| | $DT_{50}$ total system (12°C, aerobic):<br>Urea (M4):<br>5.5 d (River); 15.2 d (Pond) |
| | $DT_{50}$ water (12°C, aerobic):<br>Urea (M4):<br>5.1 d (River); 14.2 d (Pond) |
| | Radioactivity in the water phases<br>Urea (M4):<br>River: max. 6.1% (day 2), decline to 0.1% (day 12), thereafter not detectable<br>Pond: max. 11.8% (day 1), decline to 1.2% (day 21), thereafter not detectable |
| | Radioactivity in the sediment (extractable)<br>Urea (M4):<br>River: max. 0.6% (day 2), decline to 0.4% (day 6), thereafter not detectable<br>Pond: max. 1.6% (day 1), decline to 1.4% (day 12), thereafter not detectable |
| | Thiourea:<br>Detected in a study on degradation in liquid manure (max. 4.7% at day 71), for water-sediment systems no half-lives exist, according to available literature data assumed to be persistent in water-sediment systems |
| Major metabolites - name and/or code, % of applied a.i. (range and maximum) | Urea: max. 13.4% (day 1) |

**Route and rate of degradation in liquid manure**

| | |
|---|---|
| Mineralization (anaerobic) | max. 25.1% (day 105) |
| Anaerobic degradation | $DT_{50lab}$ (20°C, anaerobic): 45.4 days |
| | $DT_{90lab}$ (20°C, anaerobic): 88.8 days |
| Non-extractable residues | max. 2.7% (day 59) |
| Metabolites - name and/or code, % of applied a.i. (range and maximum) | Dicyandiamide: max. 14.5% (day 71)<br>Guanidine: max. 13.4% (day 59)<br>Thiourea: max. 4.7% (day 71) |

**Route and rate of degradation in soil**

| | |
|---|---|
| Mineralization | max. 94.6% at day 14 (aerobic)<br>max. 53.1% at day 60 (anaerobic) |
| Laboratory studies (range or median, with number of measurements, with regression coefficient) | $DT_{50lab}$ (20°C, aerobic, 100% field capacity, sandy loam):<br>1.48 days |
| | $DT_{90lab}$ (20°C, aerobic): - |
| | $DT_{50lab}$ (converted to 12°C, aerobic, 100% field capacity, sandy loam): 2.81 days |
| | $DT_{50lab}$ (20°C, anaerobic, 100% field capacity, sandy loam): 42.27 days |
| | $DT_{50lab}$ (converted to 12°C, anaerobic, 100% field capacity, sandy loam): 80.17 days |
| | Thiourea:<br>Metabolite detected in a study on degradation in liquid manure (max. 4.7% at day 71):<br>$DT_{50lab}$ (20°C, aerobic, 100% field capacity):<br>13.6 days (sandy loam); 9.4 (sandy silt loam)<br>$DT_{50lab}$ (12°C, aerobic, 100% field capacity):<br>25.7 days (sandy loam); 17.8 (sandy silt loam) |
| | degradation in the saturated zone: n.d. |
| Field studies (state location, range or median with number of measurements) | $DT_{50field}$: no field studies performed |
| | $DT_{90field}$: - |
| Anaerobic degradation | see laboratory studies |
| Soil photolysis | n.d. |
| Non-extractable residues | Laboratory studies:<br>aerobic:<br>max. 9.46% after 4 hours (day 0)<br>anaerobic:<br>9.55% after 12 hours (day 0) |
| Metabolites - name and/or code, % of applied a.i. (range and maximum) | Laboratory studies: all metabolites <10%<br>aerobic:<br>dicyandiamide, max. 0.43% at day 0<br>anaerobic:<br>dicyandiamide, max. 5.97% at day 30<br>guanylurea, max. 8.06% at day 30<br>guanidine, max. 3.15% at day 30<br>urea, max. 1.71% at day 30 |
| Soil accumulation and plateau concentration | study not required |

**Adsorption/desorption**

| | | |
|---|---|---|
| Ka , Kd<br>$Ka_{oc}$ , $Kd_{oc}$<br>pH dependence (yes / no) (if yes type of dependence) | $K_d$[1] (mL/g) | $K_{OC}$ (mL/g) |
| | No | |
| | 0.092 | 6.81 |
| | 0.059 | 4.35 |
| | 0.060 | 6.34 |
| Arithmetic mean: | | 4.38 |

**Fate and behaviour in air**

| | |
|---|---|
| Direct photolysis in air | according to the Atkinson calculation, cyanamide is stable in the atmosphere |
| Quantum yield of direct photolysis | - |
| Photo-oxidative degradation in air | - |
| Volatilization | - |

**Reference value for groundwater**

| | |
|---|---|
| According to BPR Annex VI, point 68 | - |

**Monitoring data, if available**

| | |
|---|---|
| Soil (indicate location and type of study) | - |
| Surface water (indicate location and type of study) | - |
| Ground water (indicate location and type of study) | - |
| Air (indicate location and type of study) | - |

## Chapter 5: Effects on Non-target Species

**Toxicity data of cyanamide and thiourea for aquatic species** (most sensitive species of each group)

| Species | Time-scale | Endpoint | Toxicity |
|---|---|---|---|
| **Fish** | | | |
| Cyanamide | | | |
| *Lepomis macrochirus* | 96 hours | Mortality | $LC_{50}$ = 43.1 mg a.s./l |
| Thiourea | | | |

| | | | |
|---|---|---|---|
| *Pimephales promelas* | 96 hours | Mortality | $LC_{50}$ ≥ 600 mg /l |
| **Invertebrates** | | | |
| Cyanamide | | | |
| *Daphnia magna* | 48 hours<br>21 days | immobilisation<br>reproduction | $EC_{50}$ = 3.2 mg a.s./l<br>NOEC = 0.1044 mg a.s./l |
| Thiourea | | | |
| *Daphnia magna* | 48 hours<br>21 days | immobilisation<br>reproduction | $EC_{50}$ = 5.6 mg /l<br>NOEC = 1.0 mg /l |
| **Algae** | | | |
| Cyanamide | | | |
| *Pseudokirchneriella subcapitata* | 72 hours | growth inhibition | $E_rC_{50}$ = 14.7 mg a.s./l<br>NOErC= 2.6 mg a.s./l |
| Thiourea | | | |
| *Scenedesmus subspicatus* | 96 h | growth inhibition | $E_bC_{50}$ = 4.4 mg /l<br>$EC_{10}$ = 0.6 mg /l |
| **Aquatic plants** | | | |
| *Lemna gibba* | 7 days | growth inhibition | $E_rC_{50}$ = 5.47 mg a.s./l<br>NOEC = 0.43 mg a.s./l |
| **Microorganisms** | | | |
| Cyanamide | | | |
| *Pseudomonas putida* | 19 hours | Inhibition of cell multiplication | $EC_{50}$ = 283 mg as/L (nominal)<br>NOEC = 88 mg as/L (nominal) |
| Guanidine | | | |
| *Pseudomonas putida* | 18 hours | Inhibition of cell multiplication | NOEC = 831.8 mg guanidine/L (nominal) |

**Effects on sediment organisms**

| | | | |
|---|---|---|---|
| *Chironomus riparius* | 28 days | development rate | NOEC = 1.8 mg a.s./l |

**Effects of Cyanamide on earthworms or other soil non-target organisms**

| | |
|---|---|
| Acute toxicity to earthworms<br>Eisenia foetida<br>(Annex IIIA, point XIII.3.2) | LC50 > 111.6 mg a.s./kg soil dw |
| Long-term toxicity to springtails | EC10 = 1.5 mg a.s./kg soil dw |

| | |
|---|---|
| (Annex IIIA, point XIII.3.2) | (reproduction) |
| Acute toxicity to plants<br>Allium cepa<br>(Annex IIIA, point XIII.3.2)<br>Reproductive toxicity to plants<br>A. sativa, B. rapa<br>(Annex IIIA, point XIII.3.2) | EC50 = 0.58 mg a.s./kg soil dw<br><br>NOEC ≥ 100 mg a.s./kg dw (Seedling emergence, growth and reproduction) |

**Effects of thiourea on earthworms or other soil non-target organisms**

| | |
|---|---|
| Acute toxicity to earthworms<br>*Eisenia foetida*<br>(Annex IIIA, point XIII.3.2) | $LC_{50}$ ≥ 3550 mg /kg soil dw |
| Acute toxicity to plants<br>*Avena sativa*<br>(Annex IIIA, point XIII.3.2)<br>Reproductive toxicity to plants<br>*A. sativa, B. rapa*<br>(Annex IIIA, point XIII.3.2) | $EC_{50}$ = 52.1 mg /kg soil dw<br><br>NOEC ≥ 150 mg a.s./kg dw (Seedling emergence, growth and reproduction) |

**Effects of cyanamide on soil micro-organisms**

| | |
|---|---|
| Nitrogen mineralization | NOEC = 27.2 mg a.s./kg dry weight soil |
| Carbon mineralization | Study not valid. |

**Effects of thiourea on soil micro-organisms** (Annex IIA, point 7.4)

| | |
|---|---|
| Nitrogen mineralization | NOEC ≥ 53.3 mg /kg dry weight soil |

**Effects on terrestrial vertebrates**

| | |
|---|---|
| Acute toxicity to mammals | Refer to mammalian toxicity package |
| Acute toxicity to birds | No exposure |
| Dietary toxicity to birds | No exposure |
| Reproductive toxicity to birds | No exposure |

**Effects on honeybees**

| | |
|---|---|
| Acute oral toxicity | < 51.7 µg a.s./bee |
| Acute contact toxicity | - |

**Effects on other beneficial arthropods**

| | |
|---|---|
| Acute oral toxicity | - |
| Acute contact toxicity | These studies are not relevant for the assessment of cyanamide as stable |

| | |
|---|---|
| | insecticide due to the different exposure situation over glass plates. |
| Acute toxicity to …….. | - |

**Bioconcentration**

| | |
|---|---|
| Bioconcentration factor (BCF) | <u>Cyanamide:</u><br>$BCF_{fish}$ = 0.049 L*$kg_{wet\ fish}^{-1}$ (calc.)<br>$BCF_{earthworm}$ = 0.84 L*$kg_{wet\ earthworm}^{-1}$ (calc.)<br><u>Thiourea:</u><br>$BCF_{fish}$ = 0.033 and 0.0085 L*$kg_{wet\ fish}^{-1}$ (calc.)<br>$BCF_{earthworm}$ = 0.84 L*$kg_{wet\ earthworm}^{-1}$ (calc.) |
| Depration time ($DT_{50}$) | - |
| Depration time ($DT_{90}$) | - |
| Level of metabolites (%) in organisms accounting for > 10 % of residues | - |

## Chapter 6: Other End Points

Residues

Measurable residues in food or feed from the use of cyanamide in biocidal products in PT 18 and PT 03 are not expected. Therefore, an additional exposure to humans through diet arising from the use of cyanamide as a biocide can be excluded. No MRLs specific to biocidal product uses are necessary.

# APPENDIX II: List of Intended Uses

## Summary of intended uses for PT3

ALZOGUR® is intended to be applied to the liquid manure stored underneath the slatted floor in empty pig stables to control the pathogen *Brachyspira hyodysenteriae*. The applications intend to protect fattening pigs against the pig disease dysenteria.

| Object and/or situation | Product name | Organisms controlled | Formulation | | Application | | | Applied amount per treatment | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | Type | Conc. (pure cyanamide) | method kind | number | interval between applications | | |
| Pig stables; bactericide against *Brachyspira hyodysenteriae* | ALZOGUR® | Pathogen of pig dysentery *Brachyspira hyodysenteriae* | soluble concentrate, aqueous solution | typically 50.5 % (w/w) | after dilution applied directly via the slatted floor to the liquid manure stored underneath the slatted floor in pig stables by means of a watering can or a half-automated movable dose cart (so-called "Dosierwagen") | 1-2 per year during cold seasons | Min. 126 days (duration of a fattening cycle) up to 1 year | ca. 1.5 kg cyanamide/m³ liquid manure, corresponding to 3 L ALZOGUR® per m³. | Professional use, only in empty pig stables |

## Summary of intended uses for PT18

ALZOGUR® is intended to be applied to the liquid manure stored underneath the slatted floor in empty pig stables to control dung breeding fly larvae.

| Object and/or situation | Product name | Organisms controlled | Formulation | | Application | | | Applied amount per treatment | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | Type | Conc. (pure cyanamide) | method kind | number | interval between applications | | |
| Animal housings (pig stables); insecticide to control fly larvae | ALZOGUR® | dung breeding fly species (*Musca ssp*.) | soluble concen-trate, aqueous solution | Typically 50.5 % (w/w) | after dilution applied directly via the slatted floor to the liquid manure stored underneath the slatted floor in pig stables by means of a watering can or a half-automated movable dose cart (so-called "Dosierwagen") | 1 per year during fly season | 1 year | ca. 0.5 kg cyanamide/m³ liquid manure, corresponding to 1 L ALZOGUR® per m³ | Professional use, only in empty pig stables |

# APPENDIX III – Human Health Tables for Risk Characterisation

## Table 1: Professional Users – Primary Exposure, systemic effects (cyanamide, PT18)

| Exposure Scenario | | Estimated Internal Exposure[1] | | | | Relevant NOAEL/ LOAEL & Reference Value[4] [mg/kg bw/day] | AF $MOE_{ref}$ | MOE | Exposure / AEL |
|---|---|---|---|---|---|---|---|---|---|
| | | oral uptake [mg/kg bw/day] | inhalation uptake[2] [mg/kg bw/day] | dermal uptake[3] [mg/kg bw/day] | total uptake[1] [mg/kg bw/day] | | | | |
| 1 - Application by watering can or half-automated movable cart (farmer, short-term exposure) | Tier 2a (PPE: protective gloves*, coverall*, boots) | - | $5.83x10^{-3}$ | $5.97x10^{-3}$ | 0.01 | NOAEL = 5<br>$AEL_{short-term}$ = 0.05 | 100 | 424 | 0.24 |
| | Tier 2b (PPE: protective gloves*, coverall*, boots, RPE) | - | $5.83x10^{-4}$ | $5.97x10^{-3}$ | $6.55x10^{-3}$ | | | 763 | 0.13 |
| 1 - Application by watering can or half-automated movable cart (pest control operator, long-term exposure) | Tier 2a (PPE: protective gloves*, coverall*, boots) | - | $5.83x10^{-3}$ | $5.97x10^{-3}$ | 0.01 | NOAEL = 1<br>$AEL_{medium/long-term}$= 0.01 | 100 | 85 | 1.18 |
| | Tier 2b (PPE: protective gloves*, coverall*, boots, RPE) | - | $5.83x10^{-4}$ | $5.97x10^{-3}$ | $6.55x10^{-3}$ | | | 153 | 0.65 |

[1] It is noted that for clarity reasons systemic exposure values are rounded to two decimal places. Other values are rounded to either two, one or any decimal places. However, the underlying calculations are based on unrounded exposure values.
[2] Based on the assumption of 100 % absorption by inhalation, breathing volume of 10 $m^3$ per shift and 60 kg body weight
[3] Based on the assumption of 25 % dermal absorption and 60 kg body weight
[4] based on either NOAEL of 5 mg/kg bw/d (acute maternal effects, hypoactivity) from an embryotoxicity / teratogenicity study in rats, or on NOAEL of 1 mg/kg bw/day (effects on the testes) from a 1-yr study in dogs supported by 90-d study in mature dogs and the assumption of 100 % oral absorption. By using default assessment factors of 100
* according to study by Rath, 2011: Camatril 732-gloves (Cat.III, EN 374 AJL, thickness ca. 0,40 mm, length ca. 400 mm) and coverall (type 3, EN 14605, e.g. Pro-Chem I "C")

## Table 2: Non Professional Users – Primary Exposure

| Exposure Scenario (indicate duration) | | Estimated Internal Exposure | | | | Relevant NOAEL/ LOAEL [mg/kg b.w./day] & Reference Value | AF $MOE_{ref}$ | MOE | Exposure /AEL |
|---|---|---|---|---|---|---|---|---|---|
| | | **oral uptake** [mg/kg bw/day] | **inhalation uptake** [mg/kg bw/day] | **dermal uptake** [mg/kg bw/day] | **total uptake** [mg/kg bw/day] | | | | |
| **Tier 1** (no PPE) | None as the product is only used by professionals. | | | | | | | | |
| **Tier 2** (Refinement, PPE or other risk mitigation measures – Specify) | | | | | | | | | |

## Table 3: Indirect Exposure as a result of use – Secondary Exposure of professionals

| Exposure Scenario | | Estimated Internal Exposure | | | | Relevant NOAEL/ LOAEL & Reference Value [mg/kg bw/day] | AF $MOE_{ref}$ | MOE | Exposure / AEL |
|---|---|---|---|---|---|---|---|---|---|
| | | oral uptake [mg/kg bw/day] | inhalation uptake [mg/kg bw/day] | dermal uptake [mg/kg bw/day] | total uptake [mg/kg bw/day] | | | | |
| Secondary exposure (farmer, short-term exposure) | Tier 1 (chronic scenario, worst case) | - | negligible | | | NOAEL = 5 or 1<br>$AEL_{short-term}$ = 0.05 or 0.01[1] | 100 | > 100 | < 1 |
| Secondary exposure (pest control operator, long-term exposure) | Tier 1<br>(Worst Case)<br>Chronic Scenario | - | negligible | | | NOAEL = 1 mg/kg b.w./d<br>$AEL_{medium-/longterm}$ = 0.01 mg/kg b.w./d[2] | 100 | | |

[1] based on either NOAEL of 5 mg/kg bw/d (acute maternal effects, hypoactivity) from an embryotoxicity / teratogenicity study in rats, or on NOAEL of 1 mg/kg bw/day (effects on the testes) from a 1-yr study in dogs supported by 90-d study in mature dogs and the assumption of 100 % oral absorption. By using default assessment factors of 100

[2] based on testing toxicity in an oral 1-year study in dogs (derived from a NOAEL of 1 mg/kg bw/d). The default AF of 100 and an oral absorption of 100 % was applied.

# APPENDIX IV List of studies

Data protection is claimed by the applicant in accordance with Article 60 of Regulation (EU) No 528/2012.

| Section No / Reference No | Author(s) | Year | Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/ No) | Owner |
|---|---|---|---|---|---|
| Doc II A 3.12 | Weber, K.; Creasy, D.M. | 2009 | Cyanamid: Histopathological peer review on male reproductive organs from selected studies and review on selected study reports | Yes | AlzChem Trostberg GmbH |
| Doc II A 3.12 | Dell, L. | 2018 | "Calcium Cyanamide Meta-Analysis for the assessment of possible thyroid effects in humans" | Yes | AlzChem Trostberg GmbH |
| Doc II A 3.12 | Anon. | 2001 | Data Sheet - C o l m e ® - ( Cyanamide ) - SOLUTION – ORAL ROUTE 102-100 | Yes | AlzChemn Trostberg GmbH |
| Doc II A 3.12 | Termeer, S. | 2018 | Toxicological assessment of Cyanamide-related effects in accordance with the Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (ECHA and EFSA, 2018) | Yes | AlzChem Trostberg GmbH |
| Doc II A 4 | EC | 2000 | Technical Guidance Document in support of the Directive 98/8/EC concerning the placing of biocidal products on the market, Guidance on data requirements for active substances and biocidal products (TNsG) , October 2000 | No | published |
| Doc II A 4 | FOCUS | 2006 | Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration" Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 2.0, 434 pp | No | published |
| Doc II A 4 | Beratergremium für umweltrelevante Altstoffe (BUA) | 1995 | Thioharnstoff, BUA-Stoffbericht 179 | No | published |
| Doc II A 4 | EC | 2003 | Technical Guidance Document (TGD) on Risk Assessment in support of Directive 93/67/EEC on risk assessment for new notified substances, Commission Regulation (EC) No. 1488/94 on risk assessment for existing substances (Parts I, II, III and IV) and Directive 98/8/EC of the European Parliament and the Council concerning the placing of biocidal products on the market. European Commission 2003 | No | published |

| Section No / Reference No | Author(s) | Year | Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/ No) | Owner |
|---|---|---|---|---|---|
| Doc II B 8 | Rath, A. | 2011 | Determination of operator exposure (passive dosimetry) during mixing/loading and applying a biocidal product containing cyanamide (ca. 50% w/w) on slatted floors in piggeries; SGS INSTITUT FRESENIUS GmbH, Taunusstein, Germany; Study No. IF-10/01435464; Doc. No. 575-005 | Yes | AlzChem GmbH |
| Doc II B 8 | Organisation for Economic Co-operation and Development (OECD) | 2006 | OECD SERIES ON EMISSION SCENARIO DOCUMENTS Number 14 Emission Scenario Document for Insecticides for Stables and Manure Storage Systems ENV/JM/MONO(2006)4 | No | published |
| Doc II B 8 | EC | 2003 | Technical Guidance Document (TGD) on Risk Assessment in support of Directive 93/67/EEC on risk assessment for new notified substances, Commission Regulation (EC) No. 1488/94 on risk assessment for existing substances (Parts I, II, III and IV) and Directive 98/8/EC of the European Parliament and the Council concerning the placing of biocidal products on the market. European Commission 2003 | No | published |
| Doc II B 8 | OECD | 2006 | OECD Series on Emission Scenario Documents No. 14; Emission Scenarion Document for Insecticides for Stables and Manure Storage Systems ENV/JM/MONO(2006)4 | No | published |
| Doc II B 8 | EC | 2011 | Supplement to the methodology for risk evaluation of biocides. Emission Scenarios Document for Product Type 3: Veterinary hygiene biocidal products EUR 25116 EN, 2011 | No | published |
| Doc II B 8 | EC | 2000 | FOCUS groundwater scenarios in the EU review of active substances ". Report of the FOCUS Groundwater Scenarios Workgroup, EC Document Reference SANCO/321/2000 Rev.2 | No | published |
| Doc II B 8 | EC | 2003 | FOCUS Surface water scenarios in the EU evaluation process under 91/414/EEC; SANCO/4802/2001-rev.2 final | No | published |
| Doc II B 8 | EC | 2006 | Groundwater Directive (GWD), Council Directive 2006/118/EG on the protection of groundwater against pollution and deterioration | No | published |
| Doc II B 8 | EC | 1998 | Drinking Water Directive (DWD), Council Directive 98/83/EC on the quality of water intended for human consumption | No | published |

| Section No / Reference No | Author(s) | Year | Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/ No) | Owner |
|---|---|---|---|---|---|
| Doc II B 8 | Klein, M. | 2011 | Proposals for standard scenarios and parameter setting of the FOCUS groundwater scenarios when used in biocide exposure assessment, FKZ: 360 04 035 Umweltbundesamt Dessau-Roßlau | No | published |
| Doc II B 8 | KTBL | 2005 | Faustzahlen für die Landwirtschaft; Kuratorium für Technik und Bauwesen in der Landwirtschaft e.V. (KTBL) | No | published |
| Doc II B 8 | EC | 1991 | EC Council Directive of 12 December 1991 concerning the protection of waters against pollution caused by nitrates from agricultural sources, 91/676/EEC | No | published |
| Doc II B 8 | DE | 2006 | Verordnung über die Grundsätze der guten fachlichen Praxis beim Düngen (Düngeverordnung) vom 26.01.1996; zuletzt geändert durch §12 DüngeVO vom 10.01.2006 (BGBl. I S.20) | No | published |
| Doc II B 8 | EC | 2008 | Revised guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 AND GL 38, EMEA/CVMP/ERA/418282/2005-Rev.1 | No | published |
| Doc II B 8 | EC | 1998 | Biocidal Product Directive (BPD), Directive 98/8/EC concerning the placing of biocidal products on the market | No | published |
| Doc II B 8 | ECB | 2002 | TNsG on Annex I inclusion. Technical Notes for Guidance in Support of Directive 98/8/EC of the European Parliament and the Council Concerning the Placing of Biocidal Products on the Market. Principles and Practical Procedures for the inclusion of active substances in Annexes I, IA and IB, April 2002 | No | published |
| Doc II B 8 | EC | 2011 | JRC Scientific and Technical Reports: Emission Scenarios Document for Product Type 3: Veterinary hygiene biocidal products | No | published |
| Doc II B 8 | CA Meeting | 2012 | EU COM decision for non-inclusion; document: "CA-Sept12-Doc.4.6 | No | published |
| Doc II C 13 | EC | 2006 | Groundwater Directive (GWD), Council Directive 2006/118/EG on the protection of groundwater against pollution and deterioration | No | published |
| Doc II C 13 | EC | 2000 | FOCUS groundwater scenarios in the EU review of active substances ". Report of the FOCUS Groundwater Scenarios Workgroup, EC Document Reference SANCO/321/2000 Rev.2 | No | published |

| Section No / Reference No | Author(s) | Year | Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/ No) | Owner |
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| Doc II C 13 | ECHA | 2008 | Guidance on information requirements and chemical safety assessment, Part C: PBT assessment | No | published |
| Doc II C 15 | Rath, A. | 2011 | Determination of operator exposure (passive dosimetry) during mixing/loading and applying a biocidal product containing cyanamide (ca. 50% w/w) on slatted floors in piggeries; SGS INSTITUT FRESENIUS GmbH, Taunusstein, Germany; Study No. IF-10/01435464; Doc. No. 575-005 | Yes | AlzChem GmbH |

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| Section No / Reference No | Author(s) | Year | Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
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| A3.1.1/01 | Anonymous | 2005 | Safety Data Sheet - Cyanamid F 1000 Degussa AG, Trostberg, Germany Report No.: 2.2 / REG_EU Not GLP, unpublished Doc. No.: 953-004 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A3.1.1/02 | Wenighofer, T. | 2007 | "Cyanamide F1000": Melting Temperature Austrian Research Centers GmbH Report No.: ARC--L-2583 GLP, unpublished Doc. No.: 112-002 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.1.2/01 | Wenighofer, T. | 2007 | "Cyanamdie F1000": Boiling Temperature Austrian Research Centers GmbH Report No.: ARC--L-2584 GLP, unpublished Doc. No.: 112-003 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.1.3/01 | Tognucci, A. | 2000 | Determination of the Relative Density of Cyanamide F 1000 Research and Consulting Company, Itingen, Switzerland Report No.: 744884 GLP, unpublished Doc. No.: 113-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.2.1/01 | Förster, B. | 2000 | Calculation of Henry's law Constant for Cyanamide | Yes (Data on existing | AlzChem GmbH |

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| | | | Scientific Consulting Company, Wendelsheim, Germany<br>Report No.: 102-084<br>Not GLP, unpublished<br>Doc. No.: 115-004 | a.s. submitted for the first time for entry into Annex I.) | |
| A3.2/01 | Eskötter, H. | 1991 | Determination of the Vapour Pressure of Cyanamide F 1000 in accordance with EEC-Guideline A.4<br>Battelle Institut, Frankfurt am Main, Germany<br>Report No.: BE-P-77-89-A4-01<br>GLP, unpublished<br>Doc. No.: 115-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.3.1/01 | Anonymous | 2005 | Safety Data Sheet - Alzogur<br>Degussa AG, Trostberg, Germany<br>Report No.: 4.0 / REG_EU<br>Not GLP, unpublished<br>Doc. No.: 954-012 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.3.1/02 | Anonymous | 2006 | Safety Data sheet - Cyanamid L 500<br>AlzChem GmbH, Germany<br>Report No.: ni<br>Not GLP, unpublished<br>Doc. No.: 954-015 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.3.2/01 | Anonymous | 2005 | Safety Data Sheet - Alzogur<br>Degussa AG, Trostberg, Germany<br>Report No.: 4.0 / REG_EU<br>Not GLP, unpublished<br>Doc. No.: 954-012 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.4/01 | Tognucci, A. | 2000 | Determination of the 1H-NMR-, IR-, UV/VIS Absorption and Mass Spectra of Cyanamide F 1000<br>SKW Trostberg AG, Germany<br>Report No.: 792707<br>GLP, unpublished<br>Doc. No.: 117-005 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.5/01 | Eskötter, H. | 1990 | Determination of the Water Solubility of Cyanamide F 1000 at pH 3-5, pH 7 and pH 9-11 in accordance with CIPAC Guideline MT 157.2<br>Battelle Institut, Frankfurt am Main, Germany<br>Report No.: BE-P-77-89-157-01<br>GLP, unpublished<br>Doc. No.: 114-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.6/01 | Tognucci, A. | 2000 | Determination of the Dissociation Constant of Cyanamide F 1000 in Water | Yes (Data on existing a.s. submitted for the first time | AlzChem |

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| | | | Research and Consulting Company, Itingen, Switzerland<br>Report No.: 744895<br>GLP, unpublished<br>Doc. No.: 115-003 | for entry into Annex I.) | |
| A3.7/01 | Eskötter, H. | 1990 | Determination of the Solubility of Cyanamide F 1000 in Organic Solvents in accordance with BBA Richtlinie B/7 Nr. 27 and modified to OECD-Guideline 105<br>Battelle Institut, Frankfurt am Main, Germany<br>Report No.: BE-P-77-89-105M-01<br>GLP, unpublished<br>Doc. No.: 114-002 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.9/01 | Turner, B. | 2005 | Cyanamid F 1000 - Partition CoefficientHuntingdon Life SciencesReport No.: SCI/105GLP, unpublishedDoc. No.: 114-004 | Yes(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.10/01 | Güthner, T. | 2000 | Gutachten zur Zersetzungstemperatur von Cyanamid<br>SKW Trostberg AG, Germany<br>Report No.: ni<br>Not GLP, unpublished<br>Doc. No.: 141-002 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.11/01 | Schleich, W. | 2001 | Determination of the Explosive Properties and of the Auto-ignition Temperature of ALZODEF<br>SKW Trostberg AG, Germany<br>Report No.: 064982129<br>GLP, unpublished<br>Doc. No.: 241-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.13/01 | Tognucci, A. | 2000 | Determination of the Surface Tension of Cyanamide L 500<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: 744906<br>GLP, unpublished<br>Doc. No.: 116-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.13/02 | Wenighofer, T. | 2007 | "Cyanamide L500": Surface Tension<br>Austrian Research Centers GmbH<br>Report No.: ARC--L-2586<br>GLP, unpublished<br>Doc. No.: 216-002 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.13/03 | Wenighofer, T. | 2007 | "Cyanamide F1000": Surface Tension<br>Austrian Research Centers GmbH | Yes<br>(Data on existing a.s. submitted for the first time | AlzChem GmbH |

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| | | | Report No.: ARC--L-2585<br>GLP, unpublished<br>Doc. No.: 116-002 | for entry into Annex I.) | |
| A3.15/01 | Schleich, W. | 2001 | Determination of the Explosive Properties and of the Auto-ignition Temperature of ALZODEF<br>SKW Trostberg AG, Germany<br>Report No.: 064982129<br>GLP, unpublished<br>Doc. No.: 241-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A3.16/01 | Güthner, T. | ni | Gutachten zu oxidierenden Eigenschaften von Cyanamid<br>SKW Trostberg AG, Germany<br>Report No.: ni<br>Not GLP, unpublished<br>Doc. No.: 143-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2a/01* | Wildenauer, M. | 1999 | Validierung der Methode zur Bestimmung von Cyanamid in Boden (Validation of the method for the determination of cyanamide in soil); SKW Trostberg AG, Germany; Study No.: SP990017; GLP; (unpublished); Doc. No. 434-003 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2a/02 | Wolf, S. | 2006 | Cyanamide - Validation of a confirmatory method for the determination of Cyanamide in Grapes, Soil, Bovine Muscle and Bovine Blood<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: A61244<br>GLP, unpublished<br>Doc. No.: 432-032 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2a/03* | Wolf, S. | 2008 | Revised report including amendment dated on April 29, 2008 - Cyanamide - Validation of a confirmatory method for the determination of Cyanamide in Grapes, Soil, Bovine Muscle and Bovine Blood<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: A61244<br>GLP, unpublished<br>Doc. No.: 432-034 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2b/01* | Wais, A. | 2000 | Validation of the Residue Analytical Method for Cyanamide F 1000 in Air<br>Research and Consulting Company, Itingen, | Yes (Data on existing a.s. submitted for the first time for entry into | AlzChem GmbH |

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| | | | Switzerland<br>Report No.: 744917<br>GLP, unpublished<br>Doc. No.: 436-002 | Annex I.) | |
| A4.2c/01* | Wildenauer, M. | 2000 | Validierung der Methode zu Bestimmung von Cyanamid in Oberflächenwasser (Validation of the method for determining Cyanamide in surface water); SKW Trostberg AG, Germany; Study No.: SP000005; GLP; (unpublished); Doc. No. 435-003 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2c/02* | Wildenauer, M. | 2000 | Validierung der Methode von Cyanamid in Trinkwasser; SKW Trostberg AG, Germany; Study No.: SP000004; GLP; (unpublished); Doc. No. 435-004 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2c/03 | Wolf, S. | 2007 | Cyanamide - Validation of a confirmatory method for the Determination of Cyanamide in surface water<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: B14444 102-135<br>GLP, unpublished<br>Doc. No.: 435-010 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2d/01* | Wildenauer, M. | 1999 | Validierung der Methode zur Bestimmung von Cyanamid in Blut (Validation of the method for the determination of cyanamide in blood); SKW Trostberg AG, Germany; Study No.: SP990022; GLP; (unpublished); Doc. No. 433-005 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2d/02 | Wildenauer, M. | 2000 | Validierung der Methode zur Bestimmung von Cyanamid in Rinderniere (Validation of the method for the determination of Cyanamide in bovine kidney); SKW Trostberg AG, Germany; Study No.: SP000002; GLP; (unpublished); Doc. No. 433-006 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2d/03 | Wildenauer, M. | 1993 | Validierung der Methode zur Bestimmung von Acetylcyanamid in Urin (Determination of Acetyl Cyanamide in Urine - Validation od the | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |

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| | | | Analytical Report)<br>SKW Trostberg AG, Germany<br>Report No.: SP930002<br>GLP, unpublished<br>Doc. No.: 433-008 | | |
| A4.2d/04 | Wolf, S. | 2006 | Cyanamide - Validation of a confirmatory method for the determination of Cyanamide in Grapes, Soil, Bovine Muscle and Bovine BloodResearch and Consulting Company, Itingen, SwitzerlandReport No.: A61244GLP, unpublishedDoc. No.: 432-032 | Yes(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2d/05 | Wolf, S. | 2008 | Revised report including amendment dated on April 29, 2008 - Cyanamide - Validation of a confirmatory method for the determination of Cyanamide in Grapes, Soil, Bovine Muscle and Bovine Blood<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: A61244<br>GLP, unpublished<br>Doc. No.: 432-034 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.2e/01* | Wildenauer, M. | 2001 | Validierung der Methode zur Bestimmung von Cyanamid in Trauben (Including the englisch translation: Validation of the method for determining Cyanamide in grapes and the amendment No. 1 dated 21.08.2007)Degussa AG, Trostberg, GermanyReport No.: SP010006GLP, unpublishedDoc. No.: 432-026 | Yes(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.3/01 | Wildenauer, M. | 1999 | Validierung der Methode zur Bestimmung von Cyanamid in Milch (Validation of the method for the determination of cyanamide in milk)<br>SKW Trostberg AG, Germany<br>Report No.: SP990018<br>GLP, unpublished<br>Doc. No.: 433-003 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.3/02* | Wildenauer, M. | 1999 | Validierung der Methode zur Bestimmung von Cyanamid in Muskelfleisch vom Rind | Yes<br>(Data on existing a.s. submitted for the first time | AlzChem GmbH |

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| | | | (Validation of the method for the determination of cyanamide in bovine mussle tissue)<br>SKW Trostberg AG, Germany<br>Report No.: SP990020<br>GLP, unpublished<br>Doc. No.: 433-004 | for entry into Annex I.) | |
| A4.3/03 | Wolf, S. | 2006 | Cyanamide - Validation of a confirmatory method for the determination of Cyanamide in Grapes, Soil, Bovine Muscle and Bovine Blood<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: A61244<br>GLP, unpublished<br>Doc. No.: 432-032 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A4.3/04 | Wolf, S. | 2008 | Revised report including amendment dated on April 29, 2008 - Cyanamide - Validation of a confirmatory method for the determination of Cyanamide in Grapes, Soil, Bovine Muscle and Bovine Blood<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: A61244<br>GLP, unpublished<br>Doc. No.: 432-034 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.1/01* | [redacted] | 1994 | Assessment of Acute Oral Toxicity with Cyanamide in the Rat<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 521-002 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.1/02* | [redacted] | 1973 | Determination of the acute oral toxicity of Cyanamid in albino rats<br>[redacted]<br>Report No.: ni<br>Not GLP, unpublished<br>Doc. No.: 521-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.2/01* | [redacted] | 1988 | Acute Dermal Toxicity Study in Rabbits with Aqueous Hydrogen Cyanamide<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 522-002 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |

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| A6.1.3/01* | [redacted] | 1973 | Acute inhalation toxicity study with SKW Cyanamid L500 in [redacted] ot GLP, unpublishedDoc. No.: 523-001 | Yes(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.4/01* | [redacted] | 1989 | Irritant Effects on Rabbit Skin of Aqueous Hydrogen Cyanamide 49% w/w [redacted] GLP, unpublished Doc. No.: 565-002 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.4/02* | [redacted] | 1982 | Primary Dermal Irritation/Corrosion Test with SKW-Cyanamid L 500 in Albino Rabbits [redacted] Not GLP, unpublished Doc. No.: 565-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.4/03* | [redacted] | 1984 | Primary Skin Irritation Tests With Three Aqueous Dilutions Of Alzodef in Albino Rabbits [redacted] Not GLP, unpublished Doc. No.: 565-004 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.4/04 | [redacted] | 1991 | Eye Irritation to the Rabbit of Aqueous Hydrogen Cyanamide 49% w/w [redacted] GLP, unpublished Doc. No.: 566-002 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.4/05* | [redacted] | 1974 | Eye irritation test with SKW Cyanamid L 500 in albino rabbits [redacted] Not GLP, unpublished Doc. No.: 566-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.4/06* | Reus, A.A. | 2011 | In vitro skin corrosion test with Cyanamid L 500 using EpiDerm | Yes (Data on existing a.s. submitted | AlzChem GmbH |

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| | | | reconstructed skin membranes<br>TNO Triskelion, Zeist, The Netherlands<br>Report No.: 093.01093 20018/01<br>GLP, unpublished<br>Doc. No.: 565-005 | for the first time for entry into Annex I.) | |
| A6.1.5/01* | [redacted] | 1982 | Sensitization test with SKW-Cyanamide F 1000 in Guinea Pigs (Maximization Test)<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 567-003 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.1.5/02 | [redacted] | 1988 | Test to Evaluate the Sensitizing Potential by Topical Applications, in the Guinea-Pig (Buehler test)<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 567-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.2* | Colom, H. et al. | 1999 | Absolute bioavailability and absorption profile of cyanamide in man. Journal of Pharmaco-kinetics and Biopharma-ceutics 27, 421-436 | No | published |
| A6.2/01* | [redacted] | 1993 | Metabolism of [14C]-Hydrogen Cyanamide in Rats (Preliminary and Definitive Phases)<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 512-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.2/02* | [redacted] | 1989 | Dermal Absorption of [14C]-Hydrogen Cyanamide in Male Rats<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 511-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.2/03* | [redacted] | 1989 | Investigation on the Absorption, Metabolism, and Excretion of Hydrogen Cyanamide (H2NCN) in rat and human<br>[redacted]<br>Report No.: ni | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |

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| | | | Not GLP, unpublished<br>Doc. No.: 512-004 | | |
| A6.2/04* | Obach, R. | 1986 | Bioavailability of Cyanamide in Fasted and Unfasted Rats<br>Biopharmaceutics & Drug Disposition, 1986, 7, 273-280<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 592-019 | No | published |
| A6.3.1/01* | [redacted] | 1988 | 28-Day Repeated Dose Oral Toxicity Study with Aqueous Hydrogen Cyanamide in Rats<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 532-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.3.2/01 | [redacted] | 1996 | Subacute Dermal Toxicity Study of Hydrogen Cyanamide 50 % w/w Formulation (DORMEX) in Rabbits<br>[redacted]<br>Not GLP, unpublished<br>Doc. No.: 532-002 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.3.3/01* | [redacted] | 1996 | Subacute Inhalation Toxicity Study of Hydrogen Cyanamide 50% w/w Formulation (DORMEX) in Wistar Rats<br>[redacted]<br>Not GLP, unpublished<br>Doc. No.: 532-003 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.4.1/01* | [redacted] | 1975 | Sub-chronic (90-day) toxicity study with Cyanamid L 500 in albino<br>[redacted]<br>ot GLP, unpublishedDoc. No.: 533-001 | Yes(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.4.1/02* | [redacted] | 1982 | Sub-Chronic (90-day) Oral Toxicity Study with Alzodef in Dogs<br>[redacted]<br>Not GLP, unpublished<br>Doc. No.: 533-002 | Yes<br>(Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.5/01* | [redacted] | 1989 | Chronic Toxicity Study in Dogs with Aqueous | Yes<br>(Data on existing | AlzChem GmbH |

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| | | | Hydrogen Cyanamide [redacted] GLP, unpublished Doc. No.: 537-002 | a.s. submitted for the first time for entry into Annex I.) | |
| A6.5/02* | [redacted] | 1991 | Chronic Toxicity Study in Rats with Aqueous Hydrogen Cyanamide [redacted] GLP, unpublished Doc. No.: 537-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.6.1/01* | Jagannath, D.R. | 1987 | Mutagenicity Test on Hydrogen Cyanamide in the Ames Salmonella/Microsome Reverse Mutation Assay Hazleton Labs., USA Report No.: HLA 9583-0-401 GLP, unpublished Doc. No.: 557-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.6.2/01* | [redacted] | 1988 | Evaluation of the Ability of Aqueous Hydrogen Cyanamide to Induce Chromosome Aberrations in Cultured Peripheral Human Lymphocytes [redacted] GLP, unpublished Doc. No.: 557-007 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.6.3/01* | [redacted] | 2000 | Gene Mutation Assay in Chinese Hamster V79 Cells in vitro (V79 / HPRT) with Cyanamide L 500 [redacted] GLP, unpublished Doc. No.: 557-004 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.6.3/02* | [redacted] | 1987 | Mutagenicity Test on Hydrogen Cyanamide in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay [redacted] GLP, unpublished Doc. No.: 557-002 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.6.3/03* | [redacted] | 1988 | Evaluation of the Mutagenic Activity of Aqueous Hydrogen Cyanamide in an in vitro Mammalian Cell Gene | Yes (Data on existing a.s. submitted for the first time for entry into Annex | AlzChem GmbH |

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| | | | Mutation Test with L5178Y Mouse Lymphoma Cells [redacted] LP, unpublishedDoc. No.: 557-008 | I.) | |
| A6.6.4/01* | [redacted] | 1987 | Mutagenicity Test on Hydrogen Cyanamide in the in vivo Mouse Micronucleus Assay [redacted] GLP, unpublished Doc. No.: 557-003 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.6.5 | Heidemann, A. | 2003 | Cyanamide - Summary and evaluation of mutagenicity testing Scientific Consulting Company, Wendelsheim, Germany Report No.: 102-084-03/1 Not GLP, unpublished Doc. No.: 581-008 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.7/01* | [redacted] | 1990 | Hydrogen Cyanamide up to 104 Week Oral (Drinking Water) Carcinogenicity Study in the Mouse [redacted] GLP, unpublished Doc. No.: 555-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| A6.7/02 | Angel, C.R. Olin, S.S. Robens, J.F. Schueler, R.L. Miller, G.L. Owen, L.A. King, M.S. Reichardt, W.D. Gunberg, E.W. Presley, Y.E. | 1979 | Bioassay of Calcium Cyanamide for Possible Carcinogenicity National Cancer Institute Carcinogenesis Technical Report Series 163 (1979), DHEW Publication No. (NIH) 79-1719 Report No.: na Not GLP, published Doc. No.: 592-009 | No | published |
| A6.7/02* | Ulland, B. et al. | 1979 | Bioassay of Calcium cyanamide for possible carcinogenicity; NCI Frederick Cancer Research Center, Maryland, USA; Publication: DHEW Publication No. (NIH) 79-1719; Doc. No. 592-009; Published: Yes | No | published |
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| | | | Hydrogenxyanamide<br>ABC Laboratories, Columbia, USA<br>Report No.: 38234<br>GLP, unpublished<br>Doc. No.: 722-003 | for the first time for entry into LoAAS) | |
| A7.2.1/01b* | Schmidt, J. | 1990 | Aerobic Soil Metabolism of 14C-CyanamideABC Laboratories, Columbia, USAReport No.: 38438GLP, unpublishedDoc. No.: 722-001 | Yes(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.2.1/01c* | Schmidt, J. | 1991 | Supplemental Report of the Aerobic Soil Metabolism of 14C-Cyanamide<br>ABC Laboratories, Columbia, USA<br>Report No.: 384381<br>GLP, unpublished<br>Doc. No.: 722-004 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.2.1/02* | Loehr, R.C.<br>Matthews, J.E. | 1992 | Loss of Organic Chemicals in Soil: Pure Compound Treatability Studies<br>Journal of Soil Contamination, 1992, 1 (4), 339-360<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 792-025 | No | published |
| A7.2.1/03a | Frederick, L.R. et al. | 1957 | Decomposability of Some Organic Sulfur Compounds in Soil<br>Soil Science Society Am. J., 1957, 21, 287-292<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 792-026 | No | published |
| A7.2.1/03a-d | Lashen, E.S.<br>Starkey, R.L. | 1970 | Decomposition of Thioureas by a Penicillium Species and Soil and Sewage-sludge Microflora<br>Journal of General Microbiology, 1970, 64, 139-150<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 792-023 | No | published |
| A7.2.1/03c | Harron, W.R.<br>Malhi, S.S. | 1978 | Release of Sulphate from the Oxidation of Thiourea and Ammonium Polysulphide<br>Can. J. Soil. Sci., 1978, 58, 109-111<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 792-024 | No | published |
| A7.2.1/03d | Günther, P.<br>Pestemer, W. | 1990 | Risk Assessment for Selected Xenobiotics by Biossay Methods with Higher Plants<br>Environmental | No | published |

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| | | | Management, 14, (3), 381-388<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 892-031 | | |
| A7.2.2.4/01 | Burri, R. | 2001 | Photolysis of 14C-Cyanamide on Soil Surface Under Laboratory Conditions<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: 744930<br>GLP, unpublished<br>Doc. No.: 724-002 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.2.2.4/02 a | Schmidt, J. | 1990 | Preliminary Study of the Aerobic Soil Metabolism of 14C-Hydrogenxyanamide<br>ABC Laboratories, Columbia, USA<br>Report No.: 38234<br>GLP, unpublished<br>Doc. No.: 722-003 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.2.2.4/02 b | Schmidt, J. | 1990 | Anaerobic Soil Metabolism of 14C-Cyanamide<br>ABC Laboratories, Columbia, USA<br>Report No.: 38439<br>GLP, unpublished<br>Doc. No.: 722-002 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.2.2.4/02 c | Schmidt, J. | 1991 | Supplemental Report of the Anaerobic Soil Metabolism of 14C-Cyanamide<br>ABC Laboratories, Columbia, USA<br>Report No.: 384391<br>GLP, unpublished<br>Doc. No.: 722-005 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.3.1/01* | Peter, S. | 2003 | Estimation of photochemical degradation of Cyanamide using the Atkinson Calculation Method<br>Scientific Consulting Company, Wendelsheim, Germany<br>Report No.: 102-084<br>Not GLP, unpublished<br>Doc. No.: 743-003 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.4.1.1/01 | [redacted] | 1985 | The Acute Toxicity of Hydrogen Cyanamide to the Rainbow Trout, Salmo gairdneri, in a Static Test System<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 821-004 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |

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| A7.4.1.1/02 * | [redacted]. | 1985 | Acute Toxicity of LH 21,810 A to Bluegill Sunfish (Lepomis macrochirus)<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 821-002 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.4.1.1/03 | [redacted] | 1990 | Acute Flow-Through Toxicity of Aqueous Hydrogen Cyanamide 49% (w/w) = 52% (w/v) to Carp (Cyprinus carpio)<br>[redacted]<br>GLP, unpublished<br>Doc. No.: 821-003 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.4.1.1/04 | Curtis, M.W. et al. | 1980 | Aquatic Toxicity Testing as Fundament for a Spill Prevention ProgramProceedings of the National Conference on Control of Hazardous, 1980Report No.: naNot GLP, publishedDoc. No.: 892-038 | No | published |
| A7.4.1.2/01 * | Adema, D.M.M. | 1983 | The Acute Toxicity of Alzodef to Daphnia Magna TNO, Department of Environmental Toxicology, Delft, The Netherlands<br>Report No.: R 83/198<br>Not GLP, unpublished<br>Doc. No.: 822-001 | Yes (Data on existing a.s. submitted for the first time for entry into A LoAAS) | AlzChem GmbH |
| A7.4.1.3/01 * | Seyfried, B. | 2000 | Toxicity of Cyanamide L 500 to Pseudokirchneriella subcapitata (Formerly Selenastrum capricornutum) in a 96-hour Algal Growth Inhibition Test<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: 744963<br>GLP, unpublished<br>Doc. No.: 823-003 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.4.1.3/02 | Hertl, J. | 2000 | Toxicity of SKW Cyanamide L 500 to Anabaena flos-aquae in an Algal Growth Inhibition Test<br>Ibacon GmbH, Rossdorf, Germany<br>Report No.: 6677210<br>GLP, unpublished<br>Doc. No.: 823-004 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.4.1.3/03 | Kühn, R. in Friesel et al. | 1984 | Kühn, R. in Friesel et al. (1984): Überprüfung der | No | published |

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| | | | Durchführbarkeit von Prüfungsvorschriften und der Aussagekraft der Stufe 1 und 2 des Chemikaliengesetzes - Teil VI, Forschungsbericht 10604011/08, 1984 des Instituts für Wasser-, Boden- und Lufthygiene des Bundesgesundheitsamtes Berlin, Germany, Kapitel III.5, 21-Tage-Daphnientest, Seite 51-64 (Examination of the applicability of test guidelines and of the significance of stages 1 and 2 of the Chemicals Act - Part VI , Research Report # 10604011/08, 1984 of the Institute for Water, Soil and Air Hygiene of the Federal Health Office, Berlin, chapter III.5: 21-day Daphnia test, p 51-64), Doc. No. 892-035, published | | |
| A7.4.1.3/03 * | Friesel, P. et al. | 1984 | Überprüfung der Durchführbarkeit von Prüfungsvorschriften und der Aussagekraft der Stufe 1 und 2 des Chemikaliengesetzes - Teil VI<br>Berlin, Institut für Wasser-, Boden- und Lufthygiene des Bundesgesundheitsamtes, 1984<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 892-035 | No | published |
| A7.4.1.4/01 * | Hanstveit, A.O.<br>Pullens, M.A. | 1988 | The Effect Of Aqueous Hydrogen Cyanamide On The Growth Of The Bacterium Pseudomonas Putida<br>TNO, Department of Environmental Toxicology, Delft, The Netherlands<br>Report No.: R 88/019<br>Not GLP, unpublished<br>Doc. No.: 841-003 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.4.1.4/02 | Coenen, T.M.M. | 1988 | Assessment of the acute toxicity of Guanidine nitrate on the cell multiplication of a pure culture of Pseudomonas putida bacteria. (Acute bacteria Cell | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |

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| | | | Multiplication Inhibition Test)<br>RCC NOTOX B.V., ´s-Hertogenbosch, The Netherlands<br>Report No.: 0918/PS20 | | |
| A7.4.3.1/01 | [redacted] | 1990 | Flow-Through Toxicity of Aqueous Hydrogen Cyanamide 49% (w/w) = 52 % (w/v) to Rainbow Trout (Oncorhynchus mykiss) for a 21-Day Exposure Period [redacted] Not GLP, unpublishedDoc. No.: 826-001 | Yes(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.4.3.4/01 * | Murrell, H.R.<br>Leak, T. | 1995 | Chronic Toxicity of Hydrogen Cyanamide to Daphnia magna Under Flow-Through Test Conditions<br>ABC Laboratories, Columbia, USA<br>Report No.: 41942<br>GLP, unpublished<br>Doc. No.: 827-002 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.4.3.4/02 | Kühn, R. in Friesel et al. | 1984 | Kühn, R. in Friesel et al. (1984): Überprüfung der Durchführbarkeit von Prüfungsvorschriften und der Aussagekraft der Stufe 1 und 2 des Chemikaliengesetzes - Teil VI, Forschungsbericht 10604011/08, 1984 des Instituts für Wasser-, Boden- und Lufthygiene des Bundesgesundheitsamtes Berlin, Germany, Kapitel III.5, 21-Tage-Daphnientest, Seite 51-64 (Examination of the applicability of test guidelines and of the significance of stages 1 and 2 of the Chemicals Act - Part VI , Research Report # 10604011/08, 1984 of the Institute for Water, Soil and Air Hygiene of the Federal Health Office, Berlin, chapter III.5: 21-day Daphnia test, p 51-64), Doc. No. 892-035, published | No | published |
| A7.4.3.4/02 * | Friesel, P. et al. | 1984 | Überprüfung der Durchführbarkeit von Prüfungsvorschriften und der Aussagekraft der | No | published |

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| | | | Stufe 1 und 2 des Chemikaliengesetzes - Teil VI<br>Berlin, Institut für Wasser-, Boden- und Lufthygiene des Bundesgesundheitsamtes, 1984<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 892-035 | | |
| A7.4.3.5.1/01 | Heintze, A. | 2001 | Assessment of Side Effects of Cyanamide L 500 on the Larvae of the Midge, Chironomus riparius with the Laboratory Test Method<br>GAB Biotechnologie GmbH, Niefern-Öschelbronn, Germany<br>Report No.: 20001413/01-ASCr<br>GLP, unpublished<br>Doc. No.: 824-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.4.3.5.2/01* | Hertl, J. | 2000 | Toxicity of SKW Cyanamide L 500 to the Aquatic Plant Lemna gibba in a Growth Inhbition Test<br>Ibacon GmbH, Rossdorf, Germany<br>Report No.: 6679240<br>GLP, unpublished<br>Doc. No.: 825-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.1.1/01 | Reis, K.-H. | 2002 | Effects of Cyanamide L 500 on the activity of the soil microflora in the laboratory<br>Ibacon GmbH, Rossdorf, Germany<br>Report No.: 12502080<br>GLP, unpublished<br>Doc. No.: 841-004 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.1.1/02 | Mitchell, W.R. | 1987 | Biodegradation of Guanidinium Ion in Aerobic Soil Samples<br>Bull. Environ Contain Toxicol, 1987 (39), 974-981<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 792-020 | No | published |
| A7.5.1.1/03* | Schulz, L. | 2010 | Thiourea - Effects on the activity of soil microflora (Nitrogen transformation test)BioChem Agrar GmbH, Gerichshain, GermanyReport No.: 10 10 48 015 NGLP, unpublishedDoc. No.: 841-005 | Yes(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.1.2/01* | Lührs, U. | 2001 | Acute Toxicity (14 Days) of SKW Cyanamide L 500 | Yes(Data on existing a.s. | AlzChem GmbH |

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| | | | + AHL to the Earthworm Eisenia fetida in Artificial SoilIbacon GmbH, Rossdorf, GermanyReport No.: 12081021GLP, unpublishedDoc. No.: 833-003 | submitted for the first time for entry into LoAAS) | |
| A7.5.1.2/02 * | Adema, D.M.M. | 1985 | Acute Toxicity of Dicyandiamid to the worm species Eisenia Foetida<br>TNO, Department of Environmental Toxicology, Delft, The Netherlands<br>Report No.: R 85/059 13247<br>Not GLP, unpublished<br>Doc. No.: 833-004 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.1.3/01 * | Meister, A. | 2001 | Effects of Cyanamide L500 on the Seedling Emergence of Terrestrial Non-Target Plant Species Tier II: Seedling Emergence Dose Response Test<br>Ibacon GmbH, Rossdorf, Germany<br>Report No.: 9131088<br>GLP, unpublished<br>Doc. No.: 851-003 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.1.3/02 | Friesel, P. et al. | 1984 | Überprüfung der Durchführbarkeit von Prüfungsvorschriften und der Aussagekraft der Stufe 1 und 2 des Chemikaliengesetzes - Teil VI<br>Berlin, Institut für Wasser-, Boden- und Lufthygiene des Bundesamtes, 1984<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 892-029 | No | published |
| A7.5.1.3/03 | Ballhorn, L. et al. | 1984 | Überprüfung der Durchführbarkeit von Prüfungsvorschriften und der Aussagekraft der Stufe I und II des Chemikaliengesetzes<br>Berlin, Institut für Wasser-, Boden- und Lufthygiene des Bundesamtes, 1984<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 892-030 | No | published |
| A7.5.1.3/04 * | Günther, P.<br>Pestemer, W. | 1990 | Risk Assessment for Selected Xenobiotics by Biossay Methods with Higher Plants<br>Environmental | No | published |

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| | | | Management, 14, (3), 381-388<br>Report No.: na<br>Not GLP, published<br>Doc. No.: 892-031 | | |
| A7.5.2.1/01 * | Moser, T.<br>Scheffczyk, A. | 2009 | Cyanamide: Acute and reproduction toxicity to the collembolan species Folsomia candida in artificial soil - including Recalculation of ECx values, performed by German UBA 20.05.2009<br>ECT Oekotoxikologie GmbH, Flörsheim, Germany<br>Report No.: 08BL1CR<br>GLP, unpublished<br>Doc. No.: 835-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.2.2/01 * | Förster, B. | 2009 | Cyanamide - Chronic Toxicity in Higher PlantsECT Oekotoxikologie GmbH, Flörsheim, GermanyReport No.: 08BL1PCGLP, unpublishedDoc. No.: 851-007 | Yes(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.2.2/02 * | Förster, B. | 2012 | Thiourea: Chronic Toxicity in Higher Plants<br>ECT Oekotoxikologie GmbH, Flörsheim, Germany<br>Report No.: 12BL2PC<br>GLP, unpublished<br>Doc. No.: 851-008 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.4.1/01 | Kleiner, R. | 1992 | Testing toxicity to Honeybee - Apis mellifera L. (laboratory) according to BBA Guideline VI, 23 - 1 (1991)<br>Biochem GmbH, Karlsruhe, Germany<br>Report No.: 92 10 48 014<br>GLP, unpublished<br>Doc. No.: 832-001 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.4.1/02 | Moll, M. | 2001 | Effects of SKW Cyanamide L 500 on the Parasitoid Aphidius rhopalosiphi (Hymenoptera, Braconidae) in the Laboratory - Dose Response Test<br>Ibacon GmbH, Rossdorf, Germany<br>Report No.: 6670001<br>GLP, unpublished<br>Doc. No.: 834-019 | Yes<br>(Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| A7.5.4.1/03 | Goßmann, A. | 2000 | Effects of SKW CYANAMIDE L 500 on the Predatory Mite Typhlodromus pyri | Yes(Data on existing a.s. submitted for the first time for | AlzChem GmbH |

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| | | | Scheuten (Acari, Phytoseiidae) in the Laboratory - Dose Response Design.Ibacon GmbH, Rossdorf, GermanyReport No.: 6676062GLP, unpublishedDoc. No.: 834-013 | entry into LoAAS) | |
| A8.13.3 (acc. to Annex II Titel 1, Regulation (EU) No. 582/2012 | Paul K.B. et al | 2014 | Development of a Thyroperoxidase Inhibition Assay for High-Throughput Screening | No | published |
| A8.13.3 (acc. to Annex II Titel 1, Regulation (EU) No. 582/2012 | Peachey J.E. et al | 1989 | Calcium Carbimide in Alcoholism Treatment. Part 2: medical findings of a short-term, placebo-controlled, double-blind clinical trial | No | published |
| A8.13.3 (acc. to Annex II Titel 1, Regulation (EU) No. 582/2012 | Anonymous | 2015 | List of positive studies with Cyanamide. iCSSToxCast Dashboard v2/Database prod_dashboard_v2 https://actor.epa.gov/dashboard/#chemical/420-04-2 Accessed on 28.11.2018 | No | Internet database |
| A8.13.3 (acc. to Annex II Titel 1, Regulation (EU) No. 582/2012 | Anonymous | 2018 | Medication package insert for Colme in German language. Gebrauchsanweisungen, Indikationen, Dosen. http://de.remedy-info.com/kolme.html Accessed on 23.11.2018 | No | Internet page |

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| B3.1.1/01 | Anonymous | 2005 | Safety Data Sheet - Alzogur Degussa AG, Trostberg, Germany Report No.: 4.0 / REG_EU Not GLP, unpublished Doc. No.: 954-012 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| B3.5/01 | Eskötter, H. | 1990 | Accelerated Storage Test by Heating of Cyanamide-L-500 (Alzodef) in accordance with CIPAC Handbook Method MT 46 Battelle Institut, Frankfurt | Yes (Data on existing a.s. submitted for the first time for entry into | AlzChem GmbH |

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| | | | am Main, Germany<br>Report No.: BE-P-77-89-MT46-01<br>GLP, unpublished<br>Doc. No.: 245-004 | LoAAS) | |
| B3.5/02 | Eskötter, H. | 1990 | Determination of the pH of an Aqueous Cyanamide-L 500 ( Alzodef) Dispersion / Solution in accordance with CIPAC Handbook Method MT 75.<br>Battelle Institut, Frankfurt am Main, Germany<br>Report No.: BE-P-77-90-MT75-01<br>GLP, unpublished<br>Doc. No.: 215-002 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| B3.7/01 | Melkebeke, T. | 1994 | Determination of the Storage Stability of DORMEX at 20 °C<br>RCC NOTOX B.V., ´s-Hertogenbosch, The Netherlands<br>Report No.: 074047<br>GLP, unpublished<br>Doc. No.: 245-002 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| B3.7/02 | Schmidt, J.M. | 1991 | Determination of the Aqueous Photolysis Rate of 14C-Cyanamide<br>ABC Laboratories, Columbia, USA<br>Report No.: 39035<br>GLP, unpublished<br>Doc. No.: 712-001 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| B3.8/01 | Comb, A.L. | 2000 | Alzodef Persistent Foaming<br>Huntingdon Life Sciences<br>Report No.: SCI/061/004514<br>GLP, unpublished<br>Doc. No.: 216-001 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| B3.11/01 | Biedermann, K. | 2000 | Determination of the viscosity of ALZODEF<br>Research and Consulting Company, Itingen, Switzerland<br>Report No.: 792718<br>GLP, unpublished<br>Doc. No.: 214-001 | Yes (Data on existing a.s. submitted for the first time for entry into Annex I.) | AlzChem GmbH |
| B5.10/01* | Lehmhus, J. | 2006 | Determination of the efficacy of ALZOGUR to dung flies in the laboratory, Eurofins-GAB GmbH, Stade, GermanyReport No.: 20061021/01-ELMaGLP, unpublished Doc. No.: 336-1801 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| B5.10/01 (PT3) | Schließner, Th. and Rübsamen, S. | 1981 | Zur Empfindlichkeit des Erregers der Schweinedysenterie Treponema hyodysenteria gegenüber Alzogur® (English translation of the | No | published |

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| | | | title: "The susceptibility of Treponema hyodysenteriae to Alzogur®") Tieraerztliche Umschau, 36, No. 12, December 1981, page 848-850 Doc. No. 392-020 (English translation included) (published) | | |
| B5.10/02*(PT3) | Herbst, W. | 2009 | Determination of operator exposure (passive dosimetry) during mixing/loading and applying a biocidal product containing Cyanamide (ca. 50% w/w) on slatted floors in piggeries - application via dose cart ("Dosierwagen") Scientific Consulting Company, Bad Kreuznach, Germany Report No.: ni Not GLP, unpublished Doc. No.: 575-006 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| B6.6/01 | Rath, A. | 2011 | Determination of operator exposure (passive dosimetry) during mixing/loading and applying a biocidal product containing Cyanamide (ca. 50% w/w) on slatted floors in piggeries SGS Institut Fresenius GmbH, Taunusstein, Germany Report No.: IF-10/01435464 GLP, unpublished Doc. No.: 575-005 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |
| B6.6/02 | Nickel, G. | 2011 | Determination of operator exposure (passive dosimetry) during mixing/loading and applying a biocidal product containing Cyanamide (ca. 50% w/w) on slatted floors in piggeries - application via dose cart ("Dosierwagen") Scientific Consulting Company, Bad Kreuznach, Germany Report No.: ni Not GLP, unpublished Doc. No.: 575-006 | Yes (Data on existing a.s. submitted for the first time for entry into LoAAS) | AlzChem GmbH |

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LoAAS: List of Approved Active Substances

# APPENDIX V – Assessment according to the Article 75(1)(g)-mandate of the European Commission on cyanamide "Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18" - human health part -

*The following annex presents the details of the HH risk assessment of the ED properties for cyanamide. The background of the mandate is given, followed by the two approaches for the HH risk assessment: first the quantitative and second the qualitative approach. Since this is a precedent for the risk assessment of ED properties, the approaches are presented in detail, by including the document of the two e-consultations and enclosing the summaries of the e-consultations and der BPC-WG discussions, respectively.*

## Background

As cyanamide is considered to have endocrine disrupting properties [1], the European Commission initiated a mandate according to Article 75(1)(g) of the BPR as the initial BPC opinions on cyanamide for PT 3 and PT 18 did not provide a clear conclusion on the level of the risks associated with the use of cyanamide in relation to its ED properties [2] as is illustrated in the BPC opinion by the following paragraph:
"(…) *With regards to the fact that cyanamide is considered to have endocrine disrupting properties, there is no currently agreed methodology for undertaking a risk assessment based on such properties and no agreed methodology available on how to consider the data used for the identification of whether this substance is an endocrine disruptor in risk assessment for the environment.* ***Given the exposure of cyanamide to humans and the environment, a risk related to the ED properties cannot be excluded.***"

Thus, in the scope of to the Art. 75 (1) (g) request with regard to human health, following questions of Commission needed to be adressed:

a) Based on available information, clarify whether a safe level (threshold) can be determined for the ED properties of cyanamide for human health, and if such threshold can be established, what would be this level.

b) Clarify the level of the risks for humans by:

   1. Assessing the level of risk for human health, either by a quantitative assessment or by a qualitative assessment.
   2. Providing an opinion whether the risks can be considered acceptable or not.

In order to answer the above-mentioned questions, the eCA was instructed to consider the following aspects in its assessment:

- All the data submitted in the application, as well as the conclusions of the discussions in the BPC and its Working Groups.

- Any further information submitted by the applicant or other interested parties within the scope of this request and the timeline specified by the eCA or ECHA as appropriate.

The data submitted during the public consultations on this substance organised by ECHA from 22 February to 21 April 2016 and from 26 June 2019 to 25 August 2019, including those submitted by the applicant.

The applicant was given the opportunity to provide a risk assessment on the ED properties of cyanamide. The assessment was submitted on 29 January 2021.

For this purpose, a quantitative risk assessment on the ED properties of cyanamide based on the available information was provided by the eCA and a first e-consultation was launched to address the mandate of the European Commission from 29. March - 26 April 2021.

Responses were received from eight Member States, ECHA and the applicant.The quantitative risk assessment on the ED properties of cyanamide and the responses to the first e-consultation were discussed at the BPC-WG II 2020.

Regarding the identification of a threshold for the ED properties of cyanamide, the WG did not support the values proposed by the eCA and considered that the available data would not allow defining a threshold. Also, no conclusion was drawn on the use of a MoE approach for assessing the level of risk for human health as no agreement was made on the first point. The majority of the commenting members supported performing a qualitative assessment for professionals.

Based on WG-II-2021 conclusions the eCA decided to follow a qualitative approach regarding the assessment of the general public which was presented in a second e-consultation launched from 15 July to 6 August 2021 and discussed at the WG-III-2021.
The qualitative approach addresses the questions of the risk assessment concerning ED effects of the active substance and is required for responding to the "Mandate requesting ECHA opinions under Article 75(1)(g) of the BPR – Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18".

In the following the assessments presented in the first and second e-consultations and the summaries of the comments that have been received are given. Additionally the WG discussions are reflected.

## 1st e-consultation: quantitative ED assessment of cyanamide following Article 75(1)(g)

### Background: Risk Assessment Human Health

Cyanamide is regarded to be a multi-site inhibitor interfering with the respiratory metabolism. It is known to inhibit the activity of catalase- and dehydrogenase-type enzymes.

Acute toxicity of cyanamide was moderate after oral, and lower, but measurable after dermal exposure. Inhalative uptake did not result in toxic signs but increased the sensitivity towards ethanol. Cyanamide is considered irritating to eyes, corrosive to skin and to be a sensitizer via the skin. There was no evidence for a genotoxic or a carcinogenic potential of cyanamide in humans *in vivo*. In repeat-dose studies, red blood cells, the thyroid gland, and

testes were identified as toxicological targets. In addition, fertility was impaired in the two-generation study.

The BPC-WG I-2016 agreed that a biological threshold can be determined for all toxicological effects of cyanamide and confirmed the reference values as proposed by the eCA:

| **Biocide (Assessment Report 2019)** | | | |
|---|---|---|---|
| | Value | Study | SF |
| AEL $_{acute}$ | 0.05 mg/kg bw/d | Developmental toxicity, rat, supported by human experience | 100 |
| AEL $_{medium-, long-term}$ | 0.01 mg/kg bw/d | 90-d & 1-yr, dog | 100 |
| ADI | 0.01 mg/kg bw/d | 90-d & 1-yr, dog | 100 |
| ARfD | 0.05 mg/kg bw | Developmental toxicity, rat, supported by human experience | 100 |

For details, please view the updated CAR. In short:

- For medium- and long-term toxicity, the most sensitive species was the dog. The sensitivity of spermatogenesis to cyanamide decreased in older animals as demonstrated by a common NOAEL of 1 mg/kg bw/d in the 1-yr study for effects on the testes, the red blood cells and the thymus. The NOAEL of 1 mg/kg bw/d would therefore apply to adults with established spermatogenesis ([redacted] 1989). As agreed in the BPC-WG I-2016 this NOAEL was used as the starting point for risk characterization and by using a combined assessment factor of 100 and assuming 100 % oral absorption, a **systemic Acceptable Exposure Level (AELmedium-/long-term)** of 0.01 mg/kg bw/d was derived. The NOAEL in the dog 90-d study by Til et al. 1982 was used as supportive information.
- The **systemic acute Acceptable Exposure Level (AELacute)** of 0.05 mg/kg bw/d was based on acute maternal effects (hypoactivity in 20 % of the dams) observed in an embryotoxicity/ teratogenicity study in rats on the first 1-2 days of treatment. The NOAEL was set at 5 mg/kg bw/day for hypoactivity following the first two applications ([redacted] 1989). A standard combined assessment factor of 100 was used and 100 % oral absorption was assumed.

  The most critical endpoint that may respond to single dose exposure is derived from foetal abnormality data in the rabbit developmental toxicity study. The increased foetal incidence of a specific eye abnormality (folded retina at 2 mg/kg bw/d for bilateral occurrence of retinal folds, [redacted] 1989) was considered a fixation artefact based on new data regarding the frequency of such fixation-related findings in rabbit foetuses. Hence, the developmental NOAEL of cyanamide in this study is 6 mg/kg bw/d under the conditions described, but could presumably be modulated, by the vitamin A intake.
- In rats, teratogenic effects on the diaphragm (diaphragmatic hernia) with a NOAEL of 15 mg/kg bw/day ([redacted] 1989) were presumably related to the inhibition of retinoic aldehyde dehydrogenases and a disturbed retinoic acid signaling as a result of decreased enzyme activity. Based on the data from other ALDH inhibitors, the

nutritional supply of vitamin A at the time of exposure can be expected to modulate teratogenic risk.

- The eCA also concluded in the final CAR in 2016, that based on the multiple observations of thyroid toxicity, cyanamide exhibits endocrine-disruptive properties, specifically thyroid-effects caused by the direct endocrine mechanisms of thyroid peroxidase (TPO) inhibition.

## Background: Assessment of the ED properties of cyanamide

In 2019, the eCA DE prepared an ED assessment for cyanamide based on the EFSA/ECHA Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. The ED assessment was discussed at the ED expert group (ED EG14) in June 2019. The Agency organized consultations via the BPC (BPC-33) and its Working Groups (BPC WG IV 2019).

The BPC-WG IV 2019 agreed on the conclusion as proposed by the eCA that cyanamide meets the specific scientific criteria for endocrine disruption as set out in Regulation (EU) 2017/2100. Based on the multiple observations of thyroid toxicity, the eCA concludes that cyanamide exhibits thyroid-disruptive effect caused by the direct endocrine mechanism of thyroid peroxidase (TPO) inhibition. Relevance of this finding to humans is supported by the provided TPO inhibition studies in which cyanamide was shown to be an inhibitor of human TPO activity.

For details, please view the updated CAR. In short:

For the T modality

- Sufficient data is available to draw a clear conclusion whether cyanamide meets the specific scientific criteria for endocrine disruption as set out in Regulation (EU) 2017/2100 when following the EU Guidance. The conclusion is based on the extensive *in vivo* and *in vitro* dataset.
- Adverse effects were observed on the thyroid gland in rat (follicular-cell hypertrophy / hyperplasia; changes in colloid content; thyroid weight) and dogs (thyroid weight). Furthermore, a reduction in circulating thyroxine (T4) and triiodthyronin (T3) was observed in rat and dogs.
- One of the direct modes of action responsible for the reduction of the thyroid hormones concentrations in circulation would be inhibition of thyroperoxidase (TPO). It was demonstrated that cyanamide inhibits rat, dog and human TPO in the two *in vitro* studies submitted for this evaluation.
- The BPC WG IV 2019 agree with the eCA on the relevance of the positive *in vitro* TPO inhibition tests in multiple species

For the EAS modalities:

- The available data was considered non-sufficient to draw a clear conclusion whether cyanamide meets the specific scientific criteria for endocrine disruption as set out in Regulation (EU) 2017/2100 when following the EU Guidance.
- Histopathological changes in testes/epididymides as well as effects on the spermatogenesis were observed in two species (rat and dog).

- One possible (non-EAS) mode of action responsible for the observed effects could be inhibition of retinaldehyde dehydrogenases. This enzyme catalyses the transformation of retinal to the morphogen retinoic acid (RA) in a tissue-specific manner. RA is required for spermatogenesis and female reproductive processes as well as for embryonal differentiation and development. The effects observed with cyanamide exposure in rats and rabbits, therefore, could be a consequence of the inhibition of (one of the) RA-producing enzyme(s) leading to a deficiency in locally required RA-signalling. However, no specific studies to support this hypothesized MoA were submitted.
- It is under discussion if RA deficiency meets the criteria for "other endocrine and neuro-endocrine pathways" (i.e. non-EATS) (OECD 2012, Review Paper No. 178). It is currently not addressed in the ED GD (ECHA and EFSA, 2018)
- The BPC WG IV 2019 agreed that the retinoic acid pathway does not have to be further investigated.

## Determination of a threshold for the ED properties of cyanamide

For details on the ED-related effects observed in rodents and non-rodent species in the available toxicological studies as well as the assembled, integrated and assessed lines of evidence for the T modality and effects on spermatogenesis of cyanamide in mammals, please view the updated CAR. This risk assessment focuses on the proposed modes of action and the lowest NOAEL for the key elements of the MoA.

For the T modality, the proposed MoA is depicted as following:

| Mode of Action | | Adverse Effects observed in toxicity studies<br>Lowest NOAEL for the KE |
|---|---|---|
| MIE | TPO inhibition (observed) | Only mechanistic studies available<br>Demonstrated activity of cyanamide in the range of 2.2 – 7 µM in *in vitro* (Haines 2018a & 2018b)<br>*In vivo* TPO test was positive, inducing 30 % inhibition of TPO within 30 minutes of i.p. exposure to 30, 50 or 100 mg/kg bw cyanamide ([redacted] 1979) |
| KE1 | Reduced TH synthesis | No data |
| KE2 | Reduced circulating T4 and/or T3 (observed) | Adverse effects were observed in rat and dogs<br>Due to the experimental design, statistical significance was obtained predominantly in rats, but effects were also observed in the dog.<br>Identified NOAEL of 1 mg/kg bw/d in an oral gavage 91-week study in rats ([redacted]1991) |
| KE3 | Increase in circulating TSH | No data |
| KE4/AO<br>in adult animals | Histopathological changes in thyroid (observed) | Adverse effects were observed on the thyroid gland in rat: follicular-cell hypertrophy / hyperplasia; changes in colloid content; thyroid weight<br>Identified NOAEL of 5 mg/kg bw/d in an oral gavage 28-day study in rats ([redacted] 1988) |

| Mode of Action | | Adverse Effects observed in toxicity studies<br>Lowest NOAEL for the KE |
|---|---|---|
| | | Identified NOAEL of 1 mg/kg bw/d in an oral gavage 91-week study in rats ([redacted]1991) |
| KE5 | Reduced tissue thyroid hormone concentration (proposed) | No data |
| AO<br>in progenies | Developmental abnormalities | No data – no DNT study available<br>Altered neurodevelopment (not tested) /<br>Amphibian metamorphosis (not tested) |

MIE- molecular initiating event, KE – key event

For effects on spermatogenesis, the following MoA which **is not in the scope of the ED GD** is depicted as following:

| Mode of Action | | Adverse Effects observed in toxicity studies<br>Lowest NOAEL for the KE |
|---|---|---|
| MIE | Inhibition of retinaldehyde dehydrogenases (proposed) | No data |
| KE1 | Retinoic acid deficiency in seminiferous epithelium (proposed) | No data |
| KE2 | Block of spermatogonia and Sertoli cell differentiation (proposed) | No data |
| KE3 | Histopathological changes of the testis (observed) | Histopathological changes in testes were observed in rat and dog.<br>Identified NOAEL of 1 mg/kg bw/d in an oral gavage 1-year study in dogs ([redacted]f 1989)<br>[Identified NOAEL < 0.6 mg/kg bw/d in an oral gavage 90-day study in not yet adult dogs ([redacted] 1982)*] |
| KE4 | Impaired spermatogenesis (observed) | Impaired spermatogenesis were observed in rat and dogs.<br>Identified NOAEL of 1 mg/kg bw/d in an oral gavage 1-year study in dogs ([redacted] 1989)<br>[Identified NOAEL < 0.6 mg/kg bw/d in an oral gavage 90-day study in in not yet adult dogs ([redacted] 1982)*] |
| KE5 | Decreased testis weight (observed) | Adverse effects were observed in rat and dogs. Due to the experimental settings, statistical significance could only be obtained in rats<br>Identified NOAEL of 10 mg/kg bw/d in an oral gavage 28-day study in rats ([redacted]1988), LOAEL at comparable level to body weight depression |

| Mode of Action | | Adverse Effects observed in toxicity studies<br>Lowest NOAEL for the KE |
|---|---|---|
| Adverse effect | Impaired fertility (observed) | Reduced fertility was observed in the male and female rat<br>Identified NOAEL of 7 mg/kg bw/d in an reproductive gavage study ([redacted] 1987), |

MIE- molecular initiating event, KE – key event
* Based on published data on the maturation of spermatogenesis in dogs it must be concluded that the young dogs were still immature at the end of the study so that the findings at the low dose cannot be ascribed to treatment unequivocally (for details see updated CAR DocII, ch. 3.5).

**Overall, the eCA proposed that based on the available data, a threshold for the ED properties of cyanamide can be derived.** Considering the identified / proposed modes of action, the existence of a threshold of toxicity, only above which the degree of enzyme inhibition becomes biologically relevant, can be concluded for cyanamide. This was agreed previously by the BPC-WG I-2016 when setting the reference values for human health.

The lowest relevant endocrine-related NOAELs, taking into account the adverse outcomes as well as all key events and the molecular initiating event(s), are identified for each time frame as follows:

- For medium- and long-term toxicity, a NOAEL of 1 mg/kg bw/d was identified in the 91-weeks rat as threshold for effects on the thyroid gland.
  Furthermore, a common NOAEL of 1 mg/kg bw/d was identified in the 1-yr study in dogs for effects on the testes/spermatogenesis applying to adults with established spermatogenesis. This threshold would be equivalent to the POD for the derivation of the AEL medium-, long-term.

For acute/short-term toxicity, a NOAEL of 5 mg/kg bw/d in an oral gavage 28-day study in rats was identified as threshold for effects on the thyroid gland. NOAELs for developmental effects were higher (6/15 mg/kg bw/d in rats/rabbits).

***Q1: Do you agree with the eCA on the identified threshold(s) for the ED properties?***

**Responses received from the e-Consulation**

Four MS and the applicant agreed on identified thresholds for the specific endpoints addressed in this assessment. Four other Member States expressed the opinion that a firm conclusion on the threshold for the ED properties of cyanamide cannot be drawn. The majority of MS pointed out that there are several uncertainties, including general issues (no guidance available, no global agreement on the existence of safe thresholds for ED properties) as well as limitations of the database, in particular the lack of a DNT study.

The eCA agrees, that there are several uncertainties within the current database. However, the mandate of the European Commission clearly requested a risk assessment on the available information. In addition, the eCA maintains its view that a threshold for biological adversity through TPO inhibition by cyanamide exists. While some alternative MoAs for the thyroid-modality can be excluded (e.g. TR inhibition), the threshold assumption would also apply for the remaining, theoretical alternative MoAs (e.g. enhanced hepatic TH clearance). Overall, the eCA therefore proposes that the BPC WG HH should discuss and agree on the assessment of the remaining uncertainties, taking into consideration relevant subpopulations.

**Discussion at the BPC-WG II 2020**

Several uncertainities of the presented pragmatic approach were discussed:

- There is no data on developmental neurotoxicity (DNT) available. However, as shown by the proposed MoA for the T modality, DNT effects can be caused by changes in thyroid hormone levels. Hence, neurodevelopmental effects cannot be excluded.
- Furthermore, there is no conclusion on EAS modalities available. According to the ECHA/EFSA Guidance (2018) , Further information are not requested when it is already possible to conclude that the ED criteria are met for one modality (here T modality).
- There is also no guidance or knowledge which assessement should be applied, when usind ED effects for risk assessement to derive a safe level.
- And it was pointed out that the BPR requires negligible risk.

In general, the BPC-WG was split on the question whether the ED effects regarding the T modality is based on a threshold with a slight majority considering that most likely a threshold exists. However, a clear majority considered that establishing such a threshold is not possible using the available information.

The eCA remains of the opinion that ED effects regarding the T modality is based on a threshold and the uncertanities could be addressed.

**Conclusion at the BPC-WG II 2020**

The majority of the commenting members:

- did not support the values proposed by the eCA
- considered that the available data would not allow defining a threshold

## Assessing the level of risk for human health

The discussion on reference values (POD, Assessment Factors) was already closed at the BPC-WG I 2016 and no new data was identified during the evaluation of the ED properties of cyanamide. Currently, there is guidance only on the identification of endocrine disruptors in the context of Regulation (EU) No 528/2012. The scientific debate on the general approach to risk assessment with regard to ED properties is still ongoing. Hence, a case-specific approach is adopted, following the general recommendations of the Guidance on the Biocidal Products Regulation, Volume III Parts B+C (Version 4.0, 2017).

The eCA proposed to use the Margin of Exposure (MOE) approach to assess the level of risk for human health. The MOE approach is intended to provide some indication to risk managers as to the level of concern and to help in assessing the need for, and urgency of, further action (Environmental Health Criteria 240, Chapter 5). The MOE is defined as the ratio of the POD (e.g. BMDL or NOAEL) to the theoretical, predicted or estimated exposure dose or concentration.

For details on the exposure assessment, the selected scenarios and the calculation of the estimated total uptake for professionals please view the updated CAR.

However, the eCA is of the opinion, that the calculation of a minimum MoE for each time frame is sufficient to conclude on the risk assessment for effects of cyanamide on the endocrine system. The maximum exposure can be set at the level of the agreed reference values of 0.05 and 0.01 mg/kg bw/d for acute/short-term and medium-/long-term scenarios, respectively. The resulting MoEs over the lowest endocrine-related relevant NOAEL of 5 and 1 mg/kg bw/d as identified above is 100 in both cases (note: oral absorption was set at 100 %). Thus, a minimum MoE of 100 will be assured by the agreed reference values also for the endocrine disrupting properties (please refer to MoE given in the CAR, Appendix I, Tables 1 and 3).

***Q2: Do you agree with the eCA on the use of an MoE approach for assessing the level of risk for human health?***

**Responses received from the e-Consulation**

Two MS and the applicant agreed with the proposal of the eCA to use the MoE approach for assessing the level of risk for human health. Three MS did not agree with the proposal of the eCA, referring mainly to uncertainties and a lack of guidance specific to the risk assessment for effects through endocrine MoAs. The eCA was unable to identify a clear statement on agreement/disagreement for Q2 from the responses provided by four other MS.

The BPC WG HH should discuss whether to apply the MoE or the MoS approach as proposed by the eCA or mentioned by ECHA, respectively, prefer the derivation of an endpoint specific AEL for the ED properties, or perform a qualitative risk assessment only. In addition, a need is identified to discuss and agree on the appropriateness of the proposed uncertainty factors for the exposed (sub)population – please also refer to outcome on Q1.

**Discussion at the BPC-WG II 2020**

- The applicability of the MoE approach was discussed and some concern were raised regarding: That the MoE would need to take into account how a threshold is set.
- If uncertainties could be assessed by using MoE
- And that the MoE approach is also used for genotoxic (non-threshold) carcinogens, and a threshold would not be a prerequisite for applying the MoE

**Conclusion at the BPC-WG II 2020**

There was no conclusion due to not having an agreement on Q1.

### Opinion whether the risks can be considered acceptable or not

Cyanamide is only intended for professional use and risk mitigation measures are foreseen (PT3, PT18). Considering the evidence summarised above, the eCA proposes that - in the present case of cyanamide - the risk for professionals with regard to the ED properties is considered to be acceptable as the Margin of Exposure is 100 or greater.

A risk assessment for the general public has not been performed yet. This will be done in a second step.

***Q3: Do you agree with the eCA, that the risk resulting from the intended use can be considered acceptable?***

**Responses received from the e-Consulation**

Three MS and the applicant agreed with the proposal of the eCA that the risk resulting from the intended use can be considered acceptable. Four MS did not agree with the proposal of the eCA referring to uncertainties and lack of guidance (see also above). The eCA was unable to identify a clear statement on agreement/disagreement for Q3 from the responses provided by another two MS.

The eCA DE proposes that the BPC WG HH discusses and agrees on the most suitable approach for assessment of risk resulting from the endocrine disrupting properties of cyanamide, evaluates and takes into account remaining uncertainties and finalizes the risk assessment as requested in the mandate of the European Commission based on the available information.

**Discussion at the BPC-WG II 2020**

A risk assessment for professional users with RMM in Tier 2 was presented and several members agreed to a qualitative risk assessment based on no exposure due to RMM, but expressed concern regarding a quantitative risk assessment.

A risk assessment for general public due to secondary exposure was also presented by a room document. The question was postponed to the next BPC-WG.

**Conclusion at the BPC-WG II 2020**

There was no conclusion due to not having an agreement in Q1.

The majority of the commenting members supported performing a qualitative assessment for professionals.

## 2nd e-consultation: Qualitative exposure and risk assessment for the general public within the frame of the discussion on the ED risk assessment for cyanamide

### Description of the exposure

The representative biocidal product is only used by professionals inside empty pig stables. The general public has normally no access to these buildings. Thus, exposure inside stables is not expected and has not been assessed in the CAR for cyanamide (PT 3 and PT 18). However, appropriate risk mitigation measures have been proposed to prevent access of the general public. The following measure is proposed: "Access of uninvolved third parties to

areas of application has to be excluded during/after application and cleaning."

The exposure of the general public via liquid manure is considered relevant according to the current standards of assessment. As there are no models for the application of liquid manure and the exposure of the general public, the description of the exposure for the general public regarding the qualitative assessment is based on exposure scenarios developed for the application of plant protection products, i.e. bystander and resident exposure as well as recreational exposure. These scenarios have not been taken into account for PT 3 or PT 18 active substances in the past, but have recently been considered in the assessment of one union authorisation. However, prior to WG-III-2021, these scenarios had not been actively discussed in the Working Group.

During free time the general public (e.g. residents, tourists etc.) can move around the landscape for e.g. walking, hiking, cycling or having a picnic so that a contact to treated areas such as e.g. lawns, grassland, vineyards, orchards or agriculture fields has to be taken into account. Within the frame of ED assessment the exposure of the general public, including vulnerable groups such as persons with pre-existing illness or sensitive subgroups such as children and pregnant women, is qualitatively evaluated. This assessment was not discussed in the original CAR for PT 3 and PT 18 from 2013.

The biocidal product is intended to be applied to the liquid manure stored underneath the slatted floor (in slurry canals) in empty pig stables by using a watering can or a trolley. The slurry canals can collect the liquid manure produced during a whole fattening cycle or even larger quantities of liquid manure. The slurry canals are only emptied after the end of a fattening cycle after the pigs have been housed out. Afterwards the liquid manure is removed out of the slurry canals and stored in a separate slurry tank outside the pig stables until it is used for crop manuring (according to Doc II section 8.3.1.3).

A secondary exposure due to use of liquid manure for crop manuring is considered relevant for the general public. As there are no models for the application of liquid manure exposure scenario descriptions developed for the application of plant protection products in low crops are considered.
Based on definitions given in the EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products (2014) an acute exposure is considered for bystanders because it is defined that these persons could be located within or nearby areas of application/treatment during a short time period. Residents are present (e.g. living, working) nearby areas of application/treatment and might be exposed for a longer time period.
The bystander and resident exposure to the active substance may occur during or after spreading of treated liquid manure on agricultural land when persons are passing by or living next to agricultural land where liquid manure is spread. The following pathways of exposure should be considered for bystanders and residents: spray drift (at the time of application), vapour (may occur after the substance has been applied), surface deposits and entry into treated crops regarding the potential routes of exposure (inhalation, dermal and oral (the latter only for children)).
The recreational exposure describes the contact to surfaces where treated liquid manure was applied (exposure routes: dermal and oral). The contact to the active substance may occur, when persons stay on surfaces where liquid manure was applied, e.g. on green- and grassland or on lawns. As a worst case, the direct contact of a toddler to applied liquid

manure should be considered.

At the WG-II-21 a first draft assessment regarding the exposure and risk of the general public (including via residues in food) was prepared as room document for supporting the discussion on the risk assessment in relation to ED effects for the active substance cyanamide during this WG discussion. Please note that the first draft assessment included a quantitative approach that was not discussed during WG-II-2021. However, as mentioned before the eCA decided to follow a qualitative approach regarding the assessment of the general public based on WG-II-2021 conclusions. Several WG members considered the first draft assessment very conservative. Therefore, further considerations regarding the description of the potential contact to applied liquid manure are included in section 2.2.

The following table shortly summarises the description of the exposure of the general public to be considered in the qualitative assessment:

| | |
|---|---|
| Secondary exposure due to entry/access to stables:<br>Adult, child<br>(oral, dermal, inhalation) | Not expected due to the restricted access to pig stables; has to be excluded via risk mitigation measures at product authorisation stage |
| Secondary exposure via liquid manure:<br>Adult, child<br>(oral, dermal, inhalation) | Bystander exposure scenario |
| | Resident exposure scenario |
| | Recreational exposure scenario |

*Question of the e-consultation and summary of the received comments*

In the e-consultation different questions were raised to address the aspects to be discussed with regard to the assessment for the general public:

| **Question 1:** |
|---|
| a) Taking into account that these scenarios have only recently be considered for one UA, but not for any PT 3 and PT 18 active substance before, do you agree with the eCA's opinion that the described scenarios, developed for the application of plant protection products are relevant in order to assess the exposure of the general public following manure application on agricultural land?<br>*Please note that if the HH_WG agrees with the presented scenarios, these may have to be considered for any PT 3 and PT 18 active substance (first approval and renewal) in the future.*<br>b) If yes, do you agree that these scenarios have to be taken into account for the approval process of cyanamide at this point of time, although the assessment has been finalised at BPC-16 and BPC-33?<br>c) Do you agree that the presented description considers all relevant scenarios of the exposure of the general public?<br>d) If no, which aspects should be added? |

Three commenting member states on question 1 agreed that the described scenarios are relevant in order to assess the exposure of the general public following manure application on agricultural land.

One member state noted that due to missing specific guidance on how ED effects should be addressed in risk assessment all potential ways of exposure should be carefully considered.

The aspect that there are different legal requirements for the use of liquid manure in the different member state is addressed in the description of potential risk mitigation measures (section 3.2).
One member state indicates that they have national restrictions regarding the use of liquid manure so that the presented exposure scenarios would be considered as too worst case from their point of view. Further considerations that liquid manure has a different density as liquid pesticides and that there will be a certain time between emptying the slurry canals and application were mentioned. However, the member state could agree on considering a potential exposure three days after the application of liquid manure.

Three member states agreed that the presented scenarios have to be taken into account for the approval process of cyanamide at this point of time.
According to the received comments the presented information of use and exposure has to be considered at this stage because there are new developments regarding the assessment of biocides and the active substance has been identified to have ED properties. A conclusion on the risk is required for the active substance approval and the considerations are relevant for deciding.

Three member states agreed that the presented description considers all relevant scenarios of the exposure of the general public.

The applicant pointed out that in his opinion the described scenarios are unrealistic worst case that should not be considered in the risk assessment. Further, considerations of the application of plant protection products are not appropriate for assessing the exposure to liquid manure that is applied on agricultural land.
The eCA points out that the description of potential risk mitigation measures (section 2.2) includes further considerations about exposure-reducing aspects regarding the described worst case scenarios to address the questions of a realistic exposure description.

In conclusion, all member states commenting on question 1 agreed with the description of the exposure of the general public, which has to be done for cyanamide within the frame of the discussion on the ED risk assessment. Further information of the member states has been addressed when updating the assessment.

## Description of potential risk mitigation measures

Based on the conclusions of the WG-II-2021 the eCA decided to follow a qualitative approach regarding the assessment of ED properties of the active substance.
Considering the exposure description (section 3.1) an exposure to the active substance due to the contact during and after the application of liquid manure cannot be excluded for the general public. There is only the possibility of reducing the exposure of the general public by potential risk mitigation measures that are described in the following.
The described risk mitigation measure RMM1 and RMM2 may reduce the exposure in general, while third option is only appropriate for unplanted areas.

RMM 1: Prolonged storage of liquid manure

According to Doc II section 8.3.1.3 the biocidal product is applied to the liquid manure stored underneath the slatted floor (in slurry canals) in empty pig stables by using a watering can or a trolley. The slurry canals can collect the liquid manure produced during a whole fattening cycle or even larger quantities of liquid manure. As the slurry canals are only emptied after the end of a fattening cycle after the pigs have been housed out, it is concluded that the liquid manure remains in the slurry canals during the complete fattening cycle of 126 days (manure storage time). Afterwards, the liquid manure is removed out of the slurry canals and stored in a separate slurry tank outside the pig stables until it is used for crop manuring.
It may be considered that the liquid manure is not always applied immediately to agricultural land after removal but is stored for longer periods, so that further degradation of cyanamide in liquid manure can be assumed in the case of prolonged storage. According to Doc II section 4.1.1.1.5, the DT50 value for cyanamide in the liquid manure based on an anaerobic degradation study for 105 days is calculated to be 45.4 days.

The prolonged storage of liquid manure could be a potential risk mitigation measure to reduce the active substance content in the liquid manure.
Further the feasibility of the potential risk mitigation measure has to be considered. Even if a person using liquid manure for treating agriculture land could create storage capacity, it is impossible to estimate how large the storage capacity has to be and how long the manure has to be stored.

However, it has to be noted that in various member states national regulations are in place restricting the time window for treating agriculture land. The ENV WG has already decided several times that the possible RMM of storing manure for a prolonged time is not suitable to refine the environmental risk assessment. The main argument is that liquid manure is an economic asset and that is it therefore not possible to label it with any kind of restrictions or conditions.

In addition, even if further data for prolonged degradation of the active substance in the liquid manure would be available, no conclusion could be drawn on how long the liquid manure has to be stored to reduce the content of the active substance so far that an acceptable level may be achieved, as the potential exposure of the general public cannot be compared to a threshold considering ED effects.

RMM 2: Warning signs or other measures to restrict access to treated areas

With regard to the exposure descriptions some further considerations may be taken into account.
The assumption that contact of a toddler occurs to applied liquid manure and that bystanders/residents are next to the treated area during application is the worst case. It may be assumed that the person who is responsible for the treatment ensures that nobody has access to the treated area and stays on it during application. Hence, the contact to the liquid manure may be considered first when the residues have dried (which depends on time and weather conditions). Further the contact may be considered later when the unpleasant odour of the manure has disappeared, i.e. a few days after application.
It may be assumed that the content of the active substance in liquid manure decreases after application on agricultural land based on the degradation data. Based on the information given in Doc II section 8.3.1.3 no accumulation of cyanamide in the soil from one application to the next is assumed due to the fact that the time to 99 % degradation of

cyanamide in soil is as short as 19 days (based on a DegT50 value of 2.81 days for aerobic soil degradation, normalised to 285 K).
It may be considered that the contact to the liquid manure is not immediately after application and that cyanamide further degrades on the agricultural land.

Nevertheless a realistic worst case has to be considered and potential risk mitigation measures may be required to reduce the exposure to the active substance. The contact could be prevented by warning signs or other measures to restrict the access to treated areas.
Regarding the feasibility of the potential risk mitigation measure it has to be discussed if it can be assumed as realistic that the treated areas are equipped with warning signs or other measures to prevent access to these areas.

However, liquid manure is an economic asset. That means that third parties are often collecting, re-distributing and applying the manure on agriculture land on behalf of the local farmers. The farmer who has originally treated his manure with cyanamide, will not necessarily be the same person who applies manure to agricultural land. Thus, in practice, it might not be possible to track where treated manure was applied and where access to areas has to be restricted during and after application of the manure. That is also the reason why the ENV WG has already decided in the past that a labelling of manure treated with biocidal active substances is not suitable as risk mitigation measure. The same consequently applies for warning signs or other measures to restrict access to treated areas.

Even if a direct contact to applied liquid manure is prevented by feasible risk mitigation measures and degradation data can be considered, no conclusion can be drawn how long the access to treated areas has to be restricted as the potential exposure of the general public cannot be compared to a threshold considering ED effects.

Additional consideration: Incorporation into the soil

According to the German regulation on the application of fertilisers, one possible practice in DE is incorporation of the liquid manure into soil after application, e.g. to reduce N-losses (for grassland only from 2025). There may be comparable practices in other member states. Hence, the incorporation into the soil may be considered as additional potential risk mitigation measure to reduce the availability of liquid manure and therefore of the active substance on the treated areas.

However, this practice is not applicable for all kinds of treated areas – it is not appropriate for e.g. grassland, lawns and other cultivated areas. Incorporation into the soil is only mandatory for uncultivated arable land in Germany. In the case of cultivated arable land, the liquid manure must be applied at least onto the soil using techniques close to the soil (e.g. in strips). Here, incorporation is not mandatory. The latter one is the preferred area to be treated with liquid manure for reducing N-losses. The practice can only be applied to bare soil or uncultivated fields. No information is available to assess the feasibility of this risk mitigation measure in other member states and the effect of reduction due to incorporation into the soil.

Please note that for the environmental risk assessment, an incorporation of the applied manure in soil has already been taken into account for arable land (20 cm) and for

grassland (5 cm)[6].

Furthermore, again the problem of traceability of the treatment with cyanamide will become relevant. As a farmer applying manure on agricultural land is normally not aware of the active substances that may be presented in the manure as he/she did not treat the manure himself/herself it is not possible to implement such a measure in practise.
Furthermore, please note that the ENV WG has already decided that restricting the application to either arable land or grassland is not an acceptable risk mitigation measure.

Even if other measures after liquid manure application can be considered, no conclusion can be drawn to what extend the available content of the active substance and therefore the potential exposure of the general public is reduced as both cannot be quantified and compared to a threshold considering the ED effects.

*Questions of the e-consultation and summary of the received comments*

In the e-consultation different questions were raised to address the aspects to be discussed with regard to the assessment for the general public:

**Questions 2:**

a) Do you agree that the described potential risk mitigation measures are not suitable to reduce the exposure of the active substance to the general public in a regulatory framework?
b) Are there additional risk mitigation measures that could be considered from your point of view?
c) Do you agree with the eCA that no conclusions can be drawn, independent from the practical implementation of the described potential risk mitigation measures, due to uncertainties about the magnitude of exposure reduction and feasibility?
d) Which points could be added from your point of view?
e) May there be an alternative approach for a qualitative assessment from your point of view?

All member states commenting on question 2 agreed that the described potential risk mitigation measures are not suitable to sufficiently reduce the exposure of the active substance to the general public in a regulatory framework and that no conclusions can be drawn on the amount such RMM would reduce exposure.

One member state noted that the described risk mitigation measures are not applicable. However, there is information of potential reduction of exposure – but there is no possibility of quantification. Hence, concluding on the exposure and risk is not possible.

One member state pointed out that they have national requirements with regard to the use of liquid manure so that RMM1 may be redundant and not applicable. RMM2 was also considered not suitable. The described consideration of manure incorporation into soil should be subject to national regulations from their point of view.
In general, national legislations may determine the time point when the application of liquid manure is allowed as well as the kind of agricultural land intended for application. Further different application practices may be mandatory. There are uncertainties in which member

[6] Emission Scenario Document for Insecticides for Stables and Manure Storage Systems

states which national restrictions are in place and whether these restrictions ensure a sufficient exposure reduction to the active substance.

In the opinion of one member state it is required to set risk mitigation measures for treated manure in the case of active substance approval. One example was mentioned: "Do not use the treated manure on grassland which serves for recreational purposes."
No additional risk mitigation measures were proposed by the commenting member states that could be considered.

One member state proposed to alternatively assess the mode of action for the ED effects with in the frame of a qualitative approach considering the most sensitive population.

The Applicant proposed to consider an analogous procedure as for plant protection products when applying risk mitigation measures. RMM2 may be a potential risk mitigation measure from their point of view.

In conclusion, the majority agreed that the described potential risk mitigation measures are not suitable. The feasibility of restricting the use of liquid manure is up to the ENV WG and BPC members to discuss. The majority agreed that no conclusion can be drawn regarding the magnitude of exposure reduction of the potential risk mitigation measures.

## Conclusions on exposure of general public (excluding dietary exposure)

Based on the given description of the exposure for the general public and the description of potential risk mitigation measures, there are uncertainties about the magnitude of exposure-reducing measures. These measures may in principle be expected to lead to a reduction of exposure of the general public, but the exposure to the general public cannot be excluded. This is one reason why it cannot be concluded whether these measures are sufficient to ensure an acceptable risk with regard to the ED properties of the active substance as requested in the mandate. Furthermore, all presented RMM have already been considered unsuitable in a regulatory framework by the ENV WG.

*Questions of the e-consultation and summary of the received comments*

In the e-consultation different questions were raised to address the aspects to be discussed with regard to the assessment for the general public:

| **Questions 3:** |
|---|
| a) Do you agree that the exposure of the general public cannot be excluded by any risk mitigation measures?<br>b) Do you agree that no final conclusion can be drawn regarding the risk assessment for ED properties of the active substance requested by the mandate?<br>c) If not, what is your point of view?<br>- Do you think risk mitigation measures may lead to an acceptable risk with regard to the ED properties of the active substance? If yes, which risk mitigation measures may be appropriate from your point of view? May there be additional measures from your point of view?<br>- May there be alternatives to ensure an acceptable use? |

All member states commenting on question 3 agreed that the exposure of the general public

cannot be excluded by any risk mitigation measures and that no final conclusion can be drawn regarding the risk assessment for ED properties of the active substance requested by the mandate.

One member state is of the opinion that no additional information or further aspects of assessment can be included so that BPC and SCBP have to finally conclude on acceptability.

One member state noted that the likelihood of the described exposure should be discussed in the assessment and uncertainties should be described.

One member state pointed out that a reduction of the exposure of the general public is possible. However, the described risk mitigation measures are not applicable. As no threshold of ED properties can be defined and the treated manures is widely used, they agree to not finally concluding on the acceptability of the risk.

From the applicant's point of view the exposure description reflects an unrealistic worst case and has no relevance for the assessment. Hence, the final conclusion should be that the general public is not exposed to the active substance.

In conclusion, it was agreed that the exposure of the general public cannot be excluded and no final conclusion can be drawn regarding the risk assessment for ED properties of the active substance.

## Note about the environmental e-consultation and WG discussion

Following an e-consultation addressing the arising questions regarding the environmental assessment of cyanamide requested by the mandate the members of the WG-II-2021 discussed different aspects. For details on the discussion of environmental points please refer to the final minutes of WG-II-2021. Here, the point regarding the degradation rate is given for information:

One discussion point presented the question of the need for further testing with regard to the degradation of cyanamide in liquid manure and/or for monitoring data from field applications. It was concluded that there is no need for performing new studies regarding degradation or monitoring.
This point was confirmed at the WG-III-2021 as it was concluded that it is not required for revising the current degradation assessment within the frame of responding to the mandate. For details please refer to the documents of WG-III-2021.

## Dietary risk assessment regarding ED assessment

Following the ED assessment an update of the dietary risk assessment as it is presented in the existing CAR for PT 3 and PT 18 for the active substance cyanamide is not considered necessary.

For the representative uses in PT 3 and PT 18 residues in food and feed are not expected as:
The biocidal product is applied onto manure or rinsed from the slatted floors into the liquid manure canal in the absence of animals. Thus, direct exposure of livestock is not expected (This is already described in the existing CAR for PT 3 and PT 18).

Spreading treated manure onto agricultural areas is an additional scenario that is not discussed in the existing CAR for PT 3 and PT 18. Due to the degradation of 99 % of the cyanamide within 19 days (see Doc II 8.3.1.3 in the environmental part of the existing CAR) transfer of cyanamide residues from treated manure into agricultural crops is not expected and a relevant consumer exposure is not expected from this scenario. Therefore, it is proposed to add the scenario at active substance renewal.

The dietary risk assessment could also be updated considering cyanamide MRLs for products of animal origin according to Regulation (EU) No. 1126/2014, which were not yet available when the existing CAR was drafted. However, this will not change the overall conclusion of the dietary risk assessment. Therefore, it was agreed to postpone the update to active substance renewal.

*Questions of the e-consultation and summary of the received comments*

In the e-consultation different questions were raised to address the aspects to be discussed with regard to the assessment for the general public:

| **Questions 4:** |
|---|
| a) Do you agree with the presented considerations with regard to the dietary risk assessment?<br>b) If no, which points should be added?<br>c) If no, what is an alternative approach? |

Three MS and the applicant agreed with the presented considerations regarding the dietary risk assessment of cyanamide.

One MS proposed to add an additional RMM to the dietary risk assessment introducing a period of three weeks between the application of manure and harvest of crops or grazing of livestock animals. In the opinion of the eCA DE such an RMM is not necessary as manure is typically spread on young plants and not close to harvest. Also oral uptake of manure by grazing livestock animals is not expected (see more detailed explanation above).

One MS proposed to introduce a precautionary statement informing about the existing MRLs for cyanamide at product authorisation level. A similar statement has previously been included for other substances at biocidal product authorisation.

In conclusion it was agreed to update the dietary risk assessment in the CAR at active substance renewal, as the majority of MS agreed with the considerations on dietary risk assessment presented in the e-consultation. A precautionary statement informing about existing MRLs for cyanamide is proposed in the BPC Opinion.

## Summary of WG discussion and conclusions

Following the WG-II-2021 conclusions the eCA presented a qualitative approach regarding the assessment of the general public in an e-consultation. The assessment and the received comments of other member states and the applicant were summarised above. Based on the e-consultation the qualitative assessment was discussed at the WG-III-2021. In the following the discussion and conclusions are reflected.

**Relevance of proposed exposure scenarios for secondary exposure of the general public following manure application on agricultural land:**

During the WG discussion the relevance of the described exposure scenarios for the general public was confirmed. Additional exposure scenarios for consideration were not proposed.
Due to national legislation for the application of liquid manure the described scenarios might not be realistic in two commenting member states. Nevertheless, there is uncertainty whether comparable national restrictions exist in all member states.
The applicant raises the aspect of limited time points for application of manure and of unlikely daily exposure. Further the applicant noted that the entering of treated areas by the general public would be unlikely due to the unpleaseant odour of the manure. It has to be mentioned that this point had already been considered in the qualitative assessment (please refer to section 2.2.2).

For this discussion point it was concluded that the described exposure scenarios are included in the current assessment as presented by the eCA.

In the frame of discussion on the relevance of exposure scenarios, the aspect of degradation data was raised. According to the applicant additional degradation data may be also relevant for the human health assessment. After clarification by the eCA that further degradation data would not alter the qualitative assessment, which already considered the degradation rate, and that the information is currently not available, the aspect was not further considered.
In section 2.4 the conclusions of the WG considering environmental discussion points are mentioned. With regard to the degradation assessment it was concluded that no revision is required for responding to the mandate. For details please refer to the documents of WG-III-2021.

**Applicability of proposed risk mitigation measures:**

Regarding the second discussion point it was supported that the described risk mitigation measures are not applicable for reducing the exposure and that the quantification of their impact on exposure cannot be determined.
In some member states there might not be a necessity for risk mitigation measures due to national legal restrictions. It was additionally noted that the unpleaseant odour of the manure might prevent a direct contact during/after application.
The possible approach of considering the ED mode of action (TPO inhibition), the limited exposure time (acute exposure), the potential reversibility of TPO inhibition and the low concentration of cyanamide exposure was shortly discussed.
According to the applicant there are national legislations for controlling the application of liquid manure and therefore the exposure and that these restrictions would be considered at product authorisation stage. Due to the degradation in soil and the elimination in the body the applicant would only expect low cyanamide concentrations and no ED effects.

For this discussion point it was concluded that the described risk mitigation measures cannot be considered suitable for reducing the exposure of the general public. On the other hand, some members questioned their necessity. It was not possible to conclude on the magnitude of exposure reduction of the risk mitigation measures.

**Conclusion on the risk for general public (excluding dietary risk)**

Exposure might be low but cannot be excluded for the general public. It was noted that there is no information on how low the exposure has to be for excluding risks as no threshold for ED effects of the active substance was identified by the WG.

In the qualitative assessment the eCA considers the discussion points regarding a) exposure description for the general public (section 2.1), b) potential reduction of the active substance (sections 2.2.1 and 2.2.2), c) avoiding contact to manure (section 2.2.2), d) likelikood of TPO inhibition and adverse effects caused by acute exposure (please refer to the first e-consultation in section 2), e) degradation of the active substance (sections 2.2.1, 2.4 and 3.1) and f) use pattern of liquid manure (sections 2.2.3 and 2.2.4).

The decision if the risk can be considered acceptable or not is not in the remit of the WG.

For this discussion point it was concluded that the exposure of the general public cannot be excluded. It was not possible to conclude on the risk assessment at the WG.

**Dietary risk assessment**

In conclusion it was agreed that an update of the dietary risk assessment in the AR and CAR is not needed. In addition a precautionary statement regarding the existence of MRLs for cyanamide will be added in the Draft BPC Opinion for discussion at the BPC meeting.
Regarding an RMM introducing a 3-week interval between manure application and harvest it was questioned whether this was indeed necessary.

# APPENDIX VI: Assessment according to the Article 75(1)(g)-mandate of the European Commission on cyanamide "Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18" - environmental part -

## 1. Introduction

With respect to the environment, in the scope of to the Art. 75 (1) (g) request, following questions of Commission needed to be adressed:

a. Based on available information, clarify whether a safe level (threshold) can be determined for the ED properties of cyanamide for the environment, and if such threshold can be established, what would be this level.

b. Clarify the level of the risks to the environment by:

   1. Assessing the level of risk for the environment, either by a quantitative assessment or by a qualitative assessment with particular focus on whether the exposure can be considered negligible, like for non-threshold carcinogen/mutagen substances or PBTs.

   2. Providing an opinion whether the risks can be considered acceptable or not.

In order to answer the above-mentioned questions, the eCA was instructed to consider the following aspects in its assessment:

- All the data submitted in the application, as well as the conclusions of the discussions in the BPC and its Working Groups.
- Any further information submitted by the applicant or other interested parties within the scope of this request and the timeline specified by the eCA or ECHA as appropriate.
- The data submitted during the public consultations on this substance organised by ECHA from 22 February to 21 April 2016 and from 26 June 2019 to 25 August 2019, including those submitted by the applicant.

In order to be able to answer the questions of the mandate accordingly, the following steps were taken:
In the light of the available data, the eCA provided an opinion on the risks for the environment that integrated the hazard caused by the ED properties of cyanamide as well as a series of general questions on the ED risk assessment that first needed an answer before the questions of the mandate could be answered accordingly [3]. This document underwent an e-consultation from 29 March until 26 April 2021 during which six member states, NO, CH and ECHA as well as the applicant commented [4, 5, 6, 7]. The first discussion on the proposal took place at WG-II-2021, where the majority of the commenting WG members supported the eCA's evaluation and considered that the available data would not allow defining a safe threshold [8]. However, several questions remained open, also concerning the data submitted by the applicant on the natural occurrence of

cyanamide, so a further e-consultation was initiated [9]. This e-consultation took place from 12 July until 6 August 2021 and four member states, NO as well as the applicant commented on the eCA's evaluation of the data [10, 11-17]. The final WG discussion on the COM's mandate on cyanamide took place at WG-III-2021 where all open questions could be closed accordingly [18].
The aspects discussed during the e-consultations as well as by the ENV WG meetings are explained in detail under point 4 and are summarised in a table under point 7 below.

## 2. General substance information

Cyanamide is intended to be used by the professional users as bactericide against *Brachyspira hyodysenteriae* (product type 3) and for fly control (product type 18) in pig stables. The formulation containing cyanamide is directly applied to the liquid manure stored underneath the slatted floor. For these uses an environmental risk assessment was conducted. The estimated PEC/PNEC values for surface water, sediment and soil are below the trigger value of 1, the predicted concentrations of cyanamide in groundwater below the threshold criteria of 0.1 µg/L for all scenarios. Thus, the use of cyanamide as active substance in animal housings (pig stables) indicates no unacceptable risk for the different environmental compartments. For details please refer to the latest version of the CAR of cyanamide [1].
However, cyanamide is also classified as carcinogen category 2, toxic for reproduction category 2 as well as STOT RE 2 (thyroid). Furthermore, it was identified as an endocrine disruptor for both human health as well as for the environment. The ED assessment was discussed at EDEG14 in June 2019 and agreed between member states at the HH and ENV WG IV in 2019.
The identification in the environmental sector was mainly based on available mammalian data and was supplemented by data on environmental non-target organisms from scientific literature. In line with the ECHA/EFSA ED guidance[7] and as agreed between member states at the ENV WG meeting no further data on environmental organisms were required. It is stated in the guidance, that "(…) it is recommended to strive for a conclusion on the ED properties with regard to humans and in parallel, using the same database, to strive for a conclusion on mammals as non-target organisms. Only where, based on this assessment, the criteria are not met for mammals as non-target organisms, would the assessment need to proceed to the other taxonomic groups, which may require the generation of additional data. It is sufficient that the substance meets the ED criteria in one taxonomic group in order to conclude that a substance meets the ED criteria for non-target organisms.". For details of the ED-assessment for the environmental part please refer to chapter 4.3 of the latest version of the CAR [1].

## 3. Available data/information

In accordance with the mandate of the COM, the applicant provided further information on the environmental part of the risk assessment:

- Environmental risk assessment for the endocrine disrupting (ED) properties of the active substance Cyanamide (CY) (PT 3, PT 18) [19]

[7] Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

- Regulatory aspects, Requirements of Regulation (EU) No 528/2012 (BPR) regarding the performance of human health and environmental risk assessments in relation to the alleged endocrine disrupting properties of the active substance Cyanamide [20]
- Cyanamide (CY) (PT 3, PT 18), Calculation of Predicted environmental concentrations (PEC) [21]
- Eilebrecht, S., 2020, Study report, Assessment of thyroidal- and sexual-endocrine activity thresholds and potential non-endocrine molecular initiating events of cyanamide in zebrafish embryos using gene expression profiling [22]
- Literature data [23-29]:
    - Borgert, C.J., Baker, S.P., Matthews, J.C., 2013, Potency matters: Thresholds govern endocrine activity, regulatory Toxicology and Pharmacology 67, 83-88
    - Brescia, S., 2020, Thresholds of adversity and their applicability to endocrine disrupting chemicals, Critical Reviews in Toxicology, Vol. 50, No. 3, 213–218
    - Day, P., Green, R.M., Gross, M., Weltje, L., Wheeler, J.R., 2018, Endocrine Disruption: Current approaches for regulatory testing and assessment of plant protection products are fit for purpose, Toxicology Letters 296, 10-22
    - Harper, A.R., Le, A.T., Mather, T., Burgett, A., Berry, W., Summers, J.A., 2018, Design, synthesis, and ex vivo evaluation of a selective inhibitor for retinaldehyde dehydrogenase enzymes, Bioorganic & Medicinal Chemistry 26, 5766-5779
    - Lamb, J.C., Boffetta, P., Foster, W.G., Goodman, J.E., Hentz, K.L., Rhomberg, L.R., Staveley, J., Swaen, G., Van der Kraak, G., Williams, A.L., 2014, Critical comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals – 2012, Regulatory Toxicology and Pharmacology 69, 22-40
    - Rhomberg, L.R., Goodman, J.E., Haber, L.T., Dourson, M., Andersen, M.E., Klaunig, J.E., Meek, B., Price, P.S., McClellan, R.O., Cohen, S.M., 2011, Linear low-dose extrapolation for noncancer health effects is the exception, not the rule, Critical Reviews in Toxicology, 41(1): 1–19
    - Testai, E., Galli, C.L., Dekant, W., Marinovich, M., Piersma, A.H., Sharpe, R.M., 2013, A plea for risk assessment of endocrine disrupting chemicals, Toxicology 314, 51– 59

In the course of the discussion at WG level, further documents were provided by the applicant:

- AlzChem, 2021, Negligible risk of exposure under the Biocidal Product Regulation, detailed statement of the applicant [5]
- AlzChem, 2021, Requesting zero exposure does not reflect the natural exposure of cyanamide as a natural formed compound – this aspect was not considered by the eCA and the commenting MS, detailed statement of the applicant [6]
- Wittsack, M., Rosenkranz, B., 2021, Occurrence of cyanamide as natural compound and its distribution in the environment [7]
- AlzChem, 2021, Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18”,

Comments of the applicant on the document from UBA (eCA) on the 2nd e-consultation [11]

- AlzChem, 2021, Update on monitoring study "Sampling and analysis of pig manure for cyanamide residues after stable disinfection with Alzogur under GLP conditions", detailed statement of the applicant [12]
- Fraunhofer, 2021, Study Plan, Sampling and analysis of pig manure for cyanamide residues after stable disinfection with Alzogur under GLP conditions [13]
- AlzChem, 2021, All information regarding the Cyanamide degradation in the liquid pig manure must be considered for the discussions in the forthcoming TOX and ENV WG meetings regarding ED risk assessment for Cyanamide – Summary [14]
- AlzChem, 2021, The Biocide Project by UBA confirms that cyanamide degrades 10-times faster in liquid pig manure than assumed in the CAR, detailed statement of the applicant [15]
- Fraunhofer IME, 2021, Status Overview, Studies on Cyanamide [16]
- Fraunhofer IME, 2021, Study Plan, Validation of the analytical method for determination of Cyanamide in pig manure according to SANTE 2020/12830 rev.1 (24/02/21) [17]

In addition to these documents, the applicant also participated in the above-mentioned e-consultations and discussions at the WG meetings. The comments made there can be found in the respective RCOM-tables and minutes [4, 8, 10, 18].
The information provided by the applicant was evaluated by the eCA and supplemented accordingly by own research [30-51] in order to be able to answer the questions of the mandate (see above).

## 4. General questions – Risk Assessment EDs

To be finally able to answer all questions of the COM's mandate several general aspects with regard to the risk assessment of cyanamide as an endocrine disruptor had to be considered which are summarized in this chapter. These aspects were part of the two e-consultations and were also discussed at the ENV WG-meetings II/2021 and III/2021 (see above).

### 4.1 Threshold / safe concentration limits NTOs[8]

The derivation of a threshold for EDs is a controversial issue, which has been discussed in scientific literature for quite some time [23-51]. The applicant provided a variety of publications as well as a study in zebrafish to support that safe thresholds can be derived for EDs in general and cyanamide in particular as for any other mode of action [22-29]. However, there are also at least as many publications published that discuss the opposite or at least question whether safe thresholds can be derived for EDs with sufficient certainty for the time being [30-51]. For example, in direct response to the publication by Susy Brescia (2020) [24] submitted by the applicant, an article was published by the Endocrine Society's Endocrine-Disrupting Chemicals Advisory Group that clearly contradicts the statements of the paper [35].
According to scientific literature the assessment of endocrine disruptors is associated with a range of uncertainties such as:

- occurrence of non-monotonic dose-response relationships and low-dose effects,

[8] NTO: non-target organism

- occurrence of possible time-delayed effects (induction early in life, but appearance of the adverse effect later in life),
- limited knowledge of the function of endocrine systems in environmental organisms (especially invertebrates),
- different sensitivity of different life stages (lack metabolism, lack/immaturity of endocrine signaling pathways, fluctuations in hormone levels during development/puberty/menopause, etc.),
- limited knowledge of possible species-specific sensitivity differences/uncertainty related to inter-species and intra-species extrapolation,
- availability of only few internationally accepted and validated test methods for a limited number of taxa, with limited number of endpoints and coverage of endocrine mechanisms of action (E, A, T, S),
- possible binding of a substance above a certain dose level to different receptors, potentially leading to different adverse effects at different dose levels,
- existence of additional uncertainties in the field of ecotoxicology (e.g. uncertainties introduced by temperature which for some species is an important factor influencing sexual development and sex-reversal).

Additionally, the complexity of the endocrine system with a potential crosstalk between the different axes/pathways is an important aspect to consider in this context [30-32, 34-40, 42-44, 46, 49-51].
In the eCA's opinion, further research as well as an intensive exchange between science, regulators and industry is necessary before it can be decided whether safe thresholds can indeed be derived for EDs in general and for EDs for environmental non-target organisms in particular in order to reach a well-founded decision. It needs to be considered that this question is relevant for other legislation as well, such as plant protection products and REACH. In the view of the eCA the uncertainties mentioned above cannot be dismissed out of hand and, therefore, the precautionary principle as mentioned in Article 1 of the BPR should be followed [30, 41] -i.e. based on the above-mentioned uncertainties no safe thresholds can be derived for endocrine disrupters for environmental non-target organisms - at this point in time - that cover the diversity of organisms present in the environment.
This aspect was also part of the first e-consultation and was discussed at WG II/2021 [3, 4, 8]. There, it was agreed that no thresholds/safe concentration limits can be derived with regard to environmental non-target organisms for cyanamide at this point in time due to the above-mentioned uncertainties [8]. Please refer also to point 7 below.

**4.2 Further Tests in environmental non-target organisms**

As indicated in the documents and comments provided by the applicant [4, 19, 20], the applicant has a different view on the possibility to derive a threshold for environmental NTOs and proposed a series of further studies on environmental non-target organisms, i.e. an Amphibian Metamorphosis Assay (AMA) according to OECD 231 and a Fish Short-term Reproduction Assay (FSTRA) according to OECD 229, in order to perform a quantitative risk assessment.
In the eCA's point of view these studies are not necessary and should be prevented for animal-welfare reasons as a quantitative risk assessment is not possible when no safe thresholds (e.g. PNECs) can be derived [3].
This aspect was also part of the first e-consultation and was discussed at WG II/2021 [3, 4,

8] in which the member states agreed with the eCA's position and argued, that these studies are also not necessary as cyanamide is already identified as an ED according to the EFSA/ECHA ED guidance based on the mammalian data set. The member states also questioned whether the mentioned studies would really help to clarify a threshold for cyanamide. Hence, it was agreed that the tests proposed by the applicant should be prevented for animal-welfare reasons [8]. Please refer also to point 7 below.

**4.3 Qualitative vs quantitative risk assessment**

As no safe thresholds can be derived for EDs with regard to environmental non-target organisms for cyanamide at this point in time due to the above-mentioned uncertainties, no PNEC can be determined and no quantitative risk assessment in the strict sense, i.e. by comparing PEC and PNEC, can be conducted. Also, a qualitative risk assessment, i.e. the likelihood that an effect will occur under the expected conditions of exposure, was considered to be not appropriate since the likelihood cannot be estimated regarding the high uncertainties for the effect side as described above. Hence, the only option would be to conduct a qualitative assessment of the exposure situation, which is also in line with the provisions of BPR (please refer to Annex VI "Common principles for the evaluation of dossiers for biocidal products", Assessment, Effect on the environment, principles 42-47).

The question on whether a quantitative or qualitative risk assessment is possible for cyanamide was also part of the e-consultations and was discussed at WG II/2021 and WG III/2021 [3, 4, 8, 9, 10, 18]. During the first e-consultation the member states were divided on this question. While one part was of the opinion that a qualitative assessment with particular focus on whether the exposure can be considered negligible could be possible (like for non-threshold carcinogen/mutagen substances or PBTs), another part questioned whether a qualitative assessment is possible [4].

However, taking into consideration all of the available information- including those data subsequently submitted by the applicant in course of the procedure [5-7, 11- 17], it was finally agreed at ENV WG III/2021 that neither a quantitative nor a qualitative ***risk assessment*** is possible for cyanamide at this point in time with regard to environmental non-target organisms. The only option is a qualitative ***assessment of the exposure situation*** [18]. Please refer also to point 7 below.

**4.3.1 Negligible exposure**

With regard to a qualitative assessment, in its mandate COM specifically refers to the examination of whether the exposure can be considered "negligible". However, it needs to be considered in this context, that the term "negligible" is not yet defined within the frame of the BPR, whereas the term "negligible risk from exposure" is mentioned twice in the BPR:

- **Recitals (12)**

"*With a view to achieving a high level of protection of human health, animal health and the environment, active substances with the worst hazard profiles should not be approved for use in biocidal products except in specific situations. These should include situations when approval is justified because of the* ***negligible risk from exposure*** *to the substance, human health, animal health or environmental reasons or the disproportionate negative impact for society of non-approval. When deciding if such active substances may be approved, the availability of suitable and sufficient alternative substances or technologies should also be taken into account.*"

- **Article 5(2)(a)**

"*Without prejudice to Article 4(1), active substances referred to in paragraph 1 of this Article may be approved if it is shown that at least one of the following conditions is met:*

(a) *the **risk** to humans, animals or the environment **from exposure** to the active substance in a biocidal product, under realistic worst case conditions of use, **is negligible**, in particular where the product is used in **closed systems** or under other conditions which aim at **excluding contact** with humans **and release** into the environment*".

In the eCA's point of view, based on the wording of the legal text in combination with the fact that for environmental EDs no thresholds can be derived, "negligible exposure" can only be understood as "no exposure" of the environment, i.e. no releases from the biocidal uses into environment.
This aspect was also part of the first e-consultation [3], where most member states supported the interpretation of the eCA [4]. One member state specified that in their view "negligible exposure means exposure of no concern rather than zero exposure", but agreed "that the risk to humans, animals or the environment from exposure to the active substance should be negligible where the product is used in closed systems or under other conditions where there is no release to the environment". Another member state could also not agree with the eCAs argumentation, but with the conclusion that "the substance shall not be released into the environment".
The applicant did not share these views and provided an own interpretation of the legal text [5].
However, as the interpretation of the legal text is outside the remit of the WG, this general question was not discussed in detail at the WG and no final conclusion was reached [8]. Nevertheless, the comments of member states in the working group indicate that the majority interpret the legal text as no release from biocidal uses into environment.

### 4.3.2 Intended uses of cyanamide & qualitative assessment of the exposure situation

Cyanamide is intended to be used by professional users and only in the production of fattening pigs either against dysenteria bacteria (PT 3) or for fly control (PT 18). The product is applied once to twice a year after the end of a fattening cycle, i.e. after the pigs have been housed out [1].
Cyanamide is applied via the slatted floor to the liquid manure stored underneath in piggeries. The liquid manure is stored in slurry canals. These slurry canals are dimensioned for collecting the liquid manure produced during a whole fattening cycle or for even larger quantities. The slurry canals are only emptied after the end of a fattening cycle after the pigs have been housed out. Consequently, the liquid manure remains in the slurry canals during the complete fattening cycle. According to label instruction, before the application of cyanamide, the liquid manure needs to be removed from the slurry canal as completely as possible. The liquid manure which is pumped out of the slurry canals is normally stored in a separate slurry tank outside the piggery. It is stored there until it is needed for crop manuring or - in rare cases - it is applied to agricultural land immediately after being pumped out of the slurry canals.
Releases of cyanamide into the environment were assessed in an environmental risk assessment by applying emission models to soil after manure applications on grassland and arable land followed by emission models to groundwater and surface water [1].

The following PEC-values were calculated:

Table 1: Calculated PEC-Values.

| **Compartment** | **PEC*** *(CAR, 2019)* | **PEC** *(applicant, January 2021)* |
|---|---|---|
| Surface water | 0.0351 – 2.27 µg/L | 0.00727 – 0.0146 µg/L |
| Sediment | 0.031 – 1.99 µg/$kg_{wwt}$ | 0.000168 – 0.000706 µg/$kg_{wwt}$ |
| Soil | 19.0 – 40.5 µg/$kg_{wwt}$ | 40 µg/$kg_{wwt}$ |

* The exposure assessment was evaluated and agreed on EU level with the CAR in 2016

For the detailed exposure assessment, please refer to the latest version of the Competent Authority report [1] as well as the documents provided by the applicant [21].
Based on the above-mentioned interpretation of the legal text regarding "negligible risk from exposure", the eCA is of the opinion that the exposure of the environment from the intended uses of cyanamide in PT3 and PT 18 cannot be considered "negligible", i.e. releases from the biocidal uses into the environment cannot be excluded.
The applicant provided a refined exposure assessment based on the guidance and models available for the exposure assessment of the intended uses of cyanamide in 2021 [21]. However, although the refined PEC-values are considerably lower than the agreed PEC values from the latest version of the CAR for surface water, sediment and soil (see table 1), an exposure of the environment, especially of the soil compartment, can still not be considered as negligible in our point of view, i.e. releases from biocidal uses into the environment cannot be excluded.
This aspect was also part of the e-consultations and was also discussed at WG II/2021 and WG III/2021 [3, 4, 8, 7, 9, 10, 18]. Taking into consideration all of the available information including those data subsequently submitted by the applicant in course of the procedure [5-7, 11- 17], it was finally agreed at WG III/2021 that -based on the available information- exposure of the environment from biocidal uses cannot be excluded [18]. Please refer also to point 7 below.

#### 4.3.2.1 Natural background concentration

In the context of the discussion on the question whether the releases into environment from the biocidal uses of cyanamide can be considered negligible, the applicant provided a document on the natural occurrence of cyanamide in a variety of plant species (Wittsack & Rosenkranz, 2021, [7]).[9]
According to this document, cyanamide occurs naturally in the several plant species such as *Vicia villosa, Vicia cracca, Robinia pseudoacacia.* While *Vicia cracca* is a naturally occurring plant with wide distribution, *Vicia villosa* and *Robinia pseudoacacia* are economically relevant as they are used as fodder plants, for nitrogen accumulation in soil or for bioenergy production. Based on the distribution and the cyanamide concentrations in these plant species the applicant provided a quantitative estimation of the distribution of biosynthesised cyanamide in the environment.
For this reason, he first provided a number of studies on the concentrations of cyanamide in various plant tissues. The range of the values is shown in the table 2 [7].

[9] It should be noted that the document contains an error in chapter 3.1.2. In this chapter the calculation of PECsoil_natural for cyanamide biosynthesized by *Vicia villosa* was done erroneously due to sign flaw and 0.3765 mg/kg instead of the correct value of 376.5 mg/kg was used for the PECsoil_natural calculations. The PEC values were recalculated accordingly by the applicant and can be found in Alzchem (2021) [6].

Table 2: Range of cyanamide in plant tissues.

| Plant species | Concentration cyanamide |
|---|---|
| *Vicia villosa* | 130 – 629 µg/g |
| *Robinia pseudoaccacia* | 46 – 644.5 mg/kg |
| *Vicia cracca* | 1893 – 3579 µg/g |

Based on these data on the naturally formed quantity of cyanamide as well as on the above-ground biomass production of *Vicia villosa,* the applicant calculated PEC-values in soil for the naturally occurring exposure of cyanamide based on "best case"-assumptions. This natural exposure was then compared with the soil exposure calculated for the biocidal uses. Based on these calculations the applicant concluded that the environmental exposure to biogenous cyanamide is much higher than the environmental exposure caused by biocidal uses of cyanamide (table 3, [6]).

Table 3: Comparison $PEC_{soil}$ natural biosynthesized cyanamide and $PEC_{soil}$ biocidal use.

| Concentration of biogenous cyanamide in leaves of *Vicia villosa* | $PEC_{soil}$, natural for cyanamide biosynthesised by *Vicia villosa* | $PEC_{soil}$, biocide for cyanamide from biocidal use |
|---|---|---|
| 376.5 µg/g (130 µg/g to 629 µg/g) | 5.52 to 27.6 $mg/kg_{dw}$ | max. of 0.045 $mg/kg_{dw}$ |

**Assessment of the eCA**

The eCA acknowledges the fact that cyanamide occurs naturally in plants as the applicant provided a variety of publications from scientific literature on that matter. However, the conclusions drawn by the applicant based on these data are solely based on theoretical considerations and rough estimations. No (monitoring) data are available to confirm these assumptions, so that it remains unclear to eCA whether cyanamide present in plant tissues leads indeed to a relevant background concentration in the environment and if so, to what concentrations the content in plant material really leads to and thus, what background concentration would be realistic in which environmental compartment. In addition, there will certainly be areas in the environment with no background concentration of cyanamide - namely when the corresponding plants do not occur there.

Therefore, the eCA intended not to follow the approach proposed by the applicant because of the numerous uncertainties associated with this approach. In addition, any decision taken as part of the evaluation of cyanamide in accordance with the mandate by the COM will set a precedent that will have implications for all other active substances identified as EDs within the frame of the BPR.

Hence, in the eCA's point of view, even considering that cyanamide is naturally occurring in certain plant species, the risk from exposure from the biocidal uses of cyanamide cannot be considered negligible as it cannot be proven beyond doubt whether and, if so, which background concentrations of cyanamide are indeed present in the environment.

This aspect was also part of an e-consultation and was discussed at WG III/2021 [9, 10, 11, 18]. Within the e-consultation, the commenting member states followed the assessment of the eCA. Most member states acknowledged that cyanamide is a naturally occurring substance in plants, and also the importance of considering background concentrations. However, all member states agreed on the uncertainties associated with the applicant's

proposal (e.g. unknown transfer of cyanamide from leaves to soil, no monitoring data on cyanamide in soil, distribution of the respective plants across Europe etc.) making it impossible to agree on the proposed procedure. One member state also commented that "as long as no guidance or at least no agreement is available regarding the risk assessment of substances showing ED properties, such approach is not applicable and should not be followed in order to avoid a precedent". Hence, at ENV WG III/2021 it was agreed that the data submitted by the applicant does not allow to assess reliably the environmental background levels and distribution of cyanamide in the environment [18].
Furthermore, the data provided by the applicant on the natural occurrence of cyanamide did not change the member states's view on the exposure situation- i.e. the member states agreed within the e-consultation that the risk from exposure from the biocidal use of cyanamide cannot be considered negligible even if the substance occurs naturally in certain plant species, especially given that it is unclear how cyanamide present in plant tissues could lead to a calculated relevant background concentration in the environment. In their opinion, the legal text of the BPR (Article 5(2)(a)), gives two clear examples of when negligible risk from exposure can (potentially) be considered, i.e. biocidal use in closed systems or uses under conditions which aim at excluding contact with humans and release into the environment. These are well defined and very restricted situations and it is clear that spreading of manure does not match with these descriptions. Furthermore, one member state added that without a validated methodology at the European level to carry out an ED risk assessment, for a substance clearly identified as ED, the only potential exception is that there is no additional environmental emission (in addition to the existing background concentration for natural substances).
A similar decision was then also taken at the ENV WGIII/2021-meeting: The WG agreed that with the available information exposure to the environment from biocidal uses cannot be excluded [18]. Please refer also to point 7 below.

### 4.3.3 Further studies on degradation

The applicant also intended to provide further data to demonstrate that under realistic conditions quite lower emissions of cyanamide to soil and water occur. Therefore, the applicant proposed to conduct a new biodegradation study reflecting realistic worst-case conditions of the application of cyanamide to liquid manure. In addition, the applicant intended to generate monitoring data from field applications in order to show that the calculated PEC values are still significantly overestimating the environmental exposure from the biocidal uses [19, 20, 21].
In the light of data available to the eCA by the time the document for the first e-consultation was written, the eCA was quite hesitant about requesting the proposed studies, as it remained unclear whether these studies would really provide an "added value" considering all the available information in the ED-context for cyanamide. Moreover, the eCA was questioning if a new degradation study would show significant different results, since the study already available reflects very well the test conditions currently under discussion at OECD WNT for adoption of a new test guideline. The initial aerobic conditions in the pumped-out slurry canals at the end of a fattening cycle, which the applicant claims to be beneficial for degradation of cyanamide, will not be maintained for long. With the beginning of the new fattening cycle, again, slurry will enter the slurry canals and thus anaerobic conditions will quickly return. Therefore, a deviation of the standard test procedure with anaerobic conditions seems not reasonable.
Regarding monitoring data, the eCA was (and is still) of the opinion that it should be considered that representative data must be collected under realistic conditions. Beside this

logistic aspect, also analytical limitations should be kept in mind (e.g. limits of detection). Thus, a statement on negligible exposure is also always linked to statements about the analytical boundaries. As no safe threshold values can be determined for the environment, no analytical method will be sufficiently sensitive to demonstrate that exposure is negligible. Therefore, since it cannot be clearly shown that there is no release from biocidal the uses into the environment, the eCA is of the opinion that the environmental exposure cannot be considered as negligible (= "no exposure" of the environment).
These aspects were also part of the first e-consultation and discussed for the first time at ENV WG II/2021 [3, 4, 8]. During the e-consultation, the commenting member states followed the assessment of the eCA and the WG II/2021 finally agreed that further testing with regard to the degradation of cyanamide in liquid manure and monitoring data from field applications as proposed by the applicant are not necessary (please refer also to point 7 below). The member states considered in their decision especially the applicant's statements that the additional monitoring data is intended only to show that degradation is faster than indicated by the data currently depicted in the CAR, and not to determine environmental background concentrations. The applicant further explained that, since cyanamide degrades very fast in soil, environmental background concentrations will always be very low in any case. The member states agreed that even if the exposure is considerably lowered by a new degradation study it would neither change the outcome of the evaluation nor the legal consequences on the approval of the active substance as the assessment of ED properties is only hazard based and not exposure based. Also monitoring data have no added value because no safe threshold values can be determined for the environment and no analytical method will be sufficiently sensitive to demonstrate that exposure is negligible.
Despite the clear vote of the member state at WG II/2021, the applicant submitted further documents on that matter [12- 17]. However, these documents as well as the arguments put forward by the applicant at the ENV WG III/2021- meeting did not change the group's decision- i.e. the WG didn´t see the need to perform new studies on degradation or monitoring. The already agreed CAR contains degradation studies which can enable qualitative assessment for the purpose of the COM Mandate [18]. Also, the member states's position on the exposure situation was not changed (see above). Please refer also point 7 below.

**Please note:**
In the follow-up of the ENV WG meeting III/2021, in order to get more background information on the degradation study by Kreuzig et al. (2010) cited by the applicant [15], the eCA got in touch with a colleague who was involved in that R&D-project. According to her statement, the research report under discussion is part of preliminary tests that should indeed result in the development of a draft test guideline. However, there were some weaknesses in the concept, so that a new approach was to be developed from 2010 onwards under new project management. The most critical point was that not slurry but excrement was used for testing. In the test set-up, as used for the trials from the 2010 report, some kind of artificial slurry / a slurry by choice was prepared for the study as urine and faeces were mixed. But the properties of faeces and the slurry stored in tank systems under the animal housing do not have much in common, e.g. the microbial community and the redox potential are quite different. The present report was therefore only one step on a long road to a draft test guideline, so that no regulatory consequences should be derived from it.

## 5. Public consultations

COM also asked the eCA to consider in its assessment the data submitted during the two public consultations on cyanamide organised by ECHA from 22 February to 21 April 2016 and from 26 June 2019 to 25 August 2019, including those submitted by the applicant.
Although the arguments provided during the two public consultations seem to be reasonable, the eCA is – as the BPC [52, 53] - not able to verify the information provided, to conclude whether other active substances or non-chemical alternatives can be used as an alternative for cyanamide for the intended uses in PT 3 and PT 18 or to decide whether the provided information justify an approval of cyanamide and respective products according to Article 19(5) of the BPR.
For details on the submitted comments please refer to: https://echa.europa.eu/public-consultation-on-potential-candidates-for-substitution.
This aspect was also part of the first e-consultation [3, 4]. Most member states did not comment on this aspect. However, two member states indicated that cyanamide seem to be not necessary in the respective member states. At ENV WG II/2021 the views of the member state on this aspect were collected as well [8], but as this point is outside the remit of the WG no final conclusion was reached. However, one member state explained that, in their view, stable hygiene could be seen as an alternative to the use of cyanamide. Another member state reiterated that cyanamide is not used in the member states, so that alternatives are probably available.

## 6. Acceptability of the risk

Based on the available information, it can be concluded that, based on the environmental risk assessment provided in the last version of the CAR [1], no unacceptable risks to the environment from the intended uses of cyanamide have been identified. However, the COM's mandate requires also an assessment of the acceptability of the risk in relation to the ED properties of cyanamide [2]. Based on the discussions with the other member states at ENV WG-level the following can be summarised:
A risk assessment in the strict sense, i.e. comparing "PEC/PNEC" or "exposure and effect", is not possible for cyanamide at this point in time. The member states agreed that currently no safe thresholds / safe concentrations limits can be derived for cyanamide as an identified ED due to a variety of uncertainties associated with this approach (see 4.1). They also agreed that neither a quantitative nor a qualitative risk assessment is currently possible for cyanamide at this point in time with regard to environmental non-target organisms (see 4.3). The only option is an assessment of the exposure situation with particular focus on whether the exposure can be considered negligible, like for non-threshold carcinogen/mutagen substances or PBTs. However, it needs to be considered in this context, that the term "negligible" is not yet defined within the frame of the BPR. Although the final interpretation of the term 'negligble' is outside the scope of the WG, the member states agreed that the term "negligible risk form exposure" as used in the BPR should be finally understood as "no releases into the environment" (see 4.3.1).
There is no further data (e.g. ecotoxicological effects, degradation, monitoring) that the applicant could provide to help further clarify the issues of the mandate (see 4.2, 4.3.3).
The conclusions of the qualitative assessment of the exposure situation are: i) the data submitted by the applicant on the natural occurrence of cyanamide does not allow to assess reliably the environmental background levels and distribution of cyanamide in the environment and ii) releases to the environment from the intended biocidal uses of

cyanamide cannot be excluded (see 4.3.2).
Therefore, a ***hazard*** for the environment from the ED-properties of cyanamide cannot be excluded either. This would be in line with paragraph (5) of the COM's mandate: "(…) However, as for any active substance, an approval is only possible if it is demonstrated that at least a biocidal product containing this active substance may be expected to have no immediate or delayed unacceptable effects to the human health and the environment."- i.e. for cyanamide unacceptable effects due to its ED properties cannot completely ruled out as an exposure of the environment from the biocidal uses cannot be excluded.

In this context, the ENV WG III/2021 concluded the following: "The WG agreed that, given the uncertainties (*of the assessment, supplement of the eCA, see above*) and lack of methodology, it is currently not possible to determine whether the risk is acceptable. The WG agreed that currently it is not possible to demonstrate that the risk is acceptable. Nevertheless, the WG agrees that, since exposure cannot be excluded, also risk coming from this exposure cannot be excluded." [18].

## 7. Overall Summary & conclusion

Most of the general questions listed above were also discussed within the frame of the ENV WG [8, 18]. The position of the WG members is summarised in the table below:

| # | Question | WG conclusion | Reference |
|---|---|---|---|
| 1 | Does the WG agree that currently no thresholds/safe concentration limits can be derived for EDs with regard to environmental non-target organisms for cyanamide? | The WG agreed that currently no thresholds/safe concentration limits can be derived with regard to environmental non-target organisms for cyanamide. | ENV WG II/2021 |
| 2 | Does the WG agree that no further (ecotox-) tests for cyanamide are necessary? | The WG agreed that no further tests on ED for NTO[10] should be requested at this point in time. The lack of guidance to derive a threshold makes it impossible for the MSCA[11]s to indicate which test would be required. | ENV WG II/2021 |
| 3a | Does the WG agree that the data submitted by the applicant does not allow to assess reliably the environmental background levels and distribution of cyanamide? | The WG agreed that the data submitted by the applicant does not allow to assess reliably the environmental background levels and distribution of cyanamide. | ENV WG III/2021 |
| 3b | Does the WG agree that as a consequence the data submitted by the applicant is not sufficient to show the | The WG agreed that with the available information exposure to the environment from biocidal uses cannot be excluded. | ENV WG III/2021 |

[10] NTO: non-target organisms
[11] MSCA: member states competent authority

| | | | |
|---|---|---|---|
| | biocidal contribution relative to the existing background concentrations can be considered negligible? | | |
| 4 | Does the WG agree that since exposure from the biocidal use of cyanamide cannot be excluded, neither can the risk, even though the substance might occur naturally due to certain plant species? | The WG agreed that, since exposure cannot be excluded, also risk coming from this exposure cannot be excluded. | ENV WG III/2021 |
| 5 | Does the WG agree that a quantitative risk assessment is not possible for EDs with regard to non-target organisms for cyanamide at this point in time? | The WG agreed that a quantitative risk assessment is not possible for ED with regard to non-target organisms for cyanamide at this point in time. | ENV WG II/2021 |
| 6 | Does the WG agree that a qualitative risk assessment is currently not possible for cyanamide? | The WG agreed that the current environmental background concentrations are unclear. Since there is unclear background concentration and the absence of a safe level no qualitative risk assessment can be carried out. Nevertheless, a qualitative assessment for the exposure is possible. | ENV WG II/ 2021; ENV WG III/2021 |
| 7 | Does the WG agree that the available data does not show that the risk from exposure is negligible? | The WG agreed that, since exposure from biocidal uses cannot be excluded, also risk coming from this exposure cannot be excluded. | ENV WG II/ 2021; ENV WG III/2021 |
| 8 | Does the WG see a need for further testing with regard to the degradation of cyanamide in liquid manure and/or for monitoring data from field applications as proposed by the applicant? | The WG didn´t see the need to perform new studies on degradation or monitoring. The already agreed CAR contains degradation studies which can enable qualitative assessment for the purpose of the COM Mandate. | ENV WG II/ 2021; ENV WG III/2021 |
| 9a | Does the WG agree that it is currently impossible to decide whether the risk is acceptable or not? | The WG agreed that, given the uncertainties *(of the assessment, addition of the eCA)* and lack of methodology, it is currently not possible to determine whether the risk is acceptable. | ENV WG III/2021 |
| 9b | If so, does the WG agree that | The WG agreed that currently it | ENV WG III/2021 |

| | | | |
|---|---|---|---|
| | currently it is not possible to demonstrate that the risk is acceptable (as requested by the mandate)? | is not possible to demonstrate that the risk is acceptable. Nevertheless, the WG agreed that, since exposure cannot be excluded, also risk coming from this exposure cannot be excluded. | |

Based on the discussions with the member states in the context of the ENV WG, the questions of the COM's mandate can be answered as follows:

**a) Based on available information, clarify whether a safe level (threshold) can be determined for the ED properties of cyanamide for the environment, and if such threshold can be established, what would be this level.**

*Currently no thresholds/safe concentration limits with regard to environmental non-target organisms can be derived for the ED properties of cyanamide due to a variety of uncertainties associated with such an approach.*

**b) Clarify the level of the risks to the environment by:**

**1. Assessing the level of risk for the environment, either by a quantitative assessment or by a qualitative assessment with particular focus on whether the exposure can be considered negligible, like for non-threshold carcinogen/mutagen substances or PBTs.**

*A risk assessment in the strict sense, i.e. comparing "PEC/PNEC" or "exposure and effect", is not possible for cyanamide at this point in time. Neither a quantitative nor a qualitative risk assessment can be conducted as no safe threshold can be derived with which the exposure can be compared to. The only option is an assessment of the exposure situation with particular focus on whether the exposure can be considered negligible or not. However, it needs to be considered in this context, that the term "negligible" is not yet defined within the frame of the BPR. Although the final interpretation of the term 'negligble' is outside the scope of the WG, the* member states *agreed that the term "negligible risk from exposure" as used in the BPR should be finally understood as "no releases from biocidal uses into the environment".*
*The conclusions of the qualitative assessment of the exposure situation are: i) the data submitted by the applicant on the natural occurrence of cyanamide in certain plant species does not allow to assess reliably the environmental background levels and distribution of cyanamide in the environment and ii) releases to the environment from the intended uses of cyanamide cannot be excluded.*

**2. Providing an opinion whether the risks can be considered acceptable or not.**

*Regarding the acceptability of the risk no final conclusion is possible. It was agreed*

*between the* member states *that, given the uncertainties of the assessment and lack of methodology, it is currently not possible to determine whether the risk is acceptable. The* member states *also agreed that currently it is not possible to demonstrate that the risk is acceptable. Nevertheless, the* member states *agreed that, since exposure cannot be excluded, also the risk coming from this exposure cannot be excluded.*

Please consider that any decision taken here will set a precedent for the future handling of endocrine disruptors in the frame of the BPR.

**References**

(1) Latest version of the CAR for cyanamide (product types 03 and 18) including ED assessment, eCA: Germany, November 2019; Path on S-CIRCABC: /Library/ca-reports/ca-reports_programme/a-d/Cyanamide DE/ED assessment PT3 and 18/BPC
(2) Mandate requesting ECHA opinions under Article 75(1)(g) of the BPR "Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18”
(3) DE-UBA, 2021 a, Opinion of the German Environment Agency on the Mandate of the European Commission requesting ECHA opinions under Article 75(1)g of the BPR, "Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18”
(4) DE-UBA, 2021 b, Summary and conclusion of the e-consultation on the quantitative ED assessment of Cyanamide following Article 75(1)(g), environmental part, RCOM-table first e-consultation
(5) AlzChem, 2021 a, Negligible risk of exposure under the Biocidal Product Regulation, detailed statement of the applicant on the document of the first e-consultation
(6) AlzChem, 2021 b, Requesting zero exposure does not reflect the natural exposure of cyanamide as a natural formed compound – this aspect was not considered by the eCA and the commenting MS, detailed statement of the applicant after the first e-consultation
(7) Wittsack, M., Rosenkranz, B., 2021, Occurrence of cyanamide as natural compound and its distribution in the environment
(8) ECHA, 2021 a, WG Environment, Minutes WGII2021_ENV_6-2, Draft ED risk assessment – Cyanamide, PT 3 and PT 18
(9) DE-UBA, 2021 c, 2nd e-consultation of the German Environment Agency on the Mandate of the European Commission requesting ECHA opinions under Article 75(1)g of the BPR, "Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18”
(10) DE-UBA, 2021 d, Summary and conclusion of the second e-consultation on the quantitative ED assessment of Cyanamide following Article 75(1)(g), environmental part, RCOM-table second e-consultation
(11) AlzChem, 2021 c, Evaluation of the level of the risks for human health and for the environment of cyanamide used in biocidal products of product types 3 and 18”, Comments of the applicant on the document from UBA (eCA) on the 2nd e-consultation
(12) AlzChem, 2021 d, Update on monitoring study “Sampling and analysis of pig manure for cyanamide residues after stable disinfection with Alzogur under GLP conditions”, detailed statement of the applicant
(13) Fraunhofer IME, 2021 a, Sampling and analysis of pig manure for cyanamide residues after stable disinfection with Alzogur under GLP conditions, Study Plan
(14) AlzChem, 2021 e, All information regarding the Cyanamide degradation in the liquid pig manure must be considered for the discussions in the forthcoming TOX and ENV WG meetings regarding ED risk assessment for Cyanamide – Summary
(15) AlzChem, 2021 f, The Biocide Project by UBA confirms that cyanamide degrades 10-times faster in liquid pig manure than assumed in the CAR, detailed statement of the applicant
(16) Fraunhofer IME b, 2021, Studies on Cyanamide, Status Overview

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