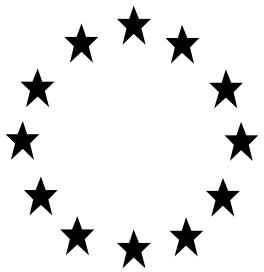
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



Cyanamide

Product-types 03 and 18
(Use in Veterinary Hygiene Biocidal Products and use in Insecticides, Acaricides and Products to control other Athropods)

July 2016

eCA: Germany

CONTENTS

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 03 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 AG, hereafter referred to as the applicant, in product-types 03 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 AG 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 AG 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.

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 03 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.

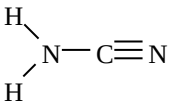
However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

[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. 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) 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: List of Intended Uses.

2.1.3. Classification and Labelling

Classification and Labelling of cyanamide

Evaluation of the submitted data under Directive 98/8/EC and 91/414/EEC resulted in the following proposal for classification and labelling:

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

	Classification	Wording
Hazard classes, Hazard categories	Acute Tox. 3(*) Acute Tox. 4(*) Eye Irrit. 2 Skin Irrit. 2 Skin Sens. 1	
Hazard statements	H301 H312 H319 H315 H317	Toxic if swallowed. Harmful in contact with skin. Causes serious eye irritation. Causes skin irritation. May cause an allergic skin reaction.

(*) Minimum classification

The RAC in its opinion from adopted 5th June 2015 concluded on the following classification:

Carc. 2	H351
Repr. 2	H361fd
Acute Tox. 3	H301
Acute Tox. 3	H311
Skin Corr. 1	H314
Skin Sens. 1	H317
STOT RE 2	H373 (thyroid).
Aquatic Chronic 3	H412

Actually, the RAC concluded for the pure cyanamide: H 412, aquatic acute: no classification; aquatic chronic: 3 without M-factor.

Table 2-2 Current labelling of cyanamide based on Regulation (EC) No 1272/2008

	Labelling	**Wording**
Pictograms	GHS06	
Signal Word	Danger	
Hazard statements	H301 H312 H319 H315 H317	Toxic if swallowed. Harmful in contact with skin. Causes serious eye irritation. Causes skin irritation. May cause an allergic skin reaction.
Suppl. Hazard statements	-	-
Precautionary statements	None listed in Annex VI	

The RAC in its opinion adopted 5 June 2015 concluded on the following labelling:
GHS08, GHS06, GHS05, Dgr, H351, H361fd, H301, H311, H314, H317, H373 (thyroid), H412

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 the RAC opinion from 5th June 2015):

	Classification	**Wording**
Hazard classes, Hazard categories	Carc. 2 Repr. 2 Acute Tox. 3 Acute Tox. 4 Skin Corr. 1 Skin Sens. 1 STOT RE 2 Aquatic chronic 3	
Hazard statements	H351 H361fd H301 H312 H314 H317 H373 H412	Suspected of causing cancer. Suspected of damaging fertility. Suspected of damaging the unborn child. Toxic if swallowed. Harmful in contact with skin. Causes severe skin burns and eye damage. May cause an allergic skin reaction. May cause damage to organs (thyroid gland) through prolonged or repeated exposure. Harmful to aquatic life with long

		lasting effects.

Table 2-4 Proposed labelling of ALZOGUR® based on Regulation (EC) No 1272/2008 (in accordance with the RAC opinion from 5th June 2015):

	Labelling	**Wording**
Pictograms	GHS05 GHS06 GHS08	
Signal Word	Danger	
Hazard statements	H351 H361fd H301 H312 H314 H317 H373 H412	Suspected of causing cancer. Suspected of damaging fertility; Suspected of damaging the unborn child. Toxic if swallowed. Harmful in contact with skin. Causes severe skin burns and eye damage. May cause an allergic skin reaction. May cause damage to organs (thyroid gland) through prolonged or repeated exposure. Harmful to aquatic life with long lasting effects.
Suppl. Hazard statements	-	-
Precautionary statements	P201+P202 P260 P264 P280 P301+P310 P303+P361+P353 P304+P340 P305+P351+P338 P308+P310 P362+P364 P405	Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Do not breathe dust/fume/ gas/mist/vapours/spray. Wash … thoroughly after handling. Wear protective gloves/protective clothing/eye protection/face protection. IF SWALLOWED: Immediately call a POISON CENTER/ doctor/… IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/ shower. IF INHALED: Remove person to fresh air and keep comfortable for breathing. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. IF exposed or concerned: Immediately call a POISON CENTER/doctor/… Take off contaminated clothing and wash it before reuse. Store locked up.

	P501 P273 P391	Dispose of contents/container to … Avoid release to the environment. Collect spillage.

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.

A CLH-dossier was prepared for cyanamide and the RAC concluded at the 33th meeting in May 2015 for the pure cyanamide: H 412, aquatic acute: no classification; aquatic chronic: 3 without M-factor. Thus, for ALZOGUR® (content of active substance = 50.5 %) the hazard category is aquatic chronic 3 without M-factor and the hazard statement is H 412.

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, 14th 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

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 non-professionals do 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 non-professionals do not have access to such buildings. Therefore, secondary exposure of non-professionals via food and/or environment is not expected. Furthermore the biocidal product is rinsed and diluted in the liquid manure after application with a factor of about 330 or 1000 in PT 3 and PT 18 respectively. Secondary dermal exposure inside the pig stable is unlikely after application and post-application (see 8.2.2.3.2). Inhalation exposure could occur during any task performed inside the treated pig stable as long as the a.s. remains in the liquid manure canal below the slatted floor but is considered negligible after application and post-application (see 8.2.2.3.2).Therefore, even if in single cases specific persons (e.g. veterinarian, technicians) enter a building after treatment exposure will be considered negligible. However, during application and cleaning, dermal and inhalation exposure cannot be excluded therefore access of uninvolved third parties has to be avoided.
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 negligible in analogy to secondary exposure of non-professionals. 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	Overall conclusion	Included RMM
1 - application by watering can or half automated movable cart – farmers, short-term exposure	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	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.

Risk Assessment for Non-Professionals

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. Non-professionals do 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 is expected. Nevertheless, it cannot be totally excluded that persons enter the buildings for specific purposes (e.g. veterinarian, technicians). However, exposure to these persons is considered negligible since the biocidal product and residues are rinsed and diluted in the liquid manure after application and since they are under supervision of the user of the biocidal product (farmer, pest control operator). Therefore, non-professional secondary exposure is not expected. A risk characterisation for non-professional secondary exposure is not required.

Safety Measures for Non-Professionals

The product will only be used by professionals in empty pig stables. Secondary exposure of the general public is considered unlikely. Therefore, special protection measures are

not considered necessary for the general public. However, 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

$PNEC_{m\ croorganisms,\ STP}$ 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 80th 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 47th 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

Cyanamide meets the criteria to be classified as carcinogen category 2 and toxic for reproduction category 2 and, thus, shall be considered as having endocrine-disrupting properties according to article 5 (1) d) of Regulation (EU) No 528/2012. No data from ecotoxicological studies concerning endocrine disrupting effects are available for cyanamide.
Since the specific scientific criteria for the determination of endocrine-disrupting properties are not yet finalized, a detailed scientific evaluation of endocrine-disrupting properties is not possible for the time being.

2.3. Overall conclusions

The outcome of the assessment for Cyanamide in product-types 03 and 18 is specified in the BPC opinion following discussions at the 16th BPC meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA web-site.

2.4. List of endpoints

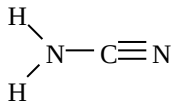
The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

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) 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) The ca. 50 % technical solution is a blue liquid.
Relative density (state purity)	$d_4^{20} = 1.23\,(21.4°C)$ (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) 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 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) (point VII.7.6.2.2)	DT50: 28.9 d at pH 5 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

Proposed classification of cyanamide based on Regulation (EC) No 1272/2008 as in the RAC opinion from 5th June 2015

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

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

	Labelling	Wording
Pictograms	GHS05 GHS06 GHS08	
Signal Word	Danger	
Hazard statements	H351 H361fd H301 H311 H314 H317 H373	Suspected of causing cancer. Suspected of damaging fertility. Suspected of damaging the unborn child. Toxic if swallowed. Toxic in contact with skin. Causes severe skin burns and eye damage. May cause an allergic skin reaction. May cause damage to organs (thyroid gland) through prolonged or repeated exposure.
Suppl. Hazard statements	-	-
Precautionary statements	(P102) P201 P202 P280	(Keep out of reach of children) Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. 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

Proposed classification of cyanamide based on Regulation (EC) No 1272/2008 as in the RAC opinion from 5th June 2015

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

Proposed 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 P391 P501	Avoid release to the environment. Collect spillage. 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 RP-HPLC-UV LOQ = 0.05 mg/kg
Air (principle of method and LOQ) (Annex IIA, point 4.2)	residue definition: cyanamide RP-HPLC-UV LOQ = 2 µg/m³
Water (principle of method and LOQ) (Annex IIA, point 4.2)	residue definition : cyanamide Ion-HPLC-UV LOQ = 0.1 µg/L (drinking water) LOQ = 0.5 µg/L (surface water) HPLC-MS/MS 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 RP-HPLC-UV LOQ = 0.05 mg/L (blood) 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*: According to Agreement of BPC-WG I-2016: exposure to corrosive concentrations: dermal absorption of 100 %; 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	
Skin sensitisation (test method used and result)	Sensitising (Magnusson & Kligman)
Respiratory sensitisation (test method used and result)	

Repeated dose toxicity

Short term

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

Subchronic

Species/ target / critical effect	
Relevant oral NOAEL / LOAEL	
Relevant dermal NOAEL / LOAEL	
Relevant inhalation NOAEL / LOAEL	

Long term

Species/ target / critical effect	
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) 3.75 mg/kg bw/d (fertility) < 1.25 mg/kg bw/d (offspring, gavage study) 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 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) 3.75 mg/kg bw/d (fertility) < 1.25 mg/kg bw/d (offspring, gavage study) 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 Rabbit: decreased foetal bw at maternally toxic dose level
Lowest relevant developmental NOAEL	Rat: 5 mg/kg bw/d 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	

Immunotoxicity

Species/ target/critical effect	

Developmental Immunotoxicity

Species/ target/critical effect	

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
$AEL_{medium-term}$	0.01 mg/kg bw	90-d & 1-yr, dog (overall NOAEL)	100
$AEL_{short-term}$			
ADI[2]	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

[2] If residues in food or feed.

MRLs

Relevant commodities	

Reference value for groundwater

According to BPR Annex VI, point 68	

Dermal absorption

Study (*in vitro*/*vivo*), species tested	
Formulation (formulation type and including concentration(s) tested, vehicle)	
Dermal absorption values used in risk assessment	

Acceptable exposure scenarios (including method of calculation)

Professional users	
Production of active substance:	Not assessed by the rapporteur under the requirements of the BPR
Formulation of biocidal product	Not assessed by the rapporteur under the requirements of the BPR
Intended uses	Liquid concentrate (512 g/l active substance)
Watering by can or half-automated movable cart in piggeries	Application solution (PT 18: 51.2 g/L active substance; PT 03: 153.6 g/L active substance)

Model: Exposure operator study (PT 03) application Frequency: 3 - 30 times a year Duration (all phases): 2-3 hours Mixing & Loading: mixing and diluting of 3 parts ALZOGUR® and 7 parts water Form of exposure: liquid, vapour (512 g/L a.s. concentrate; 153.6 g/L a.s. application solution) Application: Pouring of the diluted product on slatted pig housing floor by watering can or movable cart Form of exposure: liquid, vapour (153.6 g/L a.s. application solution) Post-application: Rinsing the slatted floor, cleaning the equipment Form of exposure: liquid, vapour (max. 153.6 g/L a.s. application solution)	Potential inhalation exposure (all phases): 0.035 mg/m3 Due to local risk assessment respiratory protective equipment (full face mask or half face mask with safety goggles) is mandatory. Actual inhalation exposure (all phases): 0.0035 mg/m3 Actual dermal exposure (all phases): 1.5 mg/person/day Acceptable with following PPE: effective chemically protective gloves, protective coverall, chemically protective boots, respiratory protective equipment (RPE) against gaseous cyanamide including a full face mask or half face mask with safety goggles
Secondary exposure	
Cleaning or any other typical work in animal housing Form of exposure: liquid, vapour Model : expert judgement	Potential inhalation exposure: negligible Potential dermal exposure: negligible
Non-professional users	The product is only use by professionals. Primary and secondary exposure is not expected.
Indirect exposure as a result of use (eg via food or feed)	Exposure of non-professionals/general public is not expected.
Combined Exposure	Combined exposure is not expected.

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 pH___5___: 4458 d pH___7___: 8444 d pH___9___: 4456 d
Photolytic / photo-oxidative degradation of active substance and resulting metabolites	Half-life: 28.9 d at pH 5 38.5 d at pH 7 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) Pond: max. 7.8% (day 21)
Distribution in water / sediment systems (active substance)	Mineralisation: River: max. 86.1% (day 28) Pond: max. 83.5% (day 28)
	DT_{50} total systems (20°C, aerobic): 2.5 d (River); 4.8 d (Pond)
	DT_{50} water (20°C, aerobic): 2.3 d (River); 4.3 d (Pond)
	DT_{50} total systems (converted to 12°C, aerobic): 4.7 d (River); 9.1 d (Pond)
	DT_{50} water (converted to 12°C, aerobic): 4.4 d (River); 8.2 d (Pond)
	Radioactivity in the water phases: River: 101.2% (day 0), decline to 0.1% (day 12), thereafter not detectable Pond: 96.7% (day 0), decline to 0.1% (day 28, end of study)
	Radioactivity in the sediment (extractable): River: max. of 4.9% (day 2), decline to 0.7% (day 28, end of study) 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): Urea (M4): 5.5 d (River); 15.2 d (Pond)
	DT_{50} water (12°C, aerobic): Urea (M4): 5.1 d (River); 14.2 d (Pond)
	Radioactivity in the water phases Urea (M4): River: max. 6.1% (day 2), decline to 0.1% (day 12), thereafter not detectable Pond: max. 11.8% (day 1), decline to 1.2% (day 21), thereafter not detectable
	Radioactivity in the sediment (extractable) Urea (M4): River: max. 0.6% (day 2), decline to 0.4% (day 6), thereafter not detectable Pond: max. 1.6% (day 1), decline to 1.4% (day 12), thereafter not detectable
	Thiourea: 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) Guanidine: max. 13.4% (day 59) Thiourea: max. 4.7% (day 71)

Route and rate of degradation in soil

Mineralization	max. 94.6% at day 14 (aerobic) 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): 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: Metabolite detected in a study on degradation in liquid manure (max. 4.7% at day 71): DT_{50lab} (20°C, aerobic, 100% field capacity): 13.6 days (sandy loam); 9.4 (sandy silt loam) DT_{50lab} (12°C, aerobic, 100% field capacity): 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: aerobic: max. 9.46% after 4 hours (day 0) anaerobic: 9.55% after 12 hours (day 0)
Metabolites - name and/or code, % of applied a.i. (range and maximum)	Laboratory studies: all metabolites <10% aerobic: dicyandiamide, max. 0.43% at day 0 anaerobic: dicyandiamide, max. 5.97% at day 30 guanylurea, max. 8.06% at day 30 guanidine, max. 3.15% at day 30 urea, max. 1.71% at day 30
Soil accumulation and plateau concentration	study not required

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} 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 21 days	immobilisation reproduction	EC_{50} = 3.2 mg a.s./l NOEC = 0.1044 mg a.s./l
Thiourea			
Daphnia magna	48 hours 21 days	immobilisation reproduction	EC_{50} = 5.6 mg /l NOEC = 1.0 mg /l
Algae			
Cyanamide			
Pseudokirchneriella subcapitata	72 hours	growth inhibition	E_rC_{50} = 14.7 mg a.s./l NOErC= 2.6 mg a.s./l
Thiourea			
Scenedesmus subspicatus	96 h	growth inhibition	E_bC_{50} = 4.4 mg /l EC_{10} = 0.6 mg /l
Aquatic plants			
Lemna gibba	7 days	growth inhibition	E_rC_{50} = 5.47 mg a.s./l NOEC = 0.43 mg a.s./l
Microorganisms			
Cyanamide			
Pseudomonas putida	19 hours	Inhibition of cell multiplication	EC_{50} = 283 mg as/L (nominal) 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 Eisenia foetida (Annex IIIA, point XIII.3.2)	LC50 > 111.6 mg a.s./kg soil dw

Long-term toxicity to springtails (Annex IIIA, point XIII.3.2)	EC10 = 1.5 mg a.s./kg soil dw (reproduction)
Acute toxicity to plants Allium cepa (Annex IIIA, point XIII.3.2)	EC50 = 0.58 mg a.s./kg soil dw
Reproductive toxicity to plants A. sativa, B. rapa (Annex IIIA, point XIII.3.2)	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 *Eisenia foetida* (Annex IIIA, point XIII.3.2)	LC_{50} ≥ 3550 mg /kg soil dw
Acute toxicity to plants *Avena sativa* (Annex IIIA, point XIII.3.2)	EC_{50} = 52.1 mg /kg soil dw
Reproductive toxicity to plants *A. sativa, B. rapa* (Annex IIIA, point XIII.3.2)	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> BCF_{fish} = 0.049 L*$kg_{wet\ fish}^{-1}$ (calc.) $BCF_{earthworm}$ = 0.84 L*$kg_{wet\ earthworm}^{-1}$ (calc.) <u>Thiourea:</u> BCF_{fish} = 0.033 and 0.0085 L*$kg_{wet\ fish}^{-1}$ (calc.) $BCF_{earthworm}$ = 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)	-	5.83×10^{-3}	5.97×10^{-3}	0.01	NOAEL = 5 $AEL_{short-term}$ = 0.05	100	424	0.24
	Tier 2b (PPE: protective gloves*, coverall*, boots, RPE)	-	5.83×10^{-4}	5.97×10^{-3}	6.55×10^{-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)	-	5.83×10^{-3}	5.97×10^{-3}	0.01	NOAEL = 1 $AEL_{medium/long-term}$ = 0.01	100	85	1.18
	Tier 2b (PPE: protective gloves*, coverall*, boots, RPE)	-	5.83×10^{-4}	5.97×10^{-3}	6.55×10^{-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

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 $AEL_{short-term}$ = 0.05 or 0.01[1]	100	> 100	< 1
Secondary exposure (pest control operator, long-term exposure)	Tier 1 (Worst Case) Chronic Scenario	-	negligible			NOAEL = 1 mg/kg b.w./d $AEL_{medium-/longterm}$ = 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 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	Publi-cation
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	Publi-cation
Doc II A 4	Beratergremium für umweltrelevante Altstoffe (BUA)	1995	Thioharnstoff, BUA-Stoffbericht 179	No	Publi-cation
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	-
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 AG
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	Publi-cation
Doc II B 8	EC	2003	Technical Guidance Document (TGD) on Risk Assessment in support of Directive 93/67/EEC on risk	No	-

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
			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		
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	Publi-cation
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	Publi-cation
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	Publi-cation
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	Publi-cation
Doc II B 8	EC	2006	Groundwater Directive (GWD), Council Directive 2006/118/EG on the protection of groundwater against pollution and deterioration	No	Publi-cation
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	Publi-cation
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	UBA
Doc II B 8	KTBL	2005	Faustzahlen für die Landwirtschaft; Kuratorium für Technik und Bauwesen in der Landwirtschaft e.V. (KTBL)	No	Publi-cation
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	Publi-cation
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	No	Publi-cation

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
			(BGBl. I S.20)		
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	Publi-cation
Doc II B 8	EC	1998	Biocidal Product Directive (BPD), Directive 98/8/EC concerning the placing of biocidal products on the market	No	Publi-cation
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	Publi-cation
Doc II B 8	EC	2011	JRC Scientific and Technical Reports: Emission Scenarios Document for Product Type 3: Veterinary hygiene biocidal products	No	Publi-cation
Doc II B 8	CA Meeting	2012	EU COM decision for non-inclusion; document: "CA-Sept12-Doc.4.6	No	Publi-cation
Doc II C 13	EC	2006	Groundwater Directive (GWD), Council Directive 2006/118/EG on the protection of groundwater against pollution and deterioration	No	Publi-cation
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	Publi-cation
Doc II C 13	ECHA	2008	Guidance on information requirements and chemical safety assessment, Part C: PBT assessment	No	Publi-cation
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 AG

Doc IIIA

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No.	Data Protection Claimed (Yes/No)	Owner

			GLP (where relevant) / (Un)Published		
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 AG
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 AG
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 AG
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 AG
A3.2.1/01	Förster, B.	2000	Calculation of Henry's law Constant for Cyanamide Scientific Consulting Company, Wendelsheim, Germany Report No.: 102-084 Not GLP, unpublished Doc. No.: 115-004	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.2/01	Eskötter, H.	1991	Determination of the Vapour Pressure of Cyanamide F 1000 in accordance with EEC-Guideline A.4 Battelle Institut, Frankfurt am Main, Germany Report No.: BE-P-77-89-A4-01 GLP, unpublished Doc. No.: 115-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.3.1/01	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	AlzChem AG

				entry into Annex I.)	
A3.3.1/02	Anonymous	2006	Safety Data sheet - Cyanamid L 500 AlzChem AG, Germany Report No.: ni Not GLP, unpublished Doc. No.: 954-015	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.3.2/01	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 Annex I.)	AlzChem AG
A3.4/01	Tognucci, A.	2000	Determination of the 1H-NMR-, IR-, UV/VIS Absorption and Mass Spectra of Cyanamide F 1000 SKW Trostberg AG, Germany Report No.: 792707 GLP, unpublished Doc. No.: 117-005	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 Battelle Institut, Frankfurt am Main, Germany Report No.: BE-P-77-89-157-01 GLP, unpublished Doc. No.: 114-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.6/01	Tognucci, A.	2000	Determination of the Dissociation Constant of Cyanamide F 1000 in Water Research and Consulting Company, Itingen, Switzerland Report No.: 744895 GLP, unpublished Doc. No.: 115-003	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 Battelle Institut, Frankfurt am Main, Germany Report No.: BE-P-77-89-105M-01 GLP, unpublished Doc. No.: 114-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.9/01	Turner, B.	2005	Cyanamid F 1000 - Partition CoefficientHuntingdon Life Sciences Report No.: SCI/105 GLP, unpublished Doc. No.: 114-004	Yes(Data on existing a.s. submitted for the first	AlzChem AG

				time for entry into Annex I.)	
A3.10/01	Güthner, T.	2000	Gutachten zur Zersetzungstemperatur von Cyanamid SKW Trostberg AG, Germany Report No.: ni Not GLP, unpublished Doc. No.: 141-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.11/01	Schleich, W.	2001	Determination of the Explosive Properties and of the Auto-ignition Temperature of ALZODEF SKW Trostberg AG, Germany Report No.: 064982129 GLP, unpublished Doc. No.: 241-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.13/01	Tognucci, A.	2000	Determination of the Surface Tension of Cyanamide L 500 Research and Consulting Company, Itingen, Switzerland Report No.: 744906 GLP, unpublished Doc. No.: 116-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.13/02	Wenighofer, T.	2007	"Cyanamide L500": Surface Tension Austrian Research Centers GmbH Report No.: ARC--L-2586 GLP, unpublished Doc. No.: 216-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.13/03	Wenighofer, T.	2007	"Cyanamide F1000": Surface Tension Austrian Research Centers GmbH Report No.: ARC--L-2585 GLP, unpublished Doc. No.: 116-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.15/01	Schleich, W.	2001	Determination of the Explosive Properties and of the Auto-ignition Temperature of ALZODEF SKW Trostberg AG, Germany Report No.: 064982129 GLP, unpublished Doc. No.: 241-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A3.16/01	Güthner, T.	ni	Gutachten zu oxidierenden Eigenschaften von Cyanamid SKW Trostberg AG, Germany Report No.: ni Not GLP, unpublished Doc. No.: 143-001	Yes (Data on existing a.s. submitted for the first	AlzChem AG

				time for entry into Annex I.)	
A4.1/01	Wildenauer, M.	1999	Validierung der Methode zur Bestimmung von Cyanamid in Cyanamid-Lösungen (50 %) (Validation of the method for the determination of cyanamide in cyanamide-solutions (50%); SKW Trostberg AG, Germany; Study No.: OA990015; GLP; (unpublished); Doc. No. 411-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A4.1/01a	Stroot, J.	2007	Validation of the analytical method for detrmining cyanamide in cyanamide solutions (50 %) in accordance to European Commission Directive 91/414 (SANCO/3030/99) – additional measurements to GLP-study OA990015, AlzChemTrostberg GmbH, Trostberg, Germany. Study no. OA070008, Doc. No. 411-005; (unpublished)	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 AG
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 Research and Consulting Company, Itingen, Switzerland Report No.: A61244 GLP, unpublished Doc. No.: 432-032	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 Research and Consulting Company, Itingen, Switzerland Report No.: A61244 GLP, unpublished Doc. No.: 432-034	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A4.2b/01*	Wais, A.	2000	Validation of the Residue Analytical Method for Cyanamide F 1000 in Air Research and Consulting Company, Itingen, Switzerland Report No.: 744917 GLP, unpublished Doc. No.: 436-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A4.2c/01*	Wildenauer,	2000	Validierung der Methode zu	Yes	AlzChem

	M.		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	(Data on existing a.s. submitted for the first time for entry into Annex I.)	AG
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 (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A4.2c/03	Wolf, S.	2007	Cyanamide - Validation of a confirmatory method for the Determination of Cyanamide in surface water Research and Consulting Company, Itingen, Switzerland Report No.: B14444 102-135 GLP, unpublished Doc. No.: 435-010	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A4.2d/03	Wildenauer, M.	1993	Validierung der Methode zur Bestimmung von Acetylcyanamid in Urin (Determination of Acetyl Cyanamide in Urine - Validation od the Analytical Report) SKW Trostberg AG, Germany Report No.: SP930002 GLP, unpublished Doc. No.: 433-008	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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, Switzerland Report No.: A61244	Yes(Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG

			GLP, unpublished Doc. No.: 432-032		
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 Research and Consulting Company, Itingen, Switzerland Report No.: A61244 GLP, unpublished Doc. No.: 432-034	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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, Germany Report No.: SP010006 GLP, unpublished Doc. No.: 432-026	Yes(Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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) SKW Trostberg AG, Germany Report No.: SP990018 GLP, unpublished Doc. No.: 433-003	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A4.3/02*	Wildenauer, M.	1999	Validierung der Methode zur Bestimmung von Cyanamid in Muskelfleisch vom Rind (Validation of the method for the determination of cyanamide in bovine mussle tissue) SKW Trostberg AG, Germany Report No.: SP990020 GLP, unpublished Doc. No.: 433-004	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 Research and Consulting Company, Itingen, Switzerland Report No.: A61244 GLP, unpublished Doc. No.: 432-032	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 Research and Consulting Company, Itingen, Switzerland Report No.: A61244 GLP, unpublished	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG

			Doc. No.: 432-034		
A6.1.1/01*	[redacted]	1994	Assessment of Acute Oral Toxicity with Cyanamide in the Rat [redacted] GLP, unpublished Doc. No.: 521-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.1.1/02*	Engel, C.	1973	Determination of the acute oral toxicity of Cyanamid in albino rats [redacted] Report No.: ni Not GLP, unpublished Doc. No.: 521-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.1.2/01*	[redacted]	1988	Acute Dermal Toxicity Study in Rabbits with Aqueous Hydrogen Cyanamide [redacted] GLP, unpublished Doc. No.: 522-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.1.3/01*	[redacted]	1973	Acute inhalation toxicity study with SKW Cyanamid L500 in rats[redacted] Not GLP, unpublished Doc. No.: 523-001	Yes(Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 AG
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 AG
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 AG

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 AG
A6.1.4/05*	[redacted]	1974	Eye irritation test with SKW Cyanamid L 500 in albino rabbits [redacted] Doc. No.: 566-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.1.4/06*	Reus, A.A.	2011	In vitro skin corrosion test with Cyanamid L 500 using EpiDerm reconstructed skin membranes TNO Triskelion, Zeist, The Netherlands Report No.: 093.01093 20018/01 GLP, unpublished Doc. No.: 565-005	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.1.5/01*	[redacted]	1982	Sensitization test with SKW-Cyanamide F 1000 in Guinea Pigs (Maximization Test) [redacted] GLP, unpublished Doc. No.: 567-003	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.1.5/02	[redacted]	1988	Test to Evaluate the Sensitizing Potential by Topical Applications, in the Guinea-Pig (Buehler test) [redacted] GLP, unpublished Doc. No.: 567-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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	Publication
A6.2/01*	[redacted]	1993	Metabolism of [14C]-Hydrogen Cyanamide in Rats (Preliminary and Definitive Phases) [redacted] GLP, unpublished Doc. No.: 512-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.2/02*	[redacted]	1989	Dermal Absorption of [14C]-Hydrogen Cyanamide in Male Rats [redacted] GLP, unpublished	Yes (Data on existing a.s. submitted	AlzChem AG

			Doc. No.: 511-001	for the first time for entry into Annex I.)	
A6.2/03*	[redacted]	1989	Investigation on the Absorption, Metabolism, and Excretion of Hydrogen Cyanamide (H2NCN) in rat and human [redacted] Report No.: ni Not GLP, unpublished Doc. No.: 512-004	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.2/04*	Obach, R.	1986	Bioavailability of Cyanamide in Fasted and Unfasted Rats Biopharmaceutics & Drug Disposition, 1986, 7, 273-280 Report No.: na Not GLP, published Doc. No.: 592-019	No	Publicati on
A6.3.1/01*	[redacted]	1988	28-Day Repeated Dose Oral Toxicity Study with Aqueous Hydrogen Cyanamide in Rats [redacted] GLP, unpublished Doc. No.: 532-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.3.2/01	[redacted]	1996	Subacute Dermal Toxicity Study of Hydrogen Cyanamide 50 % w/w Formulation (DORMEX) in Rabbits [redacted] Not GLP, unpublished Doc. No.: 532-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.3.3/01*	[redacted]	1996	Subacute Inhalation Toxicity Study of Hydrogen Cyanamide 50% w/w Formulation (DORMEX) in Wistar Rats [redacted] Not GLP, unpublished Doc. No.: 532-003	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.4.1/01*	[redacted]	1975	Sub-chronic (90-day) toxicity study with Cyanamid L 500 in albino rats [redacted] Not GLP, unpublished Doc. No.: 533-001	Yes(Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.4.1/02*	[redacted]	1982	Sub-Chronic (90-day) Oral Toxicity Study with Alzodef in Dogs [redacted] Not GLP, unpublished Doc. No.: 533-002	Yes (Data on existing a.s. submitted for the first time for entry into	AlzChem AG

				Annex I.)	
A6.5/01*	[redacted]	1989	Chronic Toxicity Study in Dogs with Aqueous Hydrogen Cyanamide [redacted] GLP, unpublished Doc. No.: 537-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
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 AG
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 AG
A6.6.2/01*	[redacted]	1988	Evaluation of the Ability of Aqueous Hydrogen Cyanamide to Induce Chromosome Aberrations in Cultured Peripheral Human Lymphocytes [redacted] Report No.: 0927/ECH 155 GLP, unpublished Doc. No.: 557-007	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.6.3/01*	[redacted]	2000	Gene Mutation Assay in Chinese Hamster V79 Cells in vitro (V79 / HPRT) with Cyanamide L 500 [redacted] Report No.: 651900 GLP, unpublished Doc. No.: 557-004	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.6.3/02*	[redacted]	1987	Mutagenicity Test on Hydrogen Cyanamide in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay [redacted] Report No.: HLA 9583-0-447 GLP, unpublished Doc. No.: 557-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.6.3/03*	[redacted]	1988	Evaluation of the Mutagenic Activity of Aqueous Hydrogen Cyanamide in an in vitro Mammalian Cell Gene Mutation Test with L5178Y Mouse Lymphoma Cells [redacted] Report No.: 0927/EL129 GLP, unpublished	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG

			Doc. No.: 557-008		
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 AG
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 AG
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 AG
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	Publication
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	Publication
A6.7/02a	Rust, U.	1987	Conversion Rate of Calcium Cyanamide (technical grade) to Hydrogen Cyanamide SKW Trostberg AG, Germany Report No.: ni Not GLP, unpublished Doc. No.: 593-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.8.1/01*	[redacted]	1989	Rat Teratology Study with Aqueous Hydrogen Cyanamide [redacted] GLP, unpublished Doc. No.: 551-002	Yes (Data on existing a.s. submitted for the first time for	AlzChem AG

				entry into Annex I.)	
A6.8.1/02*	[redacted]	1989	Oral embryotoxicity/teratogenicity study with an aqueous cyanamide solution (content 49 %) in New Zealand White Rabbits [redacted] GLP, unpublished Doc. No.: 551-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.8.1/03	Schilling, K.	2006	Position Paper - Cyanamide - Reproductive and prenatal developmental toxicity considering mechanistic aspects IRS-Consulting, Eisenberg, Germany Report No.: ni Not GLP, unpublished Doc. No.: 581-012	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.8.2/01*	[redacted]	1990	Two-Generation Reproduction Study in Rats with Aqueous Hydrogen Cyanamide (50% w/w) [redacted] GLP, unpublished Doc. No.: 543-001	Yes(Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.8.2/02*	[redacted]	1986	Oral Two-Generation Reproduction Study with an Aqueous Cyanamide Solution (Content 49 % w/w) in Rats [redacted] GLP, unpublished Doc. No.: 553-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.10	Alfonso, L. et al.	1996	Lung hypoplasia and surfactant system immaturity induced in the fetal rat by prenatal exposure to nitrofen; Biology of the Neonate 69, 94-100	No	Publication
A6.10	Allan, D. W. & Greer, J. J.	1997	Pathogenesis of nitrofen-induced congenital diaphragmatic hernia in fetal rats; Journal of Applied Physiology 83, 338-347	No	Publication
A6.10	Babiuk, R. P. et al.	2004	Reductions in the incidence of nitrofen-induced diaphragmatic hernia by vitamin A and retinoic acid; American Journal of Physiology-Lung Cellular and Molecular Physiology 286, L970-L973	No	Publication
A6.10	DeMaster, E. G. et al.	1982	Metabolic activation of cyanamide by liver-mitochondria, a requirement for the inhibition of aldehyde dehydrogenase enzymes; Biochemical and Biophysical Research Communications 107, 1333-1339	No	Publication
A6.10	DeMaster, E. G. et al.	1998	Mechanisms of inhibition of aldehyde dehydrogenase by nitroxyl, the active metabolite of the alcohol	No	Publication

			deterrent agent cyanamide; Biochemical Pharmacology 55, 2007-2015		
A6.10	Fan, X. H. et al.	2003	Targeted disruption of Aldh1a1 (Raldh1) provides evidence for a complex mechanism of retinoic acid synthesis in the developing retina; Molecular and Cellular Biology 23, 4637-4648	No	Publication
A6.10	Fukuto, J. M. et al.	2005	Nitroxyl (HNO): Chemistry, biochemistry, and pharmacology; Annual Review of Pharmacology and Toxicology 45, 335-355	No	Publication
A6.10	Hough, R. B. & Piatigorsky, J.	2004	Preferential transcription of rabbit Aldh1a1 in the cornea: Implication of hypoxia-related pathways; Molecular and Cellular Biology 24, 1324	No	Publication
A6.10	Jester, J. V. et al.	1999	The cellular basis of corneal transparency: evidence for 'corneal crystallins'; Journal of Cell Science 112, 613-622	No	Publication
A6.10	Kavlock, R. & Gray, L.	1983	Postnatal evaluation of morphological and functional effects of prenatal exposure to nitrofen in the Long-Evans rat; Journal of Toxicology and Environmental Health 11, 679-690	No	Publication
A6.10	Kinoshita, H. et al.	2000	Cyanamide-induced activation of the hypothalamo-pituitary-adrenal axis; Journal of Neuroendocrinology 12, 255-262	No	Publication
A6.10	Lee, M. J. C. et al.	1992	Prodrugs of nitroxyl as inhibitors of aldehyde dehydrogenase; Journal of Medicinal Chemistry 35, 3648-3652	No	Publication
A6.10	Luo, T. L. et al.	2006	Retinoids, eye development, and maturation of visual function; Journal of Neurobiology 66, 677-686	No	Publication
A6.10	Matt, N. et al.	2005	Retinoic acid-dependent eye morphogenesis is orchestrated by neural crest cells; Development 132, 4789-4800	No	Publication
A6.10	Mey, J. et al.	2003	Retinal dehydrogenase-2 is inhibited by compounds that induce congenital diaphragmatic hernias in rodents; American Journal of Pathology 162, 673-679	No	Publication
A6.10	Molotkov, A. et al.	2006	Retinoic acid guides eye morphogenetic movements via paracrine signaling but is unnecessary for retinal dorsoventral patterning; Development 133, 1901-1910	No	Publication
A6.10	Nakao, Y. & Ueki, R.	1987	Congenital diaphragmatic hernia induced by nitrofen in mice and rats: Characteristics as animal model and pathogenic relationship between diaphragmatic hernia and lung hypoplasia; Congenital Anomalies 27, 397-417	No	Publication
A6.10	Ostby, J. & Gray, L.	1985	The postnal effects of prenatal exposure to low doses of nitrofen	No	Publication

			(2,4- dichlorophenyl-p-nitrophenyl ether) in Sprague-Dawley rats; Toxicology 34, 285-297		
A6.10	You, L. R. et al.	2005	Mouse lacking COUP-TFII as an animal model of Bochdalek-type congenital diaphragmatic hernia; Proceedings of the National Academy of Sciences of the United States of America 102, 16351-16356	No	Publication
A6.12	Settimi, L et al.	2005	Update: hydrogen cyanamide-related illnesses--Italy, 2002-2004. Journal Morbidity and Mortality Weekly Report 54, 405-408	No	Publication
A6.12.1/01	[redacted]	1976	Bericht über die Erfahrung im Umgang mit Kalkstickstoff während meiner dreizehnjähriger betriebsärztlichen Tätigkeit(Report on the experience made in dealing with cyanamide during my thirteen years as an occupational physican [redacted] Report No.: ni Not GLP, unpublished Doc. No.: 574-003	Yes(Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.12.1/02	Schiele, R. Söll, F. Weltle, D. Valentin, H.	1981	Felduntersuchung von Personen mit langjähriger Exposition gegenüber Kalkstickstoff (Field study of workers with Long-term Exposure to Calcium Cyanamide) Zenralbl. Bakteriol. Mikrobiol. Hyg. (B), 1981, 173 (1-2), 13-28 Report No.: na Not GLP, published Doc. No.: 592-026	No	Publication
A6.12.1/03	Mertschenk, B.Borneman n, W.Pickardt, C.R.Rust, U.Schneider, J.C.Gloxhube r, C.	1993	Examinations on endocrine functions in employees from a calcium cyanamide production plantZbl. Arbeitsmed. 43, 254-258 (1993) Report No.: na Not GLP, published Doc. No.: 592-011	No	Publication
A6.12.1/04	[redacted]	1989	Clinical Examinations of Hypersensitization Towards Hydrogen Cyanamide and Calicum Cyanamide Resp. In Employees of the Calcium Cyanamide Production Plant of [redacted] Report No.: ni GLP, unpublished Doc. No.: 572-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.12.1/05	Mertschenk, B. Bornemann, W. Rust, U. Schneider, J.C. Wittmann, H.	1991	Arbeitsmedizinische Untersuchungen an Kollektiven von Beschäftigten einer Kalkstickstoffabrik Zbl. Arbeitsmed. 41, 107-119 (1991) Report No.: na Not GLP, published Doc. No.: 592-012	No	Publication

	Gloxhuber, C.				
A6.12.1/06	[redacted]	1984	Allergic reactions after Cyanamide contact [redacted] Report No.: ni Not GLP, unpublished Doc. No.: 574-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.12.1/07	Anonymous	2005	Update: Hydrogen Cyanamide - Related Illnesses - Italy, 2002-2004 MMWR Weekly, 29.04.2005, 54, 16, 405-408 Report No.: na Not GLP, published Doc. No.: 592-087	No	Publication
A6.12.2/01	[redacted]	1989	Health risk evaluation based on clinical observations during the therapeutical use of cyanamide (H2NCN) and calcium cyanamide (CaNCN) as an alcohol deterrent agent (review of the literature) nr Report No.: ni Not GLP, unpublished Doc. No.: 573-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.12.2/02	Lessenger, J.	1998	Case Study: Hypotension, Nausea and Vertigo Linked to Hydrogen Cyanamide Exposure Journal of Agromedicine, 1998, 5 (3), 5-11 Report No.: na Not GLP, published Doc. No.: 592-038	No	Publication
A6.12.2/03	Takahashi, M. et al.	2004	Intake of alcohol caused takotsubo cardiomyopathy (ampulla cardiomyopathy) in a patient with Cyanamide IRYO, 2004, 58, 12, 715-718 Report No.: na Not GLP, published Doc. No.: 592-081	No	Publication
A6.12.2/04	Ballarin, E. et al.	2005	Cyanamide-induced aplastic anemia Eur J Clin Pharmacol, 2005, 61, 467-469 Report No.: na Not GLP, published Doc. No.: 592-084	No	Publication
A6.12.4/01	Frankos, V.H.	1987	Potential Health Hazards of DORMEX (Hydrogen Cyanamide) Exposure: A Literature Review Environ Corporation, Arlington, Virginia, USA Report No.: ni Not GLP, unpublished Doc. No.: 581-003	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.12.4/02	Vázquez, J.J. Diaz de Otau, R. Guillen, F.J.	1983	Hepatitis induced by drugs used as alcohol aversion therapy. Diagnostic Histopathology, 1983, 6 (1), 29-37	No	Publication

	Zozaya, J. Pardo, F.J.		Report No.: na Not GLP, published Doc. No.: 592-020		
A6.12.4/03	Vázquez, J.J., Cervera, S.	1980	Cyanamide-induced liver injury in alcoholics The Lancet, 1980, 1 (8164), 361-363 Report No.: na Not GLP, published Doc. No.: 592-022	No	Publication
A6.12.4/04	Bruguera, M. Lamar, C. Bernet, M. Rodés, J.	1986	Hepatic disease associated with ground-glass inclusions in hepatocytes after cyanamide therapy Arch Pathol Lab Med, 1986, 110 (10), 906-910 Report No.: na Not GLP, published Doc. No.: 592-027	No	Publication
A6.12.4/05	Roman Llorente, F.J. Gracia Iglesia, E. Fojon Polanco, S. Marino Callejo, A. Pia Iglesias, G.G.	1989	Hepatotoxicidad inducida por cianamida. Revisión de las alteraciones anatomopatológicas a propósito de un caso (Cynanamide induced hepatotoxicity. A case review of anatomopathological alterations.) Anales de Medicina Interna, 1989, 6 (11), 589-590 Report No.: na Not GLP, published Doc. No.: 592-030	No	Publication
A6.12.4/06	Yokoyama, A. Sato, K. Maruyama, K. Nakano, M. Takahashi, H. Okuyama, K. Tokogi, S. Tokogi, T.	1995	Cyanamide-associated alcoholic liver disease: a sequential histological evaluation Clinical and Experimental Research, 1995, 19 (5), 1307-1311 Report No.: na Not GLP, published Doc. No.: 592-034	No	Publication
A6.12.4/07	Kawana, S.	1997	Drug eruption induced by Cyanamide (carbidmide): A clinical and hisotpathological study of 7 patients Dermatology, 1997, 195 (1), 30-34 Report No.: na Not GLP, published Doc. No.: 592-028	No	Publication
A6.12.4/08	Kojima, T. Nagasawa, N. Yashiki, M. Iwasaki, Y. Kubo, H. Kimura, N.	1997	A fatal case of drinking and cyanamide intake Japanese Journal of Legal Medicine, 1997, 51 (2), 111-115 Report No.: na Not GLP, published Doc. No.: 592-031	No	Publication
A6.12.4/09	Musaka, H. Ichihara, T. Eto, A.	1964	A new treatment of Alcoholism with Cyanamide (H2NCN) Not indicated, 38-45 Report No.: na Not GLP, published Doc. No.: 592-042	No	Publication

A6.12.4/10	Peachey, J.E. Brien, J. Roach, C.A. Loomis, Ch.W.	1981	A Comparative Review of the Pharmacological and Toxicological Properties of Disulfiram and Calcium Carbimide Journal of Clinical Psychopharmacology, 1981, 1 (1), 21-26 Report No.: na Not GLP, published Doc. No.: 592-046	No	Publication
A6.12.4/11	Peachey, J.E.	1981	A Review of the Clinical Use of Disulfiram and Calcium Carbimide in Alcoholism Treatment Journal of Clinical Psychoparmacology, 1981, 1 (6), 368-375 Report No.: na Not GLP, published Doc. No.: 592-045	No	Publication
A6.12.4/12	Jones A.W. Neiman, J. Hillbom M.	1987	Concentration- time profiles of ethanol and acetaldehyde in human volunteers treated with the alcohol-sensitizing drug, calcium carbimide Br. J. clin. Pharmac, 1988, 25 (2), 213-221 Report No.: na Not GLP, published Doc. No.: 592-047	No	Publication
A6.12.4/13	Peachey, J.E.	1980	A Study of the Calcium Carbimide-Ethanol Interaction in Man: Symptom Responses Alcohol Clin. Exp. Res., 1980, 4 (3), 322-329 Report No.: na Not GLP, published Doc. No.: 592-044	No	Publication
A6.12.4/14	Peachey, J.E.Maglana, S.Robinson, G.M.Hemy, M.Brien, J.F.	1980	Cardiovascular changes during the calcium carbimide-ethanol interactionClin. Pharmacol. Ther., 1981, 29 (1), 40-46 Report No.: na Not GLP, published Doc. No.: 592-036	No	Publication
A6.12.4/15	Tamai, H. Yokoyama, A. Okuyama, K. Takahashi, H. Maruyama, K. Suzuki, Y. Ishii, H.	2000	Comparison of cyanamide and dislufiram in effects on liver function Alcohol Clinical and Experimental Research, 2000, 24 (4), 97S-99S Report No.: na Not GLP, published Doc. No.: 592-033	No	Publication
A6.12.4/16	Moreno, A. Vazquez, J.J. Ruiz del Arbol, L. Guillen, F.J. Colina, F.	1983	Structural hepatic changes associated with cyanamide treatment: cholangiolar proliferation, fibrosis and cirrhosis Liver, 1984, 4 (1), 15-21 Report No.: na Not GLP, published Doc. No.: 592-037	No	Publication
A6.12.4/17	Suzuki, Y. Yokoyama,	2000	Cyanamide-induced liver dysfunction after abstincence in alcoholics: a	No	Publication

	A. Nakano, M. Okzyama, K.T.		long-term follow-up study on four cases Alcohol Clinical and Experimental Research, 2000, 24 (4), 100S-105S Report No.: na Not GLP, published Doc. No.: 592-032		
A6.12.4/18	Thomsen, P. Reinicke, V.	1980	Ground glass inclusions in liver cells in an alcoholic treated with cyanamide (Dipsan) Liver, 1981, 1 (2), 67-73 Report No.: na Not GLP, published Doc. No.: 592-021	No	Publication
A6.12.4/19	Anonymous	1992	Package insert - Colme-DropsSKW Trostberg AG, Germany Report No.: 1-18029 Not GLP, published Doc. No.: 593-003	No	Publication
A6.12.4/19*	Shirota, F.N. DeMaster, E.G. Kwon, C.H. Nagasawa, H.T.	1987	Metabolism of Cyanamide to Cyanide and an Inhibitor of Aldehyde Dehydrogenase (ALDH) by Rat Liver Microsomes Source: Alcohol & Alcoholism, Suppl. 1, 219-223 (1987) Report No.: Not applicable Not GLP; (published) Doc. No.: 592-003	No	Publication
A6.12.4/20	Anonymous	1992	Colme-Tropfen Packungsbeilage ni Report No.: 1-18029 Not GLP, published Doc. No.: 593-004	No	Publication
A6.12.4/21	[redacted]	2002	Erfahrungsbericht - Die Anwendung des Cyanamid (Colme R) im Anton-Proksch-Institut The use of Cyanamide (Colme R) in the Anton-Proksch-Institut [redacted] Report No.: na Not GLP, unpublished Doc. No.: 581-006	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A6.12.4/22	Niederhofer, H. Staffen, W. Mair, A.	2003	Comparison of Cyanamide and Placebo in the treatment of Alcohol Dependence of Adolescents Alcohol & Alcoholism, Vol. 38, No. 1, pp. 50-53, 2003 Report No.: na Not GLP, published Doc. No.: 592-065	No	Publication
A6.12.4/23	Krampe, H. et al.	2006	Follow-up of 180 Alocholic Patients for up to 7 years After Outpatient Treatment - Impact of Alcohol Deterrents on Outcome Alcoholism - Clinical and Experimental Research - Vol. 30, No. 1, January 2006 Report No.: na Not GLP, published Doc. No.: 592-069	No	Publication
A6.12.5/01	[redacted]	1997	Medical instructions in case of emergencies or accidents	Yes (Data on	AlzChem AG

			[redacted] Report No.: na Not GLP, unpublished Doc. No.: 573-002	existing a.s. submitted for the first time for entry into Annex I.)	
A6.12.6/01	Marconi, J. Solari, G. Gaete, S. Piazza, L.	1960	Comparative Clinical Study of the Effects of Disulfiram and Calcium Carbimide Quart. J. Studies Alc. 21, 642-654 (1960) Report No.: na Not GLP, published Doc. No.: 592-013	No	Publication
A6.12.6/02	Conde-Salazar, L. Guimaraens, D. Romero, L. Harto, A.	1981	Allergic contact dermatitis to cyanamide (carbodiimide) Contact Dermatitis 7, 329-330 (1981) Report No.: na Not GLP, published Doc. No.: 592-015	No	Publication
A6.12.6/03	Calnan, C.D.	1970	Subject - Cyanamide Contact Dermatitis Newsletter 7, 150 (1970) Report No.: na Not GLP, published Doc. No.: 592-014	No	Publication
A6.12.6/04	De Corres, L.F. Lejarazu, D.M.	1982	Allergic contact dermatitis to cyanamide Contact Dermatitis 8, 346 (1982) Report No.: na Not GLP, published Doc. No.: 592-016	No	Publication
A6.12.6/05	Goday Buján, J.J. Yanguas Bayona, I. Arechavala, R.	1994	Allergic contact dermatitis from cyanamide: report of 3 cases Contact Dermatitis, 1994, 31 (5), 331-332 Report No.: na Not GLP, published Doc. No.: 592-035	No	Publication
A6.12.6/06	Inamadar, A.C. Palit, A.	2004	Hydrogen-Cyanamide-Related Severe Cutaneous Reactions Simulating Erythema multiforme and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Exog Dermatol, 2004, 3, 26-29 Report No.: na Not GLP, published Doc. No.: 592-080	No	Publication
A6.12.6/07	Armisén, M. Rodriguez, V. Vidal, C.	2003	Allergic contact dermatitis due to colme (Calcium Cyanamide) Alergol Immunol Clin, 2003, 18, 236-238 Report No.: na Not GLP, published Doc. No.: 592-082	No	Publication
A6.12.6/08	Okazaki, F. et al.	2003	Drug eruption due to CyanamideThe Nishinihon Journal of Dermatology, 2003, 65 (3), 269-271 Report No.: na Not GLP, published Doc. No.: 592-083	No	Publication

A6.12.6/09	Trébol, I. et al.	2005	Allergic Contact Dermatitis from Cyanamide Dermatitis, March 2005, 16, 1, 32-33 Report No.: na Not GLP, published Doc. No.: 592-085	No	Publication
A6.13/01	Heinritzi, K.Bollwohn, W.	1985	Alzogur - Vergiftung beim SchweinTierärztliche Umschau, Zeitschrift für alle Gebiete der Veterinärmedizin - 40. Jahrgang, Nr. 11, 01.11.1985, pp. 914-921 Report No.: na Not GLP, published Doc. No.: 592-062	No	Publication
A7.1.1.1.1/01*	Eskötter, H.	1990	Determination of the Abiotic Degradation of Cyanamide F 1000 Batelle Institut, Frankfurt am Main, Germany Report No.: BE-P-77-90-C10-01 GLP, unpublished Doc. No.: 711-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A7.1.1.1.2/01*	Schmidt, J.M.	1991	Determination of the Aqueous Photolysis Rate of 14C-Cyanamide ABC Laboratories, Columbia, USA Report No.: 39035 GLP, unpublished Doc. No.: 712-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A7.1.1.2.1/01*	van der Hoek, E. Hanstveit, A.O.	1988	Biodegradability of Aqueous Hydrogen Cyanamide According to OECD 301 E (Modified Screening Test) TNO, Department of Environmental Toxicology, Delft, The Netherlands Report No.: R 88/021 GLP, unpublished Doc. No.: 713-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A7.1.1.2.1/02	Matla, Y.A. Hanstveit, A.O.	1990	Preliminary Determination of Some Limiting Factors for the Biodegradation of Hydrogen Cyanamide in a Standard OECD 301B Test TNO, Department of Environmental Toxicology, Delft, The Netherlands Report No.: R 90/041 GLP, unpublished Doc. No.: 713-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A7.1.2.1.2/01*	Völkel, W.	2007	Route and rate of degradation of 14C-Cyanamide in liquid manure under anaerobic conditions - Including Amendment No. 1 and No. 2Research and Consulting Company, Itingen, Switzerland Report No.: A75183 GLP, unpublished Doc. No.: 769-004	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	AlzChem AG
A7.1.2.2.2/01*	Völkl, S.	2000	14C-Cyanamide Route and Rate of Degradation in Aerobic Aquatic	Yes (Data on	AlzChem AG

			Systems Research and Consulting Company, Itingen, Switzerland Report No.: 744952 GLP, unpublished Doc. No.: 714-002	existing a.s. submitted for the first time for entry into Annex I.)	
A7.1.2.2.2/02	Rheinheimer, G. Gericke, H. Wesnigk, J	1990	Prüfung der biologischen Abbaubarkeit von organischen Chemikalien im umweltrelevanten Konzentrationsbereich [Investigation into the Biological Degradability of Organic Chemicals in Environmentally Relevant Concentrations] Source: Department of Microbiology at the Institut für Meereskunde at the Christian-Albrechts-Universität in Kiel; publication Report No.: research report 106 02 051 Not GLP; published Doc. No. 792-027	No	Publication
A7.1.3/01*	Rüdel, H.	1990	Determination of the Adsorption/Desorption of Hydrogencyanamide (Bestimmung der Adsorption/Desorption von Hydrogencyanamid)Fraunhofer Institut Report No.: SKW-01/7-13 GLP, unpublished Doc. No.: 731-001	Yes (Data on existing a.s. submitted for the first time for entry intoLoAAS)	AlzChem AG
A7.2.1/01a*	Schmidt, J.	1990	Preliminary Study of the Aerobic Soil Metabolism of 14C-Hydrogenxyanamide ABC Laboratories, Columbia, USA Report No.: 38234 GLP, unpublished Doc. No.: 722-003	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.2.1/01b*	Schmidt, J.	1990	Aerobic Soil Metabolism of 14C-CyanamideABC Laboratories, Columbia, USA Report No.: 38438 GLP, unpublished Doc. No.: 722-001	Yes(Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.2.1/01c*	Schmidt, J.	1991	Supplemental Report of the Aerobic Soil Metabolism of 14C- Cyanamide ABC Laboratories, Columbia, USA Report No.: 384381 GLP, unpublished Doc. No.: 722-004	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.2.1/02*	Loehr, R.C. Matthews, J.E.	1992	Loss of Organic Chemicals in Soil: Pure Compound Treatability Studies Journal of Soil Contamination, 1992, 1 (4), 339-360 Report No.: na	No	Publication

			Not GLP, published Doc. No.: 792-025		
A7.2.1/03a	Frederick, L.R. et al.	1957	Decomposability of Some Organic Sulfur Compounds in Soil Soil Science Society Am. J., 1957, 21, 287-292 Report No.: na Not GLP, published Doc. No.: 792-026	No	Publication
A7.2.1/03a-d	Lashen, E.S. Starkey, R.L.	1970	Decomposition of Thioureas by a Penicillium Species and Soil and Sewage-sludge Microflora Journal of General Microbiology, 1970, 64, 139-150 Report No.: na Not GLP, published Doc. No.: 792-023	No	Publication
A7.2.1/03c	Harron, W.R. Malhi, S.S.	1978	Release of Sulphate from the Oxidation of Thiourea and Ammonium Polysulphide Can. J. Soil. Sci., 1978, 58, 109-111 Report No.: na Not GLP, published Doc. No.: 792-024	No	Publication
A7.2.1/03d	Günther, P. Pestemer, W.	1990	Risk Assessment for Selected Xenobiotics by Biossay Methods with Higher Plants Environmental Management, 14, (3), 381-388 Report No.: na Not GLP, published Doc. No.: 892-031	No	Publication
A7.2.2.4/01	Burri, R.	2001	Photolysis of 14C-Cyanamide on Soil Surface Under Laboratory Conditions Research and Consulting Company, Itingen, Switzerland Report No.: 744930 GLP, unpublished Doc. No.: 724-002	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.2.2.4/02a	Schmidt, J.	1990	Preliminary Study of the Aerobic Soil Metabolism of 14C-Hydrogenxyanamide ABC Laboratories, Columbia, USA Report No.: 38234 GLP, unpublished Doc. No.: 722-003	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.2.2.4/02b	Schmidt, J.	1990	Anaerobic Soil Metabolism of 14C-Cyanamide ABC Laboratories, Columbia, USA Report No.: 38439 GLP, unpublished Doc. No.: 722-002	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.2.2.4/02c	Schmidt, J.	1991	Supplemental Report of the Anaerobic Soil Metabolism of 14C-Cyanamide ABC Laboratories, Columbia, USA	Yes (Data on existing a.s.	AlzChem AG

			Report No.: 384391 GLP, unpublished Doc. No.: 722-005	submitted for the first time for entry into LoAAS)	
A7.3.1/01*	Peter, S.	2003	Estimation of photochemical degradation of Cyanamide using the Atkinson Calculation Method Scientific Consulting Company, Wendelsheim, Germany Report No.: 102-084 Not GLP, unpublished Doc. No.: 743-003	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.4.1.1/01	[redacted]	1985	The Acute Toxicity of Hydrogen Cyanamide to the Rainbow Trout, Salmo gairdneri, in a Static Test System [redacted] GLP, unpublished Doc. No.: 821-004	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.4.1.1/02 *	[redacted]	1985	Acute Toxicity of LH 21,810 A to Bluegill Sunfish (Lepomis macrochirus) [redacted] GLP, unpublished Doc. No.: 821-002	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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) [redacted] GLP, unpublished Doc. No.: 821-003	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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	Publication
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 Report No.: R 83/198 Not GLP, unpublished Doc. No.: 822-001	Yes (Data on existing a.s. submitted for the first time for entry into A LoAAS)	AlzChem AG
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 Research and Consulting Company, Itingen, Switzerland	Yes (Data on existing a.s. submitted for the first time for	AlzChem AG

			Report No.: 744963 GLP, unpublished Doc. No.: 823-003	entry into LoAAS)	
A7.4.1.3/02	Hertl, J.	2000	Toxicity of SKW Cyanamide L 500 to Anabaena flos-aquae in an Algal Growth Inhibition Test Ibacon GmbH, Rossdorf, Germany Report No.: 6677210 GLP, unpublished Doc. No.: 823-004	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.4.1.3/03	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	Publication
A7.4.1.4/01 *	Hanstveit, A.O. Pullens, M.A.	1988	The Effect Of Aqueous Hydrogen Cyanamide On The Growth Of The Bacterium Pseudomonas Putida TNO, Department of Environmental Toxicology, Delft, The Netherlands Report No.: R 88/019 Not GLP, unpublished Doc. No.: 841-003	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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 Multiplication Inhibition Test) RCC NOTOX B.V., ´s-Hertogenbosch, The Netherlands Report No.: 0918/PS20	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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 Perio [redacted] Not GLP, unpublished Doc. No.: 826-001	Yes(Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.4.3.4/01 *	Murrell, H.R. Leak, T.	1995	Chronic Toxicity of Hydrogen Cyanamide to Daphnia magna Under Flow-Through Test Conditions	Yes (Data on existing	AlzChem AG

			ABC Laboratories, Columbia, USA Report No.: 41942 GLP, unpublished Doc. No.: 827-002	a.s. submitted for the first time for entry into LoAAS)	
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	Publication
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 GAB Biotechnologie GmbH, Niefern-Öschelbronn, Germany Report No.: 20001413/01-ASCr GLP, unpublished Doc. No.: 824-001	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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 Ibacon GmbH, Rossdorf, Germany Report No.: 6679240 GLP, unpublished Doc. No.: 825-001	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.5.1.1/01	Reis, K.-H.	2002	Effects of Cyanamide L 500 on the activity of the soil microflora in the laboratory Ibacon GmbH, Rossdorf, Germany Report No.: 12502080 GLP, unpublished Doc. No.: 841-004	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.5.1.1/02	Mitchell, W.R.	1987	Biodegradation of Guanidinium Ion in Aerobic Soil Samples Bull. Environ Contain Toxicol, 1987 (39), 974-981 Report No.: na Not GLP, published Doc. No.: 792-020	No	Publication
A7.5.1.1/03*	Schulz, L.	2010	Thiourea - Effects on the activity of soil microflora (Nitrogen	Yes(Data on existing	AlzChem AG

			transformation test)BioChem Agrar GmbH, Gerichshain, Germany Report No.: 10 10 48 015 N GLP, unpublished Doc. No.: 841-005	a.s. submitted for the first time for entry into LoAAS)	
A7.5.1.2/01 *	Lührs, U.	2001	Acute Toxicity (14 Days) of SKW Cyanamide L 500 + AHL to the Earthworm Eisenia fetida in Artificial SoilIbacon GmbH, Rossdorf, Germany Report No.: 12081021 GLP, unpublished Doc. No.: 833-003	Yes(Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.5.1.2/02 *	Adema, D.M.M.	1985	Acute Toxicity of Dicyandiamid to the worm species Eisenia Foetida TNO, Department of Environmental Toxicology, Delft, The Netherlands Report No.: R 85/05913247 Not GLP, unpublished Doc. No.: 833-004	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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 Ibacon GmbH, Rossdorf, Germany Report No.: 9131088 GLP, unpublished Doc. No.: 851-003	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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 Berlin, Institut für Wasser-, Boden- und Lufthygiene des Bundesamtes, 1984 Report No.: na Not GLP, published Doc. No.: 892-029	No	Publication
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 Berlin, Institut für Wasser-, Boden- und Lufthygiene des Bundesamtes, 1984 Report No.: na Not GLP, published Doc. No.: 892-030	No	Publication
A7.5.1.3/04 *	Günther, P. Pestemer, W.	1990	Risk Assessment for Selected Xenobiotics by Biossay Methods with Higher Plants Environmental Management, 14, (3), 381-388 Report No.: na Not GLP, published Doc. No.: 892-031	No	Publication
A7.5.2.1/01 *	Moser, T. Scheffczyk, A.	2009	Cyanamide: Acute and reproduction toxicity to the collembolan species Folsomia candida in artificial soil -	Yes (Data on existing	AlzChem AG

			including Recalculation of ECx values, performed by German UBA 20.05.2009 ECT Oekotoxikologie GmbH, Flörsheim, Germany Report No.: 08BL1CR GLP, unpublished Doc. No.: 835-001	a.s. submitted for the first time for entry into LoAAS)	
A7.5.2.2/01 *	Förster, B.	2009	Cyanamide - Chronic Toxicity in Higher PlantsECT Oekotoxikologie GmbH, Flörsheim, Germany Report No.: 08BL1PC GLP, unpublished Doc. No.: 851-007	Yes(Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.5.2.2/02 *	Förster, B.	2012	Thiourea: Chronic Toxicity in Higher Plants ECT Oekotoxikologie GmbH, Flörsheim, Germany Report No.: 12BL2PC GLP, unpublished Doc. No.: 851-008	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.5.4.1/01	Kleiner, R.	1992	Testing toxicity to Honeybee - Apis mellifera L. (laboratory) according to BBA Guideline VI, 23 - 1 (1991) Biochem GmbH, Karlsruhe, Germany Report No.: 92 10 48 014 GLP, unpublished Doc. No.: 832-001	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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 Ibacon GmbH, Rossdorf, Germany Report No.: 6670001 GLP, unpublished Doc. No.: 834-019	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
A7.5.4.1/03	Goßmann, A.	2000	Effects of SKW CYANAMIDE L 500 on the Predatory Mite Typhlodromus pyri Scheuten (Acari, Phytoseiidae) in the Laboratory - Dose Response Design.Ibacon GmbH, Rossdorf, Germany Report No.: 6676062 GLP, unpublished Doc. No.: 834-013	Yes(Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG

- key study

Doc IIIB

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
B3.1.1/01	Anonymous	2005	Safety Data Sheet - Alzogur	Yes	AlzChem

			Degussa AG, Trostberg, Germany Report No.: 4.0 / REG_EU Not GLP, unpublished Doc. No.: 954-012	(Data on existing a.s. submitted for the first time for entry into LoAAS)	AG
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 am Main, Germany Report No.: BE-P-77-89-MT46-01 GLP, unpublished Doc. No.: 245-004	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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. Battelle Institut, Frankfurt am Main, Germany Report No.: BE-P-77-90-MT75-01 GLP, unpublished Doc. No.: 215-002	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
B3.7/01	Melkebeke, T.	1994	Determination of the Storage Stability of DORMEX at 20 °C RCC NOTOX B.V., ´s-Hertogenbosch, The Netherlands Report No.: 074047 GLP, unpublished Doc. No.: 245-002	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
B3.7/02	Schmidt, J.M.	1991	Determination of the Aqueous Photolysis Rate of 14C-Cyanamide ABC Laboratories, Columbia, USA Report No.: 39035 GLP, unpublished Doc. No.: 712-001	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
B3.8/01	Comb, A.L.	2000	Alzodef Persistent Foaming Huntingdon Life Sciences Report No.: SCI/061/004514 GLP, unpublished Doc. No.: 216-001	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
B3.11/01	Biedermann, K.	2000	Determination of the viscosity of ALZODEF Research and Consulting Company, Itingen, Switzerland	Yes (Data on existing a.s.	AlzChem AG

			Report No.: 792718 GLP, unpublished Doc. No.: 214-001	submitted for the first time for entry into Annex I.)	
B5.10/01*	Lehmhus, J.	2006	Determination of the efficacy of ALZOGUR to dung flies in the laboratory, Eurofins-GAB GmbH, Stade, Germany Report No.: 20061021/01-ELMa GLP, unpublished Doc. No.: 336-1801	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
B5.10/01 (PT3)	Schließner, Th. and Rübsamen, S.	1981	Zur Empfindlichkeit des Erregers der Schweinedysenterie Treponema hyodysenteria gegenüber Alzogur® (English translation of the 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)	No	Publication
B5.10/02*(PT3)	Herbst, W.	2009	Biozide Wirksamkeit von Cyanamid L500 gegenüber Brachyspira hyodysenteriae; Institut für Hygiene und Infektionskrankheiten, Gießen, Deutschland; 06.04.2009; Doc. No. 336-0304 (unpublished)	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG
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 AG
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.: na Not GLP, unpublished Doc. No.: 575-006	Yes (Data on existing a.s. submitted for the first time for entry into LoAAS)	AlzChem AG

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LoAAS: List of Approved Active Substances