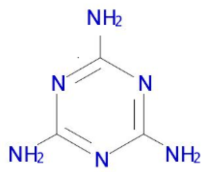
AGREEMENT OF THE MEMBER STATE COMMITTEE
ON THE IDENTIFICATION OF

Melamine

AS A SUBSTANCE OF VERY HIGH CONCERN
under Articles 57 and 59 of Regulation (EC) 1907/2006
Adopted on 15 December 2022

This agreement concerns
Melamine
EC number: 203-615-4
CAS number: 108-78-1
Molecular formula: $C_3H_6N_6$
Structural formula:



The Member State Committee agreed that:

1. **Melamine is a substance under Article 57 (f) of Regulation (EC) 1907/2006 (REACH), for which there is scientific evidence of probable serious effects to human health and the environment which give rise to an equivalent level of concern to those of other substances listed in paragraphs (a) to (e) of Article 57 of REACH Regulation.**

2. **Melamine must be added to the Candidate list of substances of very high concern**.

Annex 1: Scientific evidence for identification of substances of very high concern

The information below is based on Support Document (Member State Committee, 15 December 2022)

Melamine is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) as there is scientific evidence of probable serious effects to the environment and human health which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of the REACH Regulation.

Intrinsic properties

Degradation:

Abiotic degradation of melamine by hydrolysis and phototransformation in air and water is regarded as negligible based on experimental studies and Quantitative structure-activity relationship (**QSAR**) predictions.

The overall weight of evidence shows that degradability of melamine under environmental conditions is low: Based on QSAR data, melamine is predicted to be not readily biodegradable and hence potentially persistent. A reliable OECD TG 301C study shows that melamine is not readily biodegradable (0% degradation after 14 days). Biotic degradation of melamine was investigated in surface water over 60 days according to OECD TG 309, showing no degradation of the substance. Therefore, the degradation half-life of melamine is longer than 60 days. Additional studies with cultures of single species of bacteria or in wastewater treatment plants treating industrial effluent indicate that melamine might be degradable under specific conditions. However, these conditions are not representative of either municipal sewage treatment plants or environmental conditions and therefore are not applicable for persistency assessment under REACH.

Considering the data on abiotic and biotic degradation, the half-life of melamine in water is >60 days.

Volatility, water solubility, adsorption, distribution in the environment:

Melamine has an experimentally derived log normalised organic carbon to water partition coefficient (**K_{OC}**) of 1.81 (pH value in experiment not disclosed) indicating a low potential for adsorption on organic matter and clay minerals in the environment. The QSAR estimate for the non-ionic molecule results in a log K_{OC} of 1.51 (KOCwin from EPIsuite was applied). As melamine has a base dissociation constant **(pK_{b1})** of 7.3, non-negligible quantities of non-ionic and ionic forms of the molecule occur under environmentally relevant conditions.

For the cationic forms of melamine, a higher log K_{OC} is assumed. Thus, for the ionic melamine forms, adsorption on soil constituents such as organic matter or clay minerals is expected to be higher when compared to the non-ionic form.

As the data indicates that under environmentally relevant conditions ionic and non-ionic molecules can be found in non-negligible quantities at the same time, the log K_{OC} of 1.81 of the non-ionic form is used in the assessment of environmental fate and behaviour of melamine.

The substance's intrinsic behaviour of low volatility from water (calculated Henry's law constant 2.0e-08 Pa*m³/mol) together with its low potential to adsorb to organic matter result in a high mobility in water. Additionally, the physical-chemical substance properties indicate that the substance will partition primarily to the water compartment and will undergo environmental distribution via aqueous media, easily reaching groundwaters.

High water solubility (3.48 g/L at 20°C and pH 7.7 using EU Method A.6) and low adsorption potential of melamine make it difficult to remove melamine from water by commonly applied sewage treatment and water purification techniques as it only has a low potential to adsorb to materials and tends to remain in the water phase.

Because of melamine’s intrinsic property of high water solubility, low volatility from water and low potential for adsorption, water will be the dominant transport medium in the environment once the substance emerges in the environment. In combination with another intrinsic property, its long environmental half-life, there is a potential for widespread contamination of the water environment.

The OECD tool for Long-Range Transport Potential (**LRTP**) predicts a characteristic travel distance (CTD) of 3530 km together with an overall environmental persistence (**P_{ov}**) of 2181 days for melamine. This indicates that melamine is capable of reaching regions far away from the point of initial emission.

Distribution of melamine in the environment is influenced by the intrinsic properties of the substance, in addition to the properties and conditions of the environment. Therefore, the source of melamine emissions to the environment is not of relevance for the purpose of SVHC identification.

Toxicity:

Urinary tract toxicity after oral melamine exposure has been shown both in experimental animal studies and observational studies in humans. Following oral exposure, melamine is rapidly excreted mostly unchanged via the urine. Once the urinary concentration of melamine exceeds a certain threshold, precipitation occurs within the urinary tract leading to the formation of crystals and calculi. This is due to the chemical properties of melamine resulting in reaction within the urinary tract. Although the exact mechanisms have not been fully elucidated, it is thought that the intrinsic structural properties of melamine allow for hydrogen bonding with urinary uric acid to form a crystalline lattice structure (melamine–uric acid complexes). Melamine-related uroliths have been linked to the formation of rare urinary tract tumours in rodents (with an unusually short latency) and nephrotoxicity in humans. Epidemiological data show that the intake of high amounts of melamine leads to precipitation in the lower urinary tract and to melamine-associated formation of urinary stones in humans.

Based on these effects, there is scientific evidence of probable serious human health effects. Committee for Risk Assessment (**RAC**) has confirmed this by concluding that melamine fulfils the criteria for classification as STOT RE 2 (urinary tract) and Carc. 2. The harmonised classification has been included in the 18th ATP to CLP[1].

The observed testicular and sperm effects of melamine in an extended one-generation reproductive toxicity study conducted in rats are additional probable effects of melamine.

These effects are serious for human health because they are significant and irreversible effects. This is confirmed by the fact that they fulfil the criteria for classification (STOT RE, carcinogenicity). According to the RAC opinion, classification as STOT RE is required based on the potential to cause acute and chronic renal diseases in humans. RAC also notes that

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[1] Commission Delegated Regulation (EU) 2022/692 of 16 February 2022 amending, for the purposes of its adaptation to technical and scientific progress, Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the 18th ATP to CLP). Pursuant to the second paragraph of Article 2 of this Regulation, this new harmonised classification applies from 23 November 2023. However, pursuant to the third paragraph of that provision substances and mixtures may already be classified, labelled and packaged in accordance with this classification.

the mode of action of carcinogenesis established in experimental animals cannot be disregarded as potentially relevant in humans. Thus, melamine fulfils the criteria for classification as a suspected human carcinogen. An additional harmonised classification may be warranted based on the observed effects on reproductive toxicity. These effects are also significant when combined with environmental fate properties leading to irreversible and increasing presence in the environment for the reasons described below.

Ecotoxicity:

The observed testicular and sperm effects of melamine identified in experimental animals (rats) are considered relevant for identification of probable serious effects on the environment. They can impact reproduction and can have an effect on the population level. Rats are rodents and rodents represent approximately 42% of all mammalian species. Rodents play an important role in the environment, for example in the dispersal of seed and spores, pollination, energy and nutrient cycling, modification of plant succession and species composition. Rodents are a food source for many predators.

There is also scientific evidence of probable serious effects on fish (mortality and growth) and on aquatic invertebrates (mobility, poor condition). As supporting information, effects were observed on terrestrial birds (decreased egg shell strength). These effects are serious because they also can have an effect on population level.

These effects are also significant when combined with environmental fate properties leading to irreversible and increasing presence in the environment for the reasons described below.

Concerns arising from the substance properties

The concern raised by melamine is triggered by individual properties as well as by combination of its properties.

Concern for an irreversible and increasing presence in the environment

The combination of the substance intrinsic properties persistency, mobility and potential for being transported in the water phase over long distances lead to a potential to cause an irreversible presence in the aquatic environment, together with a widespread contamination of the aquatic environment.

Due to its low tendency for adsorption, melamine will not attach to suspended or organic matter in the environment to any significant degree.

Due to the lack of abiotic and biotic degradation of melamine, it is expected that there is no significant removal of melamine by biological processes in conventional municipal sewage treatment plants dealing with mixed sewage that predominantly originates from households. Thus, the overall amount of melamine emitted from production and use is, if at all, only marginally reduced by the treatment processes in such municipal sewage treatment plants.

It is acknowledged that sewage treatment plants that are specifically designed to treat sewage predominantly originating from industrial sites may achieve a higher removal efficiency. Such industrial sewage treatment plants are specifically designed to reflect the local situation and site specific legal requirements. Although such industrial sewage treatment plants may be relevant for melamine, no information is available about removal efficiency in such plants that would allow general conclusions about the removal efficiency to refine the release estimates nor their availability across the European Union. It is therefore assumed that manufacture and industrial applications of melamine (or its precursors) may contribute to distribution of melamine in the environment and it would have a significant cost, supporting the identified concern, to apply efficient methods even for industrial sewage treatment plants in the European Union.

Once released, melamine may remain in the environment for a long time due to its persistency.

Supporting monitoring data already confirmed occurrence of melamine in various rivers (e.g. Rhine, Meuse, Mulde, Danube), where sampling points do not influence each other because as they are located in different river catchment areas. Concentrations found exceeded the value of 0.1 µg/L. In addition, recent projects were able to identify and quantify melamine in groundwater samples in Germany and Switzerland.

In the NORMAN Empodat data base melamine was detected above limit of quantification (**LOQ**) in 958 cases and below LOQ in 267 cases in 10 countries, indicating a widespread distribution in the environment.

Due to the global water cycle and the fact that the aqueous compartments are all well connected, the high persistency and the high mobility of melamine lead to long distance transport processes in the environment. The intrinsic properties of melamine are likely to cause transport across water bodies to pristine oceans and groundwaters, raising the concern that the substance may also occur at remote locations from the origin of release.

Melamine stays in the environment even if emissions have already ceased, as can be concluded from the melamine's intrinsic properties and supported by the recurring findings in groundwater samples.

Due to the high persistency, the amount of the melamine present in the environment is expected to increase over time if continuous emission occurs. In addition, local concentrations may increase temporarily or permanently due to aridity periods e.g. as result of climate change.

Removal from the aquatic environment and from drinking water resources

Once melamine emerges in the aquatic compartment (as direct consequence of its use pattern or as result of the degradation of precursor substances) and is widely distributed in the environment, it is difficult to remove. This results from the recalcitrance of melamine against abiotic and biological processes, leading to very slow or negligible removal from the water phase.

Due to its intrinsic properties melamine will not be easily removed with natural processes or conventional drinking water purification techniques. This includes procedures such as river bank filtration or soil infiltration for groundwater enrichment, which are commonly applied on European level. Therefore, there is substantial evidence that melamine may not be removed from the water cycle, once a contamination of aquatic resources occurs. The same applies for the drinking water purification, as melamine will bypass these commonly used drinking water purification techniques and has been already found in drinking water.

Increasing exposure of humans and environmental organisms due to increasing presence in the aquatic environment and wide distribution.

Melamine is already present in surface waters. Computational models predict that, once occurring in the environment, melamine is able to remain in the environment for several years or maybe even decades and is able to reach remote regions. This is due to melamine's intrinsic property to disperse in the aquatic environment over several thousand kilometres. This means that detection of melamine and undesirable effects may occur far away from the point of the initial release.

Due to its mobility, melamine can widely distribute in the water bodies, making it difficult to control the arising concentrations and conclude on appropriate, effective measures to remove the substance from environmental aquatic media.

Depending on the level of continuation of emissions into the environment and resulting from persistency and mobility of melamine, overall concentration in the environment can be expected to increase over time. This can result in an increase of the concentrations in drinking water, too.

Consequently, exposure of environmental organisms to melamine via "natural" waters and exposure of humans via drinking water is expected to increase over time due to persistency and mobility. For these reasons and because melamine has probable serious effects, the occurrence of melamine in the environment should be prevented.

Human Health effects

Melamine has probable serious effects (urinary tract and carcinogenic effects), and therefore its presence in drinking water is a concern as it may cause effects if critical dose levels are exceeded.

Additionally, in an extended one-generation reproductive toxicity study conducted in rats, adverse histopathological changes (tubular degeneration/atrophy with related cellular debris in the epididymis) have been observed in the testis of F0 and F1 animals together with abnormal sperm cell morphology (detached head) seen both in F0 and F1 animals. Furthermore, an assessment on endocrine disrupting properties for melamine is ongoing.

Human exposure

As supporting information, ECHA notes that melamine has been repeatedly detected in human urine samples from the general population in the USA and in East Asia.

Melamine can also be ingested by infants through breast milk. Lactational and/or placental transfer was shown following exposure to melamine in animal studies.

Due to its persistence and mobility, melamine is able to reach the sources of drinking water. Continued emissions and the limits of retrievability from the aqueous phase may result in increasing concentrations in raw water in the future and humans may be exposed to increasing concentrations in drinking water, too.

Environmental effects

Due to the properties of melamine (persistency, mobility, and potential for being transported in the water phase over long distances) it is not possible to assess its (local) environmental concentration with sufficient certainty and to consider effect concentration limits for the environment by the means of standardised acute and chronic ecotoxicological tests and the assessment criteria investigated within (in short: no safe concentration limits can be derived).

One aspect that adds to the concern that the effects in the environment might currently be underestimated are sublethal effects observed in several species. In chronic fish studies mortality appeared and growth decreased (effect value in one study: no observed effect concentration (**NOEC**) 5.25 mg/L). Sub-lethal effects appeared in the long-term fish studies on the same organs as in the acute study: Kidney, liver and gills were affected with dose-dependent histological effects. Furthermore, in several fish studies there were effects on skin coloration and on blood cells, additionally the antioxidant system was impaired.

In aquatic invertebrates, the following effects were observed as well: In a chronic Daphnia test, the NOEC for reproduction was 18 mg/L. In a feeding study with Pacific white shrimp, effects on survival, growth and histological effects on the hepatopancreas, as well as effects on the antioxidant system were observed at 10 g/kg feed.

In an extended one-generation reproductive toxicity study conducted in rats, adverse histopathological changes (tubular degeneration/atrophy with related cellular debris in the epididymis) have been observed in the testis of F0 and F1 animals together with abnormal sperm cell morphology (detached head) seen both in F0 and F1 animals. Furthermore, an assessment on endocrine disrupting properties for melamine is ongoing. The observed effects on rats are considered relevant for identification of probable serious effects on the environment.

In a study with birds, effects on egg shell strength and egg shell weight were seen, that both decreased significantly after melamine exposure. These effects are important as they might be relevant for populations. In exposed hens Melamine as well as cyanuric acid were detected in the liver and kidneys. The study authors suggested that Melamine was biotransformed to cyanuric acid. This study on birds is used as supporting information in the assessment of environmental effects of melamine.

Hence the substance properties raise the concern that effects as described above or yet unknown effects could appear in the environment and lead to irreversible population-relevant effects, due to long-term exposure over the whole life and over several generations, keeping in mind continuous exposure via water and potentially increasing concentrations.

Societal concern

Efforts to purify drinking water from surface water or groundwater bodies should be as low as reasonably possible. Therefore, Member States shall introduce measures to protect the water bodies with the aim of avoiding deterioration in their quality (see Article 7.3 of the Water Framework Directive (2000/60/EC)).

The combination of melamine's intrinsic properties of persistence and mobility results in little effectivity of common and widely applied drinking water purification techniques, such as river bank filtration or soil infiltration for groundwater enrichment. Removal may only be achieved by advanced water purification techniques, if at all and at high costs that have to be paid predominantly by the society, not by the body that is responsible for the initial emission of melamine into the environment.

Exposure to humans might occur via consumption and use of contaminated drinking water. Furthermore, melamine received a harmonised classification for target organ toxicity after repeated exposure (STOT RE 2 (urinary tract)) and is likely carcinogenic to humans (Carc. 2). In case that humans may be harmed due to these potential effects, costs for medical treatment will be the result and those will be handed over predominantly to the society.

Consequently, there is societal concern regarding increasing concentrations of melamine in sources of drinking water, which requires action based on precautionary considerations.

This societal concern is further confirmed by reports that extraction of water from the Rhine and Meuse rivers was stopped due to the presence of melamine.

Concern related to co-exposure and combined effects and inability to derive a safe concentration

Melamine and other melamine analogues occur in the different environmental compartments. Therefore, co-exposure cannot be excluded. These substances can act jointly, so that exposures at comparatively low concentrations may lead to health and environmental effects. For example, combined effects due to co-exposure with other chemicals, e.g. cyanuric acid, have been reported in rats, pets and livestock. Effects occur at lower melamine concentrations following co-exposure to melamine and cyanuric acid, which is linked to the formation of highly nephrotoxic melamine–cyanuric acid crystals/stones. Potential combined effects as a consequence of co-exposure of melamine and cyanuric acid prompted the Dutch competent authority (RIVM) to lower their derived limit values for drinking water.

Therefore, appearance of undesirable effects due to additive or even synergistic mode of action cannot be excluded which adds to the concern that no safe concentration can be derived.

Overall evaluation of the concerns and summary with regard to the equivalent level of concern

The persistency, mobility and toxicity (specific target organ toxicity after repeated exposure and carcinogenicity) and the irreversibility of the contamination of the aquatic compartment compromise the quality of drinking water resources and give rise to the concern of increasing and wide spread exposure to wildlife and man via environment due to contaminated water.

Consequently, there is societal concern regarding increasing concentrations of melamine in sources of drinking water, which requires action, based on precautionary considerations. The environment provides natural drinking water sources, whose integrity needs to be ensured for future generations.

Based on these concerns the level of concern is considered very high due to the combination of the above-mentioned concerns which can be clustered into the following concern elements:

- Irreversible, wide spread and increasing presence in the environment (limited potential for removal of melamine from the aquatic environment and drinking water resources, persistency in the environment, potential to be transported to remote areas and continuous emission due to low degradation in sewage treatment plants),
- Increasing exposure of humans and environmental organisms as a result of the irreversible, wide spread an increasing presence in the environment (increasing contamination of drinking water resources, long-term exposure, exposure of remote areas),
- Concern about the effects observed and other potential effects (e.g. combined effects from concomitant exposure to similar substances)
- The combination of these concern elements results in a potential for:
    - Environmental and human health effects, potentially long-lasting and more likely in susceptible populations such as infants, which may occur in the future due to increasing exposure over time
    - Societal concern through its ubiquitous presence in and difficulty to remove from surface water and groundwater which are used as a source of drinking water

Conclusion

The combination of melamine’s substance properties causes very high concern to the environment and human health (man via environment).

The combined intrinsic properties which demonstrate scientific evidence of probable serious effects to human health and the environment and which give rise to an equivalent level of concern are the following: very high persistence, high mobility in water, potential for being transported in the water phase over long distances and toxicity. The combination of persistence and mobility of melamine lead to the difficulty of remediation from the environment and water purification. There is scientific evidence of probable serious effects for human health and the environment that may occur with increasing concentrations in the environment. These probable serious effects to human health are urinary tract toxicity, carcinogenicity and reproductive toxicity. The probable serious effects to the environment are sub-lethal effects on fish and aquatic invertebrates and reproductive toxicity in rats and other mammals.

Annex 2: Procedure

1. On 26 August 2022, Germany presented a proposal under Article 59(3) and Annex XV of the REACH Regulation on identification of Melamine as a substance which satisfy the criteria of Article 57 (f) of REACH.
2. On 2 September 2022, the Annex XV dossier was circulated to Member States and the Annex XV report was made available to interested parties on the ECHA website as required by Articles 59(3) and 59(4).
3. Melamine received comments from both Member States and interested parties on the proposal.
4. On 16 November 2022, the dossier was referred to the Member State Committee (MSC) and discussed in the MSC meeting on 13-15 December 2022.